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On the Existence of Renal Vasodilator Nerves (41893)

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Abstract. The renal vasoconstrictor responses to graded frequencies of direct electrical renal nerve stimulation and renal arterial norepinephrine injections were evaluated before and during renal alpha-1 adrenoceptor blockade in anesthetized dogs. Renal alpha-1 adrenoceptor blockade was achieved by infusing increasing doses (1, 10, 20, 40 μg/kg/min) of prazosin, a selective postsynaptic alpha-1 adrenoceptor antagonist, into the renal artery. The renal vasoconstrictor response to norepinephrine (1.5 μg) was completely abolished by 10 μg/kg/min prazosin. However, the renal vasoconstrictor response to a frequency of renal nerve stimulation which produced less renal vasoconstriction than norepinephrine (1.5 μg) in the absence of prazosin was not abolished by either 10, 20, or 40 μg/kg/min prazosin. During prazosin administration, neither renal nerve stimulation nor norepinephrine produced renal vasodilatation. Therefore, at prazosin doses two- and fourfold greater than that demonstrated to produce complete renal alpha-1 adrenoceptor blockade, no renal vasodilator responses to graded renal nerve stimulation were observed. These studies provide no evidence in support of a neural renal vasodilator mechanism in the dog.

The subject of renal vasodilator nerves has been extensively studied over the years (reviewed in (1)), often in regard to the existence of sympathetic cholinergic vasodilator fibers. Following the administration of a variety of agents with various inhibitory effects on neuroadrenergic transmission (phenoxybenzamine, phentolamine, guanethidine, hexamethonium, reserpine, hydergine, bretylium), the renal vasoconstrictor responses to renal nerve stimulation were markedly reduced or abolished and never replaced by a renal vasodilator response. Similarly, cholinergic blockade with atropine was without effect. These experiments were interpreted to indicate that there are no functional renal sympathetic cholinergic vasodilator nerve fibers. These studies provided physiological support and confirmation of Barajas and colleagues' sophisticated anatomical studies which demonstrated that the acetylcholinesterase containing nerve terminals observable in the kidney were adrenergic (2, 3).

Recently, Chapman and colleagues (4) have reexplored this question. They employed the hydrogen wash out technique to estimate renal cortical and medullary blood flow in the anesthetized rat. It was observed that whereas prazosin 1.5 μmole/kg iv abolished the reduction in renal cortical and medullary blood flow produced by renal nerve stimulation, prazosin 6 μmole/kg iv resulted in an increase in renal cortical blood flow and a decrease in renal medullary blood flow during renal nerve stimulation. It was argued that the higher dose of prazosin produced a more complete block of renal alpha-1 adrenoceptors based on a greater inhibition of the arterial pressor response to iv norepinephrine. The authors concluded that the renal nerves contained renal vasodilator fibers and, based on a reversal of the renal cortical vasodilation back to a vasoconstriction during renal nerve stimulation by combined administration of prazosin and sulpiride, suggested that the renal vasodilator fibers were dopaminergic.

In view of the possibility that renal vasodilation during renal nerve stimulation might be unmasked by a large dose of a highly selective alpha-1 adrenoceptor antagonist, we undertook studies to assess the renal vascular response to graded frequencies of renal nerve stimulation and renal arterial norepinephrine injection before and during renal alpha-1 adrenoceptor blockade with prazosin in anesthetized dogs.

Methods. Mongrel dogs of either sex and weighing between 15 and 25 kg were deprived of food for 20 hr prior to the experiment but allowed water *ad libitum*. They were anesthetized with intravenous sodium pentobarbital, 30-mg/kg initial dose and 6-mg/kg/hr maintenance dose. They were mechanically

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ventilated via an endotracheal tube to maintain arterial pO_2 above 80 mm Hg, pH between 7.35 and 7.45, and pCO_2 between 30 and 40 mm Hg. Body temperature was kept constant at 38°C by external warming. At the onset of surgery, an isotonic saline load of 300 ml was given intravenously followed by a 2.0 ml/min sustaining infusion for the remainder of the experiment. A femoral artery and both femoral veins were catheterized for measurement of arterial pressure (Statham P23Db Pressure Transducer) and administration of isotonic saline and anesthetic solutions. The left kidney was approached retroperitoneally via a left flank incision. For measurement of renal blood flow a noncannulating flow probe (Carolina) was placed around the left renal artery. An occluder was placed distal to the flow probe for zero-flow adjustments and the flow probe was calibrated *in situ* at the end of each experiment. A curved 25-gauge needle was inserted into the left renal artery against the direction of renal blood flow and connected via polyethylene tubing to a syringe pump which delivered isotonic saline at 0.5 ml/min. The left ureter was catheterized to assure free drainage of urine. The renal nerve bundle was dissected free from the renal pedicle, isolated and sectioned. The distal renal nerve bundle was placed on bipolar silver electrodes connected to a Grass S9 constant-voltage square-wave stimulator. This technique assures that all renal nerve activity passing to the kidney derives from the stimulator (1). A minimum of 60 min was allowed for equilibration and stabilization.

In the control period (renal arterial infusion of isotonic saline), the renal nerves were stimulated at supramaximal voltage of 10–30 V, 1.0 msec, and 0.5, 1, 2, 4, and 8Hz. The duration of each renal nerve stimulation was sufficient to allow for the development of a steady state change in renal blood flow (1–2 min). Following cessation of each renal nerve stimulation, sufficient time was allowed for renal blood flow to return to a steady state control level. Following the series of renal nerve stimulations, a single dose of 1.5 μg norepinephrine was injected into the renal artery. Thereafter, the renal arterial infusion was adjusted to deliver prazosin at sequentially increasing doses of 1, 10, 20, and 40 μg/kg/min. Twenty minutes were allowed to pass after the onset of a new rate of prazosin infusion prior to repetition of a series of renal nerve stimulations and norepinephrine injection as noted above. Nine dogs received the 1-, 10-, and 20-μg/kg/min doses of prazosin; seven of these nine dogs also received the 40-μg/kg/min dose of prazosin.

The outputs of the electronic pressure transducer and electromagnetic flow meter were continuously recorded on a direct writing polygraph (Beckman Dynagraph R-611). The control levels of renal blood flow prior to each frequency of renal nerve stimulation in the presence and absence of prazosin were relatively constant within each dog. The data were calculated as the percentage change in renal blood flow, control value to steady state renal nerve stimulation value, to permit comparison between dogs with different basal renal blood flow values. The data were subjected to analysis of variance with subsequent use of the Bonferroni method for simultaneous multiple comparisons (5); a significance level of 5% was chosen. Data in text, tables and figures are expressed as means ± SE.

Results. In the control period (no prazosin), norepinephrine, 1.5 μg, produced a 60% decrease in renal blood flow (Fig. 1). During the renal arterial infusion of prazosin in increasing amounts, there was a progressive dose-related decline in the renal vasoconstrictor response

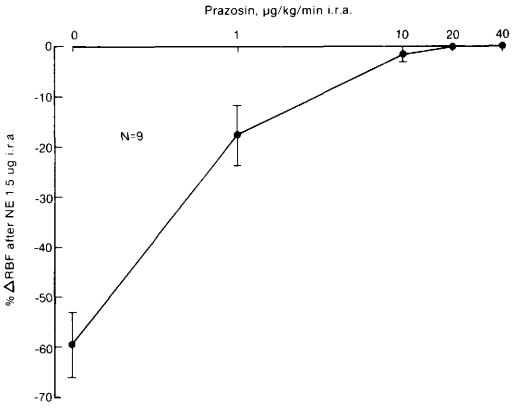

FIG. 1. The effect of renal arterial injection of 1.5 μg norepinephrine on renal blood flow (RBF) before and during graded doses of prazosin administered into the renal artery. Data are mean ± SE percentage changes (%) for $N = 9$ at 0-, 1-, 10-, and 20-μg/kg/min-prazosin doses and $N = 7$ at 40-μg/kg/min prazosin dose.

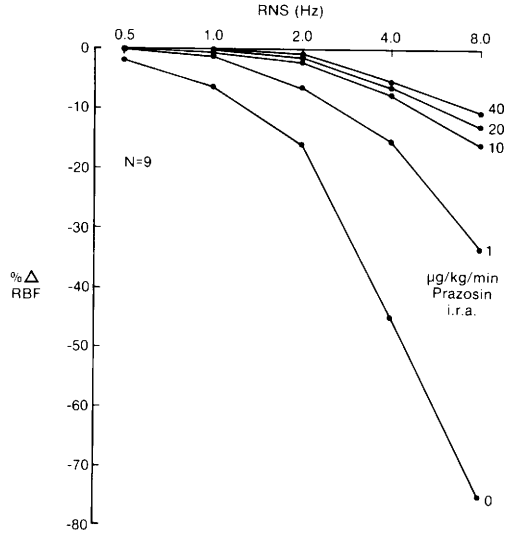

FIG. 2. The effect of graded frequencies (0.5, 1, 2, 4, and 8 Hz) of renal nerve stimulation (RNS: 10–30 V, 1 msec) on renal blood flow (RBF) before and during graded doses of prazosin administered into the renal artery. Data are mean percentage changes (%) (see Table I for mean ± SE) for $N = 9$ at 0-, 1-, 10-, and 20-μg/kg/min prazosin doses and $N = 7$ for 40-μg/kg/min prazosin dose.

to norepinephrine. Prazosin at 1 μg/kg/min reduced the response by 70% and the higher doses of prazosin abolished the response. At no time was a renal vasodilator response to norepinephrine administration observed.

During the control period (no prazosin), graded renal nerve stimulation produced frequency dependent decreases in renal blood flow without affecting mean arterial pressure (Fig. 2, Table I). During the renal arterial infusion of prazosin in increasing amounts, there was a progressive dose-related decline in the renal vasoconstrictor responses observed at all frequencies of renal nerve stimulation. Renal vasoconstrictor responses were inhibited by circa 60% at 1 μg/kg/min prazosin and by circa 80% at 10 μg/kg/min prazosin. At 20 and 40 μg/kg/min prazosin significant renal vasoconstrictor responses to renal nerve stimulation at 4 and 8 Hz were still observed. At no time was a renal vasodilator response to renal nerve stimulation observed.

In the control period (no prazosin), mean arterial pressure was 130 ± 6 mm Hg. During renal arterial infusion of prazosin, mean arterial pressure was 122 ± 5 mm Hg at 1.0 μg/kg/min, 114 ± 7 mm Hg at 10 μg/kg/min, 112 ± 9 at 20 μg/kg/min, and 105 ± 10 at 40 μg/kg/min.

Discussion. The dose of norepinephrine, 1.5 μg, produced a renal vasoconstrictor response midway between that elicited by 4- and 8-Hz renal nerve stimulation. The renal vasoconstrictor response to norepinephrine (i.e., alpha-1 adrenoceptor agonist action of native endogenous neurotransmitter) was 50% reduced by prazosin at a dose of approximately 0.5 μg/kg/min and was abolished at prazosin doses of 10 μg/kg/min and higher (20 and 40 μg/kg/min). These results are consistent with the known effects of prazosin as a potent and selective postsynaptic alpha-1 adrenoceptor antagonist (6–8) and indicate that prazosin produced total renal alpha-1 adrenoceptor blockade to norepinephrine at doses of 10 μg/kg/min and higher (20 and 40 μg/kg/min).

The situation for renal nerve stimulation, however, was different. At frequencies of renal nerve stimulation which produced much smaller renal vasoconstrictor responses than that produced by norepinephrine (1.5 μg) in

TABLE I. EFFECT OF RENAL ARTERIAL PRAZOSIN INFUSION ON RENAL BLOOD FLOW RESPONSES TO RENAL NERVE STIMULATION[a]

Prazosin (μg/kg/min, ira)	Stimulation (Hz)				
	0.5	1.0	2.0	4.0	8.0
0	−1.9 ± 0.4	−6.4 ± 1.0	−15.9 ± 1.8	−45.0 ± 6.2	−74.7 ± 7.8
1	0	−1.2 ± 0.4	−6.6 ± 1.3	−15.6 ± 2.9	−33.3 ± 5.8
10	−0.1 ± 0.1	−0.3 ± 0.2	−2.0 ± 0.9	−7.7 ± 1.7	−16.0 ± 3.0
20	0	0	−1.8 ± 1.0	−6.4 ± 1.5	−12.9 ± 2.3
40	0	0	−1.2 ± 0.9	−5.5 ± 2.2	−10.6 ± 2.6

[a] Data entries are means ± SE for percentage change in renal blood flow.

the control period, 0.5, 1, and 2 Hz, prazosin at 1 μg/kg/min (0.5 and 1 Hz) and 10 μg/kg/min (2 Hz) abolished the renal vasoconstrictor responses. Thus, based on comparison of control period renal vasoconstrictor responses, prazosin at doses which produced complete renal alpha-1 adrenoceptor blockade to norepinephrine resulted in similar findings with less potent frequencies of renal nerve stimulation. However, while renal nerve stimulation at 4 Hz decreased renal blood flow by 45% in the control period (cf. 60% with norepinephrine), this renal vasoconstrictor response was not completely abolished by the dose of prazosin, 10 μg/kg/min, which completely blocked the norepinephrine response; the higher prazosin doses, 20 and 40 μg/kg/min, were similarly ineffective. Therefore, it could be predicted, and was observed, that the 8-Hz renal nerve stimulation, producing a 75% decrease in renal blood flow during the control period, would not be completely abolished by the prazosin dose of 10 μg/kg/min which completely blocked the norepinephrine response; in addition, the higher doses (20, 40 μg/kg/min) of prazosin produced little additional inhibitory effect.

It is of interest that prazosin doses sufficient to completely block the renal vasoconstrictor responses to norepinephrine did not completely abolish the renal vasoconstrictor responses to equipotent intensities of renal nerve stimulation. This has been previously reported with the nonspecific alpha adrenoceptor antagonists, phenoxybenzamine (9) and phentolamine (10). It is possible that renal arterial infusion of alpha adrenoceptor antagonists, while clearly able to completely block renal vascular alpha adrenoceptors occupied by renal arterial infusion of norepinephrine, may not be able to completely block all the renal vascular alpha adrenoceptors occupied by release of norepinephrine from nerve terminals within the renal parenchyma.

It is important to emphasize that at a dose of prazosin (10 μg/kg/min) which was demonstrated to produce total renal alpha-1 adrenoceptor blockade to norepinephrine the renal vascular responses to graded frequencies of renal nerve stimulation were always vasoconstrictor; renal vasodilatation was never observed. Furthermore, similar observations were made with doses of prazosin, two (20 μg/kg/min) and four (40 μg/kg/min) times greater than that needed to produce complete renal alpha-1 adrenoceptor blockade to norepinephrine. Therefore, these studies provide no evidence in support of a neural renal vasodilator mechanism in the dog.

There are several major issues which deserve comment concerning these results in light of the studies of Chapman *et al.* (4). It is difficult to assess the importance of the species difference, rats versus dogs; however, sodium pentobarbital was the common anesthetic employed. A major difference was the method used for masurement of renal blood flow. Chapman *et al.* (4) used the technique of hydrogen washout. When this method was validated against directly measured renal venous outflow in dogs (11, 12), both groups noted a good correlation between renal cortical blood flow and renal venous outflow at values of renal venous outflow less than 150 ml/min/100 g; when renal venous outflow exceeded 150 ml/min 100 g, renal cortical blood flow values were uniformly lower. Although this method has been previously used in anesthetized rats (13–14), it has not been similarly validated against directly measured renal venous outflow or other more direct techniques such as electromagnetic flow meter or clearance and extraction of *p*-aminohippurate (PAH). To provide convincing evidence that the hydrogen washout technique provides reliable measurements of renal blood flow in the rat, it would seem appropriate to do validation studies such as have been done for ^{133}Xe-renal blood flow versus PAH-renal blood flow in the rat (16) and ^{133}Xe-renal blood flow versus electromagnetic flow meter-renal blood flow in the dog (17). Although the monitoring techniques, tissue electrodes for the hydrogen washout technique and external counting for the ^{133}Xe washout technique, are different, the theoretical principles underlying these various inert gas techniques are identical (18). In this regard, it is important to note that, in the dog, ^{133}Xe-renal blood flow significantly overestimated electromagnetic flow meter renal blood flow by 20% and had a high degree of variability as reflected by a coefficient of variation of 42% (17). Similarly, in the rat, although ^{133}Xe-renal blood flow and PAH-renal blood flow were in close agreement, the degree of variability was much greater with

the former than the latter technique (coefficient of variation, 32% versus 6%) (16).

In assessing the degree of completeness of renal alpha-1 adrenoceptor blockade, Chapman *et al.* (4) evaluated the arterial pressure responses to intravenous injections of norepinephrine before and after the intravenous injection of graded doses of prazosin. This approach critically depends on the assumption that inhibition of the norepinephrine (iv) induced systemic arterial pressor response by intravenous administration of the alpha-1 adrenoceptor antagonist prazosin accurately reflects the status of alpha-1 adrenoceptors located within the kidney. A proper assessent of the responses to stimulation and blockade of alpha-1 adrenoceptors located in the kidney requires the administration of alpha adrenoceptor agonists and antagonists into the renal circulation and the measurement of a specific renal, not nonspecific systemic, response (1). In the current experiments, the renal blood flow responses to the renal arterial injection of norepinephrine were measured before and during renal arterial administration of prazosin; prazosin at 10 μg/kg/min completely abolished the renal vasoconstrictor response to a dose of norepinephrine which reduced renal blood flow by 60% in the control state. This observation provides strong evidence for complete blockade of renal alpha-1 adrenoceptors and does not depend on an extrapolation from measurements of systemic arterial pressure. Another major argument of Chapman *et al.* (4) dealt with the dose range of prazosin employed; they found that prazosin at 1.5 μmole/kg did not produce full inhibition of the systemic arterial pressor response to intravenous norepinephrine whereas 6.0 μmole/kg was effective. These doses equate to 574 and 2295 μg/kg, respectively, and assuming a 10% distribution of cardiac output to a single kidney, this would equate to a kidney dose of 57.4 and 229.5 μg/kg, respectively. In the current experiments, there was 20 min of renal arterial infusion of each dose of prazosin prior to the interventions and the infusion was continued during the interventions (ca. 30 min); thus, each dose was infused for a total of 50 min. Therefore, at the prazosin doses of 1, 10, 20, and 40 μg/kg/min the total amount of prazosin infused into the kidney at each dose was 50, 500, 1000, and 2000 μg/kg and the total cumulative amount of prazosin infused into the kidney at each dose was 50, 550, 1550, and 3550 μg/kg, respectively. These latter three total cumulative doses of prazosin delivered directly into the kidney are 2.4, 6.8, and 15.5 times greater than the largest dose (presumed to have reached the kidney) employed by Chapman *et al.* (4).

A further confounding variable in interpreting the results of Chapman *et al.* (4) is that intravenous administration of prazosin 1.5 μmole/kg resulted in a decrease in mean arterial pressure from 114 ± 3 to 84 ± 2 mm Hg and, although the decrease observed with the 6.0-μmole/kg prozosin dose was not stated, it can be safely assumed to have not been less and probably was greater. Since several investigators using more direct methods for the measurements of renal blood flow have demonstrated that renal blood flow autoregulation is impaired in the rat when mean arterial pressure is less than 95–105 mm Hg (15, 19, 20), it is evident that, following prazosin administration, the rats in the study by Chapman *et al.* (4) had impaired capacity for autoregulation of renal blood flow. The authors indicate that renal cortical blood flow fell from 310 ± 13 to 223 ± 13 ml/min/100 g after prazosin 1.5 μmole/kg; it may be calculated that renal cortical vascular resistance changed little, 0.37 versus 0.38 mm Hg/ml/min/100 g. Thus, renal cortical blood flow fell in parallel with the fall in mean arterial pressure such that renal cortical vascular resistance was unchanged. The failure of renal cortical blood flow to be better maintained in the face of a reduced mean arterial pressure indicates the existence of impaired capacity for renal blood flow autoregulation. This further indicates that the renal vasculature had achieved maximal vasodilatation and, being unable to vasodilate further in response to the reduction in mean arterial pressure, exhibits a linear pressure–flow relationship wherein changes in mean arterial pressure produce parallel changes in renal blood flow (unchanged renal vascular resistance). It should be noted that, after prazosin 6.0 μmole/kg, renal nerve stimulation produced an increase of 6.1% in renal cortical blood flow in their study. In the setting of a maximally vasodilated nonautoregulating rat kidney with mean arterial pressure of 84 mm Hg (or lower), such an increase in renal cortical

blood flow could be totally accounted for by a passive flow response to a rise in mean arterial pressure of as little as 5 mm Hg. It should be noted that in the current studies, mean arterial pressure, while showing some downward trend due to unavoidable recirculation of cumulative high-dose renal arterial infusion of prazosin, remained well above the autoregulatory breakpoint of 60–70 mm Hg for the dog (21) and basal renal blood flow remained constant despite this progressive fall in mean arterial pressure (i.e., appropriate decrease in renal vascular resistance), thus exhibiting intact autoregulatory capacity.

Therefore, the absence of data validating the hydrogen washout technique for the measurement of renal blood flow in the rat, the absence of data demonstrating the presence or absence of specific renal alpha adrenoceptor blockade and the limitations of examining mechanisms for the control of renal blood flow in a kidney preparation which does not exhibit normal renal blood flow autoregulatory behavior raise strong and compelling reservations concerning the conclusions of Chapman *et al.* (4) regarding the existence of renal vasodilator nerves.

Other investigators have proposed the existence of neural dopaminergic vasodilator fibers in the kidney. The only physiological and functional study is that of Bell and Lang (22) who showed that electrical stimulation of the ventral hypothalamus in the anesthetized dog pretreated with guanethidine elicited renal vasodilator responses with 1- to 2-sec onset latency which waned within 10 sec despite continued stimulation. The renal vasodilator responses were unaffected by atropine or mepyramine but were abolished by haloperidol. Although it was not indicated whether renal denervation abolished the renal vasodilator response to stimulation, the data were interpreted to support the existence of renal vascular innervation which, on reflex activation of the renal nerves, releases dopamine as the neurotransmitter. Further studies are of an anatomical and biochemical nature. Bell *et al.* (23), using chemical determinations and fluorescence histochemical techniques, demonstrated that dog renal cortex contained more dopamine than could be accounted for by its presence in noradrenergic axons only and that it was more resistant to guanethidine depletion than in right atrium. Dinerstein *et al.* (24), using a differential fluorescence histochemical technique, identified dopamine containing neurons in the dog renal cortical vasculature. However, in the rat, renal cortical dopamine content has not been found to be greater than what would be anticipated in noradrenergic axons (25, 26) and has been interpreted as evidence against renal dopaminergic innervation in the rat (26). The effect of either renal denervation or reflex or direct renal nerve stimulation on both the urinary excretion and renal secretion of dopamine and other catecholamines has been examined by several groups of investigators. Although activation of the efferent renal nerves can cause release of dopamine into the urine and renal venous blood, approximately 50% of such dopamine release can be accounted for by dopamine synthesis from circulating L-Dopa by Dopa decarboxylase in nonneural renal tissue (27–33). Although the physiological, anatomical and biochemical studies seem to support the existence of dopaminergic nerves, there is no unambiguous evidence as to their function (34–36). That is, it needs to be shown that an alteration in the activity of efferent renal nerve fibers produces a measurable change in some renal function that is mediated by release of dopamine as neurotransmitter from those renal nerve fibers.

Thus, while the accumulated information generally favors the hypothesis concerning the existence of neural dopaminergic vasodilator fibers in the kidney, the evidence is far from conclusive. For example, an unequivocal increase in renal blood flow occurring during direct renal nerve stimulation (often during inhibition of neuroadrenergic transmission) and reversed by specific antagonists of dopamine's vascular effect has not been convincingly demonstrated and confirmed in different mammalian species. In this regard, Imbs *et al.* (25) reported that combined treatment with phenoxybenzamine and phentolamine completely blocked the renal vasoconstrictor response to renal nerve stimulation in only three of six dogs; a partial renal vasoconstrictor response persisted in the other three dogs. Thus, no evidence was found for renal vasodilator nerves. Three of the six dogs pretreated with phenoxybenzamine and phentolamine were then given indomethacin; re-

peat renal nerve stimulation elicited small renal vasodilator responses. These results raise the possibility that renal nerve stimulation (after phenoxybenzamine and phentolamine) caused the renal release of vasodilator (PGE_2, PGI_2) and vasoconstrictor (thromboxane) prostanoids with the latter predominating prior to indomethacin administration; indomethacin administration may have reduced the renal release of vasoconstrictor substances to a greater extent than vasodilator substances so that a renal vasodilator response was observed. Observations on the effect of other antagonists to vasodilator mechanisms (atropine, propranolol, mepyramine, sulpiride) were not reported. However, others have also examined this issue. Kopp *et al.* (37) stimulated the renal nerves to produce a 50% decrease in renal blood flow which was completely blocked (no residual renal vasoconstriction or vasodilation) with renal arterial administration of phenoxybenzamine. The addition of fully active doses of two structurally dissimilar prostaglandin synthesis inhibitors, indomethacin and diclofenac, did not alter the effect of phenoxybenzamine to block the renal vasoconstrictor response to renal nerve stimulation. Needleman *et al.* (38) showed that renal nerve stimulation produced renal vasoconstriction and prostaglandin release from the rabbit kidney; phenoxybenzamine completely blocked both the renal vasoconstriction and prostaglandin release whereas indomethacin, while blocking the prostaglandin release, did not affect the renal vasoconstriction. Thus, these studies, also employing renal alpha adrenoceptor blockade and prostaglandin synthesis inhibitors, do not confirm the existence of renal vasodilator nerves; therefore, the issue of the existence of renal vasodilator nerves is unresolved. Furthermore, in the absence of inhibition of neuroadrenergic transmission, there is no evidence that specific antagonists of dopamine's renal vascular action enhance the renal vasoconstrictor response to renal nerve stimulation (39).

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