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d-Amphetamine Antagonizes Prostaglandin E_1-Induced Hyperthermia and Suppression of Fixed Interval Operant Behavior in Rats[1]

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NIELSEN, J. A. AND S. B. SPARBER. *d-Amphetamine antagonizes prostaglandin in E_1-induced hyperthermia and suppression of fixed interval operant behavior in rats.* PHARMACOL BIOCHEM BEHAV 21(4) 575–581, 1984.—The experiments reported herein were designed to study the effects of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and PGE_1 on operant behavior and rectal temperature of rats. A solution containing $PGF_{2\alpha}$ or PGE_1 was infused intracerebroventricularly into rats trained to press a lever for food reward on a fixed interval 75 second (FI 75 sec) schedule. $PGF_{2\alpha}$ (10, 100 or 1000 ng/min) had no effect on FI 75 sec operant behavior. Only the highest dose increased temperature. PGE_1 (100 ng/min) had no effect, whereas higher doses (250 and 500 ng/min) produced a rate-dependent effect on behavior, increasing low rates and decreasing high rates. The two higher doses also produced convulsions after about 25 min or 20 min infusions, respectively. PGE_1 also increased temperature in a dose-dependent manner. Systemic administration of a low dose of d-amphetamine (0.5 mg/kg IP) had little or no effect on behavior or temperature. d-Amphetamine did not alter hyperthermia induced by the highest dose of $PGF_{2\alpha}$, but antagonized the PGE_1-induced hyperthermia. d-Amphetamine also antagonized all of the behavioral effects of PGE_1, including convulsions. The results are discussed in relation to the actions of PGs and d-amphetamine on catecholamine neurons in the central nervous system.

Prostaglandins d-Amphetamine Operant behavior Body temperature

IN the accompanying report we have presented data indicating that PGE_1 may inhibit the release of dopamine (DA) from central neurons *in vivo* and that it is an antagonist of effects of d-amphetamine on catecholamine metabolism or release. On the other hand, $PGF_{2\alpha}$ appeared to facilitate the release of DA and noradrenaline (NA) in a manner which seems to be different from that of d-amphetamine. As part of these series of experiments we also measured rectal temperature and fixed-interval 75-second operant behavior (FI 75 sec). The effects of PGE_1, $PGF_{2\alpha}$ and/or d-amphetamine on the latter parameters are presented herein.

Rectal temperature was measured in these experiments because PGEs and PGFs are powerful pyretic agents [8, 9, 22, 23, 36]. Stimulation of central nervous system (CNS) DA receptors may decrease body temperature [4, 5, 15, 18]. It was therefore hypothesized that DA and other catecholamines might be causally related to PG-induced temperature changes mediated in the CNS since the PGs modify CNS catecholaminergic activity *in vivo* (accompanying paper). To test this possibility we determined if d-amphetamine, which facilitates the release of DA (for review see [19]), would antagonize PGE_1-induced hyperthermia. Since $PGF_{2\alpha}$ has effects opposite to PGE_1 upon DA release (accompanying paper) it was not unreasonable to also expect that $PGF_{2\alpha}$ and d-amphetamine would have an additive action upon body temperature.

It was also determined if d-amphetamine and the PGs would interact behaviorally. Centrally administered PGs inhibited amphetamine-induced circling behavior in mice [33]. Also, while d-amphetamine has well defined rate-dependent effects on FI operant behavior [2, 6, 12, 35], the effects of PGs on FI behavior are not known. This schedule of reinforcement was used because it engenders both low and high rates of behavior. Therefore, it could be determined if $PGF_{2\alpha}$ or PGE_1 differentially alters different rates of behavior. It was also determined if a low dose of d-amphetamine altered any of the effects of PGs on FI behavior.

Our data indicate that PGE_1 and the highest dose of $PGF_{2\alpha}$ increased body temperature. A low dose of d-amphetamine, which had no effect on body temperature, antagonized

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PGE_1- but not $PGF_{2\alpha}$-induced hyperthermia. $PGF_{2\alpha}$ did not affect FI 75 sec behavior, while PGE_1 had a rate-dependent effect on behavior and also caused (behavioral) convulsions. d-Amphetamine antagonized all of the behavioral effects of PGE_1

METHOD

The drug-naive, mature male Long-Evans rats (Simonsen, Gilroy) used in experiments reported in the accompanying paper were also used in the experiments reported below, as they had their temperature and behavior monitored concurrently. They were housed individually in a room on a 12-hour day-night cycle. Food and tap water were available ad lib for several weeks. They were then gradually food-deprived to approximately 80% of their free-feeding weight (400–450 g) and shaped to lever press for 45 mg food pellets (P. J. Noyes Company,Lancaster, NH) on a continuous reinforcement schedule in a small animal operant chamber (model 143–22, BRS/LVE, Beltsville, MD). The operant chamber was enclosed in an environmental isolation chamber which was sound and light attenuating. After 4 days on the continuous reinforcement schedule they were switched to a fixed-interval schedule of reinforcement [11]. The time (seconds) from the last reinforced response to the opportunity for the next response being reinforced was gradually increased in the following manner: 2 daily hour sessions each on FI 7, 15, 30, 45, and 75 seconds. A computer-based Interact (BRS/LVE) system was programmed to control environmental contingencies and record and reduce the behavioral data. At the termination of each session, a printout was obtained which included 5 numbers representing the rats' behavior. The first number represented their responses during the first 15 seconds of each interval. The second through fifth numbers represented responding during the second through fifth 15-second segments of the interval, respectively. A continuous record of each session was also obtained on cumulative records (R. Gerbrands Company, Arlington, MA).

Cannula Implantation

The rats' response rates appeared stable after 29 daily behavioral sessions of approximately 1 hr each. Stability was evidenced by a coefficient of variability, for the last 3 sessions, of less than 33% and 10% for the response rate during the first and fifth segments, respectively, of the interval. The rats were then implanted with infusion-perfusion cannulas with cannula tips in their right lateral ventricles. Cannula construction and implantation are described in detail elsewhere [25].

The rats' operant behavior was again stable, as described above, 9 days after cannula implantation, during which time they were habituated, as evidenced by a decreased effect, to having their temperature determined and being injected (intraperitoneally) with a 0.9% saline solution. Temperature was determined by inserting a temperature probe (model 702, Yellow Springs Instrument Company, Yellow Springs, OH) 5 cm into the rat's rectum, taping it to the tail, returning the rat to its home cage, and recording its temperature from a telethermometer (model 5810, United Systems Corporation, Dayton, OH) 3 min later. The probe and tape were then removed. Stability in the temperature measures, achieved before the experiments began, was evidenced by a coefficient of variability, for the last 3 experiments, of less than 2%.

TABLE 1
EXPERIMENTAL PROTOCOL

Time (min)	Event
0	Insert rectal temperature probe. Return rat to home cage.
3	Record temperature. Remove probe. Place rat in operant chamber. Attach cannula tubing. Start behavioral session.
13	Start infusion (1 μl/min).
23	Give injection (1 ml/kg body weight, IP)
58	Stop infusion. Start push-pull perfusion (10 μl/min). (See accompanying paper for the purpose of the perfusion.)
63	Stop perfusion and behavioral session. Disconnect cannula tubing. Remove rat from operant chamber. Insert rectal temperature probe. Place rat in home cage.
66	Record temperature. Remove probe.
123	Insert rectal temperature probe.
126	Record temperature. Remove probe.

The experimental protocol is shown in Table 1. Temperature was recorded at the beginning of each experiment. Behavioral data from a 10 min baseline session was printed just before the start of the brain infusion. In this manner, we could determine if the rats' temperature and behavior were similar to that on previous days, before any drugs were administered. Behavioral data was also printed just before the intraperitoneal injection and at the end of the behavioral session.

Experimental Manipulations

See the accompanying paper for a description of the experimental manipulations.

In addition, the following manipulations were performed: no infusion-perfusion (the tubing was still connected to the cannula)/no injection (the rats were still picked up and handled as if to be injected), no infusion-perfusion/saline injection, and vehicle infusion-perfusion/no injection. By comparing these experiments with each other and with the experiments described in the accompanying paper, we could determined if infusion-perfusion with the vehicle or if saline injection affected FI 75-second behavior or rectal temperature.

PG was added to the infusion-perfusion medium twelve times, twice at each concentration of $PGF_{2\alpha}$ (10,100, and 1000 ng/μl) and PGE_1 (100, 250, and 500 ng/μl). In half of these experiments saline was injected, in the other half d-amphetamine (0.5 mg/kg) was injected.

Drugs, Infusion-Perfusion Medium

d-Amphetamine sulfate (K and K Laboratores, Inc., Plainview, NY) was dissolved in isotonic saline in a concentration of 0.5 mg of the base per ml and injected intraperitoneally in a volume of 1 ml/kg body weight. The infusion-perfusion medium contained sterile 0.9% saline to which tritium labelled dopamine (^{3}H-2-dopamine, 0.1 ng/μl, Sp. Act. 7.5 Ci/mM, New England Nuclear, Boston, MA) and

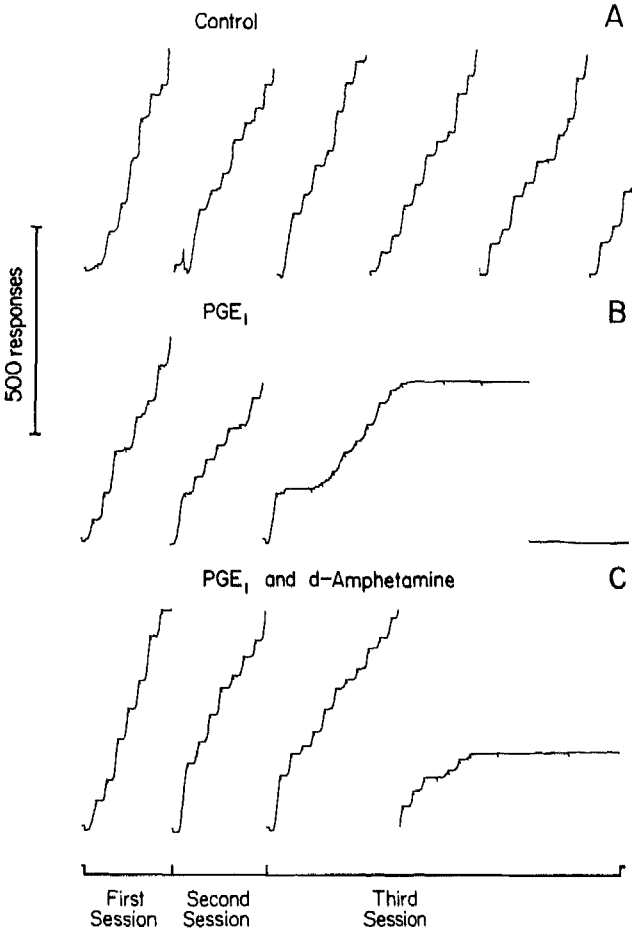

FIG. 1. Cumulative records for rat 108 demonstrating PGE_1-induced suppression of behavior and the attenuation of this effect by d-amphetamine. The rat was allowed to lever press for food reinforcement available on a fixed-interval 75-second schedule. Infusion (ICV) began at the onset of the second session and continued until the last 5 minutes of the third session when perfusion (with the same solution) was performed. The rat was injected (IP) between the second and third sessions. The infusion medium and injection were of vehicle and saline (*Panel A*), PGE_1 (250 ng/min, ICV) and saline (*Panel B*), and PGE_1 (250 ng/min, ICV) and d-amphetamine (0.5 mg/kg, IP) (*Panel C*). Responding rate is reflected by the slope of the recording. Delivery of a reinforcer is indicated as a pip on the ascending record.

$CaCl_2$ (2.3 mM) had been added. The ^{3}H-dopamine (^{3}H-DA) was included in the infusion-perfusion medium so that changes in ^{3}H-DA metabolism could be observed (see accompanying paper). Infusion and perfusion were at rates of 1 and 10 μl/min, respectively. In some experiments, $PGF_{2\alpha}$ (10, 100 or 100 ng/μl) or PGE_1 (100, 250 or 500 ng/μl) was added to the infusion-perfusion medium. The PGs (kindly supplied by Dr. J. Pike, the Upjohn Company, Kalamazoo, MI) were stored in absolute ethanol at −20°C. The ethanol in the PG stock solution was evaporated under nitrogen before the infusion-perfusion medium was added.

Data Analysis

To determine if PGs and/or d-amphetamine had effects, data were analyzed by one-way analysis of variance and correlated Student *t*-test. Significant differences between treatment means were determined by the Bonferroni [24] significant difference test. Unless otherwise noted all values are Mean±S.E. There is no measure of variability about the means in some of the tables and figures since it is not important for the calculation of the statistics in the ANOVA of a randomized block experimental design.

RESULTS

Behavior

Behavior was similar for all experiments during the 10 min session before the infusion was started. For all experiments, the number of reinforcers earned, overall response rate, or response rate during the five 15-sec segments during the 10 minute infusion that preceded the injection was not significantly different from each other or from the first 10 min.

During the 40 min following the injection there was no difference in the number of reinforcers earned (31±0), overall response rate (0.5±0.1 responses/sec), or response rate in any segment, between the nondrug experiments mentioned above.

Lever pressing controlled by FI schedule resembled that reported elsewhere [11] where lower rates of responding occurred in the beginning of the interval and higher response rates occur near the end of the interval (Fig. 1, panel A). The response rate during segment one was more variable than in later segments, on a percentage basis, but not different from previous reports [34]. Finally, behavior during nondrug experiments was similar whether the experiment was performed before, during or after the various PG and/or d-amphetamine experiments. The low degree of variability indicates that the response rate during the five 15-sec segments was quite consistent for each rat from nondrug experiment to nondrug experiment. Behavior was not apparently affected by cannula implantation.

d-Amphetamine (0.5 mg/kg) had no effect on the number of reinforcers earned (Table 2), or on the overall response rates (unpublished observations). d-Amphetamine significantly ($p<0.05$) increased the response rate during the second 15-sec segment from 0.06 to 0.20 responses/sec. It did not significantly affect the response rate in any other segment (e.g., first and fourth segment, Table 2). The effect of d-amphetamine occurred whether the experiments were performed before, during or after the various PG experiments.

Prostaglandins

The various doses of $PGF_{2\alpha}$ had no significant effect on behavior, nor did they alter d-amphetamine's effect on behavior.

PGE_1 induced convulsions which were dose-related, in that infusion of 100, 250 and 500 ng PGE_1/min produced seizures in 0, 2, and 4 out of 4 rats, respectively. The seizures occurred after about 10 μg of PGE_1 had been infused, whether at a rate of 250 or 500 ng/min, and did not appear to have any permanent effects on the parameters that were measured. Nondrug and d-amphetamine experiments performed a few days after all of the rats had experienced convulsions resulted in their temperature and behavioral profile being similar to that observed in experiments before convulsions occurred.

In order to determine the effect of PGE_1 on FI 75 sec behavior, that part of the third session where the rat was still

TABLE 2

d-AMPHETAMINE ANTAGONISM OF PGE_1'S EFFECTS ON BEHAVIOR

PGE_1 (ng/μl/min, ICV)	Behavior* 0	100	250	500
	Reinforcers			
Saline	31 ± 0	31 ± 0	21 ± 6	14 ± 6†
d-Amphetamine	31 ± 0	31 ± 0	28 ± 3	19 ± 6‡
	Response rate during segment one (responses/sec)			
Saline	0.03 ± 0.01	0.04 ± 0.02	0.06 ± 0.01†	0.09 ± 0.01†
d-Amphetamine	0.05 ± 0.01	0.07 ± 0	0.05 ± 0.01	0.05 ± 0.01‡
	Response rate during segment four (responses/sec)			
Saline	0.81 ± 0.22	0.99 ± 0.28	0.49 ± 0.20†	0.22 ± 0.15†
d-Amphetamine	0.70 ± 0.26	0.93 ± 0.29	0.66 ± 0.29	0.53 ± 0.24‡

*The behavior occurred during the 40 minutes after injection. Mean ± 1 S.E. of 4 rats.

†$p<0.05$ compared with zero PGE_1 (analysis of variance and the Bonferroni significant difference test).

‡$p<0.05$ compared with saline injection and the appropriate dose of PGE_1 (analysis of variance and the Bonferroni significant difference test).

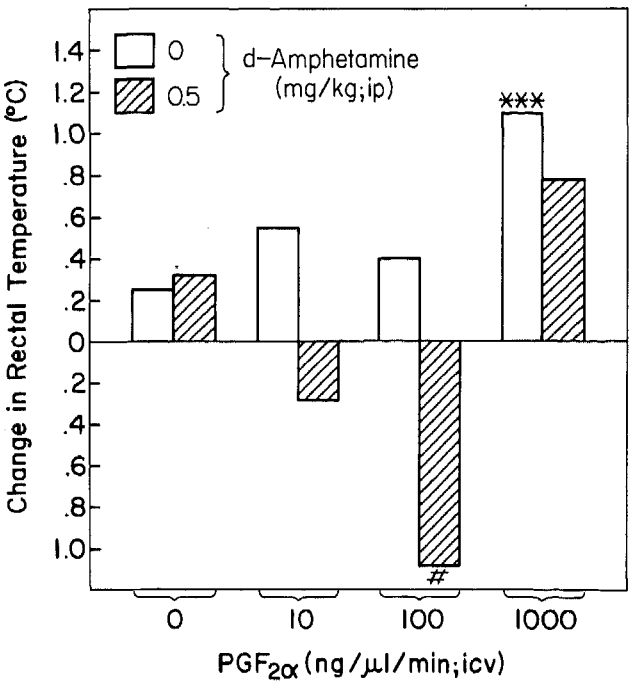

FIG. 2. The effects of $PGF_{2\alpha}$ and/or d-amphetamine on rectal temperature. ***$p<0.005$ compared with zero $PGF_{2\alpha}$; #$p<0.05$ compared with saline injection (analysis of variance and Bonferroni significant difference test). The ordinate shows the rectal temperature after the behavioral session minus the temperature before the session. The data shown is the mean of 4 rats. One standard error about each mean ranged from 0.1 to 0.3°C except for the group treated with $PGF_{2\alpha}$ (1000 ng/μl/min; ICV)-d-Amphetamine (0.5 mg/kg; IP) where one standard error was 0.4°C. See Table 1 for an explanation of the experimental protocol.

lever pressing (prior to a convulsion) was compared with the appropriate third session in other experiments. Therefore, we were comparing sessions of different durations. We were not able to scrutinize the data more closely and compare sessions of the same length, because the computer printout of data indicated the total number of responses in each segment over the entire session. The comparison of sessions of different durations seems justified, since response rates in any given segment were similar throughout the experiment.

PGE_1 produced a dose-dependent decrease in the number of reinforcers earned; an increase in the response rate during the first segment; and a decrease in response rate during the fourth segment (Table 2) and the fifth segment ($p<0.001$).

Figure 1 shows cumulative records for rat 108 demonstrating the behavioral effects of PGE_1. Panel A shows a vehicle infusion-perfusion/saline injection experiment. Panel B shows a PGE_1 (250 ng/minute) infusion-perfusion/saline injection experiment. Behavior before the infusion began was essentially indentical in both experiments. During the first 10 min of infusion PGE_1 had no effect on behavior. However, PGE_1 had an effect on behavior during the last 40 minutes of the session. Initially, PGE_1 produced a rate-dependent effect on behavior, an increase in responding early in the interval, and a decrease in responding later in the interval. Later in the session overt convulsions occurred and lever pressing was eliminated.

d-Amphetamine significantly increased the number of reinforcers earned when PGE_1 (500 ng/min) was infused, attenuated the PGE_1-induced increase in segment 1, and the PGE_1-induced decrease in behavior in segment 4 (Table 2). In addition, when the PGE_1 (500 ng/min) solution was infused, the rats had convulsions about 12 min after saline injection. However, after d-amphetamine injection, convulsions occurred later (about 19 min after injection) or not at all.

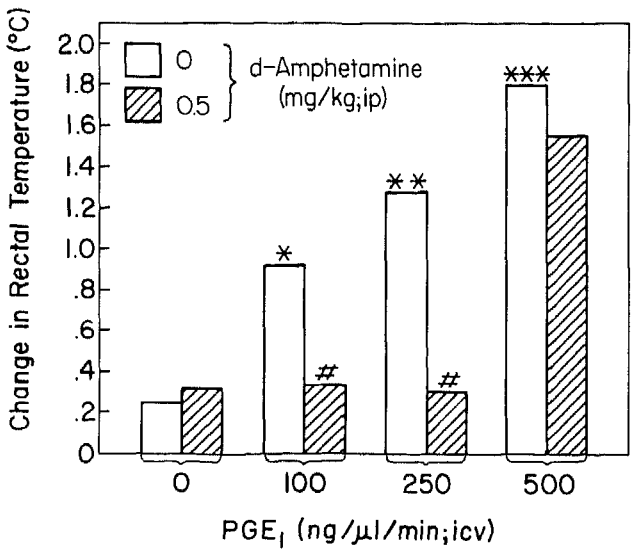

FIG. 3. d-Amphetamine attenuated PGE_1-induced hyperthermia. $*p<0.05$, $**p<0.01$, $***p<0.005$ compared with zero PGE_1; $\#p<0.05$ compared with saline injection (analysis of variance and the Bonferroni significant difference test). The ordinate shows the rectal temperature after the behavioral session minus the temperature before the session. The data shown is the mean of 4 rats. One standard error about each mean ranged from 0.1 to 0.3°C except for the group treated with $PGF_{2\alpha}$ (1000 ng/μl/min; ICV)-d-Amphetamine (0.5 mg/kg; IP) where one standard error was 0.5°C. See Table 1 for an explanation of the experimental design.

Figure 1 also shows sample cumulative records indicating d-amphetamine's antagonism of PGE_1's behavioral suppressant effect. Panel C shows an experiment where a solution containing PGE_1 (250 ng/min) was infused-perfused and d-amphetamine was injected. d-Amphetamine increased the number of reinforcers earned and attenuated both the PGE_1-induced increase in responding early in the interval and the decrease in responding late in the interval. It also delayed, to a considerable extent, the total abolition of responding which was a reflection of the appearance of convulsive behavior.

Temperature

Controls. Before the first drug experiment the rats' temperature was 37.5±0.1°C. Their temperature was not changed during the behavioral session, nor was it different 1 hour after the session. Temperature was similar for all the nondrug experiments mentioned above.

Each rat's temperature during the 6 nondrug experiments was quite consistent, indicating the reliability of our repeated-measures methodology. Since nondrug experiments were performed before, during and after the PG and/or d-amphetamine experiments, it was concluded that the rats' rectal temperature was not permanently altered by the various PG and/or d-amphetamine experiments and their consequences (*vide supra*).

d-Amphetamine. The dose of d-amphetamine used (0.5 mg/kg) had no significant effect on temperature (Fig. 2).

Prostaglandins. The 2 lower doses of $PGF_{2\alpha}$ (10 and 100 ng/min) had no effect on temperature. However, the highest dose of $PGF_{2\alpha}$ (1000 ng/min) significantly increased temperature ($p<0.001$). Although low concentrations of $PGF_{2\alpha}$ were devoid of temperature-altering effects, a combination of $PGF_{2\alpha}$ with the thermically-inactive dose of d-amphetamine (0.5 mg/kg, IP) caused a significant decrease in temperature (Fig. 2). The hyperthermia produced by the highest concentration of $PGF_{2\alpha}$ was not significantly affected by this dose of d-amphetamine.

PGE_1 caused a significant dose-dependent hyperthermia ($p<0.005$). d-Amphetamine attenuated the PGE_1-induced hyperthermia at the two lowest doses (100 and 250 ng/min) of PGE_1, but not the highest (500 ng/min) (Fig. 3).

Temperature was never different from control 1 hour after each experiment.

DISCUSSION

Nondrug experiments (infusion-perfusion of vehicle and injection of saline) were performed before, during and after the various drug experiments; no change was found in the rats' FI 75 sec behavior or rectal temperature. This indicated that the rats had recovered from any drug effects before another drug experiment was performed. Experiments where d-amphetamine was injected and the vehicle was infused and perfused were also performed before, during and after the other experiments. It was found that the above mentioned parameters did not change from one d-amphetamine experiment to another. This indicated that the rats' responsiveness to drug effects throughout the course of the experiments was consistent and reproducible. These results indicate that the problem of using the same rats for all experiments has been adequately dealt with and controlled for.

We have previously reported that fixed-ratio behavior was not affected by cannula implantation, perfusion with the vehicle medium at a rate of 10 μl/min, or addition of trace concentrations of ^{3}H-DA to the perfusion medium and subsequent perfusion [25]. The results reported here show that rectal temperature and FI behavior were also not affected by cannula implantation, injection (IP) of saline or infusion (ICV) of vehicle at a rate of 1 μl/min.

PGE_1 induced convulsions in a dose-dependent manner. The convulsions were probably not due to a nonspecific lipid effect, since infusion of a greater amount of a structurally related PG, $PGF_{2\alpha}$, produced no convulsions.

PGE_1 has been found to inhibit [3, 7, 14, 30, 31] or induce [36] seizure activity. Based on PGE_1's effect on catecholamine neurons, one might expect the latter action. d-Amphetamine inhibited PGE_1-induced convulsions, an action which could be related to PGE_1 and d-amphetamine having opposite effects on the release of catecholamines from neurons. Since catecholamines mainly decrease neuronal firing (for review see [17]), an increase in catecholaminergic neuronal activity leads to a reduction in seizure susceptibility (see [20,21]). d-Amphetamine stimulates the release of catecholamines and in moderate doses inhibits seizures (for review see [19]). One could conclude that PGE_1 may be inducing convulsions by inhibiting the release and/or postjunctional action of catecholamines, and that d-amphetamine may be attenuating PGE_1-induced convulsions by antagonizing PGE_1's actions on these processes.

d-Amphetamine also antagonized PGE_1's rate-dependent effect on FI 75 sec behavior. Both PGE_1 (this report) and d-amphetamine [6], when administered separately, increase low rates and decrease high rates of behavior. However, when they were administered in the same experiment, there was no effect on behavior. This also supports the conclusion that PGE_1 and d-amphetamine have an antagonistic relationship. This relationship has also been shown when activity

and stereotypy [28] or circling behavior [33] are monitored.

The site(s) of interaction of PGs and amphetamine is not certain. While d-amphetamine is thought to act mainly presynaptically to increase the release of DA [13,29] and block the reuptake of the neurotransmitter [10,37], PGs may be affecting DA neurons pre- and/or postsynaptically. For example, Schwarz and coworkers [32] recently reported that PGs inhibit apomorphine-induced circling in unilaterally lesioned mice, probably by affecting sites postsynaptic to the DA nerve terminal.

PGEs increase body temperature (*vide supra*). PGE_1's effect on catecholamines [25a] may be involved in this action as well. Cox and coworkers [4,5] have suggested that central DA receptors are physiologically important in thermoregulation. Stimulation of those receptors decreases body temperature in the rat [4, 5, 18]. d-Amphetamine indirectly stimulates DA receptors by facilitating DA release and, at low doses, also leads to a decrease in temperature [15]. PGE_1 might be decreasing the release of DA or otherwise modulating its action, thereby inhibiting one of the homeostatic mechanisms responsible for maintaining temperature. The result would be an increase in temperature.

Support for this model comes from the finding that a thermically inactive dose of d-amphetamine antagonized PGE_1-induced hyperthermia (this report). d-Amphetamine was not merely reducing PG-induced hyperthermia, since it had no effect on high dose $PGF_{2\alpha}$-induced hyperthermia. The fact that d-amphetamine did not antagonize the hyperthermia caused by the highest dose of PGE_1 does not necessarily detract from the model. It is probable that the highest dose of PGE_1 used was a supramaximal dose in terms of increasing temperature. In that case, the low dose of d-amphetamine might not be able to overcome this effect.

The hypothermia caused by $PGF_{2\alpha}$ plus d-amphetamine also supports the model. $PGF_{2\alpha}$ and d-amphetamine had similar effects on DA neurons, possibly increasing the release of DA (accompanying paper). Therefore, while neither was able to decrease temperature alone, their combined effect was to produce significant hypothermia. $PGF_{2\alpha}$ increased the potency of d-amphetamine, rather than vice versa, since doses of d-amphetamine higher than that used in these experiments decrease temperature [15,26], whereas a higher dose of $PGF_{2\alpha}$ produces hyperthermia ([3, 9, 16, 27], this report).

High doses of $PGF_{2\alpha}$ increase temperature (*vide supra*). The mechanism for this phenomenon is apparently not the same as that for PGE_1-induced hyperthermia, since d-amphetamine attenuated the latter, but not the former effect. It has been suggested that $PGF_{2\alpha}$-, but not PGE_1-, induced hyperthermia is mediated by serotonergic neurons [1], whereas we have suggested that PGE_1-induced hypethermia may be mediated by an alteration of dopaminergic activity.

PGE_1 produced systematic effects on the parameters that were measured in these experiments. PGE_1 produced a rate-dependent effect on operant behavior, increased temperature and induced convulsions in a dose-dependent manner. PGE_1 altered our biochemical index of dopaminergic and noradrenergic neuronal activity in a manner opposite of that of d-amphetamine [25a]. Furthermore, PGE_1 and d-amphetamine had an antagonistic relationship on essentially all of the parameters discussed herein, suggesting that PGE_1 may be an important physiological antagonist of d-amphetamine's action and/or those of similar drugs.

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