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Involvement of orexin-1 and orexin-2 receptors within the dentate gyrus of the hippocampus in the acquisition, expression and extinction of lateral hypothalamic-induced conditioned place preference in the rats

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ABSTRACT

Orexinergic projections originating from the lateral hypothalamus (LH) have an important role in the acquisition of the LH-stimulation conditioned place preference (CPP). Among the brain areas associated with reward processing, LH orexinergic neurons send projections to the dentate gyrus (DG) region of the hippocampus, and it has been shown that orexin receptors are expressed in the DG. In this study, we investigated the role of intra-DG orexin-1 (OX1) and orexin-2 (OX2) receptors on acquisition, expression and extinction of CPP induced by stimulation of the LH. Rats were unilaterally implanted by two separate cannulae into the LH and DG. The CPP paradigm was done; conditioning scores and locomotor activities were recorded by Ethovision software. The results showed that intra-DG administration of SB334867, a selective OX1r antagonist, and TCS OX2 29, a selective OX2r antagonist, (0.5, 5, 12.5 and 50 nM/0.5 μl DMSO) before carbachol microinjection (250 nM; effective dose) during the 3-days conditioning phase, dose-dependently inhibited the development of LH stimulation-induced CPP in the rats. However, this reduction in OX1r antagonist treated groups was more than that in OX2r antagonist treated animals. In addition, these antagonists decreased the expression of LH-induced CPP. Moreover, OX1r but not OX2r antagonist could shorten the extinction duration of place preference. We conclude that the orexinergic projections from the LH to DG are involved in the development, expression and extinction of CPP induced by LH stimulation.

1. Introduction

Orexin neuropeptides (also termed hypocretins) consist of two distinct peptides called orexin A and orexin B (De Lecea et al., 1998; Sakurai et al., 1998). Two groups of G-protein coupled receptors mediated the orexin actions are named orexin-1 (OX1) and orexin-2 (OX2) receptors. These orexin receptors have different affinity to binding orexins, the OX1 is

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a Gq-coupled receptor that is solely selective to orexin A and the OX2 is a Gq and Gi/o-coupled receptor which is non-selective. Orexin A and B are proteolytically produced from prepro-orexin precursor protein that exclusively expresses in posterior and perifornal regions of the lateral hypothalamus (LH) and the dorsomedial hypothalamic neurons in the rat brain (De Lecea et al., 1998; Sakurai et al., 1998). The LH orexinergic neurons extensively send projections to different areas of the brain including the locus coeruleus, ventral tegmental area (VTA), nucleus accumbens, hippocampus (HIP) and midline thalamic nuclei (Mondal et al., 1999; Sadeghi et al., 2013; Yang et al., 2013). This diffuse orexinergic system regulates multiple complex physiological functions such as feeding, arousal, sleep, stress, pain, addiction and memory processing. Orexinergic system has most considerable attention for its abilities to mediate arousal and reward functions (Harris and Aston-Jones, 2006; Safari et al., 2009; Taslimi et al., 2012). Additionally, orexin is involved in drug-seeking following extinction (maintenance), and reinstatement induced by cues or context (Aston-Jones et al., 2010). Furthermore, it is confirmed that concurrent administration of an ineffective dose of intra-LH carbachol, as a cholinergic agonist, with an ineffective dose of systemic morphine amplified reward properties of morphine and induced conditioned place preference (CPP) (Zarepour et al., 2013).

It has been revealed that there is a correlation between reward and learning and memory processing (Borgland et al., 2006; Hyman et al., 2006; Kelley, 2004; Xu et al., 2001). The HIP has a principle role in learning and memory (Farr et al., 2000; Nestler, 2001; Yang et al., 2013), and it has been shown to be involved in drug and context-induced seeking behaviors which can form addictive memories (Black et al., 2004; Corrigall and Linseman, 1988; Ferbinteanu and McDonald, 2001). The HIP has an important role in reward-related learning task such as CPP paradigm (Haghparast et al., 2013; Rashidy-Pour et al., 2014; Riahi et al., 2013). This area has been implicated in the expression and acquisition (development) of CPP in response to morphine, cocaine, and nicotine (Liu et al., 2010; Vetulani, 2001). Local infusion of morphine into the HIP (Corrigall and Linseman, 1988) and methamphetamine into dorsal HIP induced addictive behaviors in a CPP paradigm (Ricoy and Martinez, 2009). Previous studies showed that lesion of the dentate gyrus (DG) by colchicine completely prevented the acquisition and expression of cocaine-induced CPP (Hernandez-Rabaza et al., 2008). Furthermore, it has been shown that electrical stimulation of the granule cells in the DG region disrupted memory for place preference (Collier et al., 1982).

On the other hand, the expression of both orexin receptors was seen in the HIP regions such as CA1, CA2, CA3 and DG (Lu et al., 2000; Marcus et al., 2001). The DG region has the terminals of both OX1 and OX2 receptors, these axons belong to the orexinergic projecting neurons of the LH (Wayner et al., 2004). Hippocampal orexin receptors are involved in the induction of synaptic long-term potentiation (Akbari et al., 2011), and in learning and memory (Akbari et al., 2006). Based on previous studies which showed a role for the DG in development of drug addiction and reward processing, and the existence of orexin terminals and receptors in the DG, we hypothesized that the DG orexin receptors may be involved in reward behaviors. On the other hand, we previously showed that chemical stimulation of LH induced CPP (Taslimi et al., 2011). Thus in the present study, we investigated the role of intra-DG OX1 and OX2 receptors on the acquisition and expression of LH induced place preference. Additionally, diminishing the maintenance period of rewarding properties of a drug is the primary goal in addiction treatment and drug dependence. In this regard, we also used the CPP paradigm to investigate the involvement of these receptors within the DG on the extinction of LH stimulation-induced CPP in rats.

2. Results

2.1. *Effects of OX1 receptor antagonist microinjected into the DG on the acquisition of LH stimulation-induced CPP*

In this set of the experiments, the animals received different doses of SB334867 (OX1 receptor antagonist) into the DG during 3-days conditioning phase. One-way ANOVA followed by Newman–Keuls multiple comparison test [$F(7, 45)=25.63$, $P<0.0001$; Fig. 1A] clarified that the microinjection of two higher doses of SB334867 (12.5 and 50 nM) significantly decreased conditioning scores compared to carbachol-control group, but administration of maximum dose (50 nM) of this antagonist into the neighboring regions of DG (anatomical control group) did not affect conditioning score compared to carbachol-control group. Therefore, the obtained results are related to the OX1 receptor antagonist infusion into the DG during the acquisition phase. However, administration of 0.5 and 2.5 nM doses of this antagonist did not show any significant effects on conditioning scores. Furthermore, administration of maximum dose of SB334867 into the DG alone did not have any effect on the acquisition of LH-CPP. On the other hand, one-way ANOVA followed by Newman–Keuls multiple comparison test [$F(7, 45)=0.44$, $P=0.8706$; Fig. 1B] indicated that SB334867 did not change distance traveled during the 10-min test period (post-conditioning phase) in comparison with that of the vehicle- or carbachol-control groups. Therefore, blockade of the OX1 receptors in this area on the development of place preference was not due to alteration of the locomotor activity in rats.

2.2. *Effects of OX2 receptor antagonist microinjected into the DG on the acquisition of LH stimulation-induced CPP*

To investigate the effects of TCS OX2 29 (OX2 receptor antagonist) injection into the DG on the acquisition of LH-induced CPP, the animals received intra-DG administration of TCS OX2 29 during conditioning phase (acquisition period). Statistical analysis revealed that the highest dose of TCS OX2 29 (50 nM) decreased conditioning scores compare to the carbachol-control group [$F(7, 45)=17.87$, $P<0.0001$; Fig. 2A]. The other doses of this antagonist (0.5, 2.5 and 12.5 nM) did not change the conditioning scores compared to carbachol-control group. Nonetheless, sole administration of the highest dose of TCS OX2 29 (50 nM/rat) into the DG did not alter the conditioning scores. In addition, one-way ANOVA followed by Newman–Keuls test [$F(7, 45)=0.313$, $P=0.945$; Fig. 2B] indicated that none of the groups showed significant