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Prostaglandin E_1 Inhibits Acute Cell Dehydration Thirst

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GOLDSTEIN, D. J., D. J. MARANTE PEREZ, J-P. GUNST AND J. A. HALPERIN. *Prostaglandin E_1 inhibits acute cell dehydration thirst.* PHARMAC. BIOCHEM. BEHAV. 10(6) 895–898, 1979.—Intraperitoneally injected PGE_1 (100 μg/Kg) inhibits specifically the drinking induced by both IP and IV 2 M NaCl (6 ml/Kg) and compound 48/80 (100 μg/Kg, IP). Probenecid (150 mg/Kg, IP), which is not a dipsogen, has no effect on the PGE_1 induced inhibition of acute cell dehydration thirst. It is concluded the PGE_1 acts upon the peripheral mast cells, inhibiting their secretion and thus affecting the water intake associated with the activation of these cells either by hypertonicity or specific stimulants of amine release. These results raise the possibility that endogenous prostaglandins might be involved in the modulation of some of the signals which convey to the brain information on the tonicity of the body fluids.

Acute cell dehydration thirst PGE_1 Histamine Compound 48/80 Mast cells Drinking behavior

PROSTAGLANDINS of the E series have been proposed as the antidipsogenic counterparts of angiotensin [6]. Intracerebroventricular (ICV) PGE_1 reduces ICV angiotensin induced drinking [6,13], while the central inhibition of PG biosynthesis by ICV meclofenamate increases the dipsogenic response to the polypeptide [18]. We have recently reported evidence which links the mast cell and histamine to the chain of events which span from the detection of changes in osmolarity of the body fluids to the induction of thirst [7,8]. As mast cell secretion is markedly affected by the prostaglandins of the E series [15,16], it seemed interesting to explore the effects of peripheral PGs on the drinking elicited by hypertonic NaCl in the rat. The present experiments were undertaken to determine whether exogenous, IP administered PGE_1, PGE_2 and $PGF_{2\alpha}$ could modulate the drinking induced by acute cell dehydration.

METHOD

Male Sprague-Dawley rats (180–240 g) were housed individually and maintained on a 12/12 hr dark-light cycle with continuous access to food pellets and tap water. For the drinking tests distilled water was used and food was removed. For the intravenous (IV) administration of solutions, rats were lightly anesthetized with ether, the jugular vein catheterized and the free end of the catheter was left protruding from the back of the neck of the animals, which were injected when fully awake, at least two hours after the end of the anesthesia. Drugs were injected IP 5 min before the administration of drinking stimuli or making water available, in the water deprivation specificity test. After the injection of the dipsogenic stimuli, rats were placed back immediately in their home cages, where water was available. Probenecid was dissolved in distilled water with the aid of sodium hydroxide and sodium carbonate and the pH of the solution was adjusted to 7.0 with diluted hydrochloric acid. A similar procedure was used for the preparation of the PGs. Fresh PGs solutions were made weekly and kept refrigerated. The polymer amine 48/80, a selective releaser of histamine from rat mast cells [5] was diluted in saline. Compound 48/80 solutions were prepared daily, immediately before their use, avoiding light exposure.

RESULTS

After the IP injection of high doses of PGs (1 mg/Kg) the rats became apatic and flaccid and showed a marked slugishness in their drinking response to all the dipsogenic stimuli tried. This unspecific inhibition was more marked during the first 30 min after the injection of 2 M NaCl and histamine or making water available to water deprived rats. In some borderline doses the cumulative intake of water was not altered at the end of the drinking test, but the plateau was reached after a 15–30 minutes lag.

This led us to define first a dose of each of the PGs studied which did not depress the water intake induced by 24 hr of water deprivation (with food available) or change the rate of drinking. We consider this to be a very sensitive test because the amount of water drunk and the rate of drinking are highly reproducible for a given strain of rats, and 24 hr of water deprivation do not lead to a marked loss of weight. Once found, the dose of PG was further checked for unspecific effects with histamine (10 mg/Kg) and serotonin (10 mg/Kg).

The maximal doses of PGs which did not affect water

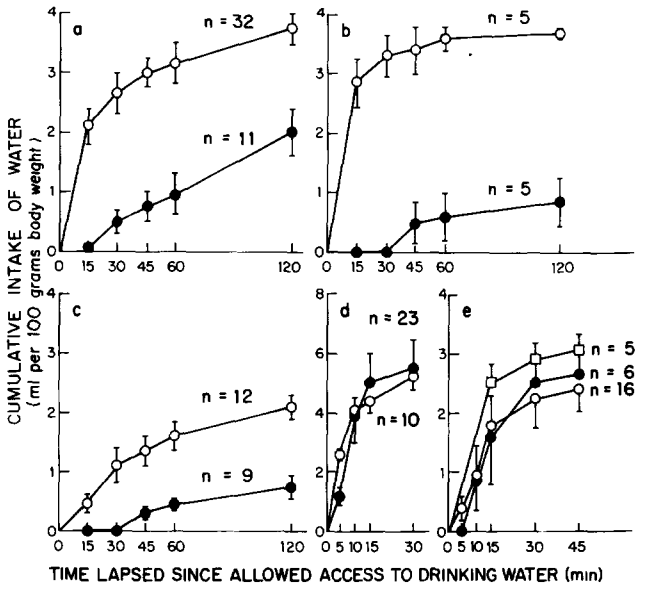

FIG 1 Influence of PGE_1 on the cumulative intake of water by rats after (a) IP 2 M NaCl, (b) IV 2 M Nacl, 6 ml/Kg, (c) compound 48/80, 100 μg/Kg, IP, (d) 24 hr deprivation of drinking water (with food available) and (e) histamine, 10 mg/Kg, IP ○, control. ●, PGE_1 pretreated animals, 100 μg/Kg, IP, 5 min before the injection of the drinking stimuli □, probenecid, 150 mg/Kg, IP, 2 hr before. Number of animals given in parentheses.

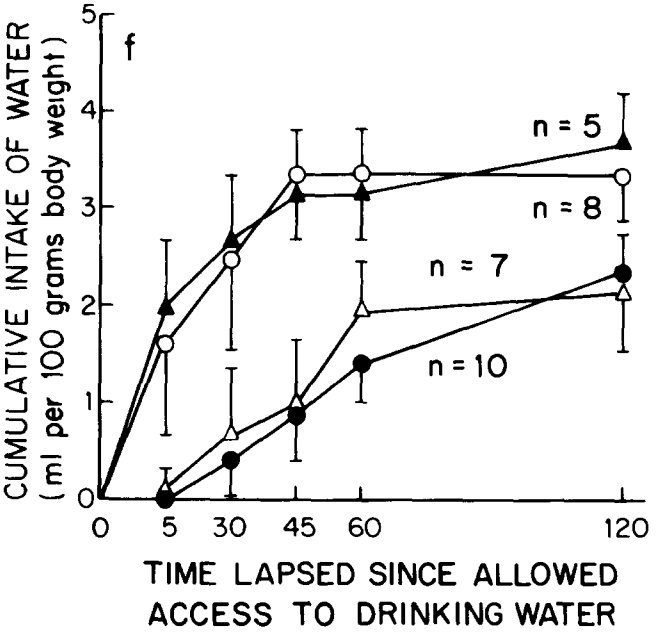

FIG. 2. Effect of probenecid pretreatment on the cumulative amount drunk by control and PGE_1 pretreated animals after the injection of IP 2 M NaCl, 6 ml/Kg. ○, 2 M NaCl· ●, 2 M NaCl + PGE_1 ▲, Probenecid + 2 M NaCl △, Probenecid + 2 M NaCl + PGE_1 The vertical bars are twice the SE. Number of animals given in parentheses

deprivation induced drinking were: PGE_1, 100 μg/Kg; PGE_2, 50 μg/Kg; $PGE_2\alpha$, 100 μg/Kg. When tested using IP 2 M NaCl (6 ml/Kg) as drinking stimulus, only PGE_1 was found to inhibit water intake, and the reduction in cumulative water intake was significant after 2 hr (Fig. 1a). At this dose, 100 μg/Kg, PGE_1 did not inhibit the drinking induced by water deprivation (Fig. 1d) nor that elicited by histamine (Fig. 1e). Serotonin induced drinking was not affected: cumulative intake of water after 1 hour, controls (n=10), 0.87 ± 0.1 ml/100 g body weight, experimentals (n=10) 0.95 ± 0.1 ml/100 g body weight). When PGE_1 (IP) was tested in conscious and unrestrained rats IV infused with 2 M NaCl (6 ml/Kg), the inhibitory effect was even more marked (Fig. 1b).

Raising the dose of PGE_2 and $PGF_2\alpha$ always resulted in depression of acute cell dehydration thirst and of that associated with the other drinking stimuli, histamine and serotonin, which pointed to a non-specific effect.

To exclude that this modification of drinking behavior could be due to a central action of the PGE_1, we blocked the brain-blood transport mechanism for weak organic acids with probenecid [2]. If the effects of PGE_1 were central, the treatment with probenecid would have resulted in a stronger depression of water intake, as the PGE_1 could not be cleared from the brain [2]. Probenecid (150 mg/Kg, IP, 2 hours before PGE_1), however, neither potentiated the inhibitory effect of PGE_1 on acute cell dehydration thirst (Fig. 2) nor affected in any other discernible way the drinking response to IP 2 M NaCl (Fig. 2) or histamine (Fig. 1e).

PGE_1 blocks the release of amines from the mast cell, the main biosynthetic and storage site of peripheral histamine [19], a dipsogenic autocoid [9,14]. If PGE_1 were exerting its peripheral action through the inhibition of mast cell secretion, it should depress the drinking induced by the mast cell activator, compound 48/80 [19]. As can be seen in Fig. 1c, the dipsogenic action of compound 48/80 was significantly inhibited by the same dose of PGE_1 which specifically depressed acute cell dehydration thirst.

DISCUSSION

Both acute cell dehydration and 48/80-induced drinking are reduced by IP PGE_1. These effects seem to be highly specific, since three other drinking stimuli, 24 hr water deprivation (with food available), histamine and serotonin elicit the same cumulative intake of water and the same rate of drinking in control animals and in animals pretreated with IP PGE_1. The fact that prostaglandin E_1 does not inhibit drinking after 24 hr of water deprivation shows that the depression of 2 M NaCl induced drinking is specific because of the PGE_1 was administered 5 min before the beginning of the drinking test, and should not, therefore, interfere with the expression of the thirst generated during the previous 24 hr of water deprivation. Having neither antihistamine nor antiserotonin effects, PGE_1 should not, and did not, affect the drinking induced by these autacoids.

The specific depression of 2 M NaCl induced drinking and that associated with compound 48/80 by IP PGE_1 gives further support to the hypothesis which links the mast cell to the behavioral response of the rat towards abrupt changes in tonicity of its body fluids. The fact that both IV and IP 2 M NaCl induced thirst are inhibited by the same dose of PGE_1 shows that the PG is exerting its action systematically and not merely blocking the mesenteric mast cells exposed to the high local concentration of salt achieved in the peritoneal

cavity after the IP injection of 2 M NaCl. The almost complete inhibition of drinking observed after IV 2 M NaCl suggests that the residual intake that follows the IP peritoneal administration of hypertonic saline to PGE$_1$ pretreated animals is in part due to a damaging effect on mesenteric mast cells, which break and release histamine into the peritoneal cavity upon exposure to concentrated NaCl (D. J. Goldstein, C. Urbina, D. J. Marante Perez and J. A. Halperin, unpublished results).

From the three PGs studied, only PGE$_1$ depressed significantly the water intake induced by 2 M NaCl. The other two, PGE$_2$ and PGE$_2\alpha$, only induced a lag of 15–30 min in the beginning of the drinking, but the rate and the cumulative intake after two hours were essentially the same as those of control rats. This is surprising, however, when it is considered that PGE$_2$ also exerts an inhibitory effect on histamine release which is as powerful as that of PGE$_1$ [16].

Probenecid has been shown to inhibit PG transport in vitro in a variety of tissues, including the brain, by blocking the organic acid transport mechanism [2]. This acid potentiates hyperthermic [20] and epileptiform [21] responses to doses of supracortically applied and ICV superfused PGs which by themselves have no effect. If the PGE$_1$ effect on drinking were central, probenecid should have reinforced its inhibitory action on 2 M NaCl induced thirst, by blocking the clearing of PGE$_1$ from brain tissue. Probenecid, however, did not modify the PGE$_1$ effect, confirming the hypothesis that the complex lipid is acting on a peripheral target to produce this effect.

The osmolarity of the extracellular fluid profoundly stimulates PGE output from the renal papilla [3] as well as from the rat stomach [1]. Maximum output of PGE is observed between 30 and 60 minutes after rising the osmolarity of the bathing or perfusing media and this is approximately the time it takes for the cumulative intake of water after 2 M NaCl to reach a plateau. One interesting possibility is that the PGEs could in fact be involved in the termination of the drinking response to hypertonic NaCl, functioning as a peripheral negative signal acting on the mast cell. In this hypothetical mechanism, the end of drinking would not be determined by the generation of satiety signals in the brain, but rather by the reduction of thirst signals triggered by histamine.

Of course, the pharmacological effects of PGE$_1$ described here cannot be taken as evidence that PGE$_1$ synthesis in the periphery has any physiological importance in the control of body fluid homeostasis, but raised the possibility that it might participate in it through its modulatory effect on mast cell function. There are some hints that point to such a role. It is well known that the injection of endotoxin in rats and mice, at doses well below the LD$_{50}$, induces a significant loss of weight whose origin has been traced to a drinking deficit [4,10]. Endotoxin is a powerful stimulant of PG synthesis [11] and it is tempting to speculate that PGE$_1$ might be implicated in the alteration of ingestive behavior.

On the other hand, the local concentration of PGE$_1$ in the proximity of the mast cells might be very high in acute cell dehydration, as has been shown to be the case in inflamed tissues [22]. This in fact raises the question of the cellular origin of the PGs that could be involved in the regulation of mast cell function in this context. The mast cell itself is able to produce a variety of pharmacologically active lipids, some of them derived from arachidonic acid [12]. In this case, the demonstration of a physiologically significant and intrinsic function of prostaglandin biosynthesis on the modulation of drinking behavior must be constructed according to the Needleman criteria [17]. Such research is presently in progress.

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