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Research Report

High-frequency stimulation of the temporoammonic pathway induces input-specific long-term potentiation in subicular bursting cells

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ABSTRACT

The subiculum (Sub) as a part of the hippocampal formation is thought to play a functional role in learning and memory. In addition to its major input from CA1 pyramidal cells, the subiculum receives input from the entorhinal cortex (EC) via the temporoammonic pathway. Thus far, synaptic plasticity in the subiculum was mainly investigated at CA1–Sub synapses. According to their spiking pattern, pyramidal cells in the subiculum were classified as bursting cells and non-bursting cells. In the present study, we demonstrate that subicular bursting cells show input-specific forms of long-term potentiation (LTP). At CA1–Sub synapses, bursting cells have been shown to express a presynaptic NMDA receptor-dependent LTP that depends on the activation of a cAMP–PKA cascade (Wozny et al., Journal of Physiology 2008). In contrast, at EC–Sub synapses the induction of LTP in bursting cells shows a high induction-threshold and relies on the activation of postsynaptic NMDA receptors, postsynaptic depolarization and postsynaptic Ca^{2+} influx. Each form of LTP is input-specific and fails to induce heterosynaptic plasticity. Taken together, our data suggest that distinct, input-specific mechanisms govern high frequency-induced LTP at subicular bursting cells' synapses.

1. Introduction

The temporal lobe including the hippocampal structure plays an important role in spatial memory formation (Malenka and Bear, 2004). Signals processed by the hippocampal trisynaptic circuit are transmitted through CA1 axons to the subiculum (Sub), which serves as the final relay of the hippocampus (Amaral and Witter, 1995). It was suggested that the Sub inter-

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Abbreviations: CA1, Cornu ammonis (region 1); DG, Dentate gyrus; EC, Entorhinal cortex; EPSC, Excitatory postsynaptic current; EPSP, Excitatory postsynaptic potential; GABA, γ-Amino butyric acid; HFS, High-frequency stimulation; IPSP, Inhibitory postsynaptic potential; LFS, Low-frequency stimulation; LTD, Long-term depression; LTP, Long-term potentiation; NMDA, N-methyl D-aspartate; PPR, Paired-pulse ratio; Sub, Subiculum

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acts between the hippocampus and the cortex, and that this interaction is required for memory formation and retrieval (de la Prida et al., 2006; Deadwyler and Hampson, 2004; Gabrieli et al., 1997; Zeineh et al., 2003). Apart from the indirect input via the trisynaptic loop, axons from layers II and III of the entorhinal cortex (EC) reach the subiculum directly via the temporoammonic pathway (Tamamaki and Nojyo, 1993; Witter et al., 1989).

For the formation of long-term memory, activity-dependent modulation of synaptic strength is thought to be an essential mechanism (Martin et al., 2000; Neves et al., 2008). Synaptic plasticity can involve either a strengthening or a weakening of synaptic coupling and is referred to as long-term potentiation (LTP) and long-term depression (LTD), respectively (Malenka and Bear, 2004). Previous studies on subicular plasticity focused on CA1–Sub synapses (Anderson et al., 2000; Commins et al., 1998; Fidzinski et al., 2008; Huang and Kandel, 2005; Kokaia, 2000; Li et al., 2005). In particular, CA1–Sub synapses onto bursting cells have been shown to express a presynaptic NMDA receptor-dependent LTP that depends on the activation of a cAMP–PKA cascade (Wozny et al., 2008a, 2008b). In a recent work we have also shown that EC–Sub synapses express low-frequency-induced LTD that is associated with heterosynaptic disinhibition of synaptic transmission at CA1–Sub synapses (Fidzinski et al., 2011). Here, we demonstrate that LTP at EC–Sub synapses is input-specific, has a high induction threshold and depends on the activation of postsynaptic NMDA receptors, suggesting that distinct, input-specific mechanisms govern high-frequency stimulation (HFS)-induced LTP at subicular bursting cells' synapses.

2. Results

Subicular pyramidal cells have been classified as bursting and non-bursting cells (Behr et al., 1996; Greene and Mason, 1996; Staff et al., 2000; Stewart and Wong, 1993; Taube, 1993). Bursting cells in the subiculum represent a specific population of pyramidal cells that can be distinguished from non-bursting cells not only by their intrinsic spiking, but also by other unique properties such as presynaptic LTP expression (Wozny et al., 2008a), bidirectional synaptic plasticity (Fidzinski et al., 2008) and a specific distribution of voltage-gated channels (Menendez de la Prida et al., 2003; Staff et al., 2000). Therefore, only bursting cells were included in the present study (Fig. 1B). Bursting cells had a mean resting membrane potential of −65.6±1.1 mV and a mean input resistance of 30.5±2.7 MΩ (n=33). Upon afferent stimulation of the EC–Sub input, subicular bursting cells responded with either monosynaptic EPSPs, or EPSPs followed by inhibitory postsynaptic potentials (IPSPs). Tetanic stimulation (4×100 Hz) that was previously shown to reliably induce LTP at CA1–Sub synapses (Wozny et al., 2008a) induced a post-tetanic potentiation at EC–Sub synapses (161.1±19.8% of baseline, n=7, $p<0.05$; Fig. 1C). This short-term plasticity did not influence synaptic transmission at CA1–Sub synapses (100.9±8.9% of baseline, n=7, p=0.9; Fig. 1D). The post-tetanic potentiation decreased back to baseline values 25 min after the stimulation paradigm (100.1±9.2% of baseline, n=7, p=0.4). In contrast, the same stimulation paradigm applied at CA1–Sub synapses induced a robust, input-specific LTP (192.3±28.9% of baseline, n=7, $p<0.05$; Fig. 1E/F).

Since the HFS protocol applied to EC–Sub synapses under control conditions failed to induce LTP, HFS was applied to EC–Sub synapses after ionotropic GABAergic transmission had been blocked by bicuculline, a procedure that is known to facilitate LTP induction in the hippocampus (Wigström and Gustafsson, 1983). Indeed, in the presence of the GABA-A receptor antagonist bicuculline, HFS at EC–Sub synapses induced a modest LTP (170.5±27.1% of baseline, n=7, $p<0.05$; Fig. 1G). EC–Sub LTP was not associated with changes in synaptic transmission at the CA1–Sub pathway (97.1.±12.8% of baseline, n=7, p=0.9; Fig. 1H). Bicuculline also facilitated induction of LTP at CA1–Sub synapses (288.0.±53.7% of baseline, n=7, $p<0.05$; Fig. 1I). The facilitated CA1–Sub LTP was stronger than EC–Sub LTP ($p<0.05$) and likewise did not elicit any discernible heterosynaptic effects on non-stimulated EC–Sub synapses (94.3±3.9% of baseline, n=7, p=0.3; Fig. 1J).

LTP induction in many brain regions depends on the summation of excitatory responses during repetitive stimulation and a sufficient depolarization of the postsynaptic membrane. We therefore analyzed summation of EPSPs during high-frequency stimuli. At EC–Sub synapses, EPSPs increased roughly twofold when compared to the first EPSP and maximum summation was reached after the third stimulus within a train (Fig. 2A). When bicuculline was present in the bath solution, summation increased to threefold, correlating with the facilitated induction of EC–Sub LTP under these conditions (Fig. 2A). At CA1–Sub synapses, summation of EPSPs was substantially stronger and longer lasting as compared to EC–Sub synapses (Fig. 2B).

The failure to induce LTP at EC–Sub synapses in the presence of inhibitory transmission, the modest LTP in the presence of GABAergic blockade and the weak synaptic facilitation during HFS suggested a higher induction threshold for EC–Sub LTP when compared to CA1–Sub synapses. We therefore tested for LTP induction at both inputs using a weaker tetanization protocol consisting of 25 pulses at a frequency of 50 Hz (25/50). Similar paradigms were shown to be sufficient for LTP induction in the dentate gyrus and in the CA1 region (for a review, see Bliss and Collingridge, 1993). As expected, the 25/50 paradigm completely failed to induce LTP when applied to EC–Sub synapses (109.9±16.8% of baseline, n=9, p=0.5; Fig. 2C). At CA1–Sub synapses, however, a robust LTP was induced (177.2±16.3% of baseline, n=11, $p<0.001$; Fig. 2C). This finding correlates with differences in the summation of EPSPs during 50 Hz stimulation, which, as shown for the 100 Hz protocol, was more pronounced at CA1–Sub synapses (Fig. 2D). A summary of changes in synaptic strength is given in Fig. 2E.

Paired-pulse analysis revealed that the LTP at CA1–Sub synapses was associated with a decrease of the PPR (1.36±0.15 at baseline vs. 1.03±0.11 after HFS, n=7, $p<0.05$; Fig. 3A), supporting a presynaptic expression mechanism as previously shown (Wozny et al., 2008a, 2008b). In contrast, no change of the PPR was observed upon induction of EC–Sub LTP, providing no evidence for a presynaptic expression (1.07±0.14 at baseline vs. 1.05±0.15 after HFS, n=7, p=0.8; Fig. 3A).

At various synapses in the central nervous system, induction of LTP depends on postsynaptic depolarization, subsequent