We have recently demonstrated that intravenous administration of the naturally occurring catecholamine, dopamine, increases effective renal plasma flow, glomerular filtration rate, and sodium excretion in normal human subjects. Since renal plasma flow increased in the absence of an alteration in mean arterial pressure, it was concluded that renal vascular resistance was decreased by dopamine. Comparable effects were observed in the dog.

The present study was undertaken to characterize these findings more fully. The effects of intravenous dopamine infusion on directly measured renal blood flow and blood pressure were compared with those of isoproterenol and norepinephrine, chosen as catecholamines with strong vasodilator and vasoconstrictor effects, respectively. In addition, renal blood flow responses to direct renal arterial injections of these three agents were studied. To determine whether the renal vascular responses to dopamine were typical of other vascular beds, comparable experiments studying femoral blood flow responses to intrarterial injections of dopamine, isoproterenol, and norepinephrine were also performed. We found that dopamine is unique among vasoactive agents, since it produces renal vasodilatation and femoral vasoconstriction.

Methods

Mongrel dogs ranging in weight from 11 to 20 kg were anesthetized by the intravenous injection of either pentobarbital, 25 mg/kg, or a combination of pentobarbital, 15 mg/kg, and barbital, 220 mg/kg. Supplemental maintenance doses were administered as needed.

Blood flow in the left femoral or left renal artery was measured continuously by means of an electromagnetic flowmeter. The kidney itself was not manipulated, and adjacent structures were disturbed minimally. Renal nerves were left intact except in four experiments in which all visible nerve structures entering the kidney were divided prior to drug administration. In experiments in which femoral artery blood flow was studied, the hind limb was acutely denervated by the division of the femoral and sciatic nerves, and circulation through the paw was occluded using a crushing device applied at the level of the lower tibia. The zero-flow baseline and phase adjustments of the flowmeter were performed immediately after application of the flow probe and at intervals throughout each experiment by mechanical occlusion of the artery distal to the flow probe. Two or three separate calibrations of each flow probe were performed during the series of experiments, using timed collections of blood over a wide range of flow rates. Reproducible linear responses were obtained with each probe. Pressure in the contralateral femoral artery was measured using a Statham P23D pressure transducer. In all studies in which drugs were administered intravenously,
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FIGURE 1

Effects of intra-arterial injections of dopamine on left renal blood flow and femoral blood pressure (expt. no. 12, table 2). Upper tracing is a continuous record of mean left renal blood flow. Lower tracing is a record of femoral arterial pressure interrupted at six-second intervals to show the six-second integrated mean. Arrows and numerals indicate injections of dopamine and doses in μg.

Mean arterial pressure was determined at six-second intervals by an on-line analogue computer.* Blood flows and blood pressures were simultaneously recorded by a Grass polygraph, the pens of which had been carefully aligned to produce synchronous recordings.

INTRANASAL DRUG ADMINISTRATION

The effects of both intravenous (iv) dopamine and iv isoproterenol infusion were studied in twelve animals. The effects of iv norepinephrine infusion were studied in six of these. The rate of drug infusion was regulated by a Harvard 600-900 pump. Isoproterenol and norepinephrine were administered at rates producing a 10 to 20 mm Hg depressor or pressor effect, respectively. The highest dose of dopamine which could be administered without an elevation of blood pressure was used. The average rate of infusion of each drug is indicated in table 1.

INTRA-ARTERIAL DRUG ADMINISTRATION

Drugs were injected in a 0.2 cc volume of 0.85% saline solution, via a 23-gauge needle inserted into the artery proximal to the flow probe. Patency of the needle was maintained by a slow infusion of 0.85% saline solution. The effects of intra-arterial (ia) dopamine injection were studied in 20 renal blood flow experiments and 14 femoral blood flow experiments. The effects of ia isoproterenol and norepinephrine injections were studied in approximately one-half of these experiments. ia drug doses ranged from 0.025 to 192 μg. In cases where recirculation of the ia drug injections affected blood pressure, only those effects which preceded the blood pressure changes were considered in the analysis of the results.

In order that the potency of dopamine as a vasoactive agent might be compared to that of isoproterenol and norepinephrine, the data were analyzed as follows. Blood flow responses were plotted against drug doses expressed on a logarithmic scale. Dose response curves were constructed by eye. The dose of isoproterenol causing 50% maximal increase in flow was compared with the dose of dopamine causing an equal increase in flow, because difficulty in determining the maximal vasodilator effect of dopamine precluded determination of the ED₅₀ for dopamine in about 50% of the experiments. The vasoconstrictor potencies of norepinephrine and of dopamine were compared by determination of the doses of each drug required to decrease control organ blood flow by 50%.

When renal vascular resistance was calculated, the peripheral resistance unit (PRU), defined as the ratio, arterial blood pressure (mm Hg)/renal blood flow (cc/min), was used. Results were analyzed statistically by means of the paired t test. Except where stated otherwise, a P value of < 0.01 was considered significant. The arithmetic mean ± standard error (SE) was used to express all results except intra-arterial drug doses, which were expressed by the geometric mean and 95% confidence limits.

The drugs used were: dopamine hydrochloride (3-hydroxytyramine hydrochloride, California Corporation for Biochemical Research, Los Angeles); norepinephrine bitartrate (Levophed, Winthrop Laboratories, New York); and dl isoproterenol hydrochloride (Isuprel, Winthrop Laboratories, New York). Doses are expressed in terms of the respective bases. The base line status of the renal circulation may be assessed from the renal blood flow per minute per gram of renal weight. In our studies flow averaged > 4 cc/g renal weight/min, a value within the published normal ranges.

*Designed and constructed by the Georgia Institute of Technology Engineering Experiment Station.

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<table>
<thead>
<tr>
<th></th>
<th>Left RBF†</th>
<th>Mean blood pressure</th>
<th>Renal resistance§</th>
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<td></td>
<td>control</td>
<td>infusion</td>
<td>control</td>
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<tr>
<td>Dopamine</td>
<td>cc/min</td>
<td>cc/min</td>
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<td>control period ± se</td>
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<td>*P</td>
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<td>*P</td>
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<td>*P</td>
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<td>12 ± 2.8</td>
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*Average drug infusion rates as follows: dopamine, 7.5 μg/kg/min; isoproterenol, 0.31 μg/kg/min; norepinephrine, 0.46 μg/kg/min.
†Average control RBF: 4.2 cc/min per g renal weight.
‡RBF: renal blood flow.
§ruw: mean blood pressure, mm Hg/renal blood flow, cc per min.
**N.S.: not significant.
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Results

EFFECTS OF INTRAVENOUS INFUSIONS OF DOPAMINE, NOREPINEPHRINE, AND ISOPROTERENOL ON RENAL HEMODYNAMICS (TABLE 1)

Dopamine infused at an average rate of 7.5 µg/kg/min caused an average increase in renal blood flow of 69 cc/min, with no significant effect on blood pressure. Renal vascular resistance decreased 30% during dopamine infusion. The infusion of isoproterenol at an average rate of 0.31 µg/kg/min produced no effect on average renal blood flow, but did decrease mean blood pressure and renal vascular resistance. It was observed that animals which could tolerate isoproterenol infusion at a rate of 0.5 µg/kg/min with a blood pressure fall not exceeding 20 mm Hg were much more likely to show an increase of renal blood flow than were animals which had a 20 mm or greater depressor response to lower doses of isoproterenol. Norepinephrine caused a decrease of renal blood flow and an increase of blood pressure and renal vascular resistance. The four animals in which renal denervation was performed seemed to respond to isoproterenol and dopamine infusions in the same manner as did the animals in which the renal nerves were left intact.

FIGURE 2

Relationship between intra-arterial doses of dopamine and changes of renal blood flow based on data from table 2. Dots and vertical lines indicate mean ± standard error. Heavy lines indicate the initial flow response, which was vasodilatation up to a dose of 6 µg and vasoconstriction at higher doses. The dashed line indicates secondary vasodilator responses.

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EFFECTS OF INTRA-ARTERIAL INJECTION OR INFUSION OF DOPAMINE, NOREPINEPHRINE AND ISOPROTERENOL ON RENAL OR FEMORAL BLOOD FLOW

The renal blood flow and systemic blood pressure responses to successive doses of dopamine injected into the renal artery are illustrated in figure 1. Table 2 presents pertinent data from 20 such experiments. Figure 2 presents in graphic form the data from table 2. The opposing renal vascular effects of dopamine are evident, as is the potency relationship between them. Flow changes can be separated into three general types, each one characteristic of a portion of the dose range of dopamine. In doses up to 6 µg, dopamine caused a dose-related increase of blood flow which was observed in each experiment. At a dose of 12 µg, there was seen in 45% of the experiments a transient initial vasoconstriction which averaged 5 ± 1% and which was 13% or less in all animals except one. At this dose the predominant effect was vasodilatation as judged by both the amplitude and duration of vasodilatation relative to vasoconstriction. As the dose of dopamine was increased above 12 µg, the relative amplitude and duration of vasoconstriction increased, frequently becoming the predominant effect in the dose range of 96 to 192 µg (table 2).

The degree of vasoconstriction produced by dopamine was variable, being completely absent at a dose of 24 µg in experiments no. 5 and 9, and at a dose of 48 µg in experiment no. 3.

Intra-arterial infusions of dopamine resulted in prompt increases of renal blood flow which were maintained for the duration of the infusion. The mean increase in blood flow was 25% at an infusion rate of 0.6 µg/kg/min, and 38% at 1.2 µg/kg/min. No evidence of vasoconstrictor effects was noted at these doses, and no changes of systemic blood pressure were seen.

The intra-arterial injection of norepinephrine invariably produced a decrease in renal blood flow. The geometric mean dose of norepinephrine producing a 50% decrease in renal blood flow was 1 µg, confidence interval 0.8 to 1.25 µg. The geometric mean of the ratio of the dopamine dose producing a 50%
<table>
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<th>Expt. no.</th>
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<th>Dopamine μg</th>
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<th>Mean†</th>
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<tr>
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<td>192</td>
<td>+</td>
<td>28/3</td>
<td>20/18</td>
</tr>
</tbody>
</table>

+ RBF: renal blood flow.

†Biphasic effects were frequently produced by doses of 6 μg or greater. At these doses, flow responses are presented in two columns separated by the sign (/). Increases in flow (+) are to the left of the (/), and decreases in flow (−) to the right.

‡ The P value is less than 0.01, except the value identified by §.
Effects of intra-arterial injections of dopamine on femoral arterial blood flow and blood pressure. Upper tracing is a continuous record of mean femoral arterial blood flow. Lower tracing is blood pressure recorded from the contralateral femoral artery. Arrows and numerals indicate injections of dopamine and doses in µg.

Figure 3

Discussion

The present study confirms by direct measurements in dogs our earlier findings using indirect methods\textsuperscript{1,2} that dopamine infusions increase renal blood flow by decreasing renal vascular resistance. Dopamine is thus quite different from other vasoactive amines. The inability of intravenous isoproterenol to increase renal blood flow consistently despite a decrease in renal vascular resistance is due to the associated depression of blood pressure. The finding that dopamine may be administered without producing a depressor effect of a magnitude similar to that of isoproterenol is probably related to the vasoconstriction which it causes by a direct action on muscular and cutaneous vascular beds.

Since it is known that dopamine exerts numerous cardiovascular effects, including a direct positive cardiac inotropic action and an indirect nerve-mediated decrease in hind limb vascular resistance,\textsuperscript{3} it was important to de-
termine whether dopamine increased renal blood flow by a direct renal effect. This question was settled by intra-arterial dopamine injections. The increases in renal blood flow following renal arterial injection of dopamine occurred too rapidly to be secondary to a systemic mode of action. They also followed doses of dopamine too small to have a systemic effect. The similarity in magnitude of the increments in renal blood flow produced by intravenous and intra-arterial dopamine infusion indicate that the direct renal vascular effects of dopamine are sufficient to account for the observed effects of intravenous infusion.

The effects of isoproterenol and norepinephrine on the femoral vascular bed were typical of their previously well-documented properties and confirmed the ability of the vascular bed in the preparation under study to respond to both vasoconstrictor and vasodilator drugs. Dopamine resembled norepinephrine qualitatively and produced only vasoconstriction. This finding is consistent with previous observations made on the innervated perfused canine hind limb. Subsequent studies have indicated that the vasoconstrictor effects of dopamine probably involve mechanisms similar to those of norepinephrine in that they may be totally blocked by the alpha-adrenergic blocking agent, phenoxybenzamine.

The combination of renal vasodilatation and femoral vasoconstriction which is produced by dopamine is interesting because it is not produced by other renal vasodilators, such as acetylcholine, histamine, bradykinin, papaverine, and the nitrates, agents which cause direct inhibition of vasomotor tone in both the limb and the kidney. It is possible to draw conclusions concerning the type of receptor with which dopamine interacts by comparing its vascular effects with those of other adrenergic agents. Isoproterenol, a sympathomimetic amine with beta-adrenergic vasodilating activity, produces both renal and skeletal muscle vasodilatation. Epinephrine has both beta-adrenergic (vasodilating) and alpha-adrenergic (vasoconstricting) activity. Small doses of this amine may produce vasodilatation of skeletal muscle, but produce only vasoconstriction of the kidney. It is reasonable to conclude that an agent which is capable of increasing renal blood flow by a beta-adrenergic mechanism will also be expected to increase limb blood flow, but that the reverse is not necessarily the case. Since dopamine could not be shown to produce vasodilatation in the limb, it is therefore unlikely that it produced renal vasodilatation by a beta-adrenergic mechanism. In support of this conclusion is the observation that the renal vasodilator responses to dopamine are not antagonized by beta-adrenergic blocking agents. It appears that dopamine may be acting on a hitherto undescribed receptor present in the kidney. Data presented recently by Eble suggest that a similar receptor may also be present in the mesenteric vascular bed of the dog.

The possibility that the renal and mesenteric vascular effects of dopamine may have physiologic significance should be considered. Dopamine is the principal catecholamine excreted in normal human urine. It has been suggested that most of the normally excreted dopamine is of renal origin. It is consistent with this possibility that the enzyme dopa decarboxylase, which is involved in the conversion of dopa to dopamine, is abundant in renal tissue. The significant amounts of dopamine present in the intestine have led Holtz to speculate that it may have a local neurohumoral function. From the standpoint of possible clinical applications, dopamine or substances with similar properties may offer the possibility of redistributing cardiac output in favor of visceral organs. Since there is evidence implicating increased renal vasomotor tone in the sodium retention of congestive heart failure, it is possible that the natriuretic effect of dopamine in this condition may be related to its direct renal vascular effect, as well as to its positive cardiac inotropic action. It would also be interesting to learn the effect of dopamine in conditions in which pathologically high renal and mesenteric vascular resistances exist, such as experimentally induced shock. It seems possible that the effects of dopamine

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might differ significantly from those of nor-epinephrine, the deleterious effects of which are being increasingly emphasized.10

Summary

The effects on directly measured renal blood flow, mean blood pressure, and calculated renal vascular resistance of intravenous infusions of dopamine, isoproterenol, and nor-epinephrine were compared. Dopamine, at doses not affecting mean blood pressure, decreased renal vascular resistance and increased renal blood flow. In contrast, isoproterenol decreased both blood pressure and renal vascular resistance but did not consistently increase renal blood flow. Renal artery injection of dopamine produced vasodilatation at doses ranging from 0.75 to 12 μg and biphasic flow responses including transient vasoconstriction at higher doses. It is concluded that the probable basis for the effect of intravenous dopamine infusion on renal blood flow is its direct renal vasodilating action.

The direct effect of dopamine on the femoral vascular bed is vasoconstriction. The combination of renal vasodilating, and femoral vasoconstricting, effects is unique and is interpreted as evidence for a renal vasodilating effect of dopamine distinct from the conventional beta-adrenergic mechanism. A possible physiological role for dopamine other than as a precursor to norepinephrine may be related to this property. It is also suggested that the ability of dopamine to alter the distribution of cardiac output in favor of visceral organs may find useful clinical applications.

References

Direct Renal Vasodilatation Produced by Dopamine in the Dog
JOHN L. McNAY, ROBERT H. McDONALD, Jr., LEÓN I. GOLDBERG and Carolyn Davis

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