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Impact of Breathing 100% Oxygen on Radiation-Induced Cognitive Impairment

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Abstract

Future space missions are expected to include increased extravehicular activities (EVAs) during which astronauts are exposed to high-energy space radiation while breathing 100% oxygen. Given that brain irradiation can lead to cognitive impairment, and that oxygen is a potent radiosensitizer, there is a concern that astronauts may be at greater risk of developing cognitive impairment when exposed to space radiation while breathing 100% O₂ during an EVA. To address this concern, unanesthetized, unrestrained, young adult male Fischer 344 × Brown Norway rats were allowed to breathe 100% O₂ for 30 min prior to, during and 2 h after whole-body irradiation with 0, 1, 3, 5 or 7 Gy doses of 18 MV X rays delivered from a medical linear accelerator at a dose rate of ~425 mGy/min. Irradiated and unirradiated rats breathing air (~21% O₂) served as controls. Cognitive function was assessed 9 months postirradiation using the perirhinal cortex-dependent novel object recognition task. Cognitive function was not impaired until the rats breathing either air or 100% O₂ received a whole-body dose of 7 Gy. However, at all doses, cognitive function of the irradiated rats breathing 100% O₂ was improved over that of the irradiated rats breathing air. These data suggest that astronauts are not at greater risk of developing cognitive impairment when exposed to space radiation while breathing 100% O₂ during an EVA.

INTRODUCTION

Future spaceflight missions are expected to include increased extravehicular activities (EVAs) during which astronauts are exposed to high-energy space radiation [photons, electrons, protons, neutrons and heavy charged (HZE) particles] while breathing 100% O₂ at a pressure of ~0.3 atmosphere (atm). Ground-based studies using air-breathing animals and simulated space radiations have reported radiation-induced brain injuries, including deleterious effects on dividing neuronal precursor cells in the hippocampus (1–3), nondividing hippocampal neurons (3, 4) and cognitive function (5–9). Recently published reviews suggest that acute radiation-induced oxidative stress and inflammation generate chronic reactive oxygen species that may ultimately result in late radiation-induced brain injury, including cognitive impairment (10–12). It is well known from both *in vitro* and *in vivo* studies that increasing the O₂ concentration increases radiation-induced damage in molecules, cells and animals (13). Thus, there is a concern that exposure to space radiations while breathing 100% O₂ may result in increased oxidative stress and neuroinflammation leading to increased late radiation-induced brain injury, including cognitive impairment.

We have been investigating radiation-induced brain injury, including cognitive impairment, for several years (14–20). Using our well characterized adult rat models, we have reported that a clinically relevant dose of fractionated whole-brain irradiation (fWBI) results in a nonsignificant reduction in cognitive function by 3 months that becomes statistically significant at 6 months, and then progressively worsens through 12 months post-fWBI (11). This cognitive impairment involves both the hippocampus as measured by the radial arm maze (14) and Morris water maze (15) tasks, as well as the perirhinal cortex, which is measured by the Novel Object Recognition task (16–18). Given that increasing the O₂ concentration increases radiation damage, we hypothesized that rats breathing 100% O₂ at 1 atm before, during and after irradiation will exhibit more severe radiation-induced cognitive impairment than those breathing air.

To test this hypothesis, unanesthetized, unrestrained, young adult male Fisher 344 × Brown Norway (F344 × BN) rats were allowed to breathe either air (21% O₂) or 100% O₂ for 30 min before, during and 2 h after whole-body irradiation with various doses of 18 MV X rays at a low dose rate of ~0.4 Gy/min. Under these simulated EVA conditions, breathing 100% O₂ at 1 atm appears to protect against radiation-induced cognitive impairment, rather than make it more severe.

MATERIALS AND METHODS

Experimental Design

Young adult male F344 × BN rats (Harlan Laboratories, Dublin, VA) were randomized into 10 groups to receive doses of 0, 1, 3, 5 or 7 Gy while breathing either air or 100% O₂ for 30 min before, during and 2 h after irradiation. Assuming a conservative relative biological effectiveness (RBE) of 6 for late brain injury from space radiation such as Fe ions (7, 21, 22), the equivalent Fe ion doses would range from 0.17–1.17 Gy. Doses of Fe ions 1 Gy are known to produce measureable cognitive impairment in rodents (5–9). Sixteen rats were entered into each of the 0, 1, 3 and 5 Gy groups, and 32 rats were entered into the 7 Gy

groups to insure that at least 16 healthy rats would be available for cognitive testing at 9 months postirradiation. However, only 6 rats had to be removed from any of the groups prior to 9 months postirradiation, and only 3 of these were in the 7 Gy groups (one air-breathing and two 100% O₂-breathing). Thus, with 30 rats in the 7 Gy groups at 9 months postirradiation, 16 rats were randomly selected from each of the 7 Gy groups for cognitive testing using a random number generator. This procedure insured that the number of cognitively tested rats in each dose group was approximately equal (14–16 rats/dose) and that none of the rats had detectable radiation-induced tumors or health problems when they were cognitively tested. All procedures in this study were approved by the Institutional Animal Care and Use Committee.

Irradiations

The rat environmental chambers, dosimetry and irradiation procedures were virtually identical to the published description of the environmental chambers, dosimetry and irradiation procedures used in our mouse carcinogenic studies (23). Briefly, 30 × 30 cm Plexiglas chambers were constructed with inlets and outlets that allowed either breathing air or 100% O₂ to freely flow at 10 L/min throughout the chamber. The only differences between the rat chambers and the mouse chambers were: the rat chamber height was 6.5 cm; there were 2 compartments per chamber; and there were 2 animals per compartment. After a 10 min flush with the appropriate gas, 2 rats were placed in each compartment and maintained in either breathing air or 100% O₂ for 30 min before the sealed chamber was rapidly transported to the linear accelerator room (~3 min) and reconnected to the in-house breathing air or 100% O₂ systems. The chambers were placed on the floor to obtain the maximum source-to-sample distance with 12 cm of water-equivalent bolus on top of the chamber to establish secondary electron equilibrium and 5 cm of water-equivalent bolus under the chamber to minimize backscatter (Table 1). Rats were irradiated with a beam of 18 MV X rays that contained a small component of neutrons from a medical linear accelerator. Dosimetry was performed with a calibrated ion chamber wrapped in bolus material, and the dose rate was ~425 mGy/min (Table 1). After irradiation, the sealed chambers were disconnected from the in-house gas systems, returned to the laboratory and reconnected to the appropriate gas for another 2 h to allow nearly complete molecular and cellular repair to occur. The unirradiated control rats were handled identically to the irradiated rats.

Cognitive Testing

Cognitive function was assessed at 9 months after irradiation using a perirhinal cortex-dependent version of the novel object recognition (NOR) task as we have previously described (16–18). Briefly, the rats were habituated to the testing arena by allowing them to explore the empty arena for 5 min a day for 5 days. After habituation, the testing sessions were divided into a sample phase and a test phase. During the sample phase (3 min), each rat was allowed to explore and become familiar with 2 identical objects located in the testing arena. After a 1 min delay in which the rat was removed from the arena and returned to its home cage, one of the 2 objects was replaced by a novel object. The left or right position of the novel object was balanced between sessions to avoid any spatial preference. The rat was then returned to the arena for 3 min, and its exploring activity recorded using EthoVision

XT software (Noldus Information Technology, Leesburg, VA). The time spent exploring the novel object, defined as placing the rat's nose within 2 cm and actively exploring it, relative to the time spent exploring the original object was then used to calculate the discrimination ratio (DR). The DR is a measure of the rat's recognition memory; the higher the DR, the better the rat's recognition memory. Each group's average DR was then calculated from the individual data and plotted versus dose.

Statistical Analysis

We first fit a 2 sample *t* test to compare the cognitive function of unirradiated rats breathing air to that of unirradiated rats breathing 100% O₂. Next, the effects of dose and breathing 100% O₂ on the cognitive function of irradiated rats were analyzed using a general linear model. As the first step, we used an *F* test to determine if there was a dose by oxygen interaction. Because the interaction was not significant ($P > 0.7$), we dropped it from the model and examined the main effects of dose and oxygen in a single model. In addition, we fit a model excluding the highest dose (7 Gy) to determine if there were any differences across the lower doses in either the rats breathing air or 100% O₂. All analyses were performed using SAS software, version 9.3. Comparisons were considered statistically significant at $P < 0.05$.

RESULTS

Breathing 100% O₂ for ~2.5 h had no statistically significant ($P > 0.7$) effect on the cognitive performance of unirradiated rats using the perirhinal cortex-dependent NOR task (Fig. 1). Also, there was no statistically significant effect of single whole-body doses on the cognitive performance measured by the NOR task from 0–5 Gy ($P_{\text{air}} > 0.4$; $P_{\text{oxy}} > 0.9$). However, the cognitive performance significantly decreased in rats breathing either air or 100% O₂ after a single whole-body dose of 7 Gy compared to the appropriate unirradiated control rats ($P < 0.001$) or rats irradiated with single doses of 1–5 Gy [$P < 0.05$; (Fig.1)]. Surprisingly, breathing 100% O₂ increased the cognitive performance of the irradiated rats at all doses (least squares mean $\pm$ SEM of all doses: 100% O₂ = 0.33 ± 0.026 ; air = 0.25 ± 0.027 ; $P < 0.05$). Thus, breathing 100% O₂ for 30 min before, during and 2 h after irradiation appears to increase cognitive performance 9 months after whole-body irradiation, rather than decrease it.

DISCUSSION

NASA uses several prebreathe and decompression protocols before and after an EVA (24, 25), which are designed to replace all of the nitrogen in the blood and tissues with oxygen prior to the EVA and return nitrogen to the blood and tissues after the EVA without producing decompression sickness. In general, these procedures include breathing >95% O₂ at 1 atm for 1 h, followed by a reduction to ~0.7 atm for 1 h, and then a reduction to ~0.3 atm for ~30 min prior to initiating the EVA. After the EVA, the procedure is reversed to restore nitrogen to the blood and tissues. Renitrogenation occurs much more rapidly than denitrogenation.

The higher respiratory rate in rats allows denitrogenation to occur more rapidly than in humans, so our 30 min prebreathe in 100% O₂ plus the transportation to the linear accelerator and set-up time after reconnecting to the inhouse gas systems were sufficient to remove >98% of the nitrogen from the blood and tissues prior to the start of irradiation. Although our dose rate was low (~425 mGy/ min) and the beam contained high energy 18 MV X rays and a small amount of neutrons, the dose rate and composition of the beam were not identical to that expected during an EVA (26–28). Moreover, our irradiations were performed while breathing 100% O₂ at 1 atm, rather than at ~0.3 atm. Finally, our decompression procedure went from 100% O₂ to air instantaneously, rather than gradually. Theoretically, all of these differences between our experimental conditions and what an astronaut would experience before, during and after an EVA, except the composition of the beam, should make the radiation-induced cognitive impairment worse rather than better. Moreover, it is unlikely that the slightly greater HZE-particle composition that astronauts are exposed to during an EVA would be sufficient to completely eliminate the protective effect of breathing 100% O₂ observed in our experiment (Fig. 1).

There appears to be little, if any, published data on irradiating cells and animals in a 100% O₂ environment that is relevant to understanding how breathing 100% O₂ could produce a protective, rather than deleterious effect on cognitive function after irradiation. It has been reported that radiation-induced cell cycle (29, 30), DNA damage (31–33) and lipid peroxidation (34–36) effects increase under hyperoxia. Theoretically, all of these phenomena should increase cognitive impairment, not decrease it. However, there is a plethora of information on the biological effects of placing humans in hyperbaric oxygen (100% O₂ environment at 2.4–3.0 atm) for single or multiple 2 h treatments, with or without irradiation (37–39). Among the known benefits of hyperbaric oxygen therapy are: 1. improved tumor response to radiation therapy (37, 40, 41); 2. stimulation of cell renewal (42, 43); 3. increased growth of new blood vessels (43–46); 4. decreased inflammation (46, 47); 5. increased ability to fight infection (48); and 6. stimulation of collagen production (39, 49, 50). With the possible exception of decreased neuroinflammation, none of these should positively affect radiation-induced cognitive impairment after breathing 100% O₂ for a single 2.5 h period.

Neuroinflammation has long been associated with radiation-induced brain injury, including cognitive impairment (11, 12). *In vitro*, a variety of inflammatory cytokines are induced in microglia and astrocytes within minutes to hours after irradiation (51–54). *In vivo*, an increase in proinflammatory mediators has also been detected within hours after irradiating rodent brains (18, 20, 55). Recently, it has been reported that hyperoxia inhibits early inflammatory response genes (38, 56), and that inhibiting early inflammatory response genes after lipopolysaccharide (LPS) challenge prevents the LPS-induced behavioral abnormality measured using trace fear conditioning (57). Thus, it is reasonable to hypothesize that short exposures to hyperoxia inhibit early inflammatory response genes or the activation of their signaling proteins, thereby decreasing radiation-induced cognitive impairment.

Recently, it has been reported that modulating changes in Homer1a expression and its signaling proteins for a period as short as 48 h may be sufficient to prevent both hippocampal- and cortical-dependent cognitive impairment at 9 months postirradiation (58).

Homer1a, a truncated form of Homer 1, is an early radiation response gene that binds to metabotropic glutamate family 1 receptors and inhibits their binding to synapses (59). This is known to alter glutamate signaling and modulate CA3-CA1 long-term potentiation (60), synaptic plasticity (60, 61) and working memory (62, 63). Consequently, it is reasonable to hypothesize that breathing 100% O₂ for a short period of time before, during and after whole-body irradiation improves cognitive function at 9 months postirradiation by blocking early radiation response genes that are involved in cognition.

Finally, it has been known for decades that breathing 100% O₂ at 1 atm causes both blood vessel constriction and reduced cardiac output (64, 65). Both of these phenomena decrease blood flow and reduce the effectiveness of breathing 100% O₂ during radiotherapy. The brain has a high metabolic rate, and its tissue oxygen concentration is ~10% when breathing air. It is well known that as the oxygen concentration increases from 1 to 10%, both radiation-induced DNA damage and radiation-induced cell kill increases by a factor of ~3 (66–68). Given that breathing 100% O₂ may produce vasoconstriction in the brains of the rats in this study, and that the brain is not expected to shift from oxic metabolism to anoxic metabolism while breathing 100% O₂ for only 2.5 h, it is reasonable to hypothesize that breathing 100% O₂ renders the brain partially hypoxic, thereby protecting it from the radiation damage that leads to cognitive impairment.

In summary, the cognitive function of rats breathing 100% oxygen at 1 atm is improved over that of rats breathing air at 9 months after single whole-body doses up to 7 Gy of 18 MV X rays (Fig. 1). Although the mechanism(s) for this unexpected result is unknown, there are two testable hypotheses. First, high levels of tissue oxygen may block early radiation response genes or inhibit activation of their signaling proteins. Second, high levels of oxygen in the blood may cause vasoconstriction that reduces blood flow and renders the brain partially hypoxic, resulting in less radiation damage to the brain. Regardless of the mechanism, these data suggest that astronauts are not at greater risk of developing cognitive impairment when exposed to space radiations while breathing 100% O₂ during an EVA.

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FIG. 1.

Unanesthetized, unrestrained, young adult male F344 X BN rats breathing 100% O₂ for 30 min before, during and 2 h after whole-body irradiation with 1–7 Gy of 18 MV X rays exhibit improved perirhinal cortex-dependent cognitive function at 9 months after irradiation compared to rats breathing air. White bars: Rats breathing air. Black bars: Rats breathing 100% O₂.

TABLE 1**Irradiation Conditions**

Beam energy	18 MV
Field size	$\sim 40 \times 40 \text{ cm}^2$
Buildup region	12 cm water-equivalent material
Backscatter region	5 cm water-equivalent material
Dose	0, 1, 3, 5, 7 Gy
Dose rate	$\sim 425 \text{ mGy/min}$