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Age as a factor in the responsiveness of the organism to the disruption of cognitive performance by exposure to HZE particles differing in linear energy transfer

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ABSTRACT

Exposure to particles of high energy and charge (HZE particles) can produce decrements in cognitive performance. A series of experiments exposing rats to different HZE particles was run to evaluate whether the performance decrement was dependent on the age of the subject at the time of irradiation. Fischer 344 rats that were 2-, 11- and 15/16-months of age were exposed to ^{16}O, ^{48}Ti, or ^{4}He particles at the NASA Space Radiation Laboratory at Brookhaven National Laboratory. As previously observed following exposure to ^{56}Fe particles, exposure to the higher LET ^{48}Ti particles produced a disruption of cognitive performance at a lower dose in the older subjects compared to the dose needed to disrupt performance in the younger subjects. There were no age related changes in the dose needed to produce a disruption of cognitive performance following exposure to lower LET ^{16}O or ^{4}He particles. The threshold for the rats exposed to either ^{16}O or ^{4}He particles was similar at all ages. Because the 11- and 15-month old rats are more representative of the age of astronauts (45–55 years old) the present results indicate that particle LET may be a critical factor in estimating the risk of developing a cognitive deficit following exposure to space radiation on exploratory class missions.

1. Introduction

During exploratory class missions, such as a mission to Mars, astronauts will be exposed to doses of radiation greater than those experienced in low earth orbit, where the space shuttle and International Space Station operate (Badhwar, 1998; Schimmerling et al., 2003; Cucinotta et al., 2013). Exposure to 10–30 cGy of particles of high energy and charge (HZE particles), has been shown to produce decrements in cognitive performance (Casadesus et al., 2004; Raber et al., 2004; Haerich et al., 2005; Shukitt-Hale et al., 2007; Rabin et al., 2011; Davis et al., 2014; Britten et al., 2012).

Previous research has shown that the dose of ^{56}Fe particles, which have a high linear energy transfer (LET), needed to disrupt cognitive performance decreases as the age at which the subject is irradiated increases (Rabin et al., 2007, 2012, 2014b). It remains to be established whether a similar relationship would be observed with lower LET particles, such as ^{4}He. This issue arises for several reasons: (1) lower LET particles would constitute a significant proportion of the radiation dose to which astronauts would be exposed within the spacecraft (Norbury and Slaba, 2014); (2) astronauts are likely to be middle-aged and exposure to HZE particles causes decrements in cognitive performance which are similar to those observed in older individuals (Joseph et al., 2000; Shukitt-Hale et al., 2007), and may be more likely to show a decrement in cognitive performance following exposure to lower doses of HZE particles compared to younger individuals; (3) the dose needed to produce a disruption of cognitive performance decreases as the LET of the specific particle decreases (Rabin et al., 2005a, 2012). Because it is possible that a minimum dose of HZE particles may be necessary to reach the threshold for the disruption of cognitive performance, it is possible that there may not be a further reduction in the threshold for the disruption of cognitive performance in old individuals, i.e., there would be no interaction between age of irradiation and the dose needed to disrupt cognitive performance. Given the relative contribution of low LET ^{4}He particles to the total dose experienced by astronauts on exploratory class missions, it would be important to determine whether or not the previously observed interaction between age of exposure to ^{56}Fe particles and threshold dose for the disruption of cognitive performance will characterize these lower LET particles.

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2. Material and methods

2.1. Subjects

The subjects for all experiments were Fischer 344 (F-344) rats. For experiments 1 (^{16}O) and 2 (^{48}Ti), old rats (11 and 15 months of age) were obtained from the colonies maintained by Charles River Laboratories for the National Institute of Aging. Two-month old F-344 rats were also obtained from Charles River Laboratories to minimize potential differences resulting from the use of different suppliers for the young and old rats. All rats were shipped directly to Brookhaven National Laboratory (BNL) by the supplier. For experiment 3 (^{4}He), two sets of 7-week old F-344 rats were obtained from Charles River Labs and shipped to the University of Maryland, Baltimore County (UMBC). These shipments were separated by 5 months. After behavioral testing on the operant task described below, the rats were shipped to BNL at 11 and 16 months of age. At BNL the rats were randomly assigned to specific doses while blinded to their prior performance on the operant task. For each experiment, 2-month old rats were shipped directly to BNL by the supplier to serve as young controls. All procedures were approved by the IACUCs of UMBC and BNL.

2.2. Radiations

Rats were given head-only exposures to HZE particles at the NASA Space Radiation Laboratory (NSRL) at BNL. The specific particles were ^{16}O (NSRL-09C: 1000 Mev/n, LET ≈ 14.2 keV/μm; 0.1 or 0.5 cGy), ^{48}Ti (NSRL-14A: 500 MeV/n, LET ≈ 134 keV/μm; 1.0 or 10.0 cGy), and ^{4}He (NSRL-16A: 1000 MeV/n, LET ≈ 0.9 keV/μm; 0.01, 0.05 or 0.1 cGy). These doses were selected based upon prior research which had established the threshold dose for the specific particles (Rabin et al., 2011). As in the original study using ^{56}Fe particles, the doses used in the present study were at or below the previously established threshold for producing a disruption of cognitive performance.

The initial sample size was ten rats/dose. For irradiation, unanesthetized rats were restrained in a well-ventilated plastic tube. Head-only exposures were accomplished by placing the head of the rat in the center of the beam and shielding the body with tungsten bricks. The nominal dose rates were adjusted so that there were multiple spills but the total irradiation time did not exceed 3–4 min; as such the animals given the higher total doses were also subjected to slightly higher dose rates. Dosimetry was provided by the staff of the NSRL using ion chambers (La Tessa et al., 2016). Non-irradiated control rats were placed in the tubes and walked about the facility for approximately 3–4 min, but were not exposed.

2.3. Behaviors

After irradiation, the rats were tested on two behavioral tasks that have previously shown changes as a function of age. The two tasks measure different aspects of cognitive performance and are dependent upon the integrity of different areas of the brain. The plus maze is a measure of baseline anxiety and is dependent upon the integrity of the amygdala; the operant task is a measure of the responsiveness of the organism to changes in environmental contingencies and the organism's motivation to work for reward. This task is dopamine-mediated and is dependent on the integrity of the striatum. The two tests were administered at different times following irradiation because plus-maze performance is spontaneous and does not require training, whereas the lever press task required training the animals to make the appropriate response. Therefore, the operant test could not be administered until all animals had learned the response.

First the rats were tested for changes in baseline levels of anxiety using the elevated plus-maze (Rabin et al., 2007). Anxiety levels are typically inferred by measuring the amount of time a rat will spend exploring the normally aversive open arms of the maze. In general, the greater the level of anxiety, the less time spent in the open arms of the maze. For the most part, exposure to HZE particles produces an increase in baseline anxiety which is shown as decreased time spent in the anxiogenic open arms of the maze (Rabin et al., 2007).

A standard rat elevated plus-maze with 43 cm arms extending from a 10 cm central area was obtained from Hamilton-Kinder, San Diego, CA (Rabin et al., 2011). The arms of the maze were approximately 90 cm above the floor. The rat's movements were tracked with a series of 36 infra-red photocells which were analyzed by computer software. Lighting was provided by a string of rope lights attached to the underside of the open arms of the maze. Each session was started by placing the rat in the central area facing the open arms of the maze and lasted 5 min. The maze was wiped down with 70% alcohol between different rats. Testing of radiation-induced changes in baseline anxiety was performed 2–3 weeks following exposure.

The second task measured performance on an ascending fixed-ratio (FR) operant task which is dependent upon the integrity of the striatum and dopaminergic system (Salamone et al., 1992, 1993). This system mediates both appetitive and aversive motivation (Salamone 1994); specifically the activational aspects of motivation and decision making as it relates to the expenditure of energy by the organism to achieve a specific goal (Salamone and Correa 2002). As such, it is a measure of the organism's ability and willingness to respond to changes in environmental contingencies and change its pattern of responding as a function of the changing task requirements. All rats were tested twice on the operant task, the first test occurring approximately 2–3 months following irradiation and the second test occurring approximately 7–8 months following exposure. Because the rats exposed to ^{4}He at 11 and 16 months of age were maintained at UMBC prior to shipment to BNL for irradiation, they were also tested on the operant task twice prior to irradiation.

The rats were trained to make a lever-pressing response to obtain a 45 mg food pellet. The training procedure involved placing the rats on a mild food deprivation schedule to maintain their body weight at approximately 90% of their weight prior to the start of the deprivation protocol. Throughout the training and testing periods the rats were weighed daily and the amount of food obtained in the operant chamber was supplemented by food provided by the experimenter as needed to maintain this body weight. Following each test of operant responding the rats were returned to an *ad lib* feeding schedule. Prior to each retest, the rats were again weighed and then placed on a deprivation schedule to reduce their body weight to approximately 90% of their current weight at the time of testing.

For the initial acquisition of the response an autoshaping procedure was utilized, which involved placing the rats in the operant chamber for 12 h. During this phase of the training, the rats were rewarded with a pellet every time the lever was pressed. Once the rats learned to press the lever to obtain food, they were trained to respond on a fixed-ratio (FR) reinforcement schedule. With a FR schedule, the rat is rewarded with a food pellet after a specific number of lever-presses: on an FR-1 schedule, every response is rewarded; whereas on an FR-20 schedule, 20 lever presses are required to obtain a single pellet; and on an FR-35 schedule, the rat must press the lever 35 times in order to obtain a single pellet. After the initial acquisition of the response, typically within a single session, the rats were introduced to the FR procedure. The training protocol for the acquisition of fixed-ratio responding involved two daily 30-min sessions at FR-1, followed on consecutive days by sessions at FR-5, FR-10 and FR-20. For testing, an ascending fixed-ratio reinforcement schedule from FR-1 to FR-35 was used. On consecutive days, the rats were run on FR-1, FR-5, FR-10, FR-15, FR-20, FR-25, FR-30, FR-35 reinforcement schedules. Each daily session was 30 min in duration and utilized only a single reinforcement schedule.

2.4. Data analysis

Initial data analysis was a 2-way (plus-maze) or 3-way (operant