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Influence of Nimodipine on Vasoconstrictor Responses in the Hindquarters Vascular Bed of the Cat

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Abstract

The beneficial effects of the calcium-entry blocking agent, nimodipine, on the cerebral circulation have been extensively studied but less is known about its peripheral vascular effects. In the present study, the effects of nimodipine on vasoconstrictor responses were investigated in the hindquarters vascular bed of the cat under constant-flow conditions.

Nimodipine decreased hindquarters vascular resistance and inhibited vasoconstrictor responses to BAY K8644 (methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate) and noradrenaline, to the α_1-adrenoceptor agonists phenylephrine and methoxamine, and the α_2-adrenoceptor agonists BHT 933 (2-amino-6-ethyl-4,5,7,8-tetrahydro-6H-oxazolo[5,4-*d*]azepine dihydrochloride) and UK 14304 (5-bromo-6-(2-imidazoline-2-yl-amino)quinoxaline). In addition to inhibiting α-adrenoceptor-mediated responses, nimodipine decreased responses to the vasoactive peptides angiotensin II and endothelin-1. Both the vasodilatory actions and inhibitory effects of nimodipine on vasoconstrictor responses were dose-dependent when the calcium antagonist was infused at rates of 0·1 and 1 $\mu g\,min^{-1}$. The results of the present study suggest that vasoconstrictor responses to α-adrenoceptor agonists and to the vasoactive peptides are dependent, in part, on an extracellular source of calcium.

It is concluded that nimodipine and related dihydropyridine calcium-entry blocking agents may be effective in the treatment of peripheral vascular disorders in which adrenergic tone is increased or plasma levels of angiotensin II or endothelin-1 are elevated.

Nimodipine is a dihydropyridine calcium antagonist which relaxes vascular smooth muscle, induces vasodilatation, and decreases arterial pressure (Towart & Kazda 1979; Kazda & Towart 1980; Towart 1981). It has been shown to have a potent relaxant effect on isolated cerebral arteries, while having less effect on arterial smooth muscle from other systemic beds (Towart 1981). Nimodipine inhibits 5-hydroxytryptamine (5-HT)-induced vasospasm in isolated rabbit basilar arteries, whereas, it had no effect on responses to 5-HT in isolated mesenteric artery from the same species (Cain & Nicholson 1989). In in-vivo experiments, nimodipine dilates the cerebral vascular bed, while producing little change in systemic arterial pressure (Haws et al 1983; Langley & Sorkin 1989; Yuan et al 1990). Nimodipine induces vasodilatation of pial blood vessels in the cat in-vivo and increases cerebral blood flow in cats, dogs, rabbits, primates and human subjects (Harper et al 1981; Schmidt & Waldemer 1990; Yuan et al 1990). Because nimodipine has been reported to have selective effects on the cerebral circulation, studies have been undertaken to determine its effectiveness in a number of cerebral vascular disorders (Alen et al 1983; Auer 1984; Langley & Sorkin 1989; Scriabine et al 1989). Although less is known about the effects of nimodipine on the systemic circulation, this agent has been reported to decrease systemic vascular resistance in conscious pigs and to reduce systemic arterial pressure in volunteers (Duncker et al 1988; Schmidt & Waldemer 1990). It is possible that in addition to the beneficial effects of nimodipine in cerebral vascular disorders, nimodipine may be useful in the treatment of systemic disorders in which vascular tone is increased (Kappelle et al 1993). Nisoldipine, another dihydropyridine calcium antagonist, has been reported to inhibit vasoconstrictor responses in the mesenteric and hindquarters vascular beds of the

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cat (Minkes et al 1989a, b). While the effects of nimodipine on the cerebral circulation have been extensively characterized, less is known about the effects of this calcium antagonist on vasoconstrictor responses in the systemic vascular bed. The present study was, therefore, undertaken to investigate the influence of nimodipine on vasoconstrictor responses in the hindquarters vascular bed of the cat in order to determine if the properties of nimodipine are similar to those reported for other calcium antagonists in the systemic circulation. The effects of nimodipine on responses to BAY K8644 (methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate—a nifedipine analogue that promotes calcium entry), noradrenaline, selective α_1- and α_2-adrenoceptor agonists and vasoconstrictor peptides (angiotensin II and endothelin-1), were investigated in the hindquarters vascular bed of the cat under constant-flow conditions.

Materials and Methods

Experimental model

Seventy-four adult cats, unselected as to sex, weighing 1·8–4·1 kg were sedated with ketamine hydrochloride (10–15 mg kg^{-1} i.m.) and were anaesthetized with pentobarbital sodium (30 mg kg^{-1} i.v.). Supplemental doses of pentobarbital were given as needed to maintain a uniform level of anaesthesia. The trachea was cannulated to ensure a patent airway, and the animals breathed room air or were ventilated with a Harvard model 607 respirator at a tidal volume of 50–70 mL and a rate of 16–20 breaths min^{-1}. Catheters were inserted into an external jugular vein and into a carotid artery for intravenous administration of drugs and measurement of systemic arterial pressure, respectively. For constant-flow perfusion of the hindquarters vascular bed, the abdominal aorta was approached through a midline incision and a small area of distal aorta was carefully cleared of surrounding connective tissue. Following the administration of heparin sodium (1000 units kg^{-1} i.v.), the aorta was ligated 3 cm above its bifurcation and catheters were inserted proximal and distal to the ligature. Blood was withdrawn from the proximal catheter and pumped at a constant flow rate through the distal catheter directly into the hindquarters vascular bed. Blood flow was maintained constant with a Sigmamotor pump model T-8, and perfusion pressure was measured by a lateral tap on the perfusion circuit located between the pump and the distal aortic catheter. The hindquarters vascular bed was denervated by ligating and cutting the lumbar sympathetic chains between L-3 and L-4. Statham P23ID pressure transducers and a Grass polygraph model 7 were used to measure systemic arterial and hindquarters perfusion pressures. Mean pressures were derived by electronic averaging of the pulsatile signals, and the pumping rate was set so that hindquarters perfusion pressure approximated systemic arterial pressure and was not changed during an experiment. The pumping rate averaged 34 ± 1 mL min^{-1} in these studies. These methods have been described previously (Minkes et al 1989a, b).

Drug administration

The selective α_1-adrenoceptor agonists used in these studies were phenylephrine hydrochloride (Sigma Chemical Co., St Louis, MO) and methoxamine hydrochloride (Glaxo Wellcome, Research Triangle Park, NC). The selective α_2-adrenoceptor agonists were BHT 933 dihydrochloride (2-amino-6-ethyl-4,5,7,8-tetrahydro-6H-oxazolo[5,4-*d*]azepine dihydrochloride; Boehringer-Ingelheim, Indianapolis, IN) and UK 14304 ((5-bromo-6-(2-imidazoline-2-yl-amino)quinoxaline) tartrate; Pfizer Inc., Groton, CT). The agonists noradrenaline hydrochloride, angiotensin II (Sigma) and endothelin-1 (Peptides International, Belmont, CA) were dissolved in 0·9 % NaCl (saline). Nimodipine and BAY K8644 (Miles, West Haven, CT) were used as the calcium-entry blocking and calcium-entry promoting agents (Schramm et al 1983). Both dihydropyridines were dissolved in a 1:4 solution of cremophor and 10 mM Tris hydrochloride, pH 7·4. The resulting suspension was warmed and 2 mL of polyethylene glycol and 10 mL of 50 mM Tris, pH 7·4, were added to make a stock solution which was stored in a stoppered brown bottle in the freezer. Working solutions were prepared in saline and were protected from room light. The solvents used did not alter baseline pressures or responses to the agonists.

The vasoconstrictor agents were injected into the perfusion circuit in small volumes (30 and 100 μL) in a random sequence, and sufficient time (5–10 min) was permitted between agonist injections for hindquarters perfusion pressure to return to baseline values. Nimodipine was infused directly into the hindquarters perfusion circuit at rates of 0·1 μg min^{-1} or 1 μg min^{-1} with a Harvard model 901 infusion pump. The infusion syringe and tubing were protected from light.

Statistical analysis

All haemodynamic data represent peak changes and are expressed in absolute units (mm Hg) as mean ± s.e. The data were analysed using the

paired t-test or one-way analysis of variance and Scheffe F-test with a Bonferroni-Dunn correction (Snedecor & Cochran 1967). A P value of less than 0·05 was used as the criterion for statistical significance.

Results

Effect of nimodipine on responses to BAY K8644 and noradrenaline

The effect of nimodipine on vasoconstrictor responses to BAY K8644 and noradrenaline was investigated in the hindquarters vascular bed of the cat, and these data are summarized in Figure 1. Injections of BAY K8644 directly into the hindquarters perfusion circuit in doses of 0·3, 1·0, and 3·0 μg caused dose-dependent increases in hindquarters perfusion pressure. The increases in hindquarters perfusion pressure in response to the nifedipine analogue that promotes calcium entry by opening L-type channels were reduced significantly during infusion of nimodipine at rates of 0·1 and 1 μg min^{-1}. Injections of nor-adrenaline into the hindquarters perfusion circuit also elicited dose-dependent increases in hindquarters perfusion pressure. During infusion of nimodipine, the increases in hindquarters perfusion pressure in response to the adrenergic agonist were reduced significantly (Figure 1).

Influence of nimodipine on responses to α_1- and α_2-adrenoceptor agonists

The effects of nimodipine on responses to selective α_1- and α_2-adrenoceptor agonists were compared, and injection of the α_1-agonists, phenylephrine and methoxamine, produced dose-dependent increases in hindquarters perfusion pressure (Figure 2). During the infusion of nimodipine, vasoconstrictor responses to both of the α_1-agonists were reduced significantly (Figure 2). The effects of nimodipine on responses elicited by the α_2-selective agonists, BHT 933 and UK 14304, were also investigated in the hindquarters vascular bed, and these data are summarized in Figure 3. Injections of BHT 933 and UK 14304 into the perfusion circuit produced dose-related increases in hindquarters perfusion pressure, and these responses were reduced significantly during infusion of nimodipine.

Effects of nimodipine on systemic arterial and hindquarters perfusion pressure

In the present experiments, infusion of nimodipine (0·1 μg min^{-1}) into the hindquarters perfusion circuit decreased hindquarters perfusion pressure from 121 ± 6 mmHg to 102 ± 5 mmHg ($P < 0·05$) and systemic arterial pressure from 118 ± 4 mmHg to 107 ± 4 mmHg ($P < 0·05$). Infusion of nimodipine (1 μg min^{-1}) into the hindquarters perfusion circuit decreased hindquarters perfusion pressure from 113 ± 5 mmHg to 72 ± 4 mm Hg ($P < 0·05$) and systemic arterial pressure from 115 ± 6 mmHg to 95 ± 6 mmHg ($P < 0·05$). The reduction in hindquarters perfusion pressure was more rapid in onset than the decrease in systemic arterial pressure, and the decreases in hindquarters and systemic arterial pressures were maintained throughout the infusion period. Hindquarters perfusion and systemic arterial pressures slowly returned toward the control value after the nimodipine infusions were ended.

Influence of nimodipine on responses to the vasoactive peptides, angiotensin II and endothelin-1

The effects of nimodipine on vasoconstrictor responses to angiotensin II and endothelin-1 are summarized in Table 1. Angiotensin II produced dose-related increases in hindquarters perfusion pressure, whereas endothelin-1 produced a biphasic change in hindquarters perfusion pressure characterized by an initial decrease followed by a secondary increase in perfusion pressure. During infusion of nimodipine, the increases in hindquarters perfusion pressure in response to angiotensin II and both components of the response to endothelin-1 were significantly reduced.

Discussion

Results of the present investigation demonstrate that nimodipine decreases hindquarters vascular resistance and inhibits vasoconstrictor responses to noradrenaline, the selective α_1- and α_2-adrenoceptor agonists, and to the vasoactive peptides angiotensin II and endothelin-1. The vasodilator and inhibitory effects of nimodipine on vasoconstrictor responses were dose-dependent when the calcium antagonist was infused at rates of 0·1 and 1 μg min^{-1}. Nimodipine has been reported to be more lipophilic than nifedipine and produces vasodilatation in cerebral vessels at lower concentrations than required for relaxation of peripheral vessels (Kazda & Towart 1980). This agent has been shown to be protective in animal models of cerebral haemorrhage and ischaemia, and this dihydropyridine has been widely used in the treatment of cerebral vascular disorders (Alen et al 1983; Auer 1984; Langley & Sorkin 1989; Scriabine et al 1989; Schmidt & Waldemer 1990). However, less is known about the effects of nimodipine in the peripheral vascular bed. In the present study, infusion of nimodipine produced decreases in hindquarters perfusion pressure and systemic arterial pressure.

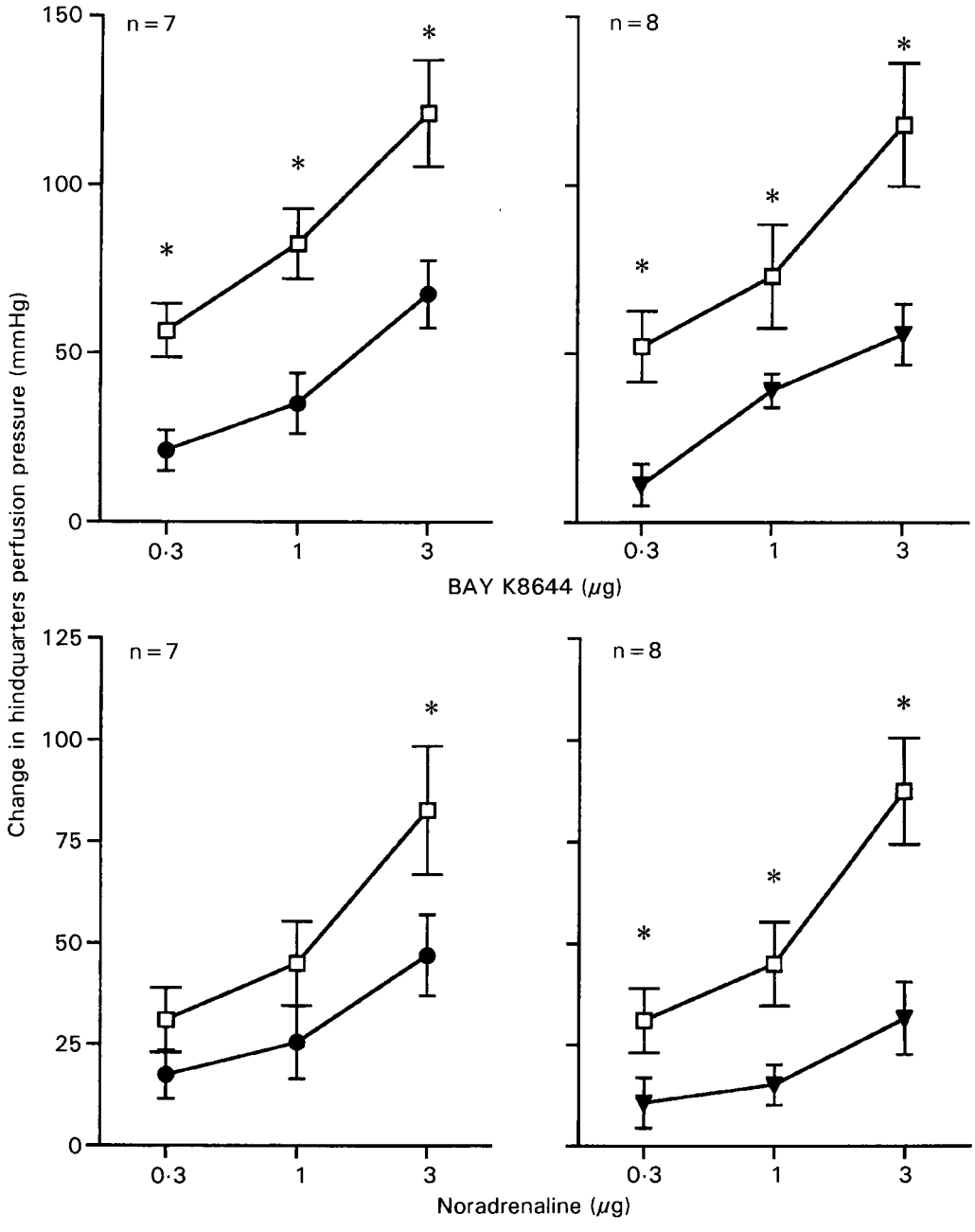

Figure 1. Influence of nimodipine on response to the calcium-entry promoting agent, BAY K8644, and noradrenaline in the hindquarters vascular bed of the cat. Responses to the calcium agonist and adrenergic agonist were determined before (□) and during infusion of nimodipine 0·1 μg min^{-1} (left, ●) or 1·0 μg min^{-1} (right, ▼) into the hindquarters perfusion circuit. n, number of animals. *$P < 0.05$ significantly different from control.

Inasmuch as blood flow was maintained constant, changes in perfusion pressure directly reflect changes in regional vascular resistance. The inhibitory effects of nimodipine on calcium entry in resistance vessel elements in the hindquarters vascular bed were assessed in experiments with BAY K8644, an agent that promotes calcium entry through dihydropyridine-sensitive, voltage-dependent channels (Schramm et al 1983; Hess et al 1984). BAY K8644 produced dose-dependent increases in hindquarters perfusion pressure and, during infusion of nimodipine, vasoconstrictor responses to BAY K8644 were attenuated. The finding that nimodipine induces vasodilatation and inhibits responses to BAY K8644 in the hindquarters vascular bed is consistent with the results of previous studies using other dihydropyridine calcium antagonists in the regional circulation of the

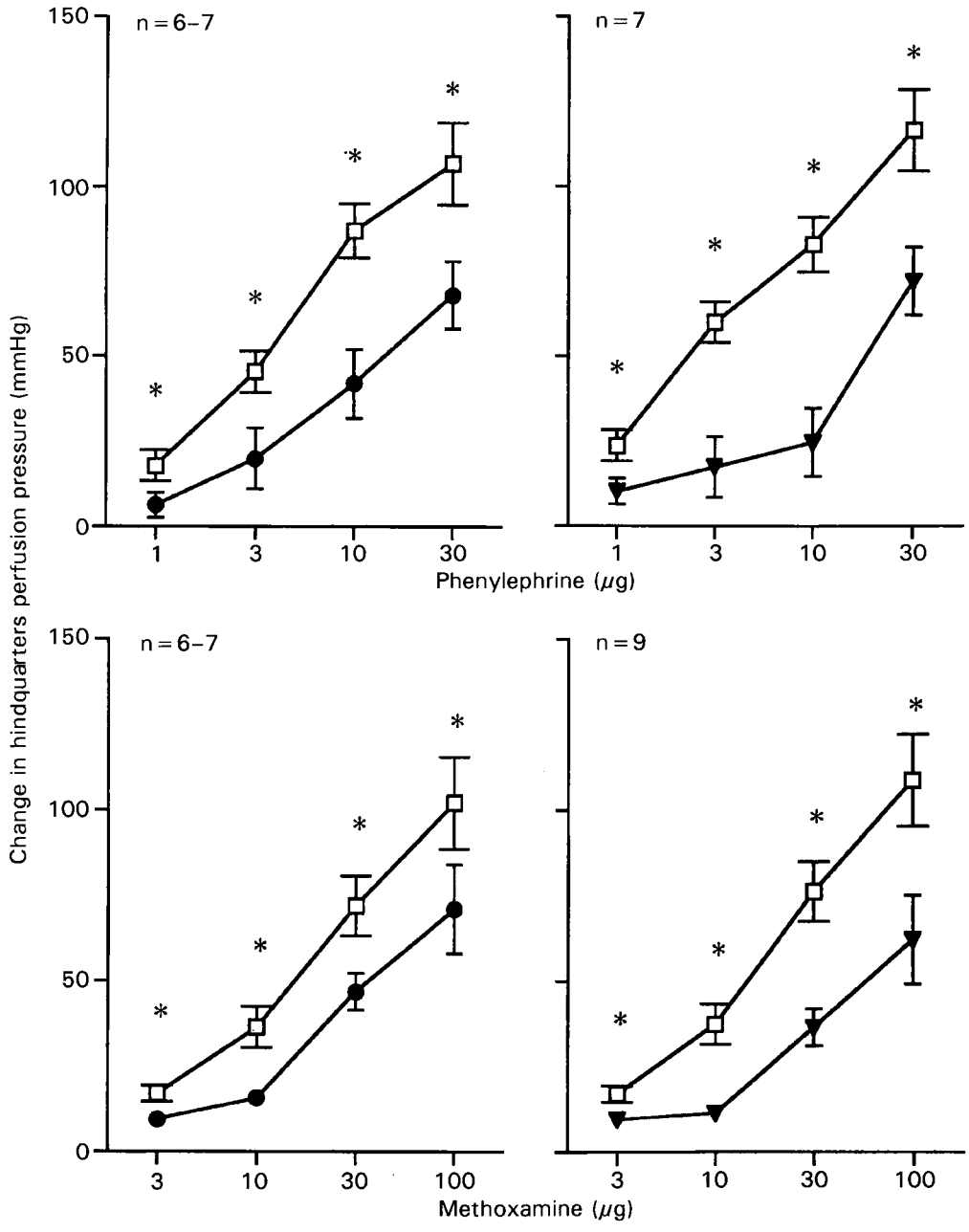

Figure 2. Influence of nimodipine on vasoconstrictor responses to phenylephrine and methoxamine in the hindquarters vascular bed of the cat. Responses to the selective α_1-adrenoceptor agonists were obtained before (□) and during infusion of nimodipine 0·1 μg min^{-1} (left, ●) or 1·0 μg min^{-1} (right, ▼) into the hindquarters vascular bed. n, number of animals. *$P < 0.05$ significantly different from control.

cat (Lippton et al 1987; Minkes et al 1989a, b). The reason for the difference in results in the present study in the cat and in previous studies showing a lack of effect of nimodipine in the systemic circulation is uncertain but may reflect differences in species, experimental preparation used, vascular bed studied, or differences in dose or rate of administration.

The presence of α_1- and α_2-adrenoceptors mediating vasoconstriction has been demonstrated in the hindquarters vascular bed of the cat (Lippton et al 1987; Minkes et al 1989a). In the present study, injections of noradrenaline produced dose-dependent increases in hindquarters perfusion pressure that were reduced by nimodipine. To ascertain if the effect of nimodipine on responses to noradrenaline was mediated by an action on a specific α-receptor subtype, the effects of the calcium antagonist on responses to selective α_1- and α_2-adrenoceptor agents were investigated. Phenyl-

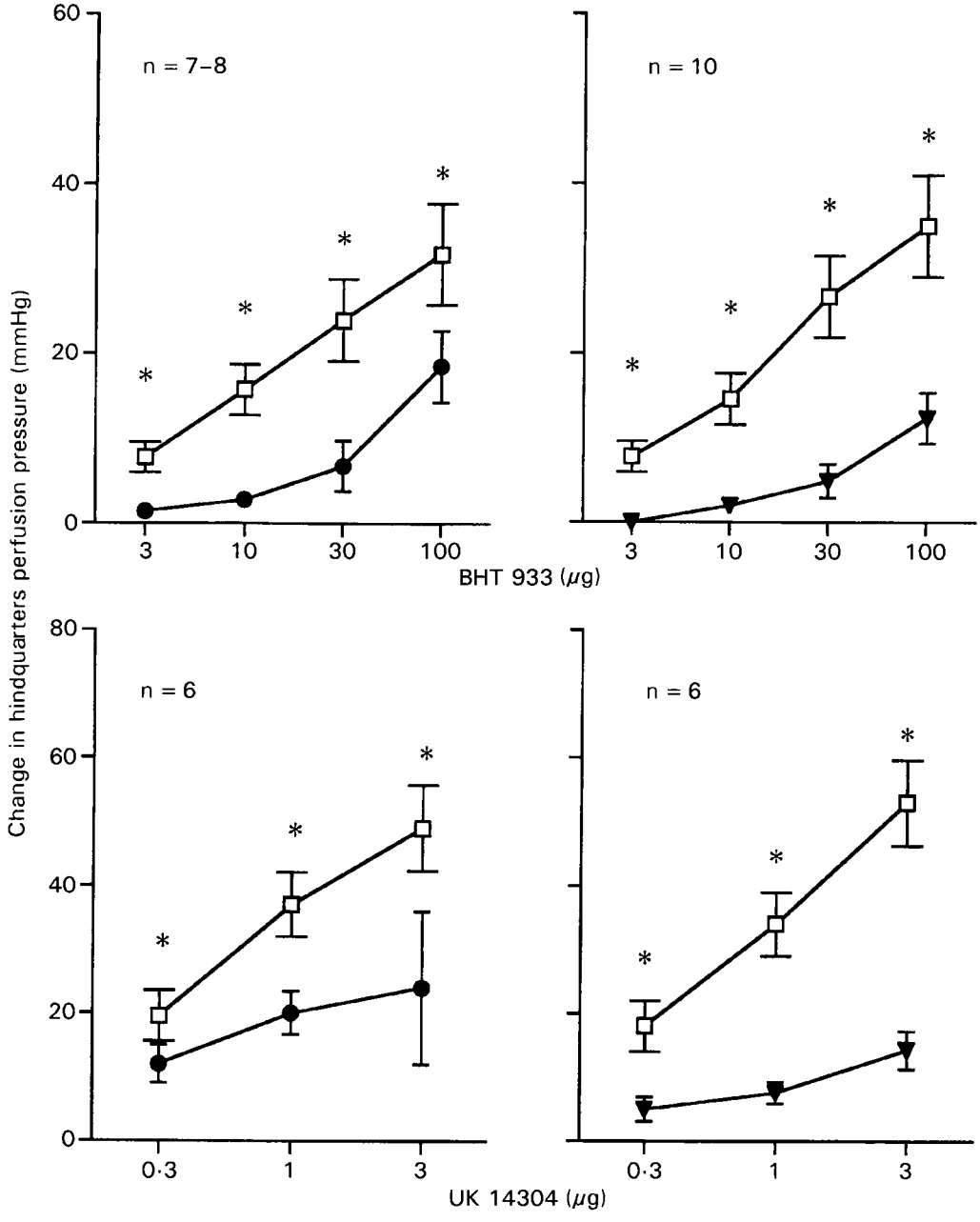

Figure 3. Influence of nimodipine on response to BHT 933 and UK 14304 in the hindquarters vascular bed of the cat. Responses to the selective α_2-adrenoceptor agonists were obtained before (□) and during infusion of nimodipine 0·1 $\mu g\,min^{-1}$ (left, ●) or 1·0 $\mu g\,min^{-1}$ (right, ▼). n, number of animals. *$P < 0.05$ significantly different from control.

ephrine and methoxamine (selective α_1-adrenoceptor agonists) and BHT 933 and UK 14304 (selective α_2-adrenoceptor agonists), produced dose-dependent vasoconstrictor responses in the hindquarters vascular bed of the cat (Lippton et al 1987; Minkes et al 1989a). During nimodipine infusion, responses to both the α_1- and α_2-adrenoceptor agonists were reduced significantly. These results show that the inhibitory effects of nimodipine on α_1- and α_2-adrenoceptor-mediated responses in the hindlimb are undifferentiated and are in agreement with previous studies with other calcium-entry blocking agents in the pulmonary and systemic vascular beds of the cat (Lippton et al 1987; Kadowitz et al 1989; Minkes et al 1989a, b). Although the present results, together with previous studies in the cat, dog, monkey and rat, suggest that α_1- and α_2-adrenoceptor-mediated responses are dependent on an extracellular source of calcium, other studies are not in agreement with this notion (Morita et al 1985; Woodman et al 1986; McGrath & O'Brien 1987; Minkes et al 1989a, b). A number

Table 1. Influence of nimodipine on responses to angiotensin II and endothelin-1 in the hindquarters vascular bed of the cat.

Vasoactive peptide	Change in hindlimb perfusion pressure (mm Hg)			
	Control	Nimodipine (0·1 $\mu g\,min^{-1}$)	Control	Nimodipine (1 $\mu g\,min^{-1}$)
Angiotensin II (n = 9)				
0·1 μg	18 ± 4	5 ± 2*	16 ± 4	3 ± 2*
0·3 μg	43 ± 10	14 ± 6	39 ± 9	13 ± 5*
Endothelin-1 (n = 6)				
0·3 nmol dilator component	11 ± 2	−4 ± 1*	−12 ± 2	−4 ± 1*
0·3 nmol constrictor component	45 ± 13	22 ± 6*	37 ± 10	12 ± 4*

n = number of animals; *response significantly different from control.

of studies, mostly in rats, provide support for the notion that α_2-adrenoceptor-mediated responses are coupled to an extracellular source of calcium, whereas α_1-adrenoceptor responses depend mostly on the release of calcium from an intracellular source (Van Meel et al 1981; Cavero et al 1983; Ruffolo et al 1984; Hicks et al 1985). The reason for the difference in results in the present study, or in other studies in the rat, showing that α_1- and α_2-receptor responses are reduced is uncertain but may be related to differences in vascular bed studied and experimental procedure employed (Van Meel et al 1981; Cavero et al 1983; Ruffolo et al 1984; Hicks et al 1985; McGrath & O'Brien 1987).

In the hindquarters vascular bed, angiotensin II produced dose-dependent vasoconstrictor responses, whereas endothelin-1 produces a biphasic change in perfusion pressure. Nimodipine infusion attenuated responses to both peptides, suggesting that an extracellular source of calcium is required in part for the actions of these peptides. These findings are consistent with previous reports showing that responses to endothelin-1 are attenuated by dihydropyridine calcium-entry blocking agents (Minkes et al 1989b). The results with nimodipine, nisoldipine and nitrendipine are similar in the peripheral vascular bed of the cat. All three calcium antagonists impair responses to noradrenaline and angiotensin II. The ability of the dihydropyridine calcium antagnoists to impair responses to angiotensin II and the other vasoconstrictor agents may suggest that extracellular calcium is required for vasoconstriction or that the refilling of intracellular pools of calcium by way of L-type channels in the plasma membrane is impaired. Alternatively, it is possible that the dihydropyridine calcium-entry blocking agents are inducing a functional antagonism of vasoconstrictor responses due to the substantial fall in baseline perfusion pressure.

In summary, the results of the present study suggest that nimodipine, an agent used in the treatment of cerebral vascular disorders, possesses vasodilator activity in the systemic vascular bed of the cat similar to that exhibited by other dihydropyridine calcium antagonists. Results of the present study show that nimodipine induces vasodilatation and attenuates vasoconstrictor responses to vasoactive peptides and to α-adrenoceptor agonists, supporting the notion that an extracellular source of calcium is required for α_1- and α_2-mediated responses in the systemic and pulmonary vascular beds of the cat (Lippton et al 1987; Kadowitz et al 1989; Minkes et al 1989a, b). In conclusion, the present results indicate that, in addition to its cerebral vasodilating activity and use in the treatment of cerebral vascular disorders, nimodipine has significant vasodilator activity and inhibits vasoconstrictor responses in the cat hindquarters vascular bed and may be useful in the treatment of peripheral vascular disorders in which adrenergic tone is elevated or production of vasoconstrictor peptides is increased.

Acknowledgements

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