Influence of morphine on medial prefrontal cortex alpha2 adrenergic system in passive avoidance learning in rats

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Abstract

The prelimbic region of the medial prefrontal cortex (mPFC) is a brain area crucial for memory, attention, and decision making. It has been shown that α2-adrenoceptors (α2-ARs) play a powerful role in regulating memory and attention functions in this region. Since many studies have demonstrated the impairment effect of morphine on memory through mPFC, we aimed to investigate the possible interaction between α2-ARs of the mPFC and morphine induced amnesia in passive avoidance learning in rats. Animals were bilaterally implanted with chronic cannulas in the mPFC, trained in the step-through type passive avoidance task, and tested 24 h after training; step-through latencies were measured. Our data indicate that post-training i.p. administration of morphine dose-dependently reduced the step-through latency, showing an amnesic effect. Post-training intra-mPFC administration of yohimbine and clonidine significantly reversed the inhibitory effect of morphine on memory retrieval. Furthermore, SKF96365 (a presynaptic calcium channel blocker) reduced yohimbine and showed slight inhibition of clonidine effect. These results suggest that α2-ARs of the mPFC may play an important role in morphine-induced amnesia.

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1. Introduction

It is well recognized that the opioid system is involved in learning and memory processes (Antonelli et al., 2007; Zarrindast and Rezayof, 2004). Our previous studies have revealed that morphine can alter memory retrieval in different paradigms such as spatial learning and passive avoidance tasks (Farahmandfar et al., 2012; Khajehpour et al., 2008). Furthermore, both pre- and post-training administration of morphine may impair memory retrieval of learned task (Ardjmand et al., 2011; Zarrindast et al., 2011).

The medial portion of the prefrontal cortex (mPFC) is associated with some processes related to a number of distinct perceptual, motor, and cognitive functions such as working memory, spatial learning, attention, and emotional response (Dalley et al., 2004; Arnsten and Li, 2005; Sara, 2009). The prelimbic area of the mPFC holds significant potential as a key structure involved in neural circuits sub-serving learning and memory functions (Fritts et al., 1998). It is also well-known that norepinephrine (NE) in the prefrontal cortex plays an important regulatory role in memory (Kobori et al., 2011; Reyes-López et al., 2010; Arnsten and Li, 2005; Sara, 2009). This site of the cortex receives important noradrenergic projections from the locus coeruleus (LC) (Heidbreder and Groenewegen, 2003; Kawahara et al., 2001; Vertes, 2006), which can be involved in different learning tasks such as place conditioning learning (Vestura et al., 2008), attentional set shifting (Newman et al., 2008), reversal learning of instrumental guided behavior (van der Meulen et al., 2007), classical conditioning (Feenstra et al., 2001; Mingote et al., 2004), and the extinction of fear conditioning (Mueller et al., 2008). Both excessive and insufficient NE levels in the PFC impair working memory; thus, an optimal amount of this neurotransmitter may be needed for normal working memory function (Arnsten and Li, 2005). The cortex NE has the highest affinity for α2-ARs which are most concentrated in superficial layers in primate PFC (Goldman-Rakic, 1990). Animals and humans have shown that NE has an important beneficial influence on spatial working memory performance through its actions at α2-ARs (Franowicz and Arnsten, 2002). There are reports showing that the α2 adrenergic antagonist yohimbine impairs PFC function or blocks the beneficial actions induced.