Brain Research 1649 (2016) 44–52

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/brainres

Research report

The effect of coactivation of muscarinic and nicotinic acetylcholine receptors on LTD in the hippocampal CA1 network

Eriko Sugisaki [a,b,*], Yasuhiro Fukushima [b,c], Satoshi Fujii [d], Yoshihiko Yamazaki [d], Takeshi Aihara [a,b]

[a] College of Engineering, Tamagawa University, 6-1-1 Tamagawagakuen, Machida, Tokyo 194-8610, Japan
[b] Brain Science Institute, Tamagawa University School of Medicine, 6-1-1 Tamagawagakuen, Machida, Tokyo 194-8610, Japan
[c] Kawasaki University of Medical Welfare, 288 Matsushima, Kurashiki, Okayama 701-0193, Japan
[d] Department of Physiology, Yamagata University of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan

ARTICLE INFO

Article history:
Received 26 February 2016
Received in revised form
14 August 2016
Accepted 18 August 2016
Available online 18 August 2016

Keywords:
Acetylcholine
Cholinergic
Interneuron
Muscarinic acetylcholine receptor
Nicotinic acetylcholine receptor
STDP

ABSTRACT

The neuromodulator acetylcholine (ACh) is considered to have a crucial effect on sensory inputs in the process of learning and memory, and ACh activates muscarinic (mAChR) and nicotinic (nAChR) acetylcholine receptors. Meanwhile in a hippocampal CA1 network including inhibitory connections, long-term potentiation (LTP) or long-term depression (LTD) is induced by the application of positive timing of the spike timing-dependent plasticity (STDP) protocol, while LTD is induced by negative timing protocol. In the previous study, the influence of ACh on LTD induced by the negative timing protocol application in the interneuron-blocked CA1 network was reported. However, the responsibility of mAChR and nAChR on pyramidal neuron and interneuron on STDP induction is still unclear. In order to clarify the role of AChRs in LTD, positive or negative timing protocol was applied in the interneuron-activated CA1 network in the presence of eserine. Consequently, the LTD induced by the positive timing protocol was switched to LTP, and the LTD by negative timing protocol was shifted toward potentiation when ACh was effective. The STDP facilitation was more effectively brought by mAChR activation on pyramidal neuron than nAChR, while mAChR on interneuron had a potential to down regulate the facilitation. These findings suggest that the direction (LTD/LTP) of STDP is determined by the activation of mAChR not only on pyramidal neuron but also on interneuron, and the magnitude of STDP is sensitively fine-tuned by nAChR. Therefore, the modulation of synaptic plasticity induced by the coactivation of mAChR and nAChR might be an important stage in integrating ACh and sensory inputs in the hippocampal CA1 network.

1. Introduction

Acetylcholine (ACh) is considered to be a versatile modulator of various brain activities, and the cholinergic system is deeply involved in learning and memory (Blokland, 1995; Hasselmo, 1999; Drever et al., 2011). Hippocampal-dependent learning and memory contributes to an increase in hippocampal extracellular ACh level (Yamamuro et al., 1995; Fadda et al., 1996, Fadda et al., 2000; Nail-Boucherie et al., 2000; Stefani and Gold, 2001), with ACh seeming to be more involved in attentional processes (Blokland, 1995).

Cholinergic neurons are mainly distributed throughout the medial septum and diagonal band of Broca (MS/DBB), and project to the CA1 area via the fimbria (Nicoll, 1985; Mesulam, 1990; Butcher et al., 1993; Cobb and Davies, 2005). The neurons of the MS/DBB act as a pacemaker for the hippocampal theta rhythm (Petsche et al., 1962; Stewart and Fox, 1990), and MS/DBB stimulation can generate slow-wave oscillations in the hippocampus (Stumpf, 1965; Monmaur and Breton, 1991; Monmaur et al., 1993; Lawson and Bland, 1993). A long-lasting excitatory postsynaptic potential (EPSP), called “slow EPSP” and caused by repetitive stimulation of cholinergic axons, can be observed in pyramidal neurons (Cole and Nicoll, 1984; Widmer et al., 2006).

Various stimulations for inducing synaptic plasticity have been studied. One such method is the spike timing-dependent plasticity (STDP) protocol. The STDP protocol is characterized by the temporal coincidence of an EPSP elicited by stimulation of a presynaptic neuron and a back-propagating action potential (BPAP) from a postsynaptic neuron firing (Magee and Johnston, 1997;

* Corresponding author at: College of Engineering, Tamagawa University, 6-1-1 Tamagawagakuen, Machida, Tokyo 194-8610, Japan.
E-mail addresses: e-sugisaki@eng.tamagawa.ac.jp (E. Sugisaki), fukushima@mw.kawasaki-m.ac.jp (Y. Fukushima), sfujii@med.id.yamagata-u.ac.jp (S. Fujii), yyamazak@med.id.yamagata-u.ac.jp (Y. Yamazaki), aihara@eng.tamagawa.ac.jp (T. Aihara).

http://dx.doi.org/10.1016/j.brainres.2016.08.024
0006-8993/

Markram et al., 1997; Bi and Poo, 1998). Presynaptic firing that precedes a postsynaptic BPAP (positive timing) induces long-term potentiation (LTP), whereas a reversal of the order (negative timing) induces long-term depression (LTD) without inhibitory connections. While, there is an LTD window in positive timing if interneurons were existed in hippocampal slices (Nishiyama et al., 2000; Tsukada et al., 2005). LTD induction by the positive timing protocol may be due to an interneuron activity and an after-hyperpolarization followed by a BPAP, whereas interneurons may largely be responsible for LTD in the negative timing protocol (Nishiyama et al., 2010). Meanwhile, interneurons barely influence LTP.

The neuromodulator ACh activates both muscarinic acetylcholine receptors (mAChRs) and nicotinic acetylcholine receptors (nAChRs). These receptors belong to metabotropic and ionotropic classes, respectively, and are widely distributed on pyramidal neurons and interneurons in the CA1 region (Levey et al., 1995; Ji and Dani, 2000; Sudweeks and Yakel, 2000; Teles-Grilo Ruivo and Mellor, 2013). The effect of individual AChR activation on synaptic plasticity in CA1 is widely reported. In a previous study (Sugisaki et al., 2011), STDP recorded on pyramidal neurons was facilitated when pyramidal neuron mAChRs were activated by ACh. Shinoe et al. (2005) revealed that LTP increase was due to an activation of postsynaptic M1 mAChRs, furthermore, M2 also participated in LTP enhancement (Shimoshige et al., 1997). If nAChR on pyramidal neuron or on presynapse was activated, nicotinic synaptic enhancement was observed (Radcliffe and Dani, 1998), and the magnitude of LTP was facilitated (Ji et al., 2001; Wang et al., 2006). Meanwhile, interneuron activities are enhanced by the activation of their own AChRs resulting in the downregulation of the pyramidal neuron activities. When α7nAChRs was activated, α7-mediated nicotinic EPSCs were elicited (Frazier et al., 1998), and the amplitude of inhibitory postsynaptic currents (IPSCs) observed on pyramidal neurons was enhanced unless otherwise desensitized (Yamazaki et al., 2005). Also, activation of nAChRs on the presynaptic terminals increased the amplitude of IPSCs (Radcliffe et al., 1999). Therefore, nicotinic activity on interneurons inhibited nearby pyramidal neuron activities (Ji et al., 2001). As for mAChRs, Zheng et al. (2011) showed that M1 mAChR activation increased a glutamate-induced postsynaptic potential. On the other hand, the activation of M2 receptors at presynaptic terminals suppress GABA release directly and M1/M3 suppress GABA release through endocannabinoid (Fukudome et al., 2004). According to these reports, the entire hippocampal CA1 network must be regulated by the synergistic action produced by the AChRs. However, how ACh, through mAChR and nAChR activation, influences the STDP learning rule in interneuron-existing network in the CA1 remains unclear. Moreover, the dependence of AChR-type specificity on STDP induction is unclear.

In the present study, to evaluate the combined influence of mAChRs and nAChRs on pyramidal neurons and interneurons in synaptic plasticity in the interneuron-activated rat hippocampal slices, which is more physiological condition than that of the previous study, eserine, a cholinesterase inhibitor, was applied to induce an ACh-treated condition. In addition, positive or negative timing of the STDP protocol was applied to induce LTD. Consequently, the combined effect of mAChR and nAChR activation on STDP was shown. Our present findings in hippocampal CA1 network indicate that the synergistic effect of AChR activations may effectively fine-tune our memory system in the presence of ACh, which is known to be related to attentional processes.

2. Results

2.1. The influence of AChR activation on STDP

First, to investigate the influence of ACh on the induction of LTD, the positive timing STDP protocol, 80 pairing stimulus of EPSP preceding a postsynaptic action potential at 5 Hz ($\Delta t = +22$ ms: Fig. 1B), was applied to the Schaffer collaterals in an interneuron-activated CA1 network in the absence or presence of different concentrations of the cholinesterase inhibitor eserine. Changes in the EPSP slope were measured before and after the application of the STDP-inducing stimulus as the magnitude of the STDP. If the post EPSP slopes were larger than pre EPSP slopes, it is defined as LTP, otherwise LTD. When an STDP-inducing stimulus was applied, LTD was induced in the absence of eserine ($70.1 \pm 7.1\%$, $n=5$, $p<0.05$; control condition; Fig. 2) as previously reported (Nishiyama et al., 2000; Tsukada et al., 2005). In the presence of 2 μM or 10 μM eserine, the LTD observed in the control condition was abolished and LTP was induced (2 μM: $111.9 \pm 2.1\%$, $n=5$, $p<0.01$; $p<0.01$ vs. control; 10 μM: $120.5 \pm 4.8\%$, $n=6$, $p<0.01$; $p<0.01$ vs. control; not significant vs. 2 μM eserine). Next, to determine whether this shift to LTP induced by the application of eserine contains an influence of interneuron activities through $GABA_AR$ activation, 25 μM picrotoxin, a $GABA_AR$ antagonist, was added. The magnitude of LTP induced in the presence of 2 μM eserine alone was significantly enhanced by the additional application of picrotoxin ($179.3 \pm 9.1\%$, $n=5$, $p<0.01$; $p<0.01$ vs. control; $p<0.01$ vs. 2 μM eserine; $p<0.01$ vs. 10 μM eserine; Fig. 2B). These results of the different magnitude of STDPs indicated that the interneuron activities also participated in cholinergically treated STDP induction.

Meanwhile, when the opposite timing protocol, 80 pairing stimulus of EPSP following an action potential at 5 Hz named negative timing protocol ($\Delta t = -15$ ms: Fig. 1B), was applied to the Schaffer collaterals, the magnitude of LTD observed in the control condition ($56.8 \pm 7.9\%$, $n=5$, $p<0.01$; Fig. 3) was reduced in the presence of 2 μM eserine ($78.7 \pm 3.6\%$, $n=5$, $p<0.05$; $p<0.05$ vs. control) and abolished in the presence of 10 μM eserine ($110.7 \pm 4.3\%$, $n=5$, $p=0.068$; $p<0.01$ vs. control; $p<0.01$ vs. 2 μM serine). These results indicated that the direction of STDP appeared to shift toward potentiation with eserine application.

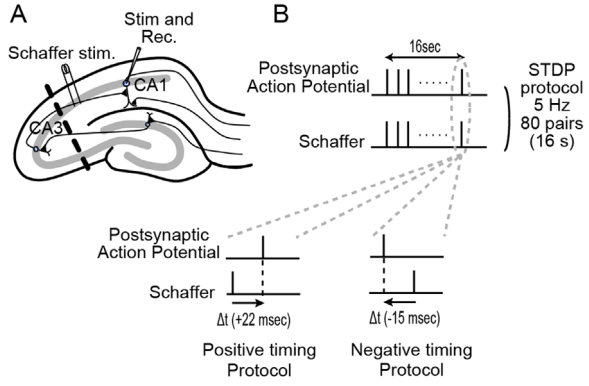

Fig. 1. Experimental procedure and stimulation pattern. **A.** Schematic drawing of a rat hippocampal slice. A stimulating electrode was placed at the Schaffer collateral. The whole-cell patch-clamp technique was used for current injection and recording of a CA1 pyramidal neuron. The dashed line indicates where the CA3 region was removed. **B.** The STDP protocol consists of postsynaptic action potentials and Schaffer stimulations applied at 5 Hz for 16 s. The two STDP-inducing protocols used in the study are shown: the positive timing protocol (bottom left), in which stimulation of the Schaffer collateral was applied prior to the postsynaptic action potential at $\Delta t = +22$ ms; and the negative timing protocol (bottom right), in which stimulation of the Schaffer collateral was applied after the postsynaptic action potential at $\Delta t = -15$ ms.