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BRIEF COMMUNICATION

Effect of Indomethacin on Water Intake of the Rat

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FEUERSTEIN, G., M. KRAUSZ AND Y. GUTMAN. *Effect of indomethacin on water intake of the rat.* PHARMAC. BIOCHEM BEHAV. 9(6) 893–894, 1978.—Indomethacin stimulated water intake in intact rats. This effect could also be demonstrated in bilaterally ureteral ligated rats, but it was totally abolished after bilateral nephrectomy. It is suggested that the stimulatory effect of indomathacin on water consumption is mediated by a renal factor.

Water consumption Indomethacin Nephrectomy

AMONG the various effects of prostaglandins (PG), those related to energy balance are poorly investigated. PG are known to affect adipose tissue [10], gastrointestinal secretions [11], and to modulate the effect of hormones such as TSH, adrenaline and GH [4].

Recent evidence demonstrated a more direct effect of PG on food and water consumption: PG of the E series depressed food intake following systemic [13] or intracerebroventricular (ICV) injections [3] while a PG antagonist, injected into the same area triggered feeding [2]. Besides, PG-E suppressed angiotensin II (A II)-evoked water intake [5] and, when administered in sufficient doses, also depressed water intake in response to other stimuli such as ICV carbachol injection or subcutaneous hypertonic saline infusion [5]. Corroborating data have been reported by Phillips and Hoffman [9], who showed that inhibitors of PG synthesis administered ICV had a potentiating effect on central A II induced water intake.

These experiments failed to demonstrate, however, any inhibitory effect of PG per se on water intake, and no attempt was made to differentiate between the effect on food and water responses. Moreover, PG synthesis inhibitors per se did not stimulate basal food or water intake when applied ICV.

In the following experiments we tried to elucidate the effect of a systematically administered PG synthesis inhibitor—indomethacin (IND)—on water consumption in the rat.

METHOD

Male rats of the Hebrew University Sabra strain, weighing 180–200 g were housed two in a cage and provided with food and tap water ad lib for the 48 hr prior to the experiments. Bilateral ureteral ligation (BLUL) was performed through a midabdominal incision (under light ether anesthesia) and both ureters were ligated 2 cm proximal to the ureterovesicular junction. Bilateral nephrectomy (BLN) was carried out by the same surgical procedures, and the kidneys were removed after renal pedicle ligature. Indomethacin (free base; kindly provided by Assia-Riesel Ltd., Tel Aviv, Israel) was dissolved in 95% ethanol, and a dose of 15 mg/kg was injected IP, in volumes not exceeding 0.15 ml. The vehicle (in equal volumes) had no effect on water intake. All experiments were conducted between 12.00 and 16.00 o'clock. BLUL- and BLN rats were treated with IND 4 and 16 hr post-operatively, respectively. Tap water only was allowed for drinking after IND injection, and water intake was measured 1, 2 and 4 hr following IND administration. Results are expressed as mean ± SE. The Student *t* test was used for statistical evaluation.

RESULTS

Figure 1 shows the cumulative water consumption at 1, 2 and 4 hr post IND. It is obvious that IND stimulated water intake in intact rats: 4 hr after IND administration the animals had consumed more than 4 times the quantity of the control rats. BLUL rats demonstrated the same spontaneous drinking behavior as intact rats, but at the end of the IND experiment water intake was stimulated to the same extent as in intact rats injected with IND. BLUL rats showed a lag in drinking response until 2 hr after IND administration, maybe as a result of the ureteral ligature, a procedure which may impede IND exertion on drinking response. Spontaneous drinking of BLN rats was in the same range as of the control and BLUL rats, but IND-stimulated water intake was totally abolished. In another series of experiments, the effect of IND on BLN rats 4 hr post-operatively was also examined, with the same results, e.g., BLN inhibited IND-stimulated water intake. Spontaneous water consumption of

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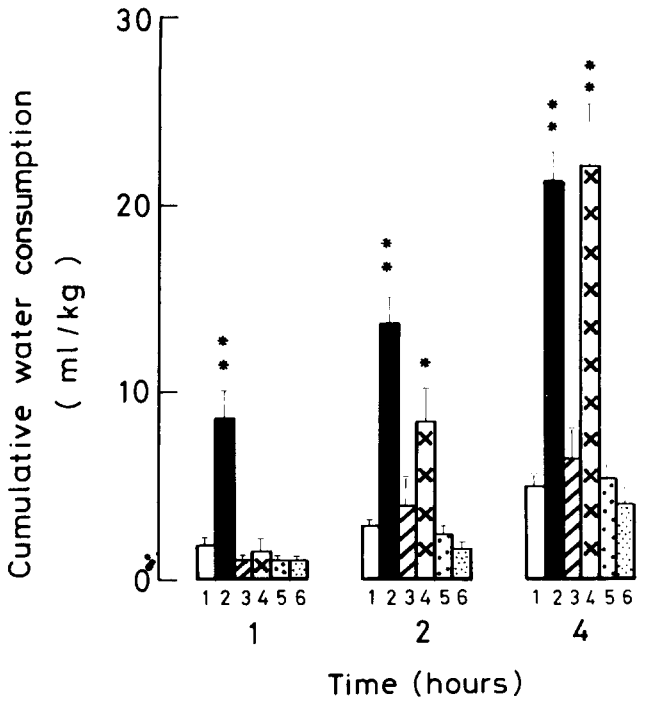

FIG. 1. Influence of indomethacin on water intake of normal, bilaterally ureteral ligated and bilaterally nephrectomized rats. (1) control, intact rats (n=35), (2) intact rats treated with IND (n=35), (3) BLUL rats (n=10), (4) BLUL treated with IND (n=10), (5) BLN rats (n=17), (6) rats BLN treated with IND (n=17). $*p<0.01$; $**p<0.001$ (compared to control rats).

control, BLUL and BLN rats was of the same magnitude throughout the experiments.

DISCUSSION

The present observation leads to the conclusion that IND, a PG synthesis inhibitor, stimulates water intake in rats. This effect persisted after acute BLUL, but was totally abolished following BLN. These results perhaps corroborate the inhibitory effect of central PG on water consumption. However, abolition of the effect of IND by BLN is not consistent with the suggestions of a pure central action. Thus, it appears that drinking response to systemic IND is mediated through a renal factor. It is well known that renal renin release mediates several drinking stimuli [6, 7, 8], but this would not be the case in IND-stimulated water intake since this drug, through inhibition of renal PG synthesis, is known to suppress renal renin release [12,14]. It might still be possible that renal PG, especially of the E and A series, exert an inhibitory effect on water intake by virtue of a central action. Alternatively, water intake stimulated by IND might evolve from IND suppression of renal PG, which are known to inhibit ADH water reabsorption [1]. Thus, IND could induce acute diuresis resulting in increased water intake. In any case, the exact mechanism of IND stimulation of water consumption awaits further elucidation.

REFERENCES

1. Anderson, R. J., T. Berl, K. M. McDonald and R. W. Schrier. Evidence for an in vivo antagonism between vasopressin and prostaglandin in the mammalian kidney. *J. clin. invest.* **56:** 420–426, 1975.
2. Baile, C. A. and F. H. Martin. Relationship between PGE, polyphloretin phosphate and α and β adrenoceptor bound feeding loci in the hypothalamus of sheep. *Pharmac. Biochem. Behav.* **1:** 539–545, 1973.
3. Baile, C. A., C. W. Simpson, S. M. Bean, C. L. McLaughlin and H. L. Jacobs. Prostaglandins and food intake of rats: a component of energy balance regulation? *Physiol. Behav.* **10:** 1077–1085, 1973.
4. Bergström, S., L. A. Carlson and J. R. Weeks. The prostaglandins: a family of biological active lipids. *Pharmac. Rev.* **20:** 1–48, 1968.
5. Epstein, A. N. and N. J. Kenney. Suppression of angiotensin-induced thirst by the E-prostaglandins. In: *Central Actions of Angiotensin and Related Hormones*, edited by J. P. Buckley and C. F. Ferrario. Oxford: Pergamon Press, Inc., 1977, pp. 417–428.
6. Gutman, Y., F. Ben-Zakein and P. Livneh. Polydipsia induced by isoprenaline and by lithium: relation to kidneys and renin. *Eur. J. Pharmac.* **16:** 380–384, 1971.
7. Gutman, Y., M. Krausz and F. Ben-Zakein. Effect of dextran on water intake and plasma renin activity. *Israel J. med. Sci.* **8:** 1770, 1972.
8. Houpt, K. A. and A. N. Epstein. The complete dependence of beta-adrenergic drinking on the renal dipsogen. *Physiol. Behav.* **7:** 897–902, 1971.
9. Phillips, M. I. and W. C. Hoffman. Sensitive sites in the brain for the blood pressure and drinking responses to angiotensin II. In: *Central Actions of Angiotensin and Related Hormones*, edited by J. P. Buckley and C. F. Ferrario. Oxford: Pergamon Press Inc., 1977, pp. 325–356.
10. Ramwell, P. W., J. E. Shaw, G. B. Clarke, M. F. Grostic, D. G. Kaiser and J. E. Pike. In: *Progress in the Chemistry of Fats and Lipids*, edited by R. Holman. Oxford: Pergamon Press Inc., 1967, Vol. 9, p. 73.
11. Robert, A., J. E. Mezamis and J. P. Phillips. Inhibition of gastric secretion by prostaglandins. *Am. J. dig. Dis.* **12:** 1073–1076, 1967.
12. Romero, J. C., C. L. Dunlop and C. G. Strong. The effect of indomethacin and other anti-inflammatory drugs on the renin-angiotensin system. *J. clin. invest.* **58:** 282–288, 1976.
13. Scatamuzzi, O. E., C. A. Baile and J. Mayer. Prostaglandins and food intake of rats. *Experientia* **27:** 256–257, 1971.
14. Speckart, P. Z., R. Zipser and R. Horton. The effect of sodium restriction and prostaglandin inhibition on the renin-angiotensin system in man. *J. clin. Endocrin. Metab.* **44:** 832–837, 1977.