Brain Research 1643 (2016) 27–34

Contents lists available at ScienceDirect

Brain Research

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

Research Report

Interaction between paired-pulse facilitation and long-term potentiation during the stimulation of the cannabinoid and vanilloid systems in the dentate gyrus

Lida Tahmasebi, Alireza Komaki*, Ruhollah Karamian, Siamak Shahidi, Abdolrahman Sarihi, Hamidreza Komaki

Neurophysiology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

ARTICLE INFO

Article history:
Received 17 October 2015
Received in revised form
9 February 2016
Accepted 25 April 2016
Available online 27 April 2016

Keywords:
Paired-pulse ratio
Synaptic plasticity
Cannabinoid
Vanilloid
Long-term potentiation
Hippocampus

ABSTRACT

Synaptic plasticity includes short-term and long-term changes in synaptic strength. Short-term plasticity can be used to assess the site mediating the long-lasting forms of synaptic plasticity such as long-term potentiation (LTP). The endogenous endocannabinoid systems can modulate LTP, and similarly, the activation of the vanilloid system has been shown to mediate synaptic plasticity in the hippocampus. In this study, we examined the interaction between short-term and long-term plasticity during the stimulation of the cannabinoid and vanilloid systems in the hippocampus of rats *in vivo*. Forty male Wistar rats, divided into four groups, were treated with the following compounds: control (saline+dimethyl sulfoxide), WIN55,212-2, capsaicin, and WIN55,212-2+capsaicin. The animals were anesthetized with urethane and then recording and stimulating electrodes were positioned at the dentate gyrus(DG) and perforant pathway(PP), respectively. Population spike (PS) amplitudes were measured before and after the induction of LTP, which was induced with high-frequency stimulation (HFS). The paired-pulse ratio (PPR) was measured before and after the induction of LTP in all groups.

We showed that WIN55,212-2 reduced the PS amplitude after HFS, whereas the vanilloid agonist increased the induction of LTP compared with the control treatment. In the present study, we found that in the presence of WIN55,212-2 and capsaicin, the induction of LTP changed the PPR. Additionally, we showed that the co-administration of cannabinoid and vanilloid agonists modulate the PPR. These findings suggest the presynaptic expression of this LTP form, and therefore, this form of LTP is caused by the increase of neurotransmitter release.

1. Introduction

Changes in synaptic strength or plasticity are proposed to underlie several cognitive processes, including learning and memory (Cazakoff and Howland, 2010). Synaptic strength is dynamic, variable, and is dependent on specific input patterns and the history of cells, and this adaptability is known as synaptic plasticity (Sylantyev et al., 2005). Synaptic plasticity can be short-term (e.g., paired-pulse facilitation [PPF] and paired-pulse depression [PPD]) or long-term (e.g., long-term potentiation [LTP] and long-term depression [LTD]) (Komaki et al., 2013). Short-term plasticity (STP), lasting from milliseconds to minutes, is important, as it allows neurons to generate an appropriate output in response to the acute change in synaptic activity (Sylantyev et al., 2005). STP may help an organism to adapt to changing environments and to alter signal processing in the hippocampus to facilitate learning and memory (Kushner et al., 2005). PPF is a relatively short-term, use-dependent form of synaptic plasticity, which occurs at most chemical synapses (including the hippocampal synapses) (Andersen and Lømo, 1967; Zucker, 1989). When a synapse is activated twice in rapid succession (typically at an interval of 20–200 ms), the magnitude of the second response is typically larger due to the facilitation of transmitter release, which is caused by the residual free Ca^{2+} in the synaptic terminal after the first conditioning pulse (Katz and Miledi, 1968). Similar to PPF, PPD can be used to study synaptic transmission (Pan et al., 2004).

Despite intensive investigation, it remained unclear whether the pre- and/or postsynaptic site is responsible for LTP expression. Several techniques that are used to understand LTP expression are difficult to perform or interpret, and the evaluation of assumptions is difficult. Thus, it would be advantageous to use a simple

* Correspondence to: Departement of Physiology, School of Medicine, Hamadan University of Medical Sciences, Shahid Fahmideh Street, Hamadan 65178/518, Iran.
E-mail addresses: alirezakomaki@gmail.com, Komaki@umsha.ac.ir (A. Komaki).

http://dx.doi.org/10.1016/j.brainres.2016.04.058
0006-8993/

technique with few assumptions that can be tested to reveal the site of LTP expression. This can be achieved by using PPF to study the site of LTP expression (Schulz et al., 1994). Paired-pulse ratio (PPR), amplitude of the second response divided by that of the first response, depends on the probability of vesicular release at the synapse (Jiang et al., 2004; Komaki et al., 2013). It has been predicted that this ratio can be used to identify the site mediating the long-term forms of synaptic plasticity, including LTP and LTD (Santschi and Stanton, 2003).

Neuromodulators regulate most forms of synaptic plasticity both short- and long-term (Lovinger, 2010; Pawlak et al., 2010). The endocannabinoid system is one of the endogenous systems that modulate this kind of synaptic plasticity (Abush and Akirav, 2010). Endocannabinoids are produced throughout the brain, and their receptor, the cannabinoid receptor 1 (CB1), is highly expressed in the cortex, hippocampus, lateral septum, nucleus accumbens, amygdala, and periaqueductal gray area (Millan, 2003). Effects of cannabinoids on synaptic plasticity are still controversial. For instance, the administration of CB1 agonists inhibits LTP induction (Nowicky et al., 1987; Collins et al., 1994; Terranova et al., 1995). On the other hand, the investigations of LTP induction in the CA1 pyramidal neurons of hippocampal slices have shown that AM281 (a CB1 antagonist) impairs the induction of LTP (de Oliveira Alvares et al., 2006; Lin et al., 2011). Furthermore, CB1 agonists induce a biphasic effect, as lower doses are LTP enhancers and higher doses are LTP suppressors (Abush and Akirav, 2010).

Transient receptor potential vanilloid 1 (TRPV1) has been shown to influence synaptic plasticity in the hippocampus (Marsch et al., 2007; Gibson et al., 2008a; Chávez et al., 2010a). TRPV1 is a calcium permeable ligand-gated cation channel, which is expressed in various peripheral non-neuronal tissues and in numerous regions of the central nervous system (CNS) such as the cerebellum, hippocampus, frontal cortex, the periventricular nuclei of the hypothalamus, and the motor neurons of the spinal cord (Montell et al., 2002). The TRPV1 channel can be activated exogenously by various ligand-like agents including capsaicin, the compound responsible for the pungency of red chili peppers (Huang et al., 2002; Montell et al., 2002).

Functions of the cannabinoid and vanilloid systems are connected with each other in the nervous system (Hermann et al., 2003; Sagar et al., 2004). Immunohistochemical studies suggest a similar distribution of TRPV1 and CB1, and these proteins extensively co-localize in areas such as the hippocampus, basal ganglia, hypothalamus, and thalamus (Cristino et al., 2006). Properties of both CB1 and TRPV1 can be modified by a variety of factors, including desensitization/internalization, heterodimerization, and phosphorylation (Varga et al., 2006; Hudson et al., 2010). Although CB1 and TRPV1 are co-expressed in several brain regions, they may have opposite roles in the regulation of neuronal activity (Di Marzo, 2010). Anatomical, electrophysiological, and neurochemical evidences support the role of the endocannabinoid/endovanilloid systems in cognition (Pan et al., 2011). Endocannabinoids, including 2-arachidonoylglycerol and anandamide, bind not only to CB1, but potentially, also to TRPV1 (Li and Burrell, 2011; Pan et al., 2011), and TRPV1 has been shown to mediate endocannabinoid-dependent plasticity in the mammalian brain (Gibson et al., 2008a; Maione et al., 2009; Chávez et al., 2010a; Grueter et al., 2010; Li and Burrell, 2011). The aim of the present study was to investigate whether LTP induction acutely induced by CB1 and TRPV1 agonists occurs at the presynaptic or postsynaptic sites, or at both. To answer this question, we analyzed the PPR of two responses evoked by two successive stimuli at given intervals, because any changes at the presynaptic sites are expected to alter the PPR (Jiang et al., 2004; Komaki et al., 2013).

2. Results

2.1. Effect of HFS on the amplitude of PS

We found that Pb exposure in the rat produces a marked decrease in LTP induction in synapses of the DG in vivo.

We examined the effect of HFS on the amplitude of PS in the DG area of the hippocampus in vivo. The evoked field potential in the DG has two components: the PS and the field excitatory postsynaptic potential (fEPSP) (Fig. 1A). We used electrophysiological recordings to measure changes in the PS amplitude. The measurements revealed that HFS directly applied to the PP-DG synapses can increase synaptic transmission by inducing the LTP of PS amplitude. As shown in Fig. 1B, the post-HFS amplitude of PS was $256.5 \pm 12.2\%$ of the pre-HFS baseline in the control group ($n=10$).

2.2. Effect of paired-pulse stimulation on PPR

Fig. 2 shows the hippocampal field potentials evoked by paired-pulse stimulation with 20 (Fig. 2**a**), 30 (Fig. 2**b**) and 40 (Fig. 2**c**) ms intervals before HFS. Paired-pulse stimulation of the PP (20–40 ms ISIs) facilitated the field potential. PPF was maximal between 20 and 30 ms, and it declined as the ISI was increased or decreased.

2.3. Effects of CB1 and TRPV1 agonists on the amplitude of PS

As both the cannabinoid and vanilloid systems regulate synaptic plasticity, and the cannabinoid and vanilloid receptors are co-expressed in numerous areas of the CNS, we investigated the effects of cannabinoid and vanilloid agonists on LTP. First, we examined the effects of the CB1 agonist WIN55,212-2 on the

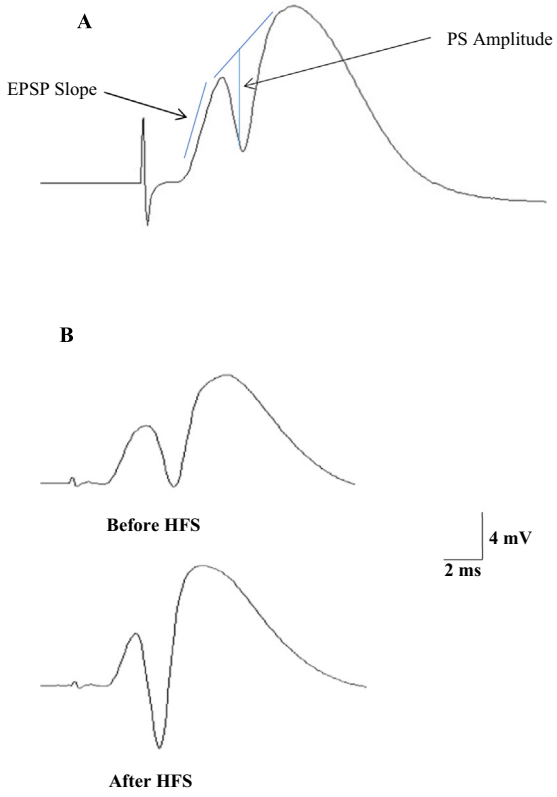

Fig. 1. Population spike (PS) amplitude and excitatory postsynaptic potential (EPSP) slope of representative field potential traces recorded in the perforant pathway (PP)-dentate gyrus (DG) synapses of the control group. Arrows indicate population spikes and the slope of EPSP (A). Representative traces of evoked field potentials in the DG recorded before and after high frequency stimulation in the control group (B).