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Critical role of CA1 muscarinic receptors on memory acquisition deficit induced by total (TSD) and REM sleep deprivation (RSD)

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ABSTRACT

Aim: Despite different theories regarding sleep physiological function, an overall census indicates that sleep is useful for neural plasticity which eventually strengthens cognition and brain performance. Different studies show that sleep deprivation (SD) leads to impaired learning and hippocampus dependent memory. According to some studies, cholinergic system plays an important role in sleep (particularly REM sleep), learning, memory, and its retrieval. So this study has been designed to investigate the effect of CA1 Cholinergic Muscarinic Receptors on memory acquisition deficit induced by total sleep deprivation (TSD) and REM sleep deprivation (RSD).

Method: A modified water box (locomotor activity may be provide a limiting factor in this method of SD) or multiple platforms were used for induction of TSD or RSD, respectively. Inhibitory passive avoidance apparatus has been used to determine the effects of SD and its changes by physostigmine (as cholinesterase inhibitor) or scopolamine (muscarinic receptor antagonist) on memory formation. Because locomotor activity and pain perception induce critical roles in passive avoidance memory formation, we also measured these factors by open field and hot-plate instruments, respectively.

Results: The results showed that TSD and RSD for 24 hours impaired memory formation but they did not alter locomotor activity. TSD also induced analgesia effect, but RSD did not alter it. Intra-CA1 injection of physostigmine (0.0001 μg/rat) and scopolamine (0.01 μg/rat) did not alter memory acquisition in the sham-TSD or sham-RSD, by themselves. Moreover, intra-CA1 injection of sub-threshold dose of physostigmine (0.0001 μg/rat) and scopolamine (0.01 μg/rat) could restore the memory acquisition deficit induced by RSD, while scopolamine could restore TSD-induced amnesia. Both drugs reversed analgesia induced by TSD. None of previous interventions altered locomotor activity.

Conclusion: According to this study, CA1 cholinergic muscarinic receptors play an important role in amnesia induced by both TSD and RSD. However further studies are needed for showing cellular and molecular mechanisms of surprising result of similar pharmacological effects using compounds with opposite profiles.

1. Introduction

Sleep is a circadian or biologic rhythm which has remained during evolution of birds and mammals; therefore, it seems functionally important. There are two types of sleep: sleep with rapid eye movements (REM) and non-REM (NREM) or slow wave sleep (Lesku et al., 2006, 2008). REM-NREM sleep cycle repeats during sleep phase and in many species total ratio of NREM to REM has been reported 4 to 1 (Hsieh et al., 2008; Tobler and Jaggi, 1987). Regarding the importance of sleep, many studies have shown that each stage of sleep has different functions so that in NREM sleep, thought, analysis and problem solving are dominant, while in REM sleep many cognitive processes such as

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memory formation will occur. Today, long-term sleeplessness is a widespread phenomenon. Long-term sleeplessness can lead to total acute sleep deprivation (SD) and chronic partial SD. Both partial and total SDs will lead to reverse changes in cognitive functions (Abel et al., 2013). First and the most important of all is that total SD impairs attention and working memory and also affects other functions such as long-term memory and decision making. According to findings, partial SD affects attention, particularly readiness (Alhola and Polo-Kantola, 2007). Different studies show that sleep is necessary in order to maintain balance of metabolism and calorie, and also keep thermal balance as well as immune adequacy of the body (Maurovich-Horvat et al., 2008).

In laboratory animals sleep is required for learning and memory consolidation and retention. Learning sessions will not improve performance unless short wave sleep phase occurs along with REM (Rasch and Born, 2013). Other studies have indicated that disturbance of REM sleep has significant and clear relationship with some neurodegenerative diseases such as psychosis and Parkinson (Anderson and Bradley, 2013). Respiratory apnea which is another common sleep disorder leads to loss of memory, reduction of concentration, and increased fatigue during the day (Pan and Kastin, 2014).

In mammals hippocampus has a central role in the early stage of memory consolidation. Hippocampus receives multimodal sensory information from different cortical sources and plays a significant role in learning process, memory, spatial coding, and also regulation of emotional behaviors as well as anxiety (Bannerman et al., 2004; Bieri et al., 2014). Sleep is a determining dimension of memory and lack of sleep can have harmful effects on memory consolidation, particularly regarding hippocampus-dependent memory (Lynch, 2004). Studies show that sleep deprivation affects different phases of memory formation. Sleep facilitates neural plasticity while SD has specific harmful effects on hippocampal synaptic plasticity (Lynch, 2004). While sleep disorder before learning may particularly affect coding phase of memory, it seems that SD after learning affects memory consolidation (Abel et al., 2013). Studies during the recent years emphasize that while acute SD may change hippocampal plasticity processes in different ways, long-term changes in signaling paths due to chronic SD can decrease neurogenesis and eventually lead to morphological changes in brain such as reduction in the size of hippocampus (Lucassen et al., 2010; Novati et al., 2011).

Reticular formation in brainstem is composed of various neuronal groups which express different neurotransmitters such as acetylcholine (Brown et al., 2012). The cholinergic system is probably important in regulation of sleep-wake states, learning and memory (Schwartz and Roth, 2008). It showed that the cholinergic neurons will be active during wakefulness and REM sleep, while they will be silent during NREM sleep (Lee et al., 2005). On a microscopic level, it indicated that prolonged wakefulness (sleep deprivation) induces increase of adenosine concentration in the basal Forebrain followed by inhibition of cholinergic and non-cholinergic systems for transition from wakefulness to sleep (Arrigoni et al., 2006; Strecker et al., 2000), then decrease of acetylcholine into cortical region showing macroscopic brain activity for sleep deprivation (Boonstra et al., 2007).

Historically, cholinergic receptors are divided into two main groups including muscarinic (mAChRs) and nicotinic (nAChRs) receptors. Five different types of muscarinic cholinergic receptors (M1–M5) are expressed in large amounts in brain by five separate simulation genes and most of them act through G protein binding receptors (Doyle, 2004; Pohanka, 2012). Every receptor subtype which is distinctively localized in the hippocampal areas regulates different processes, consisting of long term synaptic plasticity. The mAChRs have different effects on neuronal activity, because of their pre- and postsynaptic locations. Presynaptic mAChRs (M2, M4) are coupled to Gi/o and prevent voltage-gated Ca^{2+} channels, reduce cAMP-regulated signaling and prevent neurotransmitter release at cholinergic, GABAergic and glutamatergic terminals. Postsynaptic mAChRs (M1, M3, and M5) are coupled to Gq/11 and potentiate NMDA currents, regulate voltage-dependent Ca^{2+} currents and activate phospholipase C and increase of intracellular Ca^{2+} concentration (Giovannini et al., 2015).

Posterior hippocampus or CA1 which plays an important role in learning and memory has large amounts of cholinergic receptors (Parfitt et al., 2012). Despite significant studies on cognitive, cellular, and molecular effects of SD in human and biologic models, many questions are still raised regarding how to deal with negative effects of SD. Because of the close relationship between sleep, wakefulness, cholinergic system and memory, the present study aims to investigate the effects of CA1 cholinergic muscarinic receptors on memory acquisition deficit induced by total SD (TSD) and REM SD (RSD). In the present study, it is predicted that both TSD and RSD decrease memory acquisition, because of the decrease in cholinergic system activity that provides favorable conditions for neuronal plasticity and LTP production into hippocampus. Then injection of physostigmine as an acetylcholinesterase inhibitor agent (the enzyme that breaks down acetylcholine) into CA1 region of hippocampus improved memory deficit induced by SD, while scopolamine as a muscarinic receptor antagonist potentiated these memory impairment.

2. Materials and methods

2.1. Animals

Animals used in experiments were male Wistar rats with a weight range of 220-250 grams that were obtained from Institute for Cognitive Science Studies (ICSS). Animals were kept in Plexiglas cages in groups of four members under standard temperature (22 ± 2) and light/dark cycle (12/12 h), while they had free access to water and food (except some short stages of the experiment). Each group included 7 male rats and each rat was used only once. All behavioral tests were performed during light phase of light/dark cycle. All ethical issues were followed during experiments. All interventions and those orders have been illustrated in the Fig. 1.

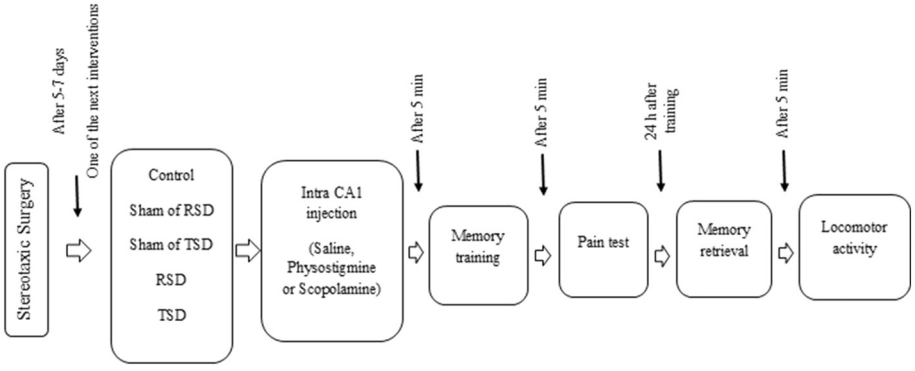

Fig. 1. All interventions and behavioral testing have been done according to the following order.