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STUDIES ON POSSIBILITY FOR ALLEVIATION OF LIFESTYLE DISEASES BY LOW-DOSE IRRADIATION OR RADON INHALATION

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Our previous studies showed the possibility that activation of the antioxidative function alleviates various oxidative damages, which are related to lifestyle diseases. Results showed that, low-dose X-ray irradiation activated superoxide dismutase and inhibits oedema following ischaemia-reperfusion. To alleviate ischaemia-reperfusion injury with transplantation, the changes of the antioxidative function in liver graft using low-dose X-ray irradiation immediately after exenteration were examined. Results showed that liver grafts activate the antioxidative function as a result of irradiation. In addition, radon inhalation enhances the antioxidative function in some organs, and alleviates alcohol-induced oxidative damage of mouse liver. Moreover, in order to determine the most effective condition of radon inhalation, mice inhaled radon before or after carbon tetrachloride (CCl_4) administration. Results showed that radon inhalation alleviates CCl_4-induced hepatopathy, especially prior inhalation. It is highly possible that adequate activation of antioxidative functions induced by low-dose irradiation can contribute to preventing or reducing oxidative damages, which are related to lifestyle diseases.

INTRODUCTION

It is widely accepted that lifestyle diseases induce reactive oxygen species (ROS). ROS, such as hydrogen peroxide (H_2O_2), hydroxyl radical (^{-}OH) and superoxide anion radicals (O_2^{-}) damage DNA, lipids and enzymes, and are highly toxic[(1)]. Overproduction of ROS initiates lipid peroxidation of cell membrane and eventually leads to various diseases[(2)]. However, animals including humans have defence system against ROS. Cells can be injured or killed when the ROS level exceeds the cellular antioxidant capacity.

Low-dose X-ray or gamma-ray irradiation promotes a small induction of ROS *in vivo* and induces the production of antioxidant substances, including superoxide dismutase (SOD), catalase and glutathione, in various organs[(3)]. The activation of antioxidative function alleviates various oxidative damages[(3, 4)].

Therapy using radon gas is performed for various diseases, which are related to lifestyle diseases, in the Misasa Medical Center of Okayama University Hospital [(5, 6)]. However, the mechanisms by which radon alleviates the symptoms of most diseases are unknown. The purpose of our study is to demonstrate the possibility that low-dose irradiation, including radon inhalation, can contribute to preventing or reducing oxidative damages, which are related to lifestyle diseases.

MATERIALS AND METHODS

Male BALB/c mice (body weight of ~25 g, age 7–8 weeks) were used in each experiment.

Experiment 1

Mice were irradiated at a dose of 0.5 Gy using an X-ray generator. At 4 h after irradiation, mouse paw oedema was measured according to Oyanagui's method[(7)]. Paw thickness and SOD activity in serum were also measured.

Experiment 2

Extirpated livers of mice were irradiated at a dose of 0.25, 0.5, 1.0 or 5.0 Gy using an X-ray generator. Livers were stored for 24 h in preservation solution (Via Span; Bristol-Myers Squibb Co., USA) at 4°C immediately after irradiation. Antioxidant-associated parameter in liver was measured at the end of this period of storage.

Experiment 3

Mice inhaled radon, and its concentration was 4000 Bq m^{-3}. Livers and kidneys were quickly excised for the analyses of antioxidant-associated parameter after inhalation for 24 h.

Experiment 4

Mice received 30 % alcohol (6 g per kg body weight) every 12 h for a total of three doses. These mice inhaled radon, where its concentrations were 20 600 and 3500 Bq m^{-3}, respectively, immediately after the first alcohol administration. At 4 h after final administration, livers and brains were quickly excised for the analyses of antioxidant-associated parameter.

Experiment 5

Mice inhaled radon for 6 h, and concentration was 180 00 Bq m^{-3}, before ($Rn+CCl_4$) or after (CCl_4+Rn) carbon tetrachloride (CCl_4; 5 % in olive oil) administration. At 24 h after CCl_4 administration, serum was obtained from the heart for the analyses of hepatic function, and livers were excised for the analyses of antioxidant-associated parameter.

RESULTS AND DISCUSSION

Experiment 1

It is well known that ischaemia-reperfusion injury is attributable to ROS. Results showed that ischaemia-reperfusion of paw contributed to paw oedema, but low-dose X-ray irradiation activated SOD activity in serum and inhibited the paw oedema. These findings suggested that low-dose irradiation activated antioxidative function and inhibited ischaemia-reperfusion injury induced by ROS (Figure 1)[8].

Experiment 2

To alleviate ischaemia-reperfusion injury with transplantation, the changes of the antioxidative function in liver graft by low-dose X-ray irradiation immediately after exenteration were examined.

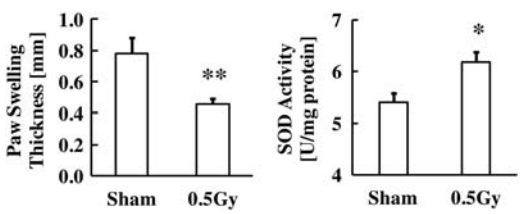

Figure 1. Changes in paw swelling thickness and SOD activity in serum 1 h of reperfusion after 1 h ischaemia. Each value indicates mean ± SEM. The number of mice per experimental point is 5. $*p < 0.05$, $**p < 0.01$ vs. Sham.

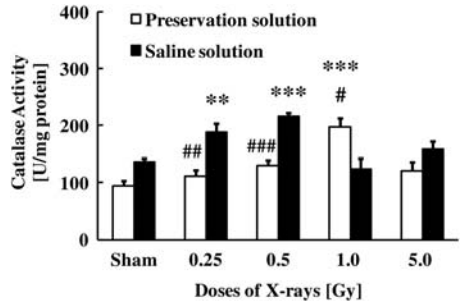

Figure 2. Changes in catalase activity in the mouse liver preserved for 24 h following irradiation. Each value indicates mean ± SEM. The number of mice livers per experimental point is 5–10. $**p < 0.01$, $***p < 0.001$ vs. each solution by sham irradiation, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ vs. physiological saline solution.

Results showed that low-dose irradiation significantly increased the catalase activity in liver grafts, suggesting the activation of antioxidative functions. However, the dose at which enhancement of antioxidative function occurs in livers stored in preservation solution, which contains glutathione, is significantly higher than that in saline solution (Figure 2)[9]. Thus, it is highly possible that low-dose irradiation inhibits ischaemia-reperfusion injury after liver transplantation. The data presented in this study provide an essential basis for future studies aimed at determination of the possibility of remission of ischaemia-reperfusion injury in livers after transplantation.

Experiment 3

Radon inhalation using this system significantly increased the SOD activity in the liver or kidney of mouse (Figure 3)[10].

Experiment 4

The effects of radon inhalation on acute alcohol-induced oxidative injury of mouse liver and brain were examined.

Assay of antioxidative functions indicated that lipid peroxide levels in both the liver and brain of the alcohol-treated mice were significantly higher than those of the saline-treated mice. However, the lipid peroxide level in the liver, but not in the brain, of alcohol-treated mice was significantly decreased by radon inhalation of a concentration of 600 or 3500 Bq m^{-3}, whereas that in the brain of saline-treated mice, but not alcohol-treated mice, was

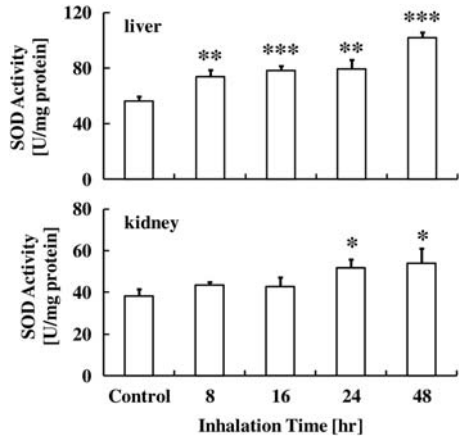

Figure 3. Changes in SOD activities in the liver and kidney of mice after radon inhalation at a concentration of 4000 Bq m^{-3}. Each value indicates mean ± SEM. The number of mice per experimental point is 5. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. control.

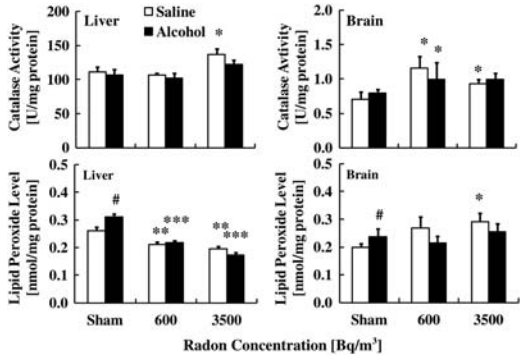

Figure 4. Changes in catalase activity and lipid peroxide level in the liver and brain of alcohol-treated mice following radon inhalation. Each value indicates mean ± SEM. The number of mice per experimental point is 4–7. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. sham inhalation, $^{\#}p < 0.05$ vs. saline.

significantly increased by radon inhalation of a concentration of 3500 Bq m^{-3}. Catalase activity in the liver was significantly increased by radon inhalation of a concentration of 3500 Bq m^{-3}. Catalase activity in brain was significantly increased by radon inhalation (Figure 4)[11]. These findings suggest that radon inhalation inhibits alcohol-induced oxidative injury of liver owing to the activation of antioxidative function. They further suggest that alcohol administration protects against oxidative injury of the brain that is induced by inhalation of a high radon concentration.

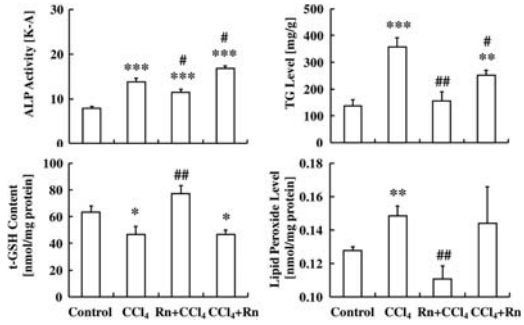

Figure 5. Protective or curative effects of radon inhalation on ALP activity in the serum and TG level, t-GSH content and lipid peroxide level in liver following CCl_4 administration. Each value indicates mean ± SEM. The number of mice per experimental point is 5–6. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. control, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. CCl_4.

Experiment 5

Furthermore, the protective or curative effects of radon inhalation on CCl_4-induced oxidative damage in liver were examined.

CCl_4 administration significantly increased the alkaline phosphatase (ALP) activity in serum, the level of triglyceride (TG) and lipid peroxide in liver, and significantly decreased total glutathione (t-GSH) content in liver, suggesting that CCl_4 administration induced hepatopathy. The ALP activity and the level of TG and lipid peroxide level of radon-inhaled mouse before CCl_4 administration were significantly lower than CCl_4-administrated mouse, suggesting that radon inhalation inhibited the hepatopathy. However, after CCl_4 administration, only the TG level in the liver of radon-inhaled mouse was significantly lower than CCl_4-administrated mouse (Figure 5). These findings suggest that prior radon inhalation is more effective than post-radon inhalation.

CONCLUSION

It is highly possible that adequate activation of the functions of the living body by low-dose irradiation or radon inhalation can contribute to preventing or reducing ROS-related injuries, which are thought to involve peroxidation.

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