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Differential effects of citalopram on sleep-deprivation-induced depressive-like behavior and memory impairments in mice☆

Afzal Misrani[a,1], Sidra Tabassum[a,1], Xi Chen[a], Shu-yi Tan[a], Ji-chen Wang[b], Li Yang[b], Cheng Long[a,c,*]

[a] School of Life Sciences, South China Normal University, Guangzhou 510631, PR China
[b] School of Psychology, South China Normal University, Guangzhou 510631, PR China
[c] Institute for Brain Research and Rehabilitation, South China Normal University, Guangzhou 510631, PR China

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ABSTRACT

Recently there is increasing concern over the association between sleep deprivation (S-Dep) and depression. Mounting evidence suggests that S-Dep might be a risk factor for depression. However, underlying molecular mechanism remains elusive and currently there is no effective therapy to negate the effects of S-Dep. In this study, we aimed to examine whether subchronic treatment of citalopram (CTM), an antidepressant, can attenuate the negative effects of S-Dep in mice. Three-month-old C57BL/6J mice were divided into control, S-Dep, CTM control and CTM + S-Dep groups. CTM and CTM + S-Dep group treated with citalopram for 5 consecutive days at a dose of 10 mg/kg per day before experimental procedure. S-Dep and CTM + S-Dep group mice were sleep deprived for 24 h using an automated treadmill method. Our results revealed that S-Dep animals displayed an increased depressive-like behavior in forced swim, tail suspension and sucrose preference test and anxiety-like behavior in the open field and elevated plus maze, as well as disrupted spatial memory in Morris water maze. Western blotting analysis revealed that S-Dep caused reductions in the levels of the plasticity- and memory-related signaling molecules i.e. pCaMKII and pCREB in the hippocampus. Moreover, S-Dep animals showed synaptic plasticity deficits in the Schaffer collateral pathway. Interestingly, subchronic CTM treatment prevented S-Dep-induced decrease in pCaMKII and pCREB levels in the hippocampus. Furthermore, CTM treatment prevented S-Dep-induced deficits in synaptic plasticity, spatial memory, depressive-like behavior in sucrose preference test and anxiety-like behavior in open field test but not in force swim, tail suspension and elevated plus maze test. This data suggests differential effects of CTM on S-Dep-associated behavioral alterations and cognitive impairments.

1. Introduction

Frequently restricted or disrupted sleep is a widespread and serious problem in our modern society (Rajaratnam and Arendt, 2001). In present-day society, sleep deprivation (S-Dep) is caused by suboptimal work schedules, around-the-clock lifestyles and psychosocial stress that collectively contribute to sleep pathology. Because sleep serves a vital function in metabolic homeostasis, energy restoration, learning-related synapse formation and neuronal reactivation; all of which are indispensable for normal brain function (Xie et al., 2013), insufficient sleep may have detrimental effects on brain function. Moreover, statistics indicate that majority of adults do not get adequate sleep every day (Roberts et al., 2011).

Anxiety and depression are highly comorbid (Cryan and Holmes, 2005) and several epidemiological studies have suggested that chronically disrupted sleep leads to pathological anxiety and depression in humans (Chapman et al., 2013; Roberts and Duong, 2014). Various reports argue that chronically disrupted sleep may gradually induce changes within the brain that are very similar to what has been reported in depressed patients (Buysse et al., 2008; Meerlo et al., 2015).

☆ Afzal Misrani, Li Yang and Cheng Long designed the study. Afzal Misrani and Sidra Tabassum carried out the behavioral and molecular experiments. Xi Chen and Shu-yi Tan performed electrophysiological experiments. Afzal Misrani, Sidra Tabassum, Xi Chen and Shu-yi Tan collected and analyzed the data. Afzal Misrani, Sidra Tabassum and Ji-chen Wang performed statistical analysis. Afzal Misrani and Sidra Tabassum wrote the manuscript. Li Yang and Cheng Long contributed to critical revision of the manuscript. All authors reviewed the manuscript before submission.

* Corresponding author at: School of Life Sciences, South China Normal University, Guangzhou 510631, PR China.
E-mail address: longcheng@m.scnu.edu.cn (C. Long).

[1] These authors contributed equally.

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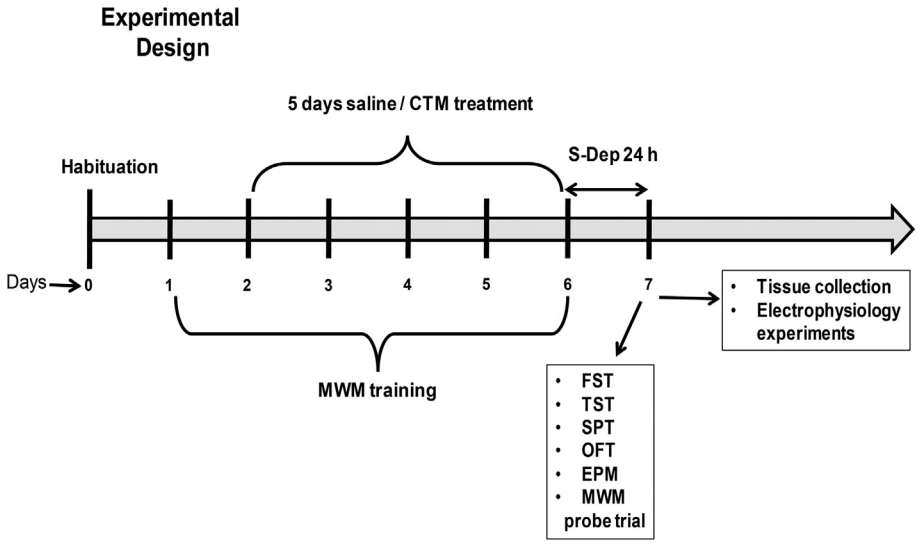

Fig. 1. Schematic illustration of the experimental procedure. Animals were assigned to one of four groups: Ctrl, S-Dep, CTM and CTM + S-Dep. S-Dep group and CTM + S-Dep group animals were subjected to 24 h total S-Dep using an automated treadmill. For behavioral experiments, mice were randomly divided and five sets of mice either from Ctrl or CTM group were tested for depressive-like behaviors using either in the FST, TST, SPT or OFT and EPM (anxiety-like behavior); S-Dep and CTM + S-Dep mice were subjected to these paradigms immediately after S-Dep procedure. Another set of animals from each of the four groups was trained in the MWM; S-Dep and CTM + S-Dep mice were sleep deprived for 24 h immediately after completion of six days training in the MWM and a probe trial was conducted next day to test spatial learning and memory. Separate sets of animals from all groups were sacrificed for tissue collection or electrophysiological experiments. Mice used for western blotting or electrophysiological experiments did not perform the behavioral tests. One set of animals only subjected to one behavioral test.

Similarly, people with a poor sleep quality are more likely to develop depression than individuals with a good sleep quality (Szklo-Coxe et al., 2010); > 90% of depressed patients complain about impairments in sleep quality (Chang et al., 2017). In contrast, short duration of total S-Dep has been shown to quickly and substantially improve depressive symptoms (with an effectiveness of 40–60%) in depression patients. However, this improvement does not last long (Allard et al., 2007; Deweerdt, 2013); as soon as sleep resumes, depressive symptoms rapidly reappear. Moreover, a relationship between S-Dep and depression has been established using a large scale community-based cohort study (Roberts and Duong, 2014), suggesting that reduced sleep quantity increases the risk of depression; which in turn increases the risk of sleep disruption. The authors provide with the evidence that adolescents with disrupted sleep report more depression, anxiety, and poor academic performance. Importantly, sleep disturbances are routinely encountered in depression and defined as risk factors for onset of depression (Neckelmann et al., 2007; Turek, 2005). However, the mechanisms underlying such impairments between insufficient sleep and depression are still poorly characterized. It has been suggested that insufficient sleep might contribute to depression through negative effects on signaling pathways involved in synaptic plasticity.

In particular, synaptic plasticity involves two key molecules, calcium/calmodulin-dependent protein kinase II (CaMKII) (Hell, 2014) and cAMP response element binding protein (CREB) (Sakamoto et al., 2011) that also play a crucial role in pathophysiology of various neuropsychiatric disorders including depression. Because of highly plastic and stress sensitive region, the hippocampus has recently received significant attention in memory, mood disorders research and pathophysiology of depression. S-Dep negatively affects hippocampal function, thereby potentially results in symptoms of depression and cognitive dysfunction. Postmortem brain samples of depression patients also show decreased levels of CREB in hippocampus (Dwivedi et al., 2003); however, antidepressant treatment to depression patients resulted in increased CREB levels (Dowlatshahi et al., 1998). Moreover, several antidepressants including fluoxetine, desipramine and reboxetine, markedly increase the enzymatic activity of CaMKII and CaMKIV in rats (Tiraboschi et al., 2004b; Vinet et al., 2004). Activation of protein kinases in the cell thus enables the phosphorylation of downstream effectors. The ability of antidepressants to trigger protein kinases in the cell and the potential for these kinases to phosphorylate CREB suggest that antidepressants can activate CREB as part of their mechanism of action. Indeed, chronic administration of different antidepressant drugs like fluoxetine, imipramine, escitalopram, rolipram, imipramine and bupropion increases phosphorylated CREB (pCREB) levels throughout the brain, including in the hippocampus, cortex, amygdala and hypothalamus (Koch et al., 2003; Thome et al., 2000). This suggests that upregulation of CREB signaling might be a common target of antidepressants.

Citalopram (CTM), is the most-frequently used antidepressant in clinical practice for the treatment of depression (Chiarotti et al., 2017; Keller, 2000). Sleep loss often causes depression. Whereas, CTM is associated with improved sleep quality in patients with depression and Alzheimer's disease (AD) (Newell et al., 2016; Shahsavand-Ananloo et al., 2013). A recent study on humans showed that CTM at a dose of 20 mg/kg/day improves sleep latency, sleep duration and the global Pittsburgh Sleep Quality Index (PSQI) (Wu et al., 2015). Importantly, acute administration of CTM facilitated memory consolidation in healthy humans and in depression models (Harmer et al., 2002). Therefore, it seems that regulation of sleep can be an essential component for understanding the pathophysiology and treatment of depression. However, the effects of CTM on S-Dep-induced depressive-like behavior and memory impairment are not well documented and the underlying molecular mechanism remains largely unknown.

In this communication, we report that subchronic CTM treatment prevents most of the S-Dep-induced behavioral alterations and maintains the basal protein levels of signaling molecules essential for synaptic plasticity, learning and memory and normal brain function. To the best of our knowledge, this is the first study to provide molecular, electrophysiological and behavioral evidence on the neuroprotective role of CTM against S-Dep-induced depressive-like behavior and cognitive impairment.

2. Materials and methods

2.1. Animal and treatments

Three-month-old C57BL/6J male and female mice from the animal house of the School of Life Sciences were used in this study. Mice were housed in a climate-controlled room (25 °C) on a 12 h light–dark cycle (lights on at 8:00 a.m.) with ad libitum access to standard rodent chow and water prior to the start of actual experiment. All animal experiments performed, were approved by the South China Normal University Animal Care and Use Committee, and were in accordance with the guidelines published in the National Institutes of Health Guide for Care and Use of Laboratory Animals.

Animals were randomly assigned into four groups: control (Ctrl),