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ROLE OF DORSAL HIPPOCAMPAL OREXIN-1 RECEPTORS IN MEMORY RESTORATION INDUCED BY MORPHINE SENSITIZATION PHENOMENON

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Abstract—The present study was examined the blockade of CA1 orexin-1 receptors (OX_1Rs) of the dorsal hippocampus in the induction or expression phase on morphine sensitization-induced memory restoration using the Morris water maze (MWM) apparatus. Results showed that pre-training administration of morphine (5 mg/kg, s.c.) increases escape latency and traveled distance, while does not alter swimming speed. This supports the impairing effect of morphine on the spatial memory acquisition in male adult rats. Also, in the retrieval session (probe trial) this treatment decreased the time spent in the target quadrant. Moreover, morphine-induced sensitization (15 or 20 mg/kg, s.c.; once daily for 3 days and followed by 5 days no drug treatment) restored the memory acquisition/retrieval deficit which had been induced by pre-training administration of morphine (5 mg/kg, s.c.). Intra-CA1 microinjection of subthreshold doses of SB-334867 (OX_1Rs antagonist; 10, 20 and 40 nmol/rat), 5 min before morphine (20 mg/kg/day × 3 days, s.c.; induction phase for morphine sensitization) did not alter restoration of memory acquisition/retrieval produced by the morphine sensitization phenomenon. In contrast, microinjection of subthreshold doses of SB-334867 (10, 20 and 40 nmol/rat) into the CA1 region in the training session, 5 min prior to morphine (5 mg/kg, s.c.; expression phase for morphine sensitization) blocked the spatial memory acquisition/retrieval in morphine-sensitized rats. In conclusion, these findings show that morphine sensitization reverses morphine-induced amnesia. Furthermore, the blockade of CA1 OX_1Rs in the expression phase, but not in the induction phase, disrupts memory restoration induced by morphine sensitization.

Key words: morphine sensitization, OX_1 receptors, CA1 regions, morris water maze, rat.

INTRODUCTION

Orexin neuropeptides including orexin-A and orexin-B are particularly produced in the lateral hypothalamus (LH; Sakurai et al., 1998). These neuropeptides have a potential role in the regulation of a variety of physiological processes such as behavioral sensitization (Borgland et al., 2006), drug-reward (Plaza-Zabala et al., 2012), and -dependence (Sharf et al., 2010b) as well as memory processing (Jaeger et al., 2002). Orexin receptors type 1 (OX_1Rs) and orexin receptors type 2 (OX_2Rs; Scammell and Winrow, 2011) are mainly responsible for the effects of the orexinergic system. OX_1Rs couple to G-proteins and their stimulation leads to the activation of protein kinases such as protein kinase A (PKA) and protein kinase C (PKC; Xu et al., 2013). In the past two decades a number of researchers reported that orexin neuropeptides may increase the neuronal excitability (Lambe and Aghajanian, 2003) or have a neuromodalatory (van den Pol et al., 1998) effect on the neuronal targets. Although the role of the orexinergic system has not been well determined in cognitive functions, this system has several connections to a variety of regions mainly those involved in the learning and memory processes such as prefrontal cortex (PFC; Peyron et al., 1998) and hippocampus (Marcus et al., 2001). In this regard, while there are studies suggesting that intra-cerebroventricular administration of orexin-A facilitates learning in the active and passive avoidance tasks (Jaeger et al., 2002; Telegdy and Adamik, 2002), others reported that treatment of animals with the orexin agonist impairs Morris water maze (MWM) performance (Aou et al., 2003) through suppression of hippocampal long-term potentiation (LTP). Additionally, Dietrich and Jenck (2010) revealed that oral administration of a dual orexin antagonist, almorexant, had no effect on learning and memory.

Recent evidences suggest the interaction between orexinergic system and opioids. Morphine administration

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Abbreviations: ANOVA, analysis of variance; LH, lateral hypothalamus; MORs, mu-opioid receptors; MWM, Morris water maze; OX_1Rs, orexin-1 receptors; PFC, prefrontal cortex.

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activates the brain dopaminergic reward pathway which originates from ventral tegmental area (VTA) and projects to the nucleus accumbens (Nac), PFC and hippocampus (Wise, 2004). The action of morphine is mainly mediated via mu-opioid receptors (MORs; Matthes et al., 1996) which are widely expressed in the reward- (Fields, 2011) and memory-(Mansour et al., 1994) related regions as well as LH (Le Merrer et al., 2009). Focusing on the effects of morphine on cognition, there is inconsistency between studies depending on the route and dose of the drug administration. While some investigations have shown that acute administration of morphine has mainly negative effects on the learning and memory, other studies indicated that chronic morphine treatment might have different effects on the cognition. For example, Miladi Gorji et al. (2008) revealed that chronic exposure to morphine had no effect on spatial learning, but impaired spatial memory. Li et al. (2001) proposed that acute administration of morphine impairs spatial memory acquisition in the MWM task. Furthermore, it has been shown that pre-training exposure to morphine impaired spatial reference and working memory (Zhu et al., 2011). Interestingly, the involvement of the orexinergic system in the effects of morphine on learning and memory is still elusive.

Since the addictive behaviors are tightly associated with alterations in learning and memory processes (for a review see Hyman, 2005), and also the orexinergic system is partly involved in the morphine- reward (Sharf et al., 2010a), withdrawal (Zhou et al., 2006) and tolerance (Ghaemi-Jandabi et al., 2014), it is important to investigate the role of the orexinergic system in morphine-induced effects on learning. In this respect, morphine-induced sensitization has been considered as an appropriate model to the exploration of behavioral sensitization. Surveys such as the one conducted by Steketee and Kalivas (2011) and Weiss (2005) have shown the involvement of behavioral sensitization in the reinstatement of drug- use and seeking behavior followed by various periods of abstinence. Behavioral sensitization development consists of two stages, namely the induction phase and the expression phase. The induction phase is responsible for the cellular and molecular alterations in the neural system underlying behavioral sensitization. In the expression phase, the induction-produced neurobiological changes present for long periods of time mediating the subsequent behavioral responses (Kalivas and Stewart, 1991). Dopaminergic (Le Marec et al., 2011), cholinergic (Rezayof et al., 2013), glutamatergic (Xia et al., 2011) and GABAergic (Zarrindast et al., 2008) neurotransmission have been found to play a pivotal role in the neurobehavioral mechanisms associated with morphine sensitization. Emerging lines of research have demonstrated that the hippocampus mediates behavioral sensitization following morphine administration (Datson et al., 2011). Also, the hippocampus has a pivotal role in processes relevant to memory formation (Shen et al., 2012) as well as drug-reward (Meyers et al., 2003). Regarding the role of the hippocampus in spatial memory, wide expression of OX_1Rs (Hervieu et al., 2001) in the CA1 region of the dorsal hippocampus and the functional interaction between morphine and the orexinergic system in the reward pathway (Harris et al., 2007), the present study was aimed to assess the effects of the dorsal hippocampal OX1Rs blockade on the spatial memory acquisition/retrieval in morphine-sensitized rats.

EXPERIMENTAL PROCEDURES

Animals

Male Wistar rats weighing 220–260 g were obtained from the Pasteur Institute, Tehran, Iran. They were maintained four per Plexiglas cage in a colony room with constant temperature (21 ± 2 °C), humidity (40–60%) and a 12/12 light–dark cycle (lights on at 7:00 am). Animals had *ad libitum* access to food and water except during the behavioral tests. Rats were allowed to get acclimated to the lab environment for at least 1 week before the experiments begin. All experimental procedures were carried out during the light phase between 9:00 and 14:00. Efforts were made to minimize the number of animals used and their suffering. The experimental protocol in this study was approved by the Research and Ethics Committee of the School of Advanced Technologies in Medicine, Tehran University of Medical Sciences and were done in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH publications No. 80–23).

Stereotaxic surgery

Rats were anesthetized by intraperitoneal injection of a ketamine and xylazine (100 and 10 mg/kg, respectively) mixture and then were placed in a stereotaxic apparatus (Stoelting Co., Wood Dale, IL, USA). Two steel guide cannulas (22-guage) were bilaterally implanted into the CA1 region of the dorsal hippocampus (AP: −3.3 mm from bregma; ML: ±2 mm from midline; DV: −2.8 mm from the skull surface) according to Paxinos and Watson's atlas (2007). The guide cannulas were secured by jeweler's screws, and the incision was closed with rapidly polymerizing dental acrylic cement. All animals were allowed to recover for 7 days following surgery and to get clear from the anesthetic effects. During the recovery period, animals were handled daily about 5 min prior to the behavioral testing.

Drugs preparation and administration procedures

Morphine sulfate (Daroopakhsh, Tehran, Iran) was dissolved in normal saline and fresh solution was administrated subcutaneously (s.c.). The selective OX_1Rs antagonist, SB-334867 (1-(2-methylbenzoxazol-6-yl)-3-[1,5] naphthyridin-4-yl-urea hydrochloride, Tocris Bioscience, Bristol, UK) was dissolved in pure DMSO to prepare a concentration of 80 mmol/l stock solution. Then this was stored at −20 °C. Concentrations of 10, 20 and 40 nmol of drug were prepared in saline from the stock solution immediately prior to the injection. The bilaterally microinjection of SB-334867 or vehicle into the CA1 regions of the dorsal hippocampus (intra-CA1)