



The effect of CA1 $\alpha 2$ adrenergic receptors on memory retention deficit induced by total sleep deprivation and the reversal of circadian rhythm in a rat model



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ABSTRACT

The $\alpha 2$ adrenergic receptors which abundantly express in the CA1 region of the hippocampus play an important role in the regulation of sleep and memory retention processes. Based on the available evidence, the aim of our study was to investigate consequences of the activation and deactivation of CA1 $\alpha 2$ adrenergic receptors (by clonidine and yohimbine, respectively) on the impairment of memory retention induced by total sleep deprivation (TSD) and the reversal of circadian rhythm (RCR) in a rat model. To this end, the water box apparatus and passive avoidance task were in turn used to induce sleep deprivation and assess memory retention. Our findings suggested that TSD (for 24 and 36, but not 12 h) and RCR (12 h/day for 3 consecutive days) impair memory function. The post-training intra-CA1 administration of yohimbine ($\alpha 2$ adrenergic receptor antagonist) on its own, at the dose of 0.1 $\mu\text{g}/\text{rat}$, decreased the step-through latency and locomotor activity in the TSD- sham treated but not undisturbed sleep rats. Unlike yohimbine, clonidine ($\alpha 2$ adrenergic receptor agonist), in all applied doses (0.001, 0.01 and 0.1 $\mu\text{g}/\text{rat}$), failed to induce such an effect. While the subthreshold dose of yohimbine (0.001 $\mu\text{g}/\text{rat}$) abrogated the impairment of memory retention induced by the 24-h TSD, it could potentiate the impairment of memory retention induced by 36-h TSD, suggesting the modulatory effect of yohimbine. Moreover, the subthreshold dose of clonidine (0.1 $\mu\text{g}/\text{rat}$) restored the memory retention deficit in TSD rats (24 and 36 h). On the other hand, the subthreshold dose of clonidine (0.1 $\mu\text{g}/\text{rat}$), but not yohimbine (0.001 $\mu\text{g}/\text{rat}$) restored the memory retention deficit in RCR rats. Such interventions however did not alter the locomotor activity. The above observations proposed that CA1 $\alpha 2$ adrenergic receptors play a potential role in memory retention deficits induced by TSD and RCR.

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1. Introduction

Cognitive functions (including but not limited to attention, memory, learning, decision making, and processing speed) are

known to be influenced by several factors, among which sleep deprivation is a well-known contributor (Cohen-Zion, Shabi, Levy, Glasner, & Wiener, 2016; Feng et al., 2016; Lo, Ong, Leong, Gooley, & Chee, 2016). Evidences have demonstrated that one and two sleepless nights may result in almost 35% and 65% decline in human cognitive functions, respectively (Buguet, Moroz, & Radomski, 2003). In general, sleep is divided into rapid eye movement (REM) and non-rapid eye movement (NREM) phases. NREM sleep itself is divided into three stages including N1, N2 and N3. Sleep deprivation on the other hand may be categorized into total

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sleep deprivation (TSD) and chronic partial sleep restriction (CPSR) (Torabi-Nami, Nasehi, & Zarrindast, 2013). Several reports have indicated that important neurotransmitters including noradrenaline play a defining role in regulating cognition following sleep deprivation (Kim et al., 2015; Uschakov et al., 2011).

The ascending noradrenergic system which originates from the locus coeruleus (LC) in brain stem projects to the prefrontal cortex and hippocampus (Mason & Fibiger, 1979; Waterhouse, Lin, Burne, & Woodward, 1983). The adrenergic system exerts its effects via two types of G protein-coupled receptors namely α and β . adrenergic receptors are divided into $\alpha 1$ and $\alpha 2$ subgroups largely expressed in the central nervous system (CNS). The $\alpha 1$ adrenergic receptors are more of post synaptic type whereas $\alpha 2$ receptors are both post- and pre synaptic (Boyajian & Leslie, 1987; Bylund et al., 1992; Dohlman, Thorner, Caron, & Lefkowitz, 1991; Jones & Palacios, 1991). Much of the available evidence support the key role of adrenergic receptors in learning and memory processes (Nasehi, Zamanparvar, Ebrahimi-Ghiri, & Zarrindast, 2016; Valizadegan, Oryan, Nasehi, & Zarrindast, 2013). However, the mechanism through which noradrenaline affects the memory function is not fully clear and seems to be at least partly related to the modulation of glutamatergic system (Hu et al., 2007).

As already indicated, inappropriate or poor sleep quality may give rise to impaired cognitive functions. Memory is considered as an important component of cognition and a key contributor to life and social interactions. Hippocampus is a brain region directly involved in memory functions. This structure plays a major role in the consolidation stage of memory formation. One of the most important parts of the hippocampal formation which involves in learning and memory is the posterior hippocampus (CA1) (Khanegheini, Nasehi, & Zarrindast, 2015; Nasehi, Tabatabaie, Khakpai, & Zarrindast, 2015). The adrenergic receptors ($\alpha 2$ -adrenoceptors) are divided into several subtypes including $\alpha 2A$, $\alpha 2B$, and $\alpha 2C$. The $\alpha 2A$ -subtype is a key $\alpha 2$ -adrenoceptor engaged in numerous effects produced by $\alpha 2$ -adrenoceptor activation (MacDonald, Kobilka, & Scheinin, 1997). Such effects include the modulation of nociception, cardiovascular function, sedation and the release of noradrenaline (Kable, Murrin, & Bylund, 2000). The involvement of this receptor subtype in memory formation has been investigated by $\alpha 2$ -adrenoceptor agonists (e.g. clonidine and guanabenz) and $\alpha 2$ -adrenoceptor antagonists including BRL-44408 and yohimbine (Galeotti, Bartolini, & Ghelardini, 2004).

An earlier investigation has postulated that $\alpha 2$ -adrenoceptors contribute to sleep propensity following sleep deprivation (Uschakov et al., 2011). Gais et al. showed that reducing the noradrenergic activity during sleep (using $\alpha 2$ -autoreceptor agonist clonidine) decreased memory performance in the human (Gais, Rasch, Dahmen, Sara, & Born, 2011). Considering the fact that sleep deprivation tends to affect our cognitive function such as memory formation (Abel, Havekes, Saletin, & Walker, 2013), the question is how to minimize or counteract such an effect in today's competitive life? To address this question, it is necessary to investigate the sleep deprivation destructive effects on various brain regions and the role of direct potentiation or blockade of different receptors in response to sleep deprivation. Based on the above, the aim of the present study was to assess the effect of CA1 $\alpha 2$ adrenergic receptors on memory retention deficit induced by TSD and the reversal of circadian rhythm (RCR).

2. Materials and methods

2.1. Animals

Subjects were Wistar rats weighing 220–250 g, obtained from the Institute for Cognitive Science Studies (ICSS). Rats were kept

in an animal house with a controlled temperature of $22 \pm 2^\circ\text{C}$ under a 12/12-h light/dark cycle. Animals were housed in groups of 4 in Plexiglas cages and had free access to water and food except for limited time of experiments and handling. Eight rats were used in each group and each animal was used once only. All behavioral tests were performed during the light phase of the light/dark cycle.

2.2. Stereotaxic surgery

Subjects were anesthetized following the intraperitoneal injection of ketamine hydrochloride (50 mg/kg) plus xylazine (5 mg/kg) and positioned in a stereotaxic apparatus (Stoelting Co, Illinois, USA). Then, the skin was incised and skull was cleaned. Later, 22-gauge guide cannulae (0.7 mm diameter) were placed (bilaterally) 1 mm above the intended site of injection according to the atlas of Paxinos and Watson (Paxinos & Watson, 2007). Stereotaxic coordinates for the CA1 areas of the hippocampus were as follow: 2 mm posterior to bregma point, 1.6 mm from the sagittal suture (on both sides) and 1.5 mm below to the skull surface. Cannulae were secured in place using the dental acrylic paste. Stainless steel stylets (27-gauge) were inserted into the guide-cannulae to keep them free of debris. All rats were allowed 5–7 days to recover from the surgery and get cleared from the effects of anesthetic agents (Hosseini, Nasehi, Radahmadi, & Zarrindast, 2013; Naseri, Hesami-Tackallou, Torabi-Nami, Zarrindast, & Nasehi, 2014; Zarrindast, Piri, Nasehi, & Ebrahimi-Ghiri, 2012).

2.3. Sleep deprivation apparatus

To minimize the level of imposed stress and physical fatigue, our study employed a modified automatic total sleep-deprivation water box apparatus (BorjSanatazma Co, Tehran, Iran) [Fig. 1A]. The apparatus comprised a Plexiglas water-tank (120 cm \times 30 cm \times 50 cm), divided into four equal boxes (30 cm \times 30 cm \times 50 cm) containing temperature-regulated water at 30°C . To maintain social stability, four rats were simultaneously submitted to the tank (one rat in each box). Two small square platforms (15 cm in diameter, with 3 mm high edges), were closely adjusted side by side. There were some holes in the surface of each platform (3 mm in diameters) to facilitate water evacuation during upward movements, and to help the rats avoid slipping or getting their paws wet. The platforms moved independently with an automatically-set plan. Initially, both platforms slightly emerged from the water level. Then, each platform alternatively moved below and above the surface of the water, forcing the animal to continuously move from one platform to another to avoid contact with water. The speed of movement was set at 1.5 cm/s. Each platform motion cycle required 20 s. During this period, each platform remained stable over the surface of the water (at 12.5 cm) for 20 s at the highest position (holding time). All rats had free access to clean water from bottles and food pellet baskets which were placed on the top of the box [Fig. 1B]. The platform went down and immediately reverted till reaching the initial position. One day before the induction of different protocols for sleep deprivation, rats were allowed 30 min to accommodate with the water box. As such, they learned to stay at the junction of both platforms, allowing them to escape from the sinking platform and avoid contact with water [Fig. 1C]. The behavioral observation during a 10-h sleep deprivation period in earlier reports has documented that animals tend to remain awake 100% of the time in the water-box (Pierard et al., 2011, 2007).

In the present research, two models for sleep deprivation including total sleep deprivation (TSD; whereby animals were continuously deprived from sleep for 12, 24 or 36 h) and reversal of circadian rhythm (RCR; during which rats were submitted to daytime sleep deprivation for 12 h over 3 days with the opportunity to catch up overnight sleep) were used. All animals were kept

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