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Interactive effects of AM251 and baclofen on synaptic plasticity in the rat dentate gyrus

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ABSTRACT

Long-term potentiation (LTP), a form of synaptic plasticity, is considered to be a critical cellular mechanism that underlies learning and memory. Cannabinoid CB_1 and metabotropic $GABA_B$ receptors display similar pharmacological effects and co-localize in certain brain regions. In this study, we examined the effects of co-administration of the CB_1 and $GABA_B$ antagonists AM251 and baclofen, respectively, on LTP induction in the rat dentate gyrus (DG).

Male Wistar rats were anesthetized with urethane. A stimulating electrode was placed in the lateral perforant path (PP), and a bipolar recording electrode was inserted into the DG until maximal field excitatory postsynaptic potentials (fEPSPs) were observed. LTP was induced in the hippocampal area by high-frequency stimulation (HFS) of the PP. fEPSPs and population spikes (PS) were recorded at 5, 30, and 60 min after HFS in order to measure changes in the synaptic responses of DG neurons.

Our results showed that HFS coupled with administration of AM251 and baclofen increased both PS amplitude and fEPSP slope. Furthermore, co-administration of AM251 and baclofen elicited greater increases in PS amplitude and fEPSP slope.

The results of the present study suggest that CB_1 receptor activation in the hippocampus mainly modifies synapses onto GABAergic interneurons located in the DG. Our results further suggest that, when AM251 and baclofen are administered simultaneously, AM251 can alter GABA release and thereby augment LTP through $GABA_B$ receptors. These results suggest that functional crosstalk between cannabinoid and GABA receptors regulates hippocampal synaptic plasticity.

1. Introduction

The hippocampus has long been considered important for learning and memory storage (Bermúdez-Rattoni, 2007; Shew et al., 2000; Bliss and Lømo, 1973; Lynch et al., 1979). It is generally believed that most information is stored at synapses in the form of modification in synaptic efficiency. In particular, two forms of synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD), have been broadly considered in the pursuit of understanding the molecular and cellular basis of learning and memory (Bliss and Collingridge, 1993; Peineau et al., 2007; Komaki and Esteky, 2005). In the hippocampal formation, LTP can be induced by repetitive activation of afferent pathways (Mott et al., 1990; Douglas and Goddard, 1975). LTP can be modulated by several neurotransmitter/neuromodulator systems (Almaguer-Melian et al., 2005). In particular, previous studies clearly demonstrate that the endocannabinoid (eCB) system is critically involved in the physiological mechanisms underlying learning and memory (Varvel and Lichtman, 2005). For example, retrograde eCB signaling modulates LTP induction, as well as glutamatergic and GABAergic transmission (Carlson et al., 2002; Chevaleyre and Castillo, 2003; Isokawa and Alger, 2005).

The eCB system has been implicated in several physiological processes, including pain modulation, appetite regulation, and cognition (Cravatt and Lichtman, 2004; Di Marzo and Matias, 2005; Jacob et al., 2012). Cannabinoids activate two types of receptors, CB_1 and CB_2, with CB_1 receptors mediating the majority of cannabinoid effects in the central nervous system (CNS; Irving et al., 2002). Cannabinoid receptors are highly expressed in the hippocampus. CB_1 receptor stimulation affects the release of a variety of neurotransmitters in the CNS (Schlicker and Kathmann, 2001), including glutamate (Irving et al., 2002; Barzegar et al., 2015) and GABA (Irving et al., 2002; Nazari et al., 2016). CB_1 receptors also participate in multiple synaptic plasticity mechanisms

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in several brain areas (Földy et al., 2006; Wilson and Nicoll, 2001; Tahmasebi et al., 2016). The eCBs were first reported to be related to short-term plasticity (Wilson and Nicoll, 2001); subsequent studies demonstrated that the eCB system is also involved in long-term synaptic plasticity. Nevertheless, the effects of cannabinoids on synaptic plasticity are controversial (Terranova et al., 1995; de Oliveira Alvares et al., 2006; Lin et al., 2011; Abush and Akirav, 2010).

CNS network functions depend on the balance between excitation and inhibition. GABA is the major inhibitory transmitter in the CNS (Shew et al., 2000). GABA exerts inhibitory effects on neurotransmission and synaptic plasticity through two types of receptors. $GABA_A$ receptors and the more recently discovered $GABA_B$ receptors are distributed throughout the brain (Brucato et al., 1995; Bowery et al., 1987). $GABA_B$ receptors, which are coupled to G proteins, are localized to both pre- and postsynaptic membranes (Safiulina and Cherubini, 2009; Bettler et al., 2004). Activation of presynaptic $GABA_B$ receptors inhibits neurotransmitter release (Poncer et al., 1997), while postsynaptic $GABA_B$ receptor activation causes the opening of potassium channels and thereby induces neuronal hyperpolarization (Safiulina and Cherubini, 2009; Lüscher et al., 1997). Previous studies showing $GABA_B$ receptor-mediated modulation of LTP induction in the dentate gyrus (DG) in vitro suggest a physiological role of $GABA_B$ receptors in learning and memory (Mott et al., 1990; Brucato et al., 1995; Mott and Lewis, 1991). Additionally, endogenous GABA has been shown to regulate LTP induction via activation of $GABA_B$ receptors (Mott et al., 1990).

Although the precise mode of action of cannabimimetic agents on hippocampal networks remains controversial, several studies have suggested that modulation of GABAergic transmission is an important component of their effects (Katona et al., 1999; Paton et al., 1998). Neurochemical (Katona et al., 1999) and electrophysiological studies (Hájos et al., 2000; Hoffman and Lupica, 2000) have revealed that cannabinoids regulate GABA release from inhibitory neurons in the hippocampus (Irving et al., 2002). Electrophysiological and immunocytochemical studies have demonstrated CB_1 receptor expression in the axon terminals of hippocampal GABAergic neurons (Hájos et al., 2000; Ronaghi et al., 2015; Andó et al., 2012) as well as abundant cell-surface CB_1 receptor immunolabeling in the axons of these neurons (Irving et al., 2002, 2000). Activation of CB_1 receptors in GABAergic neurons leads to a decrease in GABA release (Katona and Freund, 2008; Howlett et al., 2002), which results in depolarization-induced suppression of inhibition (Monory et al., 2006) and long-term depression of inhibitory GABAergic synaptic transmission (Azad et al., 2004; Albayram et al., 2011). However, several other lines of evidence have suggested that cannabinoids may also facilitate GABAergic transmission by blocking its reuptake (Varvel and Lichtman, 2005).

Although the eCB and GABAergic systems are known to play important roles in learning, memory, and synaptic plasticity, the interactive effects of these systems on LTP induction in the hippocampal DG in vivo are not clear (Fig. 1). Hence, it is crucial to understand the precise cellular functions of CB_1 and $GABA_B$ receptors in the hippocampus, as well as the role of the eCB system in the modulation of hippocampal GABAergic networks, In this study, we test the hypothesis that the effects of the eCB system on learning, memory and synaptic plasticity result, in part, from its effects on GABAergic synaptic transmission.

2. Results

2.1. Measurement of evoked potentials

We obtained field potential recordings from the granular cell layer of the DG following HFS of the perforant path (PP). Sample traces from each group are illustrated in Fig. 2. Population spike (PS) amplitude was measured from the peak of the first positive deflection of the evoked potential to the peak of the following negative deflection. Field excitatory postsynaptic potential (fEPSP) slope was measured as the slope of the line connecting the start of the first positive deflection of the evoked potential with the peak of the second positive deflection. fEPSPs and PS amplitude were calculated using eTrace data analysis software (ScienceBeam, Tehran, Iran).

2.2. Effects of HFS on PS amplitude and fEPSP slope

Investigation of HFS-induced LTP in the hippocampal DG in vivo revealed a strong enhancement of PS amplitude, which resulted in significant LTP at PP-DG synapses in the control (DMSO + Saline) group ($168.21 \pm 10.85\%$ of pre-HFS baseline; $n = 10$). Further, the mean fEPSP slope following HFS was $119.61 \pm 5.19\%$ of baseline in the control group.

2.3. Effects of CB_1 and $GABA_B$ receptor agonists on fEPSP slope and PS amplitude

HFS applied to the PP-DG area induced LTP in animals treated with AM251, as shown by an increase in fEPSP slope ($138.4 \pm 6.13\%$ of pre-HFS baseline; $n = 10$; Fig. 3). The mean PS amplitude was $231.79 \pm 22.29\%$ of baseline in the AM251 group ($n = 10$; Fig. 4). AM251 administration resulted in significantly greater fEPSP slopes in comparison with the control group ($F[3,32] = 23.85$, $P < 0.001$). PS amplitudes were also significantly higher in AM251-treated animals compared to vehicle-treated controls ($F[3,32] = 15.35$, $P < 0.01$). Baclofen treatment also resulted in significantly higher fEPSP slopes ($184.54 \pm 17\%$; $F[3,32] = 28.49$; $P < 0.001$; $n = 8$; Fig. 3) and PS amplitudes ($342.37 \pm 45.62\%$; $F[3,32] = 19.71$; $P < 0.01$; Fig. 4) in comparison with the control group.

2.4. Effects of CB_1 and $GABA_B$ agonist co-administration on fEPSP slope and PS amplitude

To evaluate the interactive effects of the eCB and GABAergic systems on synaptic plasticity, we investigated the effects of AM251 and baclofen co-administration on LTP. We found that co-administration of AM251 and baclofen resulted in larger fEPSP slopes ($191.96 \pm 29.4\%$; $n = 8$; Fig. 3) and PS amplitudes ($413.28 \pm 67.36\%$; $n = 8$; Fig. 4) than administration of either AM251 (fEPSP slope: $F[3,32] = 23.74$, $P < 0.01$; and PS amplitude: $F[3,32] = 42.56$, $P < 0.001$) or baclofen alone (fEPSP slope: $F[3,32] = 3.92$, $P > 0.05$; and PS amplitude: $F[3,32] = 3.26$, $P > 0.05$). LTP induction in the AM251 + baclofen group was also significantly increased compared to the control group, as shown by increased fEPSP slope ($F[3,32] = 37.64$, $P < 0.001$) and PS amplitude ($F[3,32] = 46.83$, $P < 0.001$).

3. Discussion

In the present study, we investigated the in vivo effects of intrahippocampal infusion of $GABA_B$ and CB_1 receptor agonists on HFS-induced LTP in the rat DG. Activity-dependent synaptic potentiation is expressed as a long-lasting increase in the synaptic component of the evoked response recorded from a large cell