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X-Irradiation at 0.5 Gy after the forced swim test reduces forced swimming-induced immobility in mice

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ABSTRACT

The forced swim test (FST) is a screening model for antidepressant activity; it causes immobility and induces oxidative stress. We previously reported that radon inhalation has antidepressant-like effects in mice potentially through the activation of antioxidative functions upon radon inhalation. This study aimed to investigate the effect of prior and post low-dose X-irradiation (0.1, 0.5, 1.0 and 2.0 Gy) on FST-induced immobility and oxidative stress in the mouse brain, and the differences, if any, between the two. Mice received X-irradiation before or after the FST repeatedly for 5 days. In the post-FST-irradiated group, an additional FST was conducted 4 h after the last irradiation. Consequently, animals receiving prior X-irradiation (0.1 Gy) had better mobility outcomes than sham-irradiated mice; however, their levels of lipid peroxide (LPO), an oxidative stress marker, remained unchanged. However, animals that received post-FST X-irradiation (0.5 Gy) had better mobility outcomes and their LPO levels were significantly lower than those of the sham-irradiated mice. The present results indicate that 0.5 Gy X-irradiation after FST inhibits FST-induced immobility and oxidative stress in mice.

Keywords: X-irradiation; forced swim test; antioxidants; brain; oxidative stress

INTRODUCTION

Low-dose X- or gamma (γ)-irradiation exerts various biological effects such as activation of the biological defense systems including antioxidative [1] and immune [2, 3] functions, inhibiting cold-induced brain injury [4] and ischemia-reperfusion injury in the mouse paw [5]. Furthermore, it ameliorates type II diabetes by maintaining insulin secretion [6]. Interestingly, both pre- [7] and post- [8] low-dose X-irradiation alleviate carbon tetrachloride-induced hepatopathy in mice. As this damage is induced by reactive oxygen species (ROS) or free radicals, activation of antioxidative functions by low-dose X- or γ-irradiation potentially mitigates the ROS- or free-radical-induced damage. We previously reported that pre- or post-treatment with α-ray emitting radon gas has antidepressant-like effects in mice [9].

Many plausible reasons have been proposed to explain why the brain is susceptible to oxidative stress [10], including high dependence on oxygen, exclusive use of glucose for energy production, tendency to accumulate metal ions, low levels of protective antioxidants and auto-oxidation of neurotransmitters [10]. In particular, lower levels of endogenous antioxidants make the brain susceptible to disrupted redox homeostasis [11, 12]. Excessive ROS are involved in the pathogenesis of brain diseases, such as stroke [13], Parkinson's disease [14], Alzheimer's disease [15] and depression [16, 17]. Both, 8-hydroxy-2′-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, and F2-isoprostanes, a marker of lipid peroxidation, are increased in depression [16].

After the 2011 nuclear accident in Fukushima, Japan, the effects of low-dose irradiation have received increasing attention. The anxiety

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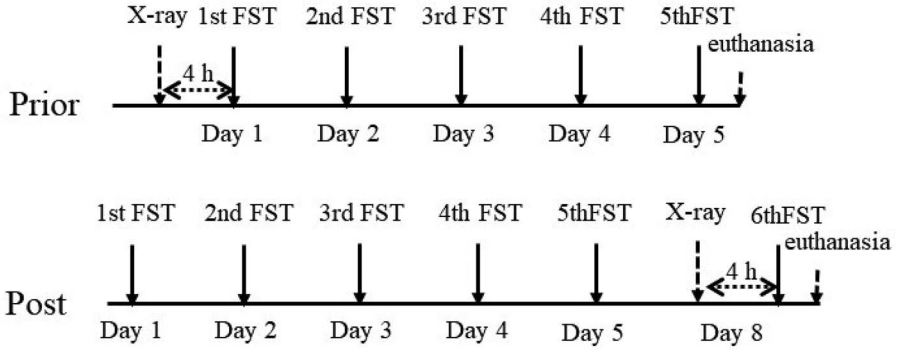

Fig. 1. Schematic representation of the experimental set-up for X-irradiation and the forced swim test (FST). (A) Timeline for experiment 1 (pre-FST X-irradiation), (B) timeline for experiment 2 (post-FST X-irradiation).

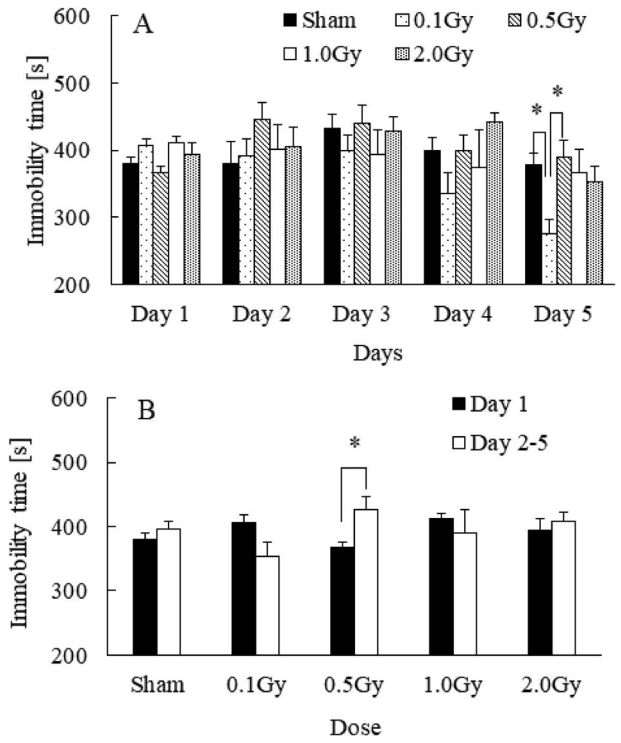

Fig. 2. Effects of X-irradiation on the forced swim test-induced immobility. (A) Average immobility time for each study group on each day of the experiment. (B) Comparison of the average immobility time on days 1 and days 2–5. Each group contained 7 mice. A significant difference was observed on day 5 for sham-irradiated and 0.5 Gy-irradiated mice ($P < 0.05$).

of exposure to radiation might cause psychological stress. Since radiation is one of the sources of oxidative stress, a combination of radiation and psychological stress is expected to cause accrued oxidative brain damage. However, we previously reported that low-dose X-irradiation inhibits oxidative stress-induced brain damage [4]. Therefore, understanding the mechanism underlying the regulation of forced swim test (FST)-induced oxidative stress upon X-irradiation may provide novel insights into its health effects. The present study aimed to examine dose-dependent changes of pre- and post-treatment with X-irradiation on FST-induced immobility, and to evaluate the levels of oxidative stress in the brain.

MATERIALS AND METHODS

Animals

Male BALB/c mice (age, 8 weeks; body weight, ∼21–26 g) were obtained from Charles River (Yokohama, Japan). Ethical approval for all experimental protocols was obtained from the animal experimentation committee of ****blind University. The mice were housed under a 12:12 h artificial light cycle (8:00 a.m. to 8:00 p.m.) at an ambient temperature of 22 ± 2°C.

FST

The FST was performed and repeated for 5 days, as described by Joram *et al.* [18]. Mice were individually placed in a transparent polymethylpentene tube (10 cm diameter × 25 cm height), filled with water to a 15-cm depth (water temperature 25 ± 1°C), and monitored for 10 min using a camera. During the test, three observers, blinded to the X-irradiation scheme, determined the immobility time of the mice. Mice were considered immobile when they ceased struggling and remained motionlessly floating in the water, making only those movements necessary to keep their heads above the water surface.

X-Irradiation

The animals received whole-body irradiation at doses of 0.1, 0.5, 1.0 or 2.0 Gy (tube voltage, 150 kV; tube current, 20 mA; filter, 0.5 mm Al and 0.2 mm Cu; distance between focus and target, 43.5 cm), delivered using an X-ray generator (MBR-1520R-3; Hitachi Power Solutions Co., Ltd., Ibaraki, Japan). During irradiation, mice were confined to a small cage (fan-shaped; radius 10 cm, height 4.5 cm, angle 30°) specific for X-irradiation. The control mice were also confined in a cage, and were sham-exposed. All mice were confined to a small cage for ∼2 min.

Experimental procedures

In experiment 1, to examine the effects of prior X-irradiation on FST-induced immobility, mice received whole-body X-irradiation 4 h before

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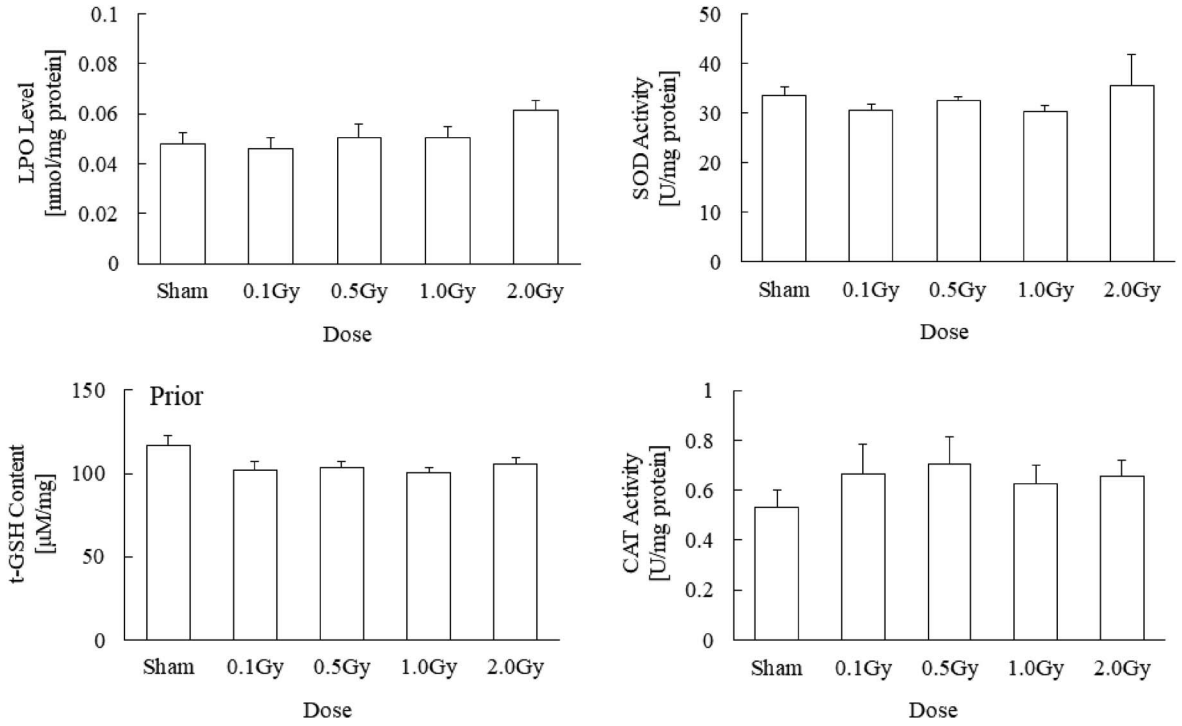

Fig. 3. Effects of prior X-irradiation on oxidative stress markers in the brains of mice receiving different doses of irradiation after the forced swim test. No significant difference was observed in the levels of oxidative stress biomarkers in response to irradiation. Each group contained 6–7 mice.

the first FST. The mice were euthanized using CO_2 after the fifth FST (Fig. 1).

In experiment 2, to examine the effects of post-X-irradiation on FST-induced immobility, FST was repeated for 5 days. Three days after the last FST experiment, mice received whole-body X-irradiation. Four hours after X-irradiation, the sixth FST was performed, after which the mice were euthanized using CO_2 (Fig.1). The brain was washed with distilled water and preserved at −80°C until the biochemical assay.

Biochemical assays

Lipid peroxide (LPO) levels were assayed using the Bioxytech LPO-586™ assay kit (OXIS Health Products, Inc., Portland, OR, USA). Briefly, the brain samples were placed in 10 mM phosphate buffer (PBS; pH 7.4) and 10 μL of 0.5 M butylated hydroxytoluene in acetonitrile was added per 1 mL of the buffer–tissue mixture. The tissue was homogenized and the homogenate was centrifuged at 15 000 × *g* for 10 min at 4°C, and the supernatant was used for the biochemical assay. The LPO assay is based on the reaction of the chromogenic reagent, *N*-methyl-2-phenylidole with malondialdehyde, a product of lipid peroxidation, and 4-hydroxyalkenals at 45°C. The optical density of the colored product was spectrophotometrically determined at 586 nm.

For the superoxide dismutase (SOD), catalase and total glutathione (t-GSH) assays, brain tissue was homogenized in 10 mM phosphate buffer (PBS; pH 7.4) and homogenates were used. SOD activity was assayed using the nitroblue tetrazolium (NBT) reduction-based SOD Assay Kit-WST (Dojindo molecular Technologies, Inc., Kumamoto, Japan) [19]. Briefly, the homogenates were centrifuged at 12 000 × *g* for 45 min at 4°C and the supernatants were used for the assay. Brain SOD activity was determined on the basis of the extent of inhibition of NBT reduction spectrophotometrically measured at 450 nm. Percentage inhibition of one-unit of enzyme activity was defined as 50% inhibition of NBT reduction.

The t-GSH content was measured using the Bioxytech GSH-420™ assay kit (OXIS Health Products, Inc.). Briefly, brain tissue homogenates were mixed with ice-cold 7.5% trichloroacetic acid solution and then centrifuged at 3000 × *g* for 10 min at 4°C. This assay is based on the formation of a chromophoric thione, which is directly proportional to the t-GSH concentration and can be measured at 420 nm.

Catalase activity was measured using an Oxiselect™ Hydrogen peroxide/Peroxidase Assay Kit (Cell Biolabos, Inc., San Diego, CA, USA). In the presence of peroxidase, the probe reacts with H_2O_2 to produce a bright pink colored product, which can be measured at 540 nm, and is directly proportional to the H_2O_2 concentration in the sample.

Protein content in each sample was measured using the Bradford method with a Protein Quantification Kit-Rapid (Dojindo Molecular Technologies, Inc.) [20].

Statistical analysis

Descriptive variables are presented as mean ± standard error of the mean (SEM) values. One-way analysis of variance (ANOVA) or

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repeated-measures ANOVA was performed to analyse the differences among different radiation doses. Each experimental group comprised samples from 6–7 animals. The pre- and post-irradiation groups were compared using the unpaired t-test, and pairwise post hoc comparisons were performed using Tukey's test. *P*-values were considered significant at $P < 0.05$.

RESULTS

Effect of prior X-irradiation on FST-induced immobility

We examined the effects of prior X-irradiation on FST-induced immobility. On Day 5, mouse immobility was significantly lower among 0.1 Gy X-irradiated mice than among sham or 0.5 Gy X-irradiated mice (Fig. 2A). Joram *et al.* [18] reported that FST-induced immobility may increase after day 2; we compared FST-induced immobility between day 1 and days 2–5. The immobility of 0.5 Gy X-irradiated mice was significantly higher during days 2–5 than on day 1 (Fig. 2B).

Modulation of oxidative stress markers in the brain upon X-irradiation prior to FST-induced immobility

To evaluate the brain levels of oxidative stress markers, levels of LPO, SOD, catalase and t-GSH were assayed. No significant differences in the levels of these markers were observed in the brains of mice subjected to irradiation and sham-exposure (Fig. 3).

Effects of post-FST X-irradiation on FST-induced immobility

We examined the effects of post-FST X-irradiation on FST-induced immobility. No significant differences in immobility were observed among the groups (Fig. 4A). The immobility of 0.1 Gy X-irradiated mice was significantly higher on day 8 than on day 1, but significantly lower on day 8 than on days 2–5 (Fig. 4B).

Modulation of brain oxidative stress markers upon X-irradiation post-FST-induced immobility

We evaluated the brain levels of oxidative stress markers in mice subjected to X-irradiation post-FST-induced immobility and observed that LPO levels in the brains of mice subjected to 0.5 Gy-irradiation was significantly lower than that of sham-irradiated mice (Fig. 5).

Differences in FST-induced immobility and oxidative stress markers in the brains of mice treated with prior or post-sham-irradiation

We compared the differences in immobility outcomes between experiments 1 and 2 and found that on day 1, the immobility was significantly higher among animals in experiment 1 than in experiment 2 (Fig. 6A). Furthermore, LPO levels were significantly higher in animals in experiment 1 than in experiment 2, whereas t-GSH levels were significantly lower in animals in experiment 2 than in experiment 1 (Fig. 6 B).

DISCUSSION

The FST is a screening model for antidepressant activity. FST-induced immobility is one of the pathological indicators of depression. Since

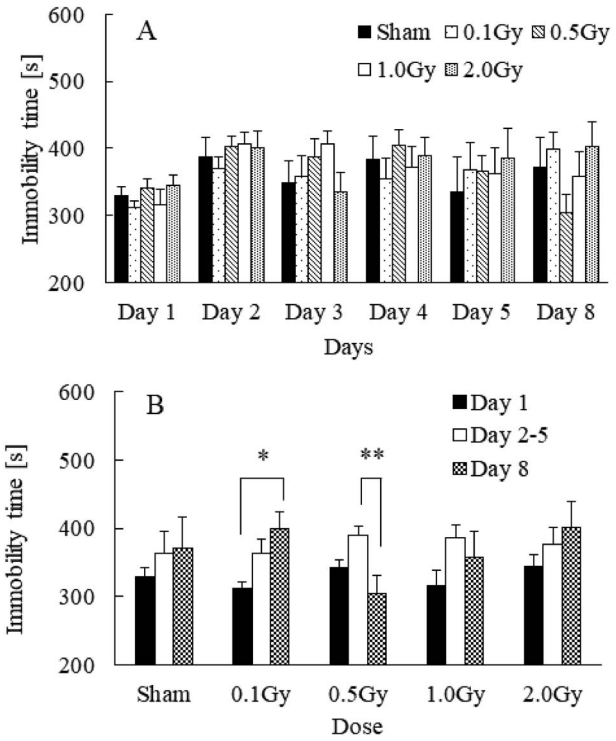

Fig. 4. Effects of post X-irradiation on FST-induced immobility. (A) Average immobility time for radiation doses on each day of the experiment. (B) Comparison of the average immobility time on day 1, days 2–5 and day 8. Each study group contained 7 mice. A significant difference was observed ($P < 0.05$) for 0.5 Gy irradiation.

FST-induced immobility can persist for at least 4 weeks, in this study we conducted and repeated FST for 5 days, as described by Joram *et al.* [18]. FST induces immobility in mice and increases the brain oxidative stress levels [21]. Oxidative stress is reportedly associated with FST-induced immobility, and the alleviation of oxidative stress improves the outcome on FST-induced immobility. For example, one study reported that guanosine administration inhibited oxidative stress in the hippocampus and reduced mouse immobility [22], while another one indicated that FST significantly decreased GSH levels [23]. In another study, tocotrienol-rich fraction-treated animals swam for a significantly longer duration than the control mice [24]. Together, these results indicate that the FST decreases antioxidant levels, thereby causing oxidative stress in the brain. Therefore, treatment with antioxidants may improve immobility outcomes in animals subjected to FST.

In this study, we focused on the effects of X-irradiation on FST-induced immobility and oxidative stress in the brain. X-Irradiation promotes ROS production, which in turn increases NF-κB levels. Increased Nuclear Factor-κB (NF-κB) levels activate Mn-SODs, thus potentially inducing antioxidative activity upon X-irradiation [25]. Low-dose irradiation increases brain SOD activity, and maximum activity is observed ~4 h after irradiation [26]. Another study reported that exposure to radon, an α-ray emitting gas,

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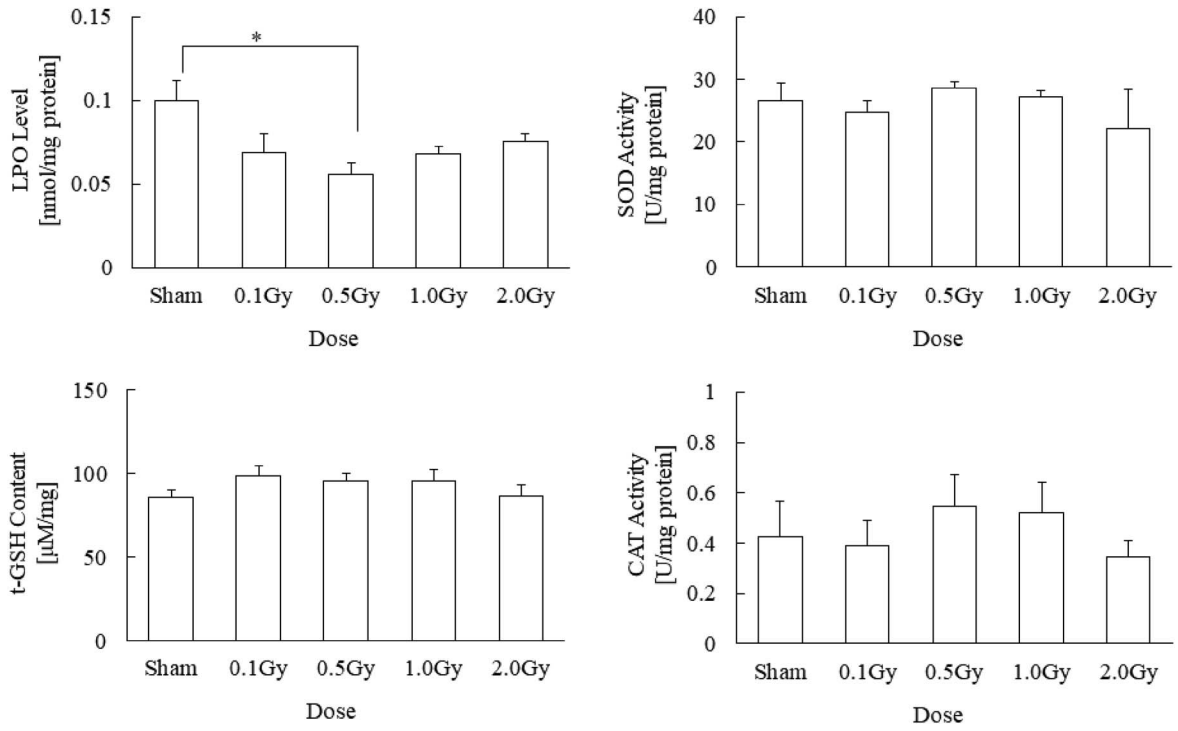

Fig. 5. Effects of post X-irradiation on oxidative stress markers in the brains of mice receiving different doses of irradiation after the forced swim test. Each study group contained 6–7 mice. A significant difference was observed in lipid peroxide levels upon irradiation treatments.

could increase SOD activity in mouse organs; however, enzyme activity returned to basal levels within 1–2 days [27]. While low-dose irradiation reportedly decreased LPO levels and increased brain SOD activity, the combined use of 0.5 Gy irradiation with ascorbic acid administration significantly decreased LPO levels, suggesting a combined effect of antioxidants [28]. Therefore, in our study, the first FST in experiment 1 was conducted 4 h after X-irradiation. Similarly, the sixth FST in experiment 2 was conducted 4 h after X-irradiation.

Herein, the results of experiment 1 show that only 0.1 Gy irradiation inhibited FST-induced immobility. To evaluate the oxidative stress levels in animals after repeating FST for 5 days, and in those exposed to X-irradiation before FST, we measured the levels of antioxidant markers such as SOD, t-GSH and catalase, and levels of LPO, an oxidative stress marker. However, no significant difference was observed in the levels of SOD, t-GSH, catalase and LPO. The activation of antioxidative functions by low-dose irradiation peaks at ∼4 h post-irradiation [26], and low-dose γ- or X-irradiation reportedly activated antioxidative functions in the brain at 6 h [29] and 24 h [4], respectively. Since in our study, the oxidative stress levels in the brain were assayed on day 5 after X-irradiation, the longer time lag in experiment 1 may have caused the levels of oxidative stress markers to return to baseline levels, thus explaining the lack of differences in antioxidant levels among different groups. Although previous studies have reported the activation of antioxidative functions in the brain, in our study, we did not obtain any direct evidence of X-irradiation (0.1 Gy)-induced enhanced antioxidative functions, and improved immobility on day 5.

The results of experiment 2 show that 0.5 Gy irradiation led to a better outcome in FST-induced immobility. Accordingly, 0.5 Gy irradiation decreased LPO levels, suggesting a reduction in oxidative stress. Notwithstanding differences in SOD, t-GSH and catalase levels between sham and 0.5 Gy-irradiated mice, catalase activity in 0.5 Gy-irradiated mice was ∼30% higher than that of sham-irradiated mice. We previously reported that low-dose X-irradiation or radon inhalation increases antioxidative functions and inhibits cold-induced brain damage [4]. Similar results were obtained in transient global cerebral ischemic injury in gerbils [30]. These findings suggest that a 30% activation of antioxidant activity, especially catalase activity, may adequately reduce FST-induced oxidative stress in the brain. The immobility time on day 8 was markedly different between mice irradiated at 0.1 Gy and 0.5 Gy. Herein, prior 0.1 Gy X-irradiation decreased FST-induced immobility on day 5, while the immobility decreased 4 h post-0.5 Gy X-irradiation. These findings suggest a response time lag between 0.1 Gy and 0.5 Gy X-irradiation.

We also compared the effects of prior or post sham-irradiation on FST-induced immobility. Since during X-irradiation, mice were confined to small cages, they probably experienced stress. To evaluate the stress levels, we compared the immobility between the sham-irradiated group between experiments 1 and 2 (sham, 0.1, 0.5 1.0 and 2.0 Gy irradiated group) from day 1 to day 5. Our results show that mice experienced stress similar to that experienced by those subjected to FST during sham-irradiation because immobility was significantly higher in experiment 1 on days 1 and 3 than in experiment 2. However,

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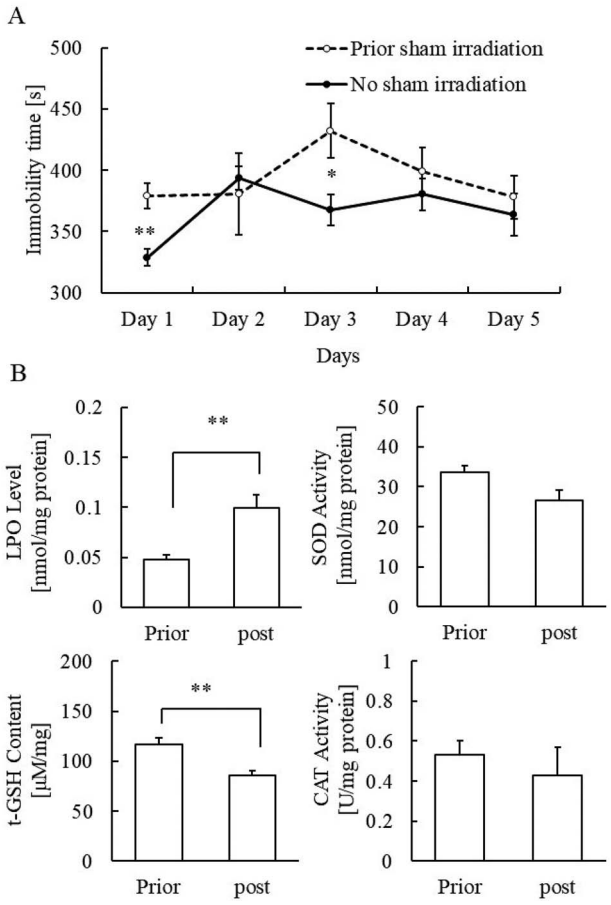

Fig. 6. (A) Differences in the forced swim test (FST)-induced immobility and oxidative stress markers in the brains of mice treated with prior or post sham-irradiation. The average immobility time on each day of the experiment is shown. The prior sham-irradiation group comprised sham-irradiated mice in experiment 1 ($n = 7$). The no sham-irradiation group comprised 0.1, 0.5, 1.0 or 2.0 Gy-irradiated mice ($n = 35$). A significant difference in immobility was observed between the prior sham irradiation group and the Gy irradiated groups on day 1 ($P < 0.01$) and day 3 ($P < 0.05$). (B) Levels of oxidative stress markers in each group. The prior group comprises sham-irradiated mice in experiment 1, while the post group comprises sham-irradiated mice in experiment 2. A significant difference ($P < 0.01$) was observed between the lipid peroxide and t-GSH levels among the sham-irradiated mice in experiments 1 and 2.

oxidative stress levels were higher in mice in experiment 2 than in experiment 1. Experimental procedures may have been responsible for these differences. In experiment 1, the immobility of 0.5 Gy-irradiated mice on day 1 was lower than that of 0.1, 1.0 or 2.0 Gy-irradiated mice; however, this difference was not significant. The same trend was observed in experiment 2.

In conclusion, the present results indicate that FST-induced immobility was inhibited by 0.1 Gy X-irradiation on day 5 in experiment 1 and 4 h after 0.5 Gy X-irradiation in experiment 2. Oxidative stress levels were reduced 4 h after 0.5 Gy X-irradiation, thus accounting for enhanced outcomes of FST-induced immobility. However, these results do not provide any direct evidence that pre-FST 0.1 Gy X-irradiation activates antioxidative functions and improves FST-induced immobility on day 5. Furthermore, this study does not provide direct evidence of 0.5 Gy X-irradiation-mediated alleviation of depression. Hence, further studies are needed to clarify whether 0.5 Gy X-irradiation could modulate depression levels.

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CONFLICT OF INTEREST

None declared.

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