Pharmacology Biochemistry & Behavior, Vol. 29, pp. 335–341. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Radiation-Induced Increases in Sensitivity of Cataleptic Behavior to Haloperidol: Possible Involvement of Prostaglandins

J. A. JOSEPH, S. B. KANDASAMY, W. A. HUNT, T. K. DALTON AND S. STEVENS

Behavioral Sciences Department, Armed Forces Radiobiology Research Institute Bethesda, MD 20814-5145

Received 1 June 1987

JOSEPH, J. A., S. B. KANDASAMY, W. A. HUNT, T. K. DALTON AND S. STEVENS. *Radiation-induced increases in sensitivity of cataleptic behavior to haloperidol: Possible involvement of prostaglandins.* PHARMACOL BIOCHEM BEHAV **29**(2) 335–341, 1988.—The effects of radiation exposure on haloperidol-induced catalepsy were examined in order to determine whether elevated prostaglandins, through an action on dopaminergic autoreceptors, could be involved in the radiation-induced increase in the potency of this neuroleptic. Cataleptic behavior was examined in animals irradiated with various doses of gamma photons (1–150 Gy) and pretreated with a subthreshold dose of haloperidol (0.1 mg/kg). This approach was chosen to maximize any synergistic effects of radiation and haloperidol. After irradiation with doses ≤30 Gy, the combined treatment of haloperidol and radiation produced catalepsy, whereas neither treatment alone had an effect. This observed catalepsy could be blocked with prior administration of indomethacin, a prostaglandin synthesis inhibitor. Animals exposed to doses of radiation ≤50 Gy and no haloperidol, however, displayed apparent catalepsy. This effect was also antagonized by indomethacin. Prostaglandins can induce catalepsy and when administered in subthreshold doses along with subthreshold doses of haloperidol, catalepsy was observed. In order to assess a possible action of prostaglandins and radiation on dopaminergic activity, the functioning of striatal dopaminergic autoreceptors was examined by determining the effects of varying concentrations of haloperidol on the K^+-evoked release of dopamine from striatal slices obtained from parallel groups of animals treated as above. Results indicated that sensitivity to haloperidol increased (higher K^+-evoked dopamine release) in slices from irradiated or prostaglandin-treated animals and that this increase in sensitivity was blocked by indomethacin. Results from both experiments suggest that radiation-induced increases in endogenous neuronal mediators, such as prostaglandins, can induce catalepsy through an action on dopaminergic autoreceptors.

Catalepsy Autoreceptor Striatum Radiation Prostaglandins Haloperidol

AN abundance of evidence suggests that exposure to high doses of ionizing radiation induces a syndrome characterized by deficits in psychomotor performance. These deficits appear primarily in tasks in which the organism is required to display physical strength, endurance, balance, and coordination. Decrements have been reported in a variety of lower animals and subhuman primates on a wide range of tasks, including active avoidance [7, 9, 11, 20, 23] and swimming [8], as well as performance on a running wheel [15], accelerod [5], or equilibrium platform [3]. Similar declines in motor function have been reported in humans accidentally exposed to high doses of radiation [4].

The mechanisms involved in this radiation-induced changes in behavior are unknown. One possibility is that radiation might alter the activity of some endogenous neuromodulator that might serve to depress or enhance synaptic transmission. Given the plethora of putative neurotransmitters and modulators that have been identified in the CNS, it is almost impossible to specify the ones most likely to be involved. However, recent evidence suggests that one set of likely candidates may be the prostaglandins, since it is known that radiation induces dramatic increases in the levels of prostaglandins in a variety of tissues [14, 16, 33–35], including brain [26]. At least two of them (PGE_2 and $PGF_{2\alpha}$) have been postulated to play a role as putative neurotransmitters or modulators [19, 28, 30, 31]. Intraventricular administration of either PGE_2 or $PGF_{2\alpha}$ was demonstrated to induce stupor, sedation, lethargy, catatonia, and cataleptic behavior [6] and to enhance haloperidol-induced catalepsy [18]. Further examination has indicated that the increased catalepsy produced by administration of haloperidol and prostaglandins could be reduced by prior inhibition of prostaglandin synthesis [24]. Thus, the increased levels of prostaglandins in the brain may play a role in some of the behavioral alterations observed after exposure to ionizing radiation.

Since catalepsy is mediated by dopaminergic mechanisms in the striatum (e.g., [12]), an action of radiation on this sys-

tem, possibly through prostaglandins as an intermediary, might have significant behavioral consequences. Previous reports have suggested that dopaminergic transmission is impaired after exposure to ionizing radiation. Although no radiation-induced changes were found in either dopamine-stimulated adenylate cyclase activity or in [^{3}H]-haloperidol binding, two important indices of striatal dopaminergic function, K^+-evoked dopamine release was shown to be transiently elevated [22]. In addition, electrical stimulation of the substantia nigra (which sends dopaminergic projections to the caudate) is significantly less effective in enhancing locomotor activity in irradiated animals [23].

An important mechanism in the regulation of dopaminergic activity is the autoreceptors found on dopaminergic terminals (e.g., see [10]). It is now widely accepted that they mediate striatal dopamine release and are controlled, in part, by inhibitory muscarinic and/or nicotinic heteroreceptors [29]. If the dopaminergic autoreceptors are inhibited, dopamine release is enhanced. Thus, application of either cholinergic agonists [29,36] or dopamine antagonists to striatal slices or synaptosomes enhances the induced release [25] or synthesis [32,37] of dopamine. Evidence indicates that prostaglandins may exert their effects on the striatum by inhibiting these striatal dopamine autoreceptors, since prostaglandins have been shown to potentiate the cataleptic behavior produced by cholinomimetic agents such as pilocarpine [1].

The purpose of the present study was to investigate whether additional deficits in striatally-mediated behavior, measured as catalepsy, could be detected after exposure to ionizing radiation and to determine whether elevated prostaglandins, through an action on dopaminergic autoreceptors, could be involved in any observed cataleptic behavior. The basic approach was to determine if catalepsy could be observed after combining subthreshold doses of haloperidol or prostaglandins (to induce catalepsy) and varying doses of ionizing radiation and whether any effect could be antagonized by pretreatment with indomethacin, a potent prostaglandin synthesis inhibitor [2]. This approach was taken to maximize any synergistic effects of haloperidol and radiation.

In order to assess a possible action of prostaglandins on dopaminergic activity, the functioning of striatal dopamine autoreceptors was examined. This was accomplished by determining the effects of varying concentrations of haloperidol *in vitro* on K^+-evoked dopamine release from striatal slices obtained from parallel groups of animals exposed to radiation and treated with prostaglandins or indomethacin.

METHOD

Animals

Male Sprague-Dawley Crl:CD(SD)BR rats (Charles River Breeding Laboratories, Kingston, NY) weighing 200–300 g were used in these experiments. Rats were quarantined on arrival and screened for evidence of disease by serology and histopathology before being released from quarantine. The rats were housed individually in polycarbonate isolator cages (Lab Products, Maywood, NJ) on autoclaved hardwood contact bedding ("Beta Chip," Northeastern Products Corp., Warrensburg, NY) and were provided commercial rodent chow ("Wayne Rodent Blok," Continental Grain Co., Chicago, IL) and acidified water (pH 2.5 using HCl) ad lib. Animal holding rooms were kept at 21±1°C with 50±10% relative humidity on a 12 hr light:dark lighting cycle with no twilight. The animals were acclimated for 1 hr in the laboratory before the beginning of any experiment.

Cataleptic Behavior

Catalepsy was scored by a method similar to that of Hamblin and Creese [17]. The front paws of the rat were placed over a bar located 10 cm above the table surface. The animal was timed until one of three events occurred: (a) one front paw touched the table surface, (b) the back feet left the table to climb upon the bar, or (c) until 60 sec has elapsed. Catalepsy was measured every 15 min over a period of 3 hr following the various treatments described below.

One hundred thirty-five animals were obtained from the vivarium and divided into three groups. The three groups were placed in clear plastic, well ventilated containers for approximately 5 min before being irradiated with one of 8 doses (1, 3, 5, 10, 30, 50, 100, or 150 Gy) of gamma photons delivered by a ^{60}Co source or sham-irradiated. Depending on its group, each animal was injected intraperitoneally (volume=1 ml/kg for all drugs used) with haloperidol (0.1 mg/kg in saline) or saline 15 min prior to being irradiated or sham-irradiated. (This dose of haloperidol had been shown in preliminary experiments not to induce catalepsy in non-irradiated animals.) The three groups were (a) haloperidol-treated and sham-irradiated (H), (b) haloperidol-treated and irradiated (H + Rad), and (c) vehicle-treated and irradiated (Rad). The dose rates were 5 Gy/min for doses <5 Gy and 10 Gy/min for doses ≥5 Gy. Dosimetry was performed using paired 50-ml ion chambers. Delivered dose was expressed as a ratio of the dose measured in a tissue-equivalent plastic phantom enclosed in a restraining tube to that measured in air.

Sixty-five animals were obtained from the vivarium and divided into four groups. For each group the indomethacin (1, 3, or 5 mg/kg, IP, dissolved in a mixture of 1% NaOH and saline, pH=6.8), haloperidol (0.1 mg/kg, IP), or their vehicles were administered 30 min and 15 min, respectively, prior to irradiation (150 Gy) or sham-irradiation. The groups were (a) indomethacin + haloperidol + radiation (I + H+ Rad), (b) indomethacin vehicle + haloperidol vehicle + radiation (Rad), (c) indomethacin vehicle + haloperidol + radiation (H + Rad) and (d) indomethacin + sham-irradiation + haloperidol vehicle (I), and (e) indomethacin + radiation (I + Rad). Group e received only the 1 mg/kg dose of indomethacin.

The intraventricular administration of prostaglandins required the implantation of a chronic cannula into the lateral ventricle. For this procedure, the rats were anesthetized with 1 ml/kg, IM, of a mixture of ketamine HCl (50 mg/kg), xylazine (5 mg/kg), and acepromazine (1 mg/kg). They were placed in a Kopf stereotaxic instrument, and the skull was exposed. A single guide cannula (Plastic Products Co., Roanoke, VA) was stereotaxically (Kopf stereotaxic instrument, David Kopf Co., Tujunga, CA) implanted into the lateral ventricle at 0.8 mm posterior to bregma and 2.5 lateral to the skull midline [27]. The cannula was lowered until cerebrospinal fluid rose in the cannula. It was then cemented in place with dental acrylic. A dummy cannula was placed in the guide cannula to keep it patent [13]. At the end of the experiment the location of the tip was histologically verified. The animals were allowed to recover for one week before being used in the experiments. Following recovery, the animals were injected with either PGE_2, $PGF_{2\alpha}$, or vehicle, ICV. From a previous preliminary experiment, concentra-

tions of PGE_2 or $PGF_{2\alpha}$ (10 nmoles in 10 μl) were chosen that do not induce catalepsy when administered without haloperidol. Both prostaglandins were stored at −4°C in 95% ethanol until use. Shortly before central administration (see below), the ethanol was evaporated by blowing nitrogen over the solution and the prostaglandin residue was redissolved in saline. Fifteen min after the central administration of one of the prostaglandins the animals were given intraperitoneal injections of either haloperidol or vehicle. Catalepsy was assessed 15 min after the injections and repeated at 30 min intervals for 180 min.

In Vitro *Release of Dopamine*

Various groups (see below) of rats were decapitated 30 min after sham-irradiation or irradiation with 150 Gy, and brains were quickly removed. The striata were dissected on ice and slices (300 mμ) were prepared using a McIlwain tissue chopper. Slices from equal numbers of animals from each treated and control group were pooled and placed into small glass vials containing a modified Krebs-Ringer basal release medium (Lo-KCl) that had been bubbled for 30 min with 95% O_2/5% CO_2. The medium contained 21 mM $NaHCO_3$, 3.4 mM glucose, 1.3 mM NaH_2PO_4, 1 mM EGTA, 0.93 mM $MgCl_2$, 127 mM NaCl, and 2.5 mM KCl (pH 7.4). The slices were washed twice in this medium and 150 μl aliquots were placed in a superfusion apparatus containing 16 parallel chambers. Typically, pooled tissue from two animals was used to fill 4 parallel chambers. The tissue and media were maintained at 37°C throughout the course of the experiment. Following placement into the superfusion chambers, the tissue was allowed to equilibrate for 30 min. It was continuously perfused with oxygenated Lo-KCl medium at the rate of 124 μl/min. Perfusate was collected on ice in tubes containing 0.3 ml of a solution of 0.1% sodium metabisulfite and 0.1% EDTA in 0.4 N perchloric acid and stored at −80°C until the dopamine content was assayed by HPLC coupled to electrochemical detection [21]. Three sets of experiments were carried out.

Striatal samples were obtained from animals exposed to 150 Gy of gamma photons and controls. Following the procedure described above, a 5-min baseline fraction was collected after the 30-min equilibration period during which the samples were perfused with the Lo-KCl buffer. The medium was then switched to one (Hi-KCl buffer) containing 30 mM KCl, 1.26 mM $CaCl_2$ (in place of EGTA), and 57 mM NaCl, as well as the other components described above (pH 7.4, 95% O_2/5% CO_2 bubbled for 30 min. To this medium was added one of four concentrations of haloperidol (0 nM, 100 nM, 500 nM, 1 μM), after which 5-min fractions were collected over 30 min.

Striatal samples were obtained from animals that had been pretreated with indomethacin (5 mg/kg, IP) or its vehicle and 30 min prior to being irradiated (150 Gy) or sham-irradiated. The samples were treated as described in the general description of the slice procedure and the first set of *in vitro* experiments.

In the third set of experiments the striatal tissue was obtained from control animals and prepared as described in the general release methods, except that after 15 min of the 30-min equilibration period, $PGF_{2\alpha}$ (final concentration 200 nM) was added to Lo-KCl medium for one-half of the tissue samples. The remaining half of the tissue samples continued to get Lo-KCl buffer without $PGF_{2\alpha}$. The final 5-min baseline perfusate was collected as described above. The medium was then switched to Hi-KCl (either with or without $PGF_{2\alpha}$) containing one of the haloperidol concentrations stated above (i.e., 0 nM, 100 nM, 500 nM, and 1 μM), after which 5-min fractions were collected and analyzed as above.

Data Analysis

Since the maximum time that an animal could remain on the bar was 60 sec, non-parametric tests were used to analyze the behavioral data. These were the Kruskal-Wallis analyses of variance and Mann-Whitney U-tests. Separate analyses were carried out for each experiment for each of 4 post-irradiation (or post-haloperidol in the case of the prostaglandin experiments) times (i.e., 15, 30, 60, 180 min). The data from the release experiments were analyzed by group × haloperidol concentration × collection fraction repeated measures analyses of variance and post hoc *t*-tests.

RESULTS

Catalepsy

This set of experiments was carried out in order to determine the radiation dose necessary to alter the cataleptic sensitivity to haloperidol. These data, for four post-irradiation time points at all radiation doses below 150 Gy, are represented in Figs. 1 and 2. The dose of haloperidol chosen for these experiments did not produce catalepsy in non-irradiated animals. (Note that tests of catalepsy between a sham-irradiated haloperidol vehicle group and the haloperidol-treated, sham-irradiated group indicated that there were no differences in the times that they remained with their forepaws on the bar. For the sake of clarity the values of this 'sham, vehicle group' are not included in the figures but are given here: mean±SEM (sec), 15 min, 3.8±0.7; 30 min, 4.8±0.6; 60 min, 5.1±0.5; 180 min, 3.9±0.5. Since no differences were seen with respect to these two groups, the haloperidol-treated group served as the control.) It can be seen from Fig. 1 that at radiation doses below 10 Gy, there were no consistent statistically significant differences among the three groups (H, H + Rad, and Rad) in the amount of time that the animals spent on the bar (all Kruskal-Wallis tests, $p>0.05$). At 10 Gy differences could be found among the three groups, especially 15 min after irradiation (Kruskal-Wallis test $p<0.05$, Mann-Whitney tests all comparisons $p<0.02$). Thirty and 60 min after irradiation the Rad and H + Rad groups significantly differed from the H group ($p<0.02$ all comparisons). At 180 min after irradiation these group differences were no longer apparent.

At 30 Gy (Fig. 2) the group differences seen briefly at 10 Gy began to be further magnified. A combined treatment of haloperidol and radiation produced a synergistic effect, so that the time the animal remained on the bar was significantly greater than that of the other two groups (all Kruskal-Wallis tests at all post-irradiation times $p<0.05$; all comparisons between H and H + Rad group remained on the bar for almost the full 60 sec, especially 60 and 180 min after irradiation (see Fig. 3). In addition, the H + Rad groups exposed to either 100 (Fig. 2) or 150 Gy showed other positive signs of catalepsy besides increased time on the bar. These included waxy flexibility when handled and a resistance to being moved. Although these behaviors were not exhibited by the Rad groups, this group (Rad) remained significantly longer on the bar than non-irradiated animals when the doses were >50 Gy (all H and Rad group comparisons, $p<0.004$ at all post-irradiation times).

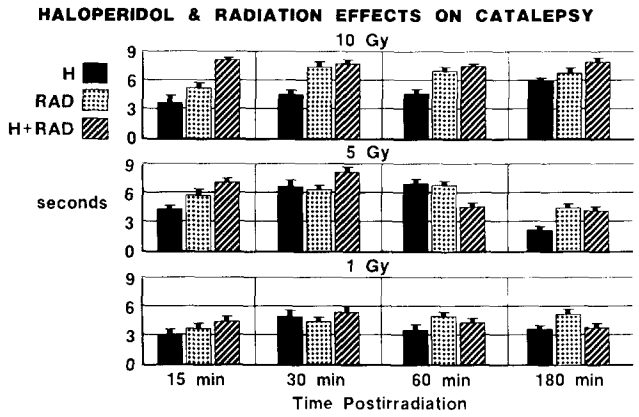

FIG. 1. Time that animals pretreated with haloperidol (0.1 mg/kg, IP) or vehicle and exposed to one of three doses of ^{60}Co irradiation (1, 5, 10 Gy) or sham-irradiated remained with their forepaws upon a stainless steel bar placed 10 cm above the table. Assessments were made at 15, 30, 60 or 180 min post-irradiation or post-sham-irradiation (see the Method section for dosimetry) (N=5 animals/group.)

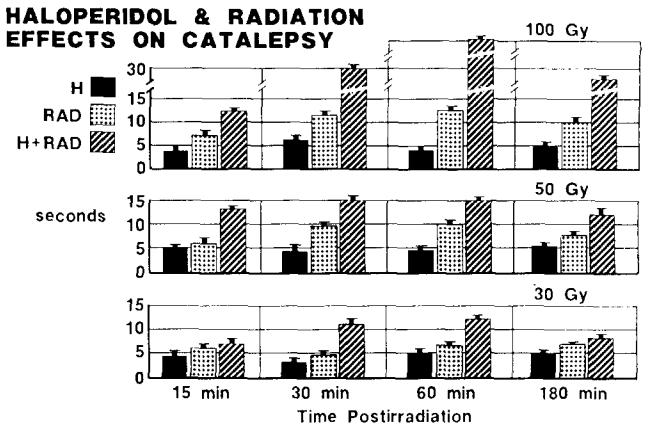

FIG. 2. Time that animals treated as in Fig. 1 and given one of three doses of ^{60}Co (30, 50, 100 Gy) could remain with their forepaws on the bar. (Note that since data for animals given 150 Gy are essentially replicated in Fig. 3 they were not shown in this figure.) (N=5 animals/group.)

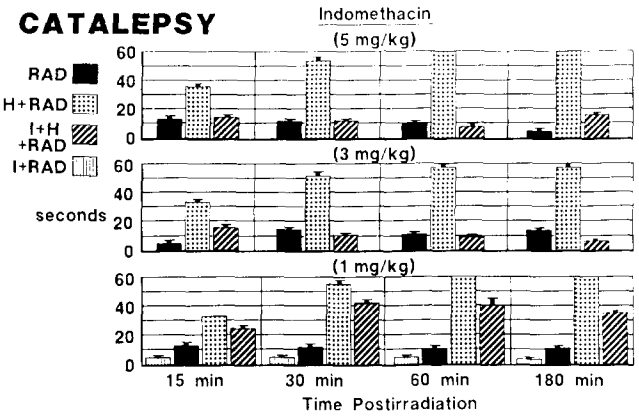

FIG. 3. The time on the bar is shown as a function of indomethacin dose and time post-irradiation (150 Gy) for four treatment groups. (Note that for the sake of clarity, since the I group responded as the I + Rad group, their data are not shown in this figure.) (N=5 animals/group.)

Since the maximal (60 sec at 60 and 180 min after irradiation) cataleptic effect was seen in haloperidol-treated animals after 150 Gy, this dose was utilized to examine the ability of the prostaglandin synthesis inhibitor, indomethacin, to antagonize this synergism. As can be seen in Fig. 3, indomethacin produced a significant dose-dependent reduction in the time that the irradiated, haloperidol-pretreated animals remained on the bar. This reduction was seen even after 1 mg/kg of indomethacin as early as 15 min after irradiation (lower left portion of Fig. 3, Mann-Whitney comparison I + H + Rad vs. H + Rad $p<0.02$). Pretreatment with either 3 or 5 mg/kg of indomethacin completely antagonized the haloperidol effects in the irradiated animals (all I + H + Rad vs. H + Rad comparisons at all post-irradiation times, all $p<0.004$). It also appeared that indomethacin also antagonized the increased time spent on the bar in the group treated with radiation and haloperidol vehicle. Comparisons between the I + Rad group and the R group indicated that the former group remained on the bar for a significantly shorter time than the Rad group (Mann-Whitney comparisons between Rad and I + Rad groups $p<0.008$). Preliminary experiments had indicated that none of the doses of indomethacin had any effect on catalepsy when given alone. Their values did not differ from those of the vehicle-treated animals (e.g., 5 mg/kg, indomethacin, time on bar (sec): mean±SEM; 15 min, 2.2±0.2; 30 min, 4.4±0.4; 60 min, 4.4±0.4; 180 min, 4.2±0.5). Moreover, no differences were seen between indomethacin-treated animals (5 mg/kg) and controls in overall activity as measured by the Digiscan Animal Activity Monitor (Model RXYZCM-16, Omnitech Electronics, Columbus, OH) for up to 3 hr following drug treatment.

These findings indicate that radiation-induced changes in prostaglandin levels may contribute to the increased time on the bar seen in both the R and the H + R groups. If prostaglandins are contributing to the reduced cataleptogenic effect, then it should be possible to produce catalepsy in animals given both haloperidol and prostaglandins. The next experiment explored these possibilities. While preliminary data had indicated that intraventricular doses of prostaglandins alone as low as 30 nmoles produced catalepsy, present results indicated that animals given 10 nmoles of PGE_2 or $PGF_{2\alpha}$, ICV, and haloperidol exhibited significantly greater times on the bar than animals given injections of the appropriate vehicles (e.g., all comparisons $PGF_{2\alpha}$ + haloperidol vs. either $PGF_{2\alpha}$ + haloperidol vehicle or $PGF_{2\alpha}$ vehicle + haloperidol, $p<0.004$ at all test times). The groups given only PGE_2, $PGF_{2\alpha}$, or haloperidol did not differ from each other in the time that they remained on the bar (all comparisons $p<0.05$; Figs. 4 and 5).

KCl-Induced Release of Dopamine From Striatal Slices

Striatal tissue from animals irradiated with 150 Gy showed a significantly greater dopamine release to various concentrations of haloperidol and 30 mM KCl than striata obtained from animals that were sham-irradiated, $F(18,120)=3.37$, $p<0.0001$; Fig. 6. These differences were seen at the 100 nM concentration of haloperidol, comparison

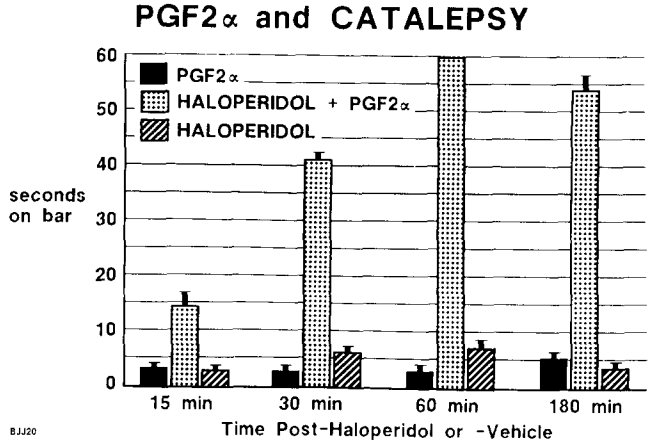

FIG. 4. The effects of intraventricular administration of $PGF_{2\alpha}$ (10 nmoles/10 μl) or vehicle or haloperidol (0.1 mg/kg, IP) on the induction of catalepsy (N=5 animals/group).

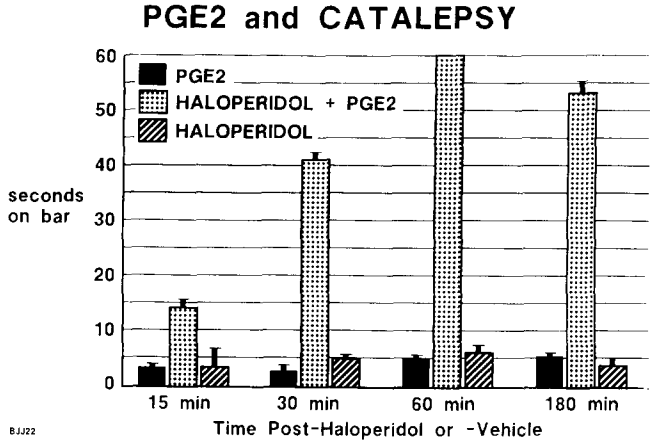

FIG. 5. The effects of intraventricular administration of PGE_2 (10 nmoles/10 μl) or vehicle or haloperidol (0.1 mg/kg, IP) or vehicle on the induction of catalepsy (N=5 animals/group).

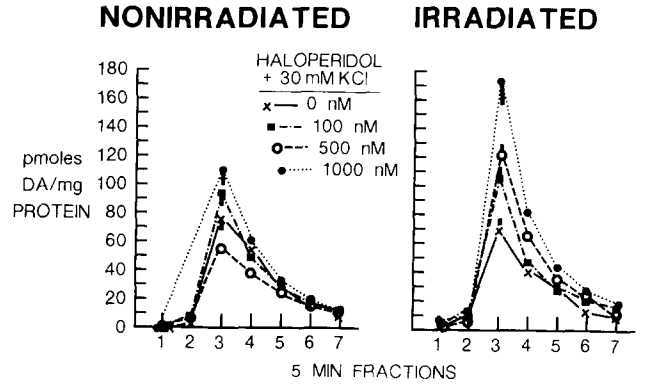

FIG. 6. The effects of irradiation (150 Gy) on the K^+-induced release of dopamine from striatal slices exposed to graded concentrations of haloperidol. Slices from equal numbers of animal from each treated and control group were pooled and placed into the superfusion chambers and maintained at 37°C. This tissue was perfused with Lo-KCl buffer (see the Method section) for 30 min. A 5-min fraction was collected after 25 min. The medium was then switched to one containing Hi-KCl (30 mM, see the Method section) and one of four concentrations of haloperidol. Five-min fractions were collected over 30 min.

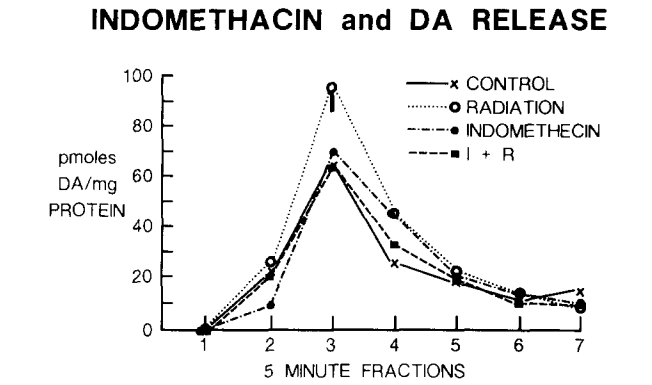

FIG. 7. The responses of striatal samples to graded doses of haloperidol obtained from animals that had been pretreated with indomethacin (5 mg/kg, IP) or its vehicle 30 min prior to irradiation or sham-irradiation. Slices were pooled for each treatment group, placed into superfusion chambers and perfused as described in Fig. 6.

of peak release in irradiated group compared to control group, $t(120)=2.04$, $p<0.05$ and were magnified at the 500 nM and 1000 nM concentrations, $t(120)=12.8$ and 10.71, respectively, $p<0.001$.

Examination of striatal tissue obtained from the I, I+ Rad, Rad, or control groups (no indomethacin or radiation) indicated a significant difference in dopamine release among the 4 groups when the tissue was exposed to 30 mM KCl and varying concentrations of haloperidol, $F(18,288)=3.39$, $p<0.00001$; Fig. 7. Subsequent post hoc comparisons indicated that this difference was the result of higher dopamine release in the R group to haloperidol than all other groups (e.g., peak release comparisons—$df=288$ R vs. I, $t=2.30$, $p<0.05$; R vs. C and R vs. I + R, $t=2.88$, $p<0.01$). No differences were seen in comparisons among the other groups (all t's <1). These findings indicate that pretreatment with indomethacin was effective in reducing the increased radiation-induced sensitivity of the striatal tissue to haloperidol.

When the striatal tissue of non-irradiated control animals was exposed to $PGF_{2\alpha}$ both prior to and during the application of varying concentrations of haloperidol, the KCl-induced release of dopamine was greater than in striatal tissue not receiving $PGF_{2\alpha}$, $F(6,132)=2.53$, $p<0.02$.

DISCUSSION

There are numerous reports that have demonstrated significant increases in prostaglandins in a variety of tissues after doses of whole-body gamma irradiation ranging from 3.0 to 10.0 Gy. These tissues included mouse [14] and guinea pig lung [33], mouse [14] and rat liver and spleen [35], as well as marrow stromal cells [16]. Most notably for the present experiments, Pausescu and colleagues [26] have shown significant increases in cerebral levels of $PGF_{2\alpha}$ after 5.0 to 7.5 Gy of whole-body gamma irradiation. As indicated above, intraventricularly administered prostaglandins can induce sedation and cataleptic behavior [6], as well as potentiate the

actions of neuroleptics [18]. Taken together the findings from these experiments suggest that the post-irradiation rise in prostaglandins may intensify the cataleptic behavior produced by haloperidol. The findings of the present experiments tend to support this suggestion.

From preliminary results, a dose of haloperidol was chosen that did not produce catalepsy in non-irradiated animals. However, the present data indicate that as increasing doses of radiation were given, the sensitivity of the animals to haloperidol increased and the H + R animals spent a proportionately greater time on the bar, especially at doses >50 Gy than the H or Rad groups. At both 100 and 150 Gy, the maximal effect was achieved in the H + Rad group at 50 min post-irradiation. In the case of the 100 Gy the effect was reduced in the H + Rad group after this time while at 150 Gy the effect remained for as long as 180 min post-irradiation. These findings indicate that the maximal sensitivity to haloperidol post-irradiation takes some time to develop and suggest that perhaps there is the induction of intermediary components which alter the catalepsy threshold. While the tissue levels of prostaglandins were not measured in these studies, numerous previous experiments have shown that the post-irradiation rise in prostaglandin concentrations occurred with 1 to 3 hr after irradiation (e.g., [33]), a time course that parallels the development of increased behavioral sensitivity to haloperidol in the present experiments.

Additional evidence for this hypothesis is provided by the present findings which showed that: (a) Pretreatment with indomethacin produced a dose-dependent reduction in post-irradiation sensitivity to haloperidol, and even significantly reduced the increased time on the bar exhibited by the Rad group. (b) While neither direct intraventricular infusion of subthreshold concentrations of prostaglandins (E_2, $F_{2\alpha}$) at nmoles, or intraperitoneal administration of haloperidol (0.1 mg/kg) produced catalepsy, there was a synergistic effect of these agents when the animals were given both prostaglandins and haloperidol. Higher concentrations of any of these agents produced catalepsy when administered alone.

A great deal of evidence has indicated that a stable balance between striatal dopamine and acetylcholine is necessary for the proper execution of various psychomotor behaviors (e.g., see [1, 12, 38]). This balance is maintained through reciprocal inhibitory control (RIC) between these two systems, and if it is altered through the actions of such compounds as prostaglandins, the threshold for motor behavioral aberrations such as catalepsy to occur is lowered. The findings cited above suggest that prostaglandins may alter the threshold for cataleptogenesis by creating an imbalance in the striatal system through inhibition of dopaminergic autoreceptors. In the present experiments, striatal tissue obtained from irradiated rats showed greater haloperidol-enhanced, K^+-evoked release than that from control animals or irradiated animals pretreated with indomethacin. Similar findings were observed in striatal tissue that had been preexposed *in vitro* to $PGF_{2\alpha}$.

In summary, the findings from these experiments indicate that the one possible mechanism for the enhanced sensitivity of irradiated animals to haloperidol may be through alterations in striatal RIC by prostaglandins. They suggest that perhaps some of the post-irradiation deficits in motor performance that have been previously reported may occur through the induction of endogenous neuronal mediators which can subsequently influence synaptic transmission. Experiments are now underway to determine: (a) the generality of these putative effects of prostaglandins to other motor behaviors, and (b) the relationship to the post irradiation striatal levels of prostaglandins generated by various doses of radiation to subsequent motor behavioral dysfunction.

ACKNOWLEDGEMENTS

This research was supported by the Armed Forces Radiobiology Research Institute, Defense Nuclear Agency, under work unit B4166. Views presented in this paper are those of the authors; no endorsement by the Defense Nuclear Agency has been given or should be inferred. Research was conducted according to the principles enunciated in the "Guide for the Care and Use of Laboratory Animal Resources, National Research Council."

REFERENCES

1. Ahtee, L. and I. Kaariainen. The role of dopamine in pilocarpine induced catalepsy. *Naunyn Schmiedebergs Arch Pharmacol* **284:** 25–38, 1974.
2. Anggard, E. and B. Samuelsson. Biosynthesis of prostaglandins from arachidonic acid in guinea-pig lung. *J Biol Chem* **240:** 3518–3521, 1965.
3. Barnes, D. J. An initial investigation of the effects of pulsed ionization radiation on the primate equilibrium function. Report No. TR-66-106. Brooks AFB, TX: United States Air Force School of Aerospace Medicine, 1966.
4. Baum, S. J., R. W. Young and H. G. Withers. Symptomatology of acute radiation effects in humans after exposure to doses of from 75 to 4500 rads (cGy) free-in-air. (PSR Note 581), Los Angeles, CA, Pacific Sierra Research Corp., 1984.
5. Bogo, V. Effect of bremsstrahlung and electron radiation on rat motor performance. *Radiat Res* **100:** 313–320, 1984.
6. Brus, R., R. Szkilnik, J. Slominska-Zurek, T. Krzeminski and Z. S. Herman. Studies on the behavioral and hypotensive effects of intraventricular prostacyclin (PGI2 in rats). *Pol J Pharmacol Pharm* **33:** 467–474, 1981.
7. Burghardt, W. F., Jr. and W. A. Hunt. Characterization of radiation-induced performance decrement using a two-lever shock-avoidance task. *Radiat Res* **103:** 149–157, 1985.
8. Casarett, A. P. Swim-tank measurement of radiation-induced behavioral incapacitation. *Psychol Rep* **33:** 731–736, 1973.
9. Casarett, A. and C. L. Comar. Incapacitation and performance in rats following split doses of fission spectrum radiation. *Radiat Res* **53:** 455–461, 1973.
10. Cebeddu, L. X., I. S. Hoffman and M. K. James. Frequency-dependent effects of neuronal uptake inhibitors on the autoreceptor-mediated modulation of dopamine and acetylcholine release from the rabbit striatum. *J Pharmacol Exp Ther* **226:** 85–94, 1983.
11. Chaput, R. L. and D. Wise. Miniature pig incapacitation and performance decrement after mixed gamma-neutron irradiation. *Aerospace Med* **41:** 290–295, 1970.
12. Costall, B. and R. J. Naylor. Neuroleptic and non-neuroleptic catalepsy. *Arzneimittelforschung* **23:** 674–683, 1973.
13. Cubells, J. F. and J. A. Joseph. Neostriatal dopamine receptor loss and behavioral deficits in the senescent rat. *Life Sci* **28:** 1215–1218, 1981.
14. Eisen, V. and D. I. Walker. Effect of ionizing radiation on prostaglandin-like activity in tissues. *Br J Pharmacol* **57:** 527–532, 1976.

15. Franz, C. G. Effects of mixed neutron-gamma total body irradiation on physical activity performance of rhesus monkeys. *Radiat Res* **101:** 434–441, 1985.
16. Gibson, D. P., R. L. De Gowin and S. A. Knapp. Effect of x-irradiation on release of prostaglandin E from marrow stromal cells in culture. *Radiat Res* **89:** 537–545, 1982.
17. Hamblin, M. W. and I. Creese. Behavioral and radioligand binding evidence for irreversible dopamine receptor blockade by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. *Life Sci* **32:** 2247–2255, 1983.
18. Herman, Z. S., J. Slominska-Zurek, A. Kryk and K. Kmieciak-Kolada. Potentiation of cataleptogenic effects of neuroleptics by prostaglandins. *Pol J Pharmacol Pharm* **30:** 639–646, 1978.
19. Hoffman, W. E. and T. J. Valigura. Independence of cardiovascular and hyperthermic effects of central prostaglandin E_2. *Brain Res* **173:** 160–163, 1979.
20. Hunt, W. A. Comparative effects of exposure to high-energy electrons and gamma radiation on active avoidance behavior. *Int J Radiat Biol* **44:** 257–260, 1983.
21. Hunt, W. A. and T. K. Dalton. An automated method for the determination of biogenic amines and their metabolites by high-performance liquid chromatography. *Anal Biochem* **135:** 269–274, 1983.
22. Hunt, W. A., T. K. Dalton and J. H. Darden. Transient alterations in neurotransmitter activity in the caudate nucleus of rat brain after a high dose of ionizing radiation. *Radiat Res* **80:** 556–562, 1979.
23. Mickley, G. A. and H. Teitelbaum. Resistance of lateral hypothalamic mediated behaviors after a supralethal dose of radiation. *Aviat Space Environ Med* **49:** 868–873, 1973.
24. Ono, N., R. Saito, T. Abiru, H-O. Kamiya and T. Furukawa. Possible involvement of prostaglandins in cataleptic behavior in rats. *Pharmacol Biochem Behav* **25:** 463–467, 1986.
25. Parker, E. M. and L. X. Cubeddu. Evidence for autoreceptor modulation of endogenous dopamine release from rabbit caudate nucleus *in vitro*. *J Pharmacol Exp Ther* **232:** 492–500, 1985.
26. Pausescu, E., R. Chirvasie, T. Teodosiu and C. Paun. Effects of ^{60}Co gamma-radiation on the hepatic and cerebral levels of some prostaglandins. *Radiat Res* **65:** 163–171, 1976.
27. Pelligrino, J. J. and A. J. Cushman. *A Stereotaxic Atlas of the Rat Brain*. New York: Meridith, 1967.
28. Poddubiuk, Z. M. A comparison of the central actions of prostaglandins A_1, E_1, E_2, $F_{1\alpha}$, and $F_{2\alpha}$ in the rat. I. Behavioral antinociceptive and anticonvulsant actions of intraventricular prostaglandins in the rat. *Psychopharmacology (Berlin)* **50:** 89–94, 1976.
29. Raiteri, M., R. Leardi, and M. Marchi. Heterogeneity of presynaptic muscarinic receptors regulating neurotransmitter release in the rat brain. *J Pharmacol Exp Ther* **228:** 209–215, 1984.
30. Ramwell, P. W., J. E. Shaw and R. Jessup. Spontaneous and evoked release of prostaglandins from frog spinal cord. *Am J Physiol* **211:** 998–1004, 1966.
31. Rosenkranz, R. P. and K. F. Killam, Jr. Effects of intracerebroventricular administration of prostaglandins E_1 and E_2 on chemically induced convulsions in mice. *J Pharmacol Exp Ther* **209:** 231–237, 1979.
32. Saller, C. F. and A. I. Salama. Dopamine synthesis in synaptosomes: Relation of autoreceptor functioning to pH, membrane depolarization, and intrasynaptosomal dopamine content. *J Neurochem* **43:** 675–688, 1984.
33. Steel, L. K. and G. N. Catravas. Radiation-induced changes in production of prostaglandins $F_{2\alpha}$, E, and thromboxane B_2 in guinea pig parenchymal lung tissues. *Int J Radiat Biol* **42:** 517–530, 1982.
34. Steel, L. K., I. K. Sweedler and G. N. Catravas. Effects of ^{60}Co radiation on synthesis of prostaglandins $F_{2\alpha}$, E, and thromboxane B_2 in lung airways of guinea pigs. *Radiat Res* **94:** 156–165, 1983.
35. Trocha, P. J. and G. N. Catravas. Prostaglandin levels and lysosomal enzyme activities in irradiated rats. *Int J Radiat Biol* **38:** 503–515, 1980.
36. Westfall, T. C., H. Grant and H. Perry. Release of dopamine and 5-hydroxytryptamine from rat striatal slices following activation of nicotinic cholinergic receptors. *Gen Pharmacol* **14:** 321–325, 1983.
37. Westfall, T., L. Naes and C. Paul. Relative potency of dopamine agonists on autoreceptor function in various brain regions of the rat. *J Pharmacol Exp Ther* **224:** 199–206, 1983.
38. Williams, J. and J. A. Davies. The action of DL-2,4-diaminobutyric acid on the cataleptogenic effects of pilocarpine and α-flupenthixol in rats. *Psychopharmacology (Berlin)* **64:** 81–83, 1979.