EFFECT OF THEOPHYLLINE ON THE RELEASE AND CONTENTS OF PROSTAGLANDINS E AND F IN RAT RENAL MEDULLA

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Accepted April 5, 1981

It has been demonstrated that prostaglandins (PGs) having physiological activity are excreted in urine of humans (1, 2), dogs (3, 4), rabbits (5, 6) and rats (7). Frolich et al. (3) and Rosenblatt et al. (4) reported that the kidney is the origin of urinary PGs and that PGs in urine reflects the synthesis of PGs in kidney and/or the release of PGs from kidney. Also, it has been shown that the excretion of urinary PGs is stimulated by furosemide (1, 5, 8, 9) and ethacrynic acid (8). Additionally, it is thought that these loop diuretics inhibit the metabolism of PGs since 15-hydroxyprostaglandin dehydrogenase and 9-keto-prostaglandin reductase have been shown to be inhibited by furosemide in vitro (10, 11). These results suggest that the inhibition of PG metabolic enzymes may play a role, at least in part, in the increase of urinary PGs induced by these loop diuretics. Oliw et al. reported that theophylline-induced natriuresis was reduced by indomethacin, and they pointed out the possibility that PG might be associated with the natriuretic effects of theophylline (12). Recently, we reported that theophylline, theobromine and caffeine remarkably increased the excretion of the urinary PGE and electrolytes with the increase of urine volume in rat (especially, theophylline was most effective), and this increase was inhibited by indomethacin (13). In the previous report, we suggested that the increase of the urine volume and the excretion of electrolytes induced by theophylline may be mediated by the intrarenal PGE. The purpose of the present work was to examine whether the renal content of PGs and the in vitro PGs release from kidney are increased by theophylline.

Male Wistar rats, weighing 220–280 g were used in all the experiments. Rats were given theophylline (50 mg/kg p.o.) or the vehicle alone and then were decapitated 2 hours later. The kidneys were quickly removed, and placed in ice-cold Krebs-Ringer bicarbonate buffer. After the capsule had been removed, the kidney was bisected in the coronal plane, sliced with a razor blade, and the medullary tissue (approx. 200 mg) was separated by careful dissection. The medullary tissue was homogenized with acidified ethanol (ethanol: HCl-200:1). PGs were immediately extracted from the medullary tissue according to the previously described procedure (14).

In the in vitro experiment, we examined the effect of theophylline on PGs release from the renal medulla. Slices of medulla (approx. 200 mg) from nontreated rats were placed in a 25 ml flask containing 2 ml of Krebs-Ringer bicarbonate buffer. Theophylline was added to the medium at the final concentration of 10^{-8} to 10^{-4} M and incubation was performed for 15 min at 37°C with 100 cycle/min shaking under an
atmosphere of 95% O₂, 5% CO₂. The extraction of PGs from the incubation medium and biological assay were performed according to the previously described procedure (7, 13).

Effects of theophylline on the contents of PGE and PGF in the renal medulla of rat are illustrated in Fig. 1. The PGE content in the renal medullary tissue was increased from 10.5±1.01 ng/g tissue to 20.1±3.41 ng/g tissue by theophylline administration (p<0.05). The amounts of PGF in the renal medullary tissue in the control and the theophylline administered group were 4.0±0.63 ng/g tissue, and 4.5±1.11 ng/g tissue, respectively.

Figure 2 shows the effect of theophylline on the release of PGs from the medullary tissue of rat kidney. In this incubation system, PGE release from the renal medullary tissue was significantly increased at the concentrations of 10⁻⁶, 10⁻⁵ and 10⁻⁴ M of theophylline. The PGE release from medullary tissue reached from 13.2±1.24 ng/100 mg/15 min to the maximum 26.0±4.66 ng/100 mg/15 min with 10⁻⁴ M of theophylline. However, no significant increase of PGE from renal medulla was evident at the concentrations of 10⁻⁸ and 10⁻⁷ M of theophylline. On the other hand, PGF release was also significantly increased at the concentrations of 10⁻³ and 10⁻⁴ M of theophylline. However, PGF release from renal medulla was lower in comparison with the level of PGE release.

There are some reports that the increase of PG release in renal medulla occurs as a result of activation of phospholipase induced by bradykinin, angiotensin II or arginine vasopressin (15), or by the hypertonic condition (16). However, the mechanism of the effect of theophylline on renal PG is obscure at present.

Most of PG in kidney is produced by medullary tissue, and it has been suggested that the interstitial cells and the collecting duct are the main sites of PG synthesis (17, 18). It has also been indicated that PGE₂ inhibits transport of sodium in the collecting tubule (19), and that of chloride in the thick ascending limb of Henle (20). These results suggest that renal PGE₂ may play an important
role in the regulation of the excretion of urinary electrolytes.

The present study showed that the content of PGE in the renal medullary tissue was increased by theophylline administration (Fig. 1) and that theophylline added in vitro increased the release of PGE from this tissue (Fig. 2). From the present and the previous results (13), it is thought that PGE release from the renal medullary tissue may be stimulated by the direct action of theophylline on kidney, so that a large amount of PGE is excreted in the urine.

REFERENCES


7) Takeuchi, K., Kogo, H. and Aizawa, Y.: Biological assay of prostaglandin using rat uterus. Folia pharmacol. japon. 71, 675-682 (1975) (Abs. in English)


12) Bohman, S.O.: Demonstration of prostaglandin synthesis in collecting duct cells and other cell types of the rabbit renal medulla. Prostaglandins 14, 729-744 (1977)