Effects of Dopamine and Isoproterenol on Renin Secretion in the Dog (36394)

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Renin release is mediated by such diverse stimuli as changes in vascular volume and sodium balance, upright posture, stimulation of renal nerves, and infusion of catecholamines. However, the exact mechanisms by which renin secretion is enhanced by these stimuli are not well understood. Winer *et al.* (1) found that renin release provoked by upright posture, and infusion of diazoxide, theophylline and ethacrynic acid could be blocked by infusion of phentolamine or propranolol. The authors suggested that renin release was possibly mediated by adrenergic receptors.

To test this hypothesis further, we studied the effects of dopamine, a naturally occurring catecholamine and a precursor of norepinephrine, and isoproterenol, a potent beta-adrenergic agonist, on renin secretion before and after beta-adrenergic blockade induced by propranolol.

Materials and Methods. Eight adult mongrel dogs (weighing 20–25 kg) were anesthetized with intravenous sodium pentobarbital (30 mg/kg) and were maintained on artificial respiration. Additional small maintenance doses of the anesthetic were administered when necessary. Aortic blood pressure was measured through a catheter connected to a Statham transducer (type P23 DB). The kidney was exposed through a subcostal incision, care was taken in handling the organ as little as possible. The renal nerves were left intact. A curved 23 gauge needle was placed in the renal artery for the infusion of drugs or 5% dextrose in water. A 19 gauge needle was placed in the renal vein, secured in place by purse string sutures for obtaining blood samples for renin assay using the method of Gunnells *et al.* (2). The renal venous catheter was kept patent by a slow infusion of 5% dextrose in water except during the collection of specimens.

Renal blood flow was measured by an electromagnetic flowmeter (Statham blood flowmeter, model SP220). The flowmeter was calibrated against known blood flow.

Drug infusion was begun 2 hr or more after surgery. The rates of infusion of the drugs were as follows: dopamine, 3 μg/kg/min; isoproterenol, 0.15 μg/kg/min; and propranolol, 0.5 μg/kg/min. After base line control values were obtained, dopamine or isoproterenol dissolved in 5% dextrose in water was infused in random order at a constant rate (1 ml/min) by a Harvard infusion pump, over a 15 min period. Each period of drug infusion was preceded and followed by a 30 min control period. At the end of each infusion period, blood pressure, renal blood flow and renin activity were measured. Dopamine and isoproterenol infusion were repeated after a 15 min infusion of propranolol, again in random order. Results are expressed in arithmetic mean ± standard deviation. Statistical significance was determined by Student's paired *t* test.

Results. Control mean blood pressure was 135 ± 15 mm Hg and remained essentially unchanged throughout the experiments. At the infusion rate used, neither dopamine nor isoproterenol produced any consistent or significant alteration in the blood pressure, either before or after propranolol. Table I summarizes the results obtained in the present

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TABLE I. Effects of Dopamine and Isoproterenol on Renal Blood Flow and Renin Activity in the Renal Venous Blood Before and After Propranolol.[a]

	Before propranolol		After propranolol	
	Renal blood flow (ml/min)	Renin activity (ng/100 ml)	Renal blood flow (ml/min)	Renin activity (ng/100 ml)
Control	202 ± 28	470 ± 130	201 ± 21	500 ± 145
Dopamine 3 μg/kg/min	232 ± 32 ($p < .01$)	333 ± 115 (NS)	228 ± 39 ($p < .05$)	461 ± 93 (NS)
Isoproterenol 0.15 μg/kg/min	214 ± 39 ($p < .05$)	1192 ± 395 ($p < .01$)	201 ± 20 (NS)	702 ± 258 (NS)

[a] The values are mean ± standard deviation. p values calculated from paired t tests are shown in parentheses. NS = statistically nonsignificant.

study.

Dopamine produced a decrease in mean renal vein renin from 470 ± 130 to 333 ± 115 ng/100 ml ($p > .05$), and an increase in renal blood flow from 202 ± 28 to 232 ± 32 ml/min ($p < .01$). After propranolol, dopamine also caused a decrease in renal vein renin from 500 ± 145 to 461 ± 93 ng/ml ($p > .05$), and an increase in renal blood flow from 201 ± 21 to 228 ± 39 ml/min ($p < .05$). Thus, beta blockade did not alter the action of dopamine on renal blood flow and renin secretion.

Isoproterenol infusion caused a significant increase in renal vein renin from 470 ± 130 to 1192 ± 395 ng/100 ml ($p < .01$), and an increase in renal blood flow from 202 ± 28 to 214 ± 39 ($p < .05$). When isoproterenol was infused after propranolol, renal vein renin increased from 500 ± 145 to 702 ± 258 ng/100 ml ($p > .05$); while renal blood flow remained unchanged. This shows that the effect on renin and renal blood flow produced by isoproterenol could be effectively blocked by propranolol.

Blood pressure, renal blood flow and renal venous blood renin remained essentially unchanged in all control periods.

Discussion. In the review articles on renin secretion, Vander (3) and also recently Davis (4) have summarized evidence for renin release affected by renal vascular receptor, macula densa receptor, renal sympathetic nerves and humoral agents as catecholamines. Stimulation of renal nerves, or activation of adrenergic receptors by endogenously released and exogenously administered catecholamines causes increases in renin secretion by kidney has been shown *in vitro* [Michelakis, Caudle, and Liddle (5)] and *in vivo* (1, 6 and 7).

The present study confirmed the findings of the previously mentioned investigators that isoproterenol significantly increased renin secretion. This increase in renin could be associated with either a decreased, unchanged or elevated blood pressure suggesting that a change in blood pressure *per se* is not an important factor in controlling renin secretion (7).

Though catecholamines have been known to be strong stimulants of renin release, the present study failed to demonstrate the catecholamine-stimulating effect of dopamine, a naturally occurring catecholamine and the immediate precursor of norepinephrine. Since both isoproterenol and dopamine caused renal vasodilation in our experiments, but only isoproterenol stimulated renin release by the kidney, the isoproterenol-induced renin secretion must be mediated by factors other than changes in renal blood flow. This study is therefore consistent with what has been reported by Ueda *et al.* (7) and Nash *et al.* (8) that no definite correlation exists between renin release and blood pressure, renal blood flow, sodium or water balance. If renin secretion were mediated by adrenergic receptors as proposed by some investigators, then dopamine which has both the alpha- and the

beta-adrenergic activities, would have caused an increase rather than a decrease in renal vein renin, unless the direct dopaminergic effect greatly prevails over both the alpha- and the beta-adrenergic effects of dopamine. Also, the renin secretion induced by isoproterenol, a pure beta agonist, would be blocked only by a beta blocker. However, it has been shown that phentolamine, an alpha blocker, was as potent as propranolol in blocking the stimulation of renin secretion by isoproterenol and that propranolol was effective in blocking methoxamine-induced secretion of renin (9). These nonspecific pharmacologic blockades of the effect of isoproterenol and methoxamine on renin secretion illustrate the difficulties involved in defining renin secretion in terms of specific alpha- or beta-adrenergic receptors. Furthermore, though Michelakis, Caudle, and Liddle (5) suggested that the renin-stimulating effect of catecholamines might be mediated through cyclic AMP, dissociation of the increased formation of cyclic AMP from the adrenergic effects has been reported by Shanfeld *et al.* (10). Thus the hypothesis of "adrenergic" mechanism in mediating the renin secretion cannot be explained on adrenergic receptor theory presently known.

While Winer, Chokshi, and Walkenhorst (9) have shown that propranolol effectively blocked catecholamine induced renin secretion, they provided no information as to the effects of beta blockade on base line renin levels. Our data indicate that, at the dose given, propranolol alone had no effect on renin secretion. This could indicate that there was very little beta-adrenergic vasodilating activity in the kidney studied. In other words, adrenergic vasodilation is not a dominant factor in determining the basal renal flow.

It has been shown that dopamine increases renal blood flow and the glomerular filtration rate in dogs [McNay, McDonald, and Goldberg (11)] and in man (12, 13) by causing a direct vasodilation. Our findings of dopamine on renal hemodynamics are similar to those reported by the above investigators. Yeh, McNay, and Goldberg demonstrated previously that haloperidol selectively attenuated renal and mesenteric vasodilation produced by dopamine thus providing additional evidence for the existence of a specific vascular receptor for dopamine in the renal and mesenteric beds (14). As the renal vasodilator effect does not seem to be responsible for the difference in renin secretion during dopamine and isoproterenol infusion, it might be possible that dopamine has a direct effect on renin secretion independent of its vascular effect. However, if this were true, the exact mechanism of dopamine effect on renin secretion is not understood at present.

Ayers, Harris, and Lefer (15) reported that dopamine caused a significant elevation in blood pressure and renin secretion in their dogs with chronic renovascular hypertension. The present study indicates that dopamine has no effect on the blood pressure of normotensive dogs and causes a slight decrease rather than an increase in renin secretion. This difference in the response of blood pressure and renin secretion to dopamine between normotensive and hypertensive animals merits further elucidation.

The unique actions of dopamine on renal blood flow and renin secretion are demonstrated in this study. The fact that the secretion of renin by the kidney can be independent from changes in renal blood flow or total renal resistance was also confirmed once more.

Summary. The effects of intra-arterial infusion of dopamine (3 μg/kg/min) and isoproterenol (0.15 μg/kg/min) on renal blood flow (RBF) and renal venous plasma renin activity (RVR) were studied in eight anesthetized dogs, before and after propranolol. Dopamine caused an increase in RBF from 201 $\pm$ 21 to 238 $\pm$ 39 ml/min ($p < .01$); and a decrease in RVR from 470 $\pm$ 130 to 333 $\pm$ 115 ng/100 ml ($p > .05$). Isoproterenol increased RBF from 202 $\pm$ 28 to 214 $\pm$ 39 ml/min ($p < .05$) and augmented RVR from 470 $\pm$ 130 to 1192 $\pm$ 395 ng/100 ml ($p < .01$). Propranolol did not alter the effects of dopamine on RBF and RVR, but effectively blocked the isoproterenol-induced vasodilation and renin secretion.

This demonstrates the unique action of dopamine on renin secretion. The presently

available evidence suggests that there probably are no specific adrenergic receptors directly mediating renin secretion by the kidney.

1. Winer, N., Chokshi, D. S., Yoon, M. S., and Freedman, A. D., J. Clin. Endocrinol. **29**, 1168 (1969).

2. Gunnels, J. C., Grim, C. E., Robinson, R. R., and Wildermann, N. M., Arch. Intern. Med. **119**, 232 (1967).

3. Vander, A. J., Physiol. Rev. **47**, 359 (1967).

4. Davis, O. J., Circ. Res. **28**, 301 (1971).

5. Michelakis, A. M., Caudle, J., and Liddle, G. W., Proc. Soc. Exp. Biol. Med. **130**, 748 (1969).

6. Bunag, R. D., Page, I. H., and McCubbin, J. W., Circ. Res. **19**, 851 (1966).

7. Ueda, H., Yasuda, H., Takabatake, Y., Iizuka, M., Iizuka, T., Ihori, M., and Sakamoto, Y., Circ. Res. **26 & 27**, Suppl. 2, 195 (1970).

8. Nash, F. D., Rostorfer, H. H., Bailie, M. D., Wathen, R. L., and Schneider, E. G., Circ. Res. **22**, 473 (1968).

9. Winer, N., Chokshi, D. S., and Walkenhorst, W. G., J. Lab. Clin. Med. **74**, 1024 (1969).

10. Shanfeld, J., Frazer, A., and Hess, M. E., J. Pharmacol. Exp. Ther. **169**, 315 (1969).

11. McNay, J. L., McDonald, R. H., and Goldberg, L. I., Circ. Res. **16**, 510 (1965).

12. Horwitz, D., Fox, S. M., and Goldberg, L. I., Circ. Res. **10**, 237 (1962).

13. McDonald, R. H., Jr., Goldberg, L. I., McNay, J. L., and Tuttle, E. P., Jr., J. Clin. Invest. **43**, 1116 (1964).

14. Yeh, B. K., McNay, J. L., and Goldberg, L. I., J. Pharmacol. Exp. Ther. **168**, 303 (1969).

15. Ayers, C. R., Harris, R. H., and Lefer, L. G., Circ. Res. **24 & 25**, suppl. 1, 103 (1969).

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