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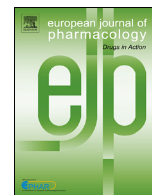

Neuropharmacology and analgesia

Tadalafil enhances working memory, and reduces hippocampal oxidative stress in both young and aged mice

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ABSTRACT

Tadalafil, a type-5 phosphodiesterase enzyme inhibitor with long half-life used to treat erectile dysfunction. Recently it has been reported that tadalafil improves cognitive function. Here, we aimed to investigate the age dependent effects of tadalafil on memory, locomotor, behavior, and oxidative stress in the hippocampus. Tadalafil was orally administered everyday (5 mg/kg) to young (2 months) and old (16 months) healthy mice for 4 weeks. Control mice from each group received equal volume of 0.9% normal saline for the same duration. Memory and locomotor activity were tested using radial arm maze and open field test respectively. The level of malondialdehyde (MDA), nitric oxide (NO), and advanced protein oxidation product (APOP) was analyzed and catalase activity was determined from the isolated hippocampus. Treatment with tadalafil in aged mice improves working memory than the corresponding tadalafil treated young mice in radial arm maze test. Tadalafil treated mice traveled less distance in the center and the mean speed of tadalafil treated aged mice was significantly lower than the tadalafil treated young mice in open field test. Tadalafil treatment elicited a decrease of MDA level in the hippocampus of aged mice than that of young mice. APOP level was decreased only in aged mice treated with tadalafil. Treatment with tadalafil decreased NO and increased catalase activity in both young and aged mice. On the basis of previous and our findings, we conclude that tadalafil treatment reduces oxidative stress while increased cGMP level in the hippocampus might be responsible for memory enhancement.

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1. Introduction

Cognitive enhancers have received much attention in contemporary neuropharmacological research. Phosphodiesterase (PDE) inhibitors may work as cognitive enhancers due to their expression of phosphodiesterases in the central nervous system (CNS) (Menniti et al., 2006). Tadalafil (CAS number 171596-29-5) is a potential phosphodiesterase 5 (PDE-5) inhibitor (Schiefer and Sparing, 2005), which has been used to treat erectile dysfunction (Donatucci et al., 2008; Porst et al., 2009). It can cross the blood brain barrier (Garcia-Barroso et al., 2013). The association of cognitive disorders with PDE-1,4,5,8,9, and 10 inhibitors has been demonstrated previously (Schmidt, 2010; Zhang, 2010) where PDE-5 and 9 were found to be a common cognitive enhancer.

Tadalafil has been reported to improve cognitive function in a mouse model of Alzheimer's disease (Garcia-Barroso et al., 2013; Zhang et al., 2013). It reduces anxiety (Liebenberg et al., 2012) and memory impairment, and improves depressive disorder (Baek et al., 2011). Tadalafil reduces the immobility time in forced swim test in rodent model and stops maternal separation induced apoptosis in the hippocampus (Baek et al., 2011).

Dentate gyrus of hippocampus is a special brain area where neurogenesis occurs (Gould et al., 1997). This neurogeneration is associated with the learning and memory processes (Deng et al., 2010; Gould et al., 1997; Kempermann et al., 1997). However, stress factors reduce the formation of granule cells in the dentate gyrus (Tanapat et al., 1998). In addition, age related oxidative stress causes memory deficits in older individuals. Oxidative stress also affects synaptic plasticity in neural networks in the hippocampus (Haxaire et al., 2012). Previous study only report that tadalafil improves memory impairment by reducing apoptotic neuronal cell death (Baek et al., 2011) and ischemia-induced apoptotic neuronal cell death (Ko et al., 2009). But the effect of tadalafil on age related cognitive deficits has not been elucidated.

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1.1. Aim of the study

We aimed to investigate the effect of tadalafil on age related memory performance, locomotor activity, and oxidative stress in the hippocampus. Hippocampus plays a critical role in memory formation that is generally affected during the aging process. Oxidative stress is a major player in declining cognitive function that is influenced by the aging process. Tadalafil might have protective properties in the hippocampus as well as in relieving age-related cognitive decline.

Elderly people mostly suffer from erectile dysfunction and PDE-5 inhibitor such as tadalafil is mostly consumed by them. Elderly people also suffer age-related cognitive dysfunction. Young mice fight against the aging differently than the elderly at the molecular, structural, functional and cognitive levels (Villeda et al., 2014). Elderly mice are less capable to counteract oxidative stress in comparison to the young mice (Villeda et al., 2014). The pharmacological agents such as tadalafil could bring different results in these age groups since other PDE-5 inhibitor (sildenafil) showed vital role in age-related cognitive dysfunction in mouse model of aging (Palmeri et al., 2013).

The availability of PDE enzymes in the CNS open a new window to investigate the effect of PDE inhibitors in enhancing cognitive function. Recently it is reported that NO-cGMP plays a vital role in improving learning and memory functions (Jin et al., 2014). The lingering of cGMP action in the CNS may facilitate memory function. Therefore, we aimed to investigate the age-related protective effect of tadalafil in hippocampus.

2. Materials and methods

2.1. Animal

Swiss-Albino male mice (*Mus musculus*) (30–35 g) were used in this study. They were housed in room temperature (25 °C) and adequate lighting condition with standard mice pellets and water. Mice were randomly divided into 4 groups. Control groups were treated with distilled water while test groups were treated with tadalafil (0.05 mg/kg) for 4 weeks. All experimental procedures were approved by the local ethical committee of North South University for animal experiments according to governmental guidelines.

2.2. Preparation of tadalafil and placebo

Tadalafil was dissolved in distilled water at a concentration of 5 mg/10 ml. The test sample was administered at single doses (5 mg/kg; per oral) for 4 weeks. The control animals received vehicle (0.9% saline).

2.3. Radial arm maze test

Eight arm radial maze test was constructed following the measurement stated by Tarragon et al. (2012). Experimental animals were introduced to 7 days of training (consecutive 3 days of habituation and 4 days of training). On the 3rd day of habituation, number of arms containing food was reduced to half and during 4 days of training only 1 arm contained food. On the day of experiment, only one arm contained food. Mice were released in the center of the maze and allowed to explore the maze. Parameters were followed as stated by Tarragon et al. (2012) and 3 trials were run for every mice. Each trial was recorded using the webcam mentioned earlier for later manual analysis. After each run, apparatus was cleaned using 70% ethanol.

2.4. Open field test

The open field test apparatus was constructed by using gray plastic wood as the material following measurements described by Walsh and Cummins (1976). The light source was a 35 W bulb suspended approximately 1 m above the apparatus for background lighting. Mice were carried to the testing room in their home cages and handled by the tail and were placed in the apparatus and were allowed to explore the field for 20 min. After each trail, apparatus was cleaned using 70% ethanol and allowed to dry. The exploration was recorded for latter analysis by using a Logitech 4 mp webcam. Video was analyzed manually using Smart (version 3.0) video tracking software developed by PanLab. During the analysis center zone and periphery zone was defined where center zone was $34.5 \times 34.5\ cm^2$.

2.5. Tissue processing

Mice were anesthetized with ketamine (0.1 ml) and perfused through the heart with cold 0.9% NaCl to remove blood from the brain tissue. Then animals were killed by decapitation. The whole brain was quickly removed carefully and kept in a petridish placed over ice. The hippocampus was dissected from the brain. Homogenate of hippocampus, 10% (w/v) was prepared in sodium phosphate buffer (30 mmol/l, pH 7.0) using an Ultra-Turrax T25 (USA) homogenizer. Homogenized tissue samples were sonicated at 5 s cycle for 150 s using an ultrasonic processor and centrifuged at 4000*g* for 10 min. Then, the upper clear supernatants were collected for the biochemical analysis.

2.6. Oxidative stress measurement

2.6.1. Estimation of lipid peroxidation

Lipid peroxidation in liver was estimated colorimetrically measuring thiobarbituric acid reactive substances (TBARS) followed by a previously described method (Niehaus and Samuelsson, 1968). In brief, 0.1 ml of tissue homogenate (Tris–HCl buffer, pH 7.5) was treated with 2 ml of (1:1:1 ratio) TBA–TCA–HCl reagent (thiobarbituric acid 0.37%, 0.25 N HCl and 15% TCA) and placed in water bath for 15 min and cooled. The absorbance of clear supernatant was measured against reference blank at 535 nm.

2.6.2. Assay of catalase (CAT) activity

Catalase activity was assayed colorimetrically at 620 nm and expressed as μmoles of H_2O_2 consumed/min/mg protein as described by Sinha (1972). The reaction mixture (1.5 ml) contained 1.0 ml of 0.01 M phosphate buffer (pH 7.0), 0.1 ml of tissue homogenate (supernatant) and 0.4 ml of 2 M H_2O_2. The reaction was stopped by the addition of 2.0 ml of dichromate–acetic acid reagent (5% potassium dichromate and glacial acetic acid were mixed in 1:3 ratio).

2.6.3. Assay of nitric oxide (NO)

NO was determined according to the method described by Tracey et al. (1995). In this study, Griess–Illosvoy reagent was modified by using naphthyl ethylene diamine dihydrochloride (0.1% w/v) instead of 1-napthylamine (5%). The reaction mixture (3 ml) containing brain homogenates (2 ml) and phosphate buffer saline (0.5 ml) was incubated at 25 °C for 150 min. Rest of process was followed as described in previous experiment of NO scavenging assay of the extract. A pink colored chromophore was formed in diffused light. The absorbance of these solutions was measured at 540 nm against the corresponding blank solutions. NO level was measured by using standard curve and expressed as nmol/gm of tissue.

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