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Research Report

Frequency-dependent changes in synaptic plasticity and brain-derived neurotrophic factor (BDNF) expression in the CA1 to perirhinal cortex projection

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ABSTRACT

The ability of a synapse to be modulated both positively and negatively may be considered as a plausible model for the formation of learning and memory. The CA1 to perirhinal cortex projection is one of the multiple hippocampal–neocortical projections considered to be crucially involved in memory consolidation. We and others have previously demonstrated the ability of this projection to undergo long-term potentiation (LTP), however it is currently unknown whether the CA1-perirhinal projection can also be modified negatively (i.e. demonstrate long-term depression (LTD)). Here we investigate whether the CA1 to perirhinal projection *in vivo* in the anaesthetised animal shows a frequency-dependent pattern of synaptic plasticity that is coupled with brain-derived neurotrophic factor (BDNF) expression. Five groups of animals were used and each group underwent one of five different stimulation protocols (1 Hz, 5 Hz, 10 Hz, 50 Hz or 100 Hz) followed by post-stimulation recordings at baseline stimulation intensity (0.05 Hz) for 1 h. Paired-pulse facilitation (PPF) recordings were taken both during baseline and 1 h post-stimulation across six inter-pulse intervals (IPIs). Following all experiments, tissue samples were taken from area CA1 and perirhinal cortex from both the unstimulated and stimulated hemispheres of each brain and analysed for BDNF. Results indicated that LTP was observed following 50 Hz and 100 Hz HFS but LTD was not observed following any low-frequency stimulation. Pre- and post-stimulation PPF recordings revealed no difference for any of the stimulation frequencies, suggesting that the plasticity observed may involve a post- rather than a presynaptic mechanism. Finally, changes in BDNF were positively correlated with stimulation frequency in the area CA1 but the same pattern was not observed in the perirhinal cortex. These findings suggest that the CA1 to perirhinal cortex projection is electrophysiologically excitatory in nature and that changes in BDNF levels in this projection may not be predictive of changes in synaptic plasticity.

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1. Introduction

The hippocampal formation (HF) is an important structure for learning and memory (Scoville and Milner, 1957; O'Keefe and Nadel, 1978; Squire, 1992). The HF is thought to play a particular role in associating different forms of sensory information (Rolls, 1996) required to form long-term memories. Although it is not the site of storage for memories, the HF acts in an integrative role to output sensory information to the neocortex for long-term storage (Squire et al., 1984; Squire, 1992; McClelland et al., 1995; Squire and Alvarez, 1995). Among the possible physiological mechanisms for memory formation and consolidation are changes in synaptic plasticity (Martin et al., 2000).

Long-term potentiation (LTP) is just one aspect of synaptic plasticity, representing a long-lasting increase in synaptic strength (Bliss and Lømo, 1973). Long-term depression (LTD) considered the converse process, is a long-lasting reduction in synaptic strength usually induced following low-frequency stimulation (LFS; Bramham and Srebro, 1987). This phenomenon has also been described in the literature. The ability of a synapse to be modulated both positively and negatively by different frequencies supports the case for changes in synaptic strength as a candidate for the physiological basis of learning and memory (Bear et al., 1987; Thiels et al., 1996). In particular, this modifiable ability of the synapse supports recent suggestions that memories are dynamic rather than static in nature, they can be updated, erased or impaired by subsequent experiences and therefore, there is a need for synapses to reflect this by also having the ability to change strength, raise or lower synaptic thresholds (Abraham and Williams, 2008) and to shift the synaptic modification range (Rioult-Pedotti et al., 2007) rather than simply being unmodifiable and locked at a certain strength.

Previously, we have described both short- and long-term synaptic plasticity in the CA1-perirhinal cortex projection. We have demonstrated that stimulation of area CA1 using a 250 Hz high-frequency stimulation (HFS) protocol results in paired-pulse facilitation (PPF) and LTP in the perirhinal cortex (Kealy and Commins, 2009). These findings agree with previous research which has demonstrated that this projection is indeed capable of sustaining long-term changes in synaptic plasticity (Cousens and Otto, 1998; Ivanco and Racine, 2000). We now wish to extend our previous findings and examine whether different stimulation frequencies have differential effects on synaptic plasticity in this pathway and whether the CA1 to perirhinal cortex projection is also capable of sustaining LTD, thus conforming to the Bienenstock–Cooper–Munro (BCM) model of biphasic synaptic modification (Bienenstock et al., 1982).

In hippocampal area CA1, a number of studies have shown that LTD can be induced by LFS (Thiels et al., 1994; Doyère et al., 1996; Citri et al., 2009; Hosseinmardi et al., 2009). NMDA-dependent homosynaptic LTD in area CA1 can be induced with LFS (1–3 Hz) of the Schaffer collateral (Dudek and Bear, 1992). Dudek and Bear (1993) later showed that this synaptic plasticity was bidirectional, LTP and LTD could be induced in the same synapses following a series of HFS and LFS protocols and these findings were later reproduced *in vivo* (Heynen et al., 1996). Further, our laboratory has demonstrated that the hippocampal output projections are also capable of being modified in an activity-dependent fashion. For example, the CA1-subiculm projection is capable of sustaining LTP (Commins et al., 1998b), while the CA1 to entorhinal cortex projection has been shown to sustain LTP following 50 Hz, 100 Hz and 250 Hz HFS protocols (Craig and Commins, 2005, 2007) and LTD following 1 Hz, 5 Hz and 10 Hz LFS protocols (Craig and Commins, 2007). In the perirhinal cortex, activity-dependent LTD has been described following 1 Hz LFS that seems to be reliant on metabotropic glutamate (mGlu) receptors (Cho et al., 2000b, 2002). Recently, kainate glutamate receptor-dependent LTD has also been identified in the perirhinal cortex and this seems to be induced via a different level of activity compared to AMPA-dependent LTD (Park et al., 2006). Interestingly, a role for perirhinal LTD in object recognition memory has been suggested as antagonism of L-type voltage-dependent calcium channels (VLDCCs) blocks object recognition memory and the induction of LTD but not the induction of LTP (Seoane et al., 2009). Furthermore, viral blockade of mGlu and AMPA receptors block perirhinal LTD *in vitro* and also recognition memory (Griffiths et al., 2008). These experiments suggest that LTD and LTP may play differential roles in perirhinal-dependent recognition memory, with an LTD-like mechanism being suggested as the process underlying this process (Warburton et al., 2003; Barker et al., 2006).

There is increasing molecular evidence to suggest that LTP and LTD are different extremes of the same process (Bienenstock et al., 1982; Bear, 2003; Yu et al., 2008). There are a number of molecular processes found to be important in LTP that are also implicated in LTD including Ca^{2+} (Mulkey and Malenka, 1992; Cummings et al., 1996), protein phosphatases (Mulkey et al., 1993, 1994; Dickinson et al., 2009), BDNF (Aicardi et al., 2004), extracellular signal-regulated kinase (ERK; Norman et al., 2000; Thiels et al., 2002; Gallagher et al., 2004), NMDA glutamate receptors (Dudek and Bear, 1992; Kirkwood et al., 1993) and AMPA glutamate receptors (Lüscher et al., 1999; Wang and Linden, 2000). The most studied model of the LTP/LTD dichotomy is the cycling of AMPA glutamate receptors to and from the postsynaptic membrane. The insertion of AMPA receptors into the postsynaptic membrane has been implicated in the induction of LTP (Shi et al., 1999, 2001; Barry and Ziff, 2002) and conversely, the endocytosis of AMPA receptors has been suggested to be the mechanism underlying LTD (Lüscher et al., 1999; Wang and Linden, 2000; Holman et al., 2007). This AMPA receptor endocytosis has been shown to be Ca^{2+}-dependent (Beattie et al., 2000) mGlu receptor-dependent (Snyder et al., 2001; Xiao et al., 2001), protein kinase C-dependent (Czarnecki et al., 2007) and Arc-dependent (Bramham et al., 2010).

The presence of BDNF can also alter the effect observed at different stimulation frequencies, suggesting that neurotrophins may play a role in modulating metaplasticity (prior synaptic activity resulting in changes in the potential for synaptic plasticity; Abraham and Bear, 1996). It has been suggested that BDNF may shift the synaptic modulation threshold, preventing the induction of LTD *in vivo* (Jiang et al., 2003). For example, at lower frequencies where LTP is normally not observed, LTP can be induced in the presence of BDNF (Figurov et al., 1996; Huber et al., 1998). Huber et al. (1998) also demonstrated that at frequencies that would normally induce strong LTD; there is an attenuation of depression in the presence of BDNF. Other studies have shown that application of BDNF in