Inhibition of Isoprenaline-Induced Increase in Plasma Renin Concentration by Vasoconstrictors[1]

Stimulation of renin secretion by the β-sympathomimetic isoprenaline has been described in rats[2] and dogs[3]. Isoprenaline infused into the isolated perfused rat kidney increases renin release[4]. This effect is antagonized by simultaneously infused angiotensin II, but in the presence of Ca^{++}-ions, only[5]. Since the vasoconstricting action of angiotensin II also depends on Ca^{++}-ions, we assumed that angiotensin II suppresses renin release by causing an intrarenal vasoconstriction. To test this assumption, we studied the effect of the vasoconstrictors angiotensin II, vasopressin and the α-sympathomimetic amine phenylephrine on the isoprenaline-induced renin release.

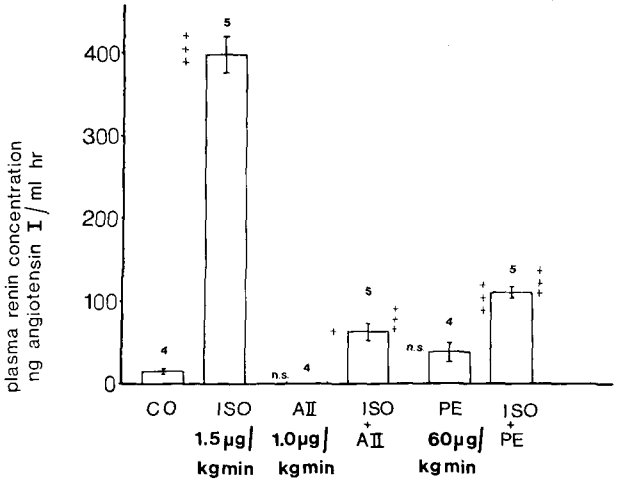

Fig. 1. Effect of angiotensin II (1.0 µg/kg min) (AII) and phenylephrine (60.0 µg/kg min) (PE) on the plasma renin concentration of controls (CO) and isoprenaline (1.5 µg/kg min) (ISO)-treated unanaesthetized rats. Renin concentration is expressed as ng angiotensin I generated by the renin in 1 ml plasma during 1 h under our conditions of incubation. Numbers of animals used are shown above each column. +, $p < 0.05$; ++, < 0.01; +++, < 0.001; n.s., not significant. Symbols at the left side of columns indicate differences between this group and the controls. Symbols at the right side of columns show differences between this group and the one treated with isoprenaline alone.

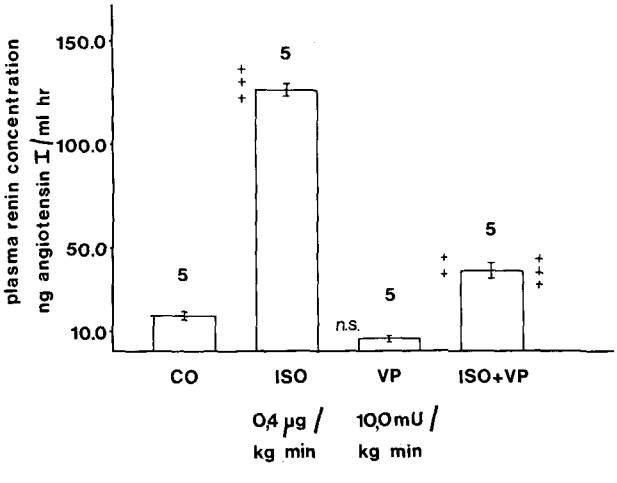

Fig. 2. Effect of vasopressin (10 mU/kg min) (VP) on renin plasma concentration of controls (CO) and isoprenaline (1.5 µg/kg min) (ISO) treated rats. For further explanation see Figure 1.

Methods. Unanaesthetized male Wistar rats (280–310 g) were used. Tail veins were cannulated for drug application. All drugs were given by constant infusion (infusion rate 0.050 ml/min). 1 ml of infusion medium contained 0.8 ml of isotonic saline, 0.1 ml 0.001 *N* HCl in which isoprenaline was dissolved, 0.1 ml of distilled water, which was the vehicle of the vasoconstrictor. Controls received the respective solvent infusions. 20 min after the start of drug infusion, 4 ml of blood were collected from the aorta of the rats lightly anaesthetized with ether. The infusion was continued during the time of collection. The plasma was separated immediately by centrifugation in a cooled centrifuge.

Renin concentration was determined by incubation of an aliquot of plasma with substrate partially purified according to SCHAECHTELIN et al.[6]. Incubation temperature was 52 °C, pH of incubation medium was 5.2. After 30 min, incubation was stopped by boiling. Angiotensin I generated was determined by radioimmunoassay[7]. Student's *t*-test was used for statistical analysis.

Studies on renal plasma flow: PAH-clearance was determined in a control group ($n = 4$) and in one ($n = 4$), which received an infusion of the α-sympathomimetic phenylephrine. Unanaesthetized rats of 310–330 g were used. Drugs were given i.v. through a cannula placed in the tail vein.

After a priming dose of PAH (1.0 mg/100 g) injected i.v., a constant infusion of PAH (5.0 mg/ml) dissolved in isotonic saline followed (infusion rate 0.050 ml/min). Mannitol (100 mg/ml) added to the infusion medium ensured a constant urine production. After 30 min of equilibration, the PAH clearance was measured during the following 20 min. During this time, the animals received the phenylephrine or solvent infusion. Urine flow rate was determined by collecting the urine. Before the test period, the bladder was emptied completely by a gentle massage of the suprapubic region. Blood was collected from the aorta at the end of the sampling period. Determination of PAH in serum and urine was made according to BRATTON and MARSHALL[8].

Studies on blood pressure and heart rate. Groups of 4 rats were used. The ventral tail artery was cannulated under light ether anaesthesia with a polyethylene cannula. Blood pressure and heart rate were recorded before and during drug infusion with a Statham transducer and a Watanabe recorder. Drugs were infused through a cannula placed in a tail vein, as in the studies on plasma renin concentration. *t*-test for paired observations was used for statistical analysis.

Results and discussion. Figure 1 shows the effect of (asp[1]-β-amid, val[5]) angiotensin II (1.0 µg/kg min) and the α-sympathomimetic amine phenylephrine (60.0 µg/kg min) on plasma renin concentration of normal and isoprenaline (1.5 µg/kg min)-stimulated rats.

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Angiotensin II given alone showed the tendency to suppress the renin levels beneath the control values, phenylephrine had no effect on the plasma renin concentration. The increase in plasma renin concentration induced by isoprenaline was markedly inhibited by simultaneous infusion of angiotensin II or phenylephrine.

Figure 2 shows a similar experiment with vasopressin (10.0 mU/kg min). Given alone, the peptide had no significant effect on plasma renin concentration. Infused in combination with isoprenaline (0.4 µg/kg min), it prevented the renin release caused by the β-adrenergic stimulation.

The effect of phenylephrine (60 µg/kg min) on the PAH-clearance of otherwise untreated animals was studied next. Since isoprenaline causes a strong antidiuresis, it was impossible to study PAH-clearance in isoprenaline-treated rats. PAH-clearance was 6.9 ml/min ($n = 4$) in controls and 7.2 ml/min ($n = 4$) in phenylephrine treated rats (not significant). This indicates that the vasoconstrictors do not suppress renin release by decreasing renal plasma flow and thus the access of isoprenaline to its intrarenal sites of action.

Finally the effects of isoprenaline and the vasoconstrictors on mean arterial pressure (MAP) and heart rate (HR) were analyzed. MAP and HR before and 10 min after the start of the infusions are given. Angiotensin II (1.0 µg/kg min) increased MAP from 104.8 to 149.3 mmHg ($p < 0.01$) and lowered HR from 460 to 315 beats/min ($p < 0.001$). Vasopressin (10 mU/ kg min) increased MAP from 90.0 to 112.0 mmHg ($p < 0.01$); HR was lowered from 478 to 302 beats/min ($p < 0.005$). Isoprenaline given alone increased HR from 470 to 540 ($p < 0.005$) and lowered MAP from 102.4 to 61.8 mmHg ($p < 0.005$). When infused simultaneously angiotensin II partially antagonized the effect of isoprenaline on MAP and HR. During the combined infusion, MAP was lowered from 92,0 to 72.0 mmHg ($p < 0.001$); HR rose slightly from 478.1 to 517.1 beats/min (n.s.). When isoprenaline and vasopressin were infused simultaneously, MAP fell slightly from 95.9 to 88.7 mmHg ($p < 0.01$) and HR rose from 498 to 507 (n.s.). Thus, 3 different vasoconstrictors markedly inhibit the isoprenaline-induced renin release and its vascular and cardiac effects.

Isoprenaline releases renin by an action on intrarenal sites[4]. The suppressive effect on renin release of angiotensin is also due to an intrarenal action[5]. The observations reported may be explained by the assumption that isoprenaline causes an intrarenal vasodilatation, e.g. in the baroreceptor area, and thus stimulates renin release. The vasoconstrictors antagonize the isoprenaline-induced vasodilation in a similar way as they inhibit its effect on systemic blood pressure. Thus they attenuate the stimulus for the baroreceptors and inhibit renin release.

The suppression of the isoprenaline-induced renin release by the vasoconstrictors strongly resembles their inhibitory effect on renin release caused by furosemide[9]. A similar mechanism was proposed to explain this phenomenon.

According to the hypothesis of GANONG[10] isoprenaline causes renin release by a direct secretomotoric stimulation of the renin-releasing cells. NOLLY et al.[11], however, could only observe a weak stimulation of renin release when they added catecholamines to an incubate of rat kidney slices. AOI et al.[12] reported a strong stimulation, but they had to use very high concentrations of epinephrine or norepinephrine. In case of a secretomotoric mechnism of the isoprenaline-induced renin release, which is still unproved, the effect of the vasoconstrictors must be due to a direct inhibitory action on the renin-secreting cells. On the molecular aspects of this action, we can only speculate.

Summary. The vasoconstrictors angiotensin II, vasopressin and the α-sympathomimetic phenylephrine significantly inhibit the renin release caused by the β-sympathomimetic isoprenaline. The mechanism of the inhibition is discussed.

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Scanning Electron Microscope Observations of the Canaliculi in the Rat Pineal Gland

Several authors have described large intercellular and pericapillary spaces in the rat pineal gland[1-8]. In these spaces there are polar terminals of the pineal cells, interstitial cells with their processes, adrenergic nerve endings, capillaries, collagenous fibres and an amorphous, weakly osmiophile substance.

After a parenchymal perfusion of a rat pineal gland, QUAY[9] observed that its canalicular system shows a 24-hour rhythm. According to the same author, this system of channels may be significant for transport activities between pinealocytes and capillaries. The rhythmic changes of the pineal parenchymal channels would be regulated partly by the release of 5-hydroxytryptamine and partly by calcium ions.

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