Intercellular Communication and Heterosynaptic Metaplasticity in the Rodent Hippocampus

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Abstract

Long-term potentiation (LTP) and long-term depression (LTD) are two forms of synaptic plasticity thought to underlie learning and memory. LTP and LTD are characterised by a persistent increase or decrease, respectively, in synaptic transmission. Synaptic plasticity is vital for neural health and cognition, however unconstrained plasticity compromises learning and, in the extreme, may be injurious. Mechanisms must therefore be in place to prevent excessive LTP and LTD. Such regulation comes in part through processes termed *metaplasticity*, whereby neuronal activity influences later plasticity induction.

The influential Bienenstock, Cooper and Munro (BCM) model of synaptic plasticity proposes a cell-wide plasticity threshold that shifts as a function of integrated postsynaptic action potential (AP) firing, such that greater AP firing raises the threshold for LTP induction and lowers the threshold for LTD induction. This homeostatic function therefore maintains synaptic plasticity within optimal bounds. Importantly, the BCM model (and more recent derivatives) posits that alterations to the plasticity threshold occur at all synapses on a given cell, whether active in generating APs or not. Recent evidence suggests that such heterosynaptic regulation of plasticity thresholds exists in the hippocampus, a brain region thought to be involved in certain forms of memory formation. In keeping with BCM predictions, strong 'priming' activity delivered to synapses in hippocampal CA1 inhibits subsequent LTP and facilitates subsequent LTD at a neighbouring pathway quiescent during priming. This metaplastic state is even able to spread heterodendritically, from the basal dendrites of stratum oriens (SO) to the apical dendrites of stratum radiatum (SR).

The principal aim of this thesis was to expand upon the previous findings of heterosynaptic and heterodendritic metaplasticity in CA1, and in particular to determine the mode of long-distance communication which allows synaptic innervation to alter plasticity thresholds at sites hundreds of microns away. To this end, extracellular and intracellular

electrophysiological experiments were conducted in acute hippocampal slices taken from rats or mice.

Various patterns of priming stimulation were delivered to synapses in SO or SR, prior to testing LTP/LTD induction in a second pathway in either stratum. Inhibition of LTP in SR could be seen following several paradigms of repeated 100 Hz priming stimulation delivered to SR or SO. Further supporting the robustness of the effect, the metaplasticity was seen at two different ages and in two different rodent species. However, priming with theta-burst stimulation did not alter subsequent plasticity. Further, repeated 100 Hz priming delivered to SR did not alter subsequent LTP in SO, which contrasts with the cell-wide metaplasticity predicted by the BCM model.

To test the importance of postsynaptic depolarization in generating the metaplasticity, individual pyramidal cells were hyperpolarized to -90 mV during SO priming via somatic injection of negative current. This procedure, delivered via sharp electrodes, abolished AP firing during priming and maintained the somatic membrane potential below resting values, thus blocking the spread of depolarization from SO to SR. However, priming under these conditions still triggered a reduction in later LTP in SR. Thus, the BCM prediction that cell-firing drives alterations to the plasticity threshold was not applicable to the current model. Certain derivatives of the BCM model implement altered membrane properties as an expression mechanism for altering LTP/LTD thresholds. However, no alterations were seen in the magnitude of the medium or slow afterhyperpolarisation, the *h* current or input resistance following priming. Instead, priming was found to require the activation of M1-acetylcholine receptors and release of Ca^{2+} from intracellular stores.

To test the possibility that intercellular communication is required for the long-distance spread of the metaplasticity, pharmacological methods were utilised to target two common intercellular modes of communication; purinergic signalling and gap junctions.

Heterosynaptic metaplasticity was found to require hydrolysis of extracellular ATP to adenosine, and activation of A_2, but not A_1 adenosine receptors. Further, heterosynaptic metaplasticity was blocked when priming occurred in the presence of the non-selective gap junction blockers carbenoxolone and meclofenamic acid, and by a connexin43-specific mimetic peptide. This latter result provides strong support that astrocytes are involved in the long-distance communication between dendritic layers. A model of neuron-astrocyte-neuron signalling is proposed as an explanation of these results.

Possible function(s) of the heterosynaptic metaplasticity are considered. The departures from the predictions of the BCM model suggest that this form of metaplasticity is not a graded, homeostatic response to postsynaptic activity in single cells. Rather, heterosynaptic metaplasticity as described in this thesis appears well placed to regulate activity at the network level, and may serve as a neuroprotective mechanism.

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List of abbreviations

AA = Arachidonic acid

AC = Adenylyl cyclase

ADP = Afterdepolarization

f/m/sAHP = Fast/Medium/Slow afterhyperpolarisation

AMPAR = α-amino-3-hyroxy-5-methyl-isoxazole-propionic acid receptor

AP = Action potential

AR = Adenosine receptor

ATP = Adenosine triphosphate

bAP = backpropagating action potential

BCM model = Bienenstock, Cooper & Munro model

BDNF = Brain derived neurotrophic factor

BK channel = Large conductance potassium channel

CA1-3 = Cornu Ammonis 1-3

CaM = Calmodulin

CaMKII = Calcium/calmodulin dependent protein kinase II

cAMP = Cyclic-adenosine monophosphate

CBX = Carbenoxolone

cGMP = Cyclic-guanosine monophosphate

CPA = Cyclopiazonic acid

CREB = Cyclic AMP response element binding protein

CSD = Cortical spreading depression

Cx43 = Connexin 43

DAG = Diacylglycerol

DG = Dentate gyrus

dH_2O = distilled hydrogen dioxide

EAAT 1= Excitatory amino acid transporter 1

EC = Entorhinal cortex

EE = Enriched environment

E-LTD = Early phase LTD

E-LTP = Early phase LTP

ER = Endoplasmic reticulum

ERK = Extracellular signal related kinase

fEPSP = Field excitatory postsynaptic potential

GABA = Gamma aminobutyric acid

GIRK = G-protein coupled, inward rectifying potassium channel

GJN = Gap junction

GLAST = Glutamate aspartate transporter

GLT = Glutamate transporter 1

GPCR = G-protein coupled receptor

HCN channel = Hyperpolarization activated, cyclic nucleotide gated channel

HF = Hippocampal formation

HFS = High frequency stimulation

hLTD = Heterosynaptic long term depression

H.M. = Henry Molaison

HSD = Heterosynaptic depression

iGluR = Ionotropic glutamate receptor

I-1 = Inhibitor 1

I_h = Hyperpolarization activated mixed cation current

I_{NMDAR} = NMDAR current

IP_3 = Inositol-bis-phosphate into inositol-1,4,5-trisphosphate

IPC = Ischemic preconditioning

KAR = Kainate receptor

LIF = Leukaemia inhibitory factor

LFS = Low frequency stimulation

LSD test = Least Significant Difference test

LTD = Long term depression

LTP = Long term potentiation

L-LTD Late phase LTD

L-LTP = Late phase LTP

mAChR = Muscarinic acetylcholine receptor

MAPK = Mitogen activated protein kinase

MFA = Meclofenamic acid

mGluR = Metabotropic glutamate receptor

nAChR = nicotinic acetylcholine receptor

NMDAR = *N*-methyl-D-aspartate receptor

NO = Nitric oxide

PKA = Protein kinase A

PKC = Protein kinase C

PKG = Protein kinase G

pl = Picoliter

PP1 = Protein phosphatase 1

PP2B = Protein phosphatase2 B

PS = Protein synthesis

PTP = Post-tetanic potentiation

PZN = Pirenzepine

R_{in} = Input resistance

RyR = Ryanodine receptor

SC = Schaffer collateral

SFA = Spike-frequency accommodation

SK channel = Small conductance potassium channel

SLM = Stratum lacunosum moleculare

SO = Stratum oriens

SP = Stratum pyramidale

SR = Stratum radiatum

tHSD = Transient heterosynaptic depression

TBS = Theta burst stimulation

VGCC = Voltage gated calcium channel

V_m = Membrane potential

1. Introduction

1.1 Thesis overview

The hippocampus is an intensely studied region of the brain. Since Donald Hebb first formalised the idea of structural or functional synaptic alteration as a mechanism of memory (Hebb, 1949), the hippocampus has been the most popular model system for investigating such changes. Hebbian changes at hippocampal synapses have been extensively researched, whether mechanistically or phenomenologically. These studies have given substantial credence to the proposed roles of synaptic plasticity in learning and memory (S. J. Martin, Grimwood, & Morris, 2000). Complementary to this, neuropsychological and systems-level studies of hippocampal function have supported the notion that this brain region is involved in certain types of memory formation (Buzsaki & Moser, 2013; Eichenbaum, 2004).

An influential model of synaptic plasticity was proposed, in which synaptic modification takes place when paired presynaptic and postsynaptic activity falls above or below a certain threshold (Bienenstock, Cooper, & Munro, 1982). According to the model, activity falling below the modification threshold will result in synaptic depression, whereas activity in excess of the threshold will produce synaptic potentiation. These aspects of the model have been validated experimentally in the hippocampus and elsewhere (Dudek & Bear, 1992; Kirkwood, Rioult, & Bear, 1996). Another important aspect of the Bienenstock, Cooper and Munro (BCM) model is that the modification threshold itself is plastic; that is, the threshold varies as a function of the cell's recent history of activity, with decreased postsynaptic cell-firing reducing the threshold and high levels of firing having the opposite effect (Bienenstock, et al., 1982). This experience-dependent shift in plasticity thresholds, termed

'metaplasticity' (Abraham & Bear, 1996), has also received experimental support (Abraham, Mason-Parker, Bear, Webb, & Tate, 2001; Kirkwood, et al., 1996).

A third aspect of the BCM model is that alterations to the plasticity threshold are driven by a global trigger, cell-firing. Thus, modifications to the threshold will hold true for all synapses on a given cell, active or not. In other words, synaptic activity which triggers sufficient firing will raise the plasticity threshold both *homosynaptically and heterosynaptically* (Bienenstock, et al., 1982). Such heterosynaptic changes have indeed been documented in multiple subfields of the hippocampus (Abraham, et al., 2001; H. Y. Wang & Wagner, 1999). Recently, a study was reported in which strong stimulation of afferents to hippocampal area CA1 produced a metaplastic shift in the plasticity threshold which spread not only heterosynaptically, but also *heterodendritically* (Hulme, Jones, Ireland, & Abraham, 2012). In this model, the metaplastic state spread to quiescent synapses hundreds of microns away from those activated during 'priming' stimulation. This report is in keeping with the cell-wide alterations to the plasticity threshold predicted by the BCM model. However, mechanistic discrepancies are evident between the metaplasticity described by Hulme and colleagues and the BCM model.

The aim of this thesis is to provide a more detailed characterisation of the model of heterosynaptic and heterodendritic metaplasticity described by Hulme et al., with particular emphasis on the mechanisms which allow the metaplastic state to spread over such considerable distances.

1.2 The hippocampal formation

The hippocampal formation (HF) of the rat is a curved structure extending from the forebrain near the septal nuclei into the temporal lobe. The HF is buried deep in

the brain, flanked on the one side by the medial edge of the cortex and on the other by the thalamus (**Fig. 1.1a**). The distinct cortical subregions that together make the HF are the entorhinal cortex (EC), dentate gyrus (DG), hippocampus proper (areas CA1-3) and subicular complex (subiculum, pre- and parasubiculum).

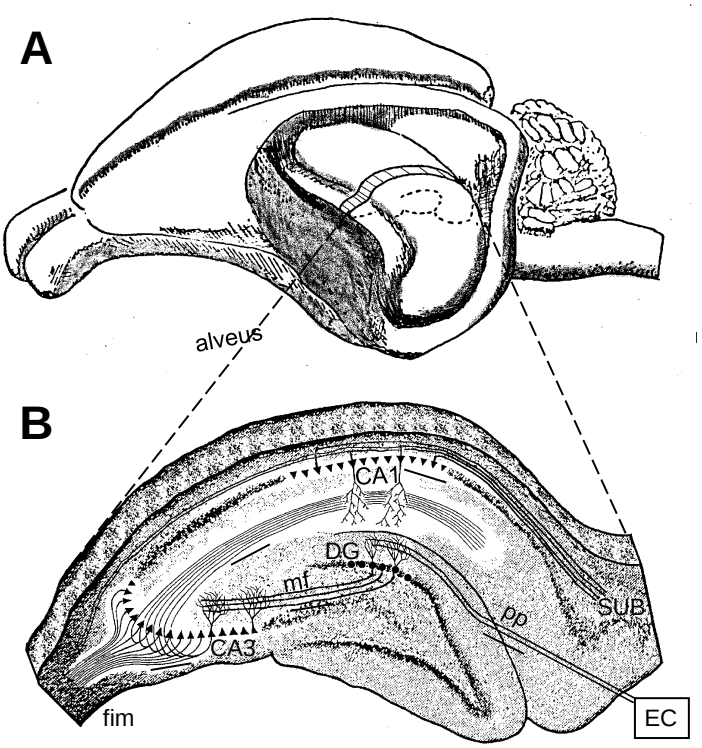

Figure 1.1. The hippocampal formation of the rat.
A: The hippocampus lying in situ. The cortex of the temporal lobe is missing to reveal the HF (original image by D. S. Kerr). **B**: Cross sectional view of the HF denoting glutamatergic pathways of the trisynaptic circuit: the perforant path (PP) extends from EC to DG; The mossy fibres (mf) travel from DG to CA3 and; the Schaffer collaterals (Sch) run from CA3 to CA1. Reciprocal connections and direct inputs from EC to CA regions are not shown. **A** and **B** modified by N. McNaughton. Reprinted with permission.

1.2.1 Hippocampal function

Perhaps the dominant view of hippocampal function relates to its role in memory. In early studies of single cell activity in hippocampus, cells were found that that fired only when the animal was in a given location in an environment (O'Keefe, 1976; O'Keefe & Dostrovsky, 1971). These ‘place cells’ were taken as evidence of a hippocampal role in spatial memory. The ‘cognitive map’ theory holds that the

function of the rat hippocampus is to allow the organism to navigate familiar environments. Accordingly, hippocampal lesions in rats produce spatial memory deficits (A. H. Black, Nadel, & O'Keefe, 1977; Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe, Nadel, Keightley, & Kill, 1975). However, spatial learning is largely intact following lesion of ventral hippocampus (E. Moser, Moser, & Andersen, 1993). Further, hippocampal lesions affect non-spatial learning also (Bunsey & Eichenbaum, 1996), and many hippocampal cells fire during non-spatial tasks (Hampson, Simeral, & Deadwyler, 1999; Wood, Dudchenko, & Eichenbaum, 1999). These findings strongly suggest a non-spatial element of hippocampal function.

Early lesion studies in primates suggested that bilateral ablation of temporal lobe structures, including the HF, triggered non-spatial memory deficits (S. Brown & Schafer, 1888). Similar observations were later made following hippocampal lesion in humans, including the famous patient Henry Molaison (H.M.: Scoville & Milner, 1957). H.M. exhibited profound anterograde amnesia and was also unable to recall information from some years leading up to his operation. Studies with H.M. and other amnesiacs suggested that hippocampal damage is associated with specific types of memory deficits. Specifically, damage to the HF does not typically disrupt acquisition of new motor skills but impairs retention of new information regarding facts or events (N. J. Cohen & Squire, 1980). These studies have been taken as evidence that the HF, along with other structures of the temporal lobe, is required for “declarative memory” (conscious recall of semantic and episodic information that can be declared or verbalised), but not “nondeclarative memory” (memory for procedures or learned actions that are expressed behaviourally without verbalisation: Squire, 1982; Squire & Zola-Morgan, 1991). The declarative memory theory has enjoyed popularity, but it is not without criticism. Opponents point to studies in which certain forms of declarative

memory were unaltered by hippocampal lesions (M. W. Brown & Aggleton, 2001; Mumby, 2001). Further, much research in the field has been conducted on animals, and it is unclear how declarative memory relates to organisms without the ability to verbalise or, possibly, consciously recall (Eichenbaum, 1997).

Episodic memory is a subdivision of declarative memory which accounts for the specific capacity to remember a personal experience or event (episode), for example details such as time, place and context (Tulving, 1972). Episodic memory is distinguished from simply knowing details or facts without an awareness of how this information came to be learned (i.e. semantic memory), and hippocampal damage in humans is associated with the loss of the former but not the latter (Vargha-Khadem, et al., 1997). However, concerns surround the literature on episodic memory due to the inability to ascertain awareness of prior experience in animal studies, and the reliance in human studies on subjective reporting without validation of truly 'remembering' an event. Nevertheless, there is evidence that rats display memory for sequences of events, at least in odour learning tasks, which are inherently episodic due to their contextual content (e.g. information on the preceding and following events). Further, hippocampal lesion severely impairs recall of temporal ordering (Agster, Fortin, & Eichenbaum, 2002; Fortin, Agster, & Eichenbaum, 2002; Kesner, Gilbert, & Barua, 2002). Notably, the firing of place cells can also be explained in an episodic memory framework whereby journeys through space are encoded as sequences of events at given locations (Eichenbaum, 2000b; Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999). Thus, place cell firing occurs when movements have some behavioural significance following a relevant experience.

A more recent derivative of the declarative memory theory, the "relational processing theory", proposes a revised view of the temporal lobe in processing

declarative memory (Eichenbaum, Otto, & Cohen, 1992). According to this theory, declarative memory is supported by a relational representation. Memories are encoded according to relevant relations between stimuli. This allows items to be encoded as distinct entities, but also as part of larger events along with the relevant relations between items. Relative to encoding of individual facts or events, relational encoding is flexible and allows associations to be applied in novel situations. According to the model, neocortical areas hold information on specific items in the short-term, prior to processing in the HF. The neocortex will ultimately be the site of long-term storage also. Parahippocampal cortices support intermediate-term retention of individual items, whereas the HF processes and organises information based on relevant relations between items (Eichenbaum, 2000a; Eichenbaum, Otto, & Cohen, 1994).

Although several different models of hippocampal function have been proposed, the functions suggested in each are not necessarily mutually exclusive. For example, relational encoding is compatible with spatial and non-spatial episodic memory. Different neurons in hippocampus fire in relation to spatial or contextual aspects of odour recognition learning (e.g. spatial location, whether the odour is the same or different as in the preceding trial or a combination of these factors). These firing patterns may therefore reflect the encoding of spatial and non-spatial aspects of events in distinct episodes, and also the associations between them (Wood, et al., 1999; Wood, Dudchenko, Robitsek, & Eichenbaum, 2000). Other theorists point to the sequential firing patterns of hippocampal neurons during encoding and replay of spatial information, and draw parallels with the binding of sequential events or items which together comprise an episode (Buzsáki, 2005; Buzsaki & Moser, 2013; O. Jensen & Lisman, 2005; Skaggs & McNaughton, 1996). The same physiological mechanism, sequential firing in cell assemblies, may therefore support spatial

navigation and episodic memory. Thus, the hippocampus may contribute to information storage in ways predicted by several models.

1.2.2 Hippocampal anatomy of the rat

The structure of the HF varies across septotemporal levels. At the extreme septal end, only the dentate gyrus and hippocampus proper are visible. The subiculum becomes apparent at roughly one third of the length, followed by the pre-, then parasubiculum, and finally the EC. Except in entorhinal areas, the HF is stratified into three layers. The deepest, containing afferent and efferent fibres, is referred to as the hilus in the DG and the stratum oriens (SO) in areas CA1-3. Next is the cell body layer, termed the granule cell layer in the DG and stratum pyramidale (SP) in the CA regions and subiculum in reference to the principle cells, granule or pyramidal, found therein. Most superficial is the molecular layer (stratum moleculare). This layer is divided into three sublayers in CA3: the stratum lucidum is the site of input from the DG; the stratum radiatum (SR) holds the apical dendrites of pyramidal cells with soma in SP; and the stratum lacunosum moleculare (SLM) contains the apical dendritic tufts. CA1 and CA2 contain SR and SLM, but not stratum lucidum.

The major excitatory pathways of the HF follow a looped course termed the "trisynaptic circuit" (Andersen, Bliss, & Skrede, 1971; see Fig. 1.1b). Input axons from the EC, the perforant path, penetrate the hippocampal fissure and synapse with DG granule cells. Granule cell axons, termed mossy fibres (Cajal, 1894), project onto pyramidal cells in CA3. In turn, axon collaterals from these cells (Schaffer collaterals: SC) synapse with CA1 pyramidal cells. Expanding the trisynaptic model, the 'polysynaptic pathway' also includes direct projections from the EC to SLM of CA1-3 via the subiculum (Hjorth-Simonsen, 1972; Steward, 1976), and recurrent CA3

collaterals (Laurberg, 1979). Several backprojections have also been characterised. These extend from CA3 to DG (Swanson, Wyss, & Cowan, 1978), CA1 to CA3 (Laurberg, 1979), subiculum to CA1 (D. M. Finch, Nowlin, & Babb, 1983) and subiculum and CA1 to EC (Köhler, 1985; Swanson, et al., 1978). These reciprocal projections allow for reverberatory circuits throughout the HF.

Entorhinal Cortex

The EC is the primary source of cortical input to the HF, and the main point of exit for output relayed back to the neocortex. The lateral EC is reciprocally connected with the perirhinal, insular, piriform, lateral frontal, parietal, temporal, occipital, and cingulate cortices. The medial EC connects preferentially to the postrhinal, medial frontal, and olfactory cortices (Burwell & Amaral, 1998a; Insausti, Herrero, & Witter, 1997). Subcortical structures which project to the EC include the amygdala, striatum, septum, hypothalamus, thalamus and brain stem (Amaral & Kurz, 1985a; Aylward & Totterdell, 1993; Canteras, Simerly, & Swanson, 1994; Pikkarainen, Ronkko, Savander, Insausti, & Pitkanen, 1999; Vangroen & Wyss, 1992b; Vertes, 1991). The EC is divided into six layers. Neocortical inputs terminating in superficial layers (I-III) synapse with entorhinal neurons, which in turn supply the axons of the PP. Afferent projections from the hippocampus extend to deeper layers (IV-VI) of the EC, which in turn project to other cortical areas.

Dentate Gyrus

The three layers of the DG are folded in a V- or U-shaped structure separated from the subiculum and CA1 by the hippocampal fissure. From the principal cell layer, granule cells project a distinctive cone-shaped dendritic arbor towards the

superficial molecular layer. These cells receive their primary inputs from the EC, but are also innervated by certain subcortical structures, namely the septum, hypothalamus and brain stem (Cowan, Raisman, & Powell, 1965; Mosko, Lynch, & Cotman, 1973; Segal, Pickel, & Bloom, 1973; Wyss, Swanson, & Cowan, 1979).

Projections from the granule cell layer take the form of unmyelinated MF axons. These fibres project to the polymorphic layer, where they sprout separate collaterals which branch and synapse with dendrites of mossy cells, pyramidal basket cells and GABAergic interneurons (Acsady, Kamondi, Sik, Freund, & Buzsaki, 1998; Ribak, Seress, & Amaral, 1985). The main MF projections continue through the polymorphic layer, terminating in CA3.

Granule cell bodies and apical dendrites receive inhibitory projections from basket cells and chandelier cells of the molecular layer. The mossy cells of the polymorphic layer send excitatory projections to the proximal dendrites of granule cells (Bramham, Torp, Zhang, Stormmathisen, & Ottersen, 1990; Laurberg & Sorensen, 1981). This projection originates both ipsi- and contralaterally, and is termed the associational/commissural projection. These feedback projections from mossy to granule cells largely follow the longitudinal axis of the HF, in either direction (Ishizuka, Weber, & Amaral, 1990; Swanson, et al., 1978). Granule cells throughout the DG project to all layers of CA3. However, axons terminating in proximal CA3 do so largely in SO and SP, whereas projections to distal CA3 terminate on the initial shafts of dendrites in stratum lucidum (Blackstad, Brink, Hem, & Jeune, 1970; Blackstad & Kjaerhei, 1961; Swanson, et al., 1978).

Hippocampus

Regions CA1-3 display relatively consistent cytoarchitecture. SP of CA1 is dense with somata, but less so in CA2 and CA3. Pyramidal cells are the principal cells of the hippocampus. Their axons traverse SO to form the alveus, alongside extrinsic fibres. The dendritic organisation of CA3 pyramidal cells varies (Ishizuka, Cowan, & Amaral, 1995). Cells located proximal to the DG have shorter dendritic arbor with little or no tufts. These cells receive limited input from the EC and heavier innervation from MF projections terminating on apical and basal dendrites. In contrast, distal CA3 cells receive MF input in apical regions only. Most CA2 pyramidal cells display similar morphology to those in distal CA3, but with slightly shorter basal dendrites in SO. A population of neurons located at the CA2-CA1 border share characteristics with CA1 cells. Pyramidal cells display a more homogenous dendritic arbor in CA1 than in CA3 and have smaller somata. CA1 pyramidal cell dendrites branch at deeper levels of SR before forming a broad plexus in SLM.

The hippocampus contains numerous GABAergic interneurons. Basket cells in SP inhibit the somata and proximal dendrites of multiple pyramidal cells (Andersen, Eccles, & Loyning, 1964; Andersen, Loyning, & Eccles, 1964). Chandelier cells in SP inhibit the proximal axons of pyramidal cells (X. G. Li, Somogyi, Tepper, & Buzsaki, 1992). Bistratified and trilaminar cells extend axon collaterals from SP and SO, respectively, synapsing onto SR or SO dendrites (Buhl, Halasy, & Somogyi, 1994; Sik, Penttonen, Ylinen, & Buzsaki, 1995). Oriens-lacunosum moleculare (O-LM) interneurons are found in SO and SR in CA3, but only SO in CA1 (McBain, Dichiara, & Kauer, 1994). O-LM cells are innervated by recurrent pyramidal cell collaterals, and extend axons to the tuft dendrites in SLM. SR contains numerous stellate-shaped interneurons (Kawaguchi & Hama, 1988). Their dendrites largely remain in this layer

and their axons terminate on pyramidal cell dendrites. Similar cells have been described in SLM (Lacaille & Schwartzkroin, 1988). The IS (interneuron-selective) neuron is found in all strata (Gulyas, Hajos, & Freund, 1996). IS neurons are innervated by all major hippocampal afferents and inhibit all other types of hippocampal interneuron, but not principal cells. Finally, "back-projection" neurons in CA1 near the SO-alveus border project back to SR of CA3, or even the hilus of the DG (Sik, Ylinen, Penttonen, & Buzsaki, 1994). These cells are innervated by CA1 pyramidal cells and are thus a direct opposite of CA3-CA1 afferent projections.

The hippocampus is heavily connected with other brain regions. SO and SR of all subfields receive projections from the amygdaloid complex, and a reciprocal projection from distal areas of CA1 has also been described in temporal portions of the HF (Ottersen, 1982; Pikkarainen, et al., 1999). SLM of distal CA1 is also bi-directionally connected with the peri- and postrhinal cortices (Swanson & Cowan, 1977). More recently, direct projections from CA1 to several cortical areas have been described (Cenquizca & Swanson, 2007): The dorsal third of CA1 projects to retrosplenial areas; projections from ventral CA1 extend to visual, auditory, somatosensory, gustatory, main and accessory olfactory, and visceral cortices, and projections from the length of CA1 (although mainly ventral areas) extend to the anterior cingulate, prelimbic, infralimbic, and orbital areas via the fornix. Subcortical connections with the hippocampus include projections from CA1-3 to the lateral septal nucleus (Swanson & Cowan, 1977), from the posterior hypothalamus to CA2 (Magloczky, Acsady, & Freund, 1994), from the thalamus to CA1 (Herkenham, 1978), and from the brain stem to CA1-3 (Pasquier & Reinososuarez, 1978).

CA3 also projects contralaterally to all CA subfields (Laurberg, 1979). The same cells give rise to these commissural projections and the SCs, and both pathways

follow a similar topography. CA3 axons traverse two-thirds the longitudinal axis of the HF, ipsi- and contralaterally (X. G. Li, Somogyi, Ylinen, & Buzsaki, 1994).

Subicular complex

The subicular complex is located between CA1 and the EC ventrally, and between CA1 and the retrosplenial cortex dorsally. This area contains the subiculum proper, and the pre- and parasubiculum. The subiculum proper has a large principal cell layer, a polymorphic layer and a molecular layer. The molecular layer contains deeper and superficial portions, analogous to SR and SLM of CA1. SO terminates at the CA1-subiculum border. The pre- and parasubiculum contain an external cell layer with smaller or larger pyramidal cell bodies, respectively.

Hippocampal output to the cortex travels extensively via the subiculum. The proximal dorsal subiculum sends axons to the deep layers of the pre- and postrhinal, and retrosplenial cortices (Witter, Groenewegen, Dasilva, & Lohman, 1989). Return connections are extended from the perirhinal cortex to the proximal subiculum, from the postrhinal cortex to the distal subiculum, and from the retrosplenial cortex to the pre- and parasubiculum (Vangroen & Wyss, 1992a; Witter, et al., 2000). Subicular contacts with other cortical regions include projections to the lateral and medial orbitofrontal, prelimbic, infralimbic, and anterior cingulate cortices (Verwer, Meijer, Van Uum, & Witter, 1997; Wyss & Vangroen, 1992). Reciprocal connections are made between the subiculum and subcortical structures including the amygdaloid complex, hypothalamus, thalamus and septum (Canteras & Swanson, 1992; Chandler & Crutcher, 1983; Pikkarainen, et al., 1999; Witter, Ostendorf, & Groenewegen, 1990; Wouterlood, Saldana, & Witter, 1990).

1.3 Cellular physiology

1.3.1 Membrane parameters and excitability

Cells in the hippocampus display a range of active and passive membrane properties. The resting membrane potential (V_m) of CA1 pyramidal neurons varies from -60 to -85 mV depending on the experimental preparation (Fricker, Verheugen, & Miles, 1999; Spruston & Johnston, 1992; Storm, 1987). Similar values have been obtained from principal cells of CA3 and DG (Keller, Konnerth, & Yaari, 1991; Staley, Otis, & Mody, 1992; Tyzio, et al., 2003), and from several hippocampal interneurons (Buchhalter & Dichter, 1991; Verheugen, Fricker, & Miles, 1999).

Estimates of the firing threshold in CA1 pyramidal cells range from -45 to -60 mV (Fricker, et al., 1999; Spruston & Johnston, 1992; Staff, Jung, Thiagarajan, Yao, & Spruston, 2000). These cells display action potentials (AP) with a half width of ~1 ms (Staff, et al., 2000), which are followed by four characteristic after-potentials (Storm, 1987, 1988, 1989; Storm, Borggraham, & Adams, 1987). The after-depolarization (ADP), is mediated by R-type voltage gated Ca^{2+} and persistent Na^{+} channels (Metz, Jarsky, Martina, & Spruston, 2005; Yue, Remy, Su, Beck, & Yaari, 2005). The fast, medium and slow after-hyperpolarizations (AHP) are mediated by a variety of K^{+} channels. For the fast AHP (fAHP), the channel in question is a voltage and Ca^{2+} gated, large K^{+} conductance (BK) type (Lancaster & Nicoll, 1987). The medium AHP (mAHP) is mediated by a mixture of BK, small conductance (SK) and muscarine-suppressed (M-type) K^{+} channels (Bond, et al., 2004; Gu, Hu, Vervaeke, & Storm, 2008; Gu, Vervaeke, Hu, & Storm, 2005; Storm, 1989). The slow AHP (sAHP) is mediated by a mixture of M-type K^{+} channel subtypes (K. S. Kim, Kobayashi, Takamatsu, & Tzingounis, 2012; Soh & Tzingounis, 2010; Tzingounis, et al., 2010; Tzingounis & Nicoll, 2008).

Lasting depolarization of CA1 neurons typically elicits a train of APs in a distinctive pattern characterized by a gradual reduction in spike-frequency (Madison & Nicoll, 1984). This "spike-frequency accommodation" (SFA) is due to the increased activity of the Ca^{2+}-activated K^+ channels mediating the AHP (Lancaster & Nicoll, 1987). Ca^{2+} influx following each AP exerts a cumulative effect on the amplitude of the AHP, thus increasing the duration of each spike-to-spike interval (Madison & Nicoll, 1984). SFA may largely be due to the activation of somatic L-type voltage gated Ca^{2+} channels and subsequent opening of co-localised SK channels (Bowden, Fletcher, Loane, & Marrion, 2001; Marrion & Tavalin, 1998). SFA is apparently a mechanism of constraining excitatory transmission, as opposed to limiting activity in general. While visible in principal cells throughout the hippocampal formation (Spruston & Johnston, 1992), SFA is typically much weaker in granule cells and GABAergic interneurons (Lacaille & Schwartzkroin, 1988; Schwartzkroin & Mathers, 1978). However, certain classes of interneuron do display SFA (Chitwood & Jaffe, 1998; Mott, Turner, Okazaki, & Lewis, 1997).

When hyperpolarized, pyramidal cells display a characteristic "sag" of V_m back towards more depolarized values (Halliwell & Adams, 1982). This "sag" is the product of the mixed-cation *h* current (I_h) which, while active at rest, becomes increasingly apparent in response to hyperpolarisation (P. R. Adams & Halliwell, 1982). Similarly, depolarization induces the deactivation of I_h and thus a hyperpolarizing "sag" (Spruston & Johnston, 1992). I_h is a feature of principal cells throughout the HF, and is also seen in several classes of interneuron (Bender, et al., 2001; Maccaferri & McBain, 1996; Spruston & Johnston, 1992). I_h is due to the activity of hyperpolarization-activated, cyclic-nucleotide-gated (HCN) channels, which are activated at potentials negative to ~ -55 mV (Maccaferri, Mangoni, Lazzari,

& Difrancesco, 1993). HCN channel activity is modulated by cyclic-adenosine monophosphate (cAMP) or cyclic-guanosine monophosphate (cGMP) binding to a domain on the C-terminus (DiFrancesco & Tortora, 1991). Cyclic-nucleotide binding induces a positive shift of < 20 mV in the channel's activation curve (Wainger, DeGennaro, Santoro, Siegelbaum, & Tibbs, 2001). The sensitivity of HCN channels to cAMP is also subject to activity-dependent change (J. Wang, Chen, Nolan, & Siegelbaum, 2002). Cellular expression of HCN channels increases travelling through the HF from DG to CA subfields to subiculum (Bender, et al., 2001; Notomi & Shigemoto, 2004). The dendritic distribution of HCN channels increases with distance from the soma (Lorincz, Notomi, Tamas, Shigemoto, & Nusser, 2002).

All HCN channel subtypes are found in the HF (Monteggia, Eisch, Tang, Kaczmarek, & Nestler, 2000; Notomi & Shigemoto, 2004). HCN1 homomers activate more rapidly and at more positive potentials, while HCN2 homomers are more sensitive to cAMP binding (C. Chen, Wang, & Siegelbaum, 2001). Heteromultimeric HCN1/2 channels display an intermediate kinetic profile which closely resembles the summed activity of I_h in CA1 pyramidal neurons, suggesting that they are the main contributors to I_h in these cells (C. Chen, et al., 2001).

1.3.2 Synaptic transmission

Glutamate

The excitatory amino acid glutamate is the main excitatory neurotransmitter in the HF (Biscoe & Straughan, 1966; Dolphin, Errington, & Bliss, 1982). Glutamate is exocytosed at presynaptic terminals, from where it binds to receptors before being taken up by excitatory amino acid transporters on neurons or glia (Danbolt, Lehre, Dehnes, Chaudhry, & Levy, 1998; Danbolt, Pines, & Kanner, 1990). Glutamate acts

primarily on three ionotropic receptor subtypes: α-amino-3-hyroxy-5-methyl-isoxazole-propionic acid (AMPA) receptors, kainate receptors, and *N*-methyl-D-aspartate (NMDA) receptors (Monaghan, Yao, & Cotman, 1985). Glutamate also activates a class of metabotropic receptor (mGluRs; Hirono, Ito, Yamagishi, & Sugiyama, 1988; Sugiyama, Ito, & Hirono, 1987).

AMPA receptors

AMPA receptors are heteromultimeric structures containing combinations of GluA1-4 subunits (Keinanen, et al., 1990). The AMPAR channel mediates Na^+ influx at resting V_m and K^+ efflux following depolarization. AMPARs on principal neurons exhibit slower deactivation and desensitization than those on interneurons (Geiger, et al., 1995). All AMPAR subunits exist as two variants, flip and flop, determined by alternative splicing of their extracellular ligand binding domain (Sommer, et al., 1990). AMPARs on pyramidal neurons mostly contain GluA2 'flip' variants, whereas nonpyramidal cells have a greater number of GluA1 'flop' variants. These subunit variants correlate strongly with cells' AMPAR desensitization profile (Lambolez, Ropert, Perrais, Rossier, & Hestrin, 1996).

The GluA2 pore-lining segment undergoes post-translational modification such that an arginine residue (R) is replaced with glutamine (Q), rendering the channel impermeable to Ca^{2+} (Sommer, Kohler, Sprengel, & Seeburg, 1991). In contrast, GluA2-lacking AMPARs are Ca^{2+} permeable (Bochet, et al., 1994).

Kainate receptors

Kainate receptors (KARs) are heteromultimers comprised of subunits GluK1-5 (formerly GluR5-7 and KA1 -2; Collingridge, Olsen, Peters, & Spedding, 2009).

GluKs 4 and 5 display the highest binding affinity, but cannot form functional channels alone (Herb, et al., 1992; Werner, Voigt, Keinanen, Wisden, & Seeburg, 1991). Ca^{2+} permeability is altered in GluK1/2-containing receptors following Q/R editing (Burnashev, Zhou, Neher, & Sakmann, 1995; Egebjerg & Heinemann, 1993).

KARs open and desensitize rapidly but recover slowly, meaning they are largely inactive (Lerma, Paternain, Naranjo, & Mellstrom, 1993). However, KARs can display EPSCs which outlast the canonical active period (Castillo, Malenka, & Nicoll, 1997). This may be due to altered desensitization following binding with certain post-synaptic density proteins (Garcia, et al., 1998). In the HF, KARs are widespread at presynaptic boutons where they modulate transmitter release (Gannon & Terrian, 1991; Herb, et al., 1992; Terrian, Connerkerr, Privette, & Gannon, 1991). KARs enhance or depress release following brief or prolonged activation, respectively, via unresolved mechanisms (Frerking, Schmitz, Zhou, Johansen, & Nicoll, 2001; Kamiya & Ozawa, 1998, 2000; Schmitz, Mellor, & Nicoll, 2001). Postsynaptic KARs modulate excitability via metabotropic pathways. KAR activation inhibits the sAHP in CA1 pyramidal cells via protein kinase A or C (PKA, PKC) (Grabauskas, Lancaster, O'Connor, & Wheal, 2007; Melyan, Wheal, & Lancaster, 2002). In CA3, GluK2 activation inhibits the sAHP and mAHP via activation of PKC, which may contribute to epileptogenesis (Fisahn, Heinemann, & McBain, 2005).

NMDA receptors

NMDA receptors are heteromultimers containing an obligatory GluN1 subunit, and additional combinations of GluN2A-D and GluN3A-B (S. L. Adams, Foldes, & Kamboj, 1995; Ikeda, et al., 1992; Monyer, et al., 1992; Moriyoshi, et al., 1991; Nishi, Hinds, Lu, Kawata, & Hayashi, 2001). GluN1 and 3 contain binding sites for

the co-agonists glycine or D-serine (Johnson & Ascher, 1987; K. Williams, Chao, Kashiwagi, Masuko, & Igarashi, 1996; Yao, Harrison, Freddolino, Schulten, & Mayer, 2008). GluN2 contains the glutamate binding site (Laube, Hirai, Sturgess, Betz, & Kuhse, 1997; Lummis, Fletcher, & Green, 1998).

Glutamate can remain bound to NMDARs for hundreds of milliseconds, allowing prolonged activation following relatively brief release (Lester, Clements, Westbrook, & Jahr, 1990). However, glycine or D-serine must be present at the agonist-binding site for the ionophore to open (Salt, 1988). V_m must also be depolarised above -50 mV or so to fully expel Mg^{2+} ions from the channel pore (Mayer & Westbrook, 1984; Mayer, Westbrook, & Guthrie, 1984). Thus, NMDARs act as coincidence detectors that open in times of conjoined pre- and postsynaptic activity (Wigstrom & Gustafsson, 1985). Once open, NMDARs are highly permeable to Ca^{2+} and monovalent cations (Ascher & Nowak, 1986).

Subunit composition alters NMDAR kinetics. Mg^{2+} unblock is slowest in GluN1/2B heteromers and fastest in GluN1/2C or GluN1/2D complexes. GluN1/2A receptors display an intermediate speed of unblocking (Clarke & Johnson, 2006). Thus, rapid depolarization causes greater unblocking of GluN1/2A heteromers. Glutamate binding is also subunit-dependent, with affinity rated as (highest to lowest) GluN1/2B → GluN1/2A → GluN1/2D → GluN1/2C (Laurie & Seeburg, 1994).

Less is known of the GluN3A/B subunits, although their presence reduces Mg^{2+} block, and also permeability and conductance (Das, et al., 1998; Matsuda, Kamiya, Matsuda, & Yuzaki, 2002; Y. F. Sasaki, et al., 2002). Interestingly, glycine or D-serine alone induce mutually occlusive currents in GluN1/3A or GluN1/3B receptors (Chatterton, et al., 2002). However, these receptors are rare in the mature HF (Chatterton, et al., 2002; Ciabarra, et al., 1995).

mGluRs

mGluRs are dimeric structures coupled to G-proteins activated upon glutamate binding (Kunishima, et al., 2000). Eight subtypes have been described, falling into three classes. G_q-coupled group I mGluRs (mGluR1 and mGluR5) accumulate at the periphery of postsynaptic densities, and stimulate the hydrolysis of inositol-bis-phosphate into inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG; Abe, et al., 1992; Aramori & Nakanishi, 1992). IP_3 activates receptors on the endoplasmic-reticulum (ER), stimulating the release of Ca^{2+} stored in this organelle (Ross, Danoff, Schell, Snyder, & Ullrich, 1992; Ross, et al., 1989; Yuzaki & Mikoshiba, 1992). Ca^{2+} and DAG together activate PKC (Sekiguchi, Tsukuda, Ase, Kikkawa, & Nishizuka, 1988; Xiang, Brammer, & Campbell, 1991).

G_i-coupled group II (mGluRs 2 & 3) and III (mGluRs 4,6,7 & 8) are largely presynaptic, found at preterminal portions of axons (group II) or at central, active zones (group III; Shigemoto, et al., 1997). These receptors are negatively coupled to adenylyl cyclase (AC); thus their activation inhibits cAMP formation and subsequent PKA activation (Okamoto, et al., 1994; Prezeau, et al., 1992; Tanabe, Masu, Ishii, Shigemoto, & Nakanishi, 1992; Winder & Conn, 1995). Presynaptic group II and III mGluRs also inhibit transmitter release (Bushell, et al., 1996).

GABA

Inhibitory transmission in the HF is mediated largely by gamma-aminobutyric acid (GABA; Alger & Nicoll, 1979; Fonnum & Stormmat, 1969). GABAergic receptors are either ionotropic $GABA_A$ and $GABA_C$Rs, or metabotropic $GABA_B$Rs. Heteropentameric $GABA_A$Rs combine $\alpha_{1\text{-}6}$, $\beta_{1\text{-}3}$, $\gamma_{1\text{-}3}$, δ ,ε ,π and $\rho_{1\text{-}3}$ subunits (Cutting, et al., 1992; Cutting, et al., 1991; Kato, 1990; Knoflach, et al., 1991;

Levitan, Blair, Dionne, & Barnard, 1988; Luddens, et al., 1990; Pritchett & Seeburg, 1990; Pritchett, et al., 1989; Schofield, et al., 1987; Shivers, et al., 1989; Wisden, et al., 1991; Ymer, et al., 1990; Ymer, et al., 1989). In the HF, the most prominent subunits are $\alpha_{1,2,4}$, β_3, γ_2 (DG) and $\alpha_{1,2,5}$, β_3, γ_2 (CA1-3), with α_4, $\beta_{1,2}$ and γ_3 present at lower levels and the remainder undetected (Sperk, Schwarzer, Tsunashima, Fuchs, & Sieghart, 1997). $GABA_A$Rs are permeable to the anions Cl^- and HCO_3^-. Cl^- influx is rapid when V_m is depolarized beyond the Cl^- reversal potential (Alger & Nicoll, 1979; Kaila, Voipio, Paalasmaa, Pasternack, & Deisz, 1993; Olsen, et al., 1984).

Heterodimeric $GABA_B$Rs combine GBR_1 and GBR_2 subunits (Jones, et al., 1998; Kaupmann, et al., 1997). Postsynaptically, they hyperpolarise V_m via PKC-dependent phosphorylation of G-protein coupled inward rectifying K^+ (GIRK) channels (Andrade, Malenka, & Nicoll, 1986; Dutar & Nicoll, 1988). Presynaptic $GABA_B$Rs inhibit transmitter release via cascades which downregulate N- and P-type voltage gated Ca^{2+} channels (Mintz & Bean, 1993; Scholz & Miller, 1991b).

Within the HF, $GABA_A$ and $GABA_B$Rs are most present in the molecular layer of the DG (Bowery, Hudson, & Price, 1987). More moderate levels are detected in the CA subfields, with $GABA_A$Rs present in all strata and $GABA_B$Rs more confined to SO and SR (Bowery, et al., 1987). $GABA_C$Rs, comprised of ρ_{1-3} subunits, have not been detected in the HF (Sperk, et al., 1997).

Purines

Several transmitters are co-released by neurons intrinsic to the HF, or are released by extrinsic afferents. Adenosine triphosphate (ATP) is co-released with glutamate (Pankratov, Lalo, Verkhratsky, & North, 2006, 2007) and is hydrolysed to ADP, AMP and adenosine by ectonucleotidases (Battastini, et al., 1995; Cunha,

Ribeiro, & Sebastiao, 1994; Nagy, Shuster, & Delgado-Escueta, 1986; Todorov, et al., 1997). ATP and ADP activate ionotropic P_{2X} and metabotropic P_{2Y} purinergic receptors (Collo, et al., 1996; Kanjhan, et al., 1999; Kidd, et al., 1995; Laitinen, Uri, Raidaru, & Miettinen, 2001; Moran-Jimenez & Matute, 2000; Rubio & Soto, 2001; Y. Sasaki, et al., 2003; Simon, Webb, & Barnard, 1997; Webb, Henderson, Roberts, & Barnard, 1998; Yu, et al., 2008). Adenosine activates its own distinct class of purinergic receptor: the P_1R.

The four subtypes of metabotropic P_1R are named A_1, A_{2A}, A_{2B}, and A_3 in reference to their endogenous ligand (Libert, et al., 1991; Maenhaut, et al., 1990; Stehle, et al., 1992; Q. Y. Zhou, et al., 1992). All are expressed throughout the HF, although A_1Rs are most common (Dixon, Gubitz, Sirinathsinghji, Richardson, & Freeman, 1996). AR subtypes are commonly divided into the inhibitory A_1- and A_3Rs (both coupled to $G_{i/0}$) and the G_s-coupled facilitatory A_{2A} and $A_{2B}Rs$ (Dickenson & Hill, 1998; Furlong, Pierce, Selbie, & Shine, 1992; Maenhaut, et al., 1990; Munshi & Linden, 1989). A G_q-coupled subset of $A_{2B}Rs$ exists in humans, but is unreported in rat brain (Linden, Thai, Figler, Jin, & Robeva, 1999; Ryzhov, et al., 2009).

Presynaptic A_1Rs limit release of excitatory but not inhibitory neurotransmitters via inhibition of N-type-Ca^{2+} channels (Lambert & Teyler, 1991; Manita, et al., 2004; Scholz & Miller, 1991a; Yoon & Rothman, 1991). Postsynaptic A_1Rs initiate a hyperpolarizing outward K^+ current (Alzheimer & Tenbruggencate, 1991; Deckert & Jorgensen, 1988). In comparison, presynaptic $A_{2A}Rs$ facilitate transmission by suppressing A_1Rs and triggering release of the neurotrophin brain derived neurotrophic factor (BDNF) (Diogenes, Assaife-Lopes, Pinto-Duarte, Ribeiro, & Sebastião, 2007; Diógenes, Fernandes, Sebastião, & Ribeiro, 2004; Lopes, Cunha, Kull, Fredholm, & Ribeiro, 2002; Lopes, Cunha, & Ribeiro, 1999).

A_3Rs weakly inhibit cAMP formation and increase IP_3 levels via PLC activation (Dixon, et al., 1996). A_3Rs are few in number and display low binding affinity for adenosine (Jacobson, et al., 1995; Q. Y. Zhou, et al., 1992). Due to their relative inactivity, A_3Rs are predominantly recruited during pathologically high levels of cell firing when adenosine levels increase dramatically (von Lubitz, et al., 1995; von Lubitz, Lin, Popik, Carter, & Jacobson, 1994).

Acetylcholine

Acetylcholine is released in hippocampus from extrinsic afferents from septal nuclei (Smith, 1974), although there are reports of cholinergic interneurons in SLM (Frotscher, Vida, & Bender, 2000). Cholinergic transmission is mediated via nicotinic (nAChR) and muscarinic (mAChR) receptors. The ionotropic nAChR family are cation-permeable pentamers combined of α ($\alpha_{2\text{-}10}$) and β ($\beta_{2\text{-}4}$) subunits (Boulter, et al., 1987; Boulter, Evans, Goldman, et al., 1986; Boulter, Evans, Martin, et al., 1986; Boulter, et al., 1990; Deneris, Boulter, Swanson, Patrick, & Heinemann, 1989; Deneris, et al., 1988; Elgoyhen, Johnson, Boulter, Vetter, & Heinemann, 1994; Elgoyhen, et al., 2001; Isenberg & Meyer, 1989; Le Novere, Zoli, & Changeux, 1996; Seguela, Wadiche, Dineleymiller, Dani, & Patrick, 1993; Wada, et al., 1988).

Five subtypes of mAChR have been cloned (Bonner, Buckley, Young, & Brann, 1987; Bonner, Young, Brann, & Buckley, 1988). These subtypes (m1-5) are assigned to one of two groups, M_1 and M_2, depending on G-protein coupling. M_1AChRs (m1, m3 and m5) are G_q-coupled and stimulate phosphoinositide turnover (or, in the case of some G_i-coupled m1AChRs, inhibit cAMP formation) (Kashihara, Varga, Waite, Roeske, & Yamamura, 1992; Pinkaskramarski, Stein, Zimmer, & Sokolovsky, 1988; Stein, Pinkaskramarski, & Sokolovsky, 1988). Activation of these

receptors initiates a “slow EPSP” attributable to the closure of resting K^+ channels (Cole & Nicoll, 1983; Madison, Lancaster, & Nicoll, 1987). M_1 activation also causes the closure of A-type, M-type, and Ca^{2+}-activated K^+ channels (P. R. Adams, Brown, & Halliwell, 1981; D. A. Brown & Adams, 1980; Cole & Nicoll, 1983, 1984a, 1984b; Nakajima, Nakajima, Leonard, & Yamaguchi, 1986). The G_i–coupled M_2 subgroup (m2 and m4) inhibits cAMP formation and N-type Ca^{2+} currents, while activating R- and T-type Ca^{2+} currents (Bidaut-Russell & Howlett, 1987; Kashihara, et al., 1992; Tai, Kuzmiski, & MacVicar, 2006; Toselli, Lang, Costa, & Lux, 1989; Toselli & Lux, 1989a, 1989b). Subtypes m1-4 are most prevalent in hippocampus, with m1AChRs widely expressed in somata and dendrites of principal cells, and m2 and m4 mostly present on interneurons, pre- and postsynaptically (Buckley, Bonner, & Brann, 1988; Levey, Edmunds, Koliatsos, Wiley, & Heilman, 1995).

1.4 Astrocytes

1.4.1 Anatomy and physiology of astrocytes

Astrocytes are small, round-bodied glial cells which make contact with neurons and the vasculature (Virchow, 1860). Astrocytic processes contact capillary walls via endfeet (Schultz, Maynard, & Pease, 1957; White, Dutton, & Norenberg, 1981), or extend to tightly ensheath synapses (A. Peters & Palay, 1965) and make contact with axonal nodes of Ranvier (J. A. Black, Waxman, & Hildebrand, 1984). Astrocytes are found throughout the HF. In CA1 they are most present in SO and SLM and are sparse in SP (Nixdorfbergweiler, Albrecht, & Heinemann, 1994). The synaptic sheath formed by astrocytes may insulate boutons and spines from transmitter spillover from nearby synapses (A. Peters & Palay, 1965). However, approximately 43% of CA1 synapses are not enveloped by an astrocytic process (Ventura & Harris, 1999).

1.4.2 Astrocytes as a neuronal support mechanism

The first functional role suggested for astrocytes was the transfer of metabolic substances from blood to neuron (Andriezen, 1893). Astrocytes respond to synaptic glutamate release by increasing metabolism of glucose to lactate, which is then transported to neurons (Pellerin & Magistretti, 1994). Lactate is the primary metabolite released by astrocytes (Dringen, Gebhardt, & Hamprecht, 1993), and astrocyte-derived lactate (the "lactate shuttle": Pellerin, Pellegri, Bittar, & Magistretti, 1997) is the main energy source for neurons (Dringen, Wiesinger, & Hamprecht, 1993; Magistretti & Pellerin, 1999).

Astrocytes are also essential for transmitter recycling. Synaptically released glutamate is rapidly bound by the neuron-specific excitatory amino acid transporter 1 (EAAT1), or the astrocyte-specific glutamate transporter 1 (GLT1) or glutamate-aspartate transporter (GLAST) (Danbolt, Stormmathisen, & Kanner, 1992; Lehre, Levy, Ottersen, Stormmathisen, & Danbolt, 1995; Rothstein, et al., 1994). Synaptic glutamate is predominantly taken up by to astrocytes (Balcar, Borg, & Mandel, 1977), largely via GLT1 (Chaudhry, et al., 1995). Once released, GABA undergoes a similar fate (Iversen & Kelly, 1975). Astrocytes convert both transmitters to glutamine which is exported to neurons (Norenberg & Martinezhernandez, 1979; Waniewski & Martin, 1986). Glutamine is converted back to glutamate, to be released or decarboxylated to GABA (Battaglioli & Martin, 1991, 1996; Bradford, Ward, & Thomas, 1978). Astrocytes also synthesize these transmitters, but to a lesser degree (Bramham, et al., 1990; Hertz, Wu, & Fedoroff, 1977; P. H. Wu, Durden, & Hertz, 1979).

1.4.3 Astrocytic signalling

There is substantial evidence of non-transporter mediated neuron-astrocyte communication. Early reports showed glutamate or GABA-mediated currents in cultured astrocytes (Bowman & Kimelberg, 1984; Hösli, Andrés, & Hösli, 1979; Kettenmann, Backus, & Schachner, 1984). Functional neurotransmitter receptors have since been found on astrocytes; among them are AMPARs (Seifert & Steinhäuser, 1995), NMDARs (A. Serrano, Robitaille, & Lacaille, 2008), mGluRs (Nicoletti, et al., 1990), mAChRs (Ulas, 1988), ARs (Porter & McCarthy, 1995) and P2Rs (Neary & Zhu, 1994). However, receptor expression varies with astrocyte subtype (Matthias, et al., 2003; A. Serrano, et al., 2008) and development (Cai, Schools, & Kimelberg, 2000; Seifert, Zhou, & Steinhauser, 1997; Sun, et al., 2013).

Astrocytes respond to iGluR and mGluR activation with, respectively, rapid influx and intracellular release of Ca^{2+} (Cornell-Bell, Finkbeiner, Cooper, & Smith, 1990; Glaum, Holzwarth, & Miller, 1990). Cytosolic Ca^{2+} signals spread within and between astrocytes as "Ca^{2+} waves", allowing long-range communication within cell networks. These waves require the formation of IP_3 (Leybaert, Paemeleire, Strahonja, & Sanderson, 1998), and are also triggered by acetylcholine (Araque, Martín, Perea, Arellano, & Buño, 2002), adenosine and ATP (Porter & McCarthy, 1996), GABA (Fraser, et al., 1995) and mechanical stimulation (Charles, Merrill, Dirksen, & Sanderson, 1991). They may also appear spontaneously (Nett, Oloff, & McCarthy, 2002; Parri & Crunelli, 2001). Evoked astrocytic Ca^{2+} signals are highly plastic. They are augmented or depressed by varying patterns of synaptic stimulation (Perea & Araque, 2005), and display lasting increases in frequency with repeated generation (Pasti, Pozzan, & Carmignoto, 1995; Pasti, Volterra, Pozzan, & Carmignoto, 1997).

Further, astrocytic A_{2B}Rs trigger widespread and sustained generation of asynchronous Ca^{2+} events lasting < 20 min (Kawamura & Kawamura, 2011).

The nature of astrocyte-astrocyte Ca^{2+} signaling has been heavily debated. These signals were first thought to spread via GJNs (Enkvist & McCarthy, 1992). Astrocytes are extensively coupled via GJNs comprised of opposed connexin43 (Cx43) hemichannels (Giaume, et al., 1991; Yamamoto, Ochalski, Hertzberg, & Nagy, 1990), which allow passage of small molecules such as Ca^{2+} and IP_3 (Saez, Connor, Spray, & Bennett, 1989). Inter-astrocytic signaling via GJNs is enhanced in an activity-dependent manner (Enkvist & McCarthy, 1994; Rouach, Glowinski, & Giaume, 2000), and is bidirectionally regulated via channel phosphorylation by serine-threonine kinases (Kwak, et al., 1995; Sáez, Martínez, Brañes, & González, 1998; Shah, Martinez, & Fletcher, 2002). However, cultured astrocytes display intercellular Ca^{2+} waves even when not coupled by GJNs (Hassinger, Guthrie, Atkinson, Bennett, & Kater, 1996). The extent of Ca^{2+} wave propagation is also independent of GJN coupling (Blomstrand, Åberg, Eriksson, Hansson, & Rönnbäck, 1999). Further, these waves are visible in Cx43-KO mutant mice (Suadicani, Brosnan, & Scemes, 2006).

An extracellular mode of communication between astrocytes has been identified. Ca^{2+} signaling between astrocytes is inhibited by blockers of purinergic receptors or by ectonucleotidases (Cotrina, Lin, & Nedergaard, 1998; Guthrie, et al., 1999). Previous reports of gap-junctional contribution to this process may be due to the inhibitory actions of GJN antagonists on $P2X_7$Rs or connexin hemichannels, a trigger (Suadicani, et al., 2006) or source (Cotrina, Lin, Alves-Rodrigues, et al., 1998) of astrocytic ATP release, respectively. Importantly, ATP triggers further ATP release from neighbouring astrocytes (C. M. Anderson, Bergher, & Swanson, 2004). ATP can

therefore trigger regenerative Ca^{2+} signals within the astrocytic network. As a caveat, GJNs may still be sufficient, if not essential, for mediating Ca^{2+} waves, as purine and GJN mediated Ca^{2+} waves can operate in tandem in culture (Paemeleire, et al., 2000).

1.4.4 Gliotransmission and the "tripartite synapse"

Astrocytes respond to Ca^{2+} mobilization by releasing glutamate (Bezzi, 1998) and D-serine (Mothet, et al., 2005). Early reports suggested astrocytic Ca^{2+} signals are followed by Ca^{2+} signals in neighbouring neurons (Nedergaard, 1994; Parpura, 1994). Subsequent studies have demonstrated gliotransmitter-mediated activation of neuronal mGluRs (Araque, Parpura, Sanzgiri, & Haydon, 1998), NMDARs (Araque, Sanzgiri, Parpura, & Haydon, 1998) GABA-Rs (Le Meur, Mendizabal-Zubiaga, Grandes, & Audinat, 2012) and purinergic receptors (Newman, 2003; J. M. Zhang, et al., 2003).

The discovery of bidirectional neuron-glia communication has led to the suggestion that astrocytes contribute to synaptic information processing. The "tripartite synapse" model (Araque, Parpura, Sanzgiri, & Haydon, 1999) postulates that gliotransmitters modulate synaptic function in response to neuronal activity. Indeed, gliotransmitters can augment or reduce excitatory and inhibitory neurotransmission (Araque, Parpura, et al., 1998; Araque, Sanzgiri, et al., 1998; Fiacco & McCarthy, 2004; J. Kang, Jiang, Goldman, & Nedergaard, 1998). A well studied form of gliotransmission is the slow inward current mediated by astrocytic glutamate acting on NR2B-containing extrasynaptic NMDARs (Araque, Sanzgiri, et al., 1998). At thalamocortical synapses, these currents persist for < 1 hr post-stimulation, and elicit burst-firing (Pirttimaki, Hall, & Parri, 2011).

Astrocytes mediate short- and long-term effects, and the astrocytic response to neuronal activity is highly plastic. Astrocytes may therefore perform highly complex,

intricate and dynamic roles in information processing. However, the tripartite synapse model remains controversial. Critics argue that genetic manipulation of astrocytic IP_3R-mediated Ca^{2+} release does not affect synaptic transmission (Fiacco, et al., 2007; Petravicz, Fiacco, & McCarthy, 2008). This may highlight insufficient understanding of the mechanisms of gliotransmitter release. However, methods used to manipulate astrocytes are often non-specific or untested in vivo, casting doubt on data they produce (Hamilton & Attwell, 2010; Nedergaard & Verkhratsky, 2012). Thus, the role of astrocytes in information processing is still controversial.

1.5 Synaptic plasticity

1.5.1 Hebb's postulate

It has long been postulated that synapses are the principal site of information storage in the brain. This theory was expanded by Donald Hebb to form what is commonly known as Hebb's Postulate (Hebb, 1949):

> *"When an Axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."*

1.5.2 Long-term potentiation

According to Hebb's postulate, information is stored via the strengthening of synapses between concurrently active cells. Early studies demonstrated a short-lasting (<5 min) potentiation of sympathetic ganglia or spinal cord synapses following tetanic

(>100 Hz) stimulation (post-tetanic potentiation: Larrabee & Bronk, 1947; D. P. C. Lloyd, 1949). Later, repeated high-frequency stimulation of rabbit PP-DG synapses in vivo was shown to persistently strengthen synaptic transmission (Bliss & Gardner-Medwin, 1973; Bliss & Lomo, 1973). This phenomenon was repeated in the rat brain, lasting < 2 months, and termed "long-term potentiation" (LTP: Douglas & Goddard, 1975). LTP has been described in all major pathways of the hippocampus (Alger & Teyler, 1976; Schwartzkroin & Wester, 1975), and throughout the brain (for example: Artola & Singer, 1987; Charpier & Deniau, 1997; Salin, Malenka, & Nicoll, 1996). LTP is expressed presynaptically as an increase in transmitter release (Malgaroli, et al., 1995; Malinow & Tsien, 1990), and postsynaptically as an increase in transmitter sensitivity (Manabe & Nicoll, 1994; Manabe, Wyllie, Perkel, & Nicoll, 1993). LTP is also accompanied by structural changes such as increased spine and synapse number (Desmond & Levy, 1981, 1985, 1986, 1988).

LTP has intuitive appeal as a synaptic memory mechanism. It is rapidly induced and can persist for at least a year (Abraham, Logan, Greenwood, & Dragunow, 2002). LTP exhibits shorter (early phase) and longer-term (late-phase) components (Krug, Lossner, & Ott, 1984). LTP is cooperative, requiring concerted activity at several input fibres to meet the potentiation threshold (K. S. Lee, 1983; McNaughton, Douglas, & Goddard, 1978). It therefore provides a mechanism capable of distinguishing salient from non-salient information. It is associative, as pairing weak with strong activity at separate inputs to the same cells potentiates both pathways (Levy & Steward, 1979; McNaughton, et al., 1978). It is input-specific, being typically observed only at synapses active during induction (Andersen, Sundberg, Sveen, & Wigstrom, 1977; G. S. Lynch, Dunwiddie, & Gribkoff, 1977). Finally, LTP is reliably (perhaps optimally) induced by naturally occurring patterns of stimulation

(Buzsaki, Haas, & Anderson, 1987; Greenstein, Pavlides, & Winson, 1988; Grover, Kim, Cooke, & Holmes, 2009; Staubli & Lynch, 1987).

1.5.3 LTP induction

The induction of LTP requires concerted pre- and postsynaptic activity to reach a threshold of postsynaptic depolarization (Dunwiddie, Madison, & Lynch, 1978; Gustafsson, Wigstrom, Abraham, & Huang, 1987; Malinow & Miller, 1986; Wigstrom & Gustafsson, 1983). This threshold is explained by the biophysical properties of the NMDAR. As noted, opening of the NMDAR channel-pore requires glutamate binding, plus sufficient postsynaptic depolarization to alleviate the Mg^{2+} block. Thus, Ca^{2+} influx via NMDARs occurs only when sustained or concerted presynaptic activity elicits sufficient postsynaptic depolarization. Thus, the NMDAR accounts for the principles of cooperativity, associativity and input-specificity (Bliss & Collingridge, 1993). That pharmacological blockade of NMDARs also blocks the induction of LTP is, therefore, no coincidence (Coan, Saywood, & Collingridge, 1987; Collingridge, Kehl, & McLennan, 1983). Interestingly, NMDAR-dependent LTP requires the activation of receptors containing both GluN2A and GluN2B subunits. Other subunit combinations produce only PTP (Volianskis, et al., 2013).

Increasing postsynaptic Ca^{2+} is both necessary and sufficient to induce LTP (G. Lynch, Larson, Kelso, Barrionuevo, & Schottler, 1983; Turner, Baimbridge, & Miller, 1982). NMDARs are the major source of spine Ca^{2+} during HFS (Alford, Frenguelli, Schofield, & Collingridge, 1993; Regehr & Tank, 1990), although VGCC-mediated Ca^{2+} entry also induces LTP (Y. Y. Huang & Malenka, 1993; Kullmann, Perkel, Manabe, & Nicoll, 1992; Mulkeen, Anwyl, & Rowan, 1987). The Ca^{2+} required for LTP can also come from internal stores gated by ryanodine receptors (RyRs) or IP_3Rs

(J. Harvey & Collingridge, 1992; Obenaus, Mody, & Baimbridge, 1989), for example following activation of G_q-coupled group 1 mGluRs (Frenguelli, Potier, Slater, Alford, & Collingridge, 1993; Petrozzino & Connor, 1994).

1.5.4 Expression of LTP

Ca^{2+} is required for activation of the serine-threonine kinases PKC and calcium-calmodulin (CaM) dependent protein kinase II (CaMKII). During HFS, PKC and CaMKII are activated following G_q-mediated Ca^{2+} and DAG mobilization, or NMDAR-mediated Ca^{2+} influx, respectively (Bramham, Alkon, & Lester, 1994; Fukunaga, Soderling, & Miyamoto, 1992). Once active, PKC translocates to the synaptic membrane (Akers & Routtenberg, 1987). PKC phosphorylates AMPARs and NMDARs at various residues on GluA1 and GluN1, which increases channel conductance (L. Chen & Huang, 1992; Jenkins & Traynelis, 2012; Moss, Blackstone, & Huganir, 1993; L. A. Raymond, Tingley, Blackstone, Roche, & Huganir, 1994). Phosphorylation also primes AMPARs for insertion into the synaptic membrane (Boehm, et al., 2006). Thus, LTP is partly expressed as a PKC-mediated increase in synaptic AMPAR and NMDAR currents (O'Connor, Rowan, & Anwyl, 1995).

The PKC isozymes α, β, γ, δ, and ε have all been implicated in LTP induction (Abeliovich, et al., 1993; Angenstein, Riedel, Reymann, & Staak, 1994; Koga, Sakai, Tanaka, & Saito, 1996; Staak, Behnisch, & Angenstein, 1995). However, the atypical ζ isoform has received particular interest. Two possible sources of PKMζ have been described. HFS-induced Ca^{2+} increases trigger activation of the protease calpain which cleaves the PKCζ isomer to expose the catalytic subunit (Suzuki, et al., 1992), rendering the newly formed PKMζ constitutively active (Sessoms, et al., 1993). Further, de-novo synthesis of PKMζ occurs during LTP maintenance from mRNA

encoding the independent catalytic domain (Hernandez, et al., 2003; Osten, Valsamis, Harris, & Sacktor, 1996). PKMζ allows for the persistent phosphorylation required to maintain LTP (P. A. Serrano, Yao, & Sacktor, 2005). Accordingly, the degree of LTP induction correlates with the post-HFS formation of PKMζ (Osten, et al., 1996).

Sustained phosphorylation is also accomplished via a persistent form of CaMKII. The binding of two Ca^{2+}/CaM complexes to a threonine residue at position 286 activates the catalytic subunit and 'traps' CaM, allowing the kinase to autophosphorylate and become constitutively active (Hanson, Meyer, Stryer, & Schulman, 1994; Meyer, Hanson, Stryer, & Schulman, 1992). LTP induction triggers the autophosphorylation of CaMKII (Fukunaga, Muller, & Miyamoto, 1995), which facilitates its translocation to the synaptic density and association with NMDARs (Gardoni, et al., 1998; K. Shen & Meyer, 1999). This association locks CaMKII in an active confirmation (Bayer, De Koninck, Leonard, Hell, & Schulman, 2001). It then phosphorylates AMPARs at ser831, increasing their conductance and allowing their delivery to the synaptic membrane (Barria, Muller, Derkach, Griffith, & Soderling, 1997; Derkach, Barria, & Soderling, 1999; Hayashi, et al., 2000; Mammen, Kameyama, Roche, & Huganir, 1997).

NMDAR activation triggers a rise in Ca^{2+} dependent AC activity, which in turn triggers cAMP formation and subsequent activation of PKA (Chetkovich, Gray, Johnston, & Sweatt, 1991; Roberson & Sweatt, 1996). This cascade contributes to the inhibition of phosphatases that is required for LTP induction (see below; Blitzer, et al., 1998; Blitzer, Wong, Nouranifar, Iyengar, & Landau, 1995). Late-phase LTP (L-LTP) also requires cAMP or PKA (Matthies & Reymann, 1993; Nguyen & Kandel, 1997). Indeed, postsynaptic dialysis of a cAMP analog is sufficient to induce L- LTP (Frey, Huang, & Kandel, 1993). PKA phosphorylates the transcription factor CREB

(cyclic-AMP response-element binding protein) which regulates the activity of several plasticity-associated genes (Sheng, McFadden, & Greenberg, 1990; Tao, Finkbeiner, Arnold, Shaywitz, & Greenberg, 1998; Ying, et al., 2002). Importantly, the cAMP-PKA-CREB pathway induces the transcription of new AMPARs, which may then be trafficked to the synapse (Nayak, Zastrow, Lickteig, Zahniser, & Browning, 1998). PKA may also activate CREB indirectly via phosphorylation of the extracellular signal-related kinase (ERK), or the mitogen-associated protein kinase (MAPK) (Davis, Vanhoutte, Pages, Caboche, & Laroche, 2000; Impey, et al., 1998; Roberson, et al., 1999). Further, neurotrophins acting on the TrkB receptor induce LTP via cAMP and ERK/MAPK-mediated CREB phosphorylation (Cavanaugh, et al., 2001; Gooney & Lynch, 2001; Ying, et al., 2002).

1.5.5 Maintenance of LTP

LTP requires protein synthesis (PS). L-LTP is prevented by the translation inhibitor anisomycin, demonstrating a need for PS from existing mRNA in the first hours of L-LTP (Krug, et al., 1984; Otani, Marshall, Tate, Goddard, & Abraham, 1989; Stanton & Sarvey, 1984). LTP induced in the presence of transcription blockers decays after 4 hrs (Frey, Frey, Schollmeier, & Krug, 1996). Thus, LTP can be divided into types 1, 2 and 3, corresponding to a decremental early phase (E-LTP), and two distinct late phases (L-LTP) requiring translation and transcription, respectively (Abraham, et al., 1993; Abraham & Otani, 1991; Racine, Milgram, & Hafner, 1983).

Translation of mRNA occurs somatically and dendritically (H. Kang & Schuman, 1996; Torre & Steward, 1996). However, newly formed proteins must then be incorporated at relevant locations. This process may be facilitated by the setting of a molecular ‘tag’ following HFS, which primes synapses to receive newly synthesized

proteins (Frey & Morris, 1997). The synaptic tag is short-lasting (< 1 hr) and can be set by weak HFS that produces only decremental LTP. This allows for the conversion of E-LTP to L-LTP if further (PS-inducing) stimulation occurs. The tag also captures proteins synthesized following strong activity at neighbouring synapses, thus allowing for the associative stabilization of LTP (Frey & Morris, 1997, 1998).

The identities of the 'tag' and its related proteins have been the subject of intense scrutiny. LTP triggers an increase in the synthesis and synaptic delivery of AMPARs (Nayak, et al., 1998; Shi, et al., 1999), and this process is directed by PKMζ (Y. D. Yao, et al., 2008). In keeping with this, the PKMζ inhibitor ZIP inhibits the setting of the tag (Sajikumar, Navakkode, Sacktor, & Frey, 2005). Alternatively, it has been postulated that mRNA released at active synapses may serve as a tag for transcriptional products formed at the soma, such as microRNA's (K. C. Martin & Kosik, 2002). However, it is likely that tagging reflects a state-change involving several steps necessary to accommodate delivery and retention of plasticity-related proteins (Redondo & Morris, 2011). These processes include spine enlargement (Kopec, Li, Wei, Boehm, & Malinow, 2006), remodeling of the actin cytoskeleton (Ramachandran & Frey, 2009) and sustained kinase activity (Ling, Benardo, & Sacktor, 2006; Redondo, et al., 2010; Y. D. Yao, et al., 2008).

As a caveat, the roles of PS and PKMζ in L-LTP have been questioned. L-LTP can be initiated in the presence of PS inhibitors (Abbas, et al., 2009; P. T. Pang, et al., 2004). Further, conventional and conditional PKCζ/PKMζ KO mice display normal LTP at 3 hrs post-HFS (Volk, Bachman, Johnson, Yu, & Huganir, 2013). While these experiments do not exclude a contribution by PS or PKMζ in L-LTP formation, they at least suggest that deficiency in either can be overcome by other means.

1.5.6 Presynaptic mechanisms of LTP and retrograde messengers

LTP is initiated postsynaptically, but involves increased neurotransmitter release. It has been proposed that LTP induction therefore induces the formation of an intercellular retrograde messenger (Bliss, Douglas, Errington, & Lynch, 1986). Arachidonic acid (AA) is an unsaturated fatty acid produced postsynaptically during HFS in an NMDAR and mGluR-dependent manner (M. A. Lynch & Voss, 1994; McGahon & Lynch, 1994; Pellerin & Wolfe, 1991). Release of AA is followed by presynaptic phosphorylation of PKC, increased glutamate release and LTP (Kato, Uruno, Saito, & Kato, 1991; Schaechter & Benowitz, 1993; J. H. Williams, Errington, Lynch, & Bliss, 1989). Further, inhibiting AA synthesis blocks LTP (Richards, Murphy, & Bliss, 1997). However, AA does not induce LTP when administered in the presence of the NMDAR blocker APV (O'Dell, Hawkins, Kandel, & Arancio, 1991).

Postsynaptic NMDAR activation also triggers the Ca^{2+}-dependent synthesis of nitric oxide (NO), which increases glutamate release (Bohme, Bon, Stutzmann, Doble, & Blanchard, 1991; O'Dell, et al., 1991; Schuman & Madison, 1991). NO can induce LTP irrespective of NMDAR activation (Arancio, et al., 1996; M Zhuo, Small, Kandel, & Hawkins, 1993). Retrograde transport of NO triggers a cascade involving activation of cGMP, the cGMP-dependent protein kinase (PKG), phosphorylation of HCN channels and enhanced glutamate release (Neitz, Mergia, Eysel, Koesling, & Mittmann, 2011; M. Zhuo, Hu, Schultz, Kandel, & Hawkins, 1994). However, it is unclear how increased HCN activity enhances transmitter release, as this inhibits presynaptic VGCCs (Z. Huang, et al., 2011).

1.5.7 Long-term depression

Whereas trains of high-frequency pulses trigger LTP, a similar number of low-frequency pulses triggers long-term depression (LTD) of synaptic transmission (Dunwiddie & Lynch, 1978). LTD is elicited typically by low-frequency stimulation (LFS) paradigms utilizing pulses at 1-15 Hz (Bramham & Srebro, 1987; Dudek & Bear, 1992). As with LTP, LTD in the hippocampus is rapidly induced, long-lasting, input-specific, saturable, reversible and dependent on postsynaptic NMDARs and Ca^{2+} (Collingridge, et al., 1983; Desmond, Colbert, De, & Levy, 1991; Dudek & Bear, 1992; Mulkey & Malenka, 1992).

1.5.8 Induction of LTD

Anatomically, LTD is characterized by a reduction in presynaptic boutons and postsynaptic spines, and synapse elimination (Becker, Wierenga, Fonseca, Bonhoeffer, & Nagerl, 2008; Nägerl, Eberhorn, Cambridge, & Bonhoeffer, 2004; Q. Y. Zhou, Homma, & Poo, 2004). Functionally, LTD is expressed presynaptically as a decrease in transmitter release (Bolshakov & Siegelbaum, 1994; Enoki, Hu, Hamilton, & Fine, 2009) and postsynaptically as a decrease in AMPAR and NMDAR currents (Luthi, et al., 2004; Xiao, Wigstrom, & Gustafsson, 1994; Xie, Berger, & Barrionuevo, 1992). A unifying model of Ca^{2+}'s role in LTP and LTD has been proposed (Lisman, 1989). According to the model, the sign of plasticity depends on the degree by which postsynaptic Ca^{2+} rises following synaptic activity. Moderate, non-NMDAR-mediated Ca^{2+} rises trigger a protein phosphatase-dependent cascade culminating in LTD, and larger Ca^{2+} transients (via NMDARs and other means) triggering a kinase-dependent pathway causing LTP. Specifically, moderate Ca^{2+} activates the Ca^{2+}/CaM-dependent protein phosphatases 2B (calcineurin/PP2B),

which dephosphorylates the small protein phosphatase inhibitor 1 (I-1). This occludes I-1 from binding to and inactivating protein phosphatase 1 (PP1), thus allowing PP1 to dephosphorylate CaMKII and trigger LTD. In contrast, larger Ca^{2+} rises activate CaMKII and Ca^{2+}-dependent adenylyl cyclases, thus favouring cAMP formation and activation of PKA. PKA then phosphorylates I-1, which inhibits PP1 to allow the induction of LTP via CaMKII-dependent means as described above. The model has received support from studies which demonstrate a critical role for CaM, PP1, PP2B and inhibitor 1 in regulating LTD (Mulkey, Endo, Shenolikar, & Malenka, 1994; Mulkey, Herron, & Malenka, 1993). However, the model does not account for the role of NMDARs, CaMKII and presynaptic changes in LTD (Desmond, et al., 1991; Pi, Otmakhov, Lemelin, De Koninck, & Lisman, 2010; Stanton, et al., 2003). Further, the model does not explain how dephosphorylation of CaMKII triggers synaptic depression.

Subsequent experiments have detailed the specific roles of kinases and phosphatases in LTP/LTD. For example, the AMPAR subunit GluA1 is dephosphorylated by PP1/2A at ser845 to produce LTD, or phosphorylated by PKA to reverse this action (repotentiation or de-depression) (Kameyama, Lee, Bear, & Huganir, 1998; H. K. Lee, Kameyama, Huganir, & Bear, 1998). Conversely, PKC or CaMKII phosphorylates GluA1 at ser831 to produce LTP, and this is reversed by PP1/2A or PP2B (depotentiation) (Jouvenceau, Billard, Haditsch, Mansuy, & Dutar, 2003; H. K. Lee, Barbarosie, Kameyama, Bear, & Huganir, 2000). These experiments elegantly demonstrate that LTP and LTD require distinct signaling cascades running in parallel, rather than the one simply being the reverse of the other. Furthermore, it appears that the molecular cascades culminating in LTP or LTD may be triggered by different subtypes of NMDAR. LTP requires signaling via GluN2A-containing

NMDARs (L. Liu, et al., 2004; Massey, et al., 2004) or, more specifically, GluN2A-2B heteromers (Volianskis, et al., 2013). Receptors containing GluN2B but not GluN2A trigger LTD (Brigman, et al., 2010; S. Duffy, Labrie, & Roder, 2007), although this subunit may not be essential in this regard (Fox, Russell, Wang, & Christie, 2006; Morishita, et al., 2007) and its involvement in LTD may be specific to the adult brain (Bartlett, et al., 2007; R. Li, Huang, Abbas, & Wigstrom, 2007).

1.5.9 Expression of LTD

Expression of LTD is largely postsynaptic, involving a reduction in number (Beattie, et al., 2000), and unitary conductance (Luthi, et al., 2004) of AMPARs. The reduction of AMPAR number requires depolymerization of the actin cytoskeleton (L. Shen, Liang, Walensky, & Huganir, 2000; Q. Y. Zhou, Xiao, & Nicoll, 2001), clathrin-coating of AMPARs and subsequent endocytosis (S. H. Lee, Liu, Wang, & Sheng, 2002; Man, et al., 2000). Further, a subset of AMPARs exists in a state of flux, moving laterally between synaptic and extrasynaptic sites (Ashby, Maier, Nishimune, & Henley, 2006; Tardin, Cognet, Bats, Lounis, & Choquet, 2003). Following weak excitation these receptors mobilize and diffuse to extrasynaptic sites (Borgdorff & Choquet, 2002; Tardin, et al., 2003). Conversely, LTP involves diffusion to the synaptic zone (Makino & Malinow, 2009). A single study has reported an extrasynaptic accumulation of AMPARs following LTD induction (Ashby, et al., 2004), although this may be due to either lateral diffusion or recycling of endocytosed AMPARs. However, LTD-induced lateral diffusion is consistent with the activity-dependent, bidirectional diffusion reported by the Choquet group (Groc, et al., 2004), and the finding that lateral diffusion is a precursor for endocytosis (Lu, et al., 2007).

As with LTP, LTD consists of distinct early (E-LTD) and late (L-LTD) phases triggered by induction paradigms of varying strength (Kauderer & Kandel, 2000). L-LTD lasts at least 8 hrs and requires de novo PS from existing mRNA, but not transcription (Manahan-Vaughan, Kulla, & Frey, 2000; Sajikumar & Frey, 2003). In fact, LTD induction may inhibit transcription via the Ca^{2+}-dependent transcriptional repressor downstream regulatory element antagonist modulator (L. J. Wu, et al., 2010). The newly synthesized proteins required for L-LTD are unidentified, but appear to be sequestered to relevant synapses via a tagging mechanism which allows for heterosynaptic late associativity (Sajikumar & Frey, 2004). Curiously, L-LTP can facilitate the heterosynaptic or heterodendritic induction of L-LTD, and vice versa. This "cross-tagging" suggests overlapping mechanisms are involved in stabilizing LTP and LTD (Alarcon, Barco, & Kandel, 2006; Sajikumar, Navakkode, & Frey, 2007; Sajikumar, et al., 2005). However, the two processes appear to require different kinase activity, as tagging in LTD does not require PKMζ but does require ERK1/2 (at least in the apical dendrites of CA1 neurons), whereas the inverse is true of LTP (Sajikumar & Frey, 2004; Sajikumar, et al., 2007). Still, it is possible that L-LTP and L-LTD involve the synthesis of the same proteins, but culminate in different forms of plasticity depending on the identity of the tag. Finally, inactive CaMKIIβ acts as a 'tag' at potentiated but subsequently quiet synapses, by sequestering activity-regulated cytoskeletal protein formed following HFS at neighbouring synapses (Okuno, et al., 2012). This 'inverse' tagging primes inactive synapses for depotentiation and depression via AMPAR endocytosis, thus providing a homeostatic counterpart to LTP induction at other synapses.

1.5.10 Presynaptic expression and retrograde messengers in LTD

LTD is associated with shrinkage of presynaptic boutons and a reduction in synaptic contacts at the CA3-CA1 synapse (Becker, et al., 2008). Further, LTD manifests partly as a reduction in the ready-release and rapidly-recycling pools of neurotransmitter (Enoki, et al., 2009; Stanton, et al., 2003; X. L. Zhang, Zhou, Winterer, Müller, & Stanton, 2006). These changes may occur directly in response to presynaptic activity, as presynaptic release of Ca^{2+} from RyR-gated stores is required for LTD (Reyes & Stanton, 1996). However, this Ca^{2+} may simply be required for transmitter release, and evidence suggests that a retrograde signalling system involving both AA and the NO-cGMP-PKG cascade also occurs in LTD (Kovalchuk, Miller, Sarantis, & Attwell, 1994; Santschi, Reyes-Harde, & Stanton, 1999; Stanton, et al., 2003; M. Zhuo, Kandel, & Hawkins, 1994). Further, presynaptic Ca^{2+} release may in fact be triggered by NO (Kakizawa, et al., 2012). However, the NO pathway may not be essential for LTD (Cummings, Nicola, & Malenka, 1994). How Ca^{2+}-cGMP-PKG signalling might induce LTD is also unclear, but may involve synergistic blockade of the cAMP-PKA pathway (Bailey, et al., 2008; Santschi, et al., 1999).

1.5.11 Metabotropic glutamate receptor-induced LTD

Non-NMDAR-mediated forms of LTD also exist. Most prominent of these is the form mediated by group I mGluRs (Bashir, Jane, Sunter, Watkins, & Collingridge, 1993; Palmer, Irving, Seabrook, Jane, & Collingridge, 1997; Stanton, Chattarji, & Sejnowski, 1991). Like NMDAR-LTD, mGluR-LTD is induced by low-frequency synaptic stimulation, although typically using paired pulses (N. Kemp & Bashir, 1999; N. Kemp, McQueen, Faulkes, & Bashir, 2000). Its expression involves internalization, and possibly lateral diffusion, of iGluRs (Ireland & Abraham, 2009;

Snyder, et al., 2001; Xiao, Zhou, & Nicoll, 2001), as well as a lowered probability of transmitter release (Fitzjohn, et al., 2001; Qian & Noebels, 2006). Finally, its maintenance is blocked by inhibitors of translation, but not transcription (Huber, Kayser, & Bear, 2000). However, these mechanisms may be developmentally regulated, with presynaptic changes involved during development and PS-dependent postsynaptic alterations visible in mature tissue (Nosyreva & Huber, 2005).

Despite their similarities, it is clear that NMDAR-LTD and mGluR-LTD are different mechanisms. The two are additive rather than occlusive, and whereas NMDAR-LTD requires serine-threonine phosphatases, mGluR-LTD does not (Schnabel, Kilpatrick, & Collingridge, 2001). Further, mGluR-LTD requires PKC for its induction (Oliet, Malenka, & Nicoll, 1997) and CaMKII for its PS-dependent consolidation (Mockett, et al., 2011). Other signaling molecules implicated in mGluR-LTD include ERK/MAPK and protein tyrosine phosphatases (Gallagher, Daly, Bear, & Huber, 2004; Moult, Correa, Collingridge, Fitzjohn, & Bashir, 2008), the latter being required for AMPAR dephosphorylation prior to endocytosis (Gladding, et al., 2009; Moult, et al., 2006). However, controversy surrounds the requirements for mGluR-LTD, as it is blocked by PKC inhibitors when induced electrically but not pharmacologically (Oliet, et al., 1997; Schnabel, Kilpatrick, & Collingridge, 1999). Further, blockade of CaMKII can augment or inhibit mGluR-LTD (Mockett, et al., 2011; Schnabel, Palmer, Kilpatrick, & Collingridge, 1999). Finally, there are reports of stable mGluR-LTD that does not require PS (Ireland & Abraham, 2009; Moult, et al., 2008) or tyrosine dephosphorylation (Ireland & Abraham, 2009).

1.5.12 Action potential-induced LTD

Repeated trains of antidromic APs can induce lasting synaptic depression (Dunwiddie & Lynch, 1978; Pockett & Lippold, 1986). This effect is most evident during blockade of excitatory synaptic transmission (Pockett, Brookes, & Bindman, 1990; Pockett & Lippold, 1986), and is facilitated by GABA(A)-mediated axonal depolarization (Bukalo, Campanac, Hoffman, & Fields, 2013). Further, the trigger for this plasticity appears to be Ca^{2+} entering via L-type VGCCs (Bukalo, et al., 2013; Christofi, Nowicky, & Bindman, 1991), suggesting a partial overlap with mechanisms implicated in homo- and heterosynaptically induced LTD (Christie, Schexnayder, & Johnston, 1997; Wickens & Abraham, 1991; see below).

1.5.13 LTP and LTD as memory mechanisms

Several lines of experimental evidence implicate LTP/LTD in learning and memory. Many signaling molecules implicated in generating or maintaining LTP are also implicated in learning and memory. For example BDNF is expressed following HFS-induced LTP (Dragunow, et al., 1993) and learning (Falkenberg, et al.), and its expression correlates with improved memory (Falkenberg, et al.). CaMKII phosphorylation is also seen post-learning (Zhao, Lawen, & Ng, 1999).

Disruption of LTP-related signaling also disrupts memory. AP-V blocks spatial learning and hippocampal LTP with similar efficacy (E. Anderson, Baudry, Lynch, & Morris, 1985), and genetic deletion of the NMDAR1 gene produces similar effects (McHugh, Blum, Tsien, Tonegawa, & Wilson, 1996; Tsien, Huerta, & Tonegawa, 1996). Pharmacologically or genetically disrupting CaMKII signaling also confers learning and plasticity deficits (Barros, et al., 1999; Beach, Hawkins, Osman, Kandel,

& Mayford, 1995; Silva, Paylor, Wehner, & Tonegawa, 1992; Silva, Stevens, Tonegawa, & Wang, 1992; Wolfman, Izquierdo, Schroder, & Izquierdo, 1999).

LTP and learning are mutually occlusive. Hippocampal LTP disrupts the subsequent acquisition of spatial memory (Castro, Silbert, McNaughton, & Barnes, 1989; McNaughton, Barnes, Rao, Baldwin, & Rasmussen, 1986; E. I. Moser, Krobert, Moser, & Morris, 1998). Likewise, associative learning disrupts subsequent hippocampal LTP (Gruart, Muñoz, & Delgado-García, 2006; Whitlock, Heynen, Shuler, & Bear, 2006), although this may be due to the engagement of metaplasticity (see below) rather than overlapping mechanisms. However, learning itself induces LTP in hippocampus (Gruart, et al., 2006; Mitsushima, Ishihara, Sano, Kessels, & Takahashi, 2011; Whitlock, et al., 2006), amygdala (McKernan & Shinnick-Gallagher, 1997; Rogan, Staubli, & LeDoux, 1997) and motor cortex (Rioult-Pedotti, Friedman, & Donoghue, 2000; Rioult-Pedotti, Friedman, Hess, & Donoghue, 1998; Ziemann, Iliać, Pauli, Meintzschel, & Ruge, 2004).

There is growing evidence that LTD is also required for learning. LTD may make an indirect contribution in this regard by priming synapses for the subsequent induction of LTP (Braunewell & Manahan-Vaughan, 2001). This view is supported by studies in which synaptically induced or AP-triggered LTD facilitated later LTP (see also metaplasticity section: Bukalo, et al., 2013; Dudek & Bear, 1992). LTD is enabled or augmented in different rat strains following exposure to novel objects (A. Kemp & Manahan-Vaughan, 2004, 2012; Manahan-Vaughan & Braunewell, 1999). Further, novelty-facilitated LTD converts short-term memory into long-term memory following inhibitory avoidance learning (Dong, et al., 2012). Thus, LTD may promote LTP and memory retention. Additionally, mice expressing a dominant-negative mutation of the regulatory subunit of PKA display reduced LTP persistence and long-

term memory retention but greater LTD and enhanced working memory and cognitive flexibility (Malleret, et al., 2010). The authors suggest that LTD facilitates new memory acquisition by restricting the amount of previously stored information, thus freeing synapses for future encoding.

LTD may be directly involved in certain forms of learning. Exploration of a novel environment facilitates LTD and reverses LTP in rats, but only when novel objects are present or familiar objects have been moved, suggesting a specific role for LTD in encoding object-space configuration (A. Kemp & Manahan-Vaughan, 2004). Similarly, object recognition or spatial object recognition is sufficient to induce LTD while inhibiting LTP in C57/Bl6 mice (Goh & Manahan-Vaughan, 2013). Thus, LTD appears to be the main cellular mechanism of learning in at least some paradigms.

1.5.14 Heterosynaptic depression

HFS delivered to one pathway induces homosynaptic LTP, but depresses responses at neighbouring, untetanised synapses (G. S. Lynch, et al., 1977). This depression may be brief, lasting only < 5 min (Alger, Megela, & Teyler, 1978), or longer-lasting (hours; Abraham & Goddard, 1983). The magnitude and duration of heterosynaptic depression (HSD) is facilitated by greater homosynaptic innervation (Abraham, Bliss, & Goddard, 1985; Abraham & Wickens, 1991).

HSD is by definition induced postsynaptically, whether by action potentials (Staubli & Ji, 1996), NMDARs (Abraham & Wickens, 1991), or VGCCs (Wickens & Abraham, 1991, but see: Scanziani, Malenka and Nicoll, 1996). However, transient heterosynaptic depression (tHSD) is *expressed* presynaptically as an inhibition of transmitter release by adenosine acting on presynaptic A_1Rs (Grover & Teyler, 1993a, 1993b). This adenosine is released in response to postsynaptic NMDAR

activation, and may come from both pyramidal cells and interneurons (Manzoni, Manabe, & Nicoll, 1994). Adenosine is secreted from dendrites in an activity dependent manner by equilibrative transporters, and then acts as a retrograde messenger on presynaptic A_1Rs (Lovatt, et al., 2012). A second presynaptic form of tHSD requires $GABA_B$R-mediated inhibition of transmitter release (Isaacson, Solis, & Nicoll, 1993). Finally, M1-AChRs may also trigger tHSD, although the downstream signaling cascade remains uncharacterized (Kozhemyakin & Kleschevnikov, 1994).

Heterosynaptic long-term depression (hLTD) shares common triggering mechanisms with homosynaptic LTD; namely NMDARs and/or VGCCs. Further, the two are mutually occlusive, suggesting overlapping mechanisms (Christie & Abraham, 1992a; Scanziani, Nicoll, & Malenka, 1996). HLTD may also require de novo PS, as its longevity correlates with the expression of the immediate early gene Zif268 (Abraham, Christie, Logan, Lawlor, & Dragunow, 1994), although it is possible that this is more relevant to the stabilization of LTP evoked in the same experiments. The spread of NMDAR-mediated hLTD may require a diffusible messenger, but is not blocked by A_1R antagonists (Scanziani, Nicoll, et al., 1996). Further, chelating postsynaptic Ca^{2+} during HFS does not affect HSD in single cells of hippocampal CA1 (Scanziani, Malenka, & Nicoll, 1996). Moreover, the requisite NMDARs are located neither at the tetanized synapses, nor at those synapses that undergo depression, as blockade of either does not inhibit hLTD (Scanziani, Malenka, et al., 1996; Scanziani, Nicoll, et al., 1996). This leaves the intriguing possibility that these NMDARs are located on other cells activated during HFS. These cells remain unidentified, however interneurons can be ruled out as hLTD is more robust in the absence of inhibition (Abraham & Wickens, 1991; Scanziani, Malenka, et al., 1996).

1.5.15 Neuromodulation of plasticity

LTP and LTD are powerfully modulated by concurrent, non-glutamatergic signaling. For example, LTP is partially inhibited by β-adrenergic receptor agonists (Dunwiddie, Roberson, & Worth, 1982). However, these same agonists enhance LTP and inhibit LTD when applied at lower concentrations (0.3 μM vs. 10 μM) (Katsuki, Izumi, & Zorumski, 1997). G_s-coupled β-adrenergic modulation also differs according to area and the stage of LTP. Blocking these receptors in CA1 has no effect on LTP induction but inhibits L-LTP, whereas the reverse is seen in DG (Swanson-Park, et al., 1999). G_s-coupled dopamine D1/D5 receptors also facilitate LTP induction and persistence (Otmakhova & Lisman, 1996; Swanson-Park, et al., 1999). In fact, LTP is promoted simply by intracellular dialysis of a G_s-activator, suggesting that signaling via these G-proteins enhances LTP regardless of the receptor ligand (S. Y. Huang, et al., 2012). Opposingly, G_{q11}-mediated signaling promotes LTD and inhibits LTP, as evidenced from several studies (Choi, et al., 2005; S. Y. Huang, et al., 2012; Seol, et al., 2007). However, exceptions to this rule have been reported (see below).

Modulation of plasticity can be achieved through many different signaling systems. Cholinergic inputs gate the characteristic “theta” EEG rhythm recorded in the hippocampus (Andersen, Bland, Myhrer, & Schwartzkroin, 1979; Gray, 1971; Malisch & Ott, 1982; Wetzel, Ott, & Matthies, 1977). Theta refers to sinusoidal EEG activity within the 4-12 Hz range, with a peak at 6-9 Hz (L. W. S. Leung, da Silva, & Wadman, 1982), and correlates with several forms of behavior and learning (Balschun, et al., 2004; Kinney, Patino, Mermet-Bouvier, Starrett, & Gribkoff, 1999; Schmidt, et al., 2013; Wetzel, et al., 1977; Wiebe & Stäubli, 2001). A single burst of

APs delivered at the peak of ACh-induced theta-like activity in hippocampal slices is sufficient to induce LTP and HSD (Huerta & Lisman, 1995). Further, ACh release during walking facilitates LTP in CA1 (L. S. Leung, Shen, Rajakumar, & Ma, 2003)

It is uncertain which receptor subtypes are involved in ACh-facilitated LTP. Early experiments demonstrated a facilitation of LTP by G_{q11}-coupled M1-AChRs (Boddeke, Enz, & Shapiro, 1992; Maeda, Kaneko, & Satoh, 1993). This was replicated in studies involving specific M1-AChR agonists which close SK channels (Buchanan, Petrovic, Chamberlain, Marrion, & Mellor, 2010). Conversely, others have found that M2-AChRs are more important for LTP facilitation (Shimoshige, Maeda, Kaneko, Akaike, & Satoh, 1997). The situation is further complicated by reports that ACh can depress synaptic transmission and block LTP (Auerbach & Segal, 1996; K. Pang, Williams, & Olton, 1993). These results reflect the promiscuous actions of ACh, which vary with concentration, receptor subtype and pattern of stimulation. For example, M1-AChRs may trigger suppressive signaling via G_{q11}-mediated phosphoinositide turnover, while concurrently initiating closure of K^+ channels. Plasticity may thus reflect the relative engagement of each mechanism.

Adenosine also modulates plasticity. Extracellular ATP accumulates during HFS and is rapidly converted to adenosine (Cunha, Vizi, Ribeiro, & Sebastiao, 1996), although extracellular adenosine may also come via direct synaptic release (H. G. Lloyd, Lindstrom, & Fredholm, 1993), or dendritic secretion (Lovatt, et al., 2012). Presynaptically, adenosine activates A_1Rs to inhibit transmitter release and LTP induction (Alzheimer, Kargl, & Tenbruggencate, 1991). Acting at A_2Rs it facilitates glutamate release and promotes, or even induces LTP (Kessey & Mogul, 1997; Kessey, Trommer, Overstreet, Ji, & Mogul, 1997). This facilitation requires an A_{2A}R-mediated suppression of A_1Rs and amplifies the effects of BDNF, including AMPAR

trafficking (Dias, Ribeiro, & Sebastião, 2012; Diogenes, et al., 2007; Diogenes, et al., 2011; Diógenes, et al., 2004; Fontinha, Diógenes, Ribeiro, & Sebastião, 2008; Lopes, et al., 2002). Less is known about the effects of $A_{2B}R$ activation on plasticity, although one study has implicated these receptors in the facilitation of LTP (Kessey, et al., 1997). Finally, low affinity A_3Rs can enhance LTP and attenuate LTD (Costenla, Lopes, de Mendonca, & Ribeiro, 2001).

1.5.16 Astrocytes and plasticity

The tripartite synapse hypothesis has fuelled interest in the possibility that astrocytes contribute to synaptic plasticity. Early reports suggested that astrocyte-derived ATP, once degraded by ectonucleotidases to adenosine, mediates transient synaptic depression (Andersson, Blomstrand, & Hanse, 2007; Pascual, et al., 2005; A. Serrano, Haddjeri, Lacaille, & Robitaille, 2006; J. M. Zhang, et al., 2003). This view has been criticised following a report that astrocytes are neither necessary nor sufficient to trigger synaptic depression (Lovatt, et al., 2012). However, this report is at odds with the absence of A_1R-dependent tHSD in dn-SNARE mice which do not exhibit vesicular gliotransmitter release (Pascual, et al., 2005).

The importance of astrocytes for hippocampal LTP has been heavily debated. IP_3R2KO mice do not exhibit the astrocyte-specific subtype 2 IP_3R, and therefore do not display IP_3-mediated Ca^{2+} events in these cells (Petravicz, et al., 2008). This mechanism is perceived as the main trigger of gliotransmitter release and a fulcrum of the tripartite synapse, yet synaptic transmission and LTP in CA1 are not altered in IP_3R2KO mice (Agulhon, Fiacco, & McCarthy, 2010). However, despite the apparent lack of a tripartite synapse-type contribution to LTP, gliotransmission is still essential for this form of plasticity. The NMDAR co-agonist D-serine is released constitutively

(i.e. not activity dependently) from astrocytes following ongoing Ca^{2+} influx via type A transient receptor potential channels (Shigetomi, Jackson-Weaver, Huckstepp, O'Dell, & Khakh, 2013). This mechanism is independent of IP_3R-mediated Ca^{2+} signalling, and is essential for NMDAR-dependent LTP in CA1 (Henneberger, Papouin, Oliet, & Rusakov, 2010; Shigetomi, et al., 2013; Y. L. Yang, et al., 2003).

The manner by which astrocytes contribute to plasticity may vary by area and the transmitter systems required. For example, optogenetic stimulation of astrocytes triggers LTD of glutamatergic parallel fibre-Purkinje cell synapses in cerebellum (T. Sasaki, et al., 2012). In the hippocampus, the same approach also triggers lasting synaptic depression but mediated via P_2YRs (J. Chen, et al., 2013). However, while these studies suggest that gliotransmitters can directly induce plasticity, the effects described are not the results of neuronal activation. In contrast, three groups have now documented forms of synaptic plasticity following stimulation of cholinergic fibres in vivo which are absent in IP_3R2KO mice, strongly suggesting astrocytic involvement. In hippocampal slices, stimulation of cholinergic inputs in the alveus evokes mAChR-dependent Ca^{2+} elevations in astrocytes, followed by glutamate release, activation of neuronal mGluRs and a presynaptic form of LTP at CA3-CA1 synapses (Navarrete, et al., 2012). In the mouse barrel cortex, combining whisker stimulation with electrical stimulation of cholinergic afferents triggers mAChR-mediated astrocytic Ca^{2+} signals and NMDAR-mediated LTP of the whisker-induced synaptic potential (Takata, et al., 2011). Stimulation of cholinergic afferents to visual cortex induces potentiation of visual responses in pyramidal neurons via an mAChR-dependent activation of primary visual cortex astrocytes (N. Chen, et al., 2012). Thus, activity dependent gliotransmission in keeping with the tripartite synapse model may contribute to plasticity induction in some cases.

1.6 Metaplasticity

In addition to modulation by concurrent signaling, synaptic plasticity is also regulated by *prior* neural activity. That is, neural activity at one point in time can alter the subsequent induction and persistence of LTP/LTD. This activity-dependent regulation of plasticity has been termed "metaplasticity" (Abraham & Bear, 1996). Metaplasticity is distinguished from neuromodulation in that the metaplastic state endures even after the subsidence of the 'priming' activity which initiated it (e.g. the presence of a neuromodulator or hormone).

1.6.1 NMDAR-mediated metaplasticity

Early demonstrations of metaplasticity highlighted the ability of transient NMDAR activation (by LFS, weak HFS, NMDA administration or single pulses in Mg^{2+}-free solution) to inhibit subsequent LTP induction in hippocampal CA1 (Coan & Collingridge, 1988; Coan, Irving, & Collingridge, 1989; Fujii, Saito, Miyakawa, Ito, & Kato, 1991; Y. Y. Huang, Colino, Selig, & Malenka, 1992). This effect lasts for less than 1 hr, and can be overcome by α-adrenergic receptor activation (Y. Y. Huang, et al., 1992; Izumi, Clifford, & Zorumski, 1992c). Similar NMDAR-mediated effects are seen in the DG (Christie, Stellwagen, & Abraham, 1995). Notably, these and other metaplasticity effects occur even when the 'priming' activity itself does not induce LTP/LTD. Metaplasticity cannot therefore be due to the saturation of plasticity.

Priming at 5 Hz also metaplastically facilitates subsequent LTD (Christie & Abraham, 1992b; Wexler & Stanton, 1993), as does priming with HFS (Holland & Wagner, 1998; Wagner & Alger, 1995). That similar priming protocols can both inhibit LTP and facilitate LTD demonstrates that metaplasticity can involve a shift in

the threshold of LTP/LTD induction rather than distinct inhibitory and facilitatory mechanisms. Accordingly, the same molecules are required to induce inhibition of LTP and facilitation of LTD; namely NMDARs, NO and PKC (Izumi, Clifford, & Zorumski, 1992a; Izumi, Tokuda, & Zorumski, 2008; O'Dell & Kandel, 1994; Stanton, 1995). These mechanisms may be critical for plasticity induction in some cases. For example, pulses occurring early in a train of LFS prime the induction of LTD by later pulses in an NMDAR-dependent manner (Mockett, Coussens, & Abraham, 2002). However metaplasticity as triggered by NMDARs need not be unidirectional, as NMDARs either inhibit or facilitate subsequent LTP in the DG, depending on the frequency of stimulation used to induce plasticity (Christie, Stellwagen, et al., 1995).

NMDAR-mediated metaplasticity typically involves a negative-feedback loop culminating in reduced NMDAR currents (I_{NMDAR}) (Kato & Zorumski, 1993; Sobczyk & Svoboda, 2007). This reduction may be due to lateral diffusion or endocytosis of receptors (Hellier, et al., 2007; Morishita, Marie, & Malenka, 2005), or alterations in receptor subunit composition (Bellone & Nicoll, 2007; Jung, Kim, & Hoffman, 2008). Importantly, I_{NMDAR} is positively and negatively regulated by G_q- and G_s-mediated signaling, respectively (MacDonald, Jackson, & Beazely, 2007). Thus, the plasticity threshold can be bidirectionally modified by several neurotransmitters acting on these G-proteins (S. Y. Huang, et al., 2012). However, while I_{NMDAR} is computationally sufficient to alter the plasticity threshold on its own (Castellani, Quinlan, Cooper, & Shouval, 2001; Shouval, Castellani, Blais, Yeung, & Cooper, 2002), it is likely that multiple metaplasticity mechanisms work in tandem to regulate LTP/LTD. One such mechanism is autophosphorylation of CaMKII. The phosphorylation state of CaMKII at Thr286 or Thr305/Thr306 bidirectionally shifts

the plasticity threshold (Mayford, Wang, Kandel, & O'Dell, 1995; Pi, et al., 2010). Further, mice expressing αCaMKII which cannot be autophosphorylated at Thr305/306 do not show reduced LTP after 10 Hz priming (L. Zhang, et al., 2005).

1.6.2 mGluR mediated metaplasticity

Glutamate metaplastically enhances of LTP via group 1 mGluRs (A. S. Cohen & Abraham, 1996). Multiple forms of this metaplasticity exist in CA1, requiring both PLC-dependent and independent signaling cascades (A. S. Cohen, Raymond, & Abraham, 1998; Ireland & Abraham, 2002). PLC-independent facilitation increases excitability via a tyrosine-phosphatase dependent reduction of the sAHP (Ireland, Guevremont, Williams, & Abraham, 2004). PLC-dependent facilitation requires mechanisms that have not been elucidated, but may involve actin remodeling and AMPAR trafficking (Horne & Dell'Acqua, 2007; Nakata & Nakamura, 2007), as trafficking of AMPARs to the extrasynaptic membrane primes their diffusion to the synapse upon HFS (M. C. Oh, Derkach, Guire, & Soderling, 2006).

mGluRs also trigger a form of metaplasticity in CA1 termed the “molecular switch” (Bortolotto, Bashir, Davies, & Collingridge, 1994). Here, prior activation of mGluRs negates the need for their activation during HFS for LTP to be seen, thus lowering the stimulus requirements for plasticity. The molecular switch can be set by as few as 8 pulses at 100 Hz, or more pulses at lower frequencies (Bortolotto, Collett, Conquet, Jia, & Collingridge, 2008). This form of metaplasticity is set with relatively little activity, providing a physiologically plausible mechanism for reducing the LTP threshold. The switch requires mGlu5 activation (Bortolotto, et al., 2005), upon which a cascade involving αCaMKII and PKC is initiated (Bortolotto & Collingridge, 1997, 2000). Similarly, priming of group I mGluRs promotes local PS, allowing relatively

weak HFS to generate L-LTP (C. R. Raymond, Thompson, Tate, & Abraham, 2000). This tagging effect can be mimicked by activating RyRs, which lie downstream of group I mGluRs (Sajikumar, Li, Abraham, & Xiao, 2009). MGluR or RyR priming also prolongs the duration of the 'tag' by initiating a switch from transient tag via CaMKII (< 60 min) to lasting tagging (at least 270 min).

mGluRs exert complex actions on subsequent plasticity in other areas of the HF. Whereas Cohen & Abraham (1996) saw no effect of DHPG on I_{NMDAR} in CA1, mGluR activation in DG induces a lasting increase in I_{NMDAR} (O'Connor, Rowan, & Anwyl, 1994; O'Connor, et al., 1995). The agonist used by O'Connor et al. (ACPD) activates both group I- and group II- mGluRs, which may account for these discrepancies. Nevertheless, the increased NMDAR current could, in theory, facilitate later LTP. On the contrary, activation of group I and group II mGluRs inhibits LTP in DG when co-active with NMDARs during priming (Gisabella, Rowan, & Anwyl, 2003). The same protocol also inhibits later mGluR-LTD (Rush, Wu, Rowan, & Anwyl, 2002; J. Wu, Rowan, & Anwyl, 2004). Thus, mGluR-mediated metaplasticity may depend equally on location, receptor subtype and co-activity of other receptors.

1.6.3 Non-glutamatergic metaplasticity

Various forms of metaplasticity have been reported that do not require NMDARs or mGluRs. For example, septal TBS delivered in vivo, that does not itself trigger glutamatergic transmission, inhibits subsequent (10 min later) LTP of the population-spike in CA1 (Newlon, Goldberg, & Hayes, 1991). This may reflect a change in the plasticity of excitability rather than blockade of synaptic LTP, and may be triggered by either GABAergic or cholinergic projections. However, LTP suppression was inversely correlated with the PTP of the pop-spike, suggesting this

metaplasticity is not due to LTP of inhibitory transmission (McLean, Caillard, Ben-Ari, & Gaiarsa, 1996; Newlon, et al., 1991).

ACh-mediated metaplasticity is diverse. MAChRs metaplastically inhibit LTP and promote LTD in cortical neurons (Seol, et al., 2007), but weakly facilitate LTP in CA1 (A. S. Cohen, et al., 1998). This latter report is in keeping with a carbachol-induced potentiation of I_{NMDAR} (J. Harvey, Balasubramaniam, & Collingridge, 1993). Further, an mAChR inhibitor blocks 5 Hz priming-facilitated LTP in DG (Christie, Stellwagen, et al., 1995). However, another study reported that septal stimulation facilitates LTP at SO synapses if septal priming occurs 5, but not 15 or 30 min prior to hippocampal HFS (Ovsepian, Anwyl, & Rowan, 2004). As with neuromodulation, these results reflect the diverse metaplastic responses elicited by different patterns of ACh release.

Another example of non-glutamatergic metaplasticity is the blockade of LTP in CA1 by prior A_2R activation (Fujii, et al., 2000). It is curious that G_s-coupled A_2Rs should be implicated in an inhibitory form of metaplasticity, given their typically facilitatory actions on LTP induction. Downstream effectors of G_s signaling are sufficient to induce LTP in the absence of synaptic activity, and G_s-activation facilitates LTP induction (Frey, et al., 1993; Seol, et al., 2007). This 'pro-LTP' state endures, enabling the metaplastic facilitation of LTP for at least 90 min (S. Y. Huang, et al., 2012). Thus, the effect detailed by Fujii and colleagues may require non-canonical A_2R signaling.

1.6.4 Heterosynaptic metaplasticity

Metaplasticity is commonly studied at the same synapses activated during experimentation. However, afferent activity at one set of synapses can alter plasticity

thresholds at heterosynaptic locations. Synaptic tagging, whereby strong input activity at one set of synapses facilitates the persistence of LTP at adjacent inputs, is one such example (Frey & Morris, 1997), and can itself be facilitated by prior RyR activation (Sajikumar, et al., 2009). The heterosynaptic *induction* of LTP is also metaplastically facilitated. Endocannabinoids inhibit local interneurons following stimulation of CA3-CA1 afferents, facilitating LTP at distances < 10 µm (Chevaleyre & Castillo, 2004). Further, HFS delivered to PP-SLM synapses facilitates later LTP in SR by triggering insertion of GluN2B-containing NMDARs (E. B. Han & Heinemann, 2013).

Heterosynaptic metaplasticity is a key concept in computational models of synaptic plasticity. The original model containing such a feature was the Bienenstock, Cooper and Munro (BCM) model (Bienenstock, et al., 1982). This model was originally devised to account for the experience-dependent formation of orientation selectivity in the developing visual cortex. The model contains three key concepts: First, changes in synaptic weight are expressed as a function (φ) of postsynaptic activity (i.e. cell firing) following afferent input activity. Low levels of postsynaptic firing during afferent input trigger synaptic depression (LTD), whereas higher levels of postsynaptic firing trigger synaptic potentiation (LTP). Second, the model contains a modification threshold (θ_{M}) denoting the crossover point on the φ function between activity that induces depression and that which induces potentiation. This threshold is not fixed but operates on a sliding scale, determined by the time-averaged level of postsynaptic firing. That is, the history of postsynaptic activation adjusts θ_{M} such that greater activity makes it harder to induce potentiation and easier to induce depression, and decreased activity has the opposite effect. This sliding threshold confers stability to the model, without which plastic changes in either direction would favour similar

changes in future. For example, LTP will raise the level of postsynaptic firing, making the further induction of LTP more likely. LTD would by comparison favour yet more synaptic depression. Thus, the plasticity threshold must be adjusted on the basis of (recent) historical activity to avoid saturating LTP or LTD (**Fig. 1.2**). Finally, the signal which alters θ_M, cell firing, is global. Thus, firing modifies θ_M across all synapses on a cell, active or quiescent. Later derivatives of the BCM model feature a similar cell-wide regulation of plasticity thresholds. However, plasticity thresholds in these later models adjust as a function of NMDAR-mediated Ca^{2+} entry (Shouval, Bear, & Cooper, 2002; Shouval, Castellani, et al., 2002; Yeung, Shouval, Blais, & Cooper, 2004).

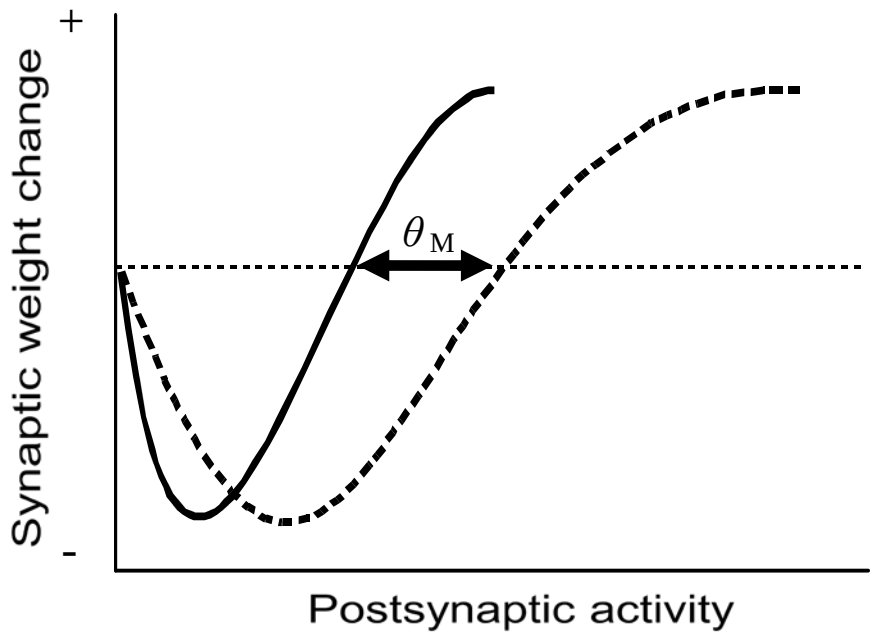

Figure 1.2. The BCM model of synaptic plasticity.
A representation of the φ function of synaptic weight change as predicted by the BCM model (Bienenstock et al., 1982). The sign and degree of synaptic weight change varies as a function of postsynaptic activity (cell-firing) following afferent activity. Lower levels of postsynaptic activity induce synaptic depression, whereas higher levels induce synaptic potentiation. The modification threshold (θ_M) is not fixed; it is regulated by the history of postsynaptic firing such that greater activity drives the rightward shift of θ_M. Thus, higher levels of postsynaptic activity trigger a homeostatic response that restricts subsequent synaptic potentiation and facilitates later synaptic depression.

A BCM-like φ function was first demonstrated at CA1 synapses in experiments where 0.5-50 Hz synaptic stimulation induced a plasticity curve with an LTP/LTD crossover point of ~10 Hz (Dudek & Bear, 1992). In follow-up experiments, and in keeping with the BCM model's sliding θ_M, LTP was facilitated by prior LTD induction (Dudek & Bear, 1993). In visual cortex θ_M is altered by sensory experience, as neurons from light-deprived rats display enhanced LTP and diminished LTD (Kirkwood, et al., 1996). This effect requires NMDAR activation rather than APs (Philpot, Cho, & Bear, 2007; Philpot, Espinosa, & Bear, 2003). However, BCM-like metaplasticity is elicited in the DG in vivo by APs alone (Abraham, et al., 2001).

To date, three groups have described heterosynaptic BCM-like metaplasticity (but for similar effects see: Roth-Alpermann, Morris, Korte, & Bonhoeffer, 2006). The first demonstrations came from the Wagner group in investigations in which strong 'priming' tetanization of SC afferents to CA1 facilitated subsequent LTD and depotentiation while inhibiting LTP at adjacent, unprimed inputs to the same stratum (Holland & Wagner, 1998; H. Y. Wang & Wagner, 1999). In the latter experiments, the authors detailed a rightward shift in the φ function following 6 x 100 Hz trains of priming stimulation, such that $\theta_{LTP/LTD}$ (analogous to θ_M) moved from ~4 Hz to ~12 Hz. The authors found that priming-induced heterosynaptic facilitation of LTD was blocked in some (but not most) cases by the NMDAR antagonist D-APV (Holland & Wagner, 1998). A second group has demonstrated a heterosynaptic inhibition of LTP at CA1 SR synapses which correlates with an L-type VGCC-dependent augmentation of the sAHP (Le Ray, De Sevilla, Porto, Fuenzalida, & Buno). Finally, the Abraham group has recently expanded on the results of Wang & Wagner (1999), demonstrating that 6 x 100 Hz priming induces a rightward shift in the φ function for SR synapses

whether priming is delivered heterosynaptically in SR or *heterodendritically* in SO (Hulme, et al., 2012).

Hulme et al.'s description of heterodendritic metaplasticity provides an important defense of the BCM prediction that strong enough activity will alter θ_M at synapses across the entire cell. Though the authors did not study the effects of priming on subsequent plasticity in SLM, and cannot therefore provide a truly cell-wide validation of BCM predictions, the results of Hulme et al. are at least consistent with this aspect of the model. In broad agreement with Wang and Wagner (1999), Hulme and colleagues found that 6 x 100 Hz priming delivered to SR or SO facilitated the induction of LTD (600 pulses at 1 Hz, repeated after 10 min). The authors also found a priming-induced reduction in LTP seen following 100 Hz stimulation, which differs from the results of Wang and Wagner but is nonetheless consistent with a rightward shift in φ as seen by those authors (compare both groups' stimulation protocols and φ functions). Further, Hulme et al. provided mechanistic insight into heterosynaptic metaplasticity in CA1. In these experiments, priming-facilitated LTD and inhibition of LTP did not to involve NMDARs, mGluRs or L-type VGCCs, or altered GABAergic transmission (Hulme, et al., 2012). In contrast, SO priming-induced the inhibition of LTP required Ca^{2+} release from IP_3-gated stores. However, the long-distance signaling cascade required for the heterodendritic spread of the metaplasticity is still poorly defined.

1.6.5 Functions of metaplasticity

Metaplasticity can be engaged by behavioural experience. For example, exposure to an enriched environment (EE) facilitates the induction (Malik & Chattarji, 2012) and persistence (S. N. Duffy, Craddock, Abel, & Nguyen, 2001) of LTP in

CA1. In contrast, stressful, fearful or painful stimuli inhibit LTP and promote LTD in this region (Artola, et al., 2006; J. J. Kim, Foy, & Thompson, 1996; Sacchetti, et al., 2002). Thus, metaplasticity has relevance beyond the confines of experimentation. Metaplasticity phenomena are in fact pertinent to several specific domains of function (Hulme, Jones, & Abraham, 2013). Metaplasticity may: (i) serve to prepare neural networks for learning; (ii) homeostatically stabilize synapses and; (iii) avoid pathological levels of synaptic potentiation or depression.

Preparedness for learning may be achieved through altered neuronal excitability. Reduced AP threshold and increased firing rates correlate with EE-induced metaplasticity (Malik & Chattarji, 2012), which in turn correlates with facilitated learning (S. N. Duffy, et al., 2001). In the amygdala, eligibility for storing new fear memories is a competitive process decided by CREB-mediated increases in excitability (J. H. Han, et al., 2007; Y. Zhou, et al., 2009). Further, learning of certain tasks correlates with a reduced sAHP and SFA (Disterhoft, Golden, Read, Coulter, & Alkon, 1988; Moyer Jr., Thompson, & Disterhoft, 1996; M. M. Oh, Kuo, Wu, Sametsky, & Disterhoft, 2003). In the case of multi-trial odour learning, which facilitates LTP (Y. Cohen, Avramoav, Barkai, & Maroun, 2011), a reduced sAHP precedes odour discrimination (Saar, Grossman, & Barkai, 1998) and correlates with acquisition of learning on a second, unrelated task (Zelcer, et al., 2006). Thus, increased excitability may promote a general learning state which metaplastically facilitates task acquisition.

Homeostatic metaplasticity refers to negative feedback mechanisms which inhibit LTP or LTD following opposing patterns of synaptic activity (Hulme, et al., 2013). By stabilizing plasticity, synaptic weights are maintained within an optimal dynamic range which promotes learning and flexibility. Unchecked LTP favours

greater synaptic potentiation, thus risking the 'overwriting' of information and minimizing the ability of other synapses to compete during encoding. In keeping with this, mutant mice lacking the PSD-95 protein display enhanced LTP but diminished spatial learning (Migaud, et al., 1998). At the opposite end of the spectrum, unbridled LTD would reduce synaptic activity to the point where synapses are no longer functional participants in the network. Thus, homeostatic inhibition or promotion of plasticity is employed to maintain optimal levels of synaptic function.

Metaplasticity stabilizes memories by rendering synapses resistant to change (Fusi, Drew, & Abbott, 2005). For example, motor learning occludes subsequent plasticity and retrograde interference following learning of a second task (Cantarero, Tang, O'Malley, Salas, & Celnik, 2013). Interestingly, plasticity occlusion is proportional to retention of the learnt task, suggesting metaplasticity facilitates retention by restricting further synaptic changes (Cantarero, et al., 2013).

There is mounting evidence that metaplasticity protects against pathological levels of neuronal activity. Repeated LTD or sensory deprivation triggers delayed synapse elimination (Kamikubo, et al., 2006; Shinoda, Kamikubo, Egashira, Tominaga-Yoshino, & Ogura, 2005; Tremblay, Lowery, & Majewska, 2010). Thus, unguarded LTD may cause widespread synapse loss which, in the extreme, could culminate in apoptosis (Jeffrey, et al., 2000; Mattson, Keller, & Begley, 1998; Mattson, Partin, & Begley, 1998). Conversely, unrestricted LTP may raise synaptic Ca^{2+} levels to the point of excitoxicity (Kostandy, 2012). In this sense, metaplasticity may be analogous to 'ischemic preconditioning' mechanisms in which adaptations to sub-lethal neuronal stimulation confer protection against later, otherwise lethal levels of synaptic activity (Youssef, Addae, McRae, & Stone, 2001; Youssef, Addae, & Stone, 2003, 2006).

1.7 Thesis objectives

Hulme et al. (2012) described a novel form of metaplasticity in which strong afferent priming stimulation homeostatically adjusts plasticity thresholds even at heterodendritic locations. This mode of metaplasticity is unique in its spatial spread, and does not require canonical triggers of metaplasticity such as NMDARs, mGluRs or VGCCs. Its dependence on postsynaptic Ca^{2+}, albeit from a different source (IP_3-gated stores), is in general agreement with Ca^{2+}-dependent models of metaplasticity. However, at the start of this thesis the effect as a whole remained poorly understood. A thorough study of the stimulus requirements for initiating the metaplastic state had not been conducted, nor had the relevant trigger of Ca^{2+} release been identified. Also, the relevance of the BCM model to this form of metaplasticity had not been fully investigated. Perhaps most importantly, a signaling mechanism had yet to be elucidated that accounts for the spread of the metaplastic state across considerable distances.

The objectives of this thesis fall into three broad categories regarding the heterosynaptic and heterodendritic metaplastic inhibition of LTP in CA1: (1) the further characterization of properties and features of the cell-wide metaplasticity effect; (2) the role of *intra*cellular signaling in mediating the effect, and; (3) the role of *inter*cellular signaling. The first objective was to replicate the cell-wide inhibition of LTP as described by Hulme et al., and conduct a detailed analysis of the patterns of priming stimulation at various dendritic locations which can or cannot elicit cell-wide metaplasticity. This objective also addressed whether the effect is age- or species-specific. Objective (2) involved investigations of the involvement of APs in triggering the heterodendritic metaplasticity, as suggested by the BCM model. As other modes of metaplasticity involve altered membrane currents, investigations under this

objective also tested whether priming-induced alterations to membrane parameters could be detected in this model. This objective also sought to address outstanding questions on the role of intracellular Ca^{2+}; specifically whether it is also required for the cell-wide facilitation of LTD and what IP_3R-coupled G-protein(s) may act as triggers for the metaplasticity effect. The focus of the final objective was the relevance of two common intercellular signaling systems, purine-mediated and GJN mediated cell-cell communication, in mediating the metaplasticity. This objective also addressed the question of what cell type(s) are required for the effect.

2. General methods

All experiments used tissue from young adult male Sprague-Dawley rats (6–8 wk), unless otherwise stated, for consistency with previous studies (Hulme, et al., 2012). Animals were sourced from a breeding colony maintained by the University of Otago. Animals were housed in standard caging of approx. 37 x 52 x 25 cm for rats (2-5animals per cage) or 10 x 10 x 20 cm for mice (single housed). Animals had free access to food and water and on a 12 h normal light/dark cycle (fluorescent lights, switched on/off at 7am/pm). All experimental protocols were approved by the University of Otago Animal Ethics Committee and conducted in accordance with New Zealand animal welfare legislation (under ethics approval code ET04/11001).

2.1 Tissue preparation

For hippocampal slices from rat brain, animals were deeply anesthetized with ketamine (100 mg/kg, i.p.) and decapitated via guillotine. Brains were rapidly removed (<1 min) then submersed in ice-cold sucrose dissection solution (mM: 210 sucrose, 26 $NaHCO_3$, 2.5 KCl, 1.25 NaH_2PO_4, 0.5 $CaCl_2$, 3 $MgCl_2$, 20 D-glucose) continuously gassed with carbogen (95% O_2-5% CO_2). The hippocampus was dissected free and transverse slices (400 µm) were made using a Sorvall tissue sectioner. Slices were transferred to a humidified recording chamber (volume ~ 750 µl) superfused at 2 ml/min with ACSF (mM: 124 NaCl, 3.2 KCl, 1.25 NaH_2PO_4, 26 $NaHCO_3$, 2.5 $CaCl_2$, 1.3 $MgCl_2$, 10 D-glucose) where they remained thinly submerged for at least 2 h while the temperature was gradually brought to 32.5°C, after which the establishment of field potential or single cell recordings was commenced. Spare slices were transferred from the dissection solution to a humidified

holding chamber for equilibration, where they were held at room temperature before being transferred as required to the recording chamber.

2.2 Extracellular recordings

Field excitatory postsynaptic potentials (fEPSPs) were taken as a measure of synaptic efficacy (**Fig. 2.1**). Synaptic potentials were chosen over population action potentials (pop-spikes) as potentiation or depression of fEPSPs directly reflects changes in synaptic efficacy, whereas changes to the pop-spike might reflect altered synaptic input *or* altered intrinsic excitability. Synaptic potentials were evoked through stimulation of Schaffer collateral afferents to the strata radiatum and oriens of hippocampal CA1 using 50 µm Teflon-insulated tungsten monopolar electrodes coupled to custom-built programmable stimulators (diphasic pulse half-wave duration 0.1 ms). Electrodes were placed centrally within each stratum (midway between the stratum pyramidale (SP) and alveus for SO potentials, and midway between the SP and stratum lacunosum moleculare for SR potentials). These electrodes were placed in order to activate distinct, independent inputs to CA1. Recordings were made using glass capillaries (OD 1 mm, ID = 0.58 mm, AM systems) pulled to form micropipettes using a P-97 Flaming/Brown micropipette puller (Sutter instrument co). Recording electrodes were made by filling micropipettes with 2 M NaCl or ACSF, which gave a final resistance of 1.5–2.5 MΩ. Recording electrodes were placed approximately 400 µm from the stimulating electrode in the same stratum. Recording electrodes were coupled to Grass® P511 A.C. amplifiers via high-impedance probes (also from Grass®). Recordings were amplified (x1000) with half-amplitude filter cutoffs set at 0.3 KHz and 3 KHz. Recordings were displayed on an Hitachi VC-6025 oscilloscope and digitized via a National Instruments BNC-2110 connector block for

recording on a PC. Stimulation, recording and offline analysis were conducted by computer using custom designed programs based on software from the Labview library.

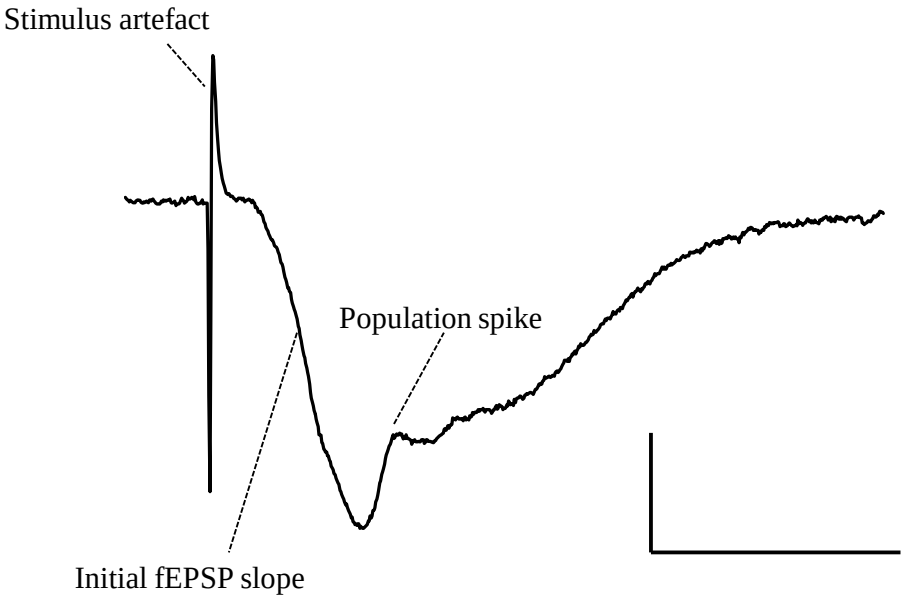

Figure 2.1. Synaptic transmission in hippocampal CA1.
Representative extracellular (field) potential from SR following stimulation of Schaffer collateral fibres. The stimulus artefact is followed by a rapid voltage deflection which gradually decays to baseline; the field excitatory postsynaptic potential (fEPSP). The fEPSP is indicative of ionotropic glutamate receptor activation, mainly AMPARs, at a population of synapses, and thus constitutes a measure of synaptic efficacy. The positive-going population spike reflects the passive current source generated by synchronous AP firing in a population of neurons in response to synaptic depolarization. Calibration bars: 1 mV, 10 ms

Slices were excluded from experimentation if synaptic potentials from either stratum failed to reach at least 2 mV amplitude at a stimulus intensity of 100 µA. After maximal fEPSP's were elicited, the stimulus intensity was adjusted to yield a response of either 1 mV amplitude (25-70 µA) or 30% of maximum slope (65-90 µA), unless otherwise stated.

To confirm that both stimulating pathways were independent, paired-pulse tests were conducted prior to LTP protocols. Pairs of pulses (50 ms interpulse interval) were delivered either via the same electrode (i.e. to the same stratum) or alternating between electrodes (and therefore between strata). Slices were included if paired-pulse facilitation of the fEPSP slope (> 10%) occurred when pulses were delivered via the same electrode, and if no cross-facilitation or depression of the second response (i.e. < 10% change in fEPSP slope) occurred when pulses were delivered via electrodes in separate strata. Baseline stimulation consisted of single pulses delivered every 30 s, alternating between stimulating electrodes. Priming stimulation was delivered after a stable period of baseline recording had been achieved (at least 15 min, assessed visually). Standard priming stimulation consisting of 600 pulses delivered to one pathway (SO or SR) as 3 x 100 Hz, 1 s trains spaced by 20 s, repeated after 5–15 min, was employed unless otherwise stated. Conditioning stimulation to induce LTP (2 x 100 Hz, 1 s trains, spaced by 30 s unless otherwise stated) or LTD (600 pulses at 10 Hz, repeated after 10 min) was delivered to a second test pathway (again, either SR or SO), 30 min after priming. Priming and conditioning stimulation was always conducted at test pulse intensity. For bath application of pharmacological agents, drugs were applied 30 min prior to priming stimulation and washed out for the 30 min between priming and conditioning.

2.3 Data analysis

For LTP and LTD experiments, changes in synaptic efficacy were analysed via measurement of the initial slopes of synaptic potentials. Baseline was calculated as the average response over the 10 min before conditioning, and all values are expressed as a percentage of this average. LTP and LTD were calculated as the

average increase or decrease, respectively, from baseline (f)EPSP magnitude during the last 10 min of recording unless otherwise stated for extracellular and intracellular experiments. All group data are presented as mean ± SEM. Recordings were not included for analysis if they did not display stability during baseline recording.

Statistical analysis was conducted using Windows Excel (Microsoft) or SPSS (IBM). Significant differences between control and primed groups were assessed by Student's *t* test or ANOVA (one-way or repeated measures with Greenhouse-Geisser corrected values, as appropriate), with α set at $p < 0.05$. Where applicable, post-hoc testing was conducted using Fisher's Least Significant Difference (LSD) test.

2.4 Drugs and reagents

All salts were obtained from BDH Laboratory Supplies. AMPCP, carbenoxolone, DPCPX and meclofenamic acid were purchased from Sigma Aldrich. MRS1754 and ZM241385 were purchased from Ascent Scientific. CNQX, pirenzepine dihydrochloride, cyclopiazonic acid and BAY 60-6583 were purchased from Tocris bioscience. Connexin 43 mimetic peptide (H-Val-Asp-Cys-Phe-Leu-Ser-Arg-Pro-Thr-Glu-Lys-Thr-OH) and inactive control peptide (H-Gly-Asp-Glu-Gln-Ser-Ala-Phe-Arg-Cys-Asn-Thr-Gln-Gln-OH) were purchased from Auspep Pty ltd. Carbenoxolone, DPCPX, meclofenamic acid, MRS1754, ZM241385, BAY 60-6583 and peptides were dissolved in dimethylsulfoxide (DMSO). Control experiments routinely involved exposure to corresponding amounts of DMSO at the relevant time-points. All other compounds were dissolved in dH_20. All drugs were diluted at least 1000-fold in ACSF before bath application or pressure ejection.

3. Characterization of heterosynaptic metaplasticity in CA1

3.1 Introduction

Wang and Wagner (1999) and Hulme et al. (2012) described a form of metaplasticity in CA1 whereby strong afferent priming stimulation heterosynaptically inhibits LTP and promotes LTD at SR synapses. This form of metaplasticity is notable for its spatial spread, as changes to the plasticity threshold are evident at SR synapses even when priming is delivered heterodendritically in SO. In this form of metaplasticity, strong afferent activity at one point restricts the potential for subsequent synaptic potentiation. The effect therefore appears to homeostatically regulate cellular activity. The apparent homeostatic nature of the effect, and its spread to quiescent synapses on the same cells, is in keeping with the predictions of the BCM model and its Ca^{2+}-based derivatives (Bienenstock, et al., 1982; Yeung, et al., 2004). Hulme and colleagues found that established triggers of homosynaptic metaplasticity, namely NMDARs, mGluRs and L-type VGCCs (A. S. Cohen & Abraham, 1996; Y. Y. Huang, et al., 1992; Yasuda, Sabatini, & Svoboda, 2003), are not required in this model. Instead, the effect requires the release of Ca^{2+} from IP_3R-gated ER stores (Hulme, et al., 2012), a mechanism not considered in previous computational models.,

While the mechanisms for triggering the metaplastic state have been partially described, the effect as a whole remains poorly understood. In particular, there are outstanding questions regarding the patterns of synaptic stimulation which can or cannot elicit the effect. The homeostatic features of computational models of plasticity suggest that stronger afferent activity would elicit greater inhibition of subsequent LTP. That is, the strength of priming would correlate with heterosynaptic LTP inhibition. However, as yet no evidence exists in support of this prediction in the CA1 model. Moreover, it remains to be seen whether the metaplasticity can be

elicited between the strata of this region, as would be expected of a truly cell-wide form of metaplasticity. These questions were addressed here by applying priming protocols of varying pulse number and duration, delivered to strata of CA1 containing the apical or basal dendrites. The robustness of the metaplasticity was further investigated by testing whether the inhibition of LTP was evident in tissue from animals of different ages, and across different rodent species.

The results showed that the heterosynaptic metaplasticity is robust in young and adult rats, and adult mice. The metaplasticity could be elicited by numerous, but not all, variations of the standard priming protocol employed by Hulme et al. The metaplasticity was also found to either be confined to a single stratum or to spread heterodendritically, depending on which synapses received priming stimulation.

Some results in this chapter have been published in the following journal articles:

Hulme, S. R., Jones, O. D., Ireland, D. R., & Abraham, W. C. (2012). Calcium-dependent but action potential-independent BCM-like metaplasticity in the hippocampus. *The Journal of Neuroscience, 32*(20), 6785-6794.

Jones, O. D., Hulme, S. R., & Abraham, W. C. (2013b). Purinergic receptor- and gap junction-mediated intercellular signalling as a mechanism of heterosynaptic metaplasticity. *Neurobiology of Learning and Memory, 105*(0), 31-39.

3.2 Methods

3.2.1 Tissue preparation

Tissue from Sprague Dawley rats was prepared as described in Chapter 2, with the exception that tissue was taken from younger (2-3 wk) male rats of the same strain for some experiments. In other experiments, slices were prepared from hippocampi of male C57/Bl6 mice (6-8 wk). As with rats, mice were sourced from the University of Otago's breeding colony. For mouse slices, animals were anesthetized with isoflurane prior to decapitation. The brain was removed and chilled as for rat tissue before horizontal slices of hippocampus embedded in cortex were prepared using a Leica VT1000 vibratome. These slices were treated as per rat slices prior to experiments.

3.2.2 Extracellular recordings

fEPSPS were elicited and recorded as detailed in Chapter 2. Electrode configuration differed according to experimental requirements. In some experiments, two stimulating electrodes were placed in SR, on either side and equidistant from a single recording electrode. In other experiments, both SR and SO were stimulated via a single electrode placed in each layer and in line with one another, with a corresponding recording electrode in each stratum (**Fig. 3.1**). For rat slices, fEPSPs in various experiments were set at 1 mV (25-70 µA), 1.5 mV (35-75 µA) or 30% of maximum slope (65-90 µA). For mouse slices, stimulus intensity was adjusted to yield fEPSPs set at 40% of maximum slope (60-90 µA).

Standard priming stimulation consisted of 3 x 100 Hz, 1 s bursts, spaced by 20 s and repeated after 5 or 15 min to give a total of 6 bursts as per the protocols of Hulme et al. (2012) and Wang & Wagner (1999). In some experiments, the number of bursts was reduced to 4 (i.e. 2 x 100 Hz, 1 s bursts, repeated after 15 min). In other

experiments, priming was delivered in a ‘massed’ form of 6 x 100 Hz, 1 s trains delivered 30 s apart, or as a series of bursts delivered within the theta frequency range (theta burst stimulation or TBS: 6 trains of 20 bursts at 5 Hz, single train delivered every 30 s, each burst consisting of 5 pulses at 100 Hz, giving a total of 600 pulses).

LTP at test synapses in SR was induced via 2 trains of 100 Hz, 1 s bursts of pulses spaced 30 s apart. In cases where SO was the ‘test’ pathway, LTP was induced via a single 1 s, 100 Hz burst due to the greater LTP seen in this stratum (see below). Data were collected and analysed as described in Chapter 2.

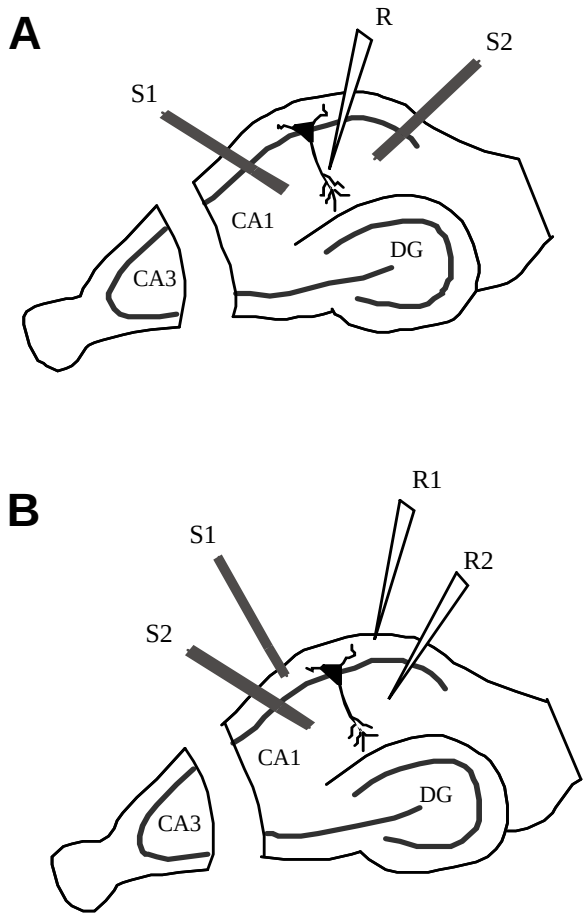

Figure 3.1. Electrode placement for field recordings.
Schematic of electrode placements in (**A**) radiatum priming and (**B**) oriens priming experiments in acute hippocampal slices. **A**: Priming stimulation was delivered via a first stimulating electrode (S1) in SR. Later conditioning was delivered via a second stimulating electrode to a separate test pathway also in radiatum (S2). FEPSPs were monitored via a single recording electrode (R). **B**: Priming delivered to SO (S1). Conditioning stimulation was delivered to SR (S2). Recording electrodes (R1, R2) were placed in both strata. Electrode positioning was counterbalanced in all groups such that priming and conditioning were delivered equally by electrodes placed closer to the CA3 or subiculum borders with CA1.

3.3 Results

3.3.1 Parameterization of heterosynaptic metaplasticity

As described by Wang & Wagner (1999) and Hulme et al (2012), 6 x 100 Hz trains of priming stimulation delivered to SR or SO induced homosynaptic LTP relative to non-primed control slices (SR priming: Control: n = 8, 99 ± 1%; Primed: n = 9, 125 ± 3%; $t_{(15)}$ = 7.06, p < 0.001, **Fig. 3.2a**; SO priming: Control: n = 7, 97 ± 6%; Primed: n = 6, 250 ± 18%; $t_{(11)}$ = 6.23, p < 0.001, **Fig. 3.2b**). In further agreement with previous results, SR or SO priming also reduced the amount of later LTP induced heterosynaptically in a test pathway in SR (SR priming: Control: n = 8, 131 ± 3%; Primed: n = 9, 118 ± 5%; $t_{(15)}$ = 2.18, p = 0.046, **Fig 3.3a**; SO priming: Control, n = 7, 135 ± 6%; Primed: n = 6, 119 ± 5%; $t_{(11)}$ = 2.44, p = 0.033, **Fig 3.3b**).

Next, the priming and conditioning protocols were manipulated to test the robustness and stimulus requirements of these effects. In SR, the 600 priming pulses were delivered as a series of 6 massed trains (30 s inter-train interval). This protocol induced a decremental form of LTP on the primed pathway (Control: n = 6, 99 ± 1%; Primed: n = 6, 128 ± 7%, $t_{(10)}$ = 4.28, p = 0.002, **Fig 3.4a**). Despite the comparatively weaker LTP on the priming pathway, the massed priming protocol still inhibited LTP in the neighbouring test pathway (Control: n = 6, 132 ± 3%; Primed: n = 6, 118 ± 2%, $t_{(10)}$ = 3.16, p = 0.010, **Fig 3.4b**). Next, the 600 priming pulses were delivered as a series of spaced shorter bursts within the theta frequency range (TBS: 6 trains of 20 bursts at 5 Hz, trains delivered every 30 s, each burst consisting of 5 pulses at 100 Hz). TBS priming yielded decremental LTP on the priming pathway (Control: n = 4, 100 ± 2%; Primed: n = 4, 119 ± 3%, $t_{(6)}$ = 5.09, p = 0.002, **Fig 3.5a**), however no effect of priming was apparent when inducing LTP at adjacent SR synapses (Control: n = 4, 122 ± 4%; Primed: n = 4, 122 ± 4%, $t_{(6)}$ = 0.06, p = 0.96, ns, **Fig 3.5b**).

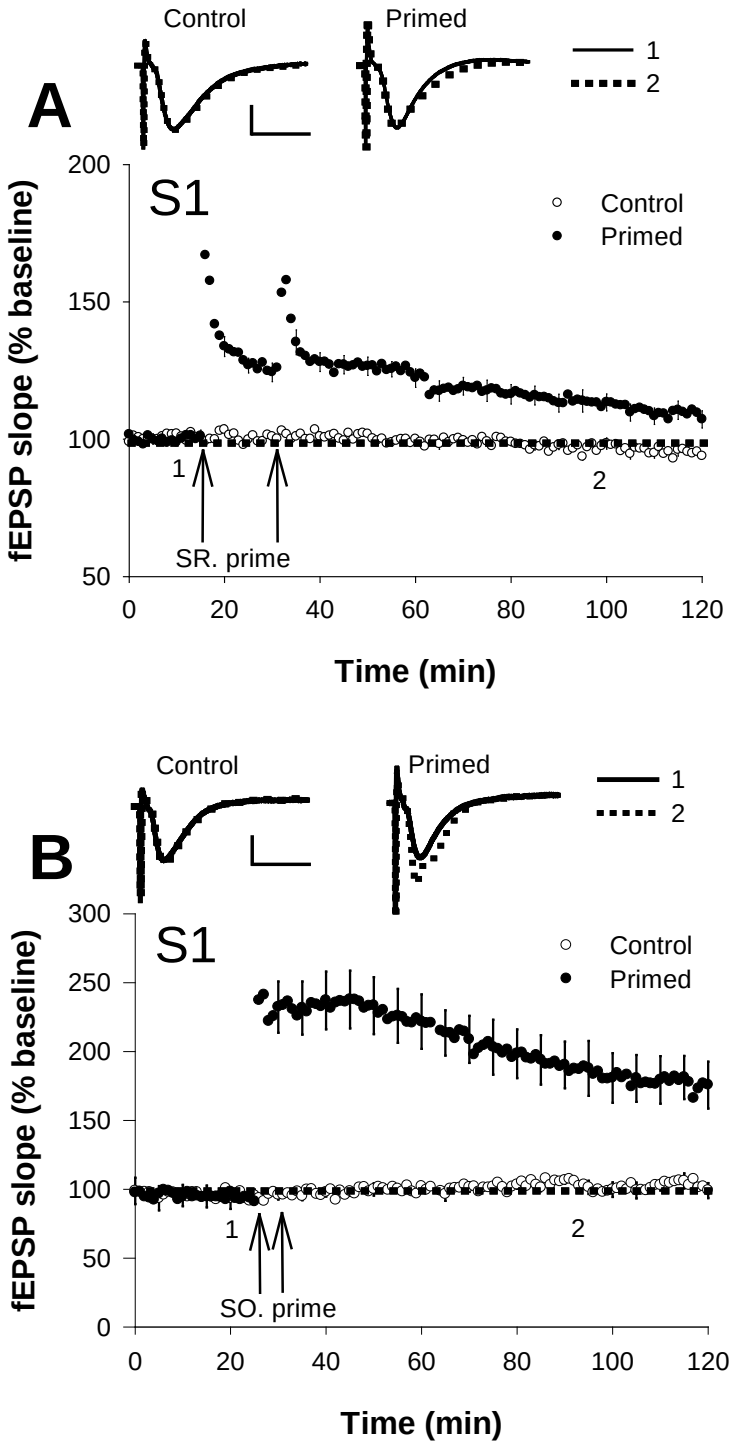

Figure 3.2. Monosynaptic effects of priming
Standard priming stimulation induced robust monosynaptic LTP when delivered to SR (**A**) or SO (**B**). Note greater magnitude of LTP following SO priming. SR or SO priming denoted by arrows marked 'SR/SO prime'. Error bars denote SEM and, for clarity, are provided for every 5th response. Inset: representative waveforms for this and all other figures are averages of the final 10 sweeps taken before (1) and post-HFS (2). Calibration bars: 0.5 mV, 10 ms.

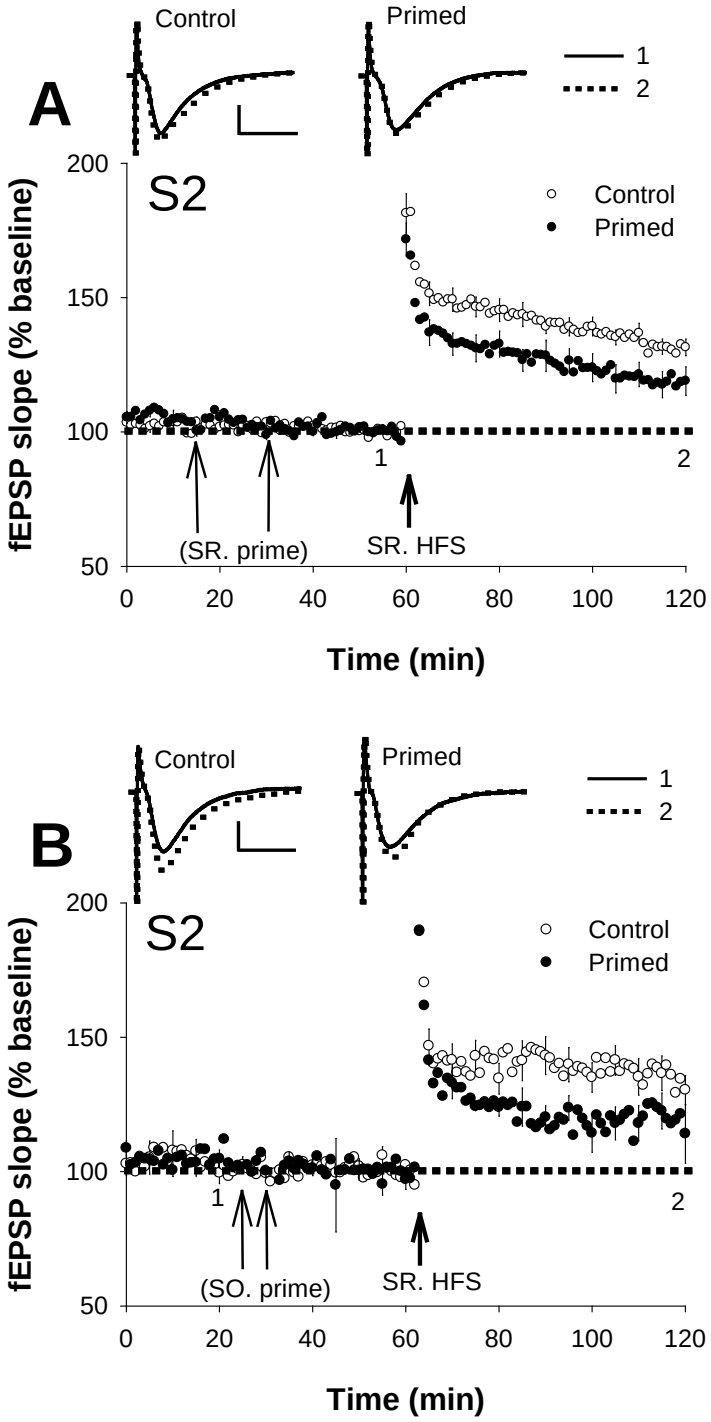

Figure 3.3. Heterosynaptic and heterodendritic effects of priming.
Standard priming stimulation delivered to afferents in SR metaplastically inhibited later LTP at adjacent synapses in the same stratum (**A**). Inhibition of LTP in SR was also seen when priming stimulation was delivered to synapses in SO (**B**). Results correspond to experiments detailed in **Fig 3.2**. SR conditioning induced at time-point marked 'SR HFS'. Calibration bars: 0.5 mV, 10 ms.

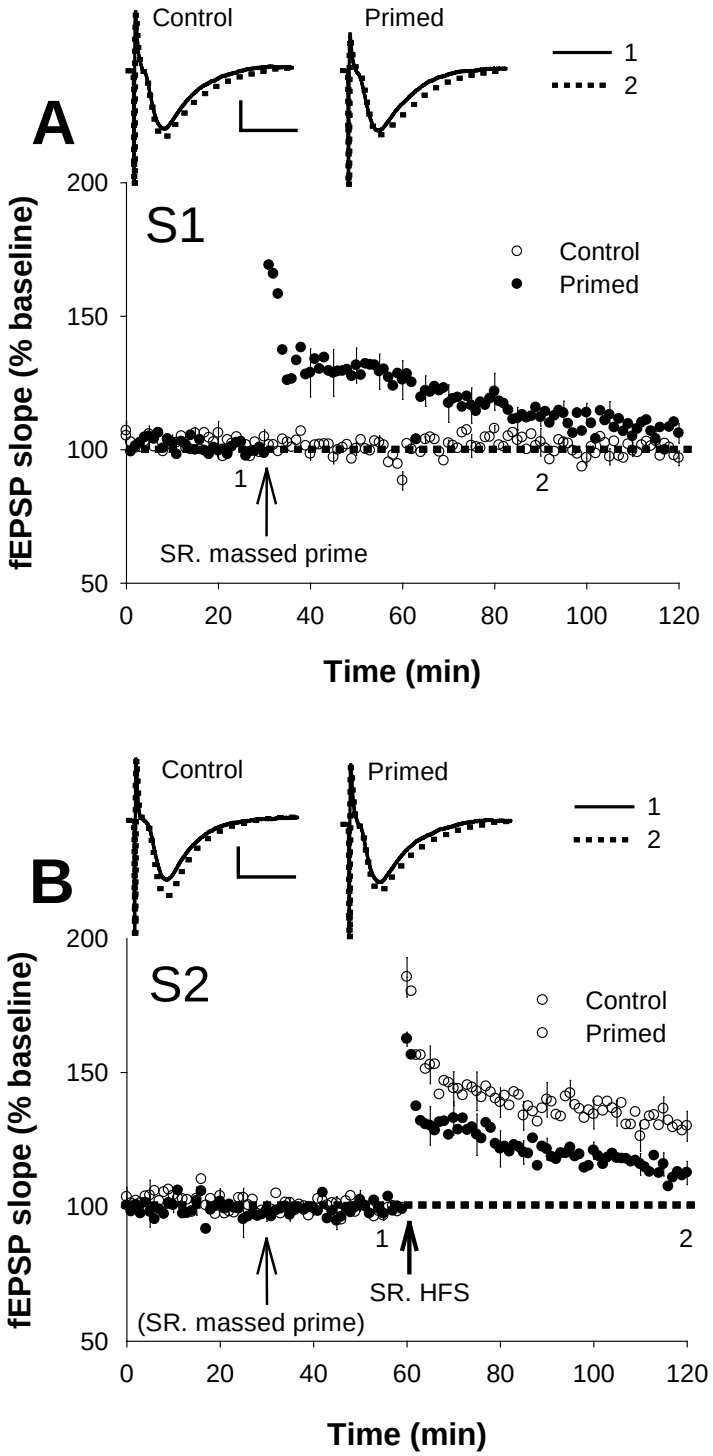

Figure 3.4. Massed priming heterosynaptically inhibits LTP in SR.
Delivering priming stimulation as 6 consecutive trains of HFS induced a decremental form of homosynaptic LTP (**A**), but still metaplastically inhibited LTP at neighbouring SR synapses (**B**). Calibration bars: 0.5 mV, 10 ms.

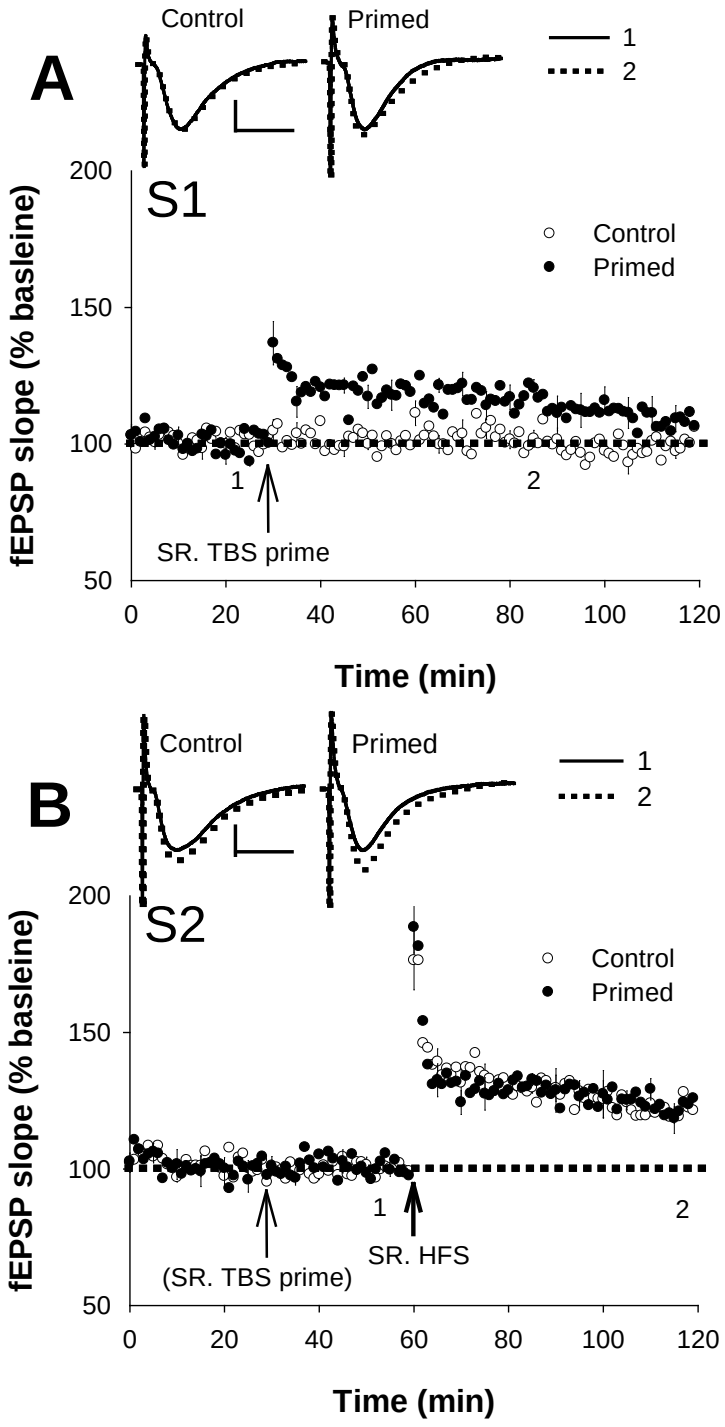

Figure 3.5. Failure of TBS priming to elicit metaplasticity.
TBS priming induced modest homosynaptic LTP (**A**) and did not alter subsequent LTP at adjacent SR synapses (**B**). Calibration bars: 0.5 mV, 10 ms.

3.3.2 Stimulus requirements of heterosynaptic metaplasticity

The stimulus requirements for generating the metaplasticity priming effect were next investigated, by reducing the number of standard SR priming trains from 3 to 2 per set (repeated after 15 min). Despite the reduced number of pulses, this protocol induced a similar amount of LTP on the primed pathway (Control: n = 8, 98 ± 2%; Primed: n = 8, 131 ± 4%; $t_{(14)}$ = 7.34, p < 0.001, **Fig 3.6a**) and significantly attenuated LTP at synapses in the neighbouring test pathway (Control: n = 8, 135 ± 3%; Primed: n = 8, 122 ± 3%; $t_{(14)}$ = 2.77, p = 0.015, **Fig 3.6b**). This reduced protocol was also effective in generating LTP in the primed pathway when delivered to SO synapses (Control: n = 9, 99 ± 1%; Primed: n = 8, 259 ± 12%, $t_{(15)}$ = 6.28, p < 0.0001, **Fig 3.7b**), and in reducing LTP heterodendritically in SR (Control: n = 9, 136 ± 6%; Primed: n = 8, 121 ± 2%, $t_{(15)}$ = 2.34, p = 0.034, **Fig 3.7b**).

3.3.3 Metaplasticity at different ages and in different rodent species

The next objective was to investigate whether the heterosynaptic metaplasticity is developmentally regulated, and whether it is expressed in mouse as well as rat hippocampus. In slices taken from 3-4 wk old rats, SO standard priming (3 × 100 Hz, repeated after 5 min) readily inhibited later LTP in SR as induced by 3 × 100 Hz trains (Control: n = 4, 141 ± 7%; Primed: n = 7, 106 ± 2%, $t_{(9)}$ = 5.57, p < 0.001, **Fig 3.8a**). SO standard priming also reduced subsequent SR LTP in slices taken from adult C57/Bl6 mice (Control: n = 4, 151 ± 9%; Primed: n = 4, 123 ± 6%, $t_{(6)}$ = 2.65, p = 0.038, **Fig 3.8b**).

3.3.4 Cell-wide vs. compartment specific induction of heterosynaptic metaplasticity

To test whether the induction of heterodendritic metaplasticity is compartment-specific, the locations of priming and subsequent conditioning were reversed. Robust LTP was induced in stratum oriens by 1 s of 100 Hz stimulation, however this was not affected by prior 6 x 100 Hz priming stimulation in stratum radiatum, even when the current intensity used during priming was increased to yield fEPSPs of 1.5 mV (Control: n = 8, 142 ± 5%; Primed 1 mV: n = 7, 161 ± 8%; Primed 1.5 mV, n = 7, *1*42 ± 7%, $F_{(2,19)} = 1.87$, $p = 0.18$, ns, **Fig 3.9**).

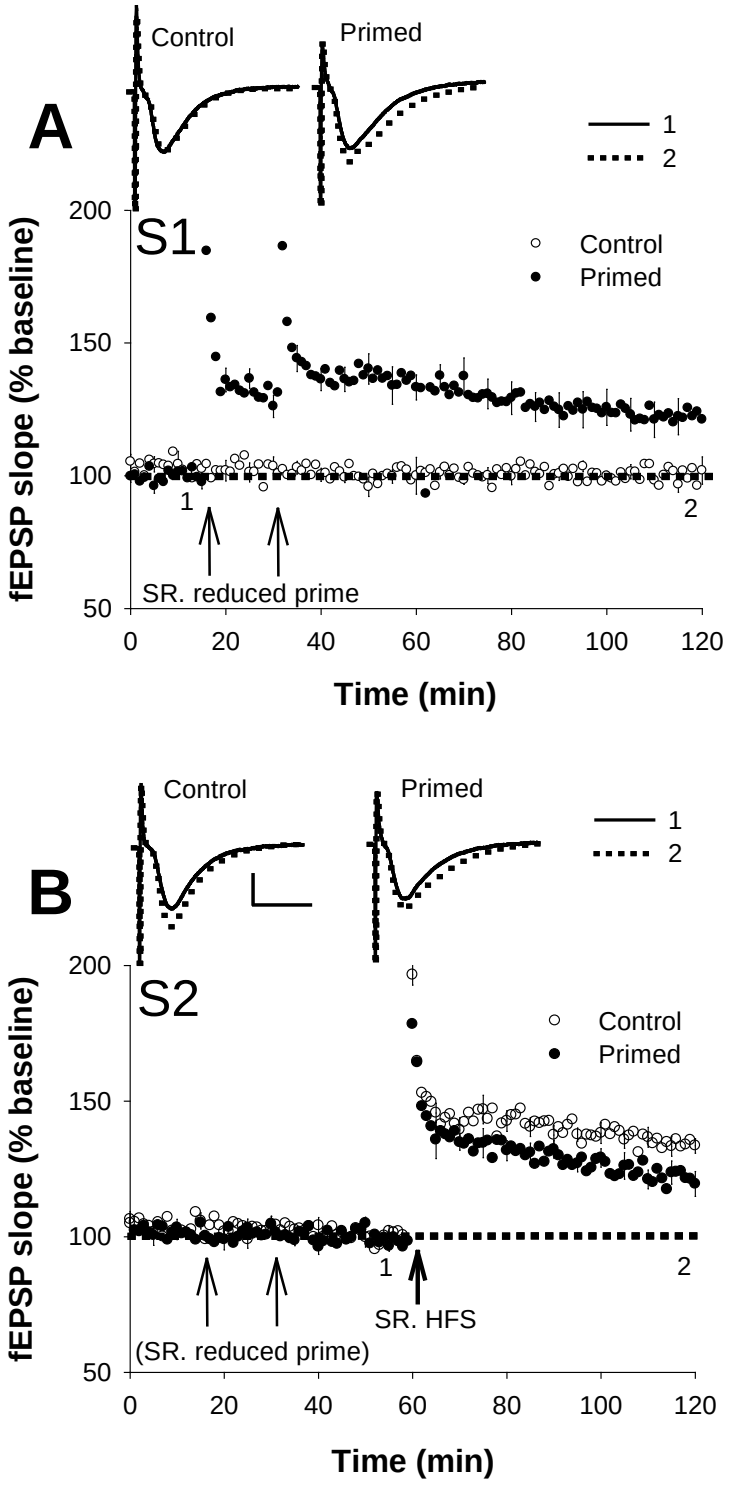

Figure 3.6. Heterosynaptic effects of a reduced priming protocol.
Reducing SR priming stimulation to 4 trains of HFS still elicited monosynaptic LTP (**A**) and still elicited metaplastic inhibition of LTP at adjacent synapses in the same stratum (**B**). Calibration bars: 0.5 mV, 10 ms.

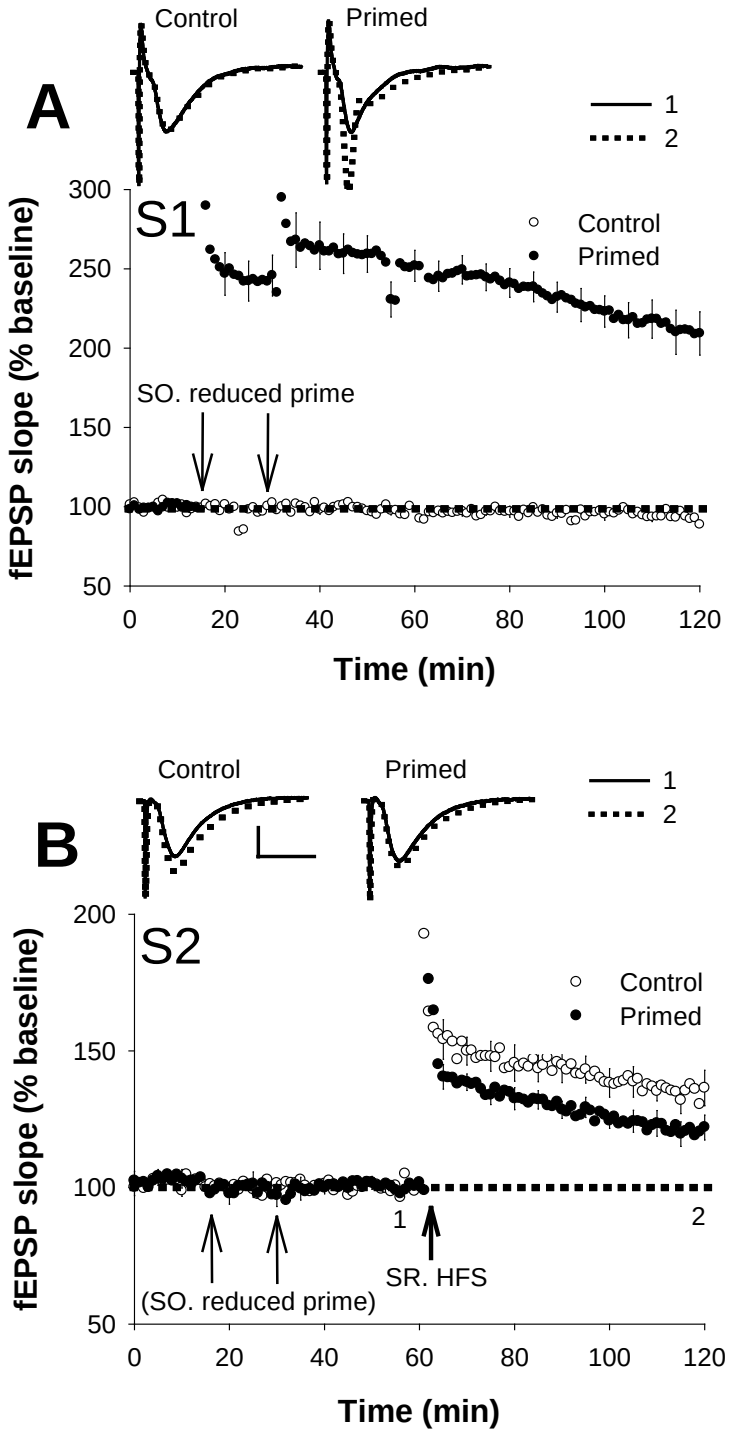

Figure 3.7. Heterodendritic effects of reduced priming.
The reduced priming protocol induced strong LTP in SO (**A**) and also inhibited subsequent LTP heterodendritically in SR (**B**). Calibration bars: 0.5 mV, 10 ms.

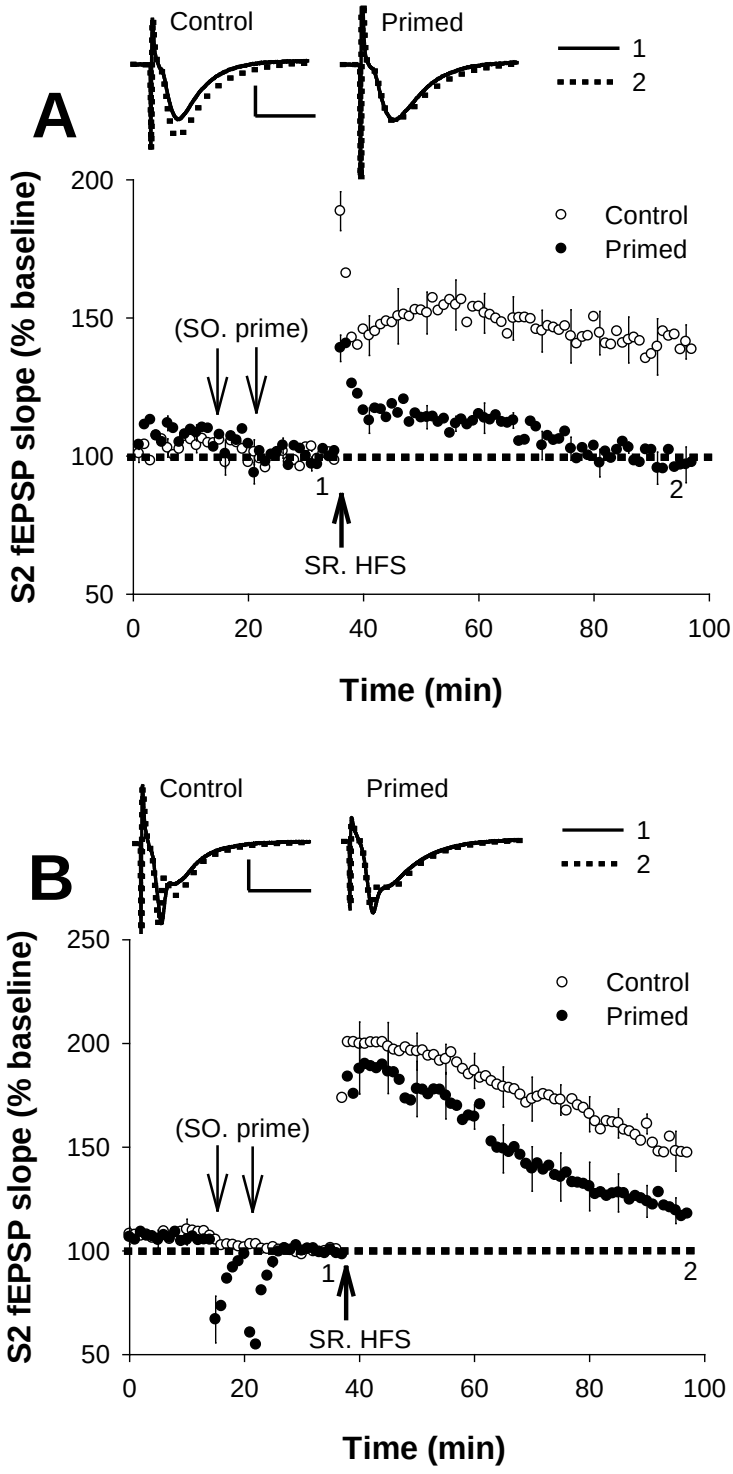

Figure 3.8. Priming-induced inhibition of LTP across age groups and rodent species. (**A**) Standard priming delivered to SO inhibited SR LTP in slices taken from 3 to 4 wk old rats (calibration bars: 0.5 mV, 10 ms). (**B**) Similar effects of SO priming were seen in slices taken from adult C57/Bl6 mice (calibration bars: 1 mV, 10 ms) Calibration bars: 0.5 mV, 10 ms.

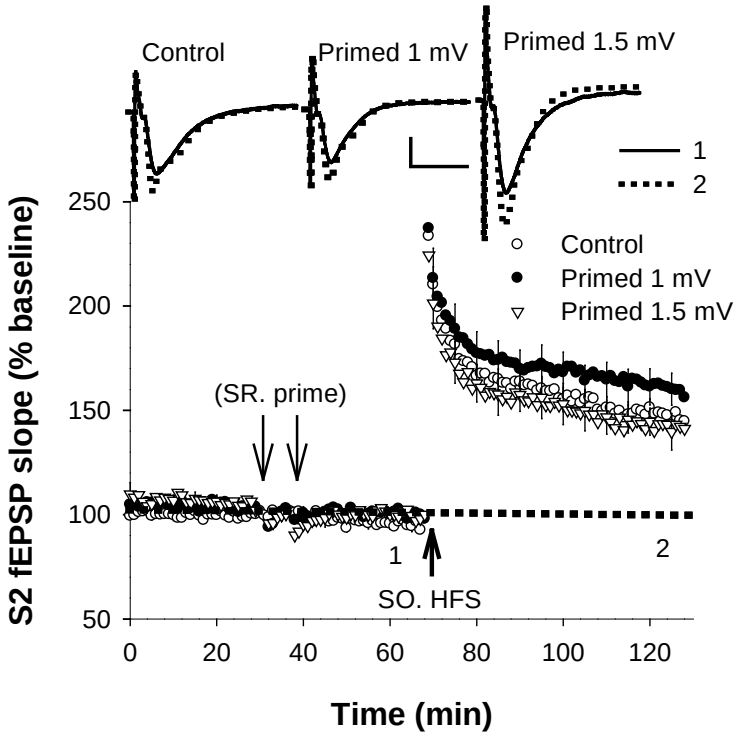

Figure 3.9. Priming is compartment-restricted.
Standard priming stimulation delivered to SR did not inhibit LTP subsequently induced in SO, even when stimulus intensity was increased. Calibration bars: 0.5 mV, 10 ms.

3.4 Discussion

3.4.1. Robustness of the heterosynaptic metaplasticity effect

Previous studies have reported a heterosynaptic inhibition of LTP in CA1 by prior high- or low-frequency stimulation (Hulme, et al., 2012; Le Ray, et al., 2004; Pavlowsky & Alarcon, 2012; H. Y. Wang & Wagner, 1999; Young & Nguyen, 2005) and in the DG (Abraham, et al., 2001). Notably, these metaplastic effects can extend between dendritic compartments located on opposite sides of the cell body (Hulme, et al., 2012; Pavlowsky & Alarcon, 2012; Young & Nguyen, 2005). Here the findings of Hulme et al. have been replicated and expanded upon to show that several high-frequency protocols, varying in number and spacing of the stimulus trains, can produce a similar level of LTP inhibition in SR, whether assessed within or between

dendritic compartments. The effect therefore appears to be quite robust and inducible under several conditions. The exception to this rule appears to be when trains of priming stimulation themselves are spaced as bursts of pulses.

In all conditions where LTP was inhibited, it was to a similar degree (~50%). This suggests a mechanism that is relatively independent of the distance between the stimulated axons and the affected synapses, although further investigation is required to determine the full spatial extent of the metaplastic state. Priming appeared to inhibit LTP to similar levels irrespective of the magnitude of LTP on the priming pathway. Indeed, LTP induced in response to SO priming was substantially greater that that seen following similar stimulation of SR synapses, yet exerted a similar influence on later LTP in SR. This apparent lack of a graded response to varying afferent activity may distinguish this phenomenon from the postulated cell-wide, homeostatic forms of metaplasticity implemented in computational models (Bienenstock, et al., 1982; Narayanan & Johnston, 2010; Yeung, et al., 2004). Instead, the similar levels of inhibition seen across priming protocols suggest that the effects of priming are 'all-or-none'. The effect also differs from the homeostatic 'shutdown' of LTP seen by other researchers, which is only evident after the vast majority of a cell's synapses have been potentiated (Roth-Alpermann, et al., 2006).

There may, however, be some variation in the extent of LTP inhibition during maturation. Priming appeared to inhibit later LTP to a larger degree in tissue from younger animals (compare **Fig 3.9b with Fig 3.10a**), suggesting that this metaplasticity is, at least in part, developmentally regulated. Glutamate transporter expression increases during development and restricts extrasynaptic diffusion of neurotransmitter (Thomas, Tian, & Diamond, 2011). However, these changes stabilize by P20, meaning that they cannot account for differences in metaplasticity seen at

different ages in the present experiments (all animals aged > 21 d). The effect was nonetheless visible in adult tissue, and further work is needed to determine whether the metaplasticity exists in the aged brain. That the metaplasticity is observable in mice indicates that the regulatory mechanism is conserved across rodent species. This latter result demonstrates that it may be possible to use transgenic mice to investigate the molecular signalling cascades underpinning the inhibition of LTP.

TBS priming did not alter subsequent plasticity. It should be noted that control slices in these experiments displayed somewhat less LTP than usual. However, this should not preclude priming stimulation from further altering subsequent plasticity. The inability of TBS priming to noticeably alter the LTP threshold is curious, as this pattern of stimulation is considered a more naturalistic model of synaptic activity than HFS (Staubli & Lynch, 1987). Repeated TBS elicits greater postsynaptic Ca^{2+} transients than HFS (Perez, Chapman, Woodhall, Robitaille, & Lacaille, 1999), and these transients include a strong IP_3R-mediated component (C. R. Raymond & Redman, 2002, 2006). Thus, given the dependence of heterosynaptic metaplasticity on IP_3-mediated Ca^{2+} release, and the failure of TBS priming to induce this form of metaplasticity, it may be that the required Ca^{2+} stores are not located postsynaptically. It is perhaps noteworthy that HFS elicits greater spillover of glutamate from the synapse than TBS, although these measurements come from mutant mice with reduced astrocytic transporter activity (Tanaka, et al., 2013). It has also been demonstrated that, at room temperature, HFS triggers glutamate release which overwhelms astrocytic GLUTs, whereas TBS does not (Diamond & Jahr, 2000). While the pertinence of these results is obscured by the experimental conditions used, they do highlight a likely greater release of transmitter during HFS than during TBS. It is tempting to suggest that HFS priming may therefore be better placed than TBS to

activate receptors at extrasynaptic locations or on astrocytes. Indeed, the magnitude of astrocyte Ca^{2+} transients is positively correlated with the number of pulses per train (Araque, et al., 2002; Barat, et al., 2012). Further, with sufficient glutamate release, transporter reversal triggers gliotransmitter efflux from astrocytes (Rossi, Oshima, & Attwell, 2000; Szatkowski, Barbour, & Attwell, 1990) However, TBS of cholinergic fibres induces Ca^{2+} transients in CA1 astrocytes and subsequent gliotransmission (Navarrete, et al., 2012). Thus, the relative efficacy of HFS and TBS in activating astrocytes remains debatable. This matter could be resolved by measuring astrocytic transporter currents and Ca^{2+} signals in response to HFS or TBS priming stimulation.

An alternative explanation is that the greater somatic depolarization elicited by TBS initiates conditions which favour subsequent LTP. Early pulses in TBS trains facilitate depolarization by subsequent bursts by triggering the activation of $GABA_B$ autoreceptors on interneurons (Mott & Lewis, 1991). Accordingly, TBS is superior to HFS in generating postsynaptic depolarization and AP firing (L. Y. Chen, Rex, Sanaiha, Lynch, & Gall, 2010; Grover, et al., 2009; Pacelli, Su, & Kelso, 1989). In fact, APs increase in number across bursts during TBS trains, whereas they rapidly decrease in number during HFS (Grover, et al., 2009). The metaplastic facilitation of LTP by AP firing has been demonstrated in two recent studies (Bukalo, et al., 2013; Hulme, et al., 2012). Thus, it is possible that TBS priming initiates facilitatory cascades which negate the inhibitory signalling associated with the heterosynaptic priming-induced attenuation of LTP.

The inability of TBS priming to inhibit later LTP also raises the question of how the heterosynaptic metaplasticity mechanisms described here might be engaged under naturally occurring circumstances. As noted, TBS is a model of theta patterned activity found in hippocampi of freely behaving animals. Naturally, TBS does not

precisely replicate the patterns of neural activity associated with the theta EEG rhythm, but it is arguably more realistic than 100 Hz HFS. Gamma oscillations in CA1 occur at frequencies of 40-100 Hz (Bragin, et al., 1995), and may therefore be sufficient for engaging heterosynaptic metaplasticity. Hippocampal gamma oscillations are suggested to be involved in information encoding and retrieval (Hasselmo, Wyble, & Wallenstein, 1996; O Jensen & Lisman, 1996), suggesting perhaps that heterosynaptic metaplasticity could be engaged by learning. Interestingly, gamma oscillations at ~100 Hz also precede the onset of seizure activity in rat and human hippocampus (Traub, et al., 2001). Thus, if gamma oscillations do generate heterosynaptic metaplasticity it may be a protective mechanism which limits synaptic excitation during seizure. Moderate concentrations (100-200 nM) of kainic acid induce gamma oscillations in hippocampal slices (Hájos, et al., 2000). This protocol could potentially be used to test the ability of gamma oscillations to generate metaplasticity.

3.4.2 Compartment-specific induction of metaplasticity

Priming stimulation delivered to SO reduced subsequent LTP induction in SR. However, the inverse configuration (SR priming) was ineffective in reducing SO LTP, even when stimulus intensity was raised. These results suggest that heterosynaptic metaplasticity as described here is not fully cell-wide, and further highlights the disparity between this mode of synaptic regulation and those featured in the BCM model and its derivatives. The amount of LTP seen in SO after priming at 1.5 mVwas less than that seen after priming at 1 mV, albeit not to a statistically significant degree. Increasing stimulus intensity further may elicit more noticeable alterations to later plasticity in SO. This is particularly plausible given that SR

priming inhibited LTP at neighbouring synapses within the same stratum. Nonetheless it remains possible that SO priming and SR priming engage different metaplasticity mechanisms that either remain confined to the dendritic layer that received priming stimulation (following SR priming), or spread across the soma (following SO priming). This may highlight a difference in the passive electrical properties of dendrites in SO and SR. For example, currents generated in SR may attenuate more heavily and thus invade SO to a lesser degree (or generate fewer APs). Or, APs generated during SR priming may attenuate more heavily as they propagate through dendrites in SO. An alternative explanation is that the apparent compartmentalisation of metaplasticity is due to differences in the protocol used to induce LTP in the test pathway (2 x HFS in SR vs. 1 x HFS in SO). Synapses in SO produce LTP more readily than those in SR (compare the amounts of LTP produced by priming stimulation in SO and SR). A single train was therefore used to induce LTP in SO in case the metaplasticity effect could be overcome by repeated HFS, and so as to make control levels of LTP induced in SO as comparable as possible with that induced in SR. It is possible however that the expression of the metaplasticity is dependent in part on the amount of synaptic activity during later plasticity induction. Such a mechanism might imply the release of factors at the time of plasticity induction which reduce LTP and promote LTD, or conversely might suggest that factors normally released at the time of plasticity induction are now absent.

3.5 Conclusions

Homeostatic regulation of synaptic plasticity thresholds is an important feature of computational models. Strong experimental support for this concept comes from in vivo studies which detail homo- and heterosynaptic metaplasticity driven by electrical

stimulation or sensory experience (Abraham, et al., 2001; Sawtell, et al., 2003). However, to date there have been few examples established in vitro which allow for the precise manipulation of pre- and postsynaptic mechanisms. Work conducted using one such model (as employed by Wang and Wagner (1999) and Hulme et al. (2012)) has been expanded upon here to show that LTP in SR of CA1 are heterosynaptically controlled by prior afferent activation in a manner that appears to homeostatically restrict subsequent synaptic potentiation. Further, this regulation can extend from basal to apical dendritic compartments. As yet, however, there is no evidence that the metaplasticity can spread in the reverse direction. This mode of metaplasticity has now been characterised further to show that it is observable across a range of priming and conditioning protocols, across two developmental ages and across two rodent species. Thus, this is a robust effect that controls the information processing capability of SR synapses.

4. Intracellular signalling and heterosynaptic metaplasticity

4.1 Introduction

4.1.1 Action potentials

Heterodendritic inhibition of LTP as described by Hulme et al. (2012) requires signalling over long distances. This could in theory be triggered by diffusible messengers (S. Y. Huang, et al., 2012). However, diffusible molecules commonly implicated in plasticity (e.g. Ras, IP_3, cAMP) have been shown to traverse only short distances (<10 μm: E. A. Finch & Augustine, 1998; C. D. Harvey, Yasuda, Zhong, & Svoboda, 2008; Rich, et al., 2000). APs or even depolarization per se, represent a more plausible trigger of a global metaplastic state. APs travel in orthograde and retrograde fashion (i.e. through axons and dendrites) (Stuart & Hausser, 1994; Stuart & Sakmann, 1994). Backpropagating APs trigger the dendritic secretion of factors such as BDNF, adenosine and endocannabinoids (Kuczewski, et al., 2008; Lovatt, et al., 2012; Ohno-Shosaku, Maejima, & Kano, 2001). Further, repeated bursts of antidromic APs reduce dendritic excitability in SR via NMDAR-dependent alterations to I_h (Narayanan & Johnston, 2007).

APs are also triggers of metaplasticity. For instance, antidromic firing in the absence of synaptic activity facilitates subsequent LTP (Bukalo, et al., 2013). On the other hand, somatic APs induced during blockade of GABAergic inhibition suppress later LTP via downregulation of R-type VGCCs (Yasuda, et al., 2003). Finally, there is evidence in vivo of AP-mediated heterosynaptic metaplasticity in the DG, as predicted by the BCM model (Abraham, et al., 2001; Bienenstock, et al., 1982). Thus, APs represent a plausible trigger for heterodendritic inhibition of LTP as seen by Hulme et al.

4.1.2 Membrane properties

Several modes of metaplasticity involve intracellular signalling cascades culminating in altered neuronal membrane properties. These changes are achieved by altering the composition or number of dendritic ion channels which regulate the orthodromic and antidromic spread of depolarization (Hoffman, Magee, Colbert, & Johnston, 1997; Sah & Bekkers, 1996). Intrinsic neuronal excitability is altered in an activity-dependent manner. For example, brief TBS or HFS triggers localised increases in dendritic excitability mediated by a downregulation of HCN channels and A-type K^+ channels (Campanac, Daoudal, Ankri, & Debanne, 2008; Fink & O'Dell, 2009; J. Y. Kim, Jung, Clemens, Petralia, & Hoffman, 2007). These mechanisms account for the increased dendritic excitability seen after weak LTP induction (Campanac, et al., 2008; Frick, Magee, & Johnston, 2004), and may facilitate further LTP (Jung, et al., 2008). However, changes to excitability can also be compensatory, making them a plausible basis for homeostatic forms of metaplasticity. For example, LTP induction at SR-CA1 synapses increases synaptic strength but concomitantly increases the sAHP (Le Ray, et al., 2004). Further, whereas I_h is downregulated after weak LTP, it is increased following stronger LTP induction (Campanac, et al., 2008; Fan, et al., 2005). I_h also provides a negative feedback mechanism for decreased synaptic strength, as this current is decreased in an mGluR-dependent manner during induction of LTD (Brager & Johnston, 2007). HCN channels are ubiquitous throughout the dendritic arbor of CA1 pyramidal cells, and LTP triggers HCN channel-mediated excitability changes both homo- and heterosynaptically(Narayanan & Johnston, 2007, 2008). Accordingly, it has been suggested that alterations to I_h could account for BCM-like cell-wide metaplasticity in this region (Narayanan & Johnston, 2010). Similarly, the proximal dendritic location of K^+ channels that

underlie the sAHP allow these channels to regulate EPSP summation from throughout the entire dendritic tree, as well as limit global activity in the form of cell firing (Power, Bocklisch, Curby, & Sah, 2011; Sah & Bekkers, 1996). Indeed, an HFS-induced increase to the sAHP has already been shown to heterosynaptically inhibit LTP at SR synapses (Le Ray, et al., 2004).

4.1.3 Intracellular calcium

Ca^{2+} is a prominent intracellular second messenger, and Ca^{2+}-dependent signalling regulates intrinsic plasticity and metaplasticity(Nelson, Krispel, Sekirnjak, & du Lac, 2003; Park, et al., 2010; Tsubokawa, Offermanns, Simon, & Kano, 2000; Yasuda, et al., 2003). Heterosynaptically primed LTD at SR synapses requires Ca^{2+} release from intracellular stores (Hulme, et al., 2012). Whether heterodendritically primed LTD in SR relies on a similar mechanism has remained an open question. Furthermore, a trigger of the Ca^{2+} release required for heterodendritic metaplasticity has remained elusive. One likely source, mGluRs, is already excluded as a candidate trigger of Ca^{2+} release in this model, as blocking these receptors during priming stimulation does not block the subsequent change in plasticity thresholds (Hulme, et al., 2012). However, other G_q-coupled GPCRs in CA1, such as the m1 subgroup of AChRs, represent possible alternatives.

The primary objective for this chapter was to investigate the contributions of various modes of intracellular signalling to the heterodendritic metaplasticity describe by Hulme et al. Specifically, the dependence of the metaplasticity on APs was investigated as a critical test of the applicability of the BCM model to this mode of metaplasticity. Possible changes in membrane parameters, including I_h and the sAHP, were investigated as an expression mechanism of the metaplasticity. Finally, it was

investigated whether heterodendritic LTD facilitation requires Ca^{2+} release from intracellular stores, and whether G_q-coupled mAChRs (a plausible trigger of Ca^{2+} release) also contribute to the metaplasticity.

Some results in this chapter have been published in the following journal article:

Hulme, S. R., Jones, O. D., Ireland, D. R., & Abraham, W. C. (2012). Calcium-dependent but action potential-independent BCM-like metaplasticity in the hippocampus. *The Journal of Neuroscience, 32*(20), 6785-6794.

4.2 Methods

4.2.1 Tissue preparation and extracellular recordings

Hippocampal slices were prepared from Sprague-Dawley rats as per the previous chapter. Extracellular recordings were conducted as per the previous experiments, with fEPSPs set at 1 mV for baseline recording. SO priming was delivered via the standard protocol of 3 x 1 s trains at 100 Hz, repeated after 5 or 15 min. LTD was induced in SR via 600 pulses at 10 Hz, repeated after 10 min.

4.2.2 Intracellular recordings

Single-cell experiments utilised intracellular sharp electrode recordings rather than whole-cell patch-clamping, in order to avoid dialysis from the cell of biochemicals required for LTP induction (Kato, Clifford, & Zorumski, 1993). Intracellular recordings were obtained using borosilicate micropipettes (1.0 mm OD, 0.5 mm ID; Sutter Instrument Co.), filled with 2 M KAc and with final resistances of 75-120 MΩ prior to impalement. Recordings were made in current-clamp mode using

an Axon Instruments HS-2A headstage coupled to an Axoclamp 2B amplifier (both from Molecular Devices Inc.). Recordings were digitized at 10 KHz via an Axon CNS Digidata 1440A and recorded using pClamp 9.0 software (again both from Molecular Devices Inc.). EPSPs were filtered with a low-pass (2 KHz), 4 pole Bessel filter prior to data analysis.

Intracellular recordings were made only from CA1 pyramidal neurons, identified via typical electrophysiological properties (depolarising voltage "sag" and heavily accommodating APs, elicited via a family of 200 ms, 0.2 nA pulses (-0.5 nA to 0.7 nA, spaced by 1 s, **Fig 4.1b**). Cells were included for experimentation if resting V_m was below -60 mV, input resistance (R_{in}) was greater than 30 MΩ, they displayed overshooting action potentials when depolarized and had EPSPs of > 8 mV amplitude in response to single 100 µA pulses with V_m held at -75 mV. Stimulation intensity was adjusted during experiments to yield EPSPs consistently between 5-8 mV (35–80 µA). The membrane potential was adjusted manually via somatic current injection, with cells routinely held at -75 mV during recording but depolarised to -65 mV during priming or conditioning stimulation. In some cases, cells were hyperpolarised to -90 mV during priming to prevent AP generation or somatic depolarization past resting values. Synaptic potentials (**Fig 4.2a**) were evoked as for extracellular experiments using single stimulating electrodes placed in SO and SR, respectively (**Fig 4.1**. R_{in} was deduced from the steady-state (i.e. post-sag) voltage deflection seen following a single -0.3 nA, 100 ms pulse delivered every 1 min (**Fig 4.2b**). Cells were held at -65 mV when generating AHPs, elicited via single trains of four APs spaced 5 ms apart, each AP generated via 1 ms, 3 nA current injection to the soma (**Fig 4.3a**). I_h was assessed by delivering 700 ms hyperpolarising current steps (-0.3, -0.5, -0.7 and -0.9 nA), spaced 2 s apart, with cells originally held at -75 mV (**Fig 4.3b**). AHP/I_h

measurements were conducted immediately before SR priming and immediately before SO conditioning. Each AHP/I_h protocol was repeated three times, spaced 30 s apart, at each timepoint, with I_h measurements beginning 30 s after the final AHP protocol ended. In control experiments, AHP and I_h measurements were taken at the same timepoints as in priming experiments. Where applicable, cells were hyperpolarised to -90 mV in control experiments to match treatment in priming experiments.

For LTP experiments, changes in EPSP slope were evaluated by comparing baseline levels with those of the final 5 min of recording (i.e. 25-30 min post-conditioning). The mAHP and sAHP were assessed by averaging measurements of maximal amplitude taken at the timepoints noted above. At these same timepoints, the peak hyperpolarisation in response to negative current steps (as noted) was taken as a an indicator of changes in the strength of I_h (Campanac, et al., 2008). Plasticity of the mAHP, sAHP and I_h was assessed by comparing the averaged values obtained at each timepoint for each current intensity.

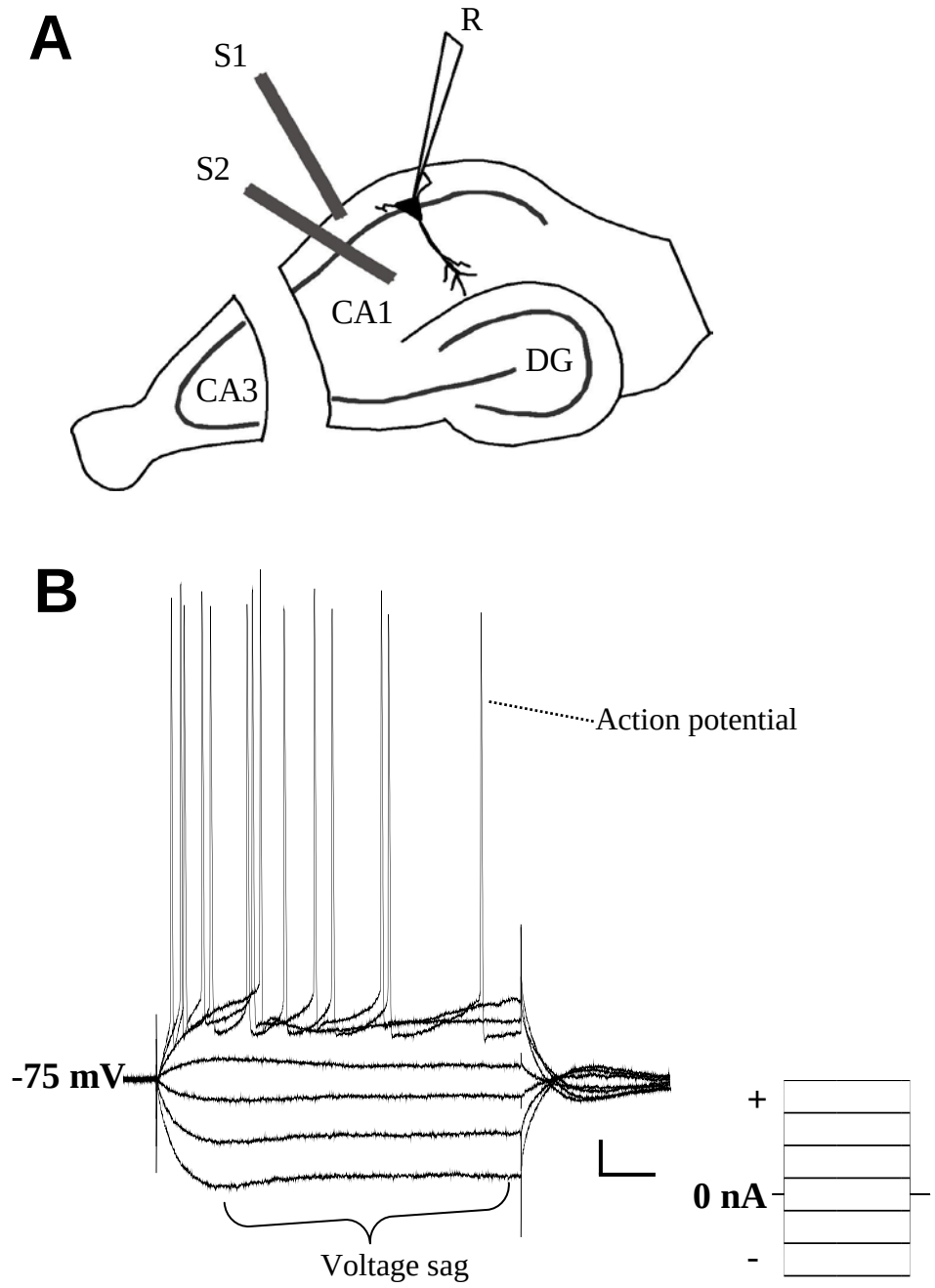

Figure 4.1. Intracellular sharp electrode recordings
A: Schematic of electrode placements for intracellular recordings with stimulating electrodes in SO for priming (**S1**) and SR for subsequent induction of LTP (**S2**). Recordings were taken via glass microelectrodes used to impale the soma of single pyramidal cells (**R**).
B: Representative current-voltage (IV) analysis taken from a pyramidal cell in CA1. Note characteristic depolarising voltage "sag" following hyperpolarisation. Also note decreasing frequency of action potentials across time during depolarising current injection (i.e. spike frequency adaptation). Calibration bars: 10 mV, 20 ms. Inset: Schematic of current steps used to generate Vm deflections.

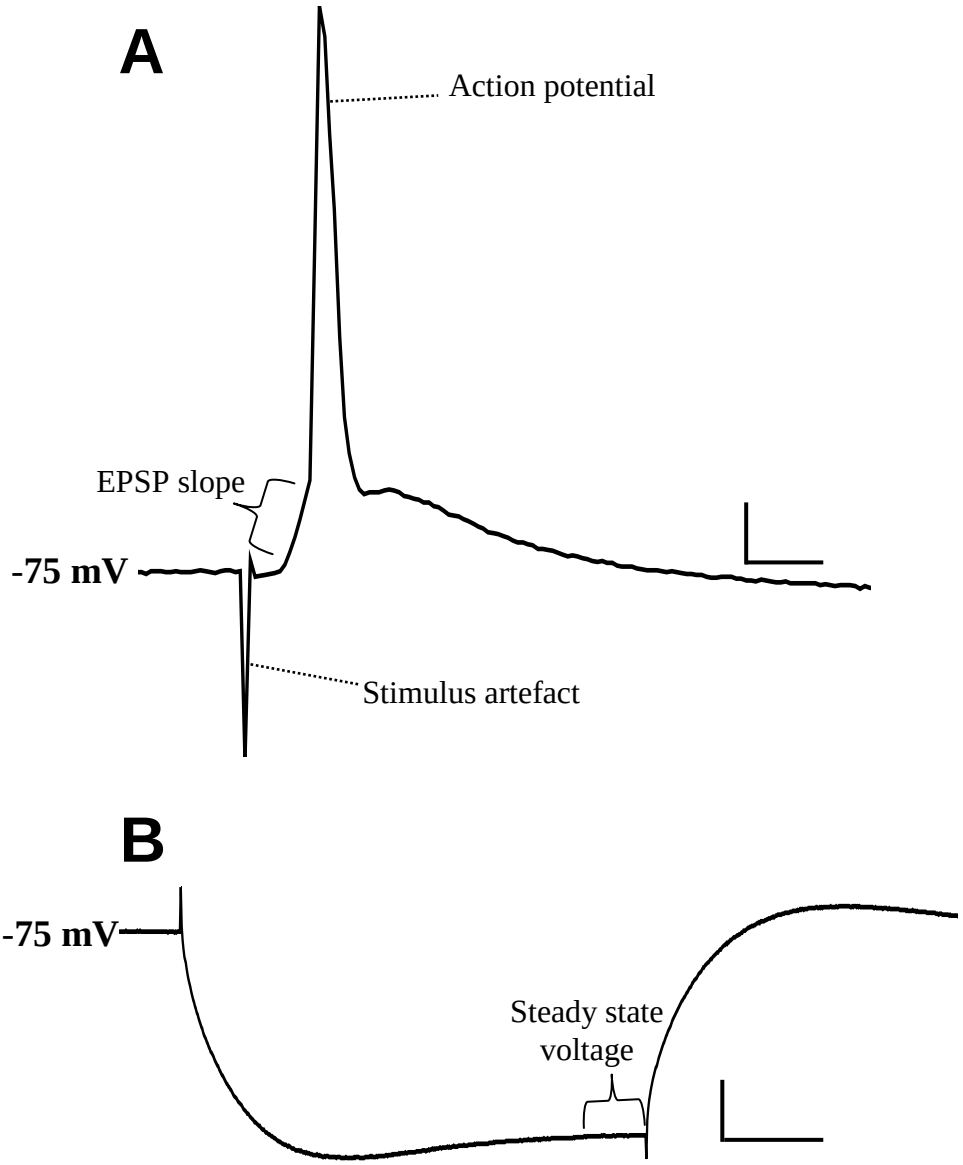

Figure 4.2. Intracellular recordings
A: Representative intracellular EPSP and AP. Synaptic efficacy was assessed via measurement of the initial slope of the EPSP, which is not confounded by the presence of APs. Calibration bars: 10 mV, 2 ms.
B: Input resistance was defined via Ohm's law (R=V/I), where the steady-state (post-sag) voltage deflection was divided by the amount of current injected. Calibration bars: 10 mV, 20 ms.

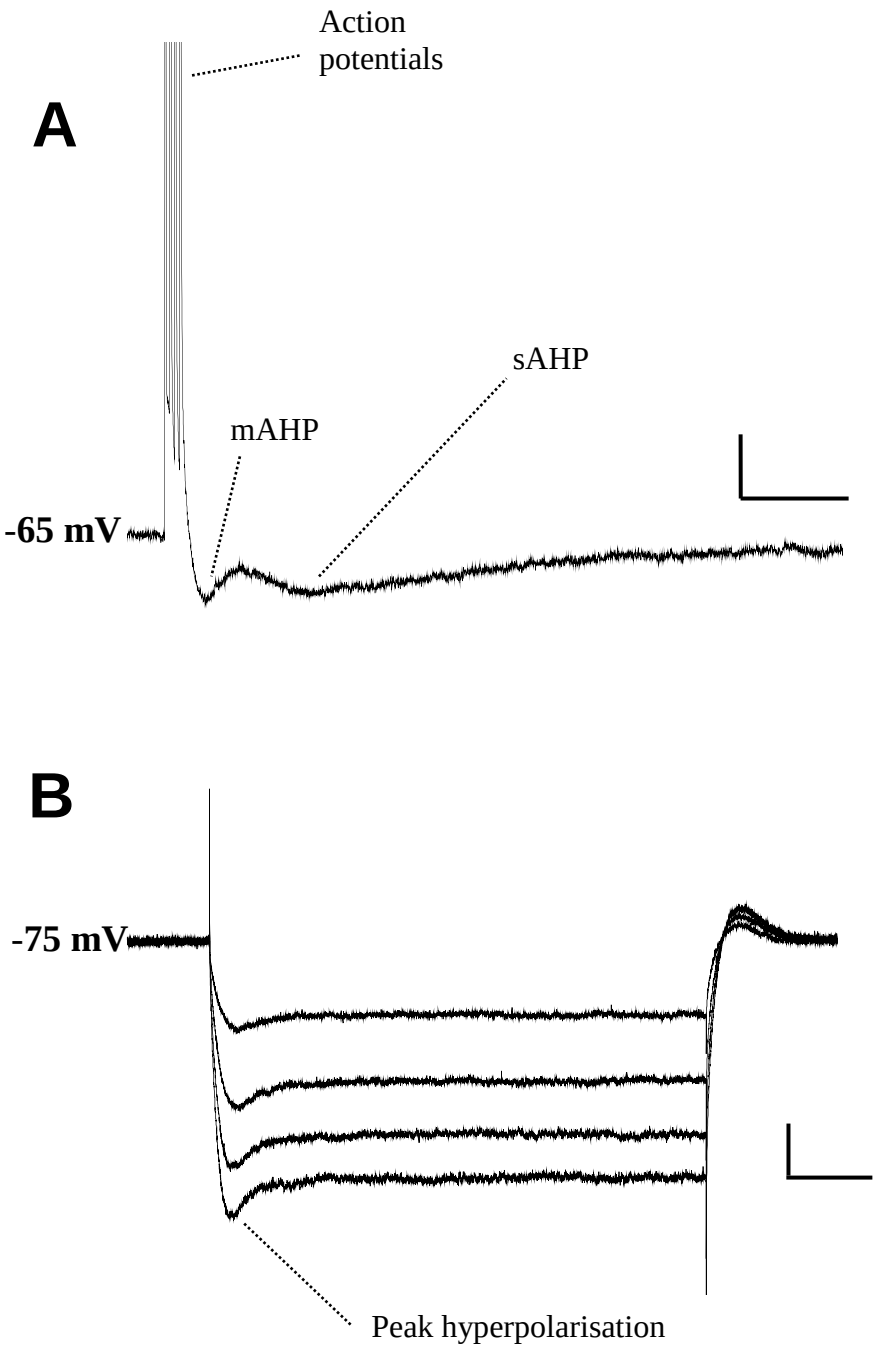

Figure 4.3. Testing for changes in afterhyperpolarisations or the *h* current
A: The medium (mAHP) and slow (sAHP) afterhyperpolarisation as induced by a train of action potentials (APs are truncated for a smaller image). Calibration bars: 10 mV, 100 ms.
B: The peak hyperpolarisation of V_m following somatic negative current injection. As the strength of I_h increases, the cell becomes less hyperpolarised in response to current injection. Thus, this measure can be taken as an initial indication of any change in the strength of I_h. Calibration bars: 10 mV, 50 ms.

4.3 Results

4.3.1 Postsynaptic depolarization is not required for heterosynaptic metaplasticity

Hulme et al. (2012) showed that hyperpolarizing individual neurons and preventing somatic action potentials during SR priming did not alter the subsequent inhibition of LTP at adjacent synapses in the same stratum. This same protocol was used to test the role of APs in SO priming. This protocol also isolated the dendritic compartments electrically, thus blocking action currents and depolarization per se from spreading from the site of priming to test synapses in SR. The number of somatic APs observed during SO priming stimulation varied (μ = 40 APs across the total 6 trains of HFS, range = 0–170, n = 8). Interestingly, the number of spikes seen during priming weakly correlated with LTP induced subsequently in SR, although not to a statistically significant degree (Pearson r = 0.637; p = 0.089, ns, **Fig 4.4**). No such correlation was evident between LTP in SR and spiking seen during IVs used to identify pyramidal cells prior to experimentation (Pearson r = 0.337; p = 0.415, ns, data not shown), suggesting that the modest correlation between priming-induced spiking and subsequent SR LTP was not due to differences in excitability *per se*. Nonetheless, spiking was absent in all cases when priming took place while the cell was hyperpolarised (**Fig 4.5**). Further, somatic V_m did not reach above -75 mV in these cases (data not shown). Accordingly, homosynaptic LTP in SO was virtually absent in these cells (Control: n = 8, 90 ± 5%; Primed: n = 8, 186 ± 23%; Primed hyperpol: n = 7, 108 ± 12%, $F_{(2,20)}$ = 11.23, p = 0.0005, **Fig 4.6a**). However, priming-induced inhibition of SR LTP was not altered when cells were hyperpolarised to -90 mV during priming stimulation (Control: n = 8, 158 ± 5%; Primed: n = 8, 125 ± 5%; Primed hyperpol: n = 7, 125 ± 10%, $F_{(2,20)}$ = 8.29, p = 0.002, **Fig 4.6b**).

4.3.2 Priming does not alter postsynaptic membrane properties

R_{in} did not differ across groups at baseline, and was not differentially altered across groups post-priming (baseline R_{in}: Control: n = 8, 37 ± 2 MΩ; Primed: n = 8, 40 ± 2 MΩ; Primed hyperpol: n = 7, 37 ± 2 MΩ, $F_{(1,20)}$ = 0.63, p = 0.54, ns; Post-priming change in R_{in}: Control: n = 8, 105 ± 4 %; Primed: n = 8, 95 ± 4 %; Primed hyperpol: n = 7, 104 ± 5 %, $F_{(1,20)}$ = 1.76, p = 0.20, ns, **Fig 4.7a**). Similarly, no group showed changes in the strength of I_h at any current intensity following priming (Control: n = 4; Primed: n = 4; Primed hyperpol: n = 5, time*condition, $F_{(1,10)}$ = 0.524, p = 0.927, ns, **Fig 4.7b**). The peak mAHP and sAHP also showed no change in any group following priming (mAHP: Control: n = 7, 91 ± 11 %; Primed: n = 7, 103 ± 10 %; Primed hyperpol: n = 6, 104 ± 7 %, $F_{(1.156,2.974)}$ = 0.398, p = 0.754, ns; sAHP: Control: 98 ± 8 %; Primed: 100 ± 8 %; Primed hyperpol: 99 ± 18 %, $F_{(1.156,2.512)}$ = 1.046, p = 0.383, ns, **Fig 4.7c**). Thus, when analysed just prior to conditioning stimulation, no membrane properties measured were significantly affected by SO priming stimulation.

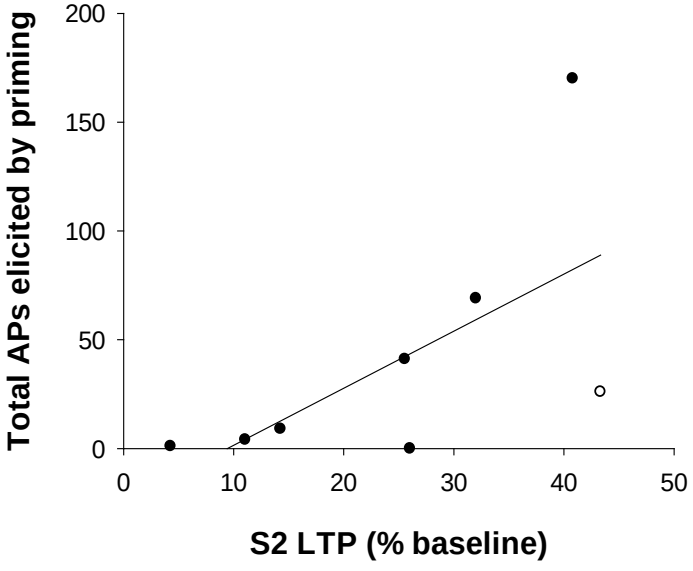

Figure 4.4. Correlation between AP firing during priming and later LTP in radiatum
SO priming in the absence of somatic hyperpolarisation induced variable amounts of cell firing. An overall trend was seen whereby greater levels of cell firing correlated positively, albeit weakly, with subsequent LTP induced at SR synapses.

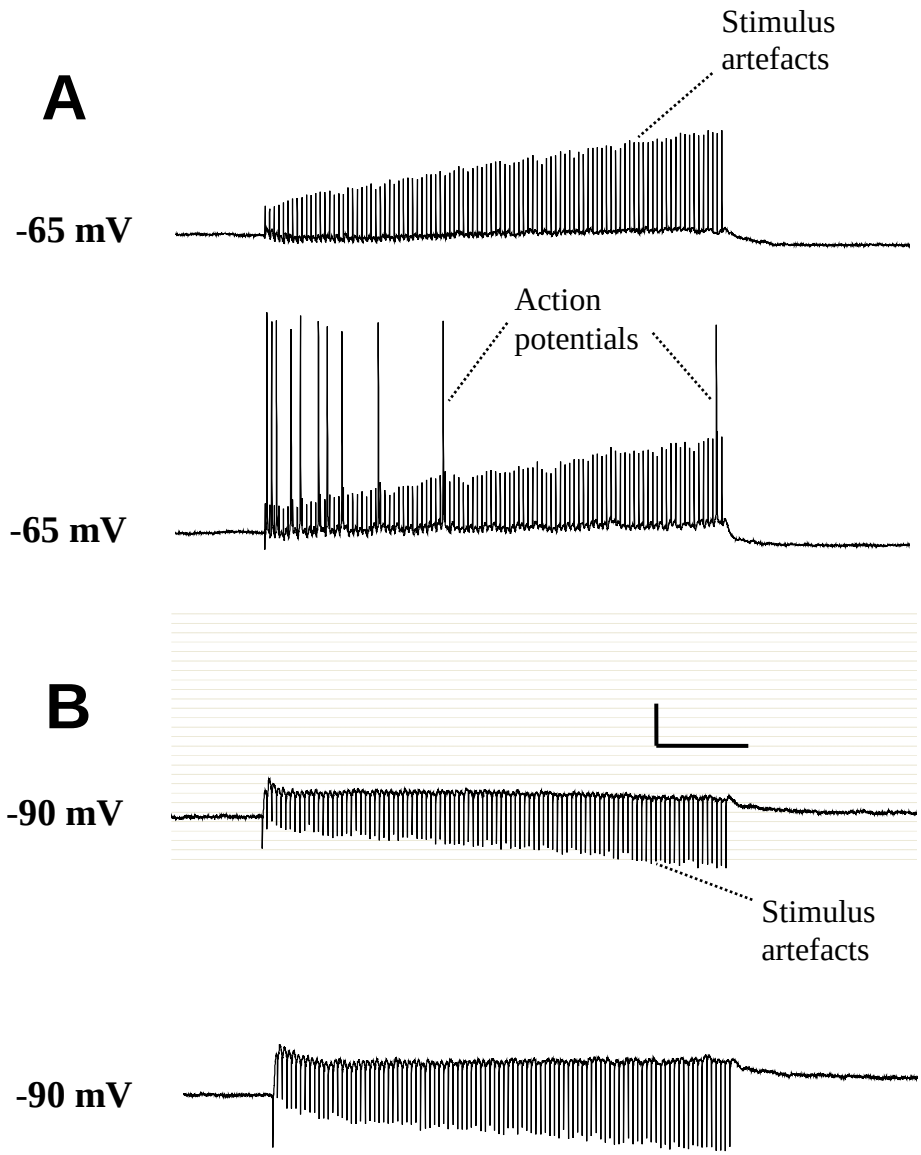

Figure 4.5. S**omatic hyperpolarisation**
Trains of 100 Hz stimulation were delivered to SO with cells held at -65 mV (i.e. close to resting V_m; **A**), or while the soma was hyperpolarised to -90 mV (**B**). Figures are representative recordings of V_m taken during the first (upper images of **A** and **B**) and last (lower images) trains of SO priming. Note the appearance of APs during the later train of regular priming, whereas no APs are evident during hyperpolarised priming. Calibration bars: 10 mV, 200 ms.

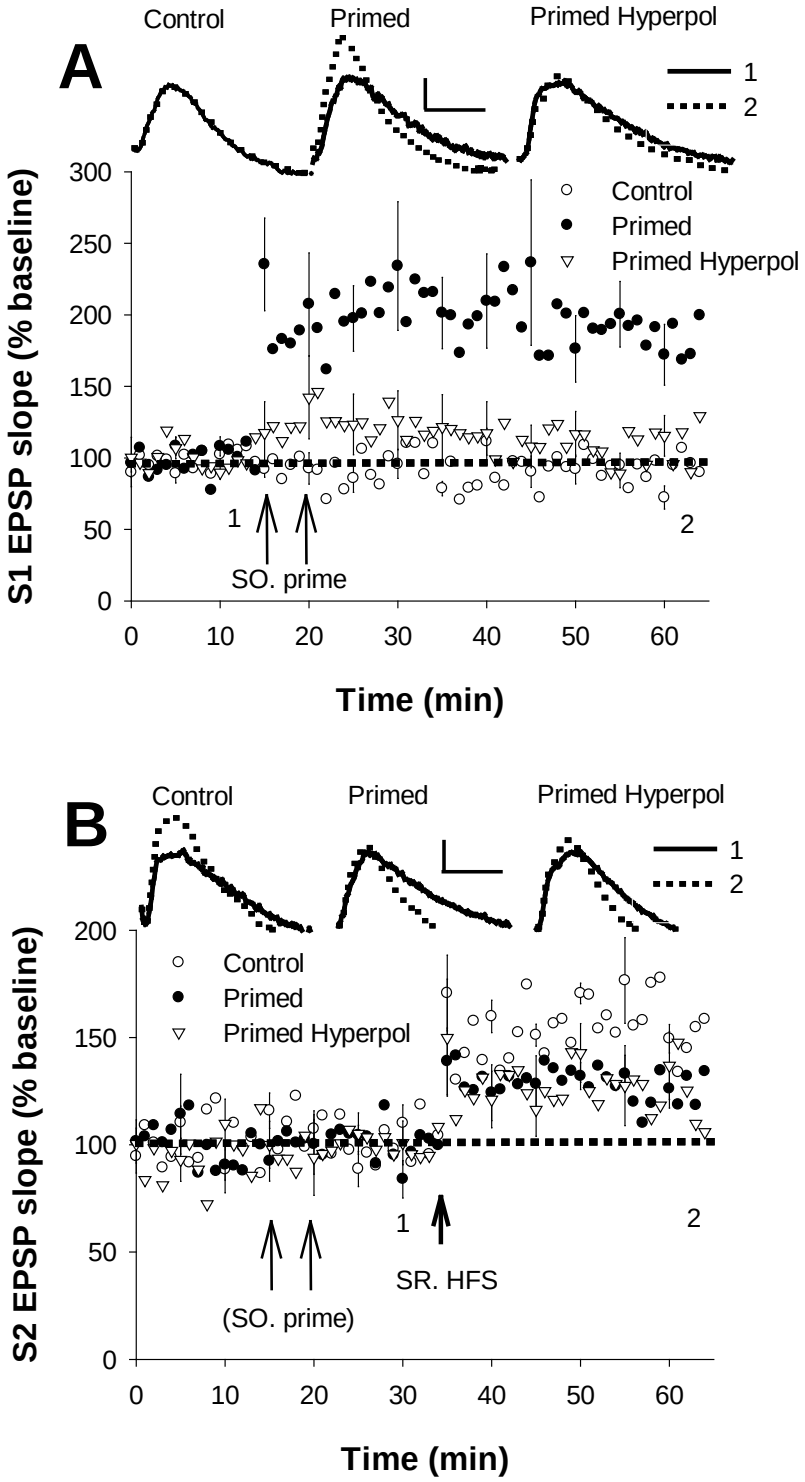

Figure 4.6. Priming during somatic hyperpolarisation
A: SO priming stimulation induced robust homosynaptic LTP (Primed) which was almost completely blocked when priming occurred during somatic hyperpolarisation to -90 mV (Primed hyperpol).
B: At SR synapses, 2x100 Hz stimulation induced LTP (Control) which was reduced following SO priming (Primed). Hyperpolarisation during priming did not alter this metaplasticity (Primed hyperpol). Calibration bars: 2 mV, 20 ms.

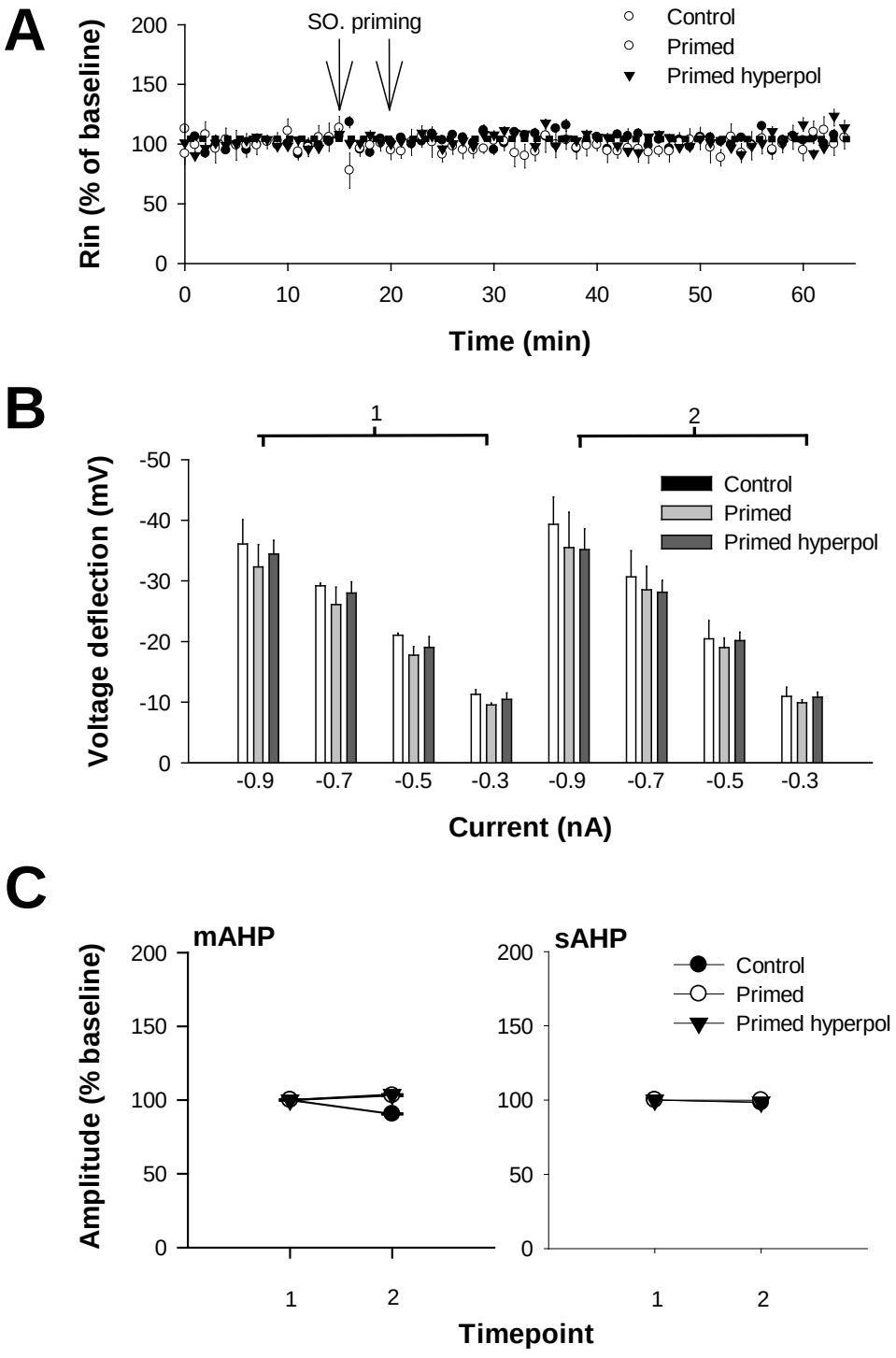

Figure 4.7. Membrane parameters are not altered by SO priming
A: No lasting changes were detected in R_{in} following SO priming in either of the primed groups.
B: The peak hyperpolarisation in response to injections of negative current at various intensities did not change following SO priming, indicating that Ih remained unaltered. Timepoints 1 and 2 refer to baseline and post-priming, respectively (see methods earlier in this chapter).
C: No group showed significant alterations in the amplitude of the mAHP or sAHP following priming. Timepoints as per **B**.

4.3.3 Intracellular Ca^{2+} and heterosynaptic metaplasticity

To test the requirement of intracellular Ca^{2+} for heterodendritic priming-facilitated LTD, the reversible sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase pump inhibitor cyclopiazonic acid (CPA; 50 μM) was bath-applied for 30 min prior to SO priming. CPA blocks refilling of intracellular Ca^{2+} stores, thus depleting them over time (Mellentin, Jahnsen, & Abraham, 2007; Seidler, Jona, Vegh, & Martonosi, 1989). CPA has only been shown to block the inhibition of LTP following heterosynaptic priming (Hulme, et al., 2012). Standard SO priming (without CPA) significantly increased the amount of LTD seen subsequently at SR synapses, however this facilitation was absent when SO priming took place in the presence of CPA (Control: n = 6, 1 ± 1%; Primed, n = 6, −12 ± 4%; Primed CPA: n = 6, -1 ± 1%, $F_{(2,17)}$ = 7.21, p = 0.005, **Fig 4.8a**). Further, SO priming in the presence of pirenzepine (PZN; 20 μM), a specific antagonist of G_q-coupled M1-AChRs, did not inhibit later SR LTP (Control: n = 5, 23 ± 4%; Primed: n = 5, 23 ± 8%, t =*-0.004*, p = 1.00, ns, **Fig 4.8b**).

4.4 Discussion

4.4.1 Postsynaptic depolarization does not trigger heterosynaptic metaplasticity

In the BCM model, APs are the key integrative unit of cellular activity. However, the proposition that alterations to θ_M are driven by AP firing was not supported here. Indeed, cell firing was remarkably variable during priming stimulation, and was in fact positively correlated with later SR LTP (although not significantly). Further, complete blockade of APs during priming did not block metaplasticity. As somatic V_m did not rise above resting levels during the hyperpolarised priming, it is also unlikely that local action currents generated during

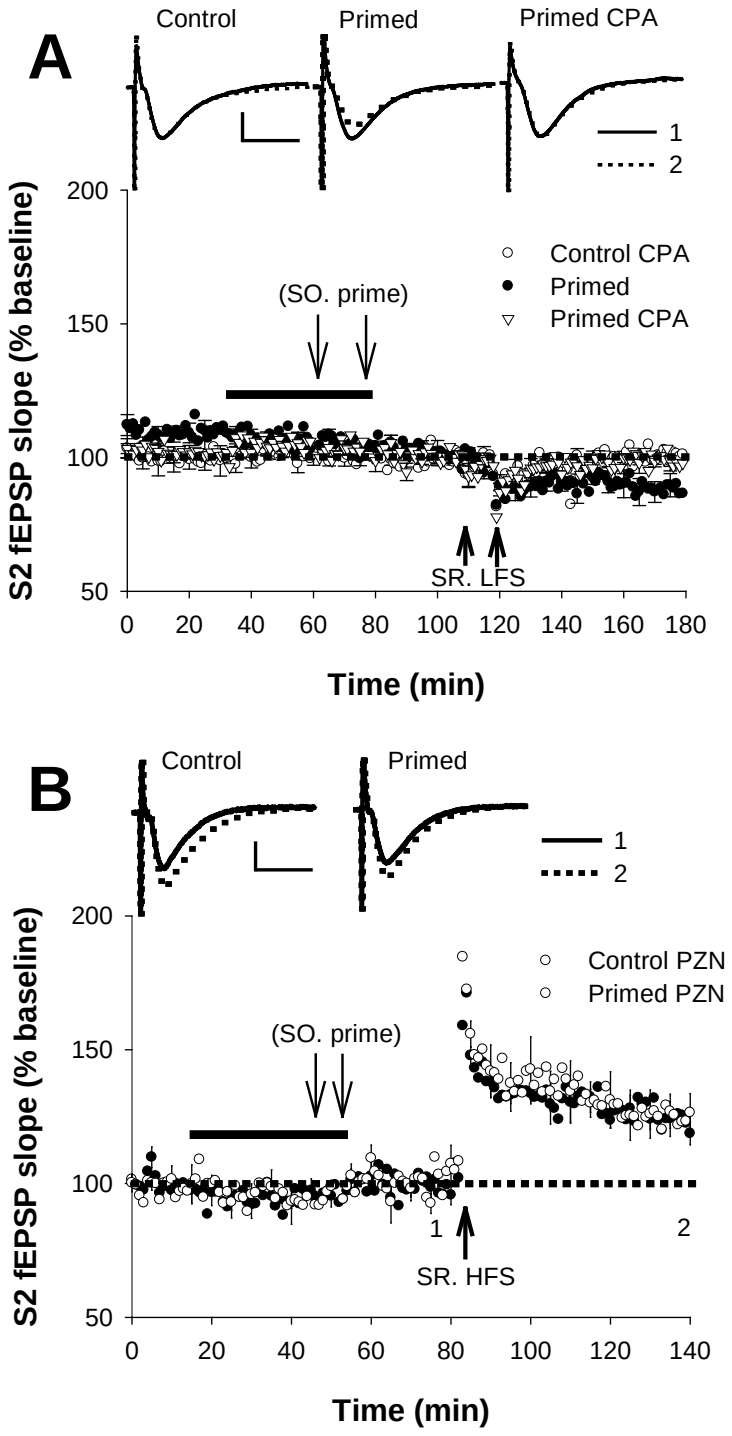

Figure 4.8. G_q-signalling and heterosynaptic metaplasticity
A: 10 Hz stimulation did not induce LTD in control slices (Control CPA), whereas the same paradigm elicited LTD in slices which received prior SO priming (Primed). However, priming in the presence of the SERCA pump inhibitor CPA had no effect on subsequent LTD induction (Primed CPA). Horizontal black bar denotes period of drug application. Calibration bars: -.5 mV, 10 ms.
B: Slices treated with the specific M1-AChR inhibitor pirenzepine during priming (Primed PZN) do not display subsequently reduced LTP. Calibration bars as per **A**.

priming could spread between dendritic compartments. This mode of communication is therefore ruled out as contributing to the metaplasticity.

Backpropagating APs could potentially mediate cell-wide metaplasticity by generating Ca^{2+} influx at both active and quiescent dendritic locations (Spruston, Schiller, Stuart, & Sakmann, 1995; Y. W. Wu, Grebenyuk, McHugh, Rusakov, & Semyanov, 2012; Yasuda, et al., 2003). In keeping with this, antidromic APs are sufficient to initiate BCM-like metaplasticity in the DG (Abraham, et al., 2001). However, several lines of inquiry suggest that APs do not regulate plasticity in such a way in CA1. In the previous chapter in was noted that TBS priming failed to alter subsequent LTP at adjacent synapses, despite the reported superiority of this protocol in generating APs. Further, Hulme et al. (2012) found that extended trains of somatic APs in fact *facilitate* subsequent LTP; an effect which has recently been verified following ectopic AP generation also (Bukalo, et al., 2013). Finally, antidromic APs convert subsequent E-LTP to L-LTP (Dudek & Fields, 2002). It is tempting to suggest that the weak correlation between priming-induced firing and subsequent LTP reflects the facilitatory effects of APs as demonstrated by Hulme et al. (2012) and Bukalo et al. (2013).

It is prudent here to compare the heterosynaptic inhibition of LTP with another model of heterosynaptic metaplasticity; synaptic tagging and capture (Frey & Morris, 1997). In both cases, strong tetanic stimulation delivered to one pathway elicits a metaplastic state that spreads to quiescent synapses in a neighbouring pathway. In both cases, the spread of the metaplastic state can extend across dendritic compartments (Alarcon, et al., 2006; Hulme, et al., 2012). Further, the priming/preconditioning protocols used to tetanize the first input in both models are often comparable (e.g. 4 s at 100 Hz in: Alarcon, et al., 2006). However, the effects of

the preconditioning stimulation can differ markedly. For example, in the classic synaptic tagging paradigm, tetanization of a first input to hippocampal CA1 facilitates the capture of L-LTP at a second input (Frey & Morris, 1997). In contrast, 4 or 6 x 100 Hz priming as employed in this thesis does not convert E-LTP to L-LTP; rather, priming inhibits the induction of LTP at nearby synapses.

Interestingly, synapses can be 'tagged' for L-LTP capture following AP firing in the absence of synaptic activity (Alarcon, et al., 2006; Dudek & Fields, 2002). This is reminiscent of the facilitation of LTP *induction* seen following AP firing by others (noted above). This might suggest that relative differences in AP firing during tetanization of the first pathway underlie the different forms of metaplasticity seen subsequently. In keeping with this, BDNF is critical for L-LTP capture (Barco, et al., 2007), and BDNF is produced in dendrites following invasion by backpropagating APs (Kuczewski, et al., 2008). BDNF also facilitates LTP induction at low concentrations (2 nM), without affecting baseline transmission, by reducing the AHP (Kramár, et al., 2004). AP-mediated BDNF signalling is therefore a plausible mechanism for metaplastically facilitating the induction *and* persistence of LTP.

It is likely that the mechanisms of L-LTP capture overlap with those involved in AP-induced facilitation of LTP induction. The question therefore becomes: why might AP firing be engaged more during HFS in the synaptic tagging paradigm, than during SR or SO priming in the experiments of this thesis? Differences in the recording environment could account for this (submerged in experiments of this thesis, interface in all synaptic tagging experiments referenced in this text), although comparisons of excitability using these two recording methods are scarce. This also raises the question of how each mechanism might be engaged separately in a physiologically realistic environment. Importantly, synaptic tagging has been

demonstrated in vivo (Shires, da Silva, Hawthorne, Morris, & Martin, 2012). Heterosynaptic metaplasticity as described in this thesis could also be tested in this way to ascertain whether this form of metaplasticity is reproducible in the living animal.

In contrast to the facilitatory role of APs described by Hulme et al. and others, Yasuda and colleagues (2003) reported that trains of APs inhibited LTP in CA1 by downregulating R-type VGCCs. However, these experiments took place in the presence of the $GABA_A$ antagonist bicuculline, and LTP was induced via pairings of EPSPs and APs. It is likely that under these conditions APs would contribute more to LTP induction than in the previous examples. Ca^{2+} influx through R-type VGCCs is triggered by back-propagating APs, whereas NMDAR-mediated Ca2+ influx is triggered by EPSPs (Christie, Eliot, Ito, Miyakawa, & Johnston, 1995; Koester & Sakmann, 1998; Markram, Helm, & Sakmann, 1995). Thus, the contribution of R-type VGCCs to LTP will depend on AP generation during induction. It is also possible that bicuculline facilitated the dendritic invasion of backpropagating APs, thus triggering greater Ca^{2+} transients. The inhibition of LTP seen by Yasuda et al. therefore reflects the loss of AP-mediated Ca^{2+} influx, which may not contribute to such a degree to LTP as induced by Hulme et al. and Bukalo et al.

Hyperpolarising cells during priming revealed two other important aspects of heterodendritic metaplasticity. First, depolarisation *per se* does not contribute to the induction of this metaplasticity. In the previous experiments of Hulme and colleagues, hyperpolarisation did not affect the ability of SR priming to inhibit LTP at neighbouring synapses in the same stratum. However, somatic hyperpolarisation as applied in these experiments might not occlude the spread of localised action currents between active and nearby quiescent synapses in the same stratum. In the present

experiments, by delivering priming to SO and testing subsequent plasticity in SR, somatic hyperpolarisation effectively kept both dendritic compartments electrically isolated. Thus, these experiments demonstrate that action currents triggered by synaptic depolarisation do not contribute to the metaplasticity. Finally, it should be noted that hyperpolarisation substantially reduced the amount of LTP seen in SO following priming. It is therefore concluded that synaptic potentiation is not necessary for the priming-induced metaplasticity. Further, this result suggests that the reduced LTP in SR is not strictly speaking a homeostatic response to potentiation of the priming pathway. This mirrors the conclusion of Holland and Wagner (1998) and Hulme et al. (2012) following experiments in which APV blocked potentiation of the priming pathway, but did not block the metaplastic effects of priming in an adjacent pathway.

4.4.2 Membrane parameters are not altered by priming

Intrinsic plasticity can dramatically alter LTP and LTD, and changes in membrane channels which govern cell firing could act as an effector of a sliding θ_M (Narayanan & Johnston, 2010). Despite several reports of such plasticity regulation, there was no evidence that these mechanisms contribute to the expression of heterodendritic metaplasticity in CA1. Channels mediating the AHPs or the *h* current did not display any change in activity following priming, thus ruling out two mechanisms known to contribute to heterosynaptic changes in excitability (Le Ray, et al., 2004; Narayanan & Johnston, 2007). It is perhaps noteworthy that the heterosynaptic changes seen in these models were measured at separate locations within the apical dendrites of SR and at distances of 150-200 µm. While these are substantial distances, they are not as great as those involved in the heterodendritic

interactions in the current experiments. Further, in the experiments described by Le Ray et al. and Narayanan and Johnston, $GABA_A$Rs were again blocked during recording. Thus, the applicability of those results to the current experiments is debatable. It is also noteworthy that the SERCA pump inhibitor CPA triggers an increase in perisomatic I_h (Narayanan, Dougherty, & Johnston, 2010), yet this compound reversed rather than induced metaplasticity in the current experiments (see below) .

The current experiments focused only on a few select membrane properties previously shown to exert heterosynaptic influence. It remains possible that other forms of intrinsic plasticity contribute to the effects of SO priming. For example, it has recently been shown that the expression of mRNA encoding for M-type K^+ channels, which regulate cell firing and LTP, is subject to activity-dependent regulation (Fontan-Lozano, Suarez-Pereira, Delgado-Garcia, & Carrion, 2011). However, given the lack of APs triggered during HFS it is unlikely that modulating the activity of this channel would have an effect on LTP as induced in the current experiments. The lack of change seen in R_{in} suggest that priming did not alter the activity of other channels either, although it is possible that such changes could be highly localised and thus detectable only with recordings from dendritic or axonal locations (Campanac, et al., 2008; Kole & Stuart, 2008).

4.4.3 Intracellular Ca^{2+} and heterosynaptic metaplasticity

Heterosynaptic and heterodendritic priming reduce subsequent LTP at SR synapses in a manner requiring Ca^{2+} from intracellular stores (Hulme, et al., 2012). Heterosynaptic priming of LTD also requires Ca^{2+} from these stores, but this had not been shown for heterodendritically primed LTD until the present experiment. Taken

together, these results demonstrate that heterosynaptic and heterodendritic regulation of LTP and LTD all require a convergent Ca^{2+} release mechanism. Thus, intracellular Ca^{2+} is a cell-wide regulator of plasticity thresholds. Consistent with this conclusion, postsynaptic Ca^{2+} is utilised as a trigger of homeostatic metaplasticity in BCM model derivatives (Yeung, et al., 2004). However, such models uniformly implement NMDARs as the relevant source of Ca^{2+}, meaning that the metaplasticity seen in the current experiments does not conform entirely to the predictions of these models. Inhibitory metaplasticity is initiated in several brain regions by G-proteins coupled to Ca^{2+} release (S. Y. Huang, et al., 2012). Given that ER Ca^{2+} stores are continuous throughout the cell it is possible that these stores could act as a cell-wide trigger of metaplasticity (Solovyova & Verkhratsky, 2003; Verkhratsky, 2002). However, it should be noted that the *cellular* source of Ca^{2+} pertinent to the current experiments (i.e. neuronal vs. non-neuronal) has not been identified.

4.4.4 Muscarinic acetylcholine receptors and heterosynaptic metaplasticity

The specific M1-AChR antagonist pirenzepine abolished the metaplastic effects of SO priming. A similar result was described by Hulme et al. (2012), but with the nonselective cholinergic antagonist atropine. These results invite parallels with the effect documented by Newlon and colleagues (1991), whereby septal TBS inhibited subsequent LTP of the CA1 population spike in vivo. There are also parallels with the inhibitory metaplastic effects of the M1-AChR agonist McN-A-343 on subsequent pairing-induced potentiation in visual cortex (Seol, et al., 2007). Metaplastic inhibition of LTP by M1-AChR activation therefore appears to be a widespread phenomenon.

The G_q signalling cascade couples M1-AChRs to IP_3 formation and liberation of Ca^{2+} from ER stores. When activated, several receptors coupled to this cascade prime the induction of LTD and inhibit the induction of LTP in multiple brain regions, including the hippocampus (S. Y. Huang, et al., 2012). M1-AChRs are the primary G_q-coupled GPCR in the hippocampus (Volk, Pfeiffer, Gibson, & Huber, 2007). They are extensively expressed in SO and SR, and with approximately equal distribution in these strata (Levey, et al., 1995). Cholinergic fibres terminating in CA1 enter this subfield from the alveus and form a dense plexus in SO (Frotscher & Leranth, 1985; Frotscher, Schlander, & Leranth, 1986; Meibach & Siegel, 1977). It is tempting to suggest that the inability of SR priming to inhibit SO LTP might be due to the lower density of cholinergic fibres in SR that could be recruited during priming. However, the equal expression of M1-AChRs in SO and SR suggests that cholinergic innervation of cells in these strata is roughly equal.

The a priori most likely alternative G_q-coupled GPCRs, group 1 mGluRs, have already been ruled out as contributing to heterosynaptic metaplasticity in CA1 (Hulme, et al., 2012). It is therefore highly likely that M1-AChRs are the trigger for Ca^{2+} release needed for the heterodendritic metaplasticity. However, the multimodal signalling of M1-AChRs means that this link cannot be taken for granted. Additional studies involving M1-AChR agonists applied in the presence of IP_3R inhibitors are necessary to resolve this issue. Furthermore, the results of Huang et al. (2012) suggest that similar effects may be accomplished by other G_q-coupled GPCRs detectable (albeit to a lesser degree) in hippocampus, such as 5-HT_2Rs (Pazos, Cortés, & Palacios, 1985). However, whether any metaplastic effects conferred by such receptors can spread heterosynaptically remains to be seen. Nevertheless, the suggestion that neuromodulators metaplastically regulate glutamatergic synapses

presents a major departure from the BCM model. This is broadly in keeping with Ca^{2+}-based BCM model derivatives, although such models commonly cite the NMDAR channel as the relevant source of Ca^{2+}. The metaplastic roles of second messenger systems such as those triggered by G_q and G_s signalling raise several questions, particularly regarding the spatial extent of the metaplastic state. Can second messengers such as IP_3 or cAMP be released or diffuse throughout the neuron? Do they trigger the synthesis or release of additional factors which then diffuse to heterosynaptic locations? More important perhaps, is what roles these mechanisms play in regulating plasticity. Can they be incorporated into homeostatic models such as the BCM, or do they serve a different purpose?

5: Intercellular communication and heterosynaptic plasticity

5.1 Introduction

Heterosynaptic or heterodendritic interactions require signalling across considerable distances. Two commonly cited modes of long distance communication are cell-cell interactions mediated by purinergic extracellular signalling and direct intercellular gap junctional signalling. Here, the possible roles of purines and gap junctions were investigated as mediators of the long-distance communication required for heterodendritic metaplasticity.

5.1.1 Intercellular signalling cascades and synaptic plasticity

Heterosynaptic and heterodendritic metaplasticity in CA1 require the release of Ca^{2+} from ER stores. However, while Ca^{2+} release is a plausible trigger of the metaplastic state, the effect as a whole remains poorly understood. In particular, the mode by which the long-range heterodendritic interactions occur remains elusive. The inhibition of SR LTP by SO priming requires a signalling cascade that is able to bridge the considerable distance between dendritic compartments. Neither postsynaptic APs nor postsynaptic depolarisation *per se* are necessary for the effect, and it is uncertain whether Ca^{2+} waves are able to propagate far enough throughout the ER to mediate these interactions (E. A. Finch & Augustine, 1998).

In lieu of a purely *intra*cellular signal transduction mechanism, it is possible that alternative modes of communication occur between distant synapses, such as *inter*cellular signalling. Intercellular interactions between adjacent neurons, or between neurons and astrocytes, have been implicated in the induction of various forms of plasticity (Andersson, et al., 2007; Bukalo, et al., 2013; Navarrete & Araque, 2010; Scanziani, Malenka, et al., 1996). Further, several models of *heterosynaptic*

plasticity require intercellular communication (Chevaleyre & Castillo, 2003; Navarrete & Araque, 2010; Scanziani, Malenka, et al., 1996). A key issue therefore is how intercellular communication might be accomplished to inhibit SR LTP following SO priming. As noted, a contribution by mGluRs, NMDARs and GABAergic signalling has already been ruled out in this regard (Hulme, et al., 2012).

5.1.2 Purinergic signalling and heterosynaptic plasticity

Heterosynaptic plasticity has long been associated with purinergic signalling. The most widely studied form of heterosynaptic plasticity is perhaps post-tetanic, heterosynaptic depression (HSD), which is widely reported to require activation of presynaptic A_1Rs (Grover & Teyler, 1993a, 1993b). In contrast, the source of relevant adenosine has become a controversial issue. Adenosine-mediated presynaptic suppression was originally considered a response to postsynaptic NMDAR activation (Bashir & Collingridge, 1992; Manzoni, et al., 1994). However, heterosynaptic depression is absent when astrocyte function (i.e. Ca^{2+} signalling) is manipulated pharmacologically (Andersson, et al., 2007; J. M. Zhang, et al., 2003). A number of studies show that the relevant source of adenosine is the extracellular hydrolysis of ATP (Cunha, et al., 1994; Cunha, et al., 1996; J. M. Zhang, et al., 2003), and this has led to the conclusion that heterosynaptic depression requires astrocyte-derived ATP (Pascual, et al., 2005; J. M. Zhang, et al., 2003). However, a recent report describes heterosynaptic depression in the absence of astrocytic activation, which instead requires dendritic secretion of adenosine via equilibrative transporters (Lovatt, et al., 2012). Regardless of the source, what is common to all these studies is a requirement for purinergic signalling in mediating heterosynaptic depression. Thus, it is possible that purines exert similarly widespread metaplastic effects.

5.1.3 Gap junctions, intercellular signalling and plasticity

Gap junctions are able to mediate cell-to-cell signalling in two ways: by electrotonic spread of depolarisation or diffusion of messenger molecules between connected cells. In CA1, ectopically generated APs spread via GJNs to neighbouring cells, where they back-propagate and induce synaptic depression (Bukalo, et al., 2013). Similarly, trains of antidromic spikes in hippocampal interneurons can spread to neighbouring cells of the same type to trigger persistent firing lasting minutes, even without somatic or synaptic depolarisation (Sheffield, Best, Mensh, Kath, & Spruston, 2011). While blocking postsynaptic depolarization in single cells during priming does not alter heterodendritic metaplasticity, it remains possible that spread of depolarization throughout the remainder of the network triggers widespread dendritic secretion of factors that can influence plasticity (Kuczewski, et al., 2008; Lovatt, et al., 2012). Spread of such factors could potentially trigger metaplasticity at adjacent synapses. Alternatively, the long-distance signalling might be accomplished by passage of IP_3 or Ca^{2+} through GJNs. The general GJN inhibitors carbenoxolone (CBX) and endothelin inhibit inter-astrocyte Ca^{2+} waves and heterosynaptic depression (Andersson, et al., 2007; Blomstrand, Giaume, Hansson, & Rönnbäck, 1999). Thus, in addition to the possible contribution of purinergic signalling, a role for GJNs in heterodendritic metaplasticity was investigated.

Some results in this chapter have been published in the following journal article:

Jones, O. D., Hulme, S. R., & Abraham, W. C. (2013b). Purinergic receptor- and gap junction-mediated intercellular signalling as a mechanism of heterosynaptic metaplasticity. *Neurobiology of Learning and Memory, 105*(0), 31-39.

5.2 Methods

5.2.1 Tissue preparation and extracellular recordings

Tissue preparation from 6-8 week old SD rats and extracellular recordings were conducted as in Chapters 3 and 4. fEPSPs in various experiments were set at 1 mV (25-70 µA), or 30% of maximum slope (65-90 µA). Standard SO priming (3 x 1 s trains at 100 Hz, repeated after 5 or 15 min) and SR conditioning (2 x 1 s trains at 100 Hz) were used in all experiments except for pressure ejection experiments.

5.2.2 Pressure-ejection

In pressure-ejection experiments, droplets of ACSF containing 300 nM of the selective A_{2B}R agonist BAY 60-6583 were ejected into SR or SO in lieu of each train of electrical priming stimulation (**Fig 5.1**). Ejections were made via low-resistance pipettes (0.7-0.8 MΩ) coupled to a picospritzer (General Valve Corporation) giving pulses of medical grade air. Pressure was maintained at 13 psi and pulse duration (4-10 ms) was adjusted to give droplets of 48-54 µm diameter (57.9-82.4 pl) as verified in mineral oil before and after experiments. Ejection pipettes were advanced ~100 µm into the tissue. In preliminary studies, ACSF or the AMPAR antagonist CNQX were ejected into SR or SO to determine a method of local delivery (i.e. only to synapses in a given stratum) that did not mechanically disrupt recordings. Delivery of 3 ejections of ACSF, 30 s apart, to SR at a distance of ~100 µm from the recording electrode did not disrupt recordings from the same stratum, whereas delivery of CNQX (50 µM) by the same protocol triggered a rapid depression of the fEPSP (recovery followed for 15 min post-ejection). Further, CNQX ejections in SO had no effect on the fEPSP in SR. Thus, sufficient, localised delivery was achieved (SR ACSF: n = 4, 101 ± 3%; SR

CNQX: n = 5, 71 ± 9%; SO CNQX 99 ± 3%, $F_{(2,10)}$ = 6.47, p = 0.016, **Fig 5.2**). The effects of ejection were assessed using field recordings as described previously.

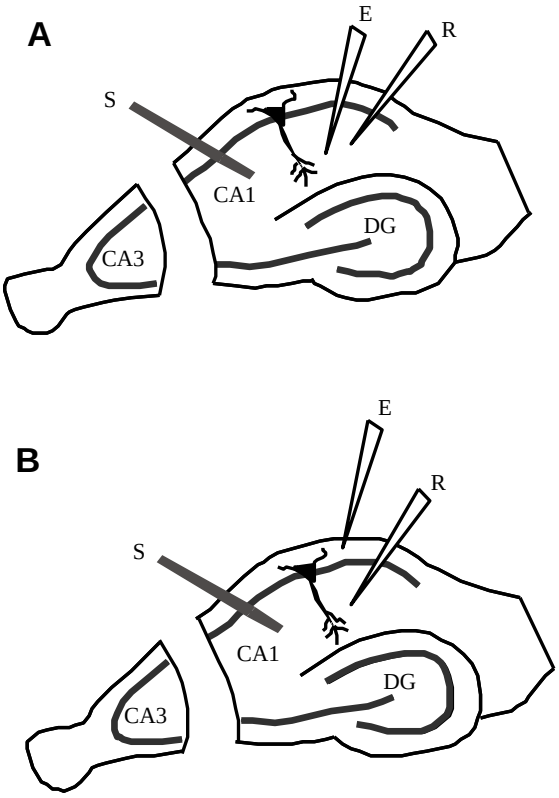

Figure 5.1. Electrode placement during pressure ejection experiments

In all experiments, a single stimulating electrode (S) and recording electrode (R) were placed in SR. A low resistance ejection pipette (E) was placed either close to the recording electrode in SR (**A**) or directly above the recording electrode but in SO (**B**).

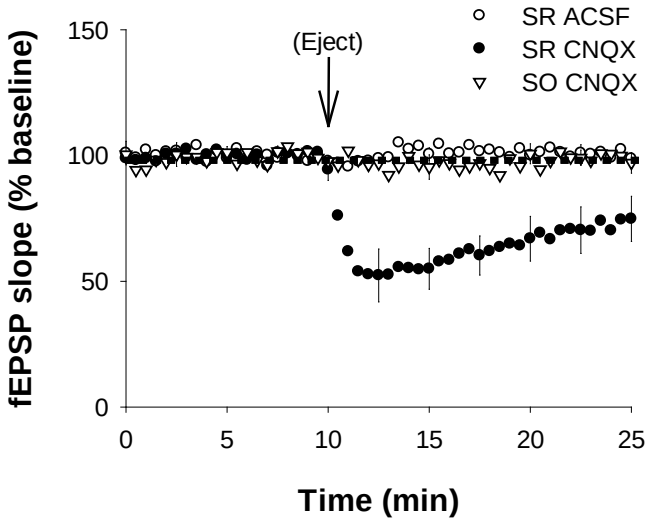

Figure 5.2. Compartment-specific delivery of pharmacological agents

The AMPAR antagonist CNQX was used to assess the ability of pressure ejection to specifically target synapses in SO or SR. Ejecting ACSF into SR had no effect on synaptic activity, whereas ejections of CNQX progressively diminished the fEPSP slope (3 ejections total, see methods). This delivery method did not affect SR synapses directly when ejections of CNQX took place in SO.

5.3 Results

5.3.1 Purinergic signalling and heterosynaptic metaplasticity

Several reports have implicated purines as mediators of heterosynaptic depression. The role of purinergic signalling in long-range heterosynaptic inhibition of LTP was therefore investigated. First, the ecto-5′-nucleotidase inhibitor AMPCP (50 nM), which blocks the conversion of the ATP metabolite AMP to adenosine (Colgan, Eltzschig, Eckle, & Thompson, 2006), was used to assess whether the inhibition of LTP requires the hydrolysis of extracellular ATP to adenosine. As per a previous report (Muzzi, et al., 2013), AMPCP caused a large depression of the fEPSP (data not shown). This depression was blocked by the adenosine A_1R antagonist DPCPX (50 nM), consistent with the recent finding that AMP acts as an A_1R agonist (Rittiner, et al., 2012). Thus, AMPCP and DPCPX were co-administered to avoid the confounding effects of the A_1R-mediated fEPSP depression. Bath-application of both compounds during SO priming blocked the long-range heterosynaptic inhibition of SR LTP, whereas priming in the presence of DPCPX alone did not (Control: n = 12, 143 ± 4%; Primed AMPCP & DPCPX: n = 9, 149 ± 6%; Primed DPCPX: n = 11, 128 ± 7%, $F_{(2,20)}$ = 3.50, p = 0.043, **Fig 5.3**).

The above data suggest that conversion of extracellular ATP to adenosine is critical for the metaplasticity effect, but that the relevant adenosine receptor is not the A_1R. Thus, selective inhibitors of A_{2A}Rs (ZM241385) and A_{2B}Rs (MRS1754) were next administered during priming stimulation. Curiously, the presence of either drug (50 nM) during priming was sufficient to block the metaplastic inhibition of LTP (Control: n = 5, 144 ± 4%; Primed: n = 8, 122 ± 2%; Primed ZM241385, n = 7, 134 ± 6%; Primed MRS1754: n = 5, 138 ± 5%, $F_{(3,21)}$ = 4.91, p = 0.009, post-hoc LSD: Control vs. Primed, p = 0.002, Primed vs. Primed ZM241385, p = 0.034,

Primed vs. Primed MRS1754, $p = 0.015$, **Fig 5.4**). This strongly suggested the involvement of A_2Rs as a trigger or mediator of the metaplasticity.

Next, the hypothesis that A_2Rs could act as a trigger of heterosynaptic communication was addressed. A_{2B}R activation triggers widespread and persistent Ca^{2+} signals in astrocytes (Kawamura & Kawamura, 2011), making this receptor a plausible trigger of the long-distance communication required for heterosynaptic metaplasticity. To this end, an A_{2B}R agonist was focally applied in either SR or SO, prior to testing LTP. Droplets of ACSF containing the specific A_{2B}R agonist BAY 60-6583 (300 nM) were pressure-ejected into either SR or SO in lieu of electrical priming stimulation. Having ascertained a suitable protocol (see section **5.2.2**), BAY 60-6583 was ejected into either SR or SO of CA1. Ejecting the agonist into either stratum reduced LTP induced 30 min later in SR in a manner very reminiscent of the effects of electrical priming stimulation (SR ejection: ACSF: $n = 4$, 32 ± 6%; BAY: $n = 4$, 9 ± 4%, $t_{(6)} = 3.13$, $p = 0.020$, **Fig 5.5a**; SO ejection: ACSF: $n = 5$, 35 ± 3%; BAY: $n = 6$, 18 ± 6%, $t_{(9)} = 2.37$, $p = 0.042$, **Fig 5.5b**).

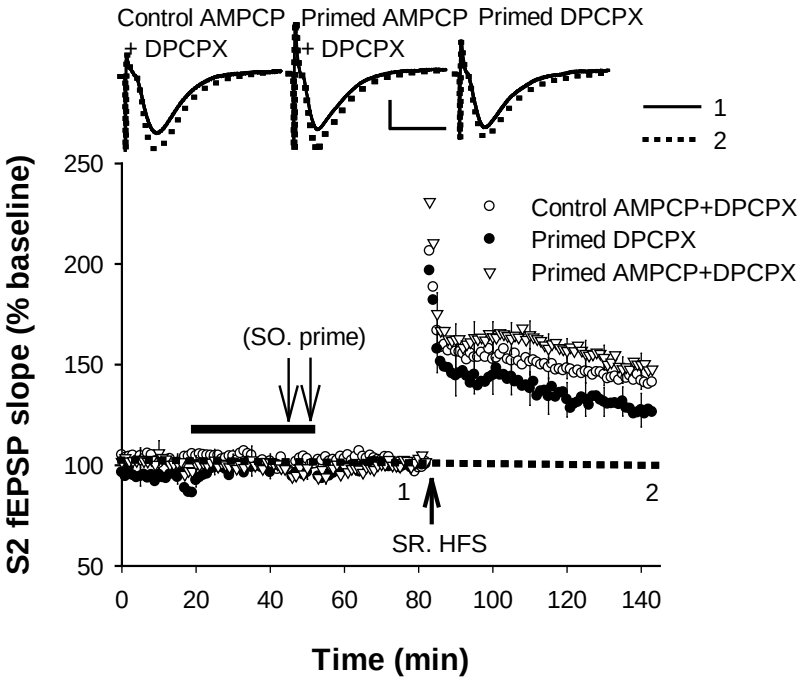

Figure 5.3. Priming requires ectonucleotidases, but not A_1Rs

Control slices treated with the ectonucleotidase inhibitor AMPCP and A_1R antagonist DPCPX displayed robust LTP after washout (Control AMPCP+DPCPX). SO priming during DPCPX wash-in reduced later SR LTP (Primed DPCPX). Priming in the presence of both drugs did not (Primed AMPCP+DPCPX).

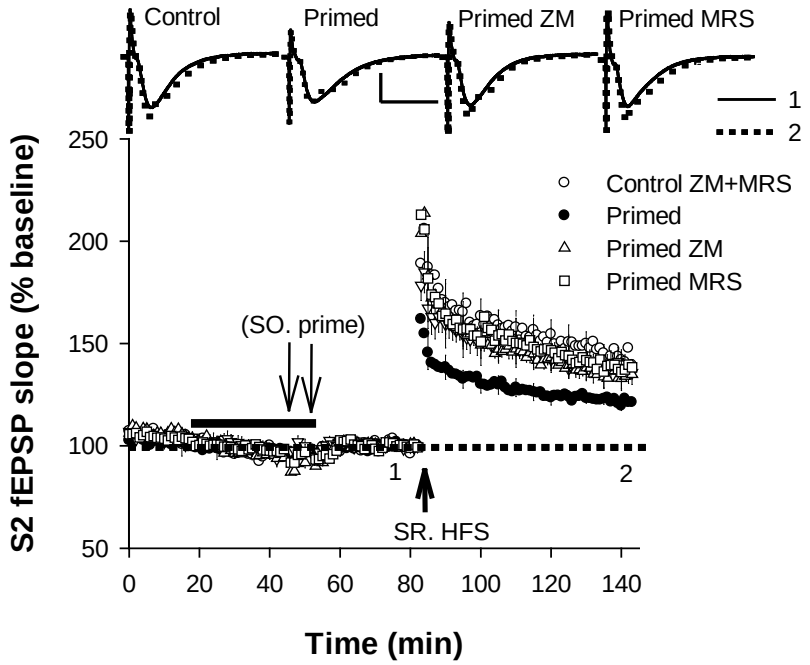

Figure 5.4. Heterosynaptic metaplasticity requires A_2 receptors

Dual application of the A_{2A}R inhibitor ZM241385 (ZM) and the A_{2B}R inhibitor MRS1754 (MRS) did not affect later SR LTP in non-primed controls (Control ZM+ MRS). SO priming reduced later SR LTP (Primed), but priming in the presence of either drug did not (Primed ZM, Primed MRS).

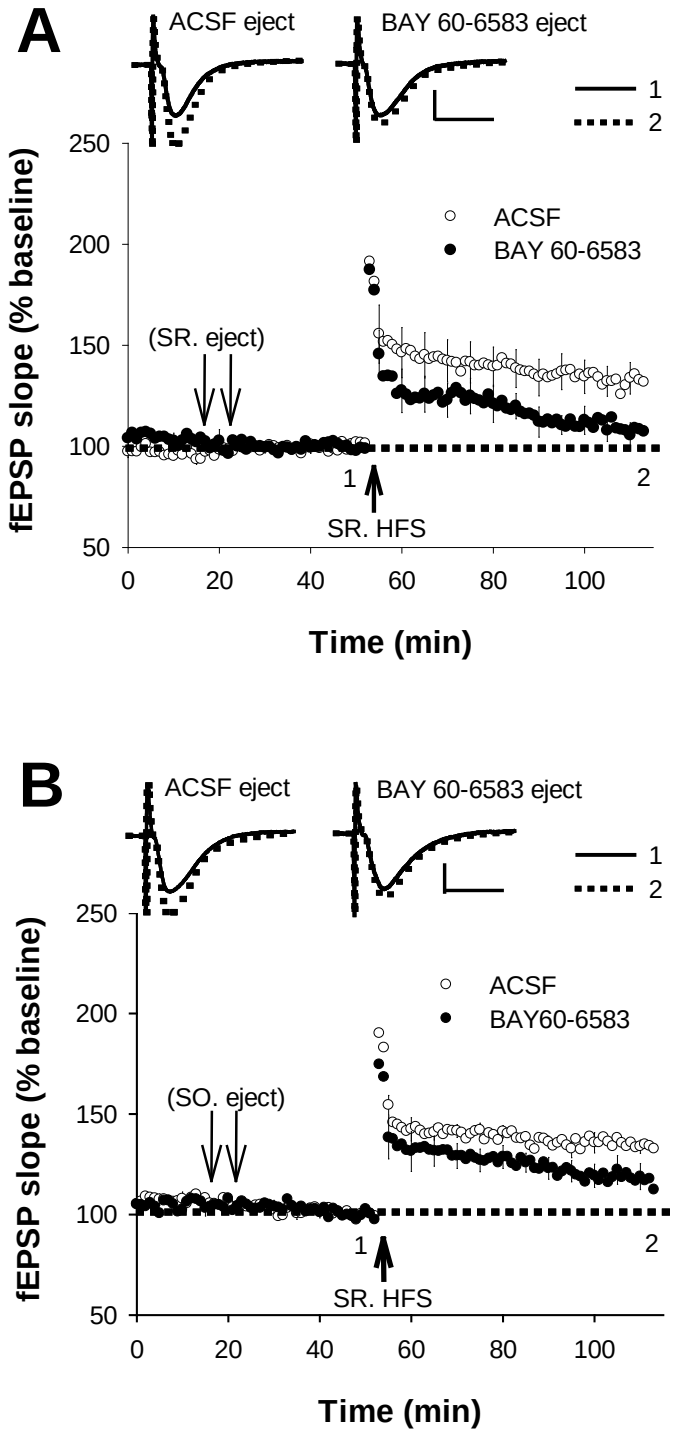

Figure 5.5. Metaplasticity induced by pressure ejection of an A_{2B}R agonist

In comparison to levels seen following ejection of ACSF, the selective A_{2B}R agonist BAY 60-6583 reduced subsequent SR LTP, whether the site of ejection was SR (**A**) or SO (**B**).

5.3.2 Gap junctions and heterosynaptic metaplasticity

The role of GJN-mediated communication was tested by priming SO synapses in the presence of the GJN inhibitor carbenoxolone (CBX, 30 μM). CBX caused a partial depression of the fEPSP which stabilised upon washout. However, robust LTP was still seen in SR after CBX washout in control experiments. Further, SR LTP was not reduced following SO priming in the presence of CBX (Control: n = 6, 130 ± 5%; Primed: n = 6, 127 ± 3%, $t_{(10)}$ = 0.53, p = 0.61 (ns), **Fig 5.6a**). Another GJN inhibitor, meclofenamic acid (MFA, 50 μM), also blocked the metaplasticity (Control: n = 5, 124 ± 4%; Primed: n = 4, 122 ± 4%, $t_{(7)}$ = 0.22, p = 0.83 (ns), **Fig 5.6b**).

While CBX and MFA experiments suggested a role for GJNs, these compounds are non-specific and could not identify which specific GJNs, and on what cell-type, are involved in the heterosynaptic metaplasticity. The role of purinergic signalling is consistent with a role for astrocytes, as release of purines from these cells is implicated in other heterosynaptic effects, as noted. Thus, it was hypothesised that specifically disrupting astrocytic communication would inhibit heterosynaptic metaplasticity. GJNs formed between astrocytes exclusively contain connexin43 (Cx43) hemichannels, whereas these proteins are not found on neurons (Rash, Nagy, & Yasumura, 1998; Rash, et al., 2003; Rash, Yasumura, Dudek, & Nagy, 2001). A specific inhibitor of Cx43 gap junctions and hemichannels (Cx43 mimetic peptide, 50 μM) was therefore used to selectively target astrocytic signalling. Cx43 mimetic peptide abolished the effects of oriens priming on subsequent radiatum LTP, whereas an inactive control peptide did not (Control both peptides: n = 5, 139 ± 4%; Primed active: n = 5, 136 ± 1%; Primed inactive: n = 7, 17 ± 6%, $F_{(2,14)}$ = 7.80, p = 0.005, **Fig 5.7**). This result strongly implicates astrocytes as mediators of the long-distance signalling required for heterodendritic inhibition of LTP.

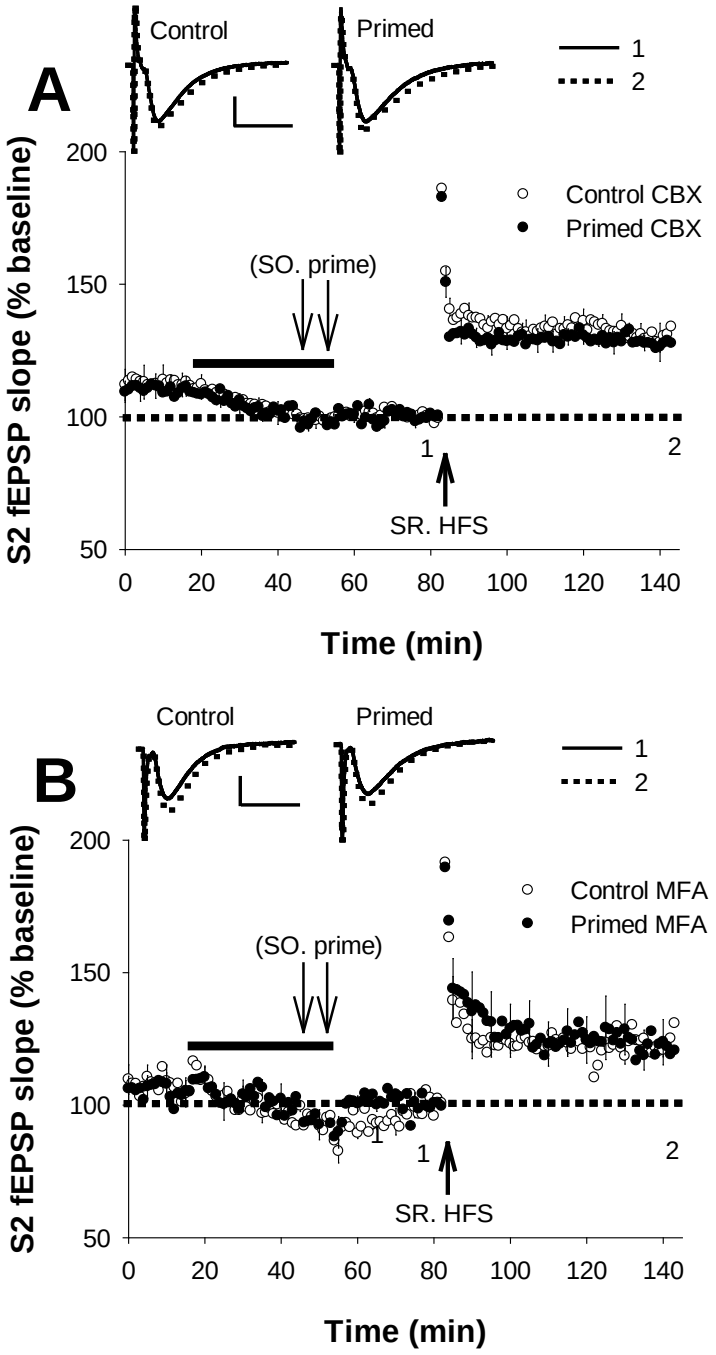

Figure 5.6. General gap junction inhibitors block heterosynaptic metaplasticity
A: Control slices pretreated with the general GJN inhibitor carbenoxolone displayed a lasting rundown of transmission, but nonetheless show robust LTP after washout (Control CBX). SO priming delivered during CBX treatment has no effect on later SR LTP (Primed CBX).
B: A second GJN inhibitor, meclofenamic acid, triggered a similar rundown of transmission without blocking LTP upon washout (Control MFA). Like CBX, this compound also blocked the metaplastic effects of SO priming on SR LTP (Primed MFA).

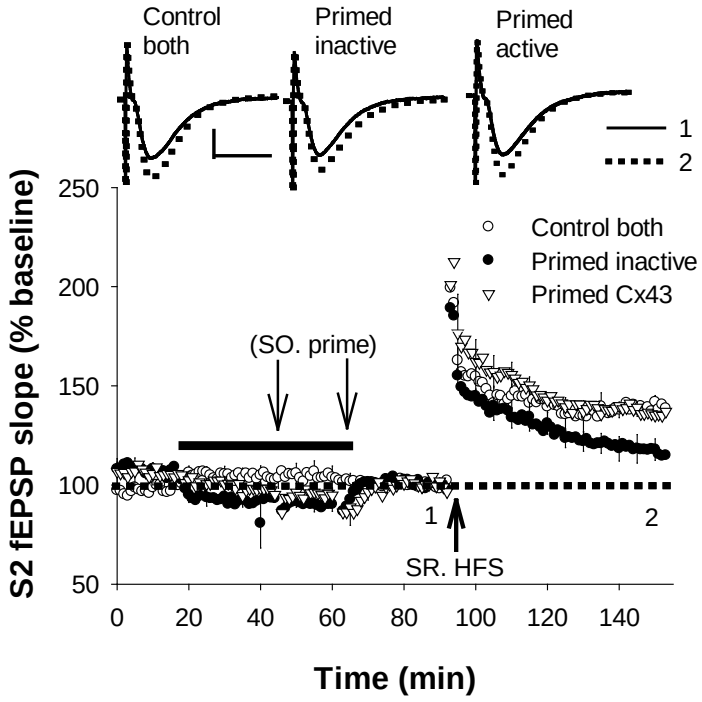

Figure 5.7. Astrocytic connexins are required for heterosynaptic metaplasticity
Connexin43 mimetic peptide, a selective inhibitor of astrocyte-specific connexin43 hemichannels, blocked the effects of SO priming on later SR LTP (Primed Cx43). In contrast, an inactive peptide did not block priming-induced inhibition of LTP (Primed inactive). Control slices treated with both peptides displayed robust LTP following washout (Control both).

5.4 Discussion

5.4.1 Purinergic signalling and heterosynaptic metaplasticity

Several groups have reported forms of heterosynaptic depression mediated by ATP or its breakdown product adenosine (J. Chen, et al., 2013; Lovatt, et al., 2012; A. Serrano, et al., 2006; J. M. Zhang, et al., 2003). The heterosynaptic metaplasticity described herein was also found to require the hydrolysis of ATP and subsequent activation of ARs; however there are clear differences between these two forms of heterosynaptic plasticity. Priming did exert an immediate depression of the neighbouring pathway in some cases (see **Fig 3.10b** for a clear example), but this depression was always short-lived and fEPSPs recovered fully between priming and conditioning stimulation, as was the case in previous studies (Holland & Wagner,

1998; H. Y. Wang & Wagner, 1999). The heterosynaptic inhibition of LTP described here was therefore not due to reduced synaptic strength at the point of tetanisation. Further, the A_1R antagonist DPCPX failed to block the metaplasticity, providing further distinction between the mechanisms of heterosynaptic metaplasticity and the canonical signalling cascade synonymous with HSD. In contrast, the metaplasticity is blocked by A_2R antagonists and mimicked by an A_{2B}R agonist.

Several potential sources of ATP could contribute to the metaplasticity. ATP is released from presynaptic terminals, nodes of Ranvier and glial cells (Cotrina, Lin, Alves-Rodrigues, et al., 1998; Fields & Ni, 2010; Pankratov, et al., 2006; Z. J. Zhang, et al., 2007). While the source of ATP required in the present model remains undetermined, it is tempting to suggest that astroglia are involved. The distance between dendritic layers is presumably too great for axonally released ATP to traverse, as this molecule is rapidly degraded by ectonucleotidases (Wall & Dale, 2013) (consider also that CNQX ejected into SO did not cross appreciably into SR), suggesting at least that the metaplasticity requires intercellular signalling. Astrocytes are also implicated in other purine-mediated effects, and while Lovatt et al. (2012) have shown that these cells are not required for adenosine-mediated depression there is still reason to believe that astrocytes are also capable of mediating such effects. First, one group has reported a transient, ATP-dependent synaptic depression in cultured neurons that is only visible when neurons are co-cultured with astrocytes (J. M. Zhang, et al., 2003). Second, ATP and adenosine mediate a heterosynaptic depression that is absent in mice expressing a dominant-negative SNARE domain selectively in astrocytes, thus blocking gliotransmitter release from these cells (Pascual, et al., 2005). Finally, optogenetic activation of GPCRs on astrocytes triggers ATP release and fEPSP depression despite bypassing neuronal activation (J. Chen, et

al., 2013). Extracellular adenosine accumulates as a result of both neuronal transporter activity and glial release of ATP (Wall & Dale, 2013). These mechanisms display vastly different kinetics (neuronal secretion being significantly faster than hydrolysis of glial ATP), making it tempting to suggest that they serve different physiological purposes. For example, distinct sources of adenosine may dominate during physiological vs. pathological events, target synaptic vs. extrasynaptic receptors, or activate receptors on neurons vs. glia (Parri, 2013).

The previously described role of M1-AChRs in heterosynaptic metaplasticity is also consistent with astrocytic involvement. Astrocytes respond to M1-AChR activation with calcium elevations derived from intracellular stores (also shown to be important in this model), and in turn release gliotransmitters which regulate plasticity (N. Chen, et al., 2012; Navarrete, et al., 2012; Takata, et al., 2011). While neurons also respond to M1-AChR activation with calcium release (de Sevilla, Nunez, Borde, Malinow, & Buno, 2008), it is at least possible that astrocytes are the relevant site of release in the present case. Careful experimentation using Ca^{2+} imaging will be needed to determine the contribution of each source of Ca^{2+} to heterosynaptic metaplasticity (see general discussion). The requirement for $A_{2B}R$ activation may also be indicative of glial involvement. Activation of $A_{2B}Rs$ induces a widespread increase in spontaneous Ca^{2+} elevations throughout the astrocytic network that persists for at least 20 min (Kawamura & Kawamura, 2011). Such lasting and widespread signalling mechanism appears well-suited to support the temporal and spatial requirements of long-range heterosynaptic metaplasticity, and is in keeping with the results of the pressure ejection experiments here in which ejection of an $A_{2B}R$ agonist in SO inhibited later LTP in SR. However, while these experiments suggest a plausible long-

distance signalling mechanism, they do not define the factors that are ultimately released to inhibit LTP.

The finding that inhibiting A_{2A}Rs blocks the effects of priming is difficult to reconcile with the known actions of this receptor. G_s-coupled A_{2A}Rs are generally considered to facilitate LTP. In fact, it has been suggested that A_{2A}R-mediated facilitation of LTP works by suppressing A_1R-mediated depression (Lopes, et al., 2002), thus improving the signal to noise ratio at active vs. non-active synapses (Cunha, 2008). Central to this hypothesis is the observation that A_{2A}R activation occurs only homosynaptically. Other facilitatory consequences of A_{2A}R activation include enhanced AMPAR currents, enhanced GABA uptake, decreased glutamate uptake and upregulated BDNF expression, which together explain the enhancement of LTP by A_{2A}Rs (Cristóvão-Ferreira, Vaz, Ribeiro, & Sebastião, 2009; Dias, et al., 2012; Jeon, et al., 2011; Matos, et al., 2012). Moreover, astrocytes are reported to release glutamate in response to A_{2A}R activation (Nishizaki, 2004). Nevertheless, a metaplastic inhibition of LTP by A_2Rs has previously been reported, albeit monosynaptically, and this effect is blocked by a compound with greater selectivity for A_{2A}Rs than A_{2B}Rs (Fujii, et al., 2000). It may be that the timing and degree of A_{2A}R activation confers differential effects on plasticity, as is the case with NMDARs and mAChRs. Alternatively, the ability of the A_{2A}R antagonist ZM241385 to block the metaplasticity may simply reflect the modest affinity of this compound for A_{2B}Rs (Ongini, Dionisotti, Gessi, Irenius, & Fredholm, 1999; Poucher, et al., 1995).

5.4.2 Gap junctions, connexins and heterosynaptic metaplasticity

Gap junctions mediate electrotonic spread of depolarisation between neurons and allow small molecules to pass between cells. In CA1 pyramidal neurons, action

potentials elicit antidromic spiking activity in electrically-coupled neighbouring cells, which invades the soma and dendrites (Schmitz, Schuchmann, et al., 2001). It is possible that priming triggers widespread antidromic and orthodromic firing in CA1. However, while such events are known to trigger metaplasticity, it is typically of a kind that facilitates LTP (Bukalo, et al., 2013; Dudek & Fields, 2002; Hulme, et al., 2012). Further, as neither APs nor somatic depolarisation are required for heterosynaptic metaplasticity it is unlikely that GJNs contribute to the heterosynaptic inhibition of LTP by eliciting such signals.

The alternative hypothesis is that astrocytic gap junctions are required for the long-range signalling which underlies heterosynaptic metaplasticity. This interpretation is complicated by the non-specific effects of CBX and MFA (Peretz, et al., 2005; Rouach, Segal, Koulakoff, Giaume, & Avignone, 2003; Tovar, Maher, & Westbrook, 2009). However, while these effects (e.g., altered NMDAR currents and cell excitability) may explain the rundown of transmission seen following administration of these compounds, they are mechanisms that have already been ruled out as contributing to the heterosynaptic metaplasticity (Hulme, et al., 2012). Further, the more specific connexin43 mimetic peptide successfully blocked the metaplasticity. This provides direct evidence of astrocytic involvement, although it remains possible that the Cx43 peptide merely compromised metabolism sufficiently to inhibit formation of the metaplastic state (Rouach, Koulakoff, Abudara, Willecke, & Giaume, 2008).

Although a role of astrocytic GJNs is possible, it is perhaps more likely that astrocytic connexins are involved in ways other than as mediating direct passage of molecules between cells. For example, connexins could be involved in an extracellular signalling cascade. The compounds used in the present experiments may

also have affected ATP-mediated signalling. Inhibition of $P2X_{(7)}$ receptors has been reported following treatment with CBX or fenamates (although not MFA specifically) (Suadicani, et al., 2006), and connexin43 mimetic peptide also blocks unapposed Cx43 hemichannels (O'Carroll, Alkadhi, Nicholson, & Green, 2008), as do MFA and CBX (X. Liu, Hashimoto-Torii, Torii, Ding, & Rakic, 2010; Weissman, Riquelme, Ivic, Flint, & Kriegstein, 2004). These hemichannels, and $P2X_{(7)}$Rs, are involved in the release of ATP from astrocytes (Pearson, Dale, Llaudet, & Mobbs, 2005; Stout, Costantin, Naus, & Charles, 2002; Suadicani, et al., 2006). Further, connexin hemichannel-mediated ATP release is required for spontaneous Ca^{2+} signals in astrocytes (Weissman, et al., 2004). Thus, further investigation is required into the possibly concerted roles of purinergic and hemichannel-mediated signalling in heterosynaptic metaplasticity. To date there are no pharmacological agents which block hemichannels but not GJNs. However, GJN-mediated communication relies on intracellular factors whereas hemichannels release signalling molecules into the extracellular space. Measuring extracellular ATP following priming stimulation in the presence or absence of GJN blockers, or $P2X_{(7)}$R antagonists, could delineate the roles of GJNs and hemichannels in the intercellular signalling mechanism described here.

6. General discussion

6.1 Introduction

The experiments of this thesis expand upon the knowledge of heterosynaptic metaplasticity in hippocampal CA1 as described elsewhere (Holland & Wagner, 1998; Hulme, et al., 2012; H. Y. Wang & Wagner, 1999). Robust, heterosynaptic metaplasticity was inducible via several priming protocols, across two age groups and in two rodent species. The effect did not require APs or somatic depolarization above resting levels, and no altered membrane parameters were observed following priming. These latter results do not support the theoretical role of AP firing as a trigger of homeostatic alterations to the plasticity threshold, as proposed in the influential BCM model of plasticity. Further, they do not support derivatives of the BCM model in which the plasticity threshold is regulated by activity-dependent changes in membrane excitability. Instead, the metaplasticity was found to require an intercellular signalling cascade involving activation of M1-AChRs, release of intracellular Ca^{2+}, hydrolysis of extracellular ATP to adenosine, activation of A_2Rs and signalling via astrocytic connexins. Taken together these findings suggest a novel mode of intercellular communication between neurons and astrocytes, which mediates lasting and widespread changes to plasticity thresholds. The findings also open up new questions to be answered in the future. For example, while several steps of the long-distance signalling cascade have been elucidated, the precise sequence of events has not. The relative contributions of neurons and astrocytes to this cascade need to be addressed, as does the identity of the molecule(s) released to ultimately inhibit LTP and promote LTD. Further, the relevance of this form of metaplasticity to neural function, and its possible interaction with other regulatory mechanisms, will be an interesting topic for future work.

6.2 Neuronal and astrocytic contributions to long-range signalling

The requirement for connexin43 confirms the participation of astrocytes in the long-distance signalling between dendritic layers. However, one of the remaining questions is how and at what stages neurons and astrocytes contribute to the induction of the metaplastic state as induced in this model system. Indeed, while the relevant M1-AChRs, ATP, A_2Rs and ER-derived Ca^{2+} could all be located on or in astrocytes, it is also possible that they are neuronal. A full explanation of the effect must account for the actions of all these molecules, and must explain neuronal and astrocytic participation. Some possible mechanisms, and how they might be tested, are considered in the following paragraphs.

Muscarinic receptors

There is no evidence to suggest that astrocytes are capable of releasing ACh, thus, at this point in time, it seems likely that priming stimulation directly recruits cholinergic afferents terminating in CA1. This suggests that M1-AChRs are likely to be involved early in the signalling cascade that triggers heterosynaptic metaplasticity. The location of the relevant mAChRs is less easily distinguished, as M1-AChRs could plausibly trigger Ca^{2+} release in neurons, astrocytes or both. It is possible that ACh activates M1-AChRs on astrocytes to triggers widespread Ca^{2+} signalling within the network, and that this underlies the wide spatial spread of the metaplasticity. Alternatively, Ca^{2+} release within neurons may spread throughout the ER to bridge these distances, although ACh has not yet been shown to be capable of eliciting such widespread Ca^{2+} release (de Sevilla, et al., 2008). A third possibility is that M1-AChRs on neurons facilitate cell firing by reducing M-channel activity, and this in turn drives the widespread activation of astrocytes. This final explanation relies on

high rates of *network* firing, and is therefore unaffected by the finding that blocking depolarisation in single cells does not alter the effects of priming. This could be tested by decreasing network excitation during priming, perhaps with AMPAR antagonists or $GABA_AR$ agonists.

Intracellular calcium

Delivery of TBS to the alveus or SO induces release of intracellular Ca^{2+} in neurons and astrocytes (Navarrete, et al., 2012). It is therefore plausible that SO priming triggers Ca^{2+} release in both cell types, although only astrocytic Ca^{2+} signalling is known to be capable of reaching the neighbouring dendritic field (de Sevilla, et al., 2008; Navarrete, et al., 2012). In any case, careful experimentation is required to determine whether the Ca^{2+} stores relevant to heterosynaptic metaplasticity, and the receptors that trigger Ca^{2+} release, are neuronal or astrocytic. In the first instance, calcium imaging experiments are required to investigate Ca^{2+} signalling in both cell types during and after priming. An important question to consider here is whether SO priming induces neuronal Ca^{2+} signals that cross the soma and reach SR. Another important matter is whether priming elicits brief Ca^{2+} events in either cell type, or whether priming triggers sustained, spontaneous Ca^{2+} events that persist after priming stimulation has abated. Further, it will be important to investigate whether the spatial spread of Ca^{2+} release throughout neuronal and astrocytic networks can be correlated to the spatial spread of the metaplastic state. This may prove useful in determining which cell type is best placed to support the long-distance spread of the metaplasticity.

Determining which receptors trigger Ca^{2+} release following priming could be accomplished by combining Ca^{2+} imaging with pharmacological inhibition of M1-

AChRs and A_2Rs. Ca^{2+} imaging while priming in the presence of the M1-AChR antagonist PZN would determine whether neuronal/astrocytic Ca^{2+} signals are abolished by this compound, and similar experiments could be used in conjunction with A_2R antagonists. Indeed, it is plausible that both receptor types initiate Ca^{2+} signalling in astrocytes at different stages of the intercellular signalling cascade. However, such experiments would not ascertain whether the effects of these compounds on heterosynaptic metaplasticity are due to their effects on Ca^{2+} signalling. Thus, it would be necessary to measure the effects of priming when Ca^{2+} signals in either cell type are selectively manipulated. This could theoretically be accomplished via the genetic deletion of M1-AChRs or A_2Rs, or by the expression of designer GPCRs under neuronal or astrocytic promoters. For example, adapted human mAChRs, which are activated by an otherwise inert ligand (Armbruster, Li, Pausch, Herlitze, & Roth, 2007), can be used to trigger Ca^{2+} release in targeted cell types in lieu of electrical priming stimulation. In contrast, single cell electroporation of calcium chelators or G-protein inhibitors could selectively abolish Ca^{2+} signalling in a given cell type during priming (Navarrete, et al., 2012). This latter approach could be used in conjunction with muscarinic agonists to determine the location of the relevant M1-AChRs. It could also be used with the A_{2B}R agonist BAY 60-6583 to test whether the metaplastic actions of this agonist require Ca^{2+} release, and in which cells.

Purinergic signalling

A second question surrounds the relevant source of ATP and the location of the A_2Rs. The requirement for Cx43-based signalling naturally suggests cell-cell interactions via GJNs comprised of these connexins. However, it is possible that ATP

is released via Cx43 hemichannels and acts as an intercellular signalling molecule, perhaps initiating the spontaneous Ca^{2+} signals seen following astrocytic $A_{2B}R$ activation (Kawamura & Kawamura, 2011). Alternatively, ATP may be released synaptically from where it could exert effects on any number of purinergic receptors, astrocytic or neuronal. There is scant evidence of a physiological role for neuronal $A_{2B}Rs$ in hippocampus other than cAMP accumulation (Kessey & Mogul, 1998). It is possible that this diffusible molecule is able to initiate widespread metaplastic inhibition of LTP, although such effects are not in keeping with the known actions of cAMP (S. Y. Huang, et al., 2012). In contrast, Kawamura and Kawamura (2012) demonstrated an astrocytic $A_{2B}R$-triggered signalling mechanism that fulfils the temporal and spatial criteria required for heterosynaptic metaplasticity. $A_{2B}R$ activation is also likely to occur downstream of M1-AChR activation, as priming with an $A_{2B}R$ agonist inhibits later plasticity but is unlikely to trigger ACh release.

6.3 How do astrocytes contribute to heterosynaptic metaplasticity?

The astrocytic network provides a plausible vehicle for long-distance communication between dendritic layers. In addition to mediating heterosynaptic communication, astrocytes may also contribute directly to the induction of the metaplastic state. As noted, astrocytes are capable of releasing several factors which induce or regulate plasticity. A key question surrounding the involvement of gliotransmission in heterosynaptic metaplasticity is whether such factors are released immediately in response to priming (i.e. in tripartite synaptic fashion) to induce a state change in neurons, or whether priming initiates a state change in astrocytes. In the latter case, priming could either trigger sustained release of gliotransmitters which act on neighbouring neurons, or trigger an occult response which predisposes astrocytes

to react differently to subsequent HFS and LFS to affect plasticity induction. The relative merits of these possibilities will be considered in the following paragraphs.

There are several signalling molecules that could be released directly by astrocytes in response to priming, which could theoretically alter subsequent plasticity. The involvement of A_{2B}Rs in heterosynaptic metaplasticity is in keeping with this possibility, as activation of these receptors triggers the release of several cytokines and growth factors from astrocytes. Among these are the interleukins 6 and 8 (Ryzhov, et al., 2009; Vazquez, Clement, Sommer, Schulz, & Van Calker, 2008), which are known to inhibit LTP (A. J. Li, Katafuchi, Oda, Hori, & Oomura, 1997; Xiong, et al., 2003), and the growth factor leukaemia inhibitory factor (LIF), which protects against glutamate-induced excitotoxicity (Moidunny, et al., 2012). Several other factors released from astrocytes, such as the cytokines interleukin 1β and TNF, are also known to inhibit LTP (Bellinger, Madamba, & Siggins, 1993; Ben Menachem-Zidon, et al., 2011; Curran & O'Connor, 2001; Sama, et al., 2008; Tancredi, et al., 2000; Tancredi, et al., 1992). Further, cytokine release from astrocytes has been documented in response to LTP induction in vivo and in vitro (Jankowsky, Derrick, & Patterson, 2000), and such release has been posited as a metaplastic mechanism of synapse stabilization (del Rey, Balschun, Wetzel, Randolf, & Besedovsky, 2013; Jankowsky, et al., 2000). Inhibitors of these molecules could be applied during and after priming stimulation to test their importance in generating heterosynaptic metaplasticity.

Gliotransmission need not occur immediately in response to priming stimulation if it is to alter subsequent plasticity. As mentioned, priming could trigger ongoing astrocytic activity. Astrocytes are capable of lasting spontaneous Ca^{2+} signals and gliotransmitter release (Kawamura & Kawamura, 2011; Pirttimaki, et al., 2011).

It may be possible to detect ongoing glia-neuron crosstalk following priming by investigating whether priming elicits sustained inward currents or Ca^{2+} signals in neurons, and whether such events are abolished when astrocytic activity is compromised genetically or pharmacologically. There are numerous gliotransmitters that could act on neurons if released following priming. Most notable here is perhaps glutamate. Sustained release of astrocytic glutamate could potentially activate GluN2B-containing NMDARs on neurons (Parri, Gould, & Crunelli, 2001). Although APV administered during priming does not block heterosynaptic metaplasticity (Hulme, et al., 2012), activation of GluN2B-containing receptors could be spontaneous and ongoing during washout of APV (Parri, et al., 2001; Pirttimaki, et al., 2011). Further, Hulme et al. would not have detected such events as they only assessed evoked NMAR currents and did not record continuously between priming and later conditioning. GluN2B-containing receptors are already implicated in the NMDAR-mediated metaplastic inhibition of LTP (Q. Yang, et al., 2011). However, activation of these receptors would also be expected to trigger a lasting reduction of I_{NMDAR} (Sobczyk & Svoboda, 2007), which Hulme et al. found to be restricted to the dendritic compartment that received priming stimulation (Hulme, et al., 2012).

The third consideration is that priming could elicit a state change in astrocytes that is not obvious until the point of plasticity induction. In this scenario, primed astrocytes would be expected either to release some factor that inhibits LTP and promotes LTD or, alternatively, not release some permissive factor that usually allows the induction of plasticity. Astrocytic release of D-serine is required for NMDAR activation and LTP; however it is unlikely that priming alters astrocytic release of this factor. First, release of D-serine is constitutive rather than activity-dependent (Shigetomi, et al., 2013). Second, priming does not alter I_{NMDAR} as measured

following stimulation of SR synapses (Hulme, et al., 2012). This leaves the possibility that astrocytes release factors at the point of plasticity induction. Such release would need to be triggered both by LFS and HFS, and while astrocytes do react to both stimulation paradigms with Ca^{2+} release (Pasti, et al., 1997; Porter & McCarthy, 1996), it is unclear what astrocytes might release that would have the dual effect of inhibiting LTP and promoting LTD. Adenosine release inhibits the induction of both plasticity phenotypes (de Mendonca, Almeida, Bashir, & Ribeiro, 1997; de Mendonça & Ribeiro, 1990; N. Kemp & Bashir, 1997), thus ruling out this gliotransmitter. Additional glutamate release would presumably enhance LTP, meaning this too is an unlikely option. It is possible that astrocytes undergo a state change that predisposes them to release cytokines in an activity dependent manner, although this would be a novel form of astrocytic plasticity.

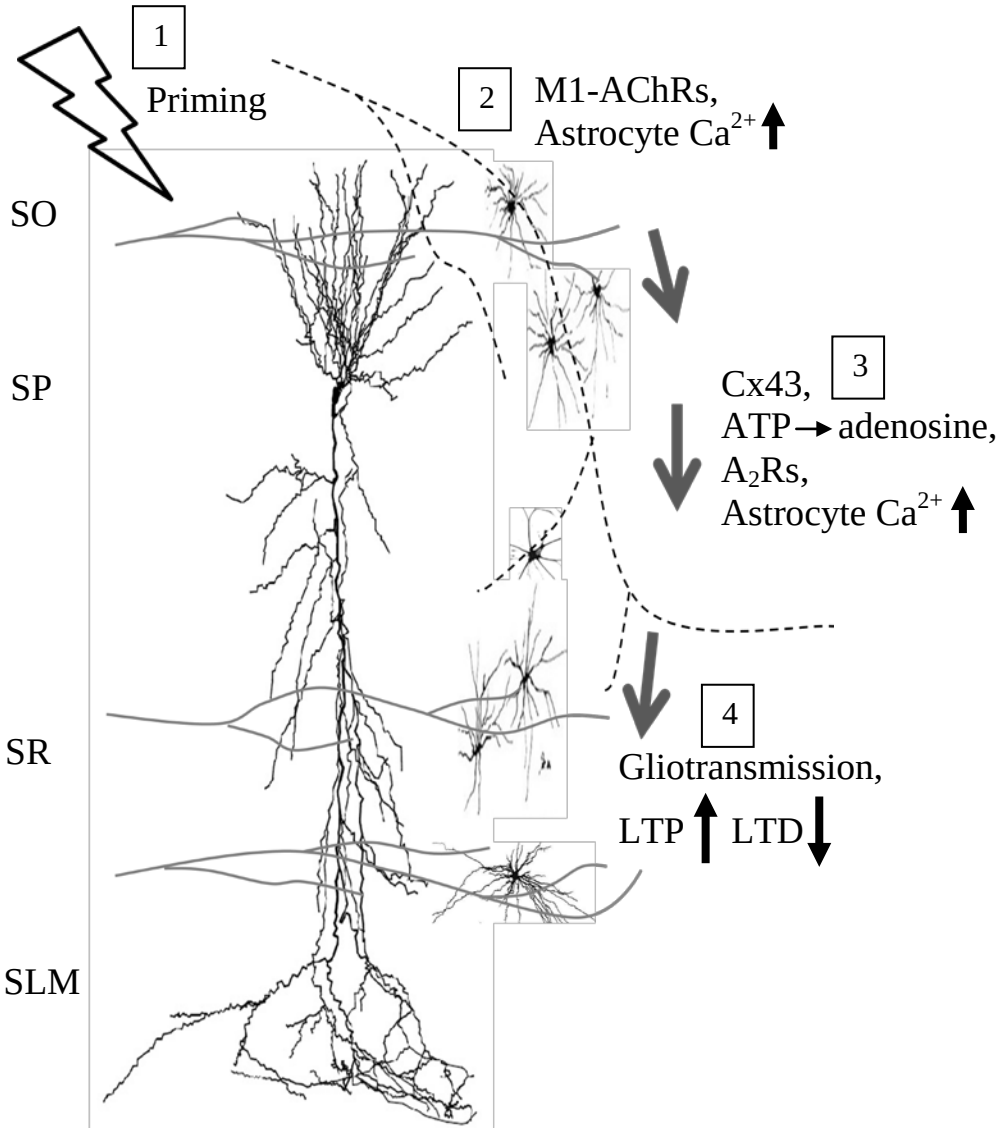

Figure 6.1. An intercellular model of heterosynaptic metaplasticity

Priming stimulation recruits glutamatergic fibres (solid, gray) from CA3, which synapse with dendrites in SO (1). Priming also depolarizes cholinergic fibres (perforated, black) which aid in the widespread recruitment of astrocytes (small cells) (2), whether by activation of astrocytic M1-AChRs or by facilitating network firing. Astrocytes respond by releasing ATP into the extracellular space, possibly via connexin43 hemichannels. This ATP is hydrolysed to adenosine, which acts on A_2Rs to trigger intercellular signalling between astrocytes, possibly via iterative Ca^{2+} mobilization and ATP release. This intercellular signalling spreads at least as far as SR (3). Astrocytic Ca^{2+} signalling also triggers gliotransmitter efflux which metaplastically inhibits LTP and facilitates LTD at synapses on nearby neurons (large cell) (4).

6.4 An intercellular model of heterosynaptic metaplasticity

Taken together, the results of the experiments in this thesis can be combined to form a plausible explanation of how neurons and astrocytes generate temporally and spatially widespread metaplasticity in CA1 (**Fig 6.1**). The results suggest that priming stimulation recruits cholinergic fibres (1), and that M1-AChRs are a likely trigger of the signalling cascade culminating in metaplasticity, whether via G_q-coupled Ca^{2+} release or by facilitated firing. It is also likely that M1-AChRs are responsible through either of these mechanisms for recruitment of astrocytes in SO (2). A parsimonious explanation of purinergic involvement is that astrocytes respond to activation by releasing ATP, which triggers widespread signalling within the astrocytic network. This signalling could be accomplished via GJNs, but given the limited evidence for purely GJN-mediated communication between astrocytes, it is more likely that connexins, in the form of hemichannels, in fact serve as the source of released ATP (3). From here, ATP is hydrolysed extracellularly to adenosine which acts on A_2Rs. Given the canonical actions of A_2R-mediated neuronal signalling, it is probable that the relevant receptors are on astrocytes. Further, given that BAY 60-6583 could prime SR synapses even when ejected into SO, it is plausible that A_{2B}Rs are the trigger of widespread intercellular communication, perhaps via the same mechanism described by Kawamura and Kawamura. The consequences of activating astrocytic A_{2B}Rs (namely, cytokine release) also provide a candidate mechanism for ultimately inhibiting LTP (4). A complete mechanistic explanation of heterosynaptic metaplasticity in CA1 is obtainable from the model, and while several components are yet to be validated they provide testable hypotheses for further experimentation.

6.5 Relevance of heterosynaptic metaplasticity

The deduced mechanisms of heterosynaptic metaplasticity in CA1 depart from those included in commonly cited computational models. The effect does not require APs or somatic depolarization, and is not a response to synaptic potentiation. Heterosynaptic metaplasticity does require a rise in free intracellular Ca^{2+}, which is broadly in keeping with Ca^{2+}-dependent models of plasticity (Yeung, et al., 2004). However, heterosynaptic metaplasticity requires Ca^{2+} from ER stores rather than via NMDARs, and is not a graded response to afferent activity. In contrast, heterosynaptic metaplasticity appears to be an all-or-nothing state induced to a similar degree by a variety of priming protocols. These differences call into question the relevance of this form of metaplasticity as a homeostatic response to postsynaptic activity. In fact, while not yet demonstrated, it appears plausible that the metaplastic inhibition of LTP could be overcome by additional priming activity if it were to trigger sufficient cell firing. Indeed, the facilitation of LTP by APs seen by others (Alarcon, et al., 2006; Bukalo, et al., 2013; Dudek & Fields, 2002; Hulme, et al., 2012) suggests that there may be competing metaplastic mechanisms, which could be engaged to various degrees by synaptic stimulation. Rather than homeostatically reducing subsequent LTP, with sufficient postsynaptic AP firing, afferent activity might engage a positive feedback mechanism that *promotes* this form of plasticity.

If this form of metaplasticity is not a compensatory response to synaptic potentiation or cell-firing, this then begs the question of what physiological purpose it might serve. Clues as to its function may be found in other heterosynaptic interactions such as transient heterosynaptic depression. THSD is generated in parallel with LTP as a means of rendering neighbouring inputs quiescent. THSD is a competitive process in which active inputs dominate over inactive ones, allowing only the most

active synapse or cells to encode information (Zhu, Lai, Hoppensteadt, & He, 2006). In keeping with this, whereas HFS induces homosynaptic LTP and tHSD at neighbouring synapses, tHSD is not seen at either input if HFS is applied to both simultaneously (Lo & Poo, 1991). Thus, tHSD maintains a sparse, economical distribution of synapses and cells devoted to encoding information (Fiete, Senn, Wang, & Hahnloser, 2010; Miller, 1996; Song, Miller, & Abbott, 2000). This could potentially be beneficial in reducing the brain's metabolic burden, and also in promoting the optimal use of neural networks by freeing up a maximal number of synapses for later learning. It is possible that the heterosynaptic metaplasticity described here is a similar but temporally sustained mechanism for decreasing competition from nearby inputs. However, the heterosynaptic metaplasticity requires neither postsynaptic depolarization nor potentiation of the priming pathway, making it difficult to envisage it as a competitive mechanism.

The enduring metaplastic state elicited by priming stimulation also bears some resemblance to lateral inhibition in sensory systems. Like HSD, lateral inhibition is a competitive process whereby the most or first active sensory neurons suppress neighbouring cells of the same type (Adesnik & Scanziani, 2010). Competing neurons are suppressed via activation of interneurons to sharpen the pattern of neuronal activity and augment perceptual resolution. It is possible that heterosynaptic metaplasticity works in a similar manner to increase the contrast between salient and non-salient information. For example, synapses strengthened by priming stimulation would be more likely to trigger cell firing, and thus more likely to cooperate in the induction of associative LTP with neighbouring synapses. Homosynaptic metaplasticity mechanisms would limit further potentiation of the primed pathway, but the potential for LTP of the neighbouring pathway would remain higher than

before priming. Thus, the potential for encoding of non-salient information would also be high unless heterosynaptic regulation of plasticity was also engaged by priming. Although the independence of heterosynaptic metaplasticity on postsynaptic firing or LTP of the priming pathway seems not to support these conclusions, it is noteworthy that such contrast, and also synaptic stabilization, could be beneficial if produced by ACh alone. As noted, the characteristic theta rhythm of the hippocampus is gated by cholinergic inputs arising in the septum. Theta is apparent during voluntary or exploratory movement and is believed to be critical for encoding, presumably by facilitating depolarization and plasticity (Buzsáki, 1989; Huerta & Lisman, 1995, 1996; Madison, et al., 1987; Vanderwolf, 1969). It is possible that cholinergic theta activity facilitates the concurrent induction of plasticity, but also triggers a metaplastic state in order to preserve encoded information from being 'overwritten' by *subsequent* neuronal activity. This would appear in keeping with the metaplastic state seen by Newlon and colleagues after theta-patterned activation of cholinergic inputs to CA1. Although such a mechanism seems at odds with the inability of TBS priming to heterosynaptically inhibit LTP, it may be that postsynaptic firing negated the effects of ACh in this paradigm.

Finally, it is possible that the heterosynaptic inhibition of LTP is a neuroprotective mechanism which adjusts plasticity thresholds to maintain network activity within safe levels of operation and avoid excitotoxicity. In this sense, heterosynaptic metaplasticity is reminiscent of the protection afforded by mechanisms termed 'ischemic preconditioning' (IPC), whereby relatively strong neural activity at one point in time confers a protective state against later, otherwise lethal metabolic challenge (Dahl & Balfour, 1964; Kitagawa, et al., 1990; Schurr, Reid, Tseng, West, & Rigor, 1986). Indeed, there is considerable mechanistic crossover between IPC and

certain forms of metaplasticity. For example, brief ‘preconditioning’ bouts of NMDAR activation ameliorate the excitotoxicity usually seen following prolonged, pathological activation of these same receptors (Hardingham, Fukunaga, & Bading, 2002; Soriano, et al., 2006). This is analogous to the inhibitory effects of NMDAR activation on later LTP (Y. Y. Huang, et al., 1992; Izumi, Clifford, & Zorumski, 1992b; L. Zhang, et al., 2005). Indeed, the same regime of NMDA pretreatment protects against later excitotoxicity and inhibits later LTP (Youssef, et al., 2006). Likewise, LTP induction ameliorates the subsequent loss of synaptic transmission following hypoxia (Youssef, et al., 2001; Youssef, et al., 2003). Thus, metaplasticity and IPC may belong to a larger family of neural responses which maintain optimal levels of neural activity. It is perhaps of relevance here that heterosynaptic metaplasticity is inducible by sustained presynaptic firing (4-6 x 100 Hz bursts) but not by a more physiologically relevant pattern of activity (TBS). This may suggest that heterosynaptic metaplasticity is a response to abnormal amounts or patterns of stimulation. A key test of this hypothesis will be to determine the minimal stimulus requirements for inducing heterosynaptic metaplasticity.

There is compelling mechanistic evidence to suggest that the heterosynaptic metaplasticity described in this thesis could function as a neuroprotective mechanism. For example, it is noteworthy that Cx43 and adenosine contribute significantly to IPC. Cx43-dependent release of paracrine signalling molecules such as ATP or glutamate is thought to contribute to neurotoxicity during prolonged ischemia (Cotrina, Kang, et al., 1998; Lin, et al., 1998; Rawanduzy, Hansen, Hansen, & Nedergaard, 1997). However, IPC is absent in both heart and brain in Cx43-deficient mice (Lin, et al., 2008; Schwanke, et al., 2002). Although the precise role of Cx43 in IPC remains elusive, there are two reasons to believe it involves release of ATP as opposed to

electrical coupling or cell-cell diffusion of Ca^{2+} or IP_3. First, brief metabolic challenge decrease intercellular communication between astrocytes, but induces opening of unapposed Cx43 hemichannels (Contreras, et al., 2002). Second, preconditioning reduces Cx43 turnover, increasing the surface expression of this protein and subsequent extracellular accumulation of ATP and adenosine (Lin, et al., 2008).

The neuroprotective effects of adenosine have been known for many years. The most widely reported mechanism of adenosine-induced neuroprotection is the activation of A_1Rs (Heurteaux, Lauritzen, Widmann, & Lazdunski, 1995; Hu, et al., 2012; Latini, Bordoni, Pedata, & Corradetti, 1999; Lauro, et al., 2010; Pérez-Pinzón, Mumford, Rosenthal, & Sick, 1996; Pugliese, Latini, Corradetti, & Pedata, 2003). In contrast, A_3Rs are desensitized during ischemia or hypoxia and contribute to neuronal injury, and their blockade enhances protection via IPC (Pugliese, Coppi, Spalluto, Corradetti, & Pedata, 2006; Pugliese, et al., 2007; Pugliese, et al., 2003). The role of A_2Rs in IPC is less clear. Whereas A_{2A}Rs have been shown not to contribute to IPC in hippocampus, they are required for NMDA preconditioning in cerebellum (Boeck, Kroth, Bronzatto, & Vendite, 2005; Pugliese, et al., 2003), suggesting location-specific roles. As noted, however, activation of astrocytic A_{2B}Rs in CA1 triggers protection against excitotoxicity by stimulating the release of LIF (Moidunny, et al., 2012). IPC also triggers an upregulation of A_{2B}Rs on astrocytes in SR (A. M. Zhou, et al., 2004). Interestingly, an IPC mechanism has been described in the heart which requires ectonucleotidase-dependent adenosine formation and activation of A_{2B}Rs (Eckle, et al., 2007). Extracellular degradation of ATP to adenosine is also induced during IPC in hippocampus (Schetinger, et al., 1998). Thus, A_{2B}R activation during preconditioning may also be a result of this pathway in the brain.

Together, these results suggest that connexin43 and purine-mediated heterosynaptic metaplasticity may ameliorate the effects of later metabolic challenge. The critical test of this hypothesis is whether SO priming is able to protect against hypoxic/ischemic insult, and whether this effect is inhibited or mimicked by the same antagonist and agonists that block or induce, respectively, heterosynaptic metaplasticity in CA1.

6.6 Metaplastic regulation of network activity

Metaplasticity allows for the fine tuning of synaptic activity homo- and heterosynaptically. Interestingly, the spatial spread of metaplastic states depends on the signalling mechanisms engaged. For example, at the level of the individual synapse, the plasticity threshold is modified as a function of prior activity, with quiescent synapses displaying greater structural growth and LTP (M. C. Lee, Yasuda, & Ehlers, 2010). This highly localised form of metaplasticity is triggered by activity-dependent remodelling of NMDAR subunit expression, with NMDAR activation triggering a reduction of functional GluN2B content in these receptors and associated Ca^{2+} influx (M. C. Lee, et al., 2010). At the branch level, later LTP is facilitated at synapses adjacent to those which undergo potentiation (C. D. Harvey & Svoboda, 2007). This facilitation of LTP spreads < 10 μm and lasts < 10 min, and requires the NMDAR-dependent activation and spread of the GTPase Ras (C. D. Harvey & Svoboda, 2007; C. D. Harvey, et al., 2008). NMDARs are therefore gatekeepers of synapse-specific and branch-specific metaplasticity. Similar effects can, however, be obtained over 20 μm of a dendritic branch via NMDAR-independent mechanisms involving mGluR activation, release of endocannabinoids and subsequent retrograde inhibition of GABAergic interneurons (Chevaleyre & Castillo, 2003, 2004). Given the

limited spread of other diffusible messengers such as cAMP and IP_3, it is possible similar spatial restrictions exist for the metaplastic effects triggered by these molecules.

Input-specific metaplasticity may also come from localised changes in excitability, for example the mGluR or NMDAR-dependent regulation of I_h noted previously (Brager & Johnston, 2007; Fan, et al., 2005). However, membrane changes such as these are well placed to exert metaplastic effects across an entire dendritic compartment. Indeed, antidromic firing at theta frequency increases I_h across 300 µm of the apical dendrite of CA1 pyramidal cells (Narayanan & Johnston, 2007). The mechanism by which antidromic firing regulates I_h at distant locations appears to involve extrasynaptic NMDAR activation by ambient Glu (Y. W. Wu, et al., 2012). However, trains of backpropagating APs accommodate heavily and do not fully invade the distal dendritic arbour (Spruston, et al., 1995), meaning that their effects on LTP or LTD are likely confined to more proximal dendritic compartments, rather than being a truly cell-wide trigger of metaplasticity. This is significant given that the gradient of apical dendritic HCN channels increases with distance from the soma in CA1 pyramidal cells. Thus, the large quantities of HCN channels in SLM are unlikely to be affected by such signalling. Nonetheless, antidromic firing may exert widespread but compartment-specific metaplasticity through these means, or by altering the properties of other ion channels, such as those that govern the AHP (Cloues & Sather, 2003), or VGCCs (Yasuda, et al., 2003).

Truly cell-wide metaplasticity is yet to be described, but may occur as a homeostatic reaction to high levels of synaptic potentiation. A homeostatic "shutdown" of LTP has been described following chemical LTP induction at all but a small portion of synapses in SR (Roth-Alpermann, et al., 2006). In these experiments,

widespread LTP blocked further synaptic enhancement, but only after potentiation was evident at a considerable number of inputs. The chemical induction protocol used is likely to have induced LTP in SO also, although this was not measured and the importance of heterodendritic LTP for the shutdown effect was not tested. Thus, it cannot be determined whether LTP shutdown requires virtually cell-wide potentiation to become manifest, or simply the potentiation of most inputs within a given compartment. Nevertheless, the authors have provided evidence of a potentially cell-wide metaplasticity mechanism.

Metaplasticity induced by SO or SR priming may also be cell-wide, although there are still outstanding issues regarding this possibility. There is, as yet, no evidence to suggest that the effect spreads to or from synapses in SLM. Indeed, it would be difficult to test for such effects given the presence of other heterosynaptic interactions between SLM and other strata mediated by GABAergic interneurons (detailed in section 1; see: Leão, et al., 2012). Further, it is not clear whether synapses in SO can be primed in such a way. If anything the failure of SR priming to alter later LTP in SO suggests otherwise, although this may be possible with stronger priming activity, as noted.

Another possibility is that heterosynaptic metaplasticity operates at the *network level*. That is, rather than being a response to strong activity in a given cell, it is in fact an adjustment of plasticity thresholds in response to strong activity in multiple cells within the network. This would allow a single signal transduction mechanism to reach a maximal number of synapses and cells, thus allowing for efficient reaction to large scale perturbations in activity. In this scenario, the metaplastic state could theoretically spread not only to quiescent synapses, but also quiescent cells not activated by priming stimulation.

Theoretically, neuronal depolarization could mediate widespread preconditioning via cortical spreading depression (CSD) (Matsushima, Hogan, & Hakim, 1996; O. Peters, Schipke, Hashimoto, & Kettenmann, 2003). However, induction of CSD typically requires massive depolarization whether induced by electrical stimulation or following haemorrhage, stroke or exposure to high levels of KCl (Dreier, et al., 2009; Gorji, et al., 2001; Leao, 1944; Nedergaard & Hansen, 1988). The mechanisms of heterosynaptic metaplasticity are a response to considerably milder activity, and may represent a more sensitive mode of spatially widespread preconditioning. Further, the widespread depolarization associated with CSD appears to facilitate rather than inhibit LTP in hippocampal slices (Wernsmann, Pape, Speckmann, & Gorji, 2006). This seems at odds with the preconditioning effects of CSD, although CSD preconditioning does not alter NMDAR signalling (Chazot, Godukhin, McDonald, & Obrenovitch, 2002) and may trigger prolonged cell firing which contributes to the facilitation of LTP (Bukalo, et al., 2013; Hulme, et al., 2012). At any rate, these results do not support the idea of neuronal depolarization as a mediating signal in network-level homeostatic metaplasticity.

The astrocytic network represents a more suitable network-level signal transduction system than neuronal depolarization. Astrocytes make contact with multiple neurons, and are thus well placed to sense network activity and exert a spatially widespread response. Indeed, astrocytic calcium waves travel significantly further than waves of neuronal depolarization during CSD (O. Peters, et al., 2003). If heterosynaptic metaplasticity is indeed a neuroprotective mechanism, then the interconnected astrocytic network could be an effective means of conferring a protective phenotype across considerable distances, thus stabilizing a maximal number of synapses and cells. Astrocytes are well placed to act as coincidence and

threshold detectors within neural networks. For example, a known trigger of heterosynaptic metaplasticity, the $A_{2B}R$, has relatively low affinity for adenosine (Beukers, den Dulk, van Tilburg, Brouwer, & Ijzerman, 2000). Thus, activation of $A_{2B}Rs$ on astrocytes could require substantial localised release and hydrolysis of ATP. To meet this threshold might require sustained activation of astrocytes via synaptically released neurotransmitters. This could come through persistent release from one neuron, but seems more likely to follow concerted transmitter release from multiple terminals. Thus, $A_{2B}R$ activation on astrocytes and its downstream consequences may only be seen when a relatively high threshold of synaptic activity is reached. Such a mechanism appears well suited to act as a trigger of neuroprotection.

6.7 Metaplasticity and neuronal homeostasis

BCM-like forms of metaplasticity act to homeostatically adjust plasticity thresholds in response to changes in neural activity. Models which incorporate a sliding plasticity threshold do so as a negative feedback mechanism which ensures stability in the face of change. Heterosynaptic metaplasticity as described in this thesis is not a homeostatic adjustment to postsynaptic firing or LTP, but could nonetheless function as a negative feedback mechanism to compensate for the possibly toxic consequences of strong activity. However, in principal, homeostatic regulation of neuronal activity is achievable without metaplasticity. Perhaps the best example of such regulation is the form of homeostatic plasticity termed ‘synaptic scaling’ (Turrigiano, Leslie, Desai, Rutherford, & Nelson, 1998). In their seminal paper, Turrigiano et al. reported that chronic increases or decreases in neuronal firing yielded compensatory decreases or increases, respectively, in the strength of synaptic

transmission. These changes displayed a slow onset (< 48 hrs), were uniform across all excitatory synapses and were accompanied by changes in intrinsic excitability that restored firing rates to pre-treatment levels (Turrigiano, et al., 1998).

Synaptic scaling is distinguishable from LTP/LTD due to its slower timescale, and from metaplasticity due to its direct regulation of synaptic strength. Scaling of synapses and excitability are of course likely to have metaplasticity consequences (Thiagarajan, Lindskog, Malgaroli, & Tsien, 2007; Thiagarajan, Lindskog, & Tsien, 2005). Indeed, chronic silencing upscales AMPAR quantity at existing synapses on CA1 pyramidal cells and also triggers formation of silent synapses, which can then be potentiated by an ensuing HFS (Arendt, Sarti, & Chen, 2013). It is also worth noting that the homeostatic regulation of firing rates bears resemblance to similar properties incorporated in the BCM model. Nevertheless, homeostatic plasticity as described by Turrigiano and colleagues could theoretically regulate network activity in the absence of metaplasticity.

If homeostatic plasticity alone can account for network stability, why would metaplasticity be required? It has been suggested that homeostatic scaling mechanisms act to compensate for altered firing rates following Hebbian changes such as LTP/LTD (Turrigiano, et al., 1998; Turrigiano & Nelson, 2000). In this model, synapses and/or excitability are scaled globally (cell-wide) to ensure that firing rates remain stable while relative changes in synaptic weight, and any information stored therein, are preserved. Such a mechanism may seem plausible at first, but is unlikely to provide sufficient regulation in the absence of additional controls afforded by metaplasticity. For example, if global scaling occurs following potentiation of a given input, then the potentiated input remains at an advantage over its neighbours when competing to store further information. This could potentially lead to the

overwriting of synaptically stored information or, in the extreme, mean unrestricted synaptic potentiation. LTD induction would naturally have the opposite effect of perpetually favoured synaptic depression. These are the very situations which computational neuroscientists seek to avoid by utilizing a sliding plasticity threshold in their models (Bienenstock, et al., 1982; Yeung, et al., 2004). Thus, global scaling requires additional regulatory mechanisms in order to ensure neuronal viability. On the other hand, if scaling were to occur locally rather than globally, then relative differences in synaptic weight would be lost, making this form of scaling non-viable for information storage without additional mechanisms which constrain synaptic strength at heterosynaptic locations, perhaps such as heterosynaptic LTD. It is noteworthy that synaptic weight changes following asymptotic heterosynaptic LTD are small compared to increases following induction of homosynaptic LTP (Abraham, et al., 1985; Abraham & Goddard, 1983; Wickens & Abraham, 1991), suggesting that this form of negative feedback would have to work in tandem with other modes of homeostasis to return postsynaptic activity to previous levels. However, homosynaptic LTD facilitates subsequent potentiation (Dudek & Bear, 1993). If this is also true of heterosynaptic LTD, a topic surprisingly unmentioned in the literature, then the potential would still exist for relative differences in synaptic weights to be lost. Thus, local (i.e. input specific) scaling can only safeguard information storage and neuronal health if accompanied by heterosynaptic LTD *and* heterosynaptic metaplasticity.

A third option might be that synaptic plasticity within a certain range is tolerable and does not require homeostatic adjustments such as synaptic scaling. In favour of this, electrically or learning-induced potentiation of synapses can be maintained for months without any global homeostatic scaling as a consequence

(Abraham, et al., 2002; Rioult-Pedotti, Donoghue, & Dunaevsky, 2007). In contrast, it appears that the synaptic modification range itself undergoes plasticity during this time, such that saturated networks can be potentiated further after a certain period of time has elapsed (Rioult-Pedotti, et al., 2007). It is therefore possible that homeostatic scaling only occurs when a relatively *high or low rate of cell firing is sustained*, perhaps pathologically. This is particularly pertinent given the prolonged experimental treatments typically used to induce scaling (at least 4 hrs: Ibata, Sun, & Turrigiano, 2008). Thus, homeostatic forms of metaplasticity, including heterosynaptic metaplasticity as described in this thesis, may serve as more immediate, sensitive and rapid responses to altered neural activity which complement slower alterations seen following chronically altered cell firing.

6.8 Concluding remarks

The experiments in this thesis describe a mechanism of long-distance intercellular communication between synapses that contributes to altered plasticity induction in a spatially and temporally widespread manner. The results present a major departure from the predictions of the BCM model and its derivatives, which rely on postsynaptic mechanisms as regulators of plasticity. Instead, these experiments have implicated the astrocytic network as a key trans-synaptic signalling system and possible regulator of LTP and LTD. This represents a novel role for this cell type and contributes to a growing body of evidence that suggests astrocytes are active participants in the processes that govern synaptic information storage. Many parametric questions remain regarding heterosynaptic metaplasticity (e.g. how quickly is it induced? What are the minimal stimulus requirements for priming to be effective? What is the spatial and temporal extent of the metaplasticity?). However, the main focus of future investigations should be a mechanistic dissection of the neuronal and astrocytic contributions to the effect. Several clues have now been provided that point to a potential trigger of the metaplasticity (ACh-induced Ca^{2+} release) and a plausible mode of communication between synapses or dendritic layers (astrocytic communication via purines, GJNs or both). The challenge now is to provide firm evidence for or against these mechanisms and to identify the mode by which the induction of LTP and LTD are ultimately altered. Further, the possibility that this form of metaplasticity serves as a neuroprotective mechanism also requires testing. This may yield further information on hitherto unknown roles of astrocytes, and the factors they release, in maintaining neural health and function.

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