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Effects of exposure to ^{56}Fe particles on the acquisition of a conditioned place preference in rats

B.M. Rabin[1], B. Shukitt-Hale[2], J.A. Joseph[2], N. Denissova[2]

1. Dept. of Psychology, UMBC, Baltimore, MD 21250 (USA)
2. Human Nutrition Research Center on Aging, USDA, Tufts Univ., Boston, MA 02111 (USA)

Abstract

Exposure to low doses of ^{56}Fe particles produces changes in neural function and behavior. The present experiments were designed to examine the effects of irradiation on the acquisition of a dopamine-mediated conditioned place preference (CPP). In the CPP procedure, rats are given an injection of the dopamine agonist amphetamine in one distinctive compartment and a saline injection in a different compartment of a three-compartment apparatus. Control rats develop a preference for the amphetamine-paired compartment. In contrast, rats exposed to 1 Gy of ^{56}Fe particles fail to develop a similar preference. The results of the experiment indicate that exposure to low doses of heavy particles can disrupt the neural mechanisms that mediate the reinforcement of behavior.

KEYWORDS: Iron-56, behavior, place preference, reinforcement, dopamine, irradiation.

1. Introduction

Exposing an organism to low doses of heavy particles can produce changes in neural functioning and behavior. More specifically, exposing rats to 1.0 to 1.5 Gy of ^{56}Fe particles produces alterations in dopaminergic activity [3, 4] and in dopamine-mediated behaviors, including motor behavior [3] and amphetamine-induced taste aversion learning [6, 7].

Dopamine is a behaviorally important neurotransmitter which is involved in the mediation of a range of behaviors, including operant responding [5] and reinforcement [1, 2]. Because exposure to low doses of heavy particles affects the functioning of the dopaminergic system, there is the possibility that these behaviors may also be affected. The present experiment was designed to begin an evaluation of the effects of exposure to ^{56}Fe particles on reinforcement using the conditioned place preference (CPP) paradigm. This procedure is standard for determining the effects of a variety of treatments on the capacity of a stimulus to reinforce learning.

2. Methods

The subjects were 37 male albino rats weighing 200-225 g at the start of the experiment. Twenty-four rats were irradiated with 1.0 Gy of 1 GeV/n ^{56}Fe particles using the Alternating Gradient Synchrotron at Brookhaven National Laboratory. The remaining rats served as non-irradiated controls.

Three days following exposure, the rats were returned to UMBC for testing. For 21 rats, amphetamine-induced CPP training was begun 3 weeks following exposure; for the remaining 16 rats, training was begun 7 weeks following irradiation. An unbiased procedure was used to establish a CPP. In this procedure, half the rats were given an injection of amphetamine (2 mg/kg, ip) in a distinctive black compartment of a three-compartment box; on alternate days, the animals were given an injection of saline in the white compartment of the box. The pattern of injections was reversed for the remaining rats, who received the amphetamine injection in the white compartment. After three injections of each compound the rats were tested for the development of a CPP by being placed in a neutral compartment and allowed to move freely between all three compartments of the apparatus for 15 min (900 sec). The amount of time spent in each compartments was recorded. A CPP to amphetamine has developed if the rats spend significantly more time in the amphetamine-paired compartment than in the saline-paired compartment.

Statistical analysis of the results was performed using a three-way analysis of variance. *Post hoc* comparisons between individual groups were performed using the Tukey-Kramer procedure to compensate for the multiple comparisons.

3. Results

The results of exposure to 1.0 Gy of 1 GeV/n ^{56}Fe particles on the acquisition of an amphetamine-induced CPP are summarized in Table I. The acquisition of an amphetamine-induced CPP in control animals is shown by the fact that the control rats spent significantly more time in the amphetamine-paired compartment than in the saline-paired compartment at both time intervals (3-week, $t = 20.16$, $p < 0.01$; 7-week, $t = 34.43$, $p < 0.01$). For the irradiated rats, there were no significant differences in the amount of time spent in either the amphetamine- or saline-paired compartment. Although there was a tendency for the irradiated rats to spend more time in the amphetamine-paired compartment than in the saline-paired compartment, this difference was not statistically significant either for the group trained three weeks ($t = 1.25$, $p > 0.05$) or seven weeks ($t = 2.07$, $p > 0.05$) following irradiation.

Comparing the performance of the rats trained three weeks following irradiation with those trai-

Table I – Time Spent in Amphetamine- and Saline-paired Compartments by Irradiated and Control Rats.

Week	Condition	n	Amphetamine-Paired (sec)	Saline-Paired (sec)
3	Radiation	15	387.0 ± 41.39*	301.67 ± 39.22
	Control	6	618.00 ± 41.98	134.67 ± 27.57
7	Radiation	9	438.11 ± 47.13	311.44 ± 38.11
	Control	7	740.71 ± 27.07	155.28 ± 93.02

* Mean ± standard error

ned seven weeks following irradiation, the data shown in Table I suggest that the rats that were run seven weeks following exposure spent a greater amount of time in one of the two injection compartments (amphetamine or saline) as compared to the neutral compartment. However, none of the *post hoc* comparisons indicated a significant change in the amount of time spent in either injection compartment as a function of time of training.

4. Discussion

Exposing rats to low doses of ^{56}Fe particles produces changes in the functioning of the dopaminergic system and in the behaviors that are mediated by dopamine. Previous research has shown that these behaviors include motor behavior [3] and amphetamine-induced taste aversion learning [6, 7]. The present experiment extends this research by showing that exposure to heavy particles can also disrupt dopamine-mediated reinforcement, as measured using the CPP procedure.

The CPP paradigm is the standard procedure for studying the capacity of a stimulus to function as a reinforcer [1, 2]. The acquisition of a conditioned place preference is shown by an increase in the amount of time spent in an environment that has been paired with a reinforcing stimulus. The neurotransmitter dopamine plays a key role in reinforcement and the administration of dopamine agonists such as amphetamine produce a place preference, as evidenced by the control rats in the present experiment. Exposing rats to low doses of ^{56}Fe particles disrupts the acquisition of an amphetamine-induced CPP. In contrast to controls which spent a significantly greater amount of time in the amphetamine-paired compartment, irradiated rats fail to develop a preference for the amphetamine paired compartment, spending approximately equal amounts of time in both the amphetamine- and saline-paired compartments. This observation indicates that exposure to heavy particles affects the neural mechanisms that mediate reinforcement.

The observation that there was no significant change in the amount of time spent in either injection compartment for the rats trained seven weeks following exposure compared to the rats trained three weeks after irradiation, indicates that there is no recovery in the radiated rats as a function of the passage of time following exposure. These results suggest that the changes in dopamine-mediated reinforcement may be relatively permanent. This interpretation would be consistent with the neurochemical data which indicates that there is no recovery of dopaminergic function as long as six months following exposure to 1 Gy of 600 MeV/n ^{56}Fe particles [3]. However, a more detailed analysis of the permanency of this effect will require the use of rats that have been trained even later following exposure.

In conclusion, the present results are in accord with the hypothesis that exposure to low doses of ^{56}Fe particles can disrupt the wide range of behaviors that are mediated by dopamine. These results, together with the results of previous research, suggest that astronauts on long-duration missions outside the magnetosphere may be at risk for disruptions of behavior that could affect their ability to successfully meet mission requirements.

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