The role of intrarenal vasoactive substances in the pathogenesis of essential hypertension


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Summary

To investigate the role of renal vasoactive substances in the pathogenesis of essential hypertension, urinary prostaglandin E excretion, urinary kallikrein excretion, plasma renin activity, plasma aldosterone concentration and urinary Na excretion were measured in normal subjects and patients with essential hypertension after stimulation of the renin-angiotensin-aldosterone system by the intravenous injection of frusemide or a low Na diet; after the inhibition of renin-angiotensin-aldosterone by an angiotensin II antagonist and after the inhibition of renal prostaglandin E synthesis by indomethacin. The urinary excretions of prostaglandin E and kallikrein, plasma renin activity and plasma aldosterone concentration increased after frusemide administration. The urinary excretion of kallikrein increased after frusemide or a low Na diet but decreased after the angiotensin II antagonist and indomethacin during Na depletion. Changes in urinary kallikrein excretion paralleled those in the renin-angiotensin-aldosterone system after various stimuli. The urinary excretion of prostaglandin E increased after frusemide. However, a dissociation between the urinary excretions of prostaglandin E and kallikrein was found during the low Na diet: the former decreased and the latter increased. The urinary excretion of prostaglandin E was closely related to urinary Na output after various stimuli. Basal levels of urinary prostaglandin E and kallikrein excretion were lower in essential hypertension than in normal subjects. The release of renal prostaglandin E and kallikrein after frusemide was also suppressed in essential hypertension compared with that in normal subjects. The data indicate that renal kallikrein-kinin and renin-angiotensin-aldosterone may interact in a dynamic fashion to maintain blood pressure, that renal prostaglandin E may be involved in renal Na handling and that the suppression of renal kallikrein-kinin and prostaglandin E in essential hypertension may be an etiological factor in essential hypertension.

Key words: essential hypertension, pathogenesis, renal prostaglandin E, renal kallikrein-kinin, renin-angiotensin-aldosterone system.

Abbreviations: KK, kallikrein-kinin; PG, prostaglandin; RA, renin-angiotensin; RAA, renin-angiotensin-aldosterone.

Introduction

It is now generally accepted that the kidney is involved in the pathogenesis of hypertension through two mechanisms. One is the renin-angiotensin system and the other the renal anti-hypertensive mechanism. Margolius, Horwitz, Pisano & Keiser (1974) reported that synthesis of renal kallikrein is regulated by aldosterone. McGiff, Itskovitz, Terragno & Wong (1976) reported that there is a close interrelationship between the renal KK system and renal PG. Thus, renal KK and PG may possibly regulate blood pressure by opposing the action of the RAA system. The present study was undertaken to investigate the role of renal vasoactive substances in the pathogenesis of essential hypertension.
essential hypertension. In addition, we examined the interrelationship between RAA, renal kallikrein, renal PG and sodium status.

Methods

The present study was carried out in 84 normal subjects and 55 patients with essential hypertension. Normal subjects were 61 men and 23 women (mean age 40.0 ± 1.6, range 18–66 years). Essential hypertensives were 35 men and 20 women (mean age 37.1 ± 1.8, range 15–63 years). All subjects were hospitalized during the study and allowed an unrestricted sodium diet. Antihypertensive medication was discontinued for at least 2 weeks before the study. Urine was collected in a bottle kept in a refrigerator and then stored at −15°C until the assay. Blood was sampled in fasting patients kept in the recumbent position for one hour. In some patients, sampling of blood and urine was performed after the following manipulations; low Na diet, frusemide injection and upright posture, infusion of angiotensin II antagonist, and administration of indomethacin.

Urinary PGE was measured radioimmunologically by using a commercial kit. After urinary PGE had been converted into PGB by alkaline treatment, the sample was acidified to pH 3–4 and extracted with ethyl acetate. The PGB fraction was then separated by silicic acid column chromatography and measured radioimmunologically with PGB antiserum. Urinary PGE was calculated by subtraction of the value of natural PGB. The overall recovery rate of added PGE was 54.8 ± 0.7%, and the estimated value was corrected by this factor.

Urinary kallikrein was measured as kininogenase activity. Urine, 0.05–0.1 ml, was incubated with 4 μg of bovine serum low-molecular-weight kininogen at 37°C for 20 min. After incubation, the sample was heated at 80°C for 20 min to terminate the enzymic reaction and the generated kinin was measured by radioimmunoassay using kallidin antiserum. In the present method, an extraction procedure for kinin was not necessary, because bovine serum low molecular weight kininogen had no cross reaction with kallidin antibody.

Plasma renin activity was determined by a modification of Haber’s method (Abe et al., 1972) and plasma aldosterone concentration with a commercial radioimmunoassay kit (Cer. Ire. Sorin.). Urinary Na was measured by autoanalyzer. The results were expressed as means ± SEM. The differences between mean values were tested by Student’s t-test.

Results

Urinary excretion of PGE and kallikrein in normal subjects and essential hypertensive patients

Resting levels of the urinary excretions of PGE and kallikrein were 736 ± 32 ng/day and 34.5 ± 4.0 μg 20 min⁻¹ day⁻¹, respectively, in 84 normal subjects, and 394 ± 29 ng/day and 18.3 ± 2.8 μg 20 min⁻¹ day⁻¹, respectively, in 55 patients with essential hypertension. The urinary excretions of PGE and kallikrein were significantly lower in patients with essential hypertension than in control subjects (PGE P < 0.001, kallikrein P < 0.001). There was a significant correlation between the urinary excretions of PGE and Na in 84 normal subjects (r = 0.39, P < 0.001) and in 51 patients with essential hypertension (r = 0.62, P < 0.001). However, the urinary excretion of kallikrein was not significantly correlated with that of Na or PGE.

Influence of low Na diet on renal vasoactive substances

Ten patients received first a diet containing 200 mmol of Na/day for at least a week, then 100 mmol and finally 30 mmol of Na, each for 3 days. PRA, PAC and urinary kallikrein excretion increased with the low Na diet. On the contrary, urinary Na and PGE excretions decreased. Thus, the low Na diet induced a dissociation between renal PGE and the kallikrein system.

Effect of frusemide on renal vasoactive substances

After the RAA system had been stimulated by frusemide injection and an upright posture for 2 h in 19 normal subjects and 16 patients with essential hypertension, urinary PGE and kallikrein excretions were measured. Values of all the variables measured increased after frusemide administration (Fig. 1). The increment of plasma renin activity and plasma aldosterone concentration was similar in normal subjects and in essential hypertension. On the contrary, the increments of urinary PGE and kallikrein excretions after frusemide administration were greater in normal subjects than in those with essential hypertension. The present results suggest that the responses of both renal PGE and renal kallikrein to frusemide are suppressed in essential hypertension.

Effect of angiotensin II antagonist on renal vasoactive substances

After the angiotensin II antagonist, 1-sarcosine-8-isoleucine angiotensin II, was infused intra-
Vasoactive substances in essential hypertension

Fig. 1. Effect of frusemide injection on urinary kallikrein (U_{kall} V) excretion, urinary PGE excretion (U_{PGE} V), plasma renin activity (PRA), plasma aldosterone concentration (PAC), urinary volume (UV) and urinary sodium excretion (U_{Na} V) in healthy subjects (n = 19) and patients with essential hypertension (n = 16). Results are presented as mean values ± SEM.

Venously at a rate of 300–600 ng/kg/min in 10 patients with essential hypertension, the urinary excretions of PGE and kallikrein were measured. During a normal Na diet, blood pressure rose as a result of the agonistic action of this analogue. The urinary excretions of PGE and Na, and plasma renin activity decreased after the administration of this drug, whereas those of kallikrein and plasma aldosterone concentration increased. During the low Na diet, blood pressure was lowered by the antagonistic action of the analogue. The urinary excretion of kallikrein and plasma renin activity decreased, while the urinary excretions of PGE and Na, and plasma aldosterone concentration did not change. The results suggest that circulating angiotensin II might be one of the regulators of urinary kallikrein excretion.

Effect of indomethacin on renal vasoactive substances

Eleven hypertensive patients were given a 90 mmol Na diet with frusemide (80 mg per day
orally) for 3 days, after which indomethacin (150 mg per day orally) was added for an additional 3 days. The urinary excretion of PGE, plasma renin activity and plasma aldosterone concentration decreased significantly after indomethacin (PGE $P < 0.05$, plasma renin activity, $P < 0.01$, plasma aldosterone concentration $P < 0.01$). The urinary excretions of kallikrein and Na decreased slightly, but the changes were not significant.

**Discussion**

Kaizu & Margolius (1975) reported that kallikrein release in the rat renal cortical cell suspension could be increased by aldosterone and reduced by spironolactone. On the other hand, Johnston, Matthews & Dax (1976) suggested that angiotensin II might be a regulator of urinary kallikrein excretion. In the present study, changes in the urinary excretion of kallikrein paralleled those of the RAA system after various stimuli. Kallikrein output increased after the administration of frusemide or a low Na diet, but it decreased after the administration of the angiotensin II antagonist and indomethacin during Na depletion. These results indicate that the renal kallikrein–kinin system may interact with the RAA system in a dynamic fashion to maintain blood pressure.

Urinary kallikrein and PGE excretion rose after frusemide, and fell after indomethacin. However, a dissociation between renal kallikrein and PGE was found after Na depletion and after the administration of the angiotensin II antagonist during a normal Na diet.

Previous reports concerning the role of renal PGE in renal Na handling have been conflicting. Intrarenal infusion of PGE induces natriuresis (Johnston, Herzog & Lauler, 1967, indicating that renal PGE may be involved in renal Na output. On the contrary, the study by Tobian, O'Donnell & Smith (1974), in which renal PGE content in the rat decreased after Na repletion, suggests that renal PGE may act as an antinatriuretic hormone. In the present study, the urinary excretion of PGE was closely related to urinary Na output after various stimuli. A significant correlation was also found between basal levels of urinary PGE and those of urinary Na. The results indicate that renal PGE may be involved in renal Na handling.

Elliot & Nuzum (1934) found that the urinary excretion of kallikrein decreased in essential hypertension. A similar result was reported by Margolius, Geller, Pisano & Sjoerdsma (1971). In the present study, basal levels of urinary PGE and urinary kallikrein were lower in essential hypertensive than in normal subjects, as also were the responses of renal PGE and kallikrein to frusemide injection. These results suggest that suppression of the renal kallikrein–kinin system and renal PGE may be an etiological factor in essential hypertension.

**References**


