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A comparison of several calcium antagonists on uterine, vascular and cardiac muscles from the rat

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1 An assessment was made of the potencies of nifedipine, gallopamil, diltiazem, cinnarizine and salbutamol as inhibitors of tension development by the uterus and cardiovascular tissues from the term pregnant rat.

2 The rank order of potency was nifedipine > gallopamil > diltiazem for those preparations on which these compounds were potent, viz. spontaneous and oxytocin-induced tension development of the uterus, spontaneous tension development of hepatic portal vein, potassium chloride (KCl)-induced pressure rises of perfused mesenteric bed and electrically-stimulated (0.5 Hz) ventricular muscle.

3 The rank order of potency of nifedipine, gallopamil and diltiazem was different for those preparations on which they exhibited low potency, viz. noradrenaline-induced pressure rises of perfused mesenteric bed and tension development of aorta.

4 Gallopamil and diltiazem, but not nifedipine, were more potent against tension development by ventricular muscle stimulated at 2.5 Hz than at 0.5 Hz, suggesting that nifedipine interacts at a different site from the other compounds.

5 Cinnarizine was less potent than the other calcium antagonists on the uterus and portal vein, was the second most potent compound against KCl-induced pressure rises of the mesenteric bed and was equipotent against responses to noradrenaline and KCl of the mesenteric bed (unlike the other compounds). This suggests that the site of action of cinnarizine differs from that of the other calcium antagonists.

6 Nifedipine, gallopamil and diltiazem, like salbutamol, exhibited selectivity for inhibition of tension development by the uterus relative to the cardiovascular tissues.

Introduction

Mechanical activity in uterine smooth muscle is dependent on the presence of extracellular calcium (Bolton, 1979). For this reason, it is predictable that tension development in this tissue should be inhibited by calcium antagonists. Gallopamil and nicardipine inhibit mechanical activity in rat uterus (Fleckenstein *et al.*, 1971; Reiner & Marshall, 1975; Csapo *et al.*, 1982) while nifedipine inhibits tension development in human isolated uterus and reduces intra-uterine pressure changes in both non-pregnant and pregnant women (Forman *et al.*, 1981). It is therefore possible that calcium antagonists could have a place in the treatment of dysmenorrhoea and of preterm labour, although the cardiovascular effects of these drugs could be a limiting factor (Nayler & Horowitz, 1983).

The objective of the present study was to compare the inhibitory effects of several calcium antagonists on the isolated uterus from the term pregnant rat with their actions on a number of isolated cardiovascular tissues from the same animals. The calcium antagonists nifedipine, gallopamil, diltiazem and cinnarizine were chosen because they may represent sub-classes of this group of compounds (Glossmann *et al.*, 1982; Spedding, 1982a; 1984). The inhibitory effects of salbutamol were also measured, as β-adrenoceptor agonists are the current treatment for preterm labour (Lippert, 1983).

A preliminary account of these findings has been published (Hollingsworth *et al.*, 1983).

Methods

All tissues were obtained from day 22 (term) pregnant Sprague-Dawley rats (250–350 g) from Manchester University Animal Unit killed before 10h 00m by cervical dislocation.

Uterus

Uterine horns were cut longitudinally, freed of foetuses and placentae and placed in Krebs solution at room temperature. Longitudinal strips (10 × 5 mm) were mounted in tissue baths at 37°C under a resting tension of 1 g. Isometric tension development was recorded on a Grass polygraph and quantified by integration (Grass 7P10B). Preparations which did not maintain regular phasic tension development during an initial 30 min stabilization period were discarded.

In experiments where the potencies of the compounds against spontaneous phasic tension development were to be measured, the integral was measured for the 15 min period from 30 to 45 min after setting up the tissue (control). At 45 min the first concentration of a compound (or equivalent vehicle) was added to the bathing fluid with successive additions at 40 min intervals (30 min for salbutamol). Integrals were measured over the last 15 min in the presence of each concentration of a compound and expressed as a % of the control integral. Another series of experiments was performed to measure the potencies of the compounds against oxytocin-induced phasic tension development. Oxytocin (0.1 mu ml^{-1}) was added to the bathing fluid 45 min after setting up the tissue and the integral measured over the next 10 min (control oxytocin response). The bathing fluid was renewed, the first concentration of compound added and 40 min later (30 min for salbutamol) the oxytocin challenge repeated. Integrals during the 10 min oxytocin periods were measured in the presence of increasing concentrations of the compounds and expressed as a % of the control oxytocin integral.

Hepatic portal vein

Hepatic portal veins, 1 to 2 cm in length, were suspended in tissue baths under 0.5 g tension. After a 30 min stabilization period, the effects of the compounds against spontaneous phasic tension development were assessed in the same manner as for the rat uterus except that integrals were counted over 10 min periods and the time between successive drug additions varied depending on the equilibration time of the drug (see Results).

Mesenteric vascular bed

The perfused mesenteric bed was set up using a modification (Warburton, 1983) of the method of McGregor (1965). The preparation was placed in a tissue bath and perfused via the cannulated anterior mesenteric artery with Krebs solution at 37°C at a rate of 5 ml min^{-1} using a Watson Marlow flow inducer (MHRE 100). Back perfusion pressure was monitored by a pressure transducer (Washington PT400) and recorded on a Grass polygraph. Base line perfusion pressure became constant during a 15 min stabilization period.

KCl (2×10^{-4} mol; approximate ED_{80}) or noradrenaline (10^{-8} mol; approximate ED_{80}) was injected as a bolus into the continuously perfusing Krebs solution every 5 min by means of a Grass stimulator (S48), which operated a Watson Marlow flow inducer (MHRE 22). The responses to KCl or noradrenaline were measured as increases in perfusion pressure; these became constant within 1 h. Inhibitory concentration-effect curves were performed by infusing the test compounds (or equivalent vehicle in control experiments) into the perfusing Krebs solution using an infusion pump (Braun Perfusor). The concentrations were increased at intervals based on preliminary experiments which assessed the time for equilibration of the response for each test compound. The control response to KCl or noradrenaline was taken as the mean pressure change produced by the agonists in the three challenges immediately before the infusion of the test compound. The mean of 3 agonist responses obtained in the presence of each concentration of the test compound were expressed as a % of the control.

Aorta

Helical strips of thoracic aorta were suspended in tissue baths at a resting tension of 1 g and tension development recorded isometrically. Cumulative concentration-effect curves were constructed to noradrenaline and repeated in the presence of increasing concentrations of the test compounds using equilibration times similar to those on portal vein. The amplitudes of the maximum responses to noradrenaline in the presence of the test compounds were expressed as a % of the initial control maximum response to noradrenaline (10^{-6} M).

Ventricular muscle

Hearts were rapidly removed into well oxygenated Krebs solution at 4°C and superfused with this solution during dissection. A longitudinal strip (6 × 1.5 mm) from the outer wall of the right ventricle was excised and suspended under 0.5 g tension in a tissue bath at 33°C. Preparations were electrically stimulated (0.5 or 2.5 Hz, 3.5 V, 2 ms) via platinum ring electrodes and tension development recorded isometrically. When twitches of constant amplitude had been obtained, the method of Harman & Poole-Wilson (1981) was used to produce partial depolarization and inactivation of fast Na^+ channels. This was achieved by changing the bathing fluid to a modified Krebs solution containing 20 mM K^+ and doubling the stimulation voltage to elicit slow Ca^{2+}-dependent twitches. Cumulative dose-response curves for the

inhibitory effects of the test compounds were then obtained having assessed equilibration times in preliminary experiments. The effect of the test compounds were expressed as % inhibition of the amplitude of the tension developed before drug addition.

Calculation of drug potencies

A regression of response (probit of % inhibition of control) against $-\log_{10}$ M of test compound was performed by the least squares method for each preparation. The $-\log_{10}$ M to produce 50% inhibition (IC_{50}) was obtained from the regression plot and a mean $IC_{50} \pm 95\%$ confidence interval was calculated for each test compound on each tissue. Relative potencies, between drugs on a tissue or for a drug between tissues, were calculated as the antilog_{10} of the differences in IC_{50}. Analysis of variance and the least significant difference test were used to examine for any variation in tension development in time- or vehicle-control experiments.

Drugs

The composition of normal Krebs solution was (mM): Na^+ 143, K^+ 5.9, Ca^{2+} 2.55, Mg^{2+} 1.2, SO_4^{2-} 1.2, $H_2PO_4^-$ 1.2, Cl^- 128, HCO_3^- 25, glucose 11. The composition of the partially depolarizing Krebs solution was (mM): Na^+ 143, K^+ 20, Ca^{2+} 2.55, Mg^{2+} 1.2, SO_4^{2-} 1.2, $H_2PO_4^-$ 1.2, Cl^- 142.1, HCO_3^- 25, glucose 11. Both solutions were gassed with 95% O_2, 5% CO_2. The following drugs were used: oxytocin (grade X, Sigma), (−)-noradrenaline bitartrate (Sigma), nifedipine (Bayer), gallopamil HCl (Knoll), (+)-*cis* diltiazem HCl (Synthelabo), cinnarizine (Janssen), salbutamol sulphate (Glaxo). Experiments involving nifedipine were performed under sodium light.

Results

Uterus

All the compounds produced a concentration-dependent inhibition of the amplitude and frequency of spontaneous and oxytocin-induced tension development; an example is shown in Figure 1. Equilibration times were 20 min for salbutamol and 30 min for the other compounds. The calcium antagonists and salbutamol were all very potent. The rank order of potency for the calcium antagonists was nifedipine ≫ gallopamil = diltiazem > cinnarizine against spontaneous tension development and nifedipine > gallopamil ≫ diltiazem > cinnarizine against oxytocin-induced tension development (Table 1). The calcium antagonists and salbutamol were less potent against oxytocin-induced than against spontaneous tension development, the relative potencies varying from 2 (gallopamil) to 26 (diltiazem) (Table 2). There was no

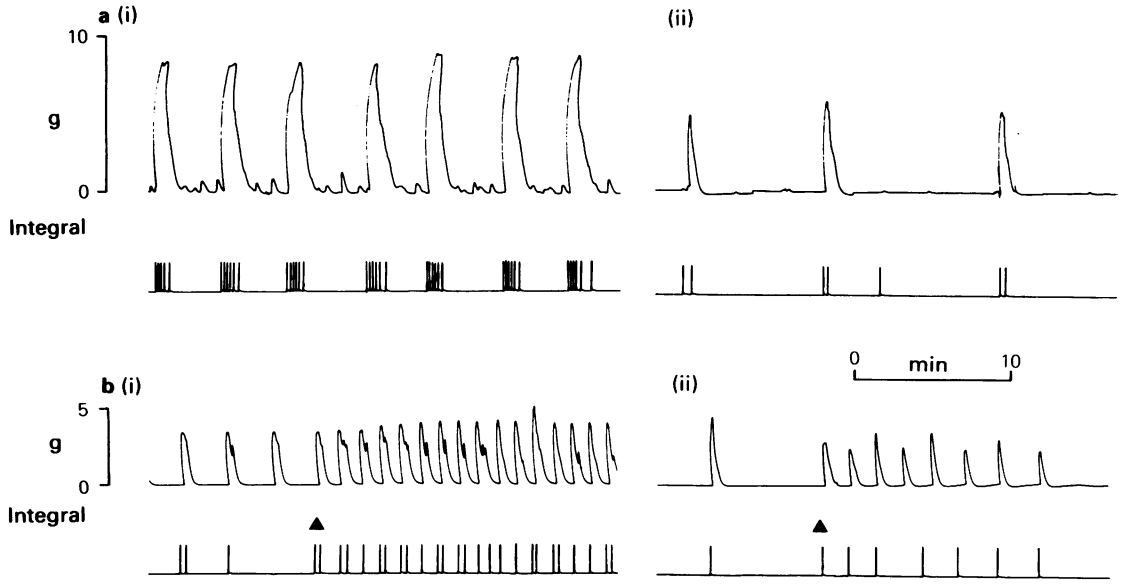

Figure 1 Traces showing (a) spontaneous tension development of the rat uterus (i) before and (ii) from 25 min after the addition of gallopamil (1.25×10^{-7} M). (b) Oxytocin-induced tension development of the uterus, (i) before and (ii) from 40 min after the addition of gallopamil (1×10^{-7} M). (▲) Addition of oxytocin (0.1 mu ml^{-1}).

Table 1 Potencies of calcium antagonists and salbutamol on isolated tissues from the day 22 pregnant rat

Drug	*Uterus* Spontaneous	*Uterus* Oxytocin (0.1 mu ml^{-1})	*Hepatic portal vein* spontaneous	*Mesenteric bed* NA (10^{-8} mol)	*Mesenteric bed* KCl (2×10^{-4} mol)	*Aorta* NA (10^{-6} M)	*Ventricular strip* Electrically stimulated (0.5 Hz)	*Ventricular strip* Electrically stimulated (2.5 Hz)
Nifedipine	9.36 ± 0.36	8.14 ± 0.80	8.22 ± 0.12	4.45 ± 0.23	7.60 ± 0.24	4.32 ± 0.31	6.86 ± 0.18	7.36 ± 0.48
Gallopamil	8.22 ± 0.46	7.94 ± 0.36	7.95 ± 0.26	5.46 ± 0.32	6.86 ± 0.33	3.92 ± 0.21	5.79 ± 0.22	7.79 ± 0.33
Diltiazem	8.18 ± 0.56	6.77 ± 0.67	6.66 ± 0.32	4.47 ± 0.32	5.64 ± 0.24	3.94 ± 0.15	5.49 ± 0.23	6.86 ± 0.51
Cinnarizine	6.87 ± 0.54	6.10 ± 0.48	5.54 ± 0.36	7.12 ± 0.18	7.09 ± 0.26	<5[a]	4.23 ± 0.46	ND
Salbutamol	9.72 ± 0.15	8.36 ± 0.59	6.26 ± 0.57	5.77 ± 0.23	<5	–[b]	–[b]	ND

Tension development was either spontaneous or induced by the agonist (NA = noradrenaline, KCl = potassium chloride) indicated. Potencies are as IC_{50}s (− log M) ± 95% confidence intervals, $n = 6–8$. [a]Cinnarizine (10^{-5} M) produced 26.8 ± 3.2% ($n = 8$) inhibition; the limit of solubility was 5×10^{-5} M. [b]See text. ND = not determined.

significant change in the integral of either spontaneous or oxytocin-induced tension development by control uteri or any suppression of tension development by vehicles ($2P > 0.05$, $n = 6–10$).

Hepatic portal vein

Equilibration times were found to be 5 min for salbutamol, 30 min for nifedipine, gallopamil and diltiazem, and 50 min for cinnarizine. The inhibitory effect of salbutamol was not maintained and by 20 min after its addition to the tissue bath, tension development was not significantly different from controls.

All the compounds produced a concentration-dependent inhibition of spontaneous tension development of portal vein; an example is shown in Figure 2a. The calcium antagonists were potent; the rank order of potency being nifedipine > gallopamil ➤ diltiazem ➤ cinnarizine (Table 1). The compounds were less potent at inhibiting spontaneous tension development by the portal vein than that by the uterus but of similar potency to that seen against oxytocin-induced tension development by the uterus (Table 2). The exception was salbutamol which was of low potency on the portal vein ($IC_{50} = 6.26$). There was no suppression of tension development in vehicle controls ($2P > 0.05$, $n = 6$).

Mesenteric vascular bed

The equilibration times were 15 min for salbutamol, 30 min for diltiazem and nifedipine and 45 min for gallopamil and cinnarizine. All the compounds, except salbutamol (against KCl), produced a concentration-dependent inhibition of KCl- and noradrenaline-induced responses of the perfused mesenteric bed; an example is shown in Figure 2b. The calcium antagonists were quite potent inhibitors of the KCl-induced responses but, except for cinnarizine, relatively impotent against noradrenaline-induced responses. The rank orders of potency were nifedipine>cinnarizine > gallopamil ➤ diltiazem and cinnarizine ➤ gallopamil > diltiazem = nifedipine respectively (Table 1).

Cinnarizine was equipotent against noradrenaline- and KCl-induced responses while the other calcium

Table 2 Relative potencies of calcium antagonists and salbutamol between tissues from the day 22 pregnant rat.

Drug	*Relative potencies* $\frac{U_{sp}}{U_{Ox}}$	$\frac{U_{sp}}{PV_{sp}}$	$\frac{U_{Ox}}{PV_{sp}}$	$\frac{U_{sp}}{M_{KCl}}$	$\frac{U_{sp}}{A_{NA}}$	$\frac{U_{sp}}{V}$
Nifedipine	17	14	0.8	58	10965	316
Gallopamil	2	2	1.0	23	19952	269
Diltiazem	26	33	1.0	365	17378	490
Cinnarizine	6	21	4	0.6	>74	437
Salbutamol	23	2884	126	>52480	ND	ND

Relative potencies are antilog$_{10}$ of the differences between tissues in IC_{50} (as − log$_{10}$ M), $n = 6–8$. U_{sp} = uterus, spontaneous. U_{Ox} – uterus contracted with oxytocin. PV_{sp} = hepatic portal vein, spontaneous. M_{KCl} = mesenteric bed contracted with potassium chloride. A_{NA} = aorta contracted with noradrenaline. V = ventricular muscle, electrically stimulated (0.5 Hz). ND = not determined.

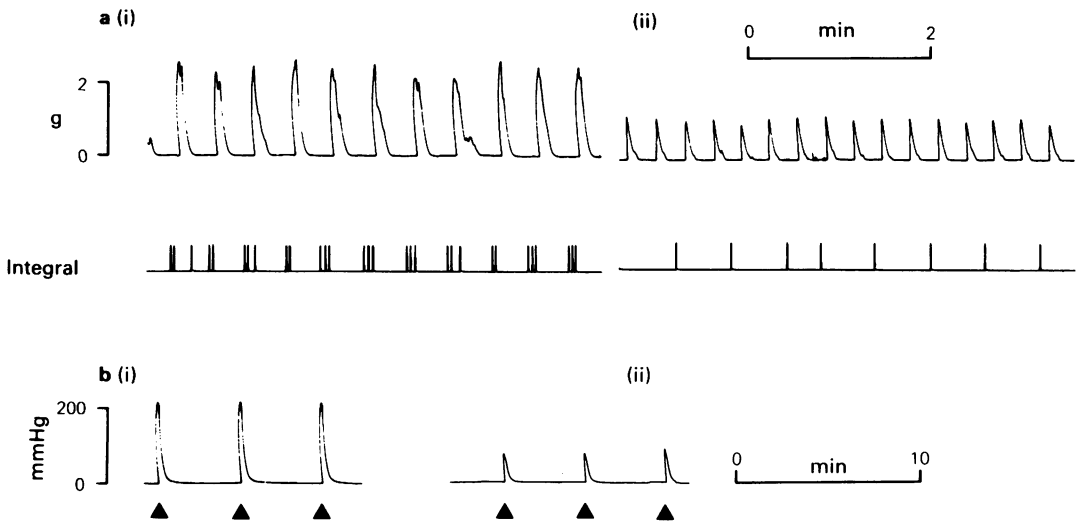

Figure 2 Traces showing (a) spontaneous tension development of the rat hepatic portal vein (i) before and (ii) from 30 min after the addition of diltiazem (2.5×10^{-7} M). (b) Increases in perfusion pressure of the perfused mesenteric bed produced by bolus injections of potassium chloride (2×10^{-4} mol) at (▲), (i) before and (ii) from 35 min after the commencement of an infusion of nifedipine (2.5×10^{-8} M).

antagonists were selective for KCl responses (Table 1). The calcium antagonists, except cinnarizine, were less potent on the mesenteric bed than on the uterus (Table 2). The potency of salbutamol against noradrenaline responses was unchanged in the presence of propranolol (0.3 or 3 μM). Infusion of vehicle had no significant effect on KCl or noradrenaline responses except for ethanol infusion (1.25%), equivalent to the highest nifedipine concentration used, which produced a mean 26% inhibition ($n = 8$) of noradrenaline responses; this was taken into account when calculating the IC_{50} for nifedipine.

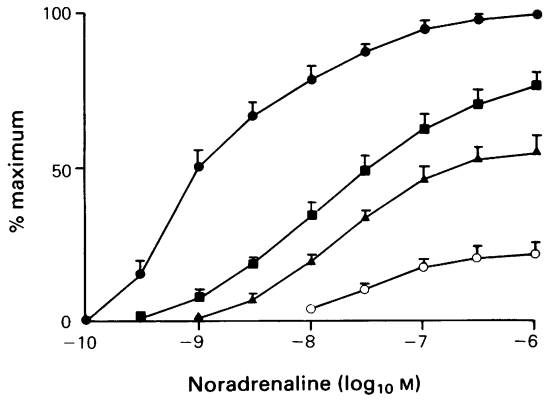

Figure 3 Concentration-effect curves for the increase in tension of the aorta induced by noradrenaline in the absence (●) and in the presence of diltiazem (■) 5×10^{-5} M, (▲) 10^{-4} M and (○) 2×10^{-4} M. The ordinate scale represents responses as % of the initial maximum response to noradrenaline (10^{-6} M). The points are the means and the vertical lines show s.e.mean ($n = 8$).

Aorta

Equilibration times were 15 min for salbutamol, 30 min for nifedipine, 45 min for gallopamil and diltiazem, and 60 min for cinnarizine. All the compounds, except salbutamol, produced a concentration-dependent reduction of the slope and maximum of the noradrenaline concentration-effect curve; this is illustrated in Figure 3 for diltiazem. The calcium antagonists had a similar low potency, this being much less than on the uterus (Table 2). Increasing concentrations of salbutamol ($n = 6$) caused parallel rightward shifts of the noradrenaline concentration-effect curves, without a reduction of the maximum, with dose ratios of 3.3 ± 1.3 (10^{-5} M), 45.4 ± 12.1 (10^{-4} M) and 3684 ± 1557 (10^{-3} M). Propranolol (10^{-6} M; $n = 4$) reduced the antagonism of noradrenaline responses by salbutamol. There was no significant change ($2P > 0.05$, $n = 10$) in the concentration-effect curves to noradrenaline when repeated 3 times in vehicle-treated controls.

Ventricular muscle

The equilibration times for the compounds were 15 min for nifedipine, gallopamil and diltiazem and 30 min for cinnarizine. All the compounds, except salbutamol, caused a concentration-dependent inhibi-

tion of electrically-stimulated tension development of ventricular muscle. The calcium antagonists were of moderate potency with a rank order, at a stimulation frequency of 0.5 Hz, of nifedipine > gallopamil = diltiazem > cinnarizine (Table 1). However, at a stimulation frequency of 2.5 Hz the rank order was changed to gallopamil = nifedipine > diltiazem. Increasing the frequency of stimulation significantly raised the potency of gallopamil and diltiazem but did not change that of nifedipine. They were less potent against tension development by the ventricular strip than on the uterus (Table 2). An effect on tension development with salbutamol was only observed in 1 out of 6 preparations when an increase was seen at 10^{-4} M. There were no significant changes in tension development in untreated control tissues over the duration of an experiment ($2P > 0.05$, $n = 6$). Hydrochloric acid (0.0005 N) and ethanol (0.125%), vehicle concentrations corresponding to the highest concentrations of cinnarizine and nifedipine used respectively, produced significant inhibition of tension development (mean of 9.2%, $n = 7$ and 17.3%, $n = 6$, respectively). These inhibitory effects were taken into account when calculating drug potencies.

Discussion

Nifedipine, gallopamil and diltiazem were potent inhibitors of the spontaneous and oxytocin-induced tension development of rat uterus, spontaneous tension development of hepatic portal vein, KCl-induced spasms of the mesenteric bed and tension development by electrically-driven ventricular muscle. Several of the inhibitory actions of these calcium antagonists, for example, gallopamil on the uterus (Fleckenstein *et al.*, 1971; Reiner & Marshall, 1975), the papillary muscle (Warburton & Weston, 1982a) and the portal vein (Warburton & Weston, 1982b), can be reversed by increasing the Ca^{2+} concentration of the medium. There is substantial support for the concept that the primary mechanism of action of nifedipine, gallopamil and diltiazem is inhibition of Ca^{2+} entry into the cell from the extracellular medium (Bolton, 1979; Nayler & Horowitz, 1983). It is therefore reasonable to conclude that this mechanism underlies the potent inhibitory actions of these compounds observed in the present study.

Cinnarizine has also been classified as a calcium antagonist with vascular selectivity (Godfraind, 1981; 1983; Van Neuten & Vanhoutte, 1981). However, it is clear from the data presented in Table 1 that this drug has a different profile of action from the other compounds. For the well-established calcium antagonists, the rank order of potency was always nifedipine > gallopamil > diltiazem, in those 5 preparations where they were potent. In contrast, cinnarizine was the least potent of the calcium antagonists on the uterus and portal vein but was the second most potent compound against KCl-evoked pressure rises in the perfused mesenteric bed. In addition, cinnarizine was equipotent against noradrenaline- and KCl-induced responses of the mesenteric bed while the calcium antagonists displayed marked differences in potency against the two agonists. An α-adrenoceptor antagonistic action of cinnarizine cannot explain its high potency against noradrenaline-induced responses on the mesenteric bed since cinnarizine was much less potent against noradrenaline-induced spasms of aortic strips. Even if inhibition of Ca^{2+} entry into the cell from the extracellular medium does underlie the potent actions of cinnarizine, the findings of the present study suggest its site of action must be different from that of the other calcium antagonists. This concept is supported by radioligand-binding studies in which cinnarizine was of low potency as an inhibitor of [^{3}H]-nifedipine binding in rabbit myocardium (Holck *et al.*, 1982).

Nifedipine, gallopamil and diltiazem exhibited their lowest potencies against noradrenaline-evoked spasms of the rat aorta and perfused mesenteric bed. There is evidence that the action of noradrenaline in these blood vessels is partially resistant to Ca^{2+} removal from the bathing medium with tension development involving mainly an intracellular Ca^{2+} pool (Godfraind & Miller, 1982; Karaki *et al.*, 1984). The low potency of these calcium antagonists is therefore perhaps predictable. However, the observed inhibitory effects of these compounds could imply some role for extracellular Ca^{2+} in the noradrenaline-induced spasms of these two tissues. Alternatively their inhibitory effects could result from an action other than that of blockade of Ca^{2+} entry into the cytoplasm. Such a possibility seems more likely since the rank order of potency for their relatively low potency actions varied and differed from that for their high potency actions. The order was gallopamil > diltiazem = nifedipine on the mesenteric bed and nifedipine > diltiazem = gallopamil on the aorta.

Furthermore these compounds possess several other pharmacological properties at high concentrations. Nicardipine, an analogue of nifedipine, is a phosphodiesterase inhibitor at 4 μM in the oestrus uterus of the rat (Nishikori *et al.*, 1981). Gallopamil at 2 and 7 μM displaces radioligands for adrenoceptors and muscarinic receptors respectively (Jim *et al.*, 1981) and has several other pharmacological actions (Nayler & Horowitz, 1983). Diltiazem at 10 μM acts as a local anaesthetic and inhibits the fast inward Na^+ current in the guinea-pig ventricle (Nakajima *et al.*, 1975) and at 80 μM binds to calmodulin from porcine coronary arteries (Johnson & Fugman, 1983).

The rank order of potency for those actions where the well established calcium antagonists were potent

was always nifedipine > gallopamil > diltiazem (except for ventricle at 2.5 Hz – see below). This rank order (or nifedipine > verapamil > diltiazem) has also been found against K^+-evoked spasms of cerebral and mesenteric arteries of the cat (Andersson *et al.*, 1983) and coronary arteries of the pig (Fleckenstein & Fleckenstein-Grün, 1980). These data provide no support for the idea that these three compounds interact at different sites in these tissues. However, in the present study gallopamil and diltiazem, but not nifedipine, exhibited the phenomenon of use-dependency with ventricular muscle, a feature well recognized with cardiac muscle (Rodenkirchen *et al.*, 1982). This gave a potency order of gallopamil = nifedipine > diltiazem at a stimulation frequency of 2.5 Hz, confirming the work of Narimatsu & Taira (1976) and Spedding (1982b). These observations, together with the markedly different profile of action of cinnarizine already discussed, suggest that the calcium antagonists employed in the present study act at different sites. This is further confirmed by the ligand-binding studies of Glossmann *et al.* (1982) and Holck *et al.* (1982) and supports the view of Spedding (1982a,b; 1984) for the existence of at least three sub-groups of calcium antagonists.

Nifedipine, gallopamil and diltiazem were potent inhibitors of tension development by the uterus and showed selectivity relative to a capacitance and resistance vessel, a vein and ventricular muscle. Such calcium antagonist selectivity could be due, for example, to differences between tissues in drug binding, in the importance of extracellular Ca^{2+} for muscle contraction or in the Ca^{2+}-channels themselves (Triggle & Swamy, 1983)—the present study cannot preferentially support any of these reasons.

Salbutamol is a moderately selective inhibitor of tension development by the uterus *in vivo* relative to its vasodepressor and cardiac chronotropic effects both in the pregnant rat (Hollingsworth & Schnieden, 1973) and in women (Liggins & Vaughan, 1973), a pattern of selectivity which was also observed in the present *in vitro* study. Indeed, salbutamol was the most potent and selective of the drugs as an inhibitor of tension development by the uterus. Nevertheless, the selectivity seen here *in vitro* with the calcium antagonists, which extends to the rat *in vivo* (Abel & Hollingsworth, 1985) plus the clinical experience already obtained with nifedipine (Forman *et al.*, 1981), suggests that these compounds may have a place in the treatment of dysmenorrhoea and preterm labour.

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