The Role of the Renin-Angiotensin System in Mediation of Adrenal Catecholamine Secretion in the Cat Induced by Intrarenal $\beta$-Adrenergic Stimulation

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SUMMARY Isoproterenol infusion (0.1 $\mu$g/kg per min) into the renal artery of the cat induced an increase in plasma renin concentration (PRC) from 14.3 ± 5.7 (mean ± SE) ng angiotensin I/ml per hr to 56.8 ± 7.7 after 70 minutes ($P < 0.05$) and an increase in catecholamine secretion rate from 38.7 ± 6.0 ng/kg per 10 min to 180.0 ± 40.0 after 70 minutes ($P < 0.001$). Intravenous infusion of the same dose of isoproterenol had no significant effect on adrenomedullary catecholamine secretion rate. Isoproterenol induced preferential norepinephrine release: the ratio of norepinephrine to epinephrine secretion changed from 11.5:23.7 during the control period to 130.0:40.1 70 minutes after the start of isoproterenol administration. Intrarenal infusion of propranolol (3.0 mg/kg per min) inhibited renal renin release and adrenal catecholamine secretion in response to intrarenal isoproterenol. Intravenous infusion (0.4 $\mu$g/kg per min) of an angiotensin II antagonist [Sar$^1$, Ileu$^8$]angiotensin II abolished the catecholamine response to intrarenal isoproterenol infusion. It is suggested that intrarenal isoproterenol infusion stimulates renal renin release and angiotensin production which, in turn, stimulates a preferential secretion of adrenomedullary norepinephrine.

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able individual variation in the basal adrenal catecholamine secretion rate of the animals, catecholamine secretion was calculated for each cat also as percent of the secretion rate during the control period, before the start of the intrarenal infusion.

Drug Infusion

Isoproterenol sulfate (Teva, Ltd.) was dissolved in 6 ml 0.9% NaCl immediately before each experiment, and infused at the rate of 0.1 µg/kg per min for a period of 30 minutes (0.2 ml/min), either intrarenally or intravenously. d,l-Propranolol (Abic, Ltd.) was dissolved, together with isoproterenol, in 6 ml 0.9% NaCl and infused at a rate of 3 mg/kg per min during 30 minutes (0.2 ml/min). [Sar¹, Ileu⁸]-angiotensin II was dissolved in 6.0 ml 0.9% NaCl. The infusion of the angiotensin II antagonist was started at the same time as isoproterenol; PRC values in control experiments were 8.6 ± 1.9, 3.6 ± 0.3 after 50 minutes (P < 0.05), and 4.1 ± 0.6 after 70 minutes (P < 0.05) in eight animals.

Thus, PRC levels were significantly reduced by propranolol infusion.

The Effect of Isoproterenol Infusion on Adrenomedullary Catecholamine Secretion Rate

The adrenomedullary catecholamine secretion rate for each cat remained constant during the entire control experiment (intrarenal infusion of 0.2 ml/min of 0.9% NaCl for 100 min; Fig. 2). Intrarenally infused isoproterenol elicited a substantial increase in adrenal catecholamine secretion 40 minutes after isoproterenol administration had begun. Secretion continued to increase, and finally reached more than five times the basal rate at the end of the experiment (from 38.7 ± 6.0 ng/kg per 10 min during the control period to 180 ± 40.0, P < 0.001). Intravenous isoproterenol, on the other hand, had no significant effect on the adrenomedullary catecholamine secretion rate (from 46.2 ± 10.7 ng/kg per 10 min during the control period to 85.5 ± 19.8—not significant). Isoproterenol induced preferential norepinephrine release: the ratio of norepinephrine to epinephrine secretion changed from 11.5:23.4 during the control period to 130.0:40.1 70 minutes after the start of isoproterenol administration (Fig. 3). Systemic blood pressure was not significantly affected by propranolol and/or isoproterenol infusion when compared to the control group (Fig. 4).

The Effect of Propranolol on Isoproterenol-Induced Adrenomedullary Catecholamine Release

Intrarenal infusion of propranolol plus isoproterenol nearly abolished the adrenal catecholamine secretion in response to intrarenal isoproterenol alone (Fig. 2). At the end of the experiment, catecholamine secretion was only 67% higher than during the control period (statistically not significant).
Isoproterenol, on the other hand, induced a 540% increase in catecholamine secretion ($P < 0.001$).

The Effect of [Sar^1, Ileu^8]angiotensin II on Isoproterenol-Induced Adrenomedullary Catecholamine Release.

Intravenous infusion of [Sar^1, Ileu^8]angiotensin II completely abolished the adrenal catecholamine response to intrarenal infusion of isoproterenol. Cats treated with the angiotensin II antagonist showed a catecholamine secretion rate similar to the basal secretion rate of control animals. The PRC rise from $12.1 \pm 3.8$ to $55.1 \pm 14.8$ ng angiotensin I/ml per hr ($P < 0.025$) was of the same magnitude as in the isoproterenol-treated group (Fig. 5).

Discussion

Our experiments demonstrate that specific β-adrenergic activation of the renal renin angiotensin system is followed by adrenomedullary catecholamine release in vivo. These experiments corroborate our observations in hypotensive hypovolemic animals (Feuerstein et al., 1977a) in which the adrenomedullary catecholamine release in response to hemorrhage could be abolished by bilateral nephrectomy. The same dose of isoproterenol administered intravenously had no effect on adrenal catecholamine secretion. A direct impact on the adre-
thermore, there were no differences between blood pressure was not followed, however, by an increase in catecholamine release. Furthermore, there were no differences between blood pressure of the different experimental groups and that of the controls.

The preferential noradrenergic response observed in our experiments (Fig. 3) is in contrast to the results reported for isolated perfused adrenal gland (Robinson, 1967; Staszewska-Barczak and Vane, 1967; Peach, 1974; Ackerly, et al., 1977). In the latter, direct stimulation of the adrenal gland by angiotensin II induced preferential epinephrine secretion. This discrepancy may be the consequence of the high concentrations of angiotensin II used in the in vitro experiments (10^{-5}-10^{-7} M angiotensin) which are far above the levels attained by spontaneous renin release in vivo. In fact, the action of angiotensin II on the sympathetic nervous system in vivo is not necessarily the result of a direct effect on the adrenal gland; it also might be influenced by indirect mechanisms such as activation of central sympathetic nuclei (Fischer-Ferraro, 1971; Katic et al., 1971; Ferrario et al., 1972). This hypothesis is supported by previous data (Feuerstein et al., 1977a) which demonstrate abolition of adrenomedullary catecholamine release in response to acute hemorrhage in animals after adrenal denervation with intact functioning kidneys as a source of renin. Adrenal denervation did not affect renal renin release in response to acute hemorrhage in animals after adrenal denervation with intact functioning kidneys as a source of renin. Adrenal denervation did not affect renal renin release in response to acute hemorrhage (unpublished data).

It should be emphasized that the noradrenergic response elicited after acute hemorrhage (Feuerstein et al., 1977a, 1977b) also was observed in our experiments after intrarenal isoproterenol infusion. The course of events points to an adrenomedullary response to hemorrhage mediated by renal stimulation and by peripherally generated angiotensin II which, in turn, activates the central nervous system. In preliminary experiments conducted in our laboratory, [Sar^{1}, Ileu^{8}]angiotensin II (0.4 g/kg per min) was injected into the lateral cerebral ventricle in cats exposed to acute hemorrhage. Doses up to 15 lg/kg of the angiotensin II antagonist failed to modulate the adrenal catecholamine response to hemorrhage. This observation awaits further investigation.

References


Role of Medullary Hemodynamics in the Natriuresis of Drug-Induced Renal Vasodilation in the Rat

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SUMMARY In contrast to most renal vasodilators, such as acetylcholine (ACh), secretin increases renal blood flow in the dog without a marked effect on sodium excretion ($U_{\text{Na}} V$). To investigate this observation, we studied the relationship between renal vasodilation, $U_{\text{Na}} V$, and papillary plasma flow (PPF) in rats, infused either with ACh or secretin into the aorta at the level of both renal arteries. ACh significantly increased GFR, PAH clearance, and $U_{\text{Na}} V$ (A + 0.35 ml/min, + 2.11 ml/min and + 1.77 /Eq/min, respectively; $P < 0.05$). PPF rose from 50 ± 2.6 ml/min 100 g (mean ± SE) in control rats to 91 ± 4.7 ml/min 100 g after ACh ($p < 0.001$). Despite a similar increase in PAH clearance after secretin (+ 2.21 ml/min; $P < 0.01$), $U_{\text{Na}} V$ remained unchanged and PPF was only slightly, although significantly, increased (from 50 ± 2.6 ml/min 100 g to 65 ± 2.75 ml/min 100 g; $P < 0.05$). Both total kidney and papillary vasodilation, and the increase in $U_{\text{Na}} V$ after ACh were blocked by previous administration of meclofenamate (M), a prostaglandin inhibitor. No effect of M in secretin-infused rats was observed. In conclusion, the relationship between total renal vasodilation and natriuresis was dissociated with secretin, but not with ACh. However, a relationship between the natriuresis and influence on papillary hemodynamics was observed with both vasodilators. Finally, the renal hemodynamic and natriuretic effects of ACh are probably mediated by prostaglandin release. Circ Res 47: 839-844, 1980

INTRARENAL infusion of vasodilator substances (e.g., acetylcholine or bradykinin) normally is associated with an increase in urinary sodium excretion. Several mechanisms have been proposed to explain this natriuretic response, such as a direct effect of the vasodilator on tubular sodium reabsorption (Parmalee and Carter, 1968; Stein et al., 1972), hemodynamic changes in the Starling forces operating at the postglomerular capillary level (Earley and Friedler, 1966), changes in the intrarenal interstitial pressure (Marchand et al., 1977), or an increase in the medullary blood flow which dissipates the medullary hypertonicity (Earley and Friedler, 1965, 1966).

In contrast with other vasodilators, intrarenal administration of secretin produces a dose-related increase in renal blood flow without a significant rise in urinary sodium excretion (Marchand et al., 1972). A recent study by Marchand et al. (1977) showed that the intrarenal infusion of secretin in the dog was associated with a significant increase in the peritubular capillary hydrostatic pressure and an unchanged interstitial pressure. On the other
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