after endotoxin was a mean of 30 mmHg below the pre-endotoxin levels of 115±10 mmHg whilst the diastolic blood pressure at this time had fallen by a mean of 37 mmHg (from 86±9 mmHg). The arterial pH was reduced from 7·468±0·035 to 7·172±0·043 units 2h post-endotoxin. In the indomethacin treated animals the blood pressure 2h after endotoxin was between 40 and 50 mmHg higher than it was before the endotoxin was administered whilst the decrease in arterial pH (from 7·513±0·038 to 7·375±0·030 units) was not as pronounced as in the animals administered endotoxin alone.

These results indicate that indomethacin not only abolishes the initial acute pulmonary vasoconstriction which follows *E. coli* endotoxin administration in the cat but that it also delays the onset of the shock phase. Possible explanations for these effects include stabilization of mast cells and lysosomes, and the inhibition of the synthesis and release, or antagonism of the vascular effects, of humoral agents such as histamine, 5-hydroxytryptamine and the prostaglandins.

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Inhibition by cinnarizine of calcium channels opening in depolarized smooth muscle

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Previous studies have shown that cinnarizine is an antagonist of several vasoactive drugs including adrenaline, angiotensin and 5-hydroxytryptamine. Cinnarizine inhibits the contraction induced by adrenaline in physiological solution but not that in a calcium-free depolarizing solution. It also inhibits the contraction induced by calcium in depolarizing solution (Godfraind & Kaba, 1969, 1972). The present experiments were designed to determine whether such inhibition is due to reduction of the permeability of the vascular smooth muscle membrane to Ca^{++}ions.

Strips 4 cm long were prepared by spiral section of rat aorta. They were bathed either in a physiological solution (NaCl 122, $NaHCO_3$ 15, KCl 5·9, $CaCl_2$ 1·25, $MgCl_2$ 1·25 and glucose 11 mM) or in a depolarizing solution (similar but containing 100 mM KCl instead of NaCl and with $CaCl_2$ added according to the concentration required).

In the presence of increasing dosages of cinnarizine (3×10^{-9}M to 2×10^{-5}M), the noradrenaline dose-effect curves were depressed non competitively whereas Ca^{++}-dose effect curves were progressively displaced to the right; this displacement reached a maximum for cinnarizine 10^{-5}M and was not characteristic of a competitive antagonism. The contraction evoked by noradrenaline in Ca^{++}-free solution containing EGTA was not depressed by cinnarizine.

In the presence of cinnarizine 10^{-5}M, there was no change in Na^+, K^+ or Ca^{++} content of rat aorta. Total $^{45}Ca^{++}$ content, determined after equilibration in radioactive solution, was not changed either in physiological solution or in depolarizing solution. Cytoplasmic $^{45}Ca^{++}$ content was estimated by measuring residual radioactivity of muscles washed in a Ca^{++}-free solution containing 2 mM La^{3+} (van Breemen, Farinas, Gerba & McNaughton, 1972). As shown in Table 1, an increase of $^{45}Ca^{++}$ content in the tissue compartment blocked by lanthanum was induced by depolarization and by noradrenaline 10^{-5}M; this increase was prevented by cinnarizine.

TABLE 1. *Cytoplasmic $^{45}Ca^{++}$ content (mmol/kg w. weight) of rat aortae immersed for 5 min± in radioactive physiological solution and during a subsequent period of 15 min. in radioactive physiological solution; in radioactive depolarizing solution or in radioactive physiological solution containing noradrenaline 10^{-5}M. Means ±S.E. of mean*

Treatment	Physiological solution	Depolarizing solution	Noradrenaline 10^{-5}M
Controls	0·055±0·002 (12)	0·088±0·004 (12)	0·089±0·004 (12)
Cinnarizine 10^{-5}M (pretreatment of 90 min.)	0·041±0·002 (12)	0·048±0·003 (12)	0·049±0·003 (12

The present results suggest that cinnarizine could act by inhibiting the opening of Ca^{++}-channels evoked by depolarization or noradrenaline and therefore by decreasing the calcium influx into the stimulated smooth muscle cell.

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Drug-induced changes in the sensitivity of the rat anococcygeus muscle

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Various types of supersensitivity occur in adrenergically innervated tissues. For example, specific supersensitivity to noradrenaline (NA) is produced by impairment of the neuronal uptake process, while non-specific supersensitivity occurs following decentralisation or reserpine treatment (Trendelenburg, 1966). Both these types of supersensitivity are indicated by leftwards shifts in the dose-% response curves. However, increased sensitivity may also be manifested as increases in the maximum response of the tissue to agonists (Cannon & Rosenblueth, 1949), with no shift in the dose-% response curve (Muir & Pollock, 1973). In this study the effects of various drugs on the sensitivity of the rat anococcygeus muscle (Gillespie, 1972) were investigated.

Adult male Wistar rats were stunned and killed by exsanguination. The anococcygeus muscles were removed and suspended in oxygenated Krebs bicarbonate solution (37° C). Responses to acetylcholine (ACh) and NA were recorded isometrically.

A specific supersensitivity (50–100 fold) to NA was produced by cocaine (10^{-5}M in the Krebs bathing medium) and 6-hydroxydopamine (6–OHDA) (2×50 mg/kg on day 1; 2×100 mg/kg on day 4; experiment on day 6). The responses to the α-agonist, oxymetazoline, which is not taken up by the nerves (Birmingham, Paterson & Wojcicki, 1970), were unaffected by these drugs, suggesting that the specific supersensitivity following cocaine and 6–OHDA resulted from impaired neuronal uptake. Reserpine (1[mg/kg]/day; 6 days) produced a 2-fold increase in sensitivity to both ACH and NA. Thyroxine (3[mg/kg]/day orally in drinking water for 2 weeks) had a similar effect. In neither of these types of supersensitivity, which were characterized by displacement of the dose-% response curves, was the maximum response to either agonist altered. Corticosterone (10[mg/kg]/day; 6 days) produced a third type of supersensitivity, similar to that produced by morphine withdrawal in other tissues (Pollock, Muir, MacDonald & Henderson, 1972) and characterized by an increase in the maximum to both agonists. In this study of morphine (300[mg/kg]/day orally in drinking water for 4 months) produced a similar pattern of supersensitivity to that produced by corticosterone.