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Indomethacin Potentiates the Operant Behavior Suppressant and Rectal Temperature Lowering Effects of Low Doses of d-Amphetamine in Rats[1]

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NIELSEN, J. A. AND S. B. SPARBER. *Indomethacin potentiates the operant behavior suppressant and rectal temperature lowering effects of low doses of d-amphetamine in rats.* PHARMACOL BIOCHEM BEHAV 21(2) 219–224, 1984.— Prostaglandins (PGs) may be important in modulating the actions of d-amphetamine. To test this hypothesis male rats were pretreated with indomethacin to inhibit PG synthesis before d-amphetamine was injected. Indomethacin (5 mg/kg, IP) was found to be without direct effect upon fixed-ratio behavior or rectal temperature, but significantly enhanced the capacity of low doses of d-amphetamine to suppress behavior and lower temperature. These effects were not due to partial food deprivation or to an increase in the concentration of d-amphetamine in brain. It is concluded that one or more of the PGs modulate the central actions of d-amphetamine, perhaps by modifying the release and/or reuptake of catecholamines, or through a postsynaptic action.

Indomethacin d-Amphetamine Prostaglandins Operant behavior Rectal temperature

NEUROPHARMACOLOGICAL and neurochemical studies have implicated the prostaglandins (PGs) as modulators of catecholaminergic synaptic transmission [2, 10, 14] and of the responsiveness of various organs to sympathetic nervous system activation [4, 6, 13]. Since d-amphetamine appears to produce most of its actions through an indirect effect on central and peripheral catecholaminergic pathways (for review, see [19]), we hypothesized that PGs may be modulators of this drug's actions.

Indomethacin, a PG synthesis inhibitor, has been shown to potentiate the hyperthermia produced by a single high dose of d-amphetamine (5 mg/kg) [8,25]. On the other hand, PGD_2 and PGE_2 inhibit amphetamine-induced circling in mice [24]. We inhibited PG synthesis with indomethacin to determine if it also potentiates the d-amphetamine-induced suppression of fixed-ratio (FR) behavior [9, 11, 28] and hypothermia [15, 17, 30]. Since we found that indomethacin potentiated d-amphetamine-induced behavioral suppression and hypothermia, it was determined if the animals body weight or the concentration of d-amphetamine in brain were important variables in the interaction between indomethacin and d-amphetamine.

METHOD

Twenty-four drug-naive, male Long-Evans rats (Simonsen, Gilroy, CA) were caged individually in a temperature (22°C) and humidity (50%) controlled room on a 12-hour light cycle. Food and tap water were available ad lib for several weeks prior to this study. The rats were then gradually food-deprived to approximately 80% of their free-feeding weights (425–500 g) and shaped to lever press for 45 mg food pellets (P. J. Noyes Company, Lancaster, NH) on a continuous reinforcement schedule [12] in a small-animal operant chamber (model 143-22, BRS/LVE, Beltsville, MD) enclosed in an environmental isolation chamber which was sound and light attenuating. The number of responses necessary for reinforcement was gradually, over the course of 7 days, increased to 30 (fixed ratio (FR) 30). A computer-based Interact system (BRS/LVE) was programmed to control environmental contingencies and record and reduce the behavioral data. At the termination of the behavior session a printout was obtained which included the number of reinforcers earned by the rat. From this data, the animal's response rate was determined. A continuous record of each session was also obtained on cumulative recorders (R. Gerbrands Company, Arlington, MA).

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

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temperature from a telethermometer (model 5810, United Systems Corporation, Dayton, OH) 3 minutes later.

The Effect of Indomethacin on d-Amphetamine-Induced Hypothermia and Behavioral Suppression

The experimental protocol involved determining the rat's temperature and then placing it within an operant chamber where it was allowed access to food reinforcers for 30 minutes on the FR 30 schedule. Immediately after this initial behavioral session, either saline, indomethacin or its vehicle was injected. Five-and-a-half hours later the rat was again placed in the operant chamber for a 60-minute session. Halfway through the session saline or d-amphetamine was injected into the rat. Temperature was recorded immediately before and after this session.

Preliminary experiments involved stabilizing the rat's behavior and temperature response to the experimental manipulations and determining whether indomethacin affected behavior or rectal temperature.

The rats were then randomly divided into 4 groups. The rats were injected with indomethacin (5 mg/kg, the only dose used in the experiments described below) or its vehicle, followed 6 hours later by 0.56 or 1.12 mg d-amphetamine/kg. The rats which received the low dose of d-amphetamine were administered 0.56 mg d-amphetamine/kg after the experimental session so that all rats received 1.12 mg d-amphetamine/kg on the day of the experiment.

The rats were then assigned to groups receiving vehicle or indomethacin, followed 6 hours later by 1.12 or 1.68 mg d-amphetamine/kg.

Effects of Body Weight on the Indomethacin-d-Amphetamine Interaction

Since indomethacin potentiated the behavioral suppressant and temperature altering effects of d-amphetamine, the next experiment was carried out to determine if the interactive effects of indomethacin and d-amphetamine were restricted to rats maintained at 80% of their free-feeding weights and/or confined to the operant chamber within a sound-attenuating enclosure.

Fourteen drug-naive, mature, male Long-Evans rats (Simonsen) were used in this experiment. After several weeks of free access to food and tap water, half the rats were slowly food deprived to 80% of their weights (400–475 g). The experimental protocol was similar to that used in the previous experiments. The major change was that the rats did not lever press for food reinforcement in an enclosed environment. Otherwise temperature determination and injections were made according to the same schedule.

Does Indomethacin Alter the Concentration of d-Amphetamine in the Brain?

All rats were habituated to the procedure by insertion of the temperature probe and injection with saline for 7 days prior to the administration of drug. Half of the food-deprived and nondeprived rats were administered indomethacin as the first drug injection, while the other half were given its vehicle. All rats were injected with d-amphetamine (1.68 mg/kg) containing d-[^{3}H]-amphetamine as the second injection. Immediately after the final temperature determination, the rats were decapitated and their brains were removed, quickly frozen, and stored at −20°C until they could be assayed for unchanged d-[^{3}H]-amphetamine as described by Axelrod [3] and Maickel and co-workers [20], and modified by Sparber and co-workers [27].

Drugs

d-Amphetamine sulfate (K and K Laboratories Inc., Plainview, NY) was prepared in isotonic saline. Indomethacin (Sigma Chemical Company, St. Louis, MO) was dissolved in isotonic saline with the aid of sodium carbonate and shaking. The pH of the solution (9.5) was adjusted to approximately 7.5 by the addition of hydrochloric acid. To determine the brain levels of d-amphetamine, 1.4 ng d-[^{3}H-(G)]-amphetamine/kg (Spec. Act. 30 Ci/mMole, New England Nuclear, Boston, MA) plus 1.68 mg d-amphetamine/kg were injected. All solutions were prepared daily and injected (IP) in a volume of 1 ml/kg of body weight. Drug doses are expressed as the base.

Data Analysis

Data were analyzed by either a paired Student t-test, with each rat serving as its own control, to determine if d-amphetamine altered FR 30 behavior or rectal temperature, or by a group Student t-test to determine if indomethacin altered the d-amphetamine-induced effects on behavior, temperature, or the amount of d-amphetamine in brain. A critical p value of 0.05 was set as that required to indicate a statistically reliable effect of experimental manipulation. All values represent the mean±S.E.

All experiments were carried out early in the day. The experimental designs were such that balanced orders of injections and use of equipment, etc., enabled us to take into account those variables which otherwise could not be controlled for (e.g., diurnal variation).

RESULTS

During the preliminary experiments, the rats' initial rectal temperature was 37.7±0.1°C. Their temperature 6 hours later, just before the 60-minute behavior session, was 38.0±0.1°C. During the 60-minute behavior session a significant elevation in temperature (1.0±0.1°C) was observed. The rate of lever pressing for all subjects on the last day prior to initiating drug experiments was 1.80±0.12, 1.91±0.13, and 2.10±0.15 responses/second for the three 30-minute sessions, respectively. There was no systematic baseline shift in their temperatures or response rates during the period required to complete the experiments. The experimental groups did not differ from each other in terms of their temperatures (Fig. 1) or response rates (Fig. 2) during experiments when saline was injected. Saline, indomethacin or its vehicle failed to affect temperature or behavior in any experiment where d-amphetamine was not administered.

The second group of rats' temperatures the day before the first drug treatment were similar to baseline temperatures determined for the first group of rats, including the temperature elevation (0.7±0.1°C) between the second and third determinations.

The Effect of Indomethacin on d-Amphetamine-Induced Hypothermia and Behavioral Suppression

The spontaneous increase in temperature which occurred during the 60-minute behavioral session was not affected by the lowest dose of d-amphetamine (0.56 mg/kg) (Fig. 1, panel A, open versus cross-hatched columns). When indomethacin was injected 6 hours earlier, the combination blocked the

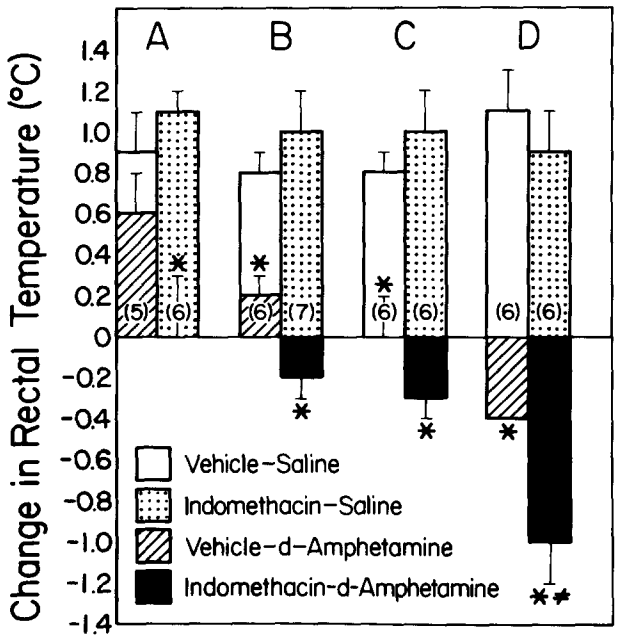

FIG. 1. Indomethacin potentiated d-amphetamine-induced hypothermia. Indomethacin or its vehicle was injected 6 hours before saline or d-amphetamine. Rectal temperature was determined before the first injection and 30 minutes before and after the second injection. The data shows the last temperature minus the first temperature. The histograms represent the means, numbers in parentheses represent the group size, and the vertical lines represent 1 S.E. The S.E. for the vehicle-d-amphetamine group depicted in panel D was less than 0.1. The dose of d-amphetamine was 0.56 mg/kg (panel A), 1.12 mg/kg (panels B and C), and 1.68 mg/kg (panel D). The dose of indomethacin was always 5 mg/kg. *$p<0.05$ compared with the same rats treated with vehicle-saline or indomethacin-saline (2-tailed, paired t-test); *‡$p<0.05$, rats treated with indomethacin and d-amphetamine were compared with those treated with vehicle and the same dose of d-amphetamine (2-tailed Student t-test).

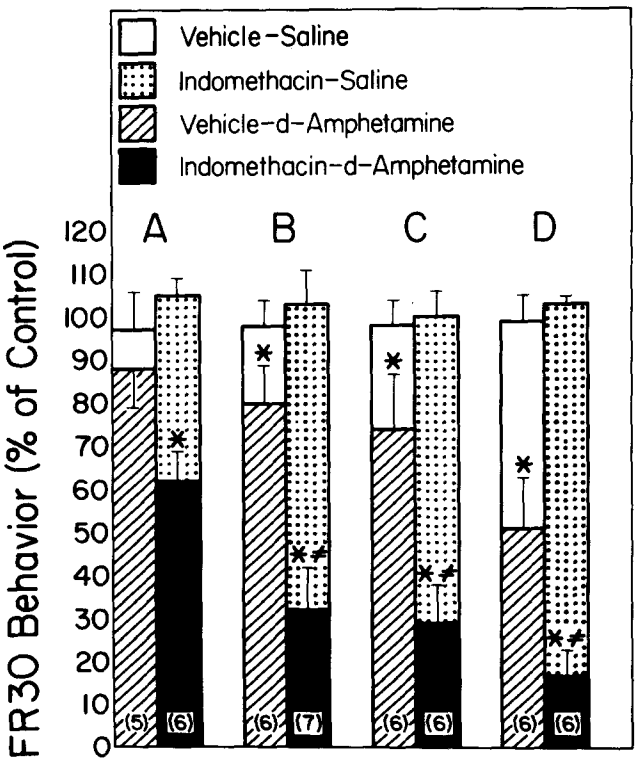

FIG. 2. Indomethacin potentiated d-amphetamine-induced suppression of FR 30 behavior. For a description of the protocol and dosages, see the legend to Fig. 1. The FR 30 behavior occurred during a 30 minute session following the second injection. The control (vehicle-saline) response rates (responses/second) were: panel A—1.92; panel B—1.98; panel C—2.01; panel D—1.89. *$p<0.05$ compared with the same rats treated with vehicle-saline or indomethacin-saline (2-tailed, paired t-test); *‡$p<0.05$, rats treated with indomethacin and d-amphetamine were compared with those treated with vehicle and the same dose of d-amphetamine (2-tailed Student t-test).

temperature elevation (Fig. 1, panel A, cross-hatched versus solid column; Note—there was zero change in rectal temperature in the indomethacin-d-amphetamine group [solid column]). The spontaneous increase in temperature was blocked in both experiments by 1.12 mg d-amphetamine/kg, given without indomethacin (Fig. 1, panels B and C, open versus cross-hatched columns). Pretreatment with the PG synthetase inhibitor had no effect on this action of d-amphetamine (Fig. 1, panels B and C, cross-hatched versus solid columns). When the highest dose of d-amphetamine (1.68 mg/kg) was administered, there was a small hypothermic effect (Fig. 1, panel D, cross-hatched column). This dose of d-amphetamine combined with indomethacin pretreatment resulted in a clear cut hypothermia, the rats' temperature measured 2°C less than that determined under the same experimental conditions in which indomethacin vehicle and saline were injected (Fig. 1, panel D, cross-hatched versus solid columns).

The FR operant behavior was not significantly affected by the lowest dose of d-amphetamine (Fig. 2, panel A, open versus cross-hatched columns). However, when 0.56 mg d-amphetamine/kg was administered to rats treated 6 hours earlier with indomethacin, a significant reduction in FR 30 responding, to about 60% of control, occurred (Fig. 2, panel A, cross-hatched versus solid columns). The highest dose (1.68 mg/kg) suppressed responding to about 50% of control rates (Fig. 2, panel D, cross-hatched column). Pretreatment with indomethacin, combined with the highest dose of d-amphetamine, virtually eliminated FR 30 responding (Fig. 2, panel D, solid column).

Figures 3 and 4 show sample cumulative records from individual rats demonstrating the dose-dependent, rate-decreasing action of d-amphetamine and its potentiation by pretreatment with a behaviorally inactive dose of indomethacin.

Effects of Body Weight on the Indomethacin-d-Amphetamine Interaction

d-Amphetamine (1.68 mg/kg) attenuated the rise in the rats' temperatures in both the deprived and nondeprived state (Table 1). Indomethacin potentiated this effect, placing the rats in a hypothermic state. The magnitude of these effects was the same in deprived and nondeprived rats and similar to those seen earlier (Table 1 and Fig. 1, panel D, solid column).

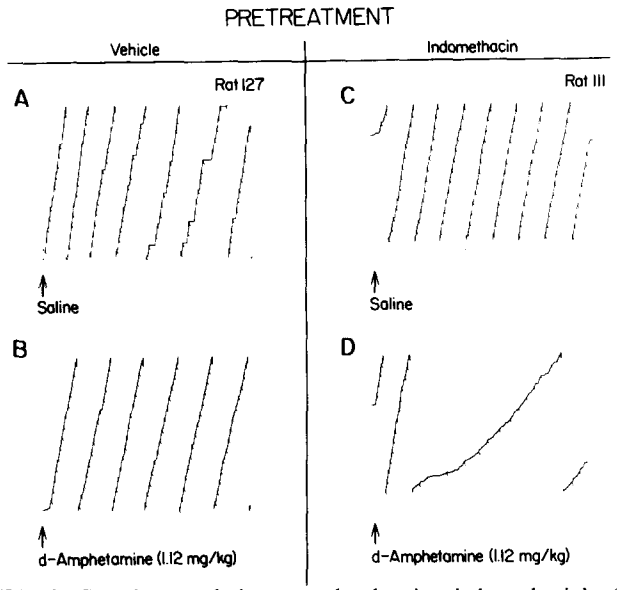

FIG. 3. Sample cumulative records showing indomethacin's (5 mg/kg, IP) potentiation of the slight, but significant (Fig. 2) behavioral suppressant action of d-amphetamine (1.12 mg/kg, IP). The rats' (127 and 111) lever-pressing behavior during a 30 minute FR 30 session after saline (panels A and C) or d-amphetamine (panels B and D) is depicted. Indomethacin (rat 111) or its vehicle (rat 127) was injected 6 hours before d-amphetamine or saline. Response rate is reflected by the slope of the recording. Delivery of a reinforcer is indicated as a pip on the ascending record.

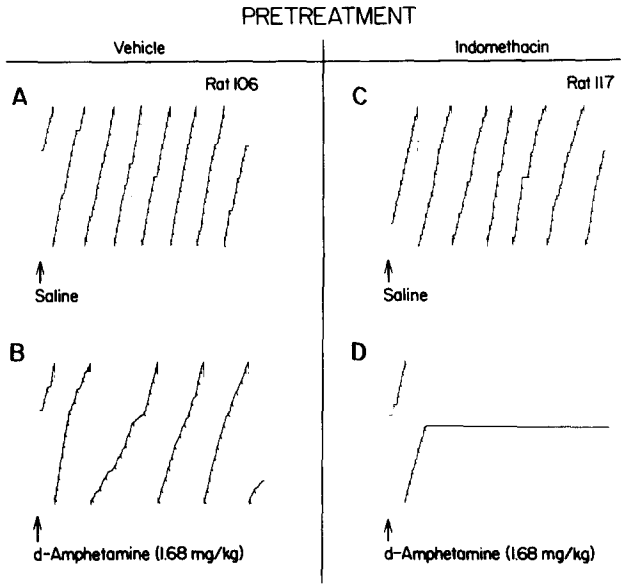

FIG. 4. Sample cumulative records showing indomethacin's (5 mg/kg, IP) potentiation of the behavioral suppressant action of d-amphetaminae (1.68 mg/kg, IP). See legend to Fig. 3 for a fuller description of the records.

Does Indomethacin Alter the Concentration of d-Amphetamine in the Brain?

The amount of d-amphetamine in whole brain 30 minutes after administration of 1.68 mg d-amphetamine/kg to nondeprived rats was 1.13±0.15 mg/g of brain. The amount of d-amphetamine in brain was not affected by depriving rats to 80% of their free-feeding weight prior to injection of 1.68 mg/kg (1.07±0.15 μg/g). Pretreatment with indomethacin resulted in a concentration of 0.81±0.16 μg d-amphetamine/g of brain in food deprived, and 0.89±0.15 μg d-amphetamine/g of brain in nondeprived rats. The deprived and nondeprived rats pretreated with vehicle were grouped together, since deprivation had no significant effect, and compared with the combined deprived and nondeprived rats pretreated with indomethacin. It was determined that indomethacin caused a significant ($p<0.05$) decrease in the concentration of unchanged d-amphetamine in rat brain 30 minutes after injecting the drug.

DISCUSSION

The consistent increase in rectal temperature which we observed during the day is currently inexplicable. Handling may have been partially responsible, since it has been reported that handling of mice resulted in a body temperature rise [7]. Additionally, circadian fluctuation of body temperature may also have contributed to this phenomenon [23]. Regardless of the cause for the slight elevation in temperature, a low dose of d-amphetamine blocked this phenomenon and a higher dose of d-amphetamine converted the temperature to a hypothermic state. These data are in agreement with those of Jellinek [15], who reported a drop of 0.5°C 30 minutes after injecting rats with 1 mg d-amphetamine/kg.

It has previously been demonstrated that doses of d-amphetamine similar to those used in the present study suppressed FR behavior in rats [9, 11, 28]. As expected, such was the case in these experiments. The degree of suppression was consistent with the choice of doses, allowing us to determine any effects, regardless of the direction of the interactive effect.

Indomethacin enhanced the effects of d-amphetamine. The low dose of d-amphetamine (0.56 mg/kg) alone had no effect on rectal temperature or FR behavior, but its combination with indomethacin significantly attenuated the rise in the rats' temperature and significantly decreased behavior. In addition, the PG synthesis inhibitor significantly increased the magnitude of the temperature-lowering effect of the high dose of d-amphetamine and the behavioral suppressant effect of both the middle and high doses of d-amphetamine. This indicates that FR 30 behavior was a more sensitive measure than rectal temperature of indomethacin's interactive effect with d-amphetamine.

Several factors were eliminated as possible explanations of indomethacin's potentiation of d-amphetamine-induced hypothermia. It was not due to the rats' performing an operant behavior, being confined within an isolation chamber, or altering their body weight so that food pellets could be used as reinforcers to maintain the operant. In addition, indomethacin's potentiation of d-amphetamine-induced behavior suppression was not due to an increase in the amount of d-amphetamine in whole brain after treatment with the PG synthetase inhibitor. In fact, indomethacin significantly decreased the brain levels of d-amphetamine. The reason for this effect is not clear; however, it may be suggested that the PG synthetase inhibitor's potentiation of d-amphetamine's actions would have been even greater if the amount of unchanged d-amphetamine in the brain had been comparable in the rats pretreated with indomethacin and its vehicle.

Central nervous system PGs appear to be important modulators of d-amphetamine's actions. Schwarz and coworkers [24] have shown that PGD_2 and PGE_2 inhibit

TABLE 1

FOOD DEPRIVATION DOES NOT ALTER d-AMPHETAMINE'S EFFECT UPON RECTAL TEMPERATURE OR ITS INTERACTION WITH INDOMETHACIN*

	Change in Rectal Temperature (°C) (Mean ± S.E.)			
Body Weight	Vehicle + Saline	Vehicle + d-Amphetamine	Indomethacin + Saline	Indomethacin + d-Amphetamine
100%	0.7 ± 0.1 (3)	−0.2 ± 0.0†	0.8 ± 0.1 (4)	−0.5 ± 0.2†‡
80%	0.6 ± 0.1 (3)	−0.2 ± 0.1†	0.7 ± 0.2 (4)	−0.6 ± 0.1†‡

*The rats were administered vehicle or indomethacin (5 mg/kg, IP) followed 6 hours later by d-amphetamine (1.68 mg/kg, IP). Numbers in parenthesis represent group sizes.

†$p<0.05$ Compared with the same rats treated with indomethacin and saline or vehicle and saline (2-tailed, paired t-test).

‡$p<0.05$ All rats receiving vehicle and d-amphetamine (100% and 80%) compared with all rats receiving indomethacin and d-amphetamine (2-tailed Student t-test).

amphetamine-induced circling in mice. Our data indicate that indomethacin can significantly augment d-amphetamine's capacity to lower temperature and alter FR operant behavior. The involvement of the CNS prostaglandins in mediating these effects is supported by several findings. Indomethacin has been shown to inhibit CNS prostaglandin synthesis [1,16] and augment the hyperthermia caused by a high dose of d-amphetamine [8,25]. In fact, the experiments described herein may be underestimating the importance of PGs in the actions of d-amphetamine because indomethacin (2.5 and 10 mg/kg, IP) only inhibited PG synthesis to about 40% of control 5 hours after administration [16]. Finally, acetaminophen, an agent which can inhibit peripheral [31] but not central [1] PG synthesis, did not modify the d-amphetamine-induced increase in body temperature [8].

Prostaglandins might be affecting d-amphetamine's action by modulating CNS catecholaminergic neurons [24]. PGEs and d-amphetamine have opposite actions on the release of noradrenaline from central nervous tissue *in vitro*, with PGEs inhibiting [26,29] and d-amphetamine increasing its release [19]. In addition, when the lateral ventricles of conscious, freely-moving rats were perfused with [^{3}H]-dopamine, d-amphetamine (0.5 mg/kg) significantly increased the amount of the [^{3}H]-noradrenaline metabolite [^{3}H]-3-methoxy-4-hydroxyphenylethyleneglycol in perfusate [22]. Infusion of PGE_1 (intracerebroventricularly) antagonized this effect. Therefore, indomethacin might be potentiating the actions of d-amphetamine by allowing greater increased release of noradrenaline via inhibition of PGE synthesis.

On the other hand, prostaglandin's effect on CNS dopamine neurons may be involved in both the hypothermic and hyperthermic effects of d-amphetamine. It has been hypothesized that the hypothermic [17] and hyperthermic [30] actions of d-amphetamine are mainly dependent on a central dopaminergic mechanism. We have observed that when the lateral ventricles of conscious, freely-moving rats were perfused with [^{3}H]-dopamine, d-amphetamine (0.5 mg/kg) significantly decreased the amount of the [^{3}H]-dopamine metabolites [^{3}H]-3,4-dihydroxyphenylacetic acid, [^{3}H]-homovanillic acid, and [^{3}H]-3-methoxytyramine in perfusate [22]. Therefore, one must conclude that the biphasic effect of d-amphetamine upon body temperature is due to different mechanisms, hypothermia the direct result of low doses and hyperthermia secondarily due to a central, a peripheral lipolytic, and a behavioral stimulatory action. If facilitated release of catecholamines is involved in both body temperature responses to d-amphetamine, inhibition of PG(E) synthesis would be expected to augment both actions. This might explain how peripherally administered PGE_1 antagonised d-amphetamine-induced hyperthermia [5], and d-amphetamine's (0.5 mg/kg) antagonism of centrally administered PGE_1-induced hyperthermia [21]. Indomethacin, possibly by inhibiting PGE synthesis, potentiated hyperthermia produced by a high dose of d-amphetamine [8,25], as well as hypothermia produced by a low dose of d-amphetamine (this report).

Indomethacin's potentiation of d-amphetamine's effects may be important clinically. Indomethacin has been reported, in a single clinical case, to potentiate the hypertensive effect of phenylpropanolamine [18], a compound which, like d-amphetamine, facilitates the release of noradrenaline. Our data suggest that indomethacin-like drugs (prostaglandin synthetase inhibitors) may potentiate the effects of d-amphetamine-like drugs.

In summary, indomethacin potentiated the operant behavior suppressant and temperature lowering actions of low doses of d-amphetamine, perhaps by inhibiting the synthesis of PGEs which may modulate catecholamine neurons in a manner resulting in an effect opposite to d-amphetamine.

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