Amphetamine-induced taste aversion learning in young and old F-344 rats following exposure to ^{56}Fe particles

K. L. Carrihill-Knoll · B. M. Rabin ·
B. Shukitt-Hale · J. A. Joseph · A. Carey

Received: 5 December 2006 / Accepted: 27 March 2007 / Published online: 3 May 2007
© American Aging Association 2007

Abstract Exposure to ^{56}Fe particles produces changes in dopaminergic function and in dopamine-dependent behaviors, including amphetamine-induced conditioned taste aversion (CTA) learning. Because many of these changes are characteristic of the changes that accompany the aging process, the present study was designed to determine whether or not there would be an interaction between age and exposure to ^{56}Fe particles in the disruption of an amphetamine-induced CTA. One hundred and forty F-344 male rats 2-, 7-, 12-, and 16-months old, were radiated with ^{56}Fe particles (0.25–2.00 Gy, 1 GeV/n) at Brookhaven National Laboratory. Three days following irradiation, the rats were tested for the effects of radiation on the acquisition of a CTA produced by injection of amphetamine (3 mg/kg, i.p.). The main effect of age was to produce a significant decrease in conditioning day sucrose intake; there was

no affect of age on the acquisition of the amphetamine-induced CTA. Exposing rats to ^{56}Fe particles disrupted the acquisition of the CTA produced by injection of amphetamine only in the 2-month-old rats. These results do not support the hypothesis of an interaction between age and exposure to ^{56}Fe particles in producing a disruption of amphetamine-induced CTA learning. As such, these results suggest that the aging produced by exposure to ^{56}Fe particles may be endpoint specific.

Keywords ^{56}Fe particles · Aging · Amphetamine · Conditioned taste aversion · F-344 rats

Introduction

A conditioned taste aversion (CTA) is produced when a novel taste solution is paired with an unconditioned stimulus such that the organism will avoid intake of that solution at a subsequent presentation. The acquisition of a CTA can be influenced by a variety of factors, including the nature of the unconditioned stimulus (Glowa et al. 1994; Grigson and Freet 2000), the strain (Glowa et al. 1994; Grigson and Freet 2000; Foynes and Riley 2004; Kosten et al. 1994; Lancellotti et al. 2001), and the age (Misanin et al. 1988; Misanin et al. 2002a; Valliere et al. 1988) of the rat. Previous research, using lithium chloride (LiCl) to produce a CTA in Lewis and Fischer-344

K. L. Carrihill-Knoll · B. M. Rabin (✉)
Department of Psychology, University of Maryland
Baltimore County,
Baltimore, MD 21250, USA
e-mail: rabin@umbc.edu

B. Shukitt-Hale · J. A. Joseph · A. Carey
Human Nutrition Research Center on Aging, USDA-ARS,
Tufts University,
Boston, MA 02111, USA

rats, has shown that there are a series of age-related changes in CTA learning (Misanin et al. 1988; Misanin et al. 2002a, b; Valliere et al. 1988). Overall, these studies indicate that older rats are more sensitive to the effects of pairing LiCl with a novel solution. Compared with younger rats, older rats are more likely to acquire a CTA across a range of CS-US intervals (Misanin et al. 1988; Ingram and Peacock 1980), are more resistant to the extinction of the CTA (Guanowsky et al. 1983; Ingram and Peacock 1980), and are less responsive to the disruptive effects of US pre-exposure on the acquisition of a CTA (Valliere et al. 1988).

Exposing rats to heavy particles (HZE particles), a ground-based model for exposure to cosmic rays, disrupts the functioning of the dopaminergic system (Joseph et al. 1992, 1993) and the behaviors that are dependent upon the integrity of that system (Joseph et al. 1992; Rabin et al. 1998, 2003; Shukitt-Hale et al. 2000, 2003). In addition to the effects of irradiation on cognitive performance, exposure to ^{56}Fe particles disrupts the acquisition of an amphetamine-induced CTA, but does not affect the acquisition of a CTA produced by administration of lithium chloride (Rabin et al. 1998, 2000). Because amphetamine is a dopamine agonist, the development of an amphetamine-induced CTA requires an intact dopamine system (Rabin et al. 1998), and the disruption of dopaminergic function by heavy particle irradiation interferes with behaviors that are dependent upon the integrity of that system. Overall, the deficits observed following exposure to HZE particles are similar to those that are observed in old animals, which suggest that exposure to low doses of HZE particles produces “accelerated aging” (Joseph et al. 1992, 1993, 2000).

Because both the aging process (Baker et al. 1997; Friedman and Gerhardt 1992; Shukitt-Hale et al. 2002) and exposure to HZE particles disrupt dopaminergic function (Joseph et al. 1992, 1993), it is possible that there may be an interaction between age and irradiation, such that exposing older rats to lower doses of ^{56}Fe particles will interfere with the acquisition of an amphetamine-induced CTA. Previous studies have shown that exposing rats to doses of ^{56}Fe particles which do not affect operant performance in young rats (≈ 2 months of age) produces deficits in performance in older animals (Rabin et al. 2003, 2005). Similarly, lower doses of ^{56}Fe particles are needed with older rats to produce decreases in

exploration of the open arms of the elevated plus-maze than are needed for younger rats (Rabin et al. 2007). Therefore, it is possible that a similar effect would be observed with CTA learning such that a lower dose of radiation would be required to disrupt amphetamine-induced CTA learning in older rats than in younger rats.

The purpose of the present experiment was to determine: (1) whether there were any systematic effects of age on the acquisition of an amphetamine-induced CTA in F-344 rats, as previously reported for LiCl-induced CTA learning; and (2) whether the effects of exposure to ^{56}Fe particles on amphetamine-induced CTA learning varied as a function of the age of the rat.

Materials and methods

Subjects

One hundred and forty Fischer-344 (F-344) male rats, aged 2, 7, 12 and 16 months ($n=10$ rats/dose) at the time of radiation, were obtained from the National Institute of Aging contract colonies. Although previous research on the effects of exposure to ^{56}Fe particles has utilized Sprague-Dawley (S-D) rats, F-344 rats were selected for this experiment because they are the standard strain used in aging studies.

The rats were housed in AAALAC-accredited facilities at Brookhaven National Laboratory (BNL). They were maintained on a 12-h light/dark cycle in a temperature and humidity controlled room. Food and water were continuously available except as required by the experimental protocol. The research protocol was approved by the Institutional Animal Care and Use of Committees of UMBC and BNL.

Radiation

Rats were exposed to ^{56}Fe (1 GeV/n) particles using the NASA Space Research Laboratory (NSRL) at BNL. At first, 7- and 16-month-old rats were exposed to 0.5 or 1.5 Gy of ^{56}Fe particles at a nominal dose rate of 1.0 Gy/min. The 2- (0.5, 1.5 or 2.0 Gy) and 12-month-old (0.25, 0.5 or 1.5 Gy) rats were exposed to ^{56}Fe particles 6 months following the first groups of rats. The control rats at each age (0 Gy) were not irradiated.

These radiation doses were selected in order to bracket doses that have been previously reported to be effective in altering the responsiveness of rats to injection of amphetamine. This research has shown that doses between 0.8 and 1.5 Gy of ^{56}Fe particles (1 GeV/n) disrupt the acquisition of an amphetamine-induced CTA in 2-month-old S-D rats (Rabin et al. 2000). Therefore the doses for this experiment were intended to evaluate the effectiveness of both lower and higher doses of ^{56}Fe particles on CTA learning as a function of age.

During radiation, rats were placed in a well-ventilated plastic restraining tube which restricted the movement of the rat. The plastic tube was placed perpendicular to the beam and positioned so that the head of the rats was in the center of the beam. As such, the rat's shoulders may have also received some radiation.

Procedure

Four days prior to irradiation, the rats were placed on a 23.5-h water deprivation schedule, which was maintained for the duration of the experiment. Three days after irradiation, on the conditioning day, the rats were presented with a single calibrated drinking tube containing a 10% sucrose solution for the 30-min drinking period, and intake measured. Immediately following the drinking period, all rats were injected with amphetamine (3 mg/kg, ip). Twenty-four hours later, on test day, the rats were again presented with a calibrated drinking tube containing the 10% sucrose solution for the 30-min drinking period, and intake was measured. A CTA is shown by a significant reduction in test-day sucrose intake in comparison with conditioning-day intake.

These particular experimental parameters were selected so that the results of the current experiments using F-344 rats would be consistent with the results of previous research using S-D rats. Specifically, the 3-day interval was selected because previous experiments on the effects of exposure to HZE particles (Joseph et al. 1992) had shown a maximal reduction in dopamine release 3 days following exposure to ^{56}Fe particles. In addition, research on the disruption of amphetamine-induced CTA learning has utilized a single injection of amphetamine on the conditioning day and a 24-h interval between conditioning and test days.

Statistical analyses

To evaluate the effects of exposure to 1 GeV/n ^{56}Fe particles on CTA learning, three separate analyses of variance (ANOVA) were performed: (1) a two-way ANOVA comparing conditioning and test day sucrose intake of the non-irradiated rats (0 Gy) across all the age groups; (2) a three-way ANOVA for the three doses (0 Gy, 0.5 Gy and 1.5 Gy) that were common to all four age groups; and (3) a series of two-way ANOVAs across all dose ranges within each individual age group. Post-hoc comparisons between individual groups of rats were made using the Fisher's protected *t*-tests.

Results

Figure 1 presents the effects of age on conditioning and test-day sucrose intake of young (2- and 7-months old), mature (12-months old) and adult (16-months old) non-irradiated rats. These data show that there is a decrease in conditioning-day sucrose intake as a function of age, and further decrease in test-day in-

Fig. 1 Effects of age on conditioning- and test-day sucrose intake (ml) in non-irradiated rats. The control rats were taken to the accelerator but were not exposed to ^{56}Fe particles. Conditioning day was 3 days following this procedure. The rats were tested at different ages: young (2 and 7 months), mature (12 months) and adult (16 months) rats. Error bars indicate the standard error of the mean (s.e.m). **a** Significantly different ($P < 0.05$) than age-dependent conditioning-day intake; **b** significantly different ($P < 0.05$) than conditioning-day intake of the 2-month-old rats; **c** significantly different ($P < 0.05$) than the test day intake of the 2-month old rats

take at all ages following injection of amphetamine. The initial two-way ANOVA comparing the conditioning day intake with the test-day intake of the non-irradiated rats across all age groups indicated significant main effects for age ($F[3,77]=34.35$, $P<0.01$), and for day ($F[1,77]=266.03$, $P<0.01$). The age by day interaction was not significant ($F[3,77]=0.44$, $P>0.10$), indicating that the test day reduction in sucrose intake was observed in all groups of rats regardless of age.

Post-hoc comparisons indicated that at all ages there was a significant decrease in test-day intake compared with conditioning-day intake. In addition, compared with the sucrose intake of the 2-month-old rats, there were significant reductions in the intake of

the 7-, 12- and 16-month-old rats on both conditioning and test days. There were no significant differences in conditioning and test-day sucrose intake between the latter three groups of rats.

Figure 2 presents the effects of radiation on conditioning- and test-day sucrose intake as a function of age. Initially, a three-way ANOVA was performed for the doses (0 Gy, 0.5 Gy and 1.5 Gy) that were common to all four age groups. The results show that the main effects for age ($F[3,113]=86.67$, $P<0.01$); for radiation dose ($F[2,113]=9.51$, $P<0.01$); and for day ($F[1,102]=653.99$, $P<0.01$) were significant. All two-way interactions were also significant, as was the triple interaction ($F[6,114]=3.84$, $P<0.01$).

Fig. 2 Conditioning- and test-day sucrose intake (ml) as a function of dose and age of exposure/testing. **a** 2-month-old rats; **b** 7-month-old rats; **c** 12-month-old rats; **d** 16-month-old rats. The data for the non-irradiated rats is redrawn from Fig. 1

To provide a more detailed analysis of the relationship between age and exposure to ^{56}Fe particles, a series of two-way ANOVAs was run to analyze the effects of radiation at each age separately. At all ages, there was a significant decrease in test day sucrose intake compared with conditioning day intake (all P values < 0.05). The main effect for dose was significant in the 2-, 12- and 16-month-old rats (all P values < 0.05). However, only for the 2- and 16-month-old ($F[3,35] = 6.86$, $P < 0.01$; $F[2,27] = 6.41$, $P < 0.01$, respectively) rats was the day by dose interaction significant, indicating that the response of the rats to injection of amphetamine varied as a function of both radiation dose and age. For the 2-month-old rats, post hoc analysis using Fischer's protected t -test showed that a significant reduction in test-day sucrose intake compared with conditioning-day intake was observed at all radiation doses except for the rats exposed to 0.50 Gy of ^{56}Fe particles. None of the individual comparisons were significant in the 16-month-old rats.

Discussion

Considering initially the effects of age on conditioning-day sucrose intake in the control (non-irradiated) rats, the data show that there is a significant decrease in intake as a function of age. This decrease has not been reported by previous investigators who have studied the effects of aging on taste aversion learning. The reasons for the decreased intake in the current study are not immediately obvious. One possibility is that may be related to the fact that the present experiment utilized F-344 rats from the N.I.A.-supported colonies in contrast to the other previous studies which utilized Wistar rats (Misanin et al. 1988, 2002a, b; Glowa et al. 1994; Guanowsky et al. 1983). It is possible that adult and old F-344 rats respond differently to sucrose than do Wistar rats. While strain differences have been reported in the acquisition of a CTA, these studies have used young rats and the differences that are observed are on the effects of specific stimuli and manipulations on CTA learning (Grigson and Freet 2000; Foynes and Riley 2004; Kosten et al. 1994; Lancellotti et al. 2001).

It is also possible that effect of aging on conditioning-day sucrose intake is masked, to some extent, when the data are presented as preference score (Moron

et al. 2002) or when a two-bottle test is used (Misanin et al. 1988, 2002a, b; Ingram and Peacock 1980; Guanowsky et al. 1983). Because of the difficulties associated with the use of an accelerator to irradiate the rats, the present experiment and related previous experiments (Rabin et al. 1998, 2000, 2003) have utilized a one-bottle test to decrease the possibility that the neophobic response of rats would interfere with the intake of the novel sucrose solution. While the use of a single-bottle test was adopted to minimize the neophobic response to the novel sugar solution, it still remains possible that the differences in conditioning-day sucrose intake as a function of age may reflect age-dependent changes in neophobia. Alternatively, it is possible that the deprivation schedule produced different levels of thirst as a function of the animal's age. The lack of pre-conditioning water intake does not permit the evaluation of these alternatives. However, research using S-D rats in which water intake was monitored indicates that exposure to different doses of heavy particles does not differentially affect water intake.

Despite the decreased conditioning-day sucrose intake in the older control rats compared with the 2-month-old rats, a significant reduction in test-day intake was observed in non-irradiated rats at all ages. As such, increasing age does not affect the ability of the rat to acquire an amphetamine-induced CTA. These results are consistent with the results of previous studies which have shown that older rats are more likely to acquire an aversion under a variety of conditions than are younger rats (Misanin et al. 1988, 2002a; Valliere et al. 1988; Ingram and Peacock 1980). In the present experiment, the amount of the decrease in test-day sucrose intake was greatest in the 7-month-old rats. There was no further reduction in test-day sucrose intake in the 12- and 16-month-old rats, probably due to a "floor" effect which limited the reduction in test-day intake.

With regard to the effects of exposure to heavy particles on amphetamine-induced CTA learning, the present results show that exposing 2-month-old F-344 rats to 0.5 Gy of ^{56}Fe particles reduces the intensity of an amphetamine-induced CTA. These results are consistent with the results of previous experiments using Sprague-Dawley (S-D) rats, which also showed a disruption of amphetamine-induced CTA learning following exposure to ^{56}Fe particles (Rabin et al. 1998, 2000). For the rats exposed to 0.5 Gy of ^{56}Fe

particles (1 GeV/n), the test-day sucrose intake following injection of amphetamine was not significantly different than the conditioning-day intake, indicating a disruption of the amphetamine-induced CTA learning. Although the basic response to irradiation was the same, strain differences are shown as differences in the dose of heavy particle radiation needed to produce the disruption of CTA learning: 0.5 Gy for the F-344 rats compared with 0.8 Gy for the S-D rats exposed to 1 GeV/n ^{56}Fe particles.

As shown in Fig. 2, only the 2-month-old rats showed a significant disruption of amphetamine-induced taste aversion learning following exposure to ^{56}Fe particles. Exposing the 7-, 12- and 16-month-old rats to ^{56}Fe particles did not disrupt the acquisition of an amphetamine-induced CTA; there were reductions in test-day sucrose intake at all ages and doses. These results indicate that exposing older rats (7-, 12- and 16-months of age) to heavy particles did not produce any effects on CTA learning above those produced by the age of the animal.

Although the data are interpreted in terms of the disruption of amphetamine-induced CTA learning by exposure to ^{56}Fe particles, alternate interpretations are available. Grigson and collaborators (Grigson et al. 1998, 2002; Schroy et al. 2005) have proposed that the treatment with drugs of abuse, such as cocaine, morphine and amphetamine, do not cause a taste aversion per se. Rather, treatment with these drugs suppresses intake of the normally preferred sucrose solution by interfering with the reinforcing aspects of the solution. In this interpretation, the sucrose becomes a conditioned stimulus predicting the forthcoming presentation of the more rewarding amphetamine. This effect, called the anticipatory contrast effect, is observed when saccharin is paired with drugs of abuse or when a weaker saccharin solution is paired with a subsequent stronger solution (Grigson and Freet 2000; Schroy et al. 2005). Additional support comes from the observation that ibotenic acid lesions of the gustatory thalamus disrupt the avoidance of the saccharin produced by injection of drugs of abuse, but not by injection of lithium chloride (Grigson and Freet 2000; Schroy et al. 2005; Reilly et al. 2004). Rabin et al. (1998) have reported similar results following exposure to heavy particles. Following exposure to ^{56}Fe particles, rats continue to show a lithium chloride-induced CTA, but fail to show a CTA following injection of amphetamine. This observation

would be consistent with the anticipatory contrast effect hypothesis proposed by Grigson and collaborators. However, in contrast to the support provided by the selective effects of ibotenic acid applied to the gustatory thalamus or parabrachial nucleus, heavy particle irradiation affects the entire brain non-selectively. Although the studies using exposure to heavy particles are consistent with the anticipatory contrast effect hypothesis, the data do not provide unequivocal support. The present results, however, do indicate that the effects of treatment with amphetamine are consistent across all ages tested, and that there may be enhanced effects in the older rats.

Because the effect of exposure to ^{56}Fe particles is to produce “accelerated aging” (Joseph et al. 1992, 1993, 2000), it was hypothesized that there would be an interaction between age and irradiation in the ^{56}Fe -induced disruption of amphetamine-induced CTA learning. The present results do not support this hypothesis. Exposure to the lowest dose of ^{56}Fe particles (0.50 Gy) did disrupt the acquisition of the dopamine-mediated amphetamine-induced CTA in the younger rats (2-months old), a finding that is consistent with previous research (Rabin et al. 1998, 2000). However, a significant disruption of CTA learning was not observed in the older rats (7-, 12-, and 16-months old). For these animals, an age-related decrease in both unconditioned and conditioned sucrose intake seems to have been the primary effect. In contrast to the results observed with other endpoints and with younger rats, exposure to HZE particles did not produce additional effects on the acquisition of an amphetamine-induced CTA.

Previous research using a ground-based model for exposure to cosmic rays has shown that irradiation affects the functioning of the dopaminergic system (Joseph et al. 1992, 1993, 1999) and the behaviors that are dependent upon the integrity of that system (Rabin et al. 2000, 2003; Shukitt-Hale et al. 2000, 2003). The radiation-induced changes are also characteristic of the aged organism. In general, the behavioral changes produced by exposure to heavy particles interact with the those that occur as a part of the aging process, such that ^{56}Fe -induced deficits in performance that are not observed in younger organisms are observed in older ones (Rabin et al. 2005) and lower doses of HZE particles are needed to produce deficits in older rats than are needed to produce equivalent deficits in younger ones (Rabin

et al. 2007). The results of the present experiment show that the disruption of an amphetamine-induced, dopamine-mediated CTA produced by exposure to 0.5 Gy of ^{56}Fe particles in 2-month-old rats does not occur in older F-344 rats, either radiated or non-irradiated. In contrast to other dopamine-mediated behavioral endpoints, the effect of exposure to HZE particles does not parallel the effects of aging in that aging does not disrupt the acquisition of an amphetamine-induced CTA. The factors that may be responsible for the discrepancy between the effects of exposure to ^{56}Fe particles and aging on CTA learning, compared with other behavioral endpoints, are not certain. It is, however, possible that the significant decrease in unconditioned sucrose intake as a function of aging interferes with the heavy-particle-induced disruption of the amphetamine-induced CTA.

In summary, there are two components to the present experiment: first, an evaluation of the effects of age on the acquisition of an amphetamine-induced CTA; and second, the possible interaction between age and heavy particle irradiation on amphetamine-induced taste aversion learning. With regard to the first hypothesis, the major finding of the present experiment is that aging is associated with a significant decrease in sucrose intake on the conditioning day. Despite the decrease in sucrose intake, all rats acquired a CTA following injection of amphetamine. With regard to the second hypothesis, exposure to ^{56}Fe particles disrupted the acquisition of a CTA only in the 2-month-old rats exposed to the lowest tested dose of radiation (0.5 Gy). There were no significant effects of irradiation in the older rats (7-, 12-, or 16-months old) on amphetamine-induced CTA. These results suggest that possible interactions between exposure to HZE particles and age may be dependent upon the specific endpoint under consideration.

Acknowledgements This study was supported by grants from the National Aeronautics and Space Administration. We also wish to thank N.I.A. for providing access to their colonies of aged rats.

References

- Baker LJ, Baker TB, Kesner RP (1997) Taste aversion learning in young and adult rats. *J Comp Physiol Psychol* 91:1168–1178
- Foynes MM, Riley AL (2004) Lithium-chloride-induced conditioned taste aversion in the Lewis and Fischer 344 rat strains. *Pharmacol Biochem Behav* 79:303–308
- Friedman MN, Gerhardt GA (1992) Regional effects of aging on dopaminergic function in the Fischer-344 rat. *Neurobiol Aging* 14:560–569
- Glowa JR, Shaw AE, Riley AL (1994) Cocaine-induced conditioned taste aversions: comparison between effects in LEW/N and F344/N rat strains. *Psychopharmacol* 114:229–232
- Grigson PS, Freet CS (2000) The suppressive effects of sucrose and cocaine, but not lithium chloride, are greater in Lewis than in Fischer rats: evidence for the reward comparison hypothesis. *Behav Neurosci* 114:353–363
- Grigson PS, Reilly S, Shimura T, Norgren R (1998) Ibotenic acid lesions of the parabrachial nucleus and conditioned taste aversion: further evidence for an associative deficit in rats. *Behav Neurosci* 112:160–171
- Grigson PS, Lyuboslavsky P, Tanase D (2002) Bilateral lesions of the gustatory thalamus disrupt morphine—but not LiCl—induced intake suppression in rats: evidence against the conditioned taste aversion hypothesis. *Brain Res* 858:327–337
- Guanowsky V, Misanin JR, Riccio DC (1983) Retention of conditioned taste aversion in weanling, adult, and old age rats. *Behav Neur Biol* 37:173–178
- Ingram DK, Peacock LJ (1980) Conditioned taste aversion as a function of age in mature male rats. *Exp Aging Res* 6:113–123
- Joseph JA, Hunt WA, Rabin BM, Dalton TK (1992) Possible “accelerated aging” induced by ^{56}Fe heavy particle irradiation: implications for manned space flights. *Radiat Res* 130:88–93
- Joseph JA, Hunt WA, Rabin BM, Dalton TK, Harris AH (1993) Deficits in striatal muscarinic receptor sensitivity induced by ^{56}Fe heavy particle irradiation: further “age-radiation” parallels. *Radiat Res* 135:257–261
- Joseph J, Shukitt-Hale B, McEwen J, Rabin BM (1999) Magnesium activation of GTP hydrolysis or incubation in S-adenosyl-L-methionine reverses ^{56}Fe -induced decrements in oxotremorine-enhancement of K^+ -evoked striatal dopamine release. *Radiat Res* 152:637–641.
- Joseph JA, Shukitt-Hale B, McEwen J, Rabin BM (2000) CNS-induced deficits of heavy particle irradiation in space: The aging connection. *Adv Space Res* 25:2057–2064
- Kosten TA, Miserendino, MJD, Chi S, Nestler EJ (1994) Fischer and Lewis rat strains show differential cocaine effects in conditioned place preference and behavioral sensitization but not in locomotor activity or conditioned taste aversion. *J Pharmacol Exp Ther* 269:137–144
- Lancelotti D, Mayer BM, Glowa JR, Houghtling RA, Riley AL (2001) Morphine-induced conditioned taste aversions in the LEW/N and F344/N rat strains. *Pharmacol Biochem Behav* 68:603–610
- Misanin JR, Greider DL, Hinderliter CF (1988) Age differences in the outcome of long-delay taste-aversion conditioning in rats. *Bull Psychon Soc* 26:258–260
- Misanin JR, Collins M, Rushanan S, Anderson MJ, Goodhart M, Hinderliter CF (2002a) Aging facilitates long-trace taste-aversion conditioning in rats. *Physiol Behav* 75:759–764
- Misanin JR, Goodhart MG, Anderson MJ, Hinderliter CF (2002b) The interaction of age and unconditioned stimulus intensity on long-trace conditioned flavor aversion in rats. *Dev Psychobiol* 40:131–137

- Moron I, Ballarsteros MA, Candido A, Gallo M (2002) Taste aversion learning and aging: a comparison with the effect of dorsal hippocampal lesions in rats. *Physiol Res* 51: S21–S27
- Rabin BM, Joseph JA, Erat S (1998) Effects of exposure to different types of radiation on behaviors mediated by peripheral or central systems. *Adv Space Res* 22:217–225
- Rabin BM, Joseph JA, Shukitt-Hale B, McEwen J (2000) Effects of exposure to heavy particle on a behavior mediated by the dopaminergic system. *Adv Space Res* 25: 2065–2074
- Rabin BM, Joseph JA, Shukitt-Hale B (2003) Long-term changes in amphetamine-induced reinforcement and aversion in rats following exposure to ^{56}Fe particles. *Adv Space Res* 31:127–133
- Rabin BM, Joseph JA, Shukitt-Hale B (2005) A longitudinal study of operant responding in rats irradiated when 2 months old. *Radiat Res* 164:552–555
- Rabin BM, Carrihill-Knoll K, Carey A, Maloney B, Shukitt-hale B, Joseph JA, Foster BC (2007) Elevated plus-maze performance of Fischer 344 rats as a function of age and exposure to ^{56}Fe particles. *Adv Space Res* (in press)
- Reilly S, Bornovalova M, Trifunovic R (2004) Excitotoxic lesions of the gustatory thalamus spare simultaneous contrast effects but eliminate anticipatory negative contrast: evidence against a memory deficit. *Behav Neurosci* 118:365–376
- Schroy PL, Wheeler RA, Davidson C, Scalera G, Twining RC, Grigson PS (2005) Role of gustatory thalamus in anticipation and comparison of rewards over time in rats. *Am J Physiol Regul Integr Comp Physiol* 288:R966–R980
- Shukitt-Hale B, Casadesus G, McEwen JJ, Rabin BM, Joseph JA (2000) Spatial learning and memory deficits induced by ^{56}Fe radiation exposure. *Radiat Res* 154:8–33
- Shukitt-Hale B, McEwan JJ, Szprengiel A, Joseph JA (2002) Effect of aging on the radial arm water maze — a test of spatial learning and memory. *Neurobiol Aging* 25: 223–229
- Shukitt-Hale B, Casadesus G, Cantuti-Castelvetri I, Rabin BM., Joseph JA (2003) Cognitive deficits induced by ^{56}Fe radiation exposure. *Adv Space Res* 31:119–126
- Valliere WA, Misanin JR, Hinderliter CF (1988) Age-related differences in the US pre-exposure effect on conditioned taste aversion in rats. *Bull Psychonom Soc* 26:64–66