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Effect of Prostaglandin E_1 and its Biosynthesis Inhibitor Indomethacin on Drinking in the Rat[1]

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PÉREZ GUAITA, M. F. AND E. CHIARAVIGLIO. *Effect of prostaglandin E_1 and its biosynthesis inhibitor indomethacin on drinking in the rat.* PHARMAC. BIOCHEM. BEHAV. **13**(6) 787–792, 1980.—In the rat, injection of prostaglandin E_1 (PGE_1) 0.5, 1.0 or 2.0 μg into the 3rd brain ventricle (3rd b.v.) inhibited the water deprivation-induced water intake in a dose-related fashion. The 1.0 μg dose of PGE_1 also inhibited the intake of 1.8% sodium chloride in rats depleted of body sodium by intraperitoneal dialysis, and of food in food deprived rats during a 60 min test period. Prostaglandin E_1 (1 μg) depressed the dipsogenic effect of angiotensin II (AII) or carbachol injected through the same cannula. Water-deprived rats pretreated with the PG synthetase inhibitor indomethacin, in two different doses, showed enhanced water intake. The pretreatment with indomethacin also enhanced the dipsogenic effect of various doses of AII injected into the 3rd b.v. The antagonistic action of PGE_1 on water-deprivation, or AII-induced water intake, and the enhancement of water intake after blocking PGs synthesis, suggests the involvement of PG in the regulation of thirst.

Prostaglandin E_1 Indomethacin Water intake

THE homeostatic regulation of body water depends on the action of two central mechanisms: thirst and secretion of antidiuretic hormone (ADH). In rats, it has been proposed that both mechanisms are under the direct control of angiotensin II (AII). Administration of AII into the blood stream or directly into the brain elicits drinking behavior. The sensitivity of the brain to injections of 1 p-mole, or less, of the octapeptide, may reflect a physiological mechanism [11] rather than a pharmacological one.

Prostaglandin E_1 (PGE_1) injected into the third ventricle of the conscious goat, mimics AII in stimulating drinking and release of ADH [1]. However, the action of prostaglandin on thirst mechanisms is a subject of controversy. While an agonistic effect to AII has been reported in the goat [1], PGE_1 injected into the lateral ventricle in rats antagonizes the dipsogenic effect of AII [15]. Low doses of PGE_1, given by the intraventricular route, affect water balance without altering other responses [15]. Since prostaglandins are present in the brain [7], the effect is possibly indicative of a physiological process.

The aim of the present experiments was to study the effect of PGE_1 on the mechanisms of thirst. The effect of PGE_1 on water-deprivation- and AII-induced drinking and the effect of blocking PG synthesis is reported.

GENERAL METHOD

Male albino rats weighing between 200–300 g at the beginning of the experiment were used.

Cannulae Implantation

Stainless steel cannulae were aimed at the 3rd brain ventricle under ether anaesthesia by means of a stereotaxic instrument. The cannulae tips were lowered to −1.5 mm at the level of A 6.8, on the midline according to the atlas of König and Klippel [16]. After surgery the rats were individually caged and one week was allowed for recovery.

Deprivation Experiments

Four groups of rats were designated: (1) deprived of water but not food; (2) deprived of food but not water; (3) depleted of body sodium by peritoneal dialysis; (4) maintained on water and food ad-libitum.

Injections

All the intracerebro-ventricular (ICV) injections were made in a volume of 1 μl. The injector needle was extended 0.5 mm further from the tip of the cannula. During the injection, the rats were manually restrained. After the injection, they were transferred to the test cages with distilled water to drink. The amount of water drunk was recorded for periods of 5, 15, 30 and 60 minutes. No food was presented during the drinking test.

Testing

The animals were tested in individual cages. The water

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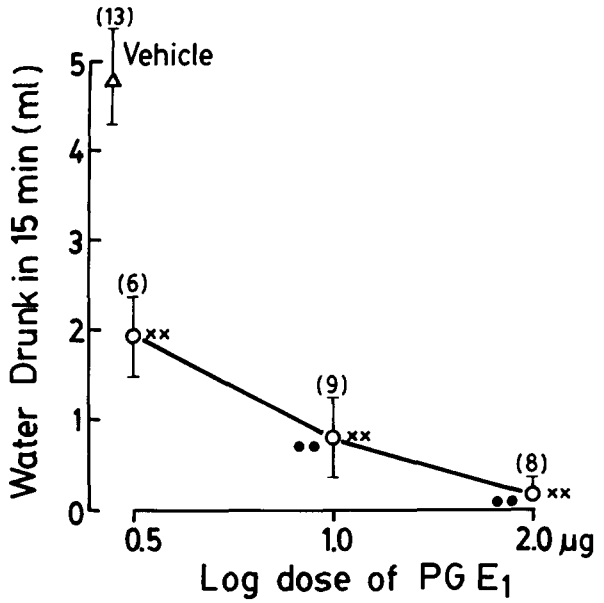

FIG. 1. Mean amount of water drunk (±SE, of mean, number of observations in parentheses) by water-deprived rats during 15 min, in response to intracranial injections of various doses of prostaglandin E_1 (PGE_1). $\times\times p<0.01$ when compared with water-deprived rats injected with the PG vehicle. $\bullet\bullet p<0.01$ when compared with the 0.5 µg dose.

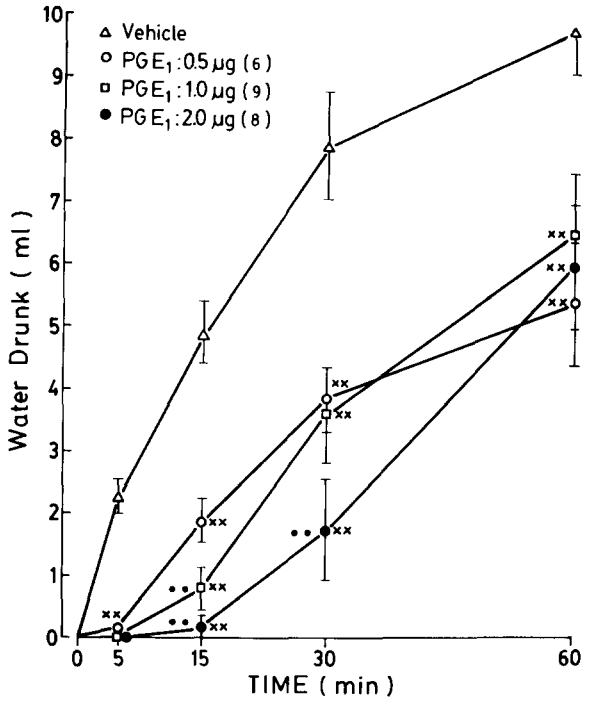

FIG. 2. The pattern of cumulative mean amounts (±SE of mean) of water drunk by water-deprived rats in response to intracranial injection of various doses of PGE_1. $\times\times p<0.01$ when compared with water-deprived rats injected with the PG vehicle. $\bullet\bullet p<0.01$ when compared with the 0.5 µg dose.

was offered in graduated tubes and the volume ingested was recorded at the end of 5, 15, 30 and 60 minutes.

Analysis of Results

Statistical analyses were performed by the two-way analysis of variance (ANOVA) and a posteriori test of Duncan for any two means comparisons.

EXPERIMENT 1: EFFECT OF VARIOUS DOSES OF PGE_1 ON WATER INTAKE INDUCED BY WATER DEPRIVATION

METHOD

A group of cannulated rats was deprived of water for 24 hours. In order to insure an equal state of dehydration, water was removed for one hour, restored for a half hour, and removed again for 24 hours. Food was available at all times. After this period the water deprived rats were injected with crystalline Prostaglandin E_1 (PGE_1). (The PG was kindly supplied by Dr. John Pike of the Upjohn Company.)

A stock solution was made by dissolving 10 mg of PGE_1 in 1 ml of ethanol. The injected solution was freshly prepared each time by taking an aliquot of the stock solution and given up to volume with 0.2 M phosphate buffer or 0.15 M NaCl. Three doses of PGE_1 were used: 0.5, 1.0 and 2.0 µg. Immediately after the injection the rats were tested for water intake. Water-deprived rats injected with the PG vehicle were used as control.

RESULTS

As shown in Fig. 1, the rats deprived of water and injected with the PG vehicle drank 4.9 ± 0.44 ml water in 15 minutes. The ICV injection of PGE_1 significantly inhibited the amount of water drunk. The dose of 0.5 µg reduced the water intake to 1.9 ± 0.36 ml. Compared with the control test the difference was significant, $p<0.01$. The dose of 1.0 µg decreased water intake to 0.82 ± 0.34 ml, $p<0.01$. With 2 µg PGE_1, the water intake was virtually abolished (0.12 ± 0.12 ml) 15 min after the injection.

Figure 2 shows the pattern of cummulative drinking by 3 groups of water-deprived rats injected with different doses of PGE_1. Water intake was prevented for all doses at the beginning of the experiment. Fifteen minutes after injection, the water intake was dose-related, increasing during the 60 min observed, although the difference with the control group remained statistically significant. The interaction between different time and drug dose was significant at $F<0.001$.

EXPERIMENT 2: EFFECT OF PGE_1 ON SODIUM APPETITE

METHOD

A group of rats were depleted of sodium by intraperitoneal dialysis (IPD). The technique, which has been described previously [8], consists of an IP injection of 5% glucose solution warmed to body temperature in a volume equivalent to 10% body weight, which is then removed 1 hour later by inserting an 18 gauge needle into the peritoneal cavity. The removed dialyzate had 94.8 ± 6.2 mEq/l of NaCl (N=5) or 0.87 mEq/100 g rat body weight. The dialysed rats were then caged individually with distilled water as the only drink for 20 hours. After this treatment the animals develop a strong Na appetite. Then they were tested for 1.8% NaCl intake given in choice with distilled water. The rats were ICV can-

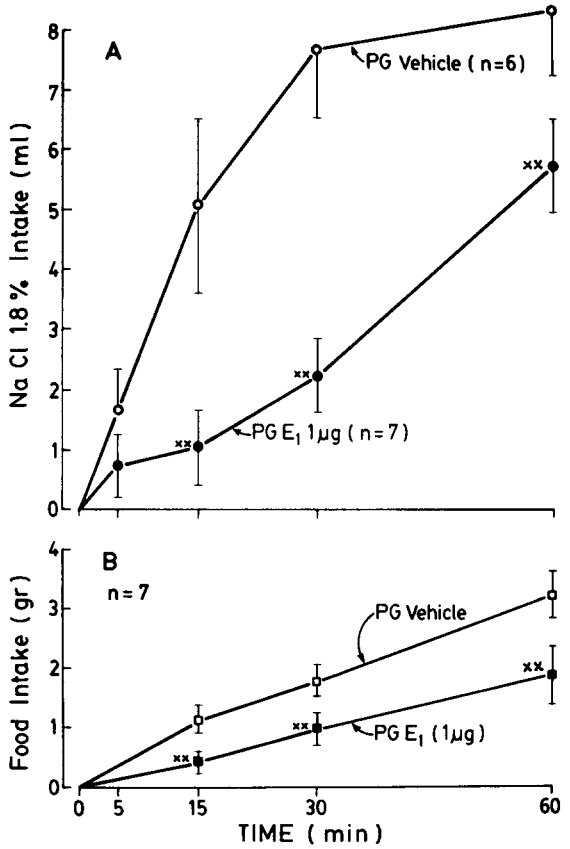

FIG. 3. The cumulative mean amounts (±SE of mean) of NaCl and food ingested during one-hour test by sodium depleted (A) or food-deprived (B) rats, in response to intracranial injection of 1.0 µg of prostaglandin E_1 (PGE_1) or PG vehicle. $\times\times p<0.01$ when compared with rats injected with the PG vehicle.

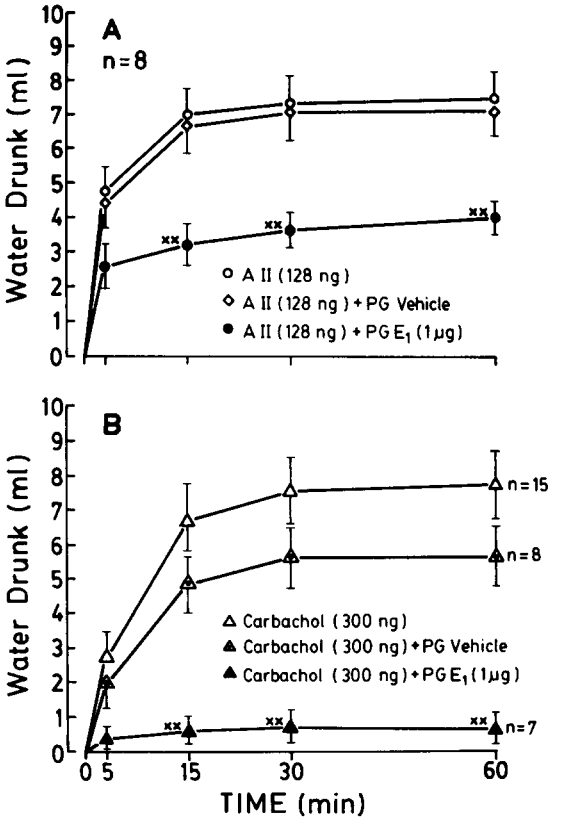

FIG. 4. The cumulative mean amounts of water drunk (±SE of mean) by rats intracranially injected with angiotensin II (A) or carbachol (B) after 1.0 µg of PGE_1 injected through the same cannula. $\times\times p<0.01$, when compared with rats injected with the PG vehicle.

nulated as described, and after a week they were depleted of sodium again, but this time, before the test, the rats were ICV injected with 1 µg of PGE_1. In a third test, the sodium depleted rats were ICV injected with the PG vehicle (0.2 M phosphate buffer) before being tested for NaCl intake.

RESULTS

Prostaglandin E_1 in dose of 1.0 µg rat substantially reduced the intake of 1.8% sodium chloride and water (Fig. 3A). The reduction from control values was 79% ($p<0.01$) for the first 15 min test period, and 80% ($p<0.01$) at the 30 min test. During the 60 min test, the inhibition was 31%. The drinking pattern was similar to that of water-deprived rats injected with 1.0 µg of PGE_1 (Fig. 2). Significant interaction effects were obtained by ANOVA ($F<0.001$). The intake of water after PG vehicle was 1.4 ± 0.38 ml, 2.1 ± 0.31 ml and 2.3 ± 0.80 ml for 15, 30 and 60 min test period. After PGE_1 injection, the volume drank was 0.3 ± 0.15 ml, 0.6 ± 0.18 ml and 1.5 ± 0.20 ml, respectively. The reduction from control values was 78%, 71% and 34% at each time observed.

EXPERIMENT 3: EFFECT OF PGE_1 ON FOOD INTAKE

METHOD

Seven rats were trained to ingest their entire daily ration of food as powered standard laboratory diet in a two-hour test session. The animals were food deprived for the remaining 22 hours per day. Water was available ad lib during both the test and the deprivation periods. After 5 days the intake had stabilized. Then the rats were ICV cannulated. After a recovery period of one week, they were deprived of food for 40 hours, and tested for food intake immediately after an ICV injection of 1 µg of PGE_1. After recovery of body weight, a second test was run, but this time 1 µl of the PG vehicle was ICV injected.

RESULTS

The food-deprived rats injected with the PG vehicle ate 1.11 ± 0.13 g food during 15 min. The ICV injection of PGE_1 (1.0 µg) decreased food intake to 0.40 ± 0.10 g ($p<0.01$). The difference persisted at the 60 min, as it is shown in Fig. 3B, and is statistically significant. The two-way ANOVA shown a significant interaction effect ($F<0.001$).

EXPERIMENT 4: EFFECT OF PGE_1 ON CARBACHOL, AND AII-INDUCED THIRST

The antidipsogenic action of PGE_1 was exerted on the water-deprivation induced drinking. The present experiment was designed to test the effect of PGE_1 on the water intake induced by two well-known dipsogens: carbachol and Angiotensin II (AII).

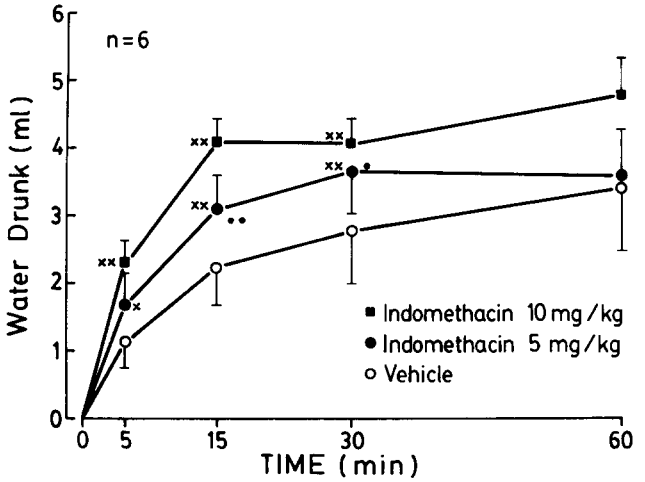

FIG. 5. The cumulative mean amounts (±SE of mean) of water drunk by water-deprived rats pretreated with two doses of indomethacin. $\times\times p<0.01$, $\times p<0.05$ when compared with water-deprived rats injected with the vehicle. $\bullet\bullet p<0.01$, $\bullet p<0.05$ when compared with the 10 mg/kg dose.

METHOD

Non-deprived, cannulated rats were tested for their drinking response to 300 ng of carbachol (carbamylcholine chloride, Sigma). In the following days, PGE_1 (1.0 μg) or PG vehicle (0.2 M phosphate buffer) in that sequence were injected through the same cannula 3 min before the carbachol injection. Drinking response was recorded. At least two days were allowed between tests. The test for the effect of PGE_1 on AII-induced drinking was conducted in the same manner as the carbachol test reported above. Each rat received an ICV injection of 128 ng AII (Synthetic Asn^1-Val^5-angiotensin octapeptide (AII) Hypertensin CIBA to test the ability of the peptide to evoke drinking. On the following days, either 1 μg of PGE_1or PG vehicle were ICV administered 3 min before the AII injection. The drinking test was conducted as described above.

RESULTS

As shown in Fig. 4, non-deprived rats injected with AII drank 7.0 ± 0.74 ml water during the first 15 min after the injection, averaging a total of 7.6 ± 0.79 ml for the 60 min test period. The pre-injection of PG vehicle did not change the dipsogenic action of AII. However, the pre-treatment with PGE_1 prevented the dipsogenic action of AII. The inhibition of water intake compared with the group injected with the vehicle was 51% at the 15 min test ($p<0.01$) and 44% at the end of 60 min test ($p<0.01$) (Fig. 4A). The pretreatment with PGE_1 also prevented the dipsogenic action of carbachol: 300 ng of the latter evoked an intake of 6.8 ± 0.89 ml water in 15 min and a cumulative intake of 7.7 ± 0.80 ml for the 60 min test (Fig. 4B). The injection of the PG vehicle reduced the 1 hour intake by 26%, but the difference was not statistically significant. The pretreatment with PGE_1 lowered the dipsogenic effect of carbachol to 0.5 ± 0.29 ml water ($p<0.01$) at 15 min and 0.6 ± 0.29 ml ($p<0.01$) at the 60 min test, compared with the groups injected with PG vehicle. The interaction between treatment was significant ($F<0.001$).

EXPERIMENT 5: ENHANCEMENT OF WATER DEPRIVATION-INDUCED DRINKING BY INHIBITION OF PG SYNTHESIS

As the exogenous administration of PGE_1 inhibited water intake in water-deprived rats, the aim of this experiment was to determine if the inhibition of the endogenous level of PGs could affect water intake.

METHOD

A group of six rats were deprived of water for 10 hours. Two hours before the drinking test started, the rats received an IP injection of the PG synthesis inhibitor indomethacin (Indocid, Merck, Sharpe and Dohme) dissolved in 0.15 M NaCl, in amount of 5 or 10 mg/kg. Three days of recovery were allowed between tests. Control injections were 0.15 M NaCl. Another control group of six rats, no-deprived was injected with 10 mg/kg of indomethacin.

RESULTS

As shown in Fig. 5, rats deprived of water for 10 hours, and IP injected with 0.15 M NaCl, drank 2.2 ± 0.48, 2.7 ± 0.69 and 3.4 ± 0.97 ml water during 15, 30 and 60 min, respectively. The administration of 10 mg/kg indomethacin substantially increased water intake to 4.0 ± 0.24 ml in 15 min ($p<0.01$). This level of significance was maintained through the 60 min test. The percentages of increase were 80.4%, 46.0% and 40.0% at 15, 30 and 60 min respectively. The dose of 5 mg/kg indomethacin increased the intake of water slightly but non-significantly. The percentages of increase were 35.5%, 31.6% and 6.7% at 15, 30 and 60 min respectively. The two-way ANOVA shown a significant interaction effect ($F<0.001$). The water intake of non-deprived rats was not affected by the administration of 10 mg/kg of indomethacin.

EXPERIMENT 6: ENHANCEMENT OF AII-INDUCED DRINKING BY INHIBITION OF PG SYNTHESIS

Exogenous PGE_1 not only inhibited the water deprivation-induced drinking but also the drinking evoked by the ICV injection of AII. A remaining question was whether the endogenous inhibition of PG synthesis enhances the dipsogenic action of AII. The next experiment was designed to answer this question.

METHOD

Angiotensin II, in doses of 1, 5 or 32 ng, was ICV injected into non-deprived rats pretreated with indomethacin (5 mg/kg), as described in Exp. 5. Control rats, ICV injected with the same dose of AII, received an IP injection of the vehicle (0.15 M NaCl). The drinking test was conducted immediately after the AII injection.

RESULTS

Figure 6 shows the intake of water evoked by different doses of AII ICV injected in rats pretreated with indomethacin. In the first 5 min after 1.0 ng AII administration, water intake did not increase significantly, whereas 5.0 and 32.0 ng raised water intake from 1.1 ± 0.36 ml to 2.8 ± 0.86 ml ($p<0.01$) and 1.8 ± 0.73 to 3.7 ± 0.50 ml ($p<0.01$) respectively, compared with the control rats receiving AII and the indomethacin vehicle (Fig. 6A). Sixty minutes after AII administration, water intake was enhanced at all doses in rats treated with indomethacin. The dose of 1.0 ng of AII

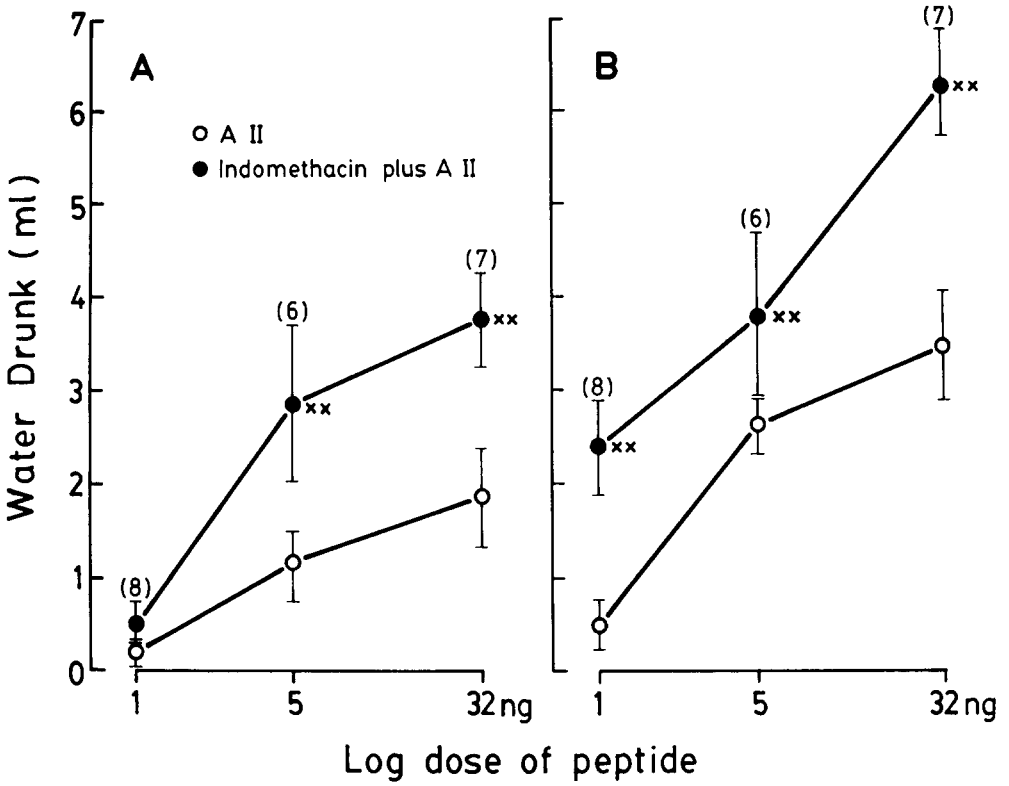

FIG. 6. Mean amount of water drunk (±SE of mean, number of observations in parentheses) during 5 (A) and 60 (B) min, by rats injected with AII, or AII after pretreatment with indomethacin. $\times\times p<0.01$ when compared with rats injected with AII alone.

raised water intake from 0.5 ± 0.26 ml to 2.3 ± 0.54 ml ($p<0.01$). The dose of 5.0 ng of AII raised water intake from 2.6 ± 0.37 ml to 3.7 ± 0.91 ml ($p<0.01$). The dose of 32.0 ng of AII increased drinking from 3.0 ± 0.72 ml to 6.3 ± 0.76 ml, and is statistically significant ($p<0.01$). See Fig. 6B. The interaction between different drug dose was significant, $F<0.001$.

DISCUSSION

These experiments show that PGE_1 may be a modulator of water intake in the rat. This conclusion is based on the depression of water intake observed after ICV injection of PGE_1 and the enhancement of water intake seen after endogenous inhibition of PG synthesis.

The inhibition of water intake by PGE_1 was dose related. Fifteen minutes after injection of PGE_1, the dose of 0.5 μg reduced water intake of water-deprived rats by 60% whereas the dose of 2 μg almost completely abolished water intake. Inhibition of water intake by PGE was previously reported in the rat [15]. However, in conscious goat PGE_1 elicited drinking [1]. This antagonistic action of PGE_1 on water intake regulation may reflect species variation. In the present experiment inhibition of water intake lasted at least 60–90 min. This effect is transient, a fact that could be related to the rapid inactivation of PG "in vivo" by enzymatic processes, which degrade endogenous as well as exogenously administered PG [19]. Prostaglandin E_1 induced fever in the rat, and effect which might interfere with motivated behavior. However, the effective dose was above the range needed to inhibit water intake [15]. In the present experiment the effect of PGE_1 on body temperature has not been monitored.

Prostaglandin E_1 also inhibited the ingestion of sodium solutions in sodium-depleted rats, but this effect could reflect a general rejection to drink, rather than a specific action on the regulation of sodium appetite. It is worth noting that the pattern of cumulative intakes of sodium solution in sodium-depleted rats, and water in water deprived rats, after administration of 1 μg of PGE_1, was similar (see legends, Figs. 2 and 3). The reduction of food intake after PGE_1 injection should be related to the prandial-drinking habit of the rat demonstrated by Kenney and Epstein [15]. However, PGs have been implicated in the hypothalamic control of energy balance [2] although the reports are controversial [17].

Since the antidipsogenic action of PGE_1 is exerted also on AII-induced drinking, this antagonistic effect suggests that PGE_1 and AII may interact to regulate water intake.

The water intake induced by carbachol, a synthetic dipsogen that mimics the action of acetylcholine, was also inhibited by PGE_1. An interaction between PG and acetylcholine, taking place at the receptor level has been reported [3].

The decrease in water, saline and food intake induced by PGE_1 seems to be specific to the ingestive behavior rather than a general depression. PGE_1-treated rats observed in their test cages immediately after injection showed a slight depression lasting no more than 10 minutes. However, the intake was still significantly low at 30 and 60 minutes when the animals has recovered the general activity.

Perhaps the strongest evidence for PG modulation on

water intake was given by the experiment in which an inhibitor of PG synthesis was used. In this experiment, it was demonstrated for the first time that blocking the PGs synthesis enhanced water-deprivation-induced drinking.

A large body of evidence suggests that a battery of enzyme systems for the synthesis of PG are present in the brain [7]. Indomethacin is known to block PG synthetase in a competitive irreversible fashion [12]. Although indomethacin inhibits other enzyme systems, higher concentration of the drug than that was used in this experiment is required.

A role known for the renal renin-angiotensin system is to produce vasoconstriction [6,11]. In addition, the intracerebral administration of AII induces a marked increase in water intake [10]. Since the brain may contain an intrinsic renin-angiotensin system [9] (although this is controversial) [19] and the components required for the formation of AII are present within the CNS [13] it was postulated that the dipsogenic action of AII could be due to its vasoconstrictor effect. This forms the basis for the "ischemic hypothesis" of AII-inducing drinking, suggested by Nicolaidis and Fitzsimons [18]. The vasoconstriction produced by angiotensin in the blood vessels of the highly vascularized circumventricular organs would be detected by receptors within the vessel's walls and transduced as thirst. The results of the present experiment may be explained through this hypothesis. The vasoplegic effect of PGE_1, opposite to the vasoconstrictor effect of AII, may interfere specifically with angiotensin-induced drinking. On the other hand, blocking PG biosynthesis enhanced the dipsogenic action of exogenously administered angiotensin and increased water intake induced by water deprivation, which has an angiotensin-mediated component [11]. Nevertheless, a constrictor property of prostaglandins on cerebral vessels has also been reported [7].

Other evidence for the interaction between PGs and angiotensin is that PGs of the E series are released by different organs in response to angiotensin stimulation [4]. This fact has been interpreted as a physiological antagonistic mechanism to AII-vasoconstriction [5].

The possibility that PGs may act indirectly by increasing the rate of formation of the deaminated metabolite of 5-hydroxytriptamine (5-HT) [14] should also be considered. However, this would not be the case since PGE_1 inhibits water intake in water-deprived rats pretreated with 5-HT synthesis inhibitor, p-chlorophenylalanine (PCPA) (Pérez Guaita and Chiaraviglio, unpublished results).

The physiological role of PGs on the central regulation of water intake is still speculative. Two facts are worth noting, however. The first is the antagonistic effect of PGE_1 on water deprivation, and AII-induced drinking in the rat suggesting an interaction between the two potent vasoactive substances of opposite sign. The second is the enhancement of water intake after blocking PGs synthesis, suggesting that endogenous PGs are involved in the mechanisms which control water intake.

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