Neuroscience Letters xxx (2014) xxx–xxx

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

Q1 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 xxx

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.

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.

Q2 * 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/

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 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

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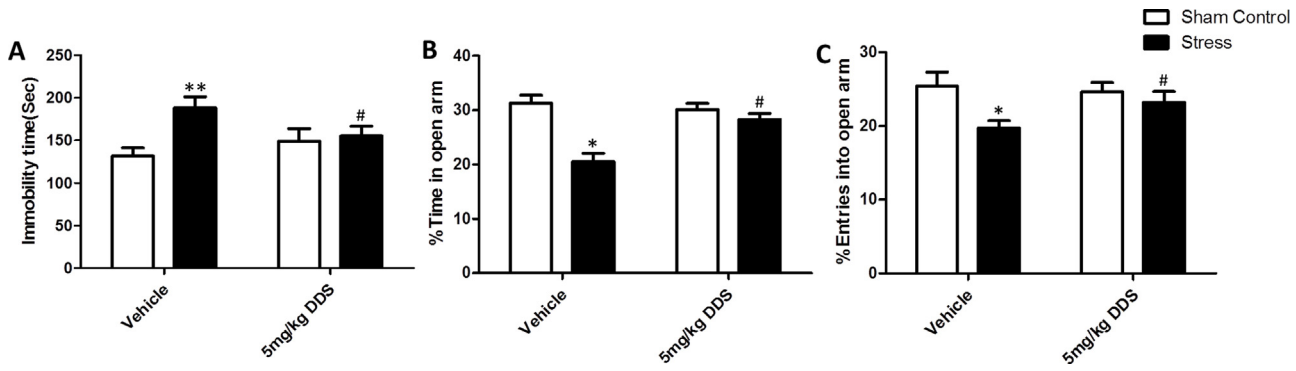

Fig. 1. Effect of dapsone administration on surgical stress induced depressive and anxiety like behavior in aged mice. (A) Total immobility time during the last 4 min in forced swim test were quantified, (B) percentage of total time spent in open arms during a 5 min session in elevated plus maze, (C) percentage of total entries into open arms during a 5 min session in elevated plus maze. Data were shown as mean ± S.E.M. (error bars) and were analyzed by two way ANOVA followed with bonferroni post hoc test. $n = 7$ for each set of test. $^{*}p < 0.05$, vs. sham control; $^{**}p < 0.01$, vs. sham control; $\#p < 0.05$, vs. stress.

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 protein bands were developed with ECL system (Millipore, Bedford, MA, USA).

2.6. Real-time PCR analysis

Real-time PCR was carried out as reported previously [21]. Total RNA was extracted from brain tissues (containing hippocampus and cerebral cortex) by TRIZOL (Invitrogen, CA, USA). The expression levels of NOX2, NOX4 were examined by RT-PCR by using Takara SYBR RT-PCR Kit (Takara, Dalian, China); GAPDH was used as an internal control. The following primers were used: NOX4: 5′-CCAGAATGAGGATCCCAGAA-3′ (forward) and 5′-AAAACCCTCGAGGCAA- AGAT-3′ (reverse); NOX2: 5′-CAGGAGTTCCAAGATGCCTG-3′ (forward) and 5′-GATTGGCCTGAGATTCATCC-3′ (reverse); GAPDH: 5′-GATAATGGCAAAC- TTGTCGTCG-3′ (forward) and 5′-ACATTGGAGCATCGGGTGAG-3′ (reverse). Data were analyzed with the $2^{-\Delta\Delta CT}$ method.

2.7. Statistic analysis

Data are expressed as mean ± S.E.M. and are analyzed in GraphPad Prism 5.0 Version (GraphPad Software, San Diego, CA, USA). Two-sample comparisons were carried out using Student's *t* test. Multiple comparisons were conducted using two-way ANOVA followed by bonferroni post hoc test. *p* value < 0.05 was considered statistically significant.

3. Results

3.1. Surgical stress induced depressive and anxiety like behavior in aged mice were improved by dapsone administration

To investigate whether DDS pretreatment improved surgical stress induced depressive and anxiety like behavior in aged mice, we evaluated the performance of mice by FST and EPM tests. Student's *t* test revealed that chloral hydrate anesthesia did not induce depressive like behavior according to FST; the total immobility time of the sham control group (131.55 ± 9.84 s) and mice without anesthesia (128.40 ± 7.43 s) was similar between the groups ($p > 0.05$). No significant difference was observed between sham control mice and non-anesthetized mice in the EPM test: the percentage of time spent in open arms and open arms entries in the sham control group were 31.25 ± 2.99% and 25.43 ± 1.89%, respectively, compared with 32.58 ± 5% and 24.2 ± 2.71%, respectively, in non-anesthetized mice ($p > 0.05$), implicating that chloral hydrate also did not induce anxiety. Mice in the stress group have a significantly longer immobility time in FST compared with the sham control mice (Fig. 1A, $^{**}p < 0.01$), indicating that surgical stress induced depressive like behavior. Pretreatment with 5 mg/kg DDS reduced the immobility time of mice following surgery (Fig. 1A, $\#p < 0.05$). In EPM test, mice in the stress group spent less time on open arms compared with the sham control mice (Fig. 1B, $^{*}p < 0.05$); the total entries to open arms also declined (Fig. 1C, $^{*}p < 0.05$), suggesting that surgical stress led to anxiety like behavior. However, mice in the stress + DDS group showed increased time spent on open arms as well as open arms entries compared with the stress group (Fig. 1B and C, $\#p < 0.05$). There was no significant difference between the sham control group and the DDS group in behavioral tests. These results suggested that dapsone administration improved surgical stress induced depressive and anxiety like behavior in aged mice.

3.2. Brain oxidative stress in aged mice exposed to surgical stress was suppressed by dapsone administration

Since oxidative stress has been demonstrated to be closely involved in stress induced depressive and anxiety like behavior [6,7], we next investigated whether dapsone could modulate brain oxidative stress by measuring brain ROS and MDA levels. ROS levels represented by DCFH-DA fluorescence intensity in anesthetized and non-anesthetized mice were 99.10 ± 4.19% and 97.58 ± 5%, respectively, ($p > 0.05$). The MDA contents in anesthetized and non-anesthetized mice were 1.056 ± 0.09 nmol/mg protein and 1.022 ± 0.11 nmol/mg protein, respectively, ($p > 0.05$). No difference in MDA and ROS levels were observed in the sham control group and the DDS group. As shown in Fig. 2, surgical stress elevated brain ROS and MDA levels significantly (Fig. 2A, $^{*}p < 0.05$; Fig. 2B, $^{**}p < 0.01$). However, pretreatment with 5 mg/kg DDS remarkably alleviated the increase of brain oxidative stress levels caused by surgical stress (Fig. 2A, $\#p < 0.05$; Fig. 2B, $\#\#p < 0.01$). These results revealed that dapsone is effective in inhibiting surgical stress induced brain oxidative damage.

3.3. Surgical stress induced NADPH oxidase expression was inhibited by dapsone administration

Previous studies suggested that NOX is closely associated with elevation of oxidative stress in depression and anxiety behavior caused by stress response [6,7]. To figure out the underlying mech-

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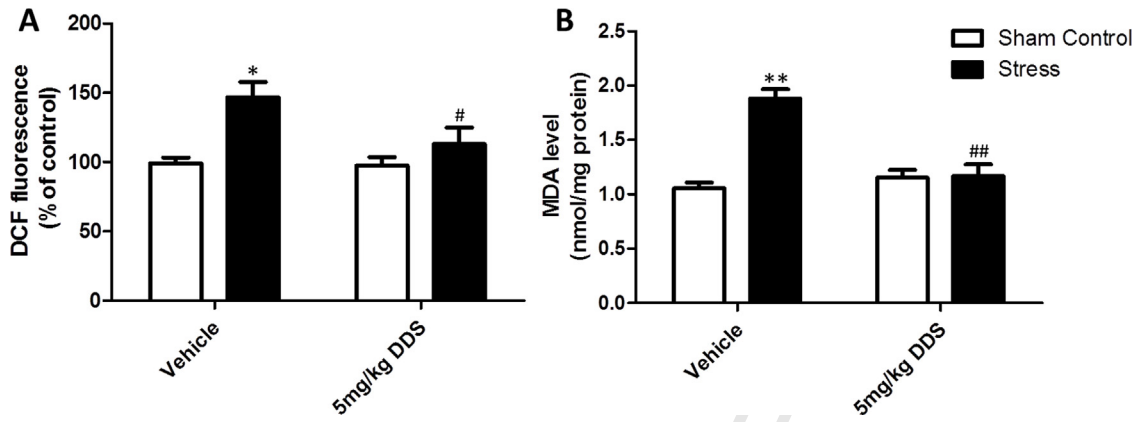

Fig. 2. Surgical stress induced brain oxidative stress was suppressed by dapsone administration. (A) Reactive oxygen species (ROS) levels in brain tissues (containing hippocampus and cerebral cortex) were represented via measuring DCFH-DA fluorescence intensity; (B) malondialdehyde (MDA) levels in brain tissues (containing hippocampus and cerebral cortex) were measured by MDA assay kit. Data were expressed as mean ± S.E.M. (error bars) and were analyzed by two way ANOVA followed with bonferroni post hoc test. $n = 5$. $^{*}p < 0.05$, vs. sham control; $^{**}p < 0.01$, vs. sham control; $\#p < 0.05$, vs. stress; $\#\#p < 0.01$, vs. stress.

anisms by which dapsone down-regulated brain oxidative stress; we further examined brain NOX levels. The mRNA and protein levels of NOX were quantified, respectively, in brain tissues containing hippocampus and cerebral cortex in all four groups. DDS treatment alone has no effect on brain NOX levels as shown in Fig. 3. In accordance with our observations in oxidative stress, brain NOX2 and NOX4 mRNA levels were up-regulated by surgical stress (Fig. 3A; $^{**}p < 0.01$); the protein levels of NOX2 and NOX4 were also increased in stress group (Fig. 3B–b, $^{**}p < 0.01$; Fig. 3B–c,$^{*}p < 0.05$). However, pretreatment with 5 mg/kg DDS markedly down-regulated brain NOX2 and NOX4 levels in mice following surgery as revealed by real-time PCR and western blot analysis (Fig. 3A and B, $\#p < 0.05$). These findings suggested that DDS may decrease brain oxidative stress via modulating NOX2 and NOX4 levels.

4. Discussion

Maladaptation of stress response is regarded as a risk factor for various neuropsychiatric disorders, including depression and anxiety. The pathogenesis of stress related depression and anxiety is not well understood yet. Hippocampal neuronal dysfunction and dysregulated glucocorticoid release subsequent to stress response may contribute to depressive and anxiety like behavior [22,23]. Recent studies also demonstrated that elevated brain oxidative stress mediated by up-regulation of NOX is involved in stress induced depressive and anxiety like behavior [6,7]. Surgical stress response is closely correlated with post-surgical cognitive dysfunction and mood disorders, especially in aged population [24]. In the present study, we used a well-established mice model to study the effect of dapsone in surgical stress induced depressive and anxiety like behavior. Mice received abdominal surgery could develop brain inflammation and oxidative damage as well as disturbed hormone release [15,25–27]. For example, it is reported that circulating glucocorticoid levels were increased in rodent abdominal surgery models [26,27], and our unpublished data found that glucocorticoid (GC) levels and GC related pathways are up-regulated in this model. These pathological changes, consistent with other stress models and clinical studies [6,24], suggested that mice underwent abdominal surgery are suitable to investigate surgical stress related mood disorders. The FST test and EPM test were applied to evaluate depressive and anxiety like behavior, respectively. Our behavioral test results demonstrated that surgical stress led to both depressive and anxiety like behavior.

There are evidences that mice following abdominal surgery may develop mild and transient pain which could not be evaluated clearly according to several researches [28,29]. While the locomotion and other spontaneous activities in mice following surgery were not suppressed at 24 h after surgery [14,28]. The mild pain response may be caused by surgical incision or inflammation. It is unclear whether DDS can reduce pain directly but perhaps it can help to limit pain via anti-inflammatory activity indirectly.

Elevation of brain oxidative stress is an important pathological change in various stress models [6,7,25]. Similar to the observations in repeated restraint stress models and chronic unpredictable stress models [6,30], we observed an increase of brain oxidative stress in aged mice following surgery as indicated by quantification of ROS and MDA levels. It has been reported that DDS was capable of inhibiting the generation of ROS and lipid peroxidation products both in vivo and in vitro [13,14,16]. Treatment with DDS in aged mice following surgery not only improved mood disorders, but also attenuated brain oxidative damages. These findings were consistent with previous studies that DDS administration protects animals from spinal cord injury [31] or focal ischemia [12,13] through preventing oxidative damages.

Previous studies demonstrated that NOX plays a pivotal role in stress induced depression and anxiety via elevating brain oxidative stress levels [6,7]. NOX2 and NOX4 are predominant enzymes of NOX family in mediating brain oxidative stress [32]. In the present study, up-regulation of brain NOX levels in aged mice following surgery was in line with the results reported in restraint stress model [6]. DDS has been found to inhibit NOX4 expression in mice exposed to paraquat and further decreasing superoxide generation [10,14]. While in this study, we observed that DDS pretreatment concomitantly suppressed NOX2 and NOX4 levels in brain. This may partially explain how DDS treatment decreased brain oxidative stress in aged mice following surgery. Evidence in restraint stress model proved that up-regulation of NOX level is closely linked with high levels of glucocorticoids [6]. Our previous study on green tea polyphenols proved that the conventional antioxidant exerted antidepressant-like effects through normalizing HPA axis function [17]. Whether DDS could modulate organismal glucocorticoid levels in surgical stress model needs in-depth study.

In addition to brain oxidative damages, neuroinflammation has also been characterized in stress related psychiatric disorders [33]. As for surgical stress, activation of inflammation-associated signaling pathway and elevation of proinflammatory cytokines (for example: IL-1β, TNF-α) are closely linked to depression and cognitive impairment [34]. DDS has long been used as anti-inflammatory agent [12]. Given that DDS possesses anti-inflammatory effect, it is likely that DDS improves surgical stress induced behavioral

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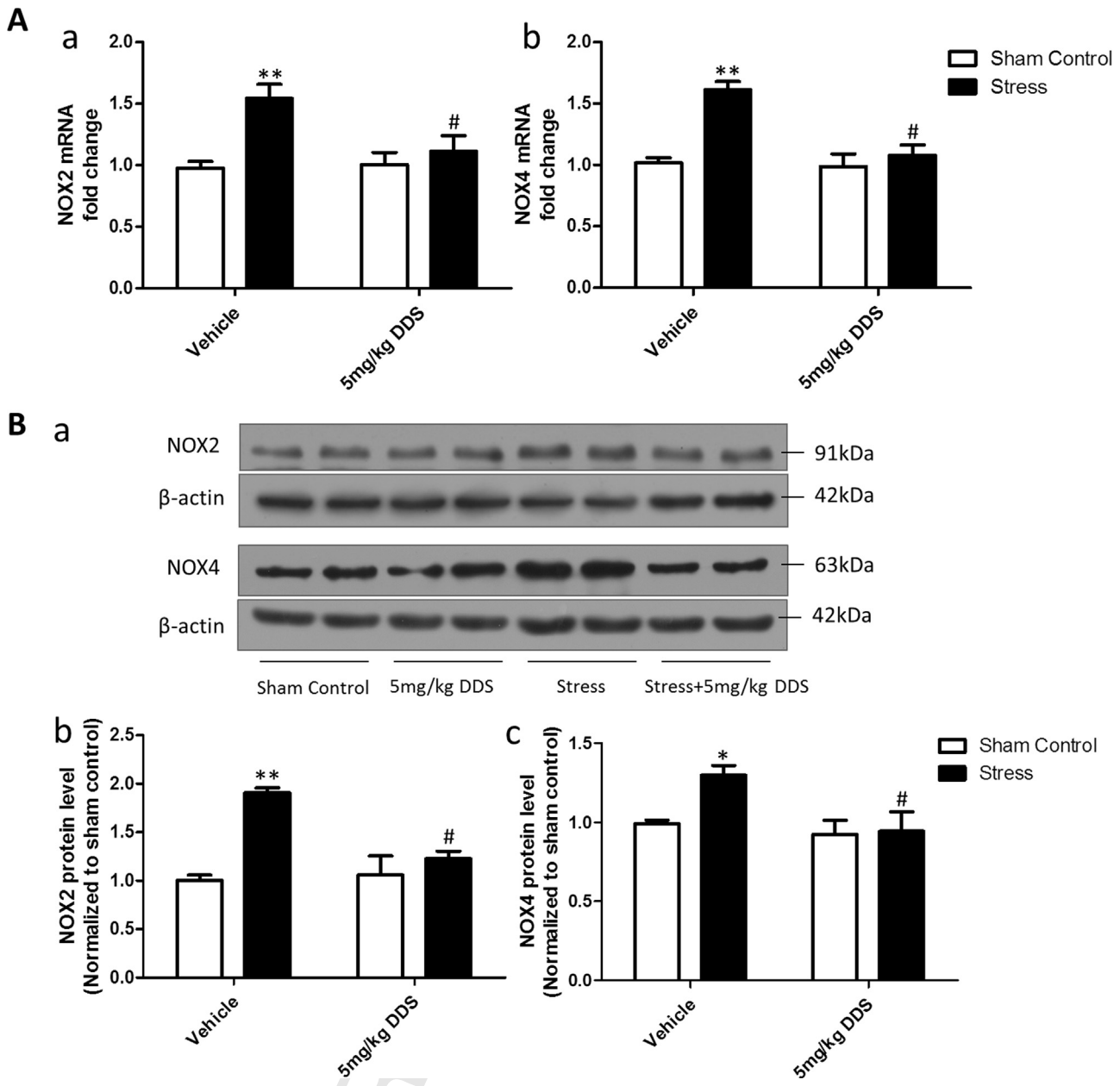

Fig. 3. Surgical stress induced NADPH oxidase (NOX) expression was inhibited by dapsone administration. (A) Real-time PCR analysis of NOX2 (a) and NOX4 (b) levels in brain tissues (containing hippocampus and cerebral cortex) of sham control, stress, DDS and stress + 5 mg/kg DDS group; (B) representative NOX2 and NOX4 western blot images; (a) quantitative results of NOX2 (b) and NOX4 (c) in brain tissues (containing hippocampus and cerebral cortex) of sham control, stress, DDS and stress + 5 mg/kg DDS group. Data were expressed as mean ± S.E.M. (error bars) and were analyzed by two way ANOVA followed with bonferroni post hoc test. $n = 5$. $^{*}p < 0.05$, vs. sham control; $^{**}p < 0.01$, vs. sham control; $\#p < 0.05$.

changes and oxidative damage through inhibiting neuroinflammation.

It should be noted that early clinical case reports pointed out that very few individuals taken modest dose of DDS could develop transient depression symptoms which disappeared after withdrawal of DDS [35,36]. In the present study, we did not observe depression symptoms in mice treated with 5 mg/kg DDS alone (DDS group) in behavioral tests, implicating that the applied dose was safe.

5. Conclusion

Collectively, the present study demonstrated that DDS is potent in improving surgical stress induced depressive and anxiety like behavior in aged mice via suppressing brain oxidative stress, and this effect is partially mediated by modulating NOX level. Our research indicates that DDS could be a potent intervention for surgical stress related mood disorders through anti-oxidative effect.

Conflict of interest

The authors declare no competing financial interests.

Acknowledgements

This work was supported by the National High Technology Research and Development Program of China (973 Program No. 2012CB911000, No. 2012CB911004) and the National Natural

Science Foundation of China (NSFC; Grants No. 81171015 and No.81371205).

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Please cite this article in press as: T. Zhang, et al., Surgical stress induced depressive and anxiety like behavior are improved by dapsone via modulating NADPH oxidase level, Neurosci. Lett. (2014), http://dx.doi.org/10.1016/j.neulet.2014.11.045