Effects of various sympathicomimetic drugs on renal hemodynamics in normotensive and hypotensive dogs

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Mills, Lewis C., John H. Moyer and Carrol A. Handley. Effects of various sympathicomimetic drugs on renal hemodynamics in normotensive and hypotensive dogs. Am. J. Physiol. 198(6): 1279-1283. 1960.—The effects of L-epinephrine, L-norepinephrine, phenylephrine, methoxamine, metaraminol and mephentermine on renal hemodynamics were studied in six groups of dogs. Although comparable rises in blood pressure were obtained, there were marked differences in the effects on renal hemodynamics. While infusion of mephentermine led to only slight reductions in glomerular filtration rate and renal blood flow, and only a slight increase in renal vascular resistance, methoxamine produced a marked fall in flow and a marked increase in resistance. The other agents tested had effects which were intermediate between these two. The effects of these same drugs on renal hemodynamics were also compared in dogs made hypotensive by bleeding. While blood pressure increased significantly in all groups, glomerular filtration rate and renal blood flow increased significantly only during infusion of methoxamine, metaraminol and phenylephrine. Since assays relative to the inherent vasodilator properties of these agents revealed epinephrine to be the only agent with marked activity, it seems unlikely that the observed effects were due to this factor. It is concluded that the observed changes were due to a greater reactivity of renal vascular vasoconstrictor adrenergic receptors with certain sympathicomimetic drugs than those of the vasculature in general.

Previous experimental work by Ahlquist (1) has shown not only differences in response of a given vascular bed to a series of sympathicomimetic drugs, but also differences in response of various vascular beds to the same sympathicomimetic agent. For example in the renal vascular bed of dogs, epinephrine produced a marked vasoconstrictor effect, norepinephrine a moderate vasoconstrictor effect, and isopropylarterenol a slight vasodilator effect. However, in the femoral vascular bed the vasoconstrictor effects of epinephrine and norepinephrine were approximately of the same magnitude, and isopropylarterenol produced a marked vasodilator effect. Ahlquist postulated that there were separate vasoconstrictor and vasodilator receptors in the blood vessels, that the ratio of the two types of receptors varied from one vascular bed to another, and that there were differences in the ability of the amines tested to react with one or both types of receptors. Therefore, in the renal vascular bed in which vasodilator receptors were thought to be few in proportion to vasoconstrictor receptors, epinephrine produced the most marked vasoconstrictor effect and isopropylarterenol only a slight vasodilator effect.

In the femoral bed where there were greater numbers of vasodilator receptors, the vasoconstrictor effect of epinephrine was diminished by its own vasodilator action, that of norepinephrine only slightly diminished since it reacts very little with vasodilator receptors, and that of isopropylarterenol potentiated since it reacts chiefly with vasodilator receptors.

Since the above article was published, several new sympathicomimetic agents have been synthesized. The present experiments were designed to extend the above observations in regard to renal vascular hemodynamic responses to such drugs.

METHODS

Two types of experiments were made. In the first sympathicomimetic amines were given to normotensive dogs, and in the second to hypotensive dogs. In each, six groups of normal female dogs weighing 10–20 kg were studied. All groups were anesthetized with sodium pentobarbital, 25 mg/kg of body weight, following which an infusion of 250 ml of 5% glucose in water was given over a 45-minute period. The dogs were then given a priming dose of creatinine (25 mg/kg) and
$p$-aminohippuric acid (PAH) (5 mg/kg), and an intravenous infusion of normal saline containing these substances (creatinine—4.0 gm/l. and PAH—1.0 gm/l.) was given at the rate of 0.25 ml/kg/min. A Foley catheter was inserted into the urinary bladder for collection of urine specimens, and a small polyethylene catheter was placed in one femoral artery for collection of arterial blood samples and determination of mean blood pressure with a mercury manometer. Urinary and plasma sodium and potassium were determined with a Beckman flame photometer. Other chemical methods and techniques employed have been previously described (2).

Forty-five minutes after the infusion of creatinine and PAH had been started, three to four successive 10-minute control periods were done for determination of glomerular filtration rate (GFR) (creatinine clearance), renal plasma flow (RPF) (PAH clearance), and urinary and plasma sodium and potassium. In the experiments in normotensive animals an infusion of normal saline containing the sympathicomimetic drug to be studied was started intravenously immediately following the control periods. For these purposes no attempt was made to give the same amount of the drug to each dog, but rather to give sufficient drug to elevate the blood pressure to the same level in each dog. Initially an attempt was made to raise the mean blood pressure to a level of 30% above the control.

As soon as the blood pressure had stabilized, renal clearances were again measured during two to six consecutive 10-minute periods. In most instances the rate of the infusion was then increased to obtain a further rise in blood pressure (approximately 60% above control levels) and clearances were again determined.

From 11 to 23 dogs were studied in each of six drug groups. In analyzing the data, the average of at least two consecutive clearance determinations at a given blood pressure level was used as the value for that drug period. When more than three clearance determinations were obtained at a given blood pressure level,
Phentermine (Wyamine)—40 mg/l.; metaraminol (Aramine)—50 mg/l.; L-norepinephrine (Levophed)—normal saline were as follows: L-epinephrine—normal saline were as follows: L-epinephrine—

After the blood pressure had been elevated and stabilized at the control level, glomerular filtration rate and renal plasma flow were measured again. There were animals were bled after three to four consecutive . For key to abbreviations, see tables 1 and 2.

The following amounts of each agent were given: L-epinephrine—0.5 mg; L-norepinephrine—0.5 mg; phenylephrine—0.5 mg; methoxamine—1.0 mg; metaraminol—1.0 mg; mephentermine—1.0 mg. These concentrations were selected in order to obtain equivalent blood pressure responses during the drug periods, without having extremely large differences in the amount of extra fluid infused during these periods. The structural formulas of these drugs are shown in figure 1.

Additional experiments were also done to determine which, if any, of these agents besides epinephrine possessed significant vasodilator activity. Seven dogs were anesthetized with sodium pentobarbital, and an indwelling femoral artery catheter connected to a mercury manometer was used for blood pressure measurements. Following a suitable control period (usually 20 min.), phenoxybenzamine, 2 mg/kg, was injected intravenously, and after the blood pressure had again stabilized, the agent to be tested was given as a single intravenous injection.

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Results

The effects of these agents on blood pressure and renal hemodynamics in the experiments in normotensive animals are summarized in Table 1. In the 'A' group in which there was less than 40% rise in mean blood pressure, the mean percentage rise of pressure for each drug was comparable; however, in spite of this, there were marked differences in the effects on renal hemodynamics. During infusion of mephentermine, there was no significant change in glomerular filtration rate or renal blood flow (RBF); renal vascular resistance (RVR), urine volume and urine potassium increased. Infusion of metaraminol on the other hand produced a marked reduction in GFR and RBF, a marked increase in RVR, and a moderate depression of urine volume and sodium and potassium excretion. The other agents tested were intermediate in effect between mephentermine and methoxamine.

In the 'B' groups in which blood pressure increased 40% or more, the same relative effects were obtained in that there was no significant change in GFR and RBF during mephentermine administration, a marked reduction with metaraminol and the other agents again had intermediate effects. However, with the exception of the dogs receiving mephentermine, there was a greater reduction in GFR and RBF, and a larger increase in RVR in group B than in group A. Owing to the extreme reduction in blood flow (possibly in part due to a decrease in renal tubular extraction of PAH) in many of the dogs receiving metaraminol absolute values for renal vascular resistance could not be calculated accurately by the method used; however, there is no question as to the marked degree of preferential renal vasoconstriction which occurred in these animals.

In addition, it should be noted that although the dogs receiving metaraminol had the most marked absolute increase in mean blood pressure as well as the highest actual mean blood pressure during infusion of the drug, these animals had the least reduction, with the exception of the mephentermine group, in GFR and RBF. This was considered to exclude definitely the possibility that the large differences in renal hemodynamic responses observed were due to the slight differences in blood pressure responses obtained.

Because of the greater decrease in RBF than in GFR, the filtration fraction increased in all groups. This indicates a relatively greater increase in efferent arteriolar resistance than in afferent arteriolar resistance. The hematocrit increased significantly in all but the group A methoxamine animals, but more in response to metaraminol and phenylephrine than to the other drugs. Urine flow increased in those animals receiving mephentermine (235 and 337% of control values in the A and B groups, respectively), but declined in those given methoxamine (44 and 18%). Urinary sodium excretion generally paralleled the change in urine volume increasing to 40% in the A group and 64% in the B group during administration of methoxamine and decreasing to 34 and 21% in response to methoxamine. Urinary potassium increased slightly in the mephentermine groups (130 and 125%, respectively) and decreased to 52 and 20% in the methoxamine groups. The other drugs had intermediate effects on urine flow and sodium and potassium excretion; these changes in general paralleled those in GFR. There was no significant alteration in plasma sodium concentration. Plasma potassium concentrations increased significantly during phenylephrine and methoxamine administration.

The effects of each drug on blood pressure and renal hemodynamics during control, posthemorrhage, and drug periods are summarized in Table 2. The amount of hemorrhage, and the fall in blood pressure in the post-hemorrhage periods were comparable for each group. Concurrently there was a marked and highly significant fall in GFR and RBF. With administration of the sympathicomimetic drug, there was a highly significant rise in blood pressure, and with the exception of the group receiving mephentermine, blood pressure was approximately at control levels. Mephentermine was less potent under these circumstances and with the concentration used (300 mg/l.) it was not usually possible to attain control levels. During the drug periods, GFR and RBF increased significantly when mephentermine, metaraminol and phenylephrine were given, but not during administration of norepinephrine, epinephrine or methoxamine (Table 2). Renal vascular resistance was calculated by the formula RVR = MBP/RBF. In the case of the former three drugs, RVR which had increased as a result of hemorrhage decreased with administration of the vasopressor agent. In contrast administration of norepinephrine, epinephrine and methoxamine led to a further rise in renal vascular resistance.

As anticipated, urine flow diminished after hemorrhage. Significant increases of urine flow occurred only when GFR increased (Table 3). Urine sodium and...
potassium were also measured. Changes in their excretion paralleled those in urine volume, although there was less tendency for the sodium to increase and more tendency for the potassium to increase during the drug periods.

In the experiments designed to test for vasodilator activity of these agents only epinephrine and isopropylnoradrenaline had marked activity (fig. 2). Injection of metaraminol, methoxamine and norepinephrine led to a slight initial rise in blood pressure followed by a slight fall below control levels, suggesting that there may have been slight vasodilator activity. Methoxamine and phencyclamine had no vasodilator effect. Since a slight rise was observed with some of the agents suggesting that adrenergic blockade might not have been complete, metaraminol, methoxamine and epinephrine were injected into dogs pretreated with phenoxybenzamine, 5 mg/kg in doses of 0.1 mg, 0.5 mg, and 5 mg at 20-minute intervals. Under these conditions epinephrine produced a marked vasodilator response, methoxamine had no effect, and metaraminol produced a slight rise followed by a minimal depression in blood pressure.

**DISCUSSION**

The results of these studies, which show marked differences in renal hemodynamic responses to the sympathicomimetic agents tested, suggest that there is a definite selectivity of certain of these drugs for renal vasoconstrictor adrenergic receptors as compared to those of the general vasculature. Although measurements of renal extraction of PAH were not made in the hypertensive animals, it seems unlikely that calculated changes in renal plasma flow are due to decreased extraction alone, since the drugs had the same relative effects on renal hemodynamics in both the normotensive and hypertensive animals, and since GFR, which would not be affected by this mechanism, paralleled the changes in RPF. It is unlikely that these changes are due to variations in the ability of the drugs to stimulate vasodilator adrenergic receptors, or due to differences in the number of such receptors from one vascular system to another. If, indeed, this was a significant factor one would expect epinephrine which has marked ability to stimulate vasodilator receptors to produce more renal vasoconstriction than any other drug studied since, to obtain the same rise in systemic blood pressure, more vasoconstriction would have to occur in vascular beds having few vasodilator receptors (such as the renal vascular bed) in order to compensate for the vasodilator effect in other areas. In addition, none of the other agents studied had significant vasodilator properties.

In the interpretation of the results the possible effects of these drugs on cardiac output and blood viscosity must also be taken into consideration. If a given drug produced a fall in cardiac output, significantly more vasoconstriction might be required by such a drug to produce an identical rise in blood pressure as compared to drugs such as epinephrine which causes a rise in cardiac output (3) or metaraminol which produces no change in cardiac output (4). Although there were undoubtedly some changes in cardiac output, it is again unlikely that this factor is responsible for the large differences observed.

In addition, if one uses the change in hematocrit as an index to possible changes in blood viscosity, there is not enough difference between one group to another to account for the effects on renal hemodynamics.

Therefore, although it is likely that some of the observed changes were due to differing effects on cardiac output and blood viscosity, or due to differences in vasodilator properties (excluding epinephrine), it would seem that the major differences in effect were due to a difference in reactivity of renal vasoconstrictor adrenergic receptors as compared to those of the general vasculature.

Similar studies in normotensive human subjects (5), in which infusions of metaraminol, norepinephrine and methoxamine were given, have shown identical qualitative results, but it would seem that the human renal vasculature is relatively less sensitive. The human data serve as a further confirmation of changes observed here.

The drugs used in this study were supplied by courtesy of the following companies: methoxamine, Burroughs Wellcome & Co., Inc.; metaraminol, Merck Sharp & Dohme, Inc.; norepinephrine, Winthrop Laboratories, Inc.; methylergometrine, Wyeth Laboratories, Inc.

**REFERENCES**