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Research Report

Plastic and metaplastic changes in the CA1 and subicular projections to the entorhinal cortex

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ABSTRACT

The hippocampal formation (HF) is a brain structure critically involved in memory formation. Two major pathways have been identified in the rat; one projection targets the hippocampus via perirhinal cortex and lateral entorhinal cortex (LEC) while another targets the hippocampus via postrhinal cortex and medial entorhinal cortex (MEC). Areas CA1 and subiculum constitute major output structures of HF and target many cortical structures including EC. These return projections are also anatomically segregated with distinct regions of CA1 and subiculum projecting to either the LEC or MEC. We have previously demonstrated that the projections from CA1 and subiculum to the EC are capable of sustaining short- and long-term plastic changes. Here we detail a physiological topography that exists along the hippocampal output projections, equating well with the known anatomy. Specifically, field excitatory postsynaptic potential (fEPSP) responses in LEC are stronger following distal CA1 and proximal subiculum stimulation, compared to either proximal CA1 or distal subiculum stimulation. In addition, fEPSP responses in MEC are stronger following proximal CA1 stimulation compared to distal CA1. We also demonstrate that the distal CA1-LEC, proximal CA1-MEC and proximal subiculum-LEC projections are all capable of frequency-dependent plastic effects that shift the response from LTD to LTP. In addition, responses in distal CA1-LEC projection seem to show metaplastic capabilities. We discuss the possibility of dissociation between LEC and MEC projections, which may suggest two functional circuits from the HF to the cortex and may have implications in information processing, memory research and hippocampal seizure spread to the cortex.

1. Introduction

The hippocampus is a medial temporal lobe structure that is critically involved in the formation of declarative memories (Ogden and Corkin, 1991; Scoville and Milner, 1957). Evidence for this ascertain derives from lesion (Jarrard, 1983, 1993), patient (Cipolotti et al., 2006), imaging (Schacter and Wagner, 1999), and the plastic capabilities of this structure (Martin et al., 2000). Long-term potentiation (LTP), a long-lasting form of synaptic change considered a realistic model of learning and memory was first identified along the perforant pathway (the major input projection to the hippocampus; Bliss and Lomo, 1973; Bliss and Collingridge, 1993). Other forms of activity-dependent changes have been demonstrated throughout the hippocampal circuit, including among others, long-term depression (LTD), paired-pulse facilitation and depression (PPF/D), post-synaptic potentiation (PST) and augmentation (Thomsom, 2000). PPF and PPD are short-term plastic changes

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at the synapse elicited by a brief spike pair. PPF is the phenomenon whereby the field excitatory postsynaptic response (fEPSP) to a second stimulus is enhanced relative to the first, if the second stimulus is delivered relatively quickly after the first (Katz and Miledi, 1970; Zucker, 1989).

It has been increasingly clear that it is not just simply a matter of whether plastic changes can be induced at a particular synapse; rather synapses should be viewed as being dynamic. The dynamic nature of synapses should be seen in terms of the duration of change (short-term changes in the range of milliseconds, in the case of PPF/D to more longer-term changes hours to days, in the case of LTP/D), degree of change and direction of change. Some synapses for example, may demonstrate an increase in efficacy (facilitation and potentiation), while others may decrease (depression). This dynamism is important in the developing cortex (Bienenstock et al., 1982) and is now clear that memory formation and storage may also depend on such changes (Bear et al., 1987).

Traditionally LTP and LTD have been treated as independent entities, evidence, however, now suggests that these processes are bi-directional modifications of the same synaptic mechanism (Castellani et al., 2001; Dudek and Bear, 1993; Heynen et al., 2000). Experimental data obtained from the developing visual cortex have led to a biphasic synaptic modification rule known as the Bienenstock-Cooper-Munro rule (BCM; Bienenstock et al., 1982), with the crossover point from LTD to LTP known as the modification threshold (θm). This threshold is not fixed but varies according to prior postsynaptic activity (Dudek and Bear, 1993). This activity-dependent modulation, termed metaplasticity (Abraham and Bear, 1996) can result from a number of different factors including changes in receptor function, prior synaptic activity and stress (Dudek and Bear, 1992; Garcia, 2001; Gisabella et al., 2003; Van Dam et al., 2004; Wu et al., 2004).

Neuroanatomical research over the last number of years (Witter et al., 2000) has suggested the existence of two parallel pathways through the hippocampal formation that may be involved in separately processing functionally different types of information. The first pathway arises in the perirhinal cortex, projects through the lateral entorhinal cortex (LEC) and terminates in different layers of the dentate gyrus, CA3 and the distal CA1 and proximal subiculum. The second pathway arises in the postrhinal cortex and targets the proximal CA1 and distal subiculum as well as different layers of dentate gyrus and CA3 via the medial entorhinal cortex (MEC). More recent research (Kloosterman et al., 2003) has indicated that the segregation of information is maintained on the return projections from the hippocampus to the cortex. Tracing studies, for example, have shown that the proximal CA1 and distal subiculum target mainly the MEC whereas the distal CA1 and proximal subiculum target the LEC (Kloosterman et al., 2003; Tamamaki and Nojyo, 1995). The importance of identifying hippocampal–cortical projections that are physiologically as well as anatomically connected lies in the suggestion that one or all of these projections may serve as functional routes along which memories may be retained. Indeed, many current theories of memory formation highlight the importance of hippocampal–cortical interactions for the consolidation of declarative memories (Nadel and Moscovitch, 1997; Rolls, 1996; Squire, 1992). Furthermore, some theories (Rolls, 1996) specify that the backprojections from the hippocampus to the neocortex must undergo activity-dependent changes in order for memories to be retained in the long-term.

Recently we have demonstrated that the projection from CA1-EC and subiculum-EC can undergo activity-dependent changes in the form of PPF and LTP (Craig and Commins, 2005, 2006); however, as suggested above it is becoming increasingly recognised that it is not simply a question of whether synapses can become potentiated or not, but rather, it is important to understand the full range of dynamic plastic capabilities of a particular synapse to fully appreciate the role of plasticity in memory formation.

In a first set of experiments we aim to detail electrophysiologically the topographical nature of the CA1 and subicular projections to EC, from this, we wish to examine the plastic and metaplastic capabilities of these projections. Specifically, we aim to elucidate whether the CA1 and/or subicular-EC projections are capable of frequency-dependent plasticity, that is, are the projections capable of shifting from LTD to LTP simply by varying the frequency applied to the particular synapse. In other words, does each projection fit the BCM model of synaptic plasticity and if so what is the modification threshold of each projection? Furthermore once a change has occurred in the responsiveness of a projection, is that projection capable of further change by applying a second stimulation at any give frequency?

2. Results

2.1. *General description of electrode placement sites*

2.1.1. *Lateral EC responses following CA1 stimulation*

In all cases ($n=6$) a response was evoked in the LEC following stimulation in area CA1. Figs. 1a (first panel) and b (upper panel) shows the distribution of the approximate final positions of all stimulating and recording sites. Fig. 1a (second panel) shows 3 representative Nissl-stained coronal slices with proximal, medial and distal CA1 electrode tracks, while Fig. 1b (lower panel) shows an electrode track in LEC. The final stimulating sites were positioned along the entire proximo-distal extent of CA1. The positions of the stimulating electrodes were all located between 3.1 mm and 5.8 mm posterior to Bregma. In addition the final positions of the recording electrodes in LEC were all located between 6.7 mm and 7.2 mm posterior to Bregma.

The recording electrode was first lowered to 6 mm below the surface of the brain and allowed to settle in the LEC. Then, the stimulating electrode was slowly lowered towards the proximal CA1 with stimulation conducted at a rate of 0.05 Hz. When the maximal fEPSP response was achieved in the LEC, the stimulating electrode was allowed to settle for 10 min and various features of the fEPSP were noted, including amplitude, slope and latency of response. The response occurred at a mean latency value of 14.67±0.34 ms and had a mean peak amplitude value of 0.34±0.08 mV and a slope of 0.1±0.02 mV/ms. While recording electrode remained in place in LEC the stimulating electrode was then removed