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Research report

Tempol prevents chronic sleep-deprivation induced memory impairment

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ABSTRACT

Sleep deprivation is associated with oxidative stress that causes learning and memory impairment. Tempol is a nitroxide compound that promotes the metabolism of many reactive oxygen species (ROS) and has antioxidant and neuroprotective effect. The current study investigated whether chronic administration of tempol can overcome oxidative stress and prevent learning and memory impairment induced by sleep deprivation. Sleep deprivation was induced in rats using multiple platform model. Tempol was administered to rats via oral gavages. Behavioral studies were conducted to test the spatial learning and memory using radial arm water maze. The hippocampus was dissected; antioxidant biomarkers (GSH, GSSG, GSH/GSSG ratio, GPx, SOD, and catalase) were assessed. The result of this project revealed that chronic sleep deprivation impaired both short and long term memory ($P<0.05$), while tempol treatment prevented such effect. Furthermore, tempol normalized chronic sleep deprivation induced reduction in the hippocampus activity of catalase, GPx, and SOD ($P<0.05$). Tempol also enhanced the ratio of GSH/GSSG in chronically sleep deprived rats treated with tempol as compared with only sleep deprived rats ($P<0.05$). In conclusion chronic sleep deprivation induced memory impairment, and treatment with tempol prevented this impairment probably through normalizing antioxidant mechanisms in the hippocampus.

1. Introduction

Sleep is the state of natural rest observed in most animals (Moreira et al., 2004). It is a restorative process that regulates homeostasis of autonomic, neuroendocrine and immune system (Cirelli, 2004; Moreira et al., 2004; Steiger et al., 1987), which is essential for the physical and mental health of a human being. Sleep has been broadly classified into two stages: non rapid eye movement (NREM) sleep and rapid eye movement (REM) or paradoxical sleep (Gyton, 2006; Silber et al., 2007).

Sleep deprivation is a commonplace occurrence in modern culture, which is a condition of not having enough sleep. Numerous studies have demonstrated that sleep deprivation in laboratory animals produces memory deficits in several behavioral tasks, such as avoidance tasks (Dubiela et al., 2013), Morris water maze task (Saadati et al., 2015), and radial water maze task (Alzoubi et al., 2012a,b,c; Mhaidat et al., 2015b). While the mechanisms that are responsible for the occurrence of memory deficits following sleep deprivation are not clearly understood, some of the effect of sleep deprivation has been hypothesized to be due to free radicals accumulation during prolonged waking as a result of enhanced metabolic activity, and inability of antioxidants defense mechanism to scavenge progressively accumulated free radicals (Alzoubi et al., 2012, 2013b,c; Mhaidat et al., 2015b).

Tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl) is an antioxidant that works as a superoxide dismutase mimetic (Samuni et al., 1991). It directly reacts with both carbon-centered and peroxy radical (Chateauneuf and Ingold, 1988) and thus prevents the reduction of hydrogen peroxide to the hydroxyl radical (Samuni et al., 1991). Furthermore, tempol can oxidize reduced transition metals that would otherwise serve to catalyze the formation of the hydroxyl radical via the Fenton reaction (Samuni et al., 1990; Soule et al., 2007; Wilcox, 2010; Wilcox, 2008). The antioxidant effect of tempol was observed in many studies, where tempol has been shown to preserve mitochondria against oxidative damage and improve tissue oxy-

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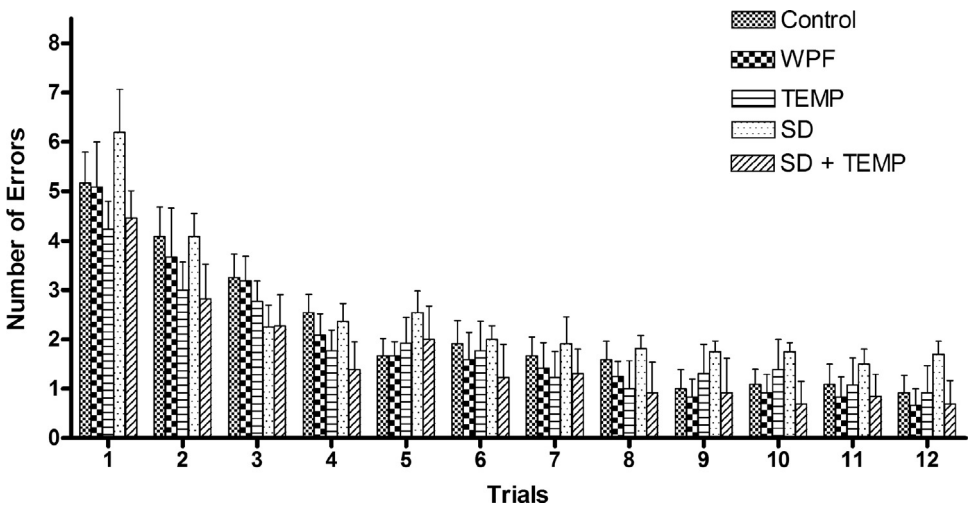

Fig. 1. Animals' performance during RAWM. Comparison of (control), wide platform (WPF), tempol (TEMP, 80 mg/kg), chronic sleep deprivation (SD), and chronic sleep deprivation with tempol (SD + TEMP). Each animal was trained for six consecutive trials separated by 5 min rest, then another six consecutive trials (the learning phase). Similar learning performance was observed among all tested groups, indicating normal learning in sleep deprivation and/or tempol treated groups. Performance of animals was compared based on the average number of errors committed in each trial (n = 12–14/group).

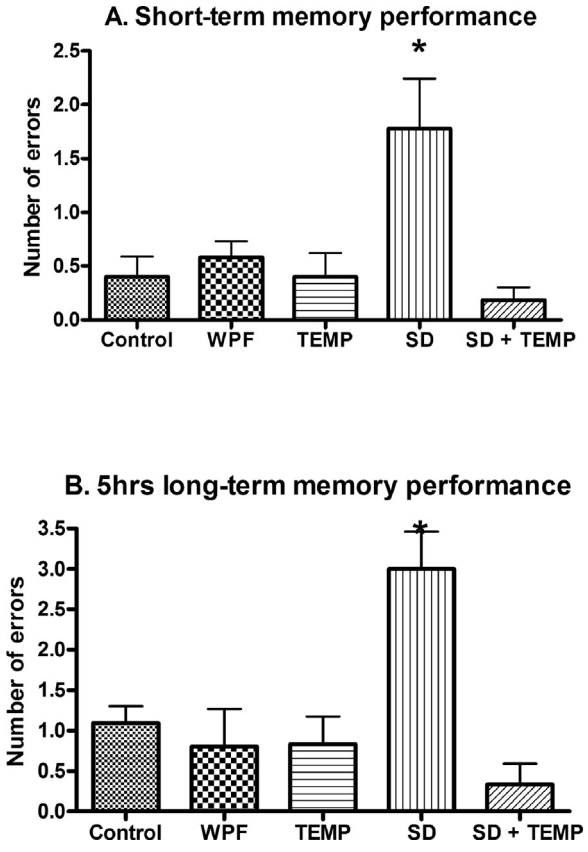

Fig. 2. Animals performance at memory tests. Short-term memory test was carried out 30 min after the end of the acquisition phase (A), whereas long-term memory test was carried out 5 h after the end of the acquisition phase (B). Sleep deprivation induced both short- and long-term memory impairment, which was prevented by tempol treatment. * Indicates significant difference from all other groups (P < 0.05, n = 12–14, one-way ANOVA).

genation (Alzoubi et al., 2013a,d,e; Khabour et al., 2014). In this study, the effects of tempol on chronic sleep deprivation induced oxidative stress and memory impairment were investigated.

2. Materials and methods

2.1. Animals and treatments

Adult male Wister rats weighing 180–200 g were used in this study. The animals were housed in metal cages (4–5 rats per cage) under hygienic conditions and maintained at normal room temperature with free access to food and water. Animals were housed on a 12 h light/dark cycle (light on 7 am) at 25 °C. All experimental procedures were performed during the light cycle. The study was approved by animal care and use committee of the Jordan University of Science and Technology.

Animals were randomly assigned into five groups: control, sleep deprivation (SD), wide platform (WPF), tempol, and tempol + SD. The tempol and tempol + SD groups were treated with tempol (Sigma Chemical Co., Saint Loius, MO, USA) at a dose of 80 mg/kg, via oral gavage once daily for 6 weeks. This dose was used by a number of previous studies and shown to be effective in protection against cognitive function impairment in conditions other than sleep deprivation (Ahmed et al., 2014; Talebianpoor and Mirkhani, 2012). The control, SD, and WPF groups were administered normal saline, i.p., once daily for 6 weeks. The SD and tempol + SD groups were subjected to sleep deprivation 8 h/day for 6-weeks. All manipulations including SD, tempol and normal saline administration were started on the same day, and continued for 6 weeks. The radial arm water maze (RAWM) training was carried out immediately after 6 weeks of treatment. SD and/or tempol treatments continued throughout the RAWM testing days.

2.2. Induction of sleep deprivation

Sleep deprivation was induced using columns in water (modified multiple platform) model as previously described (Aleisa et al., 2011a,b; Alhaider et al., 2010a,b, 2011, 2012a). This method has been reported to interfere with total sleep, but it mainly eliminates REM sleep (Grahnstedt and Ursin, 1985). Furthermore, to test the effect of possible stresses of the tank environment, wide platforms (diameter: 12 cm) were used to allow the rats to sleep without falling in the water (the WPF group).