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The influence of diltiazem and nifedipine on renal function in the rat

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1 The effect of intravenous administration of the calcium-entry blocking drugs, diltiazem and nifedipine, on renal haemodynamic and tubular function was examined in denervated kidneys of pentobarbitone-anaesthetized rats. Infusion of vehicle for the compounds had no effect on renal function which was stable for the duration of the experiments.

2 Diltiazem was infused at 5, 10 and 20 $\mu g\,kg^{-1}\,min^{-1}$. Blood pressure did not change following 5 $\mu g\,kg^{-1}\,min^{-1}$ diltiazem but was significantly reduced, by 12 mmHg, after 10 $\mu g\,kg^{-1}\,min^{-1}$ and by 17 mmHg after 20 $\mu g\,kg^{-1}\,min^{-1}$. Renal blood flow was not affected by any dose of diltiazem while at the lowest dose of drug, glomerular filtration rate (g.f.r.) was significantly increased, by 24%.

3 Absolute and fractional sodium excretion were increased significantly, 154% and 77% respectively, by 5 $\mu g\,kg^{-1}\,min^{-1}$ diltiazem, 20% and 24% respectively, by 10 $\mu g\,kg^{-1}\,min^{-1}$ diltiazem, but were unchanged by 20 $\mu g\,kg^{-1}\,min^{-1}$.

4 Infusion of nifedipine at 0.5, 1.0 and 2.0 $\mu g\,kg^{-1}\,min^{-1}$ decreased systemic blood pressure by 9, 9 and 20 mmHg, respectively. Renal blood flow was increased (7%) by 1.0 $\mu g\,kg^{-1}\,min^{-1}$ only, while g.f.r. did not change at any dose.

5 Urine flow, absolute and fractional sodium excretions were increased, 127%, 96% and 90% respectively, by 0.5 $\mu g\,kg^{-1}\,min^{-1}$ nifedipine, 127%, 197% and 194% respectively, by 1.0 $\mu g\,kg^{-1}\,min^{-1}$, while these variables remained unchanged by a dose of 2.0 $\mu g\,kg^{-1}\,min^{-1}$.

6 These data show that doses on diltiazem and nifedipine, which had little or no effect on blood pressure, had minimal actions on renal haemodynamics. However, at 5 and 10 $\mu g\,kg^{-1}\,min^{-1}$ diltiazem and 0.5 and 1.0 $\mu g\,kg^{-1}\,min^{-1}$ nifedipine these compounds exhibited direct tubular actions, causing both a diuresis and natriuresis, while at the highest dose of each drug these actions were masked by a concomitant reduction in blood pressure.

Introduction

Calcium-entry blocking drugs are becoming widely used in the treatment not only of cardiac disease (Flaim & Zelis, 1982) but also of hypertension (Lederballe Pedersen, 1983; Klein *et al.*, 1983). There is accumulating evidence which indicates that the calcium-entry blockers have an important action on the kidney causing an increased sodium and water excretion. The exact mechanisms underlying this effect on the kidney are unclear. Systemic administration of these compounds is associated with a number of changes in cardiovascular function, such as a fall in blood pressure, vasodilatation and blockade of adrenergic transmission, each of which could influence indirectly the tubular handling of sodium and water. Yamaguchi *et al.* (1974) have shown that administration of diltiazem to the dog increased both renal blood flow and glomerular filtration rate while Marre *et al.* (1982) demonstrated that nifedipine decreased renal vascular resistance in the isolated perfused kidney of the rat and suggested that the changed renal haemodynamics were responsible for the natriuresis and diuresis. In contrast, methoxyverapamil in the rat (Brown & Churchill, 1983) and verapamil and nifedipine in the dog (Dietz *et al.*, 1983) had a natriuretic and diuretic action without affecting renal haemodynamics. These results indicated that such compounds could act directly on tubular reabsorptive processes.

The renal nerves themselves can directly influence the rate of sodium reabsorption from the cells of the proximal tubule and the ascending limb of the loop of Henle (DiBona, 1982; DiBona & Sawin, 1982). This action has been shown to be mediated through α-adrenoceptors (Zambraski *et al.*, 1976; DiBona &

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Johns, 1980) and it has recently been found that the calcium-entry blocking drugs can interfere with noradrenergic transmission at various neuroeffector junctions (Vanhoutte & Rimele, 1982). The possibility exists that diuresis and natriuresis might result from blockade of noradrenergic transmission in the kidney by calcium-entry blocking drugs (Bonjour *et al.*, 1969).

An attempt was made in the present study to overcome the complicating factors of blood pressure and the renal nerves. Firstly, a range of doses was chosen of two chemically dissimilar calcium-entry blocking drugs, diltiazem and nifedipine, which caused little or no fall in blood pressure. Secondly, the kidney was denervated to remove any possible neural influence on sodium and water handling caused by reflex activation of the renal sympathetic nerves due to changes in blood pressure. The results showed that 5 and 10 $\mu g\,kg^{-1}\,min^{-1}$ diltiazem and 0.5 and 1.0 $\mu g\,kg^{-1}\,min^{-1}$ nifedipine caused small variable changes in renal haemodynamics but large increases in sodium and water excretion. A preliminary account of these studies has been presented to the Pharmacological Society (Johns, 1984).

Methods

Male albino Sprague-Dawley rats (360–420g) were anaesthetized with sodium pentobarbitone, 60 mg kg^{-1} i.p., supplemented with small i.v. bolus doses as required. A carotid artery was cannulated for blood pressure measurements (Statham P23Db pressure transducer linked to a Grass model 7 polygraph) and removal of blood samples. The right jugular vein was cannulated and an infusion of saline (150 mmol l^{-1} NaCl) was begun at 6.6 ml h^{-1} (Braun Unita I infusion pump). The left kidney was exposed using a ventral mid-line incision, the ureter cannulated for urine collection and the renal artery cleared to allow the fitting of an electromagnetic flow probe (Carolina EP100 series) for measurement of renal blood flow (Carolina FM501 flowmeter linked to a Grass model 7 polygraph). All visible nerves to the kidney were isolated and sectioned.

Renal function measurements

On completion of surgery 2 ml of a solution containing 10 mg ml^{-1} inulin in saline was given i.v. over 2 min and the infusion changed to this same solution for the remainder of the experiment. Measurements were begun 2 h later. Arterial blood samples (0.35 ml) were removed, centrifuged and the plasma stored while the cells were resuspended in saline and infused back into the animal.

The experimental procedure consisted of 4 clearance periods each of 20 min duration, two before and two following drug administration. Immediately the first two clearances had been completed, the infusion was changed to one containing the drug and 30 min later two further clearances were measured. A mean value of the two clearances, before the drug, was compared to the mean value of the two clearances estimated during the drug administration.

Inulin in plasma and urine was assayed as previously described (Johns *et al.*, 1976) and plasma inulin levels were measured at the beginning and end of each pair of clearance periods. Glomerular filtration rate was calculated as the clearance of inulin (Arundell & Johns, 1982) and renal blood flow was measured from the calibrated paper trace obtained from the Grass polygraph at 5 min intervals throughout each clearance period. Plasma and urinary sodium concentrations were measured using a Beckman flame photometer. Absolute sodium excretion was calculated as the product of urinary sodium concentration and urine flow rate. Fractional sodium excretion, which represents a measure of the tubular handling of sodium independent of changes in sodium load, was calculated from the division of sodium clearance (absolute sodium excretion divided by plasma sodium concentration) by glomerular filtration rate.

Drug infusions

A vehicle for infusion was prepared which consisted of a 1:1 (v/v) mixture of glycofurol:ethanol diluted 1:10 with saline. This was infused into the animals during the second pair of clearance periods at a rate of 0.6 ml h^{-1}.

A stock solution of diltiazem was prepared fresh every 48 h by dissolving the compound in a 1:1 (v/v) mixture of glycofural:ethanol. Solutions to be infused were prepared from this stock by diluting at least 1:10 with saline and infused at a rate of 0.6 ml h^{-1}. Diltiazem was infused at three dose levels, 5, 10 and 20 $\mu g\,kg^{-1}\,min^{-1}$.

Stock solutions of nifedipine were also prepared by dissolving the drug in the 1:1 glycofurol:ethanol mixture and were stored deep frozen for no longer than four days. The solutions to be infused were prepared by diluting the stock solution by at least 1:10 with saline and infused at a rate of 0.6 ml h^{-1}. During nifedipine infusion all syringes, containers and cannulae were covered with silver foil in order to minimize any breakdown due to light exposure. Nifedipine was administered at three dose levels, 0.5, 1.0 and 2.0 $\mu g\,kg^{-1}\,min^{-1}$.

Statistics

The absolute and percentage changes quoted in the text represent the means of the individual changes recorded in each animal. Mean values ± s.e.mean are

Table 1 Effect of diltiazem on renal function in the denervated rat kidney

	Diltiazem					
	5 μg kg^{-1} min^{-1} (*n* = 6)		10 μg kg^{-1} min^{-1} (*n* = 5)		20 μg kg^{-1} min^{-1} (*n* = 6)	
	Pre-drug	*Post-drug*	*Pre-drug*	*Post-drug*	*Pre-drug*	*Post-drug*
Systemic blood pressure (mmHg)	121 ± 7	115 ± 7	121 ± 5	107 ± 5***	118 ± 6	97 ± 4†
Left renal blood flow (ml min^{-1} kg^{-1})	17.86 ± 1.64	17.70 ± 2.09	16.19 ± 0.91	15.46 ± 1.04	16.73 ± 0.79	18.20 ± 1.53
Left glomerular filtration rate (ml min^{-1} kg^{-1})	3.30 ± 0.20	4.12 ± 0.46*	2.98 ± 0.26	2.85 ± 0.21	3.65 ± 0.21	3.52 ± 0.15
Left urine flow rate (μl min^{-1} kg^{-1})	28.5 ± 3.2	53.0 ± 8.8	35.8 ± 3.4	42.7 ± 4.0*	31.7 ± 4.6	29.8 ± 3.4
Left absolute sodium excretion (μmol kg^{-1} min^{-1})	4.33 ± 0.83	9.14 ± 2.03*	6.56 ± 0.79	7.89 ± 0.99***	5.44 ± 1.09	5.59 ± 1.22
Left fractional sodium excretion (%)	1.21 ± 0.19	2.02 ± 0.32*	1.85 ± 0.10	2.39 ± 0.17***	1.47 ± 0.37	1.47 ± 0.31

Data are expressed as means ± s.e.mean. Values for *P* are calculated from the absolute change for each variable from a mean of the two clearances before and a mean of the two clearances following the drug. *n* represents the number of animals used. * $P<0.05$, ** $P<0.02$, *** $P<0.01$, † $P<0.001$.

used. Statistical analysis was undertaken using the paired Student's *t* test within groups and the unpaired Student's *t* test between groups. Differences were taken to be statistically significant when $P<0.05$.

Results

Vehicle infusion

In a group of 6 rats the first two clearance periods were made, the saline infusion changed to one containing the vehicle and the two final clearances were then undertaken. Systemic blood pressure was 123 ± 6 mmHg over the first two clearances and remained unchanged, 117 ± 5 mmHg, during the second two clearance periods. Renal blood flow and glomerular filtration rate did not change over the course of the experiment being 18.04 ± 1.59 ml min^{-1} kg^{-1} and 3.20 ± 0.31 ml min^{-1} kg^{-1}, respectively, during the first and 18.98 ± 1.53 ml min^{-1} kg^{-1} and 3.46 ± 0.29 ml min^{-1} kg^{-1}, respectively, over the second set of clearances. Urine flow, and absolute and fractional sodium excretions remained stable throughout the period of measurement being 41.9 ± 4.7 μl min^{-1} kg^{-1}, 9.30 ± 0.80 μmol kg^{-1} min^{-1} and 2.62 ± 0.35%, respectively, during the first two clearance periods and 44.5 ± 5.5 μl min^{-1} kg^{-1}, 9.92 ± 0.06 μmol kg^{-1} min^{-1} and 2.51 ± 0.28%, respectively over the second set of clearance periods. Clearly, the vehicle for the drug had no effect itself on either renal haemodynamics, sodium or water excretion.

Diltiazem infusion

Table 1 shows the effect of diltiazem on systemic and renal variables. Diltiazem, 5 μg kg^{-1} min^{-1}, had no effect on either systemic blood pressure or renal blood flow but there was a significant ($P<0.05$) increase in glomerular filtration rate of approximately 24%. Diltiazem (5 μg kg^{-1} min^{-1}) did not change urine flow and significantly increased ($P<0.05$) absolute and fractional sodium excretions by 154% and 77%, respectively.

Diltiazem infusion at 10 μg kg^{-1} min^{-1} decreased systemic blood pressure significantly ($P<0.01$), by 14 mmHg, but had no effect on either renal blood flow or glomerular filtration rate. At this dose diltiazem significantly increased urine flow by 20% ($P<0.05$), absolute sodium excretion by 20% ($P<0.01$) and fractional sodium excretion by 24% ($P<0.01$).

Infusion of diltiazem at 20 μg kg^{-1} min^{-1} significantly ($P<0.001$) depressed systemic blood pressure, by 17 mmHg, but had no effect on any other renal haemodynamic or functional variable measured. Figure 1 presents a comparison of the systemic and

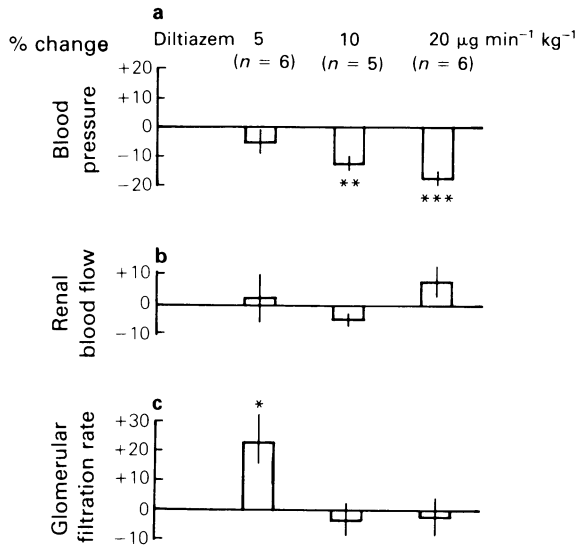

Figure 1 The percentage changes in (a) systemic blood pressure, (b) renal blood flow and (c) glomerular filtration rate which occur when diltiazem was infused intravenously at 5, 10 and 20 $\mu g\,kg^{-1}\,min^{-1}$. Each column represents the mean of n animals and vertical lines show s.e.means. The levels of significance are: $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

renal haemodynamic responses to the increasing doses of diltiazem while Figure 2 shows the pattern of renal functional responses to the different doses of the drug.

Nifedipine infusion

Table 2 presents the systemic and renal responses induced by nifedipine. At 0.5 $\mu g\,kg^{-1}\,min^{-1}$ nifedipine there was a small but significant ($P<0.01$) reduction in systemic blood pressure of 10 mmHg while both renal blood flow and glomerular filtration rate did not change. However, this dose of nifedipine caused a significant and sustained increase in urine flow, 127% ($P<0.01$), and in absolute and fractional sodium excretions, 96% ($P<0.02$) and 90% ($P<0.02$), respectively.

Nifedipine at 1.0 $\mu g\,kg^{-1}\,min^{-1}$ significantly ($P<0.02$) decreased systemic blood pressure by 11 mmHg, caused a small, but significant ($P<0.05$), increase in renal blood flow of 7%, and had no effect on glomerular filtration rate. At this dose of nifedipine there were significant increases in urine flow, 127% ($P<0.01$), absolute sodium excretion, 197% ($P<0.02$), and fractional sodium excretion, 194% ($P<0.02$).

Nifedipine infused at 2.0 $\mu g\,kg^{-1}\,min^{-1}$ caused a significant ($P<0.001$) decrease in systemic blood

Table 2 Effect of nifedipine on renal function in the denervated rat kidney

	Nifedipine					
	0.5 $\mu g\,kg^{-1}\,min^{-1}$ ($n=5$)		1.0 $\mu g\,kg^{-1}\,min^{-1}$ ($n=6$)		2.0 $\mu g\,kg^{-1}\,min^{-1}$ ($n=5$)	
	Pre-drug	*Post-drug*	*Pre-drug*	*Post-drug*	*Pre-drug*	*Post-drug*
Systemic blood pressure (mmHg)	125 ± 6	115 ± 4***	114 ± 5	104 ± 5**	116 ± 4	93 ± 4†
Left renal blood flow (ml $min^{-1}\,kg^{-1}$)	27.45 ± 3.21	27.73 ± 2.70	17.37 ± 1.11	18.49 ± 1.05*	23.89 ± 1.91	22.82 ± 1.03
Left glomerular filtration rate (ml $min^{-1}\,kg^{-1}$)	4.62 ± 0.38	4.61 ± 0.32	2.48 ± 0.49	2.25 ± 0.34	3.70 ± 0.19	3.68 ± 0.15
Left urine flow rate (μl $min^{-1}\,kg^{-1}$)	34.7 ± 1.6	77.1 ± 7.9***	30.1 ± 5.7	69.9 ± 15.4***	38.2 ± 8.8	48.7 ± 8.1
Left absolute sodium excretion (μmol $kg^{-1}\,min^{-1}$)	9.32 ± 1.14	17.68 ± 1.88**	4.52 ± 1.26	11.81 ± 3.22**	7.50 ± 2.07	8.24 ± 1.82
Left fractional sodium excretion (%)	1.48 ± 0.15	2.81 ± 0.46**	1.77 ± 0.57	5.09 ± 1.60**	1.67 ± 0.35	2.08 ± 0.43

Data are expressed as means ± s.e.mean. Values for P are calculated from the absolute change for each variable from a mean of the two clearances before and a mean of the two clearances following the drug. n represents the number of animals used. $^{*}P<0.05$, $^{**}P<0.02$, $^{***}P<0.01$, †$P<0.001$.

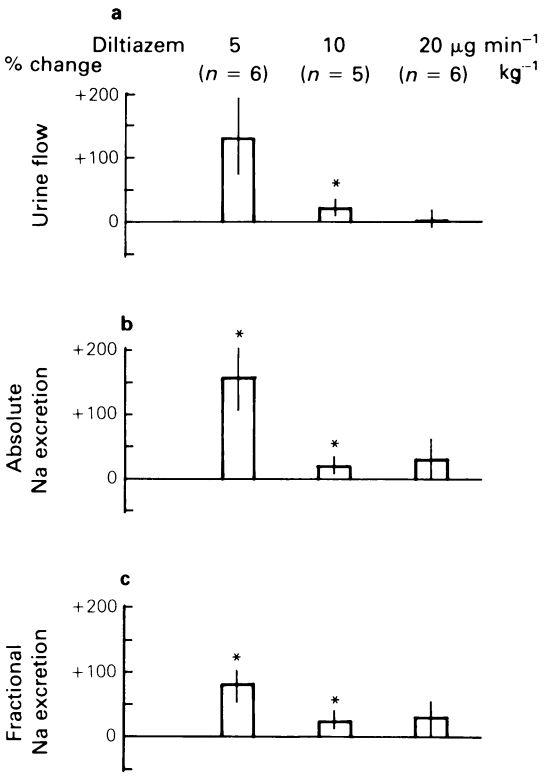

Figure 2 The percentage changes in (a) urine flow, (b) absolute and (c) fractional sodium excretions induced by intravenous diltiazem infusion at 5, 10 and 20 $\mu g\,kg^{-1}\,min^{-1}$. Each column represents the mean of *n* animals and vertical lines show s.e.means. The significance levels are indicated as in Figure 1.

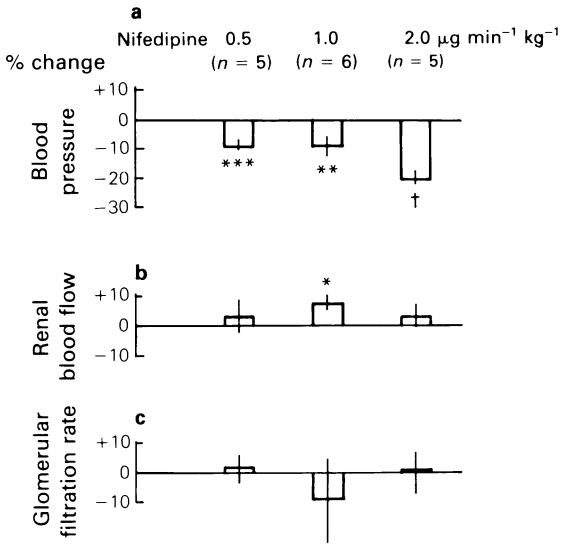

Figure 3 The changes in (a) systemic blood pressure, (b) renal blood flow and (c) glomerular filtration rate resulting from intravenous nifedipine infusion 0.5, 1.0 and 2.0 $\mu g\,kg^{-1}\,min^{-1}$. Each column represents the mean of *n* animals and vertical lines show s.e.means. The levels of significance are: * $P<0.05$; ** $P<0.02$; *** $P<0.01$; † $P<0.001$.

pressure (23 mmHg) but had no effect on either renal blood flow or glomerular filtration rate. Urine flow, absolute and fractional sodium excretions did not change following administration of this dose of nifedipine. A comparison of the systemic and renal haemodynamic responses to the increasing doses of nifedipine are shown in Figure 3 and the changes in renal function induced by nifedipine are shown in Figure 4.

Discussion

The results of the present study show that both diltiazem and nifedipine cause dose-related depressions in systemic blood pressure. Such an action of the calcium-entry blocking drugs is well recognized and probably represents a major effect of these compounds on vascular smooth muscle causing vasodilatation (Janis & Scriabine, 1983). The finding that renal blood flow was not changed at any dose of diltiazem and only minimally increased by the intermediate dose of nifedipine suggests that these compounds do not have important actions on the renal vasculature. Similar observations have been found using other calcium-entry blocking drugs given intravenously, such as methoxyverapamil (Brown & Churchill, 1983), felodipine (DiBona & Sawin, 1983) and nifedipine (Hof, 1983) and nifedipine given into the renal artery (Dietz *et al.*, 1983). Further, it is clear that, in the face of the fall in blood pressure caused by diltiazem and nifedipine, renal blood flow could be effectively maintained and indicated that the autoregulatory ability of the kidney was not affected by these drugs.

Diltiazem increased glomerular filtration rate when given at the lowest dose rate and it is of interest that in one other study using diltiazem in the dog (Yamaguchi *et al.*, 1974) glomerular filtration rate increased with increasing doses of drug. The mechanisms involved in this response are unclear but the possibility exists that at low doses the compound had a differential effect on the afferent and efferent arteriolar resistances such that there was an increase in filtration pressure and hence filtration rate. However, neither diltiazem nor nifedipine at the two highest doses used had any effect on glomerular filtration rate. Similarly, in other studies using intravenous administration of either

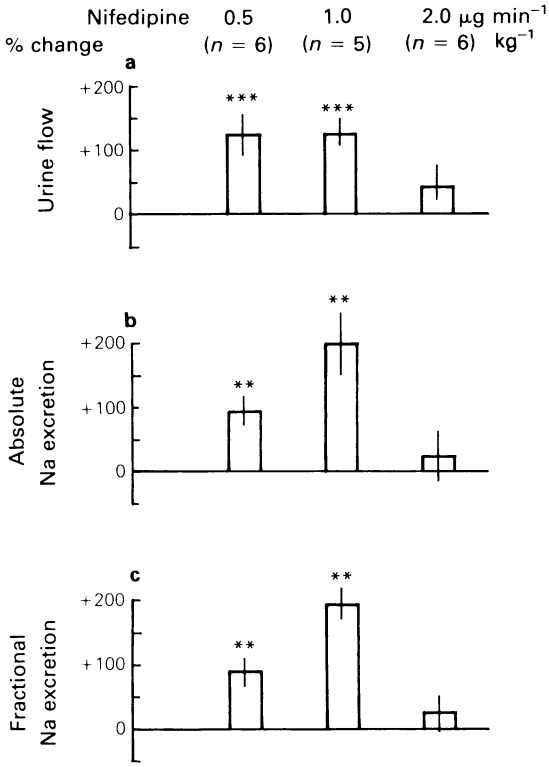

Figure 4 The percentage changes in (a) urine flow, (b) absolute and (c) fractional sodium excretions which occur following administration of nifedipine at 0.5, 1.0 and 2.0 $\mu g\,kg^{-1}\,min^{-1}$. Each column represents the mean of n animals and vertical lines show s.e.means. The significance levels are as in Figure 3.

methoxyverapamil (Brown & Churchill, 1983) or felodipine (DiBona & Sawin, 1983), or close renal arterial infusion of verapamil or nifedipine (Dietz *et al.*, 1983; Marre *et al.*, 1982) no change in filtration rate was observed which supports the present results. Taken together this evidence indicates that these compounds have a minimal effect on glomerular filtration rate.

At the lowest doses of diltiazem and nifedipine there was an approximate doubling of absolute sodium excretion. In the case of diltiazem this could have been due to an increase in glomerular filtration rate but as fractional sodium excretion was also increased significantly it is probable that the drug was having a direct action on tubular reabsorptive processes. In spite of the falls in blood pressure and minimal changes in renal haemodynamics caused by the two lower doses of diltiazem and nifedipine there was an increased output of sodium and water from these denervated kidneys. This provides further support for the contention that diltiazem and nifedipine were having a direct action on the tubular reabsorptive processes. Similar findings have been described by others using intravenous methoxyverapamil (Brown & Churchill, 1983), felodipine (DiBona & Sawin, 1983) and intra-renal arterial infusions of verapamil and nifedipine (Dietz *et al.*, 1983) into innervated kidneys, or nifedipine given into the isolated perfused kidney (Marre *et al.*, 1982).

The highest doses of both diltiazem and nifedipine had no effect on either water, absolute or fractional sodium excretions but did cause large reductions of blood pressure. It is known (Selkurt, 1951) that pressure directly influences sodium reabsorption along the renal tubules, with a reduction in pressure causing a reduction in sodium excretion. Thus, such a fall in pressure caused by the calcium-entry blocking drugs would have over-ridden any diuretic or natriuretic effect of diltiazem or nifedipine. Nevertheless, the compounds were probably exerting a tubular action at these high dose levels as a fall in blood pressure of this magnitude in the absence of drugs would have markedly reduced water and sodium excretion and this did not occur in their presence. Support for this argument comes from the observation that intra-renal arterial administration of diltiazem, which had no effect on blood pressure, did produce dose-related increases in sodium excretion (Yamaguchi *et al.*, 1974).

The present study demonstrates that systemic administration of two chemically dissimilar calcium-entry blocking drugs, diltiazem and nifedipine, causes dose-dependent decreases in blood pressure. At doses which had little or no effect on blood pressure there were minor changes in renal haemodynamics but large increases in water and sodium output which suggest a direct tubular action. The natriuretic and diuretic activity of nifedipine appeared to be greater than that obtained with diltiazem at doses which caused similar reductions in blood pressure. The diuretic and natriuretic activities of diltiazem and nifedipine at high doses were over-ridden by the tubular effects of the large falls in systemic pressure caused by the drugs. This study in the denervated kidney provides further evidence to show that the calcium-entry blockers directly inhibit sodium reabsorption by the kidney tubules.

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