Effects of Angiotensin I Converting Enzyme Inhibitors on the Renal Excretory Function, Hemodynamics and Renin Release in Isolated Perfused Rat Kidney

Tohru OGIHARA, M.D., Mamoru YOSHIKAWA, M.D.,
Toshiyuki YASUI, M.D., Haruyuki NAKANE, M.D.,*
Yoko NAKANE, M.D.,* and Takao SARUTA, M.D.

SUMMARY

Direct renal effects of angiotensin I converting enzyme inhibitors (CEIs), captopril, SA446 and MK421, were examined in isolated rat kidneys perfused with a renin-substrate-free medium. Among three CEIs, only captopril induced a significant natriuresis, whereas SA446 and MK421 did not. U_{KV} , renal vascular resistance and creatinine clearance were not affected by any of these CEIs. Renin release from perfused rat kidneys were not influenced by CEIs under the present experimental conditions.

These results suggest that among three different types of CEIs, only captopril possesses natriuretic action in the isolated perfused rat kidney and that this action may be independent of its inhibitory action on angiotensin converting enzyme. It is also suggested that these three CEIs themselves do not have a direct effect on the renal vascular bed.

Additional Indexing Words:

Captopril SA446 MK421

IN man and animals, it has been reported that CEIs induced natriuresis which seems disproportionate to the blood pressure level achieved by CEI administration.¹⁾⁻⁴⁾ The mechanism of CEI-induced natriuresis has been suggested to be related to the inhibition of angiotensin I converting enzyme (ACE).

Recently, we have reported that captopril induced natriuresis in isolated perfused rat kidney, in the absence of angiotensinogen, kininogen and aldosterone.⁵⁾ This observation suggests that captopril-induced natriuresis in the isolated perfused rat kidney may be independent of its inhibitory action on

From the Department of Internal Medicine, School of Medicine, Keio University, Shinanomachi, Shinjuku-ku, Tokyo, and * the Department of Internal Medicine, Urawa City Hospital, Saitama.

Address for reprint: Takao Saruta, M.D., Department of Internal Medicine, School of Medicine, Keio University, 35, Shinanomachi, Shinjuku-ku, Tokyo 160, Japan.

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Fig. 1. Effects of captopril, SA446 and MK421 on urine volume in the isolated perfused rat kidney.

ACE or kininase II.

In order to further investigate the mode of direct renal action of CEIs, the effects of three different types of CEIs, captopril (Squibb Laboratories), SA446 (Santen Laboratories) and MK421 (Merck Sharp Laboratories), on renal hemodynamics and excretory function were examined in isolated perfused rat kidney. We also examined whether these effects are based on the blockade of local angiotensin II (AII) formation by studying renin release from the isolated kidneys.

MATERIALS AND METHODS

Under pentobarbital anesthesia, following an injection of 100 units of

Fig. 2. Effects of captopril, SA446 and MK421 on urinary sodium excretion ($U_{Na}V$) in the isolated perfused rat kidney.

heparin into the jugular vein, the right kidney of male Wistar rats (weight, 300–450 Gm) was cannulated without interruption of blood flow,⁶⁾ isolated, and perfused in vitro at a stable perfusion pressure (80 mmHg) with 75 ml of recirculating Krebs-Ringer bicarbonate buffer containing 5% or fraction V bovine serum albumin, 5.5 mM of glucose and 1 mg of creatinine.⁷⁾

Thirty-one rats were divided into 4 groups: control group ($n=10$), captopril-administered group ($n=6$), SA446-administered group ($n=9$), and MK421-administered group ($n=6$). The observation period began after a 20 min-equilibration period. One mg of captopril, 2.0 mg of SA446, or 2.2 mg of MK421 was injected in the recirculating medium (6.1×10^{-5} M, 6.0×10^{-5} M, and 6.0×10^{-5} M in the perfusate, respectively) at 20 and 40 min of the observation period. The renal function and perfusate renin concentration were measured for 1 hour and compared with data from the control period (0–20 min). The glomerular filtration rate (GFR) was estimated by

Fig. 3. Effects of captopril, SA446 and MK421 on urinary potassium excretion (U_KV) in the isolated perfused rat kidney.

measuring creatinine clearance. The perfusate renin concentration was measured by a previously described method.⁸⁾ Values are reported as means $\pm$ SEM. A non-paired t-test was used to determine statistical significance.

RESULTS

As shown by Figs. 1-3, captopril induced significant increases in urine volume and $U_{Na}V$, whereas slight changes in these variables induced by SA446 and MK421 were not statistically significant. U_KV was not affected by CEIs. Similarly, CEIs did not affect renal vascular resistance (Fig. 4). Although a gradual decrease in GFR was observed in all groups, there was no significant difference in GFR between the control group and CEI-administered

Fig. 4. Effects of captopril, SA446 and MK421 on renal vascular resistance in the isolated perfused rat kidney.

groups (Fig. 5). Fig. 6 shows the renin concentration in the recirculating medium of isolated perfused kidneys determined in control, captopril-administered and SA446-administered groups. In the CEI-administered groups tested, perfusate renin concentrations did not differ from the control group.

DISCUSSION

In vivo studies in man and animals have reported that CEIs induce natriuresis and renal hemodynamic changes.¹⁾⁻⁴⁾ The possible mechanisms of CEI-induced natriuresis *in vivo* have been suggested as follows: (1) vasodilatory and tubular actions due to reduction of angiotensin II and/or accumulation of kinins,^{3),9)-16)} (2) vasodilatory and tubular actions due to stimulation of prostaglandin (PG) synthesis caused by an accumulation of kinins,¹⁷⁾⁻¹⁹⁾ and (3) reduction of aldosterone.^{20),21)} All these mechanisms are related to

Fig. 5. Effects of captopril, SA446 and MK421 on creatinine clearance in the isolated perfused rat kidney.

the inhibition of ACE, and actions of CEIs other than ACE inhibition have been poorly documented.

In our previous study, we suggested that changes in circulating AII, kinins, PGs and aldosterone are not likely to be related to the captopril-induced natriuresis in the isolated perfused rat kidney, since, in the isolated perfusion system, the perfusate lacks renin substrate, aldosterone and probably kininogen.⁵⁾ However, it is possible that the formation of AII, kinins and PGs are still present within the isolated kidney and that the captopril-induced natriuresis may depend on its inhibitory action on intrarenal ACE. Among the three CEIs tested in the present study, only captopril induced a significant natriuresis, despite the fact that all three agents have similar ACE-inhibition properties. These three CEIs did not affect U_{KV} , renal vascular resistance and creatinine clearance. This difference between captopril and SA446 and MK421 on renal action suggests that the natriuretic action of captopril may be independent of its inhibitory action on ACE in isolated perfused rat kidney. Moreover, the lack of significant stimulation of renin release in CEI-administered groups suggests that the effects of CEIs on intrarenal AII

Perfusate Renin Concentration (mean $\pm$ S.E.M.)

Fig. 6. Effects of captopril and SA446 on renin release in the isolated perfused rat kidney.

formation is negligible in this system for feedback control of renin release by AII. Since renin release from the isolated kidney is not influenced by captopril and SA446 (compared with the control group), captopril-induced natriuresis in the isolated perfused rat kidney may be independent of its inhibitory action on local AII formation.

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