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Effect of nitrendipine on renal cortical and papillary autoregulation in hypertensive rats

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Abstract

Renal cortical and papillary perfusions were assessed by laser-Doppler flowmetry and autoregulatory indices. There was cortical autoregulation (autoregulatory index of 0.31 ± 0.08) in Wistar from 160 to 100 mm Hg, but not in the papilla, which was abolished by nitrendipine, 0.125 and 0.25 $\mu g\ kg^{-1}\ min^{-1}$. In SHRSP the cortex, but not the papilla, exhibited autoregulation from 180 to 120 mm Hg (autoregulatory index of 0.27 ± 0.10) but not during low and high doses of nitrendipine. The non-clipped kidney cortex of 2KlC Goldblatt rats autoregulated from 190 to 130 mm Hg (autoregulatory index of 0.20 ± 0.13), but was inhibited only by the higher dose of nitrendipine. In mature Wistar and SHRSP cortical autoregulation is blocked effectively by nitrendipine whereas the 2K1C Goldblatt hypertensive rats are relatively resistant.

Keywords: Kidney; Autoregulation; Ca^{2+} channel antagonist

1. Introduction

A characteristic feature of the kidney is that it can powerfully autoregulate its blood flow over a wide range of perfusion pressures. There are two major mechanisms which underlie this phenomenon. Firstly, there is a myogenic hypothesis whereby increased pressure at the vascular smooth muscle of the afferent and efferent arterioles causes depolarisation and a resultant vasoconstriction of these resistance vessels to maintain flow at a constant level (Arendshorst et al., 1975). Secondly, the tubuloglomerular feedback mechanism is one whereby the flow of the tubular fluid past the macula densa causes a feedback response resulting in decreased filtration pressure of that nephron via afferent arteriolar constriction (Holstein-Rathlou et al., 1991). The exact contribution of each of these mechanisms in regulating renal blood flow autoregulation is currently being debated (Cupples et al., 1990).

There is increasing evidence that the efficiency of autoregulation varies at different regions of the kidney. Studies utilising laser-Doppler flowmetry (Roman and Kaldunski, 1988) have shown that there is good autoregulation of flow in the cortical regions which parallel that of whole kidney blood flow (Cupples et al., 1990). However, the situation regarding the deeper regions is less clear, insofar as Cohen et al. (1983), using dual slit videomicroscopy to measure red cell velocity, were able to demonstrate autoregulation in the papilla whereas studies by Fenoy and Roman (1991), using laser-Doppler flowmetry, were unable to find autoregulation in these areas. Indeed, these latter workers suggested that autoregulation of flow in the papillary regions only occurred under conditions of hydropenia and was not present in volume expanded animals.

The ability of the kidney to autoregulate whole organ blood flow in hypertensive states has been investigated. Studies undertaken in the spontaneously hypertensive rat (SHR) have yielded conflicting views with reports by Arendshorst (1979) and Iversen et al. (1987) demonstrating good autoregulation of total renal blood flow, albeit set to a higher level, whereas that of Dibona and Rios (1988) reported it to be deficient, even though both groups used similar experimental techniques and conditions. Observations by Roman and Kaldunski (1988), measuring regional perfusion with a laser-Doppler flowmeter, found cortical au-

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toregulation to be normal in the SHR, which contrasted with our own recent findings (Huang et al., 1994) of deficient cortical autoregulation in the stroke-prone spontaneously hypertensive rat (SHRSP). This latter study was undertaken using young immature rats and it was possible that the full myogenic capacity of the kidney had not developed. The situation regarding the renovascular form of hypertension has received less attention but Iversen et al. (1986), using the unclipped kidney of the 2K1C rat, found good whole kidney autoregulation over a higher pressure range than the normotensive controls but again this was not supported by the work of Ploth et al. (1981) using rats which had been subjected to a shorter period of renal artery clipping who demonstrated deficiencies in the autoregulation of total renal blood flow.

The aim of this study was to examine the effect of the Ca^{2+} channel antagonists on regional autoregulation of blood flow in adult mature normotensive and in stroke-prone spontaneously hypertensive (SHRSP) and 2K1C Goldblatt hypertensive rats in which the renin-angiotensin system had been chronically stimulated. In this way, potential differences in the myogenic responses and dependence on extracellular Ca^{2+} might become apparent. This was approached using laser-Doppler flowmetry to measure cortical and papillary perfusion over a range of pressures from a maximum of 180 to a minimum of 50 mm Hg to generate autoregulatory curves. Studies were then undertaken in the presence of two dose levels of nitrendipine which have been previously shown to attenuate autoregulation (Huang et al., 1994).

2. Materials and methods

2.1. 2K1C Goldblatt rat preparation

Three groups of male Wistar rats, 85–95 g underwent preparative surgery 4 weeks before the terminal experiment. They were briefly anaesthetised with an O_2-N_2O-fluothane mixture, the right kidney was exposed retroperitonally, its artery cleared close to the aorta and a 0.2 mm 'U' shaped silver clip was slipped onto the artery and its ends clamped shut. The abdominal musculature and skin were sutured in separate layers and intramuscular antibiotics and analgesics given and the animals allowed to recover. Three weeks later the animals were subjected to a second procedure to create a papillary window.

2.2. Papillary window preparation

All animals were subjected to this procedure which was essentially the same as that described by Roman and Smits (1986). The animals were anaesthetised as described in the previous section and the left kidney was exposed retroperitonally. A small area of the dorsal surface of the cortex was removed over the point where the ureter entered the kidney using a sharp scalpel. Once any bleeding had been stopped, the kidney was replaced in the peritoneal cavity, the abdominal musculature and skin sutured in turn and, following administration of intramuscular antibiotics and analgesics, the animals were allowed to recover. The animals were then taken for experimentation 7 days later.

2.3. Experimental procedure

On the day of the experiment, rats were anaesthetised with sodium pentobarbitone (60 mg kg^{-1}, i.p.) and cannulae inserted into the left femoral and jugular veins for infusion of saline, drugs and supplementary doses of anaesthetic. Cannulae were also placed in the right carotid and left femoral arteries for measurement of arterial pressure above and below the left renal artery, respectively (Statham P23ID linked to a Grass model 7 polygraph). The left kidney was exposed via a mid-line abdominal incision and ligatures were placed around the aorta above and below the left renal artery and attached to a screw device to allow the aorta to be constricted such that perfusion pressure at the kidney could be raised or lowered as required. Further ligatures were placed around the mesenteric and coeliac arteries. The kidney was freed of perirenal fat, its artery, vein and ureter cleared and was then placed in a plastic holder to expose its dorsal surface. During this procedure the kidney was denervated and was thus not subject to reflex neural influences. The fatty infiltration at the papillary window area of the cortex was dissected away to expose the papilla and if bleeding occurred this was minimised by local application of a small pad of cotton wool soaked in thrombin (100 U ml^{-1}).

2.4. Cortical and papillary perfusion measurements

Laser-Doppler measurements of perfusion were made with a Perimed PF3 and a PF303 probe of 1 mm diameter. The Laser-Doppler flowmeter was calibrated such that one perfusion unit was equivalent to a 10 mV output. Perfusion measured in this way represents the product of the velocity and concentration of moving blood cells in the volume of tissue under the probe. The probe was closely applied to the tissue (0.5–1.0 mm) and four measurements of 1–2 min duration were made at different sites on the cortex and one measurement was taken over the papilla. Background recordings were taken at each site of cortex and papilla after a ligature had been tied around the renal artery and vein.

Renal perfusion was increased to its maximal level by two means, firstly by occluding the mesenteric and coeliac arteries and secondly by injecting intravenously 1–2 ml blood collected from donor rats. Cortical and papillary perfusions were estimated at these highest levels and then, by adjusting the degree of constriction of the aortic loop, renal perfusion presure was lowered in steps of 10 mm Hg to the lowest value of 50 mm Hg. At each pressure level, cortical and papillary perfusions were measured. Each animal in groups I and II was subjected to two sets of pressure reductions while in other groups each rat underwent only one set of pressure reductions. An autoregulary index was calculated for both cortex and papilla as follows: Autoregulatory index = [(Perfusion 1 − Perfusion 2)/Perfusion 1]/[(Renal perfusion pressure 1 − Renal perfusion pressure 2)/Renal perfusion pressure 1].

This ratio was put forward by Semple and Dewardener (1959) and an index of zero indicates perfect autoregulation of perfusion while an index of one indicates no autoregulation and approximates to a fixed resistance.

2.5. Hormone infusion

The changes in systemic and renal perfusion pressure of this nature could lead to large changes in the level of humoral factors acting on the kidney. In order to minimise the influence of these changes, the approach of Roman and Cowley (1985) was used in which a range of hormones were infused exogenously to achieve high but stable plasma levels. The following hormones were given as a cocktail: aldosterone (66 ng kg^{-1} min^{-1}), hydrocortisone (60 μg kg^{-1} min^{-1}), vasopressin (0.17 ng kg^{-1} min^{-1}) and noradrenaline (333 ng kg^{-1} min^{-1}). The hormone cocktail was dissolved in normal saline immediately prior to use and infused in a volume of 33 μl min^{-1} 100 g^{-1} body weight.

2.6. Drugs

Nitrendipine was dissolved at 1 mg ml^{-1} in a 969:60:100 polytheylene glycol-400:glycerol:water mixture and aliquots were stored deep frozen and used within 1 week. This stock solution was diluted with saline and when nitrendipine was infused, all syringes, containers and cannulae were covered with aluminium foil to prevent breakdown of nitrendipine due to exposure to light.

2.7. Experimental protocol

Normal saline (150 mmol NaCl) was infused at 33 μl min^{-1} 100 g^{-1} body weight as soon as the venous cannula had been placed and this was maintained for the duration of the experiment. The initial cortical and papillary perfusion measurements were taken 1 h after completion of surgery and used to establish baseline values. The hormone cocktail was then infused and continued throughout the experiment. Once the new stable levels had been reached (after 30 min) a further set of measurements were taken to give the starting values for the experiment.

2.8. Animal groups

Eight groups of rats were studied.

Group I ($n = 9$) were Wistar rats (225 ± 7 g) in which two sets of measurements were taken. Once the highest blood pressure was achieved, perfusion measurements at each pressure level were undertaken as described above. Following the first set of pressure manipulations, nitrendipine was given at 0.125 μg kg^{-1} ml^{-1} and 30 min later, the kidney was subjected to a second set of pressure reductions.

Group II ($n = 6$) were also Wistar rats (226 ± 5 g) which were treated identically to group I except that nitrendipine was given at 0.25 μg kg^{-1} min^{-1} in the second part of the experiment.

Group III ($n = 6$) were stroke prone spontaneously hypertensive rats (SHRSP), 181 ± 8g, in which saline was infused throughout and acted as a control group. Once the highest blood pressure was achieved, perfusion measurements were undertaken.

Group IV ($n = 6$) were SHRSP (189 ± 10 g) which were infused with nitrendipine, 0.125 μg kg^{-1} min^{-1} i.v. for 30 min before the perfusion measurements at various renal perfusion pressures were undertaken.

Group V ($n = 6$, 190 ± 4 g) this group was identical to groups III and IV except that nitrendipine was given at 0.25 μg kg^{-1} min^{-1}.

Groups VI ($n = 8$, 249 ± 5 g), VII ($n = 8$, 257 ± 7 g), and VIII ($n = 7$, 267 ± 8 g) comprised 2KlC Goldblatt rats, which were given either vehicle (group VI), or 0.125 μg kg^{-1} min^{-1} nitrendipine (group VII) or 0.25 μg kg^{-1} min^{-1} nitrendipine (group VIII).

2.9. Statistics

Renal perfusion pressure, cortical and papillary perfusion were recorded at each pressure level and absolute changes obtained. Within each group of rats the absolute changes in each of the variables following nitrendipine administration was calculated and compared using a Student's paired t-test. Autoregulatory curves were generated using a 'set-point' which was closest to the initial baseline pressure for each group of rats and percentage deviations from this level were calculated and presented in the Tables and Figures. Autoregulatory indices for each treatment and group of rats were estimated over defined ranges and differ-

Table 1
Basal variables of all groups of rats

Group	n	Body weight (g)	Age (week)	Base line		
				RPP (mm Hg)	Cortical perfusion (PU)	Papillary perfusion (PU)
Wistar 0.125 $\mu g\ kg^{-1}\ min^{-1}$ nitrendipine	9	225 ± 7	7.9 ± 0.2	103 ± 3	152 ± 7	174 ± 17
Wistar 0.25 $\mu g\ kg^{-1}\ min^{-1}$ nitrendipine	6	226 ± 5	7.5 ± 0.3	108 ± 4	145 ± 12	208 ± 24
SHRSP control	6	181 ± 8 [a]	11.4 ± 0.8 [a]	131 ± 4 [a]	157 ± 15	198 ± 24
SHRSP 0.125 $\mu g\ kg^{-1}\ min^{-1}$ nitrendipine	6	189 ± 10 [a]	11.9 ± 0.8 [a]	133 ± 5 [a]	176 ± 14	222 ± 26
SHRSP 0.25 $\mu g\ kg^{-1}\ min^{-1}$ nitrendipine	6	190 ± 4 [a]	11.6 ± 1.1 [a]	132 ± 2 [a]	170 ± 11	221 ± 11
2K1C control	8	249 ± 5 [a]		135 ± 5 [a]	122 ± 6 [a]	209 ± 23
2K1C 0.125 $\mu g\ kg^{-1}\ min^{-1}$ nitrendipine	8	257 ± 7 [a]		156 ± 6 [a]	110 ± 5 [a]	169 ± 24
2K1C 0.25 $\mu g\ kg^{-1}\ min^{-1}$ nitrendipine	7	267 ± 8 [a]		144 ± 5 [a]	121 ± 11 [a]	208 ± 22

Base line: data obtained before infusion of hormone cocktail. n = number of rats tested. RPP: renal perfusion pressure in mm Hg. PU: perfusion unit. [a] $P < 0.05$ compared with Wistar data.

ences from 1 were calculated and comparisons between groups were undertaken using a one way analysis of variance (ANOVA) followed by a post-hoc Bonferroni-Dunn test. Analyses were undertaken using Super ANOVA software (Abacus Concepts) and significant differences were taken when P was less than 0.05.

3. Results

The baseline values of body weight, age, renal perfusion pressure, cortical and papillary perfusions for groups I to VIII are presented in Table 1 and show that the SHRSP rats were older and lighter than the Wistars, that the SPSHR and 2K1C Goldblatt rats had a higher blood pressure and the cortical perfusion was lower in the 2K1C Goldblatt hypertensive rats. Table 2 shows that in group I rats, initial blood pressure was 103 ± 3 mm Hg (Table 1) and the highest pressure achieved following hormone infusion, occlusion of the mesentric and coeliac arteries and transfusion of blood was approximately 160 mm Hg. As renal perfusion pressure was gradually reduced in group I animals from 160 to 100 mm Hg, there was only a small fall in cortical perfusion and the autoregulatory index (Table

Table 2
Cortical and papillary perfusion achieved at each pressure in Wistar rats

0.125 $\mu g\ kg^{-1}\ min^{-1}$ nitrendipine			0.25 $\mu g\ kg^{-1}\ min^{-1}$ nitrendipine		
RPP (mm Hg)	Cortical perfusion (PU)	Papillary perfusion (PU)	RPP (mm Hg)	Cortical perfusion (PU)	Papillary perfusion (PU)
Saline					
160	170	160	160	182	170
148	150 ± 10	138 ± 26	150	177	165
139	146 ± 12	163 ± 15	138	162 ± 7	208 ± 33
129	145 ± 11	167 ± 17	130	163 ± 6	205 ± 28
119	140 ± 11	156 ± 15	120	162 ± 7	189 ± 26
109	136 ± 11	143 ± 14	110	161 ± 6	178 ± 23
99	130 ± 11	136 ± 15	100	157 ± 8	166 ± 21
89	124 ± 12	136 ± 15	90	149 ± 9	148 ± 19
79	117 ± 12	114 ± 14	80	140 ± 10	137 ± 19
69	104 ± 10	101 ± 13	70	123 ± 11	124 ± 19
59	87 ± 9	87 ± 13	60	104 ± 15	112 ± 20
50	69 ± 10	74 ± 15	50	86 ± 13	98 ± 19
After nitrendipine					
140	123	165	140	145	155
130	143 ± 20	143 ± 15	130	144 ± 6	146 ± 29
120	136 ± 17	133 ± 14	120	138 ± 5	150 ± 24
110	131 ± 18	121 ± 16	110	129 ± 4	138 ± 23
100	119 ± 15	109 ± 15	100	120 ± 5	126 ± 24
90	112 ± 15	99 ± 15	90	106 ± 8	114 ± 23
79	100 ± 14	84 ± 15	80	106 ± 8	114 ± 23
69	88 ± 14	73 ± 16	70	81 ± 10	88 ± 18
60	83 ± 14	66 ± 16	60	70 ± 10	78 ± 15
50	66 ± 11	48 ± 13	50	54 ± 10	68 ± 14

RPP: renal perfusion pressure. PU: perfusion unit.

3) of 0.31 ± 0.08, which was significantly different from 1 ($P < 0.05$), indicated that there was effective autoregulation whereas papillary perfusion decreased steadily (an autoregulatory index of 1.04 ± 0.18, Table 3). Further reduction of perfusion pressure, from 100 to 50 mm Hg was associated with autoregulatory indices (Table 3) not different from 1 which demonstrated that neither cortex nor papilla were capable of autoregulating over this pressure range. Administration of nitrendipine into the group I rats reduced blood pressure by 16 ± 3 mm Hg ($P < 0.001$), increased cortical perfusion by 23 ± 7 perfusion units ($P < 0.05$) from its baseline levels (Table 1) but had no effect on papillary perfusion. Renal perfusion pressure was then maximally elevated and decreased in a step-wise fashion (Table 2). Under these conditions, cortical perfusion did not appear to autoregulate over the higher pressure range (the autoregulatory index was not different from 1) which contrasted with that obtained in the absence of nitrendipine, and over the lower pressure range (100–50 mm Hg) autoregulation was not apparent in either cortex or papilla as shown by the autoregulatory indices (Table 3).

In the second group of Wistar rats, the initial test of pressure reduction showed cortical but not papillary perfusion to be well maintained over the high pressure range (Table 2) and produced a pattern of autoregulatory indices (Table 3) very comparable to group I, that is good autoregulation in cortex but not papilla from 160 to 100 mm Hg, and from 100 to 50 mm Hg there was no autoregulation at either site. Following infusion of the high dose of nitrendipine, pressure fell by 18 ± 3 mm Hg ($P < 0.01$) and there were significant (both $P < 0.05$) increases in both cortical and papillary perfusions of 19 ± 5 and 17 ± 6 perfusion units, respectively, from the baseline levels (Table 1). Thereafter, pressure was raised to its highest level and it was found that perfusion in the cortex and papilla decreased steadily when pressure was lowered (Table 2) and there was no indication of autoregulation at any pressure level by either vascular region as shown by the autoregulatory indices (Table 3). The full autoregulatory curves for the cortex are shown in Fig. 1.

The second series of studies were undertaken in SHRSP (groups III to V) which were slightly lighter than the Wistar rats, but were much older, approximately 12 weeks versus 8 weeks, and had elevated blood pressure, 132 versus 105 mm Hg. The manoeuvre to raise perfusion pressure resulted in starting pressures of around 180 mm Hg (Table 4), and in preliminary experiments there was excessive bleeding from various sites, it was therefore difficult to undertake two autoregulatory curves in one animal, consequently, only one test was undertaken. The group III rats were the control SHRSP and over the pressure range, 180–120 mm Hg, the cortex, but not papilla, was able to maintain perfusion at a relatively stable level (Table 4) and exhibited good autoregulation, as shown by the autoregulatory indices (Table 3). Over the pressure range 120–50 mm Hg, neither site was able to maintain perfusion and the autoregulatory indices indicated that there was no autoregulation (Table 3). In the group IV rats, administration of nitrendipine decreased blood pressure by 10 ± 2 mm Hg ($P < 0.01$) and increased cortical perfusion by 12 ± 3 perfusion units ($P < 0.05$) from baseline values (Table 1) but did not change papillary perfusion. It was apparent that over both the high (180–120 mm Hg) and low (120–50 mm Hg) pressure ranges perfusion fell gradually in both cortex and papilla (Table 4) and neither the cortex nor papilla could autoregulate in response to the pressure changes (Table 3) and indicated that cortical autoregulation had been blunted compared to the group III animals which had not received the drug. The group V SHRSP were given the high dose of nitrendipine which decreased blood pressure by 11 ± 2 mm Hg but caused

Table 3
Autoregulatory indices

Group	RPP range (mm Hg)		Cortical AI		Papillary AI	
	Range 1	Range 2	In range 1	In range 2	In range 1	In range 2
Wistar						
Saline	160–100	100–50	0.31 ± 0.08 [f]	0.81 ± 0.14	1.04 ± 0.18	0.90 ± 0.04
(Nit. 0.125 $\mu g\ kg^{-1}\ min^{-1}$)	140–100	100–50	0.90 ± 0.15 [b]	0.90 ± 0.06	1.04 ± 0.22	1.28 ± 0.09
Wistar						
Saline	160–100	100–50	0.26 ± 0.09 [f]	0.89 ± 0.13	0.94 ± 0.17	0.86 ± 0.07
(Nit. 0.25 $\mu g\ kg^{-1}\ min^{-1}$)	140–100	100–50	0.80 ± 0.02 [b]	1.20 ± 0.09	1.16 ± 0.08	0.94 ± 0.08
SHRSP saline	183–120	120–50	0.27 ± 0.10 [f]	1.34 ± 0.11	0.94 ± 0.19	0.89 ± 0.05
SHRSP (nit. 0.125 $\mu g\ kg^{-1}\ min^{-1}$)	180–120	120–50	0.87 ± 0.06 [a]	1.18 ± 0.11	1.09 ± 0.31	1.13 ± 0.11
SHRSP (nit. 0.25 $\mu g\ kg^{-1}\ min^{-1}$)	173–120	120–50	0.82 ± 0.18 [a]	1.35 ± 0.15	0.91 ± 0.06	1.12 ± 0.10
2KIC saline	190–130	130–50	0.20 ± 0.13 [f]	1.07 ± 0.07	0.97 ± 0.17	0.91 ± 0.17
2K1C (nit. 0.125 $\mu g\ kg^{-1}\ min^{-1}$)	200–130	130–50	0.35 ± 0.12 [e]	1.04 ± 0.06	0.86 ± 0.12	1.09 ± 0.10
2KIC (nit. 0.25 $\mu g\ kg^{-1}\ min^{-1}$)	190–130	130–50	0.75 ± 0.03 [a]	1.13 ± 0.04	0.88 ± 0.11	1.11 ± 0.06

RPP: renal perfusion pressure. AI: autoregulatory index. Nit.: nitrendipine. [a,b,c] Significantly different from 1 at $P < 0.05$, 0.01 and 0.001, respectively. [e,f,g] Significantly different from control, which was obtained during saline infusion, at $P < 0.05$, 0.01 and 0.001, respectively.

Table 4
Cortical and papillary perfusion achieved at each pressure in SHRSP

Saline			Nitrendipine 0.125 $\mu g\ kg^{-1}\ min^{-1}$			Nitrendipine 0.25 $\mu g\ kg^{-1}\ min^{-1}$		
RPP (mm Hg)	Cortical perfusion (PU)	Papillary perfusion (PU)	RPP (mm Hg)	Cortical perfusion (PU)	Papillary perfusion (PU)	RPP (mm Hg)	Cortical perfusion (PU)	Papillary perfusion (PU)
173	167 ± 9	153 ± 38	171	173 ± 10	191 ± 26	173	180 ± 31	177 ± 16
160	154 ± 8	198 ± 20	160	160 ± 7	184 ± 17	160	188 ± 18	181 ± 11
150	151 ± 7	183 ± 20	150	149 ± 8	172 ± 17	150	179 ± 19	170 ± 12
140	150 ± 7	175 ± 19	140	142 ± 8	163 ± 17	140	164 ± 19	163 ± 13
130	145 ± 8	166 ± 18	130	133 ± 6	154 ± 15	130	155 ± 19	152 ± 12
120	140 ± 7	159 ± 18	120	124 ± 7	147 ± 14	120	146 ± 21	139 ± 12
110	125 ± 6	150 ± 18	110	116 ± 8	138 ± 13	110	137 ± 20	129 ± 12
100	108 ± 8	135 ± 15	100	104 ± 9	126 ± 11	100	125 ± 20	119 ± 12
90	99 ± 9	123 ± 14	90	92 ± 11	108 ± 13	90	109 ± 18	105 ± 8
80	82 ± 9	113 ± 13	80	82 ± 10	93 ± 12	80	95 ± 17	94 ± 8
70	71 ± 8	101 ± 13	70	70 ± 9	81 ± 11	70	74 ± 11	76 ± 6
60	54 ± 7	88 ± 13	60	59 ± 7	70 ± 11	60	54 ± 6	61 ± 4
50	42 ± 6	73 ± 12	50	41 ± 4	54 ± 8	50	39 ± 6	48 ± 5

RPP: renal perfusion pressure. PU: perfusion unit.

significant increases in cortical and papillary perfusions of 27 ± 6 ($P < 0.01$) and 14 ± 5 ($P < 0.05$) perfusion units, respectively, from the baseline levels (Table 1). Following raising of renal perfusion pressure to the highest values, the step-wise reduction in pressure was associated with gradual falls in both cortical and papillary perfusions (Table 4) and resulted in autoregulatory indices (Table 2) which were not significantly different from 1 for both cortex and papilla over the high and low pressure ranges, demonstrating that at the cortex, nitrendipine had blocked autoregulation. The full autoregulatory curves are presented in Fig. 2.

The third study (group VI-VIII) was undertaken in 2K1C Goldblatt rats and the left kidney weights of these animals, at 1.39 ± 0.03 g, were all significantly ($P < 0.001$) higher than the right kidneys, at 1.07 ± 0.02 g, by approximately 30% which was taken to be due to the constraining influence of the clip on the right kidney. Blood pressure and cortical and papillary perfusions were similar in all three groups of 2K1C Goldblatt hypertensive rats (Table 1). Blood pressure was significantly ($P < 0.001$) higher, at 145 ± 4 mm Hg, than that of normotensive Wistar rats, of approximately 105 mm Hg, while cortical perfusion at 118 ± 4 perfusion units was significantly ($P < 0.001$) lower than 149 ± 6 perfusion units of Wistar rats whereas papillary perfusion was comparable to that of normotensive Wistar rats (195 ± 13 versus 188 ± 14 perfusion units). In the group VI 2K1C Goldblatt rats, as renal perfusion pressures were reduced to 130 from 190 mm Hg cortical perfusion remained relatively stable (Table 5) and had an autoregulatory index of 0.20 ± 0.13 (Table

Table 5
Cortical and papillary perfusion achieved at each pressure in 2K1C rats

Saline			Nitrendipine 0.125 $\mu g\ kg^{-1}\ min^{-1}$			Nitrendipine 0.125 $\mu g\ kg^{-1}\ min^{-1}$		
RPP (mmHg)	Cortical perfusion (PU)	Papillary perfusion (PU)	RPP (mmHg)	Cortical perfusion (PU)	Papillary perfusion (PU)	RPP (mmHg)	Cortical perfusion (PU)	Papillary perfusion (PU)
190	123 ± 8	295 ± 3	190	115 ± 12	203 ± 12	190	170	260
180	125 ± 5	256 ± 30	180	128 ± 15	196 ± 6	183	160 ± 1	260 ± 15
170	128 ± 8	221 ± 19	171	125 ± 9	189 ± 10	173	145 ± 4	226 ± 26
160	128 ± 7	211 ± 19	161	126 ± 11	178 ± 11	161	143 ± 8	225 ± 28
150	127 ± 7	202 ± 18	151	123 ± 12	173 ± 14	150	141 ± 12	201 ± 25
141	131 ± 8	203 ± 20	141	125 ± 14	179 ± 21	140	134 ± 12	197 ± 23
130	127 ± 8	189 ± 18	130	122 ± 15	168 ± 20	130	128 ± 10	181 ± 23
121	119 ± 6	178 ± 18	120	115 ± 14	156 ± 20	120	124 ± 12	171 ± 22
111	106 ± 6	163 ± 17	110	109 ± 13	148 ± 20	110	115 ± 12	159 ± 21
100	95 ± 5	151 ± 17	100	99 ± 13	137 ± 23	100	107 ± 12	146 ± 19
90	78 ± 5	139 ± 17	90	92 ± 13	120 ± 23	90	98 ± 9	129 ± 20
80	70 ± 5	119 ± 16	80	79 ± 12	105 ± 22	80	88 ± 8	116 ± 19
70	62 ± 5	102 ± 16	70	69 ± 12	90 ± 21	70	71 ± 8	94 ± 17
60	50 ± 6	88 ± 14	60	57 ± 10	77 ± 20	60	52 ± 7	78 ± 14
50	41 ± 4	66 ± 9	50	46 ± 9	60 ± 16	50	40 ± 6	56 ± 9

RPP: renal perfusion pressure. PU: perfusion unit.

3), consistent with efficient autoregulation, but below this pressure range cortical perfusion fell gradually and gave an autoregulatory indices of 1.07 ± 0.07 (Table 3) which indicated no autoregulation was occurring. By contrast, papillary perfusion decreased steadily with reduction in pressure (Table 5) and gave autoregulatory indices (Table 3) which indicated there was no autoregulation over either pressure range.

Administration of the nitrendipine at 0.125 μg kg^{-1} min^{-1} in group VII 2K1C Goldblatt hypertensive rats had no effect on blood pressure and papillary perfusion but cortical perfusion was significantly ($P < 0.05$) increased by some 20 perfusion units from baseline values (Table 1). Once pressure had been raised to its highest level, as it was reduced over the range 190–130 mm Hg (Table 5) cortical perfusion was relatively constant and gave an autoregulatory index of 0.35 ± 0.12 (Table 3) indicating good autoregulation, while below this pressure range, no autoregulation was apparent. Again, papillary perfusion gave autoregulatory index values (Table 3) which were not different from 1 indicating that this vascular region did not autoregulate.

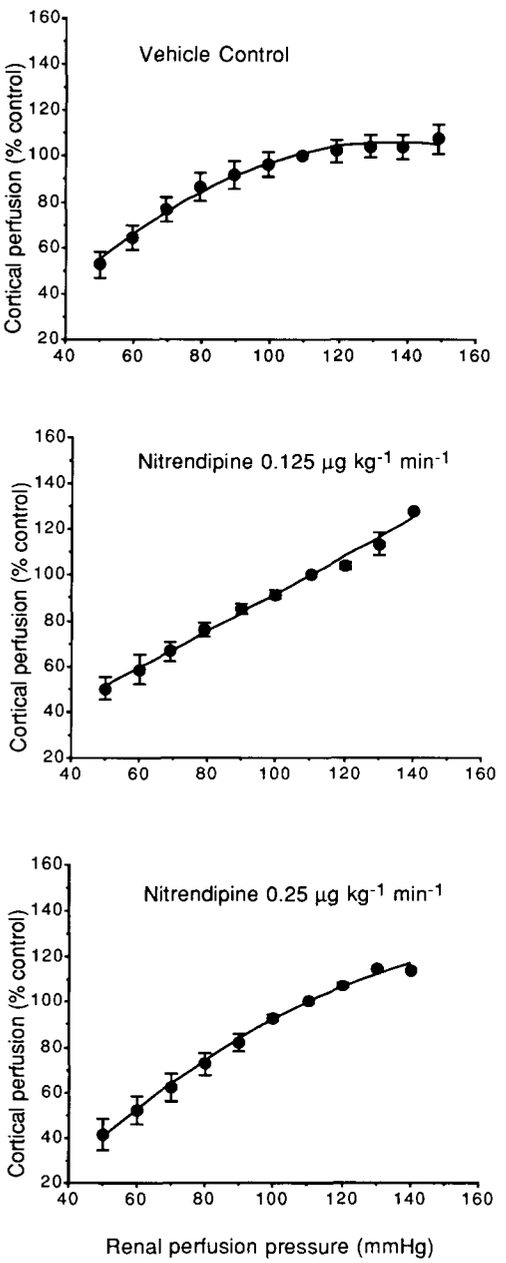

Fig. 1. Shows the percentage changes in cortical perfusion in Wistar rats from baseline pressures during either vehicle infusion or administration of nitrendipine at 0.125 and 0.25 μg kg^{-1} min^{-1}.

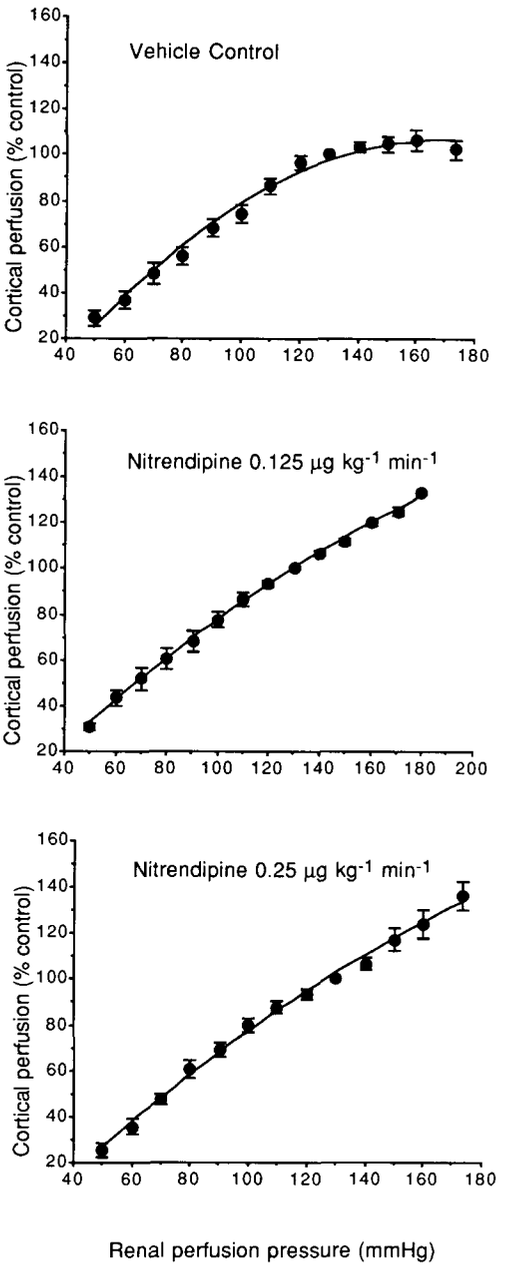

Fig. 2. Shows the percentage changes in cortical perfusion in groups of SPSHR from baseline pressures during the infusion of vehicle or nitrendipine at 0.125 or 0.25 μg kg^{-1} min^{-1}.

The autoregulatory indices for cortex and papilla were similar in Groups VI and VII and indicate that nitrendipine had no effect at this dose level. Following administration of the nitrendipine at 0.25 μg kg^{-1} min^{-1} in group VIII animals, blood pressure was decreased by 13 mm Hg ($P < 0.01$) but at the same time cortical perfusion increased significantly by 21 perfusion units whereas papillary perfusion did not change from the baseline values. Renal perfusion pressure was then increased maximally and there were gradual reductions in both cortical and papillary perfusions as pressure was reduced from the highest to the lowest values (Table 5). This gave rise to autoregulatory indices (Table 3) which were not significantly different from 1 at either pressure range for both cortex and papilla. The full autoregulatory curves are given in Fig. 3 and show that in the group VIII rats there was a blockade of cortical autoregulation over the higher pressure range compared to the control group and the group VII given the low dose of nitrendipine.

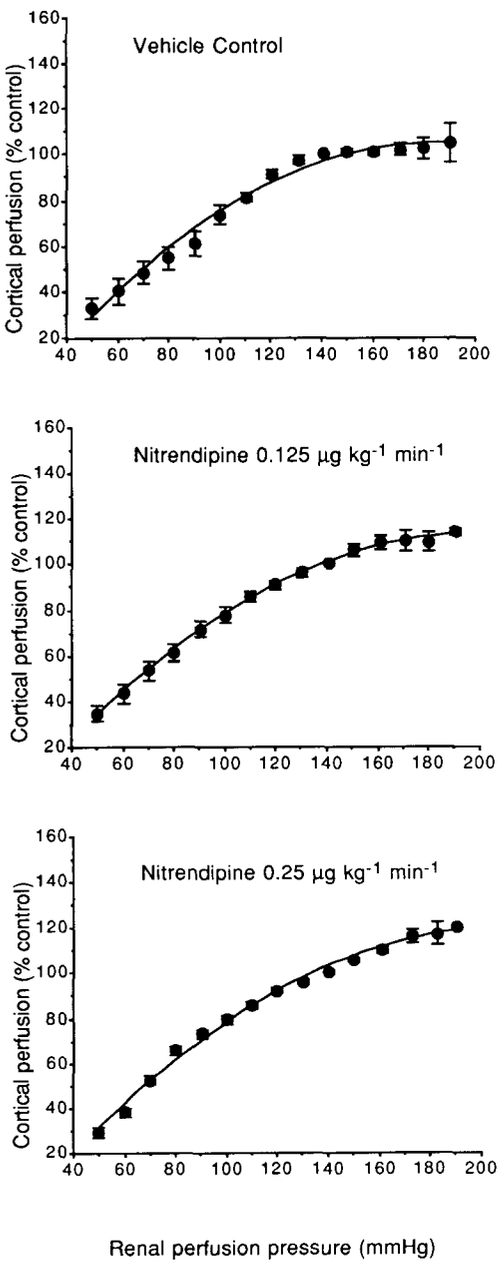

Fig. 3. Shows the percentage changes in cortical perfusion in groups of 2K1C Goldblatt rats from baseline pressures during the infusion of vehicle or nitrendipine at 0.125 or 0.25 μg kg^{-1} min^{-1}.

4. Discussion

The aim of this study was to examine the characteristics of blood flow autoregulation in two models of hypertension, a genetic and renovascular form, and to determine whether this phenomenon was affected by the Ca^{2+} channel antagonists. Measurement of regional blood flow, in the cortex and papilla, was undertaken using laser-Doppler flowmetry and the validity of this technique for measuring quantitative changes in perfusion in both cortex and papilla has been validated by Roman and co-workers (Roman and Smits, 1986; Smits et al., 1986) although no absolute measure of blood flow can be produced using this method. In order to get a wide pressure range over which to examine autoregulation two strategies were utilized to achieve a maximal pressure. One approach was based on that of Roman and Cowley (1985) in which replacement hormone and catecholamines were given in order to maintain high (some 4–5 times) but stable plasma levels and the mesenteric and coeliac arteries were tied off to increase peripheral resistance. A second way was that of transfusing 1–2 ml blood from donor rats into the experimental animal. These particular manoeuvres were very necessary as the Ca^{2+} channel antagonist itself caused decreases in blood pressure which had the potential of reducing the pressure range over which measurements could be taken.

The normotensive rats demonstrated good cortical autoregulation down to approximately 100 mm Hg but below this pressure and until 80 mm Hg was reached perfusion gradually decreased, and thereafter perfusion fell much more steeply as pressure was reduced. This pattern of perfusion over this pressure range was very similar to that observed previously but in 130 g rats (Huang et al., 1994) compared with 230 g in the present study and correlates closely with that previously observed (Roman and Kaldunski, 1988) using normotensive rats and laser-Doppler flowmetry. It was evident that perfusion through the papillary region was pressure dependent as from the highest to the lowest pressure there was no indication of autoregulation at any stage. This corresponds to our own previous findings in young rats (Huang et al., 1994) and those of Fenoy et al. (1992) in adult rats. The reason for this

lack of papillary autoregulation is not apparent but may be the consequence of the relative volume expansion in the animals, as previous reports of Fenoy and Roman (1991) and Cohen et al. (1983) have indicated that papillary autoregulation occurs under conditions of hydropenia but is lost during volume expansion.

Administration of both low and high doses of nitrendipine caused an increase in perfusion within the cortex which probably represents its action at the resistance vessels causing hyperpolarization and hence dilation. Furthermore, autoregulation by the cortex was effectively abolished because as perfusion pressure was reduced there was a proportionate decrease in cortical perfusion. This finding was very similar to that reported previously for both young and adult normotensive rats (Huang et al., 1994; Fenoy et al., 1992). There is good in vitro evidence (Fleming et al., 1987; Carmines and Navar, 1989) to show that the Ca^{2+} channel antagonists have a preferential action at the afferent arterioles to cause vasodilatation, and this is the major resistance bed within the kidney and probably accounts for the largest component of the myogenic response to pressure. Interestingly, the degree of vasodilatation induced by the nitrendipine in the renal cortex was similar in both normotensive and hypertensive rats and therefore provided no evidence to support the view that the vasculature of the hypertensive rats were more sensitive to the Ca^{2+} channel antagonist. The observations of the present study emphasise not only that the Ca^{2+} channel antagonists cause dilatation but can also prevent the musculature from responding appropriately to changes in perfusion pressure.

Basal blood pressure in the SHRSP was some 20 mm Hg higher than that of the Wistars and it was apparent that the maximum pressures achieved at the start of the autoregulation experiment were greater, 180 versus 160 mm Hg. In the SHRSP autoregulation of cortical perfusion was efficient down to 120 mm Hg, but below this pressure, cortical perfusion decreased with pressure. This increase in the limit of autoregulation of cortical perfusion suggests that the vasculature has been reset to operate effectively over a higher pressure range. These observations in the mature SHRSP correlated well with the findings of whole kidney renal blood flow by Arendshorst (1979) and Iversen et al. (1987) and with the laser-Doppler findings of Roman and Kaldunski (1988) using the SHR. The Ca^{2+} channel antagonists at both doses caused significant increases in cortical perfusion in the SHRSP even though blood pressure itself was reduced, reflecting a marked vasodilatation in the kidney, similar to the pattern observed in the normotensive rat. In the presence of both low and high doses of nitrendipine cortical autoregulation was abolished in these mature SHRSP which was consistent with our previous findings with the young SHRSP (Huang et al., 1994). Thus, these findings extend the original observations of Fenoy et al. (1992) in the SHR, that in these genetic models of hypertension the vasculature and its response to perfusion pressure is blocked by the Ca^{2+} channel antagonists.

It was of interest that even though the 2K1C Goldblatt rats had only been subjected to 3 weeks of renal artery occlusion and had been subjected to the papillary window surgery, they had blood pressures some 30–50 mm Hg greater than the normotensive Wistars. It is recognised that in this relatively short time phase, the hypertension was probably renin dependent (Sen et al., 1979). The data showed quite clearly that the cortex, but not papilla, of the unclipped kidney autoregulated perfusion quite well but only down to approximately 130 mm Hg which was slightly greater than the SHRSP, but much higher than the autoregulatory limit in the Wistar. Interestingly, these observations support the report of Iversen et al. (1986) who measured total renal blood flow in the unclipped kidney 2K1C Goldblatt rats, although their animals were 10 weeks post-clipping which may be a renin independent phase. However, these findings do not support the observations of Ploth et al. (1981) using essentially the same animal weights, clip size and 3–4 weeks post-clipping, who found that total renal blood flow was not autoregulated. The reasons for these conflicting findings are not clear and remain to be clarified.

Administration of the Ca^{2+} channel antagonist to the 2K1C Goldblatt rats decreased blood pressure only at the higher dose, but increased cortical perfusion at both dose levels. Interestingly, the low dose of nitrendipine had no effect on autoregulation cortical perfusion from 180 to 130 mm Hg which was in marked contrast to the action of the compound in the normotensive and SHRSP groups. The reason for this is unclear, but one factor might be the high level of circulating angiotensin II which is likely to have been present (Sen et al., 1979) chronically in these rats 3 weeks post-clipping. Indeed, the basal levels of cortical perfusion were significantly less in the 2K1C Goldblatt rats than in the Wistar or SHRSP. It may be that the chronic elevation of angiotensin II could have increased the bulk and tone of the resistance vessels such that they were still able to undergo further vasodilatation as renal perfusion pressure was reduced and thereby contributed to the autoregulatory response. This may suggest that in the 2K1C Goldblatt rats the myogenic responses evoked during perfusion pressure changes may be more dependent upon intracellular Ca^{2+} stores compared with the normotensive and SHRSP with extracellular Ca^{2+} moving into the cells. Nevertheless, the higher dose of nitrendipine effectively abolished the ability of the cortex to autoregulate its perfusion.

In neither of the SHRSP nor 2K1C Goldblatt hypertensive rats was it possible to demonstrate autoregulatory capacity within the papilla over either the high or low pressure range examined. This was very similar to the situation found in the normotensive rats suggesting that myogenic control of perfusion in this area was limited. Furthermore, although the nitrendipine caused elevations in basal levels of papillary perfusion, particularly at the higher doses, it had no effect on the pressure-perfusion relationship of the papilla.

These studies set out to compare the ability of cortex and papilla to autoregulate perfusion in adult Wistar compared to SHRSP and 2K1C Goldblatt hypertensive rats and to determine their sensitivity to the Ca^{2+} channel antagonist nitrendipine. The findings demonstrated good perfusion autoregulation in the cortex of normotensive, SHRSP and Goldblatt rats, albeit with the pressure range being elevated in the hypertensive models. There was no evidence of papillary autoregulation in either normotensive or hypertensive rats at any pressure range. Autoregulation of cortical perfusion was abolished by the low dose of nitrendipine in normotensive and SHRSP, but was unaltered in the 2K1C Goldblatt rats. The reason for this resistance to nitrendipine in the 2K1C Goldblatt rats is uncertain and deserves further investigation.

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