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The Antidipsogenic Action of Peripheral Prostaglandin E_2[1]

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KENNEY, N. J., K. E. MOE AND K. M. SKOOG. *The antidipsogenic action of peripheral prostaglandin E_2.* PHARMAC. BIOCHEM. BEHAV. 15(2) 263–269, 1981.—Intraperitoneal (IP) injection of 50 μg/kg prostaglandin E_2 (PGE_2) suppresses water intake elicited by cellular dehydration, intracerebroventricular injection of angiotensin II (A II) and, for a shorter duration, water deprivation. At a dose of 100 μg/kg, IP PGE_2 reduces drinking to all of these stimuli as well as to hypovolemia. A 10 μg/kg dose of PGE_2 has no effect on drinking under any of the conditions tested. Intraperitoneal PGE_2, at either 50 or 100 μg/kg, does not support the formation of a conditioned taste aversion suggesting that PGE may act via specific inhibition of drinking rather than by producing a generalized malaise. Although both central and peripheral administration of PGE suppresses water intake, the findings that peripheral PGE_2 reduces drinking to cellular dehydration but has minimal effects on drinking due to hypovolemia are in marked contrast to the actions reported for intracranial PGE. In addition, peripheral PGE_2 reduces body temperature whereas centrally applied PGE induces thermogenesis. These data may indicate differential roles and/or mechanisms by which central and peripheral PGE may control water intake.

Water intake Prostaglandins Cellular dehydration Hypovolemia Angiotensin II
Water deprivation Conditioned taste aversion Body temperature

THE prostaglandins are naturally-occurring, unsaturated fatty acids synthesized and released by virtually every tissue of the body (see [2] for review). Present data indicate that the prostaglandins of the E series (PGEs) may play an important role in the regulation of body fluid and electrolyte content. For example, increased brain levels of PGE have been shown to stimulate the release of vasopressin [18]. Augmentation of renal PGE levels inhibits the water conserving effects of vasopressin [10]. In addition, PGE has been implicated in the modification of the filtering and reabsorption of sodium at the nephron [1,15].

One of the major mechanisms by which PGE might act to control fluid content of the body may be through the inhibition of water intake. Intracranial administration of PGE_1 or PGE_2 (10 ng per rat or more) is a potent suppressor of water intake stimulated by the central [12] or peripheral [11] administration of angiotensin II (A II). Drinking elicited by hypovolemia induced by polyethylene-glycol treatment is also reduced following low-dose, central administration of PGE_1 [12]. Water-deprivation-induced drinking is more resistant to suppression by central PGE administration; doses of 1 μg or more are required to reduce intake under these conditions [11,12]. On the other hand, water intake in response to cellular dehydration is unaffected by the intracerebroventricular (IVT) injection of PGE [11,12].

The effect of central PGE on water intake is not limited to situations in which exogenous PGE is applied to brain. Some evidence now suggests that stimulation of endogenous synthesis of PGE also inhibits water consumption elicited by central A II. IVT administration of arachidonic acid, the precursor of PGE_2, suppresses drinking to intracranially administered A II [5,6]. This effect can be eliminated by pretreatment with indomethacin, an inhibitor of PG synthesis [5,6]. Bradykinin, a peptide which stimulates the production of endogenous PGE [16], also suppresses drinking to centrally administered A II [11].

Although prostaglandins function locally and are not believed to pass from periphery to brain or vice versa [2], recent reports indicate that the antidipsogenic action of the E prostaglandins is not confined to centrally administered or produced PGE. Suppression of endogenous PG synthesis through the intraperitoneal injection of indomethacin results in increased water intake by water-replete Sabra rats over a 4-hr test period [4]. Chronic oral administration of indomethacin results in increased water consumption and decreased latency to the onset of drinking by rats in which drinking is stimulated by intravenous infusion of A II [13].

The role of peripheral PGE in controlling water intake may differ from that of central PGE, however. First, central administration of PGE is effective in reducing intake stimulated by both IVT and intravenous (IV) administration of A II [11,12]. Suppression of plasma PGE by indomethacin augments drinking to IV A II but has no effect on drinking induced by the intracranial administration of the dipsogen

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[13]. Second, as mentioned above, IVT PGE administration has no effect on drinking stimulated by cellular dehydration [12]. Goldstein *et al.* [9] have reported, however, that when injected into the peritoneum, both PGE_1 and PGE_2 significantly suppress intake in response to IV hypertonic saline infusion.

In this paper we examine the effect of intraperitoneal injection of PGE_2 on water intake induced by cellular dehydration, intracranially administered A II, polyethyleneglycol induced hypovolemia, and water deprivation.

GENERAL METHOD

Subjects

Adult male Long-Evans rats weighing between 270 and 370 g were used in all studies. Animals were housed individually in standard hanging cages and had ad lib access to both food (Purina pellets) and water except as noted below. All dipsogen tests were conducted in the light portion of a 12:12 light:dark sequence.

Prostaglandin E_2

Prostaglandin E_2 (PGE_2), crystalline free-acid, was generously supplied by Dr. John Pike of the Upjohn Company. PGE_2 was dissolved in 95% ethanol and diluted to the appropriate concentration with 0.2% sodium carbonate in a 1:9 mixture. Fresh solutions were made for each test day.

Statistical Analyses

All statistical tests for experiments measuring water intake were performed on non-cumulative intake data obtained for each time-interval tested unless otherwise stated. For Experiment 2 (body temperature) tests were conducted on changes of core temperature from baseline. For experiments in which the control measures were repeated, an overall analysis of variance (ANOVA) was performed to test for significant differences among control values. As a result of these tests, control values were averaged for presentation and for further analysis.

An overall two-way (dose × time) repeated measures ANOVA was conducted for each portion of Experiment 1 and for Experiment 2. If the overall F value was significant, a series of planned orthogonal comparisons was performed to locate the source of the treatment effect with regard to both time and drug dose. These comparisons were conducted on components of the overall treatment sum for each time interval. The F value was computed using a conservative error term specific to each comparison rather than a composite error term derived from the overall ANOVA [14].

The analysis for Experiment 3 consisted of an overall one-way ANOVA performed on the proportion of total fluid intake consumed as saccharin by each animal. Planned orthogonal comparisons as described above were conducted for each control-experimental group comparison.

EXPERIMENT 1A: CELLULAR DEHYDRATION

METHOD

Ten rats were tested once per day on each of ten consecutive days. On each test day, all rats received subcutaneous injections of 0.75 ml 1 M NaCl per 100 g body weight after which they were returned to their cages where no water was available. Fifteen minutes after the hypertonic saline injection, each animal received an intraperitoneal (IP) injection of either PGE_2 (Days 2, 4 and 9) or the carrier solution of the PG (9 parts 0.2% sodium carbonate : 1 part 95% ethanol). PGE_2 was administered in doses of 10, 50 and 100 μg/kg, in descending order of concentration in 1 ml/kg of the carrier solution. After the IP injection, rats were returned to their cages where water was available in calibrated burets. Water intake was measured to the nearest 0.1 ml every 5 min for the first 30 min and at the end of the first hour following the IP injection.

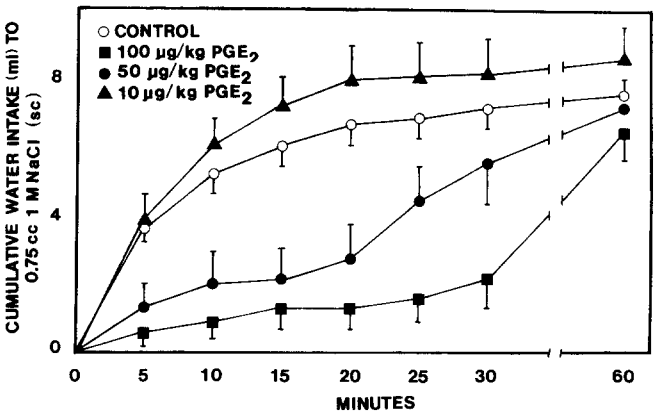

FIG. 1. Cumulative water intake (mean ± standard error) of rats in response to a hypertonic saline challenge. Animals were pretreated with an intraperitoneal injection of prostaglandin E_2 (PGE_2) in doses of 10, 50, or 100 μg/kg or PGE_2 vehicle.

RESULTS

Water intake stimulated by cellular dehydration was markedly suppressed by IP injection of PGE_2 administered in doses of 50 or 100 μg/kg (Fig. 1). Injection of 10 μg/kg PGE_2 had no effect on water consumption in response to this dipsogen.

Rats treated with 50 μg/kg PGE_2 drank significantly less water than on control days during the first 5 min of the test session (average intake = 1.3 ± 0.6 ml vs 3.6 ± 0.4 ml on control days, $p<0.001$). Intakes on the PGE_2 test day continued to be less than those on control days for the first 15 min of the test session ($p<0.005$ for the 10–15 min interval). During the fifth test-session interval (20–25 min), water consumption of rats when treated with 50 μg/kg PGE_2 increased over control levels (average intake = 1.7 ± 0.6 ml on the PGE_2 test day vs 0.3 ± 0.1 ml on control days, $p<0.05$) and by 30 min, total intake of rats on the PGE_2 test day was statistically equal to that observed on control days.

When treated with 100 μg/kg PGE_2, rats drank less than on control days during the first 5 min of the test session (average intake = 0.6 ± 0.4 ml vs 3.6 ± 0.4 ml on control days, $p<0.005$). Intakes remained significantly suppressed from control levels during the second and fourth test-session intervals ($p<0.01$ and $p<0.005$, respectively). No compensation for the suppression of intake occurred until the final 30 min of the test session (30–60 min). During this interval, water consumption on the 100 μg/kg test day averaged 4.3 ± 0.8 ml compared to 0.4 ± 0.1 ml on the control days ($p<0.005$). Total consumption on the 100 μg/kg test day equalled that on control days at the end of the test session.

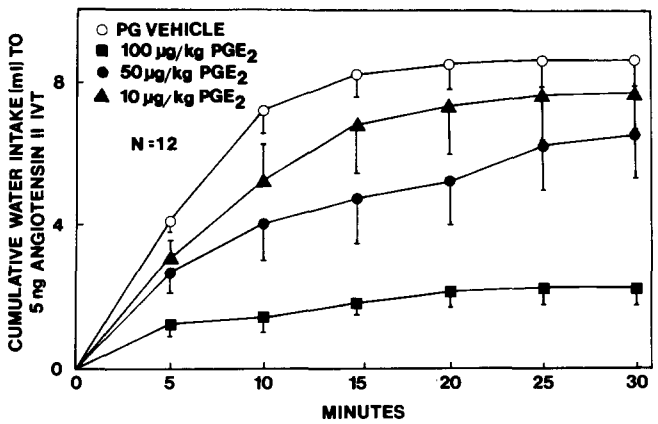

FIG. 2. Cumulative water intake (mean ± standard error) of rats in response to an introcerebroventricular injection of 5 ng angiotensin II immediately following intraperitoneal injection of prostaglandin vehicle or prostaglandin E_2 (10, 50, or 100 µg/kg).

EXPERIMENT 1B: ANGIOTENSIN II

METHOD

Rats were fitted with unilateral 23-ga stainless-steel cannulae stereotaxically aimed for the left lateral cerebral ventricle under pentobarbital anesthesia (see [8] for details). Approximately 1 week was allowed for recovery from surgery. Testing was carried out in three-day blocks. On each test day, 5 ng of Asp-1, Iso-5 angiotensin II (A II, Calbiochem) dissolved in 1 µl isotonic saline was injected through the ventricular cannula. On the first and the third days, the A II injection was immediately preceded by an IP injection of PG vehicle (1 ml/kg). On the intervening day, rats received an IP injection of PGE_2. PGE_2 was injected in doses of 10, 50 and 100 µg/kg. Animals were returned to their cages where water was available in calibrated burets immediately following the A II injection. Cumulative water intakes were measured every 5 min for the next 30 min.

Two criteria were employed to determine the accuracy of the cannula placement. The first was a behavioral criterion for the patency of the cannula. The failure of an animal to drink at least 3 ml in the 30 min following a 5-ng A II injection on any control day was taken as an indication that the cannula was not patent. The second criterion was histological. Postmortem histological examination was used to determine the exact placement of the cannula. Only data from the 12 animals that met the patency criterion and whose cannulae terminated in the lateral ventricle were included in the analysis.

RESULTS

As with drinking due to cellular dehydration, water intake elicited by IVT A II was unaffected by treatment with 10 µg/kg PGE_2 but was reduced by higher levels of the PG (Fig. 2). When drinking was stimulated by IVT A II treatment, 85% of the total test-session drinking occurred during the first 10 min on control days. When the rats were treated with 50 µg/kg PGE_2 in conjunction with this dipsogen, drinking was significantly suppressed during this time ($p<0.025$ for the first and $p<0.01$ for the second 5-min interval). During the third and fourth intervals, intakes on the PGE_2-treatment

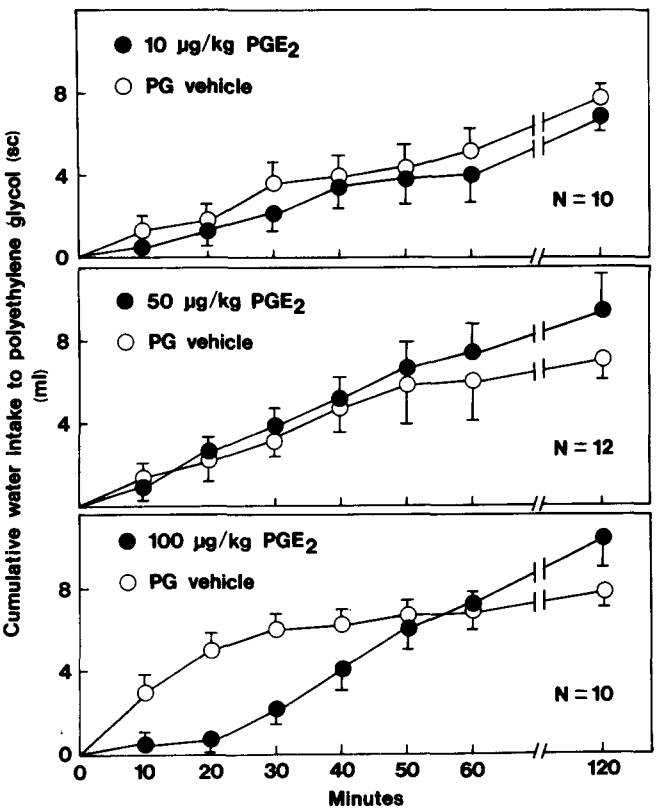

FIG. 3. Cumulative water intake (mean ± standard error) of rats receiving a subcutaneous injection of 5 ml 20% polyethylene glycol when pretreated with intraperitoneal prostaglandin vehicle or 10, 50, or 100 µg/kg prostaglandin E_2.

day equalled those on the control days. During the fifth test-session interval (20–25 min), however, intakes on the test day increased over control values and total consumption equalled that on control days at the end of the test period (30 min).

When the dose of PGE_2 was raised to 100 µg/kg, water intake was significantly suppressed from control levels during both the first and second test-session intervals ($p<0.001$ for both comparisons). No compensation for this suppression occurred; intakes during the remaining test-session intervals were equal to those on control days. Total consumption on the 100 µg/kg test day remained significantly lower than on control days at the end of the 30-min test session ($p<0.001$).

EXPERIMENT 1C: HYPOVOLEMIA

METHOD

The effect of PGE_2 in doses of 10, 50 and 100 µg/kg on water intake stimulated by hypovolemia was measured in 3 separate groups of animals (n=10, 12, and 10, respectively). Each animal was tested twice: once with the PGE_2 and once with the PG carrier solution. Within each PGE_2-dose group, the order of the PGE_2 and the PG vehicle injections was counterbalanced with half of the rats receiving PGE_2 on the first test while the remaining animals were tested first with the PG vehicle. For all tests, hypovolemia was induced by the subcutaneous injection of 5 ml of a 20% polyethylene-

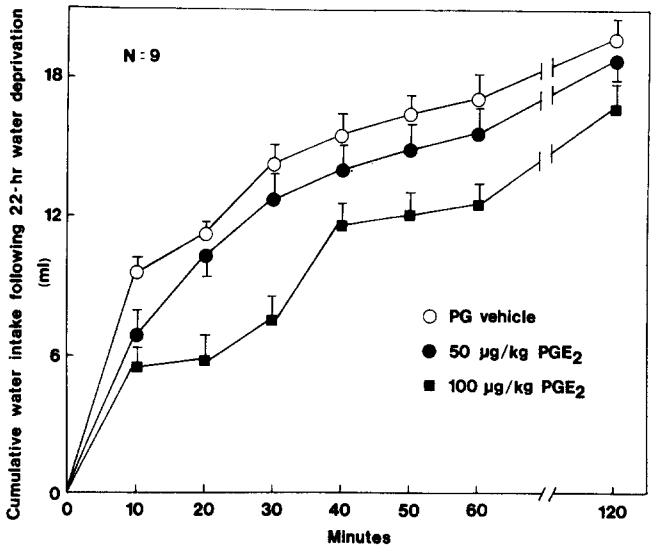

FIG. 4. Cumulative water intake (mean ± standard error) of 22-hr water-deprived rats for the first 2 hr of a 4 hr water access period following intraperitoneal administration of prostaglandin vehicle or 50 or 100 µg/kg prostaglandin E_2.

glycol (PEG) solution. The PEG was dissolved in isotonic saline and injected between the scapulae while the animals were under light ether anesthesia. The dipsogen was injected 6 hr prior to the PGE_2 or PG vehicle. No water was available during the delay period. Immediately following the injection of PGE or PG vehicle, animals were returned to their cages where water was available in calibrated burets. Water intakes were measured every 10 min during the first hour of water access and at the end of the second hour. The two hypovolemia tests were separated by 7–9 days during which time the rats were maintained on ad lib food and water.

RESULTS

Intraperitoneal injection of PGE_2 in doses of 10 or 50 µg/kg had no effect on drinking elicited by hypovolemia (Fig. 3). At 100 µg/kg, IP PGE_2 significantly reduced the amount of water consumed during the first and second test-session intervals ($p<0.005$ and $p<0.01$, respectively). Intakes of rats when treated with 100 µg/kg PGE_2 were slightly though insignificantly greater than control levels throughout the remainder of the test session. By the 40-min measure, total water consumption on the PGE_2 test day was no different than that on the control day and remained equal to control levels for the rest of the test session.

EXPERIMENT 1D: WATER DEPRIVATION

METHOD

Nine rats were deprived of water, but not of food, for 20 hr each day. After a 6-day adaptation period, testing began and continued for the next 5 days. Days 1, 3 and 5 were control days on which the PG vehicle (1 ml/kg) was injected IP immediately prior to water access. On Day 2, all rats received IP injections of 100 µg/kg PGE_2, while on Day 4 all received 50 µg/kg of the PG. Water intakes were measured every 10 min for the first hour of water access and at the end of the second, third and fourth hours.

RESULTS

Water-deprivation induced drinking was reduced by 30% during the first 10 min of water access after treatment with 50 µg/kg PGE_2 ($p<0.05$, Fig. 4). However, during the second 10 min interval, water consumption on the PGE_2 treatment day was significantly greater than that on control days (average intake = 3.5 ± 0.7 ml on the 50 µg-test day and 1.6 ± 0.2 ml on control days, $p<0.05$). At the end of this segment (20 min) total water intake on the PGE_2 test day equalled that observed on control days and remained equal throughout the remainder of the test session.

When the animals were injected with 100 µg/kg PGE_2, drinking was significantly reduced from control levels during the first 2 test-session intervals ($p<0.005$ for each comparison). Intakes of rats when treated with this dose of the PG were equal to those on control days during all other test-session intervals with one exception. During the fourth interval (30–40 min) intakes on the PGE_2 test day were significantly greater than control (4.0 ± 0.7 ml on the PGE test day and 1.3 ± 0.2 ml on the control days, $p<0.005$). This augmentation of intake did not totally compensate for the earlier reduction. Total water intake at the end of the 4-hr water-access period on the 100 µg/kg PGE_2 test day remained significantly below that on control days (average total intake = 19.3 ± 1.0 ml on the test day vs 24.5 ± 1.2 ml on control days, $p<0.01$).

DISCUSSION

PGE_2, administered peripherally, like PGE applied to brain, is antidipsogenic. The water-intake suppressant effects of IP PGE_2 are both dose and dipsogen dependent. When administered at a dose of 10 µg/kg, IP PGE_2 has no effect on water intake elicited by any of the dipsogens tested. At a dose of 50 µg/kg, drinking stimulated by either cellular dehydration or by IVT A II is suppressed by the PGE_2. In both cases, animals compensate for the suppression such that within 30 min after the PGE_2 treatment intakes reach control levels. IP injection of 50 µg/kg PGE_2 also reduces intake elicited by water deprivation but only during the first 10 min of water access. In this case, rats compensate for the suppression within 20 min following the PGE_2 treatment. Intake in response to polyethylene-glycol induced hypovolemia is unaffected by 50 µg/kg PGE_2.

At the highest dose tested (100 µg/kg), IP PGE_2 is a general suppressor of water intake. When drinking is elicited by hypovolemia or cellular dehydration, total water intake is reduced early in the test session but returns to control levels within 1 hr. In the case of water deprivation, complete compensation for the PGE_2-suppressant effects is not seen even 4 hours after treatment. Animals drinking in response to IVT A II were only monitored for 30 min during which time intakes on the 100 µg/kg PGE_2 test day remained significantly below control levels.

While comparison across dipsogenic conditions is difficult, it appears that the effectiveness of IP PGE_2 in reducing water intake is not related to the potency of the dipsogenic stimulus as measured by the total amount of water consumed under control conditions. Drinking elicited by polyethyleneglycol, the least potent stimulus (4.3 ± 0.5 ml consumed in the first 30 min), is least affected by IP PGE_2. Drinking is reduced only following the injection of 100 µg/kg of the PG. Water intake in response to deprivation, the most potent stimulus (14.3 ± 0.9 ml consumed in 30 min), is slightly reduced for 10 min following treatment with 50 µg/kg PGE_2

TABLE 1

BASELINE CORE TEMPERATURE (°C) AND CHANGES OF CORE TEMPERATURE FROM BASELINE FOLLOWING IP INJECTION OF PGE_2 OR ITS CARRIER SOLUTION (MEAN ± SEM)

Condition	Baseline Core Temperature (°C)	Time after Injection (min) 10	20	30	60
PG vehicle	37.41 ± 0.04	+0.6 ± 0.1	+0.9 ± 0.1	+0.8 ± 1.0	+0.2 ± 0.1
10 μg/kg PGE_2	37.30 ± 0.10	+0.4 ± 0.1	+0.6 ± 0.1	+0.8 ± 0.1	+0.4 ± 0.1
50 μg/kg PGE_2	37.79 ± 0.09	−0.4 ± 0.1	−0.7 ± 0.2	−0.3 ± 0.2	−0.4 ± 0.2
100 μg/kg PGE_2	37.59 ± 0.12	−0.5 ± 0.1	−0.7 ± 0.1	−0.4 ± 0.1	−0.2 ± 0.2

but quickly returns to control levels. Treatment of water-deprived rats with 100 μg/kg PGE_2 results in a suppression of ingestion without total compensation even after 4 hours. Drinking induced by hypertonic-saline injection (7.1 ± 0.6 ml drunk in 30 min) or IVT A II (8.6 ± 0.7 ml drunk in 30 min) is markedly reduced following injection of either 50 or 100 μg/kg PGE_2.

EXPERIMENT 2

Intracranial injection of PGE_1 or PGE_2 results in a marked increase of body temperature in most species studied including rat [3]. This increase of body temperature may partially underlie the antidipsogenic action of central PGE [5,12]. In this study we examine the effect of peripheral PGE_2 treatment on body temperature.

METHOD

The effect of IP PGE_2 or its carrier solution on body temperature was measured in 8 rats over a 5 day period. On Days 1 and 5, all animals received IP injections of PG vehicle (1 ml/kg). On Days 2, 3 and 4, PGE_2 was injected in doses of 10, 50 and 100 μg/kg respectively. Body temperature was measured by means of a YSI telethermometer (probe inserted 6 cm beyond anus) immediately prior to the IP injection. Temperature measures were repeated 10, 20, 30 and 60 min after the injections. Temperature changes on the two PG vehicle injection days did not differ and were averaged for presentation.

RESULTS

Intraperitoneal injection of the PG carrier solution resulted in a rise of core temperature which reached a maximum increase of 0.9 ± 0.1°C 20 min after treatment ($p<0.001$, Table 1). By 30 min, temperatures on control days had returned to baseline levels.

When rats were treated with 10 μg/kg PGE_2, body temperature also increased over baseline (Table 1), although at 10 min after the injection the increase of temperature on the PG test day was significantly less than that on the control days (average increase = 0.4 ± 0.1°C on the 10 μg/kg test day vs 0.6 ± 0.1°C on the vehicle days, $p<0.05$). At all other times, the increase of core temperature following IP injection of 10 μg/kg PGE_2 equalled that following the injection of PG vehicle.

Treatment with either 50 or 100 μg/kg PGE_2 reduced body temperature from pretest levels (Table 1). In both cases, the greatest decrease from baseline occurred 20 min after the PGE_2 injection ($p<0.005$ for 50 μg/kg and $p<0.001$ for 100 μg/kg). Thirty minutes after the 50 μg/kg PGE_2 injection, core temperature was not statistically different from baseline.

When temperature changes on the 50 μg/kg PGE_2-test day were compared to changes following the injection of PG vehicle, core temperature on the PGE-treatment day was significantly suppressed from control at all time intervals ($p<0.001$ at 10, 20 and 30 min and $p<0.01$ at 60 min).

When rats were treated with 100 μg/kg PGE_2, core temperature remained significantly suppressed from baseline for 30 min ($p<0.025$). In this case, temperature returned to baseline by 60 min. When compared to changes of temperature on vehicle injection days, treatment with 100 μg/kg PGE_2 resulted in a significant reduction of core temperature for the first 30 min of the test session ($p<0.001$ for all comparisons). At 60 min, the change of core temperature on this PGE-test day did not differ from the changes observed on control days.

When analyzed in terms of change from baseline temperature, core temperature modifications following the 100 μg/kg PGE_2 injection did not differ from those following the 50 μg/kg treatment for the first 30 min of the test session. At the 60-min measure, the suppression of temperature following the 50 μg/kg injection was significantly greater than that following the 100 μg/kg dose of the PG ($p<0.05$).

DISCUSSION

In contrast to the thermogenic action of centrally administered PGE, peripheral injection of PGE_2 at doses of 50 or 100 μg/kg reduces body temperature. The effects of these two doses of the PG do not differ until 1 hour after injection when the suppression of temperature following the 50 μg/kg dose is greater than that following injection of 100 μg/kg PGE_2. While similar mechanisms may underlie the modifications of both core temperature and drinking following IP PGE_2-treatment, the finding that the two highest doses of the PG tested have equivalent effects on body temperature but, in many cases, dissimilar effects on water intake suggests that the two effects may be separable under some conditions.

EXPERIMENT 3

The results of the first experiment demonstrate that IP injection of PGE_2 reduces water ingestion to specific dipsogenic stimuli. It could be argued that the suppression of intake following such PGE_2 administration does not reflect a specific inhibition of drinking but rather results from a general malaise that interferes with the animals' performance. Although the distinction between specific inhibition and gen-

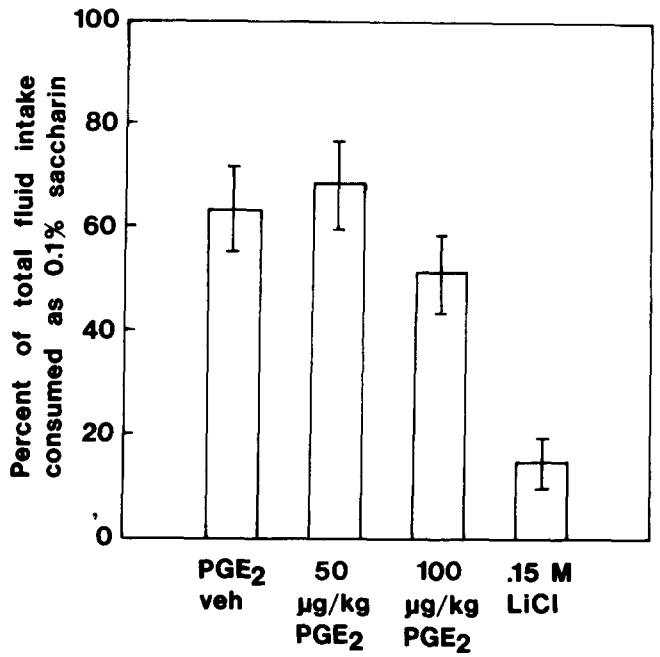

FIG. 5. Percent of total fluid intake consumed as 0.1% saccharin in a two-bottle, saccharin vs water choice test the day after first exposure to saccharin and subsequent intraperitoneal injection of prostaglandin vehicle, 0.15 M lithium chloride (LiCl), or 50 or 100 µg/kg prostaglandin E_2 (PGE_2).

eral malaise is difficult to demonstrate (see [17] for a discussion of a similar problem in analyzing the role of cholecystokinin in inhibiting food intake), the conditioned taste aversion phenomenon first described by Garcia and Koelling [7,8] is often used as one measure of malaise or toxicity. If a rat is made ill shortly after consuming a novel substance, a conditioned aversion (or reduction of intake) to that substance will be demonstrated on subsequent exposure. In this study, we pair IP PGE_2 treatment with the presentation of a novel saccharin solution to determine whether such PGE treatment will support the formation of a conditioned taste aversion.

METHOD

Twenty-four rats were deprived of water, but not of food, for 23 hr each day. Water was made available in 100-ml graduated cylinders for 1 hr per day. The position of the water cylinder on the cage was alternated from right to left each day. By the end of a 12-day training period, daily water intake and body weight had stabilized.

On the conditioning day (Day 13), a 0.1% sodium-saccharin solution was presented in lieu of water. Immediately following the 1-hr saccharin presentation, each animal received an IP injection of one of the following drugs: (1) PG vehicle (1 ml/kg, n=6), (2) 50 µg/kg PGE_2 (n=6), (3) 100 µg/kg PGE_2 (n=6) or (4) 0.15 M lithium chloride (volume (ml) = 2% body weight (g), n=6). Lithium chloride (LiCl) is a substance frequently used for inducing conditioned taste aversions. On Day 14, all rats were tested in a two-bottle preference situation. During the 1-hr fluid-access period, each animal was presented with both water and the 0.1% saccharine solution. The two solutions were of equal temperature and all animals were forced to taste each solution. Total intake of both saccharin and water was measured at the end of the hour. A decrease in the proportion of fluid taken as saccharin on this test day by animals in any of the drug-treatment groups as compared to those in the control (PG vehicle) group was taken as evidence for the induction of a conditioned taste aversion by the drug treatment.

RESULTS

In comparison to PG-vehicle treated rats, only the animals injected with LiCl formed a conditioned taste aversion to the saccharine solution (Fig. 5). Saccharine-solution consumption accounted for only 14.4 ± 4.7% of the total fluid intake of rats in the LiCl-treatment group compared with 63.6 ± 7.9% for rats receiving the PG carrier solution ($p<0.01$). Saccharin consumption by animals injected with either 50 or 100 µg/kg PGE_2 did not differ from that of rats in the control condition. Animals treated with 50 µg/kg PGE_2 consumed 68.3 ± 8.3% of their total fluid intake as saccharin. For rats treated with 100 µg/kg PGE_2, saccharin consumption accounted for 51.2 ± 6.9% of the total intake.

DISCUSSION

Intraperitoneal injection of 50 or 100 µg/kg PGE_2, when associated with the consumption of a novel saccharine solution, does not serve as an unconditioned stimulus for the formation of a conditioned taste aversion. The failure of the PGE_2 injections to elicit a taste aversion suggests that IP injection of PGE_2, in the doses tested, does not induce malaise. Although the taste aversion paradigm is not a totally reliable assessor of illness [17], these results, in addition to the determination of the differential effects of PGE injection on water intake dependent on the dipsogen eliciting the behavior (Experiment 1), support the contention that the reduction of water intake following peripheral injection of PGE_2 is due to a specific antidipsogenic action of the PG rather than to general malaise.

GENERAL DISCUSSION

PGE_2, administered peripherally, is antidipsogenic. When injected at a dose of 50 µg/kg, IP PGE_2 markedly suppresses water consumption in response to cell dehydration or intracranially administered A II and, less markedly, to water deprivation. At 10 µg/kg, PGE_2 treatment has no effect on water intake elicited by any of the dipsogens tested. At 100 µg/kg, IP PGE_2 reduces drinking, at least transiently, to all dipsogens tested.

In spite of its marked effects on water intake, IP injection of PGE_2 does not support the formation of a conditioned taste aversion when paired with the presentation of a novel saccharine solution. Thus, the reduction of water intake induced by peripheral PGE_2 treatment appears to be indicative of a specific inhibition of drinking rather than to the induction of a generalized state of malaise.

The determination of specific antidipsogenic action of the E prostaglandins is not new. The suppression of water intake induced by A II, water deprivation, and hypovolemia but not cellular dehydration by intracranially administered PGE is well documented [11,12]. The data presented here, however, suggest that peripheral, as well as central, PGE may be involved in the control of water intake.

While both central and peripheral PGE are antidipsogenic, analysis of the specific effects of central and peripheral PGE treatment on water ingestion reveals marked

differences in the action of the PG dependent on the route of administration. Most notably, while central administration of PGE is an extremely effective suppressor of water intake in response to polyethylene-glycol treatment [12], peripheral administration of PGE_2 has only transient effects on drinking under this condition and then only when administered in the generally antidipsogenic dose of 100 μg/kg (Experiment 1C). In addition, while central PGE treatment has no effect on drinking induced by cellular dehydration [12], peripheral PGE_2 treatment, at doses of 50 or 100 μg/kg, reduces intake to this stimulus (Experiment 1A).

The effects of central and peripheral PGE treatment on body temperature are also opposed. Central injection of PGE has long been recognized as inducing hyperthermia [3]. Although the pyrogenic and antidipsogenic effects of IVT PGE appear separable at low doses [12], an increase of body temperature does accompany the decrease of water intake elicited by IVT PGE under most conditions [5,12]. IP administration of PGE_2 does not cause hyperthermia (Experiment 2). At a dose of 10 μg/kg, IP PGE_2 elicits a rise of core temperature no greater than that resulting from treatment with the PG carrier solution alone. When administered in doses of 50 or 100 μg/kg, IP PGE_2 significantly reduces body temperature. The reduction of body temperature and the suppression of water intake induced by the IP PGE_2 treatment do not appear to be strictly related in that while the two highest doses of the PGE_2 tested have differential effects on water intake under most conditions, their effects on body temperature are similar. Further research is needed to verify this apparent independence.

Our finding that drinking induced by IVT A II is suppressed by peripherally administered PGE_2 is in apparent contradiction to the report that suppression of peripheral PGE levels by indomethacin has no effect on water intake to this stimulus [13]. Since plasma PGE_2 levels under normal conditions, as well as following the IP injections used in the studies reported here, are not known, it may be that the suppression of intake elicited by IVT A II by peripheral PGE_2 represents a pharmacological action of supranormal levels of the PG and is not indicative of a physiologically relevant control system. On the other hand, indomethacin, the drug used to block PG synthesis in the previous work [13], acts at the cyclo-oxygenase step of PG production, thus blocking not only PGE synthesis but also synthesis of all PGs. The failure of such PG synthesis blockade to augment drinking may, therefore, indicate that other PGs normally act to oppose the PGE suppression of water consumption to this stimulus. The role of endogenous PGE in controlling fluid intake to the other dipsogenic challenges tested here remains to be determined.

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