Neuroscience Letters 585 (2015) 103–108

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Short communication

Surgical stress induced depressive and anxiety like behavior are improved by dapsone via modulating NADPH oxidase level

Tao Zhang[a], Xiaosheng Tian[a], Qiudian Wang[a], Yawei Tong[a], Hecheng Wang[a], Zhengqian Li[a,b], Lunxu Li[a,b], Ting Zhou[a], Rui Zhan[a], Lei Zhao[a], Yang Sun[a], Dongsheng Fan[c], Lin Lu[d], Jing Zhang[e], Yinglan Jin[a], Weizhong Xiao[c,**], Xiangyang Guo[b,**], Dehua Chui[a,c,*]

[a] Neuroscience Research Institute and Department of Neurobiology, Peking University Health Science Center, 38 Xueyuan Road, Haidian District, Beijing 100191, China
[b] Department of Anesthesiology, Peking University Third Hospital, Beijing 100191, China
[c] Department of Neurology, Peking University Third Hospital, Beijing 100191, China
[d] Peking University Sixth Hospital and National Institute on Drug Dependence, Beijing 100191, China
[e] Department of Pathology, University of Washington School of Medicine, Seattle 98104, WA, USA

HIGHLIGHTS

- Surgical stress induces depressive and anxiety like behavior in aged mice.
- Elevation of brain oxidative stress was observed in mice following surgical stress.
- Dapsone suppressed surgical stress induced brain oxidative stress.
- Dapsone improved surgical stress induced depressive and anxiety like behavior.
- Effect of dapsone on surgical stress was mediated by inhibiting NADPH oxidase.

ARTICLE INFO

Article history:
Received 5 August 2014
Received in revised form 3 November 2014
Accepted 26 November 2014
Available online 28 November 2014

Keywords:
Surgical stress
Depressive like behavior
Anxiety like behavior
Dapsone
Oxidative stress
NADPH oxidase

ABSTRACT

Surgical stress induced depression and anxiety like behavior are common complications among aged individuals suffering from surgery. Recent studies proposed that accumulation of oxidative stress is involved in the etiology of stress induced depression and anxiety. Dapsone possesses antioxidant properties, however, whether dapsone is effective in modulating surgical stress induced brain oxidative damage remains uncertain. The present study aimed to investigate the effect of dapsone on surgical stress induced depressive and anxiety like behavior, and brain oxidative stress in a well-established surgical stress model. Depressive and anxiety like behavior accompanied by elevated brain oxidative stress were observed in aged mice underwent abdominal surgery. Pretreatment with 5 mg/kg dapsone significantly improved the behavioral disorder and ameliorated brain oxidative stress in this model. Further investigation, revealed that surgical stress increased brain NADPH oxidase level, while pretreatment with dapsone abrogated the elevation of NADPH oxidase triggered by surgical stress. These findings suggest that dapsone is effective in improving surgical stress induced brain oxidative damage via down-regulating NADPH oxidase level in aged mice.

1. Introduction

The surgical stress response, activated by afferent neuronal input to the brain from the site of injury, could lead to profound endocrine–metabolic changes [1,2]. Maladaptation of surgical stress is closely associated with adverse outcomes in patients following surgery [2]. It has been recognized as one of the risk factors in the pathogenesis of post-surgical depression and anxiety; especially in geriatric surgical population [3,4]. Although it

Abbreviations: NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; NOX, nicotinamide adenine dinucleotide phosphate oxidase; DDS, dapsone; EPM, elevated plus maze; FST, forced swim test; DCFH-DA, 2'-7'-dichlorofluorescein-diacetate; MDA, malondialdehyde.

* Corresponding author at: Neuroscience Research Institute and Department of Neurobiology, Peking University Health Science Center, 38 Xueyuan Road, Haidian District, Beijing, 100191, China. Tel.: +86 10 82802920.
** Corresponding authors.
E-mail address: dchui@bjmu.edu.cn (D. Chui).

http://dx.doi.org/10.1016/j.neulet.2014.11.045
0304-3940/

is not totally understood why aged individuals are more susceptible to surgical stress than young individuals, evidences indicate that progressive loss of resilience to stress response during aging may be responsible for higher susceptibility of aged to surgical stress [5].

Depression and anxiety are common mood disorders among individuals; while the underlying mechanisms are not fully clarified. Recent studies demonstrated that accumulation of oxidative stress was involved in the pathogenesis of stress induced depression and anxiety [6,7]. Mice underwent repeated restraint stress showed significantly increased brain oxidative stress characterized by excessive levels of reactive oxygen species (ROS) and accumulation of malondialdehyde (MDA), a lipid peroxidation product caused by the attack of ROS on lipid components of cell membranes [6,8]. ROS and MDA levels are recognized oxidative stress markers in stress related mood disorders [8]. NADPH oxidase (NOX) is the key enzyme that mediates the generation of oxidative stress [6]. Researches revealed that stress response could up-regulate brain NOX expression and further increase brain oxidative stress level [6]. Eliminating oxidative stress by anti-oxidants or NOX inhibitor was reported to provide beneficial effects against depression and anxiety [6,7].

Dapsone (DDS), a traditionally used anti-leprosy agent [9], has been demonstrated to possess antioxidant activity recently. For example, DDS is able to suppress ROS production in neutrophils and diploid fibroblasts [10,11]; it can also inhibit lipid peroxidation in ischemia models [12,13]. The mechanism by which DDS decreases ROS generation was partially due to its inhibition on NOX expression based on previous researches [10,14]. However, whether DDS could mitigate stress induced brain oxidative damage in aged mice is to be elucidated, and the effect of DDS on stress induced depressive and anxiety like behavior is also unclear.

The present study aimed to investigate whether DDS is effective in improving surgical stress induced depressive and anxiety like behavior and the underlying mechanisms in a well-established surgical stress model. We hypothesized that DDS may mitigate surgical stress induced depressive and anxiety like behavior via modulating brain NOX and oxidative stress levels in aged mice.

2. Materials and methods

2.1. Animals and surgical stress procedure

Aged (20 months old) male C57BL/6 mice were kept in groups of 3–4 mice per cage at standardized housing conditions with free access to food and water under a 12/12 h light/dark cycle. All experimental procedures were approved by Peking University Biomedical Ethics Committee Experimental Animal Ethics Branch. Mice were divided into 4 groups ($n = 7$ for each group): sham control group (sham control), DDS group (DDS), surgical stress group (stress), surgical stress + DDS group (stress + DDS).

The surgical stress procedure was performed according to previous report with a minor modification [15]. Mice were deeply anesthetized by intraperitoneal (i.p.) injection of 5% chloral hydrate prior to the surgery. The surgical site was sterilized and a 1.5 cm incision was made in the upper left quadrant of abdomen through the skin and muscle wall. The internal organs were gently manipulated for 1 min by inserting a sterile probe into the body cavity. The muscle and skin were then closed and mice were placed back to their home cages. The duration of abdominal surgery was 20–25 min. Animals in sham control group were anesthetized and treated in the same manner except for the surgery.

2.2. Drug administration

DDS was purchased from Sigma–Aldrich (St. Louis, MO, USA). DDS was dissolved in dimethyl sulfoxide (Sigma–Aldrich, St. Louis, MO, USA) and diluted with saline solution before administration. The final concentration of dimethyl sulfoxide in vehicle was limited to 0.05% (v/v). The following treatment paradigm was applied: sham control group: i.p. injection of vehicle; stress group: i.p. injection of vehicle 1 h prior to the surgery; DDS group: i.p. injection of 5 mg/kg body weight DDS; stress + DDS group: i.p. injection of 5 mg/kg body weight DDS 1 h prior to the surgery. The dosage of DDS was applied as reported previously [16].

2.3. Behavioral tests

Forced swim test (FST) and elevated plus maze (EPM) were performed 2 days after the surgery (1 day for recovery and 1 day for adaption to test environment). All tests were performed in light phase of activity cycle. For FST test, mice were individually placed into a polycarbonate cylinder (25 cm in height, 10 cm in diameter) containing 10 cm of water maintained at 24–26 °C. The movement in the cylinder was monitored by video for 6 min, and the total immobility time during the last 4 min was recorded. Immobility was defined as lack of active, escape-directed behaviors except the necessity to keep floating [17].

The EPM test was performed as described previously to measure anxiety level [18]. Movement of mouse in EPM was tracked for 5 min via an overhead camera. The ratio of open arm time to total arm time and the open arm entries to total entries were calculated and analyzed. All behaviors were evaluated by experienced raters blind to the treatment.

2.4. Detection of oxidative stress

Brain tissues containing hippocampus and cerebral cortex were dissected immediately after mice finished the behavioral tests. To measure ROS level, we conducted 2'-7'-dichlorofluorescein-diacetate (DCFH-DA) assay as previously described [19]. Briefly, tissues containing hippocampus and cerebral cortex were homogenized in phosphate buffer at pH 7.4 (10% wt/vol) and centrifuged at 11,000 g for 15 min at 4 °C. Supernatants were collected and DCFH-DA (Sigma–Aldrich, St. Louis, MO, USA) was added to a final concentration of 100 μM. The mixture was incubated in 37 °C in darkness for 30 min and then the reaction was stopped by cooling down on ice and fluorescence intensity (λexc485 nm, λem525 nm) was read in a flexstation 3 microplate reader (Molecular devices, Sunnyvale, CA, USA), the results were normalized to protein concentration and expressed as % of the value of sham control [19]. To measure lipid peroxidation products, we quantified the brain MDA level through a spectrophotometer method according to the description of the assay kit (Nanjing Jiancheng Bioengineering Institute, China). MDA contents were corrected for protein concentration [20].

2.5. Western blot analysis

Western blots were performed as described previously [21]. Brain tissues (containing hippocampus and cerebral cortex) were lysed in RIPA buffer and protein concentration was quantified by BCA kit (Pierce). 60 μg proteins were separated by SDS-PAGE electrophoresis and were transferred to 0.45 μm polyvinylidene difluoride (PVDF) membranes (Millipore, Bedford, MA). Primary antibodies against NOX2 (1:3000, Santa Cruz), NOX4 (1:4000, Abcam), and β-actin (1:5000, Sigma) were reacted with the membranes in 4 °C overnight. The membranes were incubated with peroxidase-conjugated secondary antibodies, respectively, and