The action of cinnarizine on noradrenaline-sensitive calcium influx and efflux in vascular smooth muscle

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It has recently been reported that, in the rat aorta, the turnover of the calcium fraction resistant to displacement by lanthanum provides an estimate of Ca^{2+} fluxes across the smooth muscle cell membrane (Godfraind, 1976). Noradrenaline increased the rate of ^{45}Ca uptake into the La-resistant fraction. Once this fraction was loaded with ^{45}Ca, noradrenaline also increased the rate of ^{45}Ca efflux. For both influx and efflux, the increased rate corresponded to a Ca turnover of 30 μ-mol ^{45}Ca kg^{-1} min^{-1}. This increased influx of Ca appeared to control the tonic component of the contraction which is dependent on the calcium concentration of the bathing fluid. Cinnarizine is a non-competitive antagonist for noradrenaline in rat aorta. It reduced in a dose-dependent manner the tonic component of the contraction and blocked the noradrenaline evoked calcium influx (Godfraind, 1974).

The purpose of the present experiments was to examine the action of cinnarizine on the rate of calcium exchange into the La-resistant Ca fraction, considering not only the Ca influx but also the Ca efflux.

Contractility and ^{45}Ca exchange were studied as reported elsewhere (Godfraind, 1976). The action of cinnarizine was analyzed after a preincubation of 90 minutes.

In unstimulated strips, a slight depression of ^{45}Ca uptake in the La-resistant fraction was observed with cinnarizine (10^{-5} M). Lower concentrations reduced the initial rate of uptake, but the ^{45}Ca content measured after the 5 min preincubation in the radioactive solution preceding the addition of noradrenaline (10^{-5} M) was not different from controls.

Cinnarizine concentrations between 10^{-8} M and 10^{-5} M reduced the noradrenaline-sensitive ^{45}Ca uptake into the La-resistant fraction. In agreement with previous results (Godfraind, 1974), 50% inhibition was achieved with cinnarizine (8×10^{-7} M) which reduced to 50% of its maximum the Ca_n-dependent tonic contraction evoked by noradrenaline. Cinnarizine (10^{-5} M) abolished the noradrenaline-sensitive ^{45}Ca influx and the tonic contraction. The noradrenaline-sensitive Ca efflux was slightly depressed by cinnarizine (3×10^{-7} M) but this depression was not increased with cinnarizine (10^{-5} M).

The observation that Ca influx and efflux sensitive to noradrenaline are differently affected by cinnarizine indicates that inward and outward Ca fluxes occurring during alpha-adrenoceptor stimulation might result from the opening of two distinct channels in the cell membrane.

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Alpha and beta adrenoceptors in the hepatic portal venous vascular bed of the dog

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The distribution of adrenoceptors in the portal venous vascular bed of the dog is not fully established. α-Adrenoceptor agonists such as noradrenaline and adrenaline cause dose-dependent portal vasoconstriction (Green, Hall, Sexton & Deal, 1959; Shoemaker, 1964; Richardson & Withrington, 1977a) and although intraportal isoprenaline does not reduce portal vascular resistance (Hanson, 1973; Hirsch, Ayabe & Glick, 1976), this does not exclude the possibility of a β-adrenoceptor population which may contribute to the responses elicited by mixed α- and β-adrenoceptor agonists.

The hepatic portal venous vascular bed of 11 chloralose-urethane anaesthetized dogs (9.6–11.5 kg) was perfused at constant flow with blood derived from the superior mesenteric vein (Richardson & Withrington, 1977a). The control systemic arterial pressure was 140.0 ± 11.3 mmHg (mean ± 1 s.d.) and the inferior vena cava pressure (IVCP) 1.8 ± 0.8

mmHg. The hepatic portal venous flow (HPVF) was 241.7 ± 63.2 ml/min and the hepatic portal venous pressure (HPVP) 5.42 ± 1.82 mmHg. The hepatic portal vascular resistance (HPVR), calculated as (HPVP–IVCP)/HPVF was 0.017 ± 0.008 mmHg ml^{-1} min, or 0.051 ± 0.026 mmHg ml^{-1} min 100 g liver weight.

Isoprenaline was injected on 39 occasions in 9 preparations (100 ng–100 μg intraportally): in no experiment was there a dose-dependent reduction in HPVR, the maximum fall being under 5%, and doses over 1 μg tended to cause small increases in HPVR. Similar responses were obtained when a background portal 'tone' was induced by intraportal infusions of noradrenaline (1, 5 & 10 μg/min).

Phenylephrine, noradrenaline and adrenaline were injected intraportally in graded increasing doses: the only response was portal vasoconstriction. The thresholds, and doses which doubled the HPVR were: phenylephrine ($n = 4$) 0.5 to 5.0 μg and 6.3 (± 3.0) × 10^{-7} mol (mean ± s.e. mean); noradrenaline ($n = 4$), 100 ng and 2.5 (± 0.8) × 10^{-8} mol; adrenaline, the most potent, ($n = 4$), 100 ng and 6.5 (± 0.3) × 10^{-9} mol.

The form and position of these dose-response curves to intraportal phenylephrine, noradrenaline and adrenaline were unaffected by propranolol (250 μg/kg, i.v.): the doses of each substance required to double the HPVR were not significantly altered by β-adrenoceptor blockade ($P>0.30$, $n = 3$, paired t-test). In contrast, phentolamine (1.0 mg/kg. i.v.) caused a shift of the portal vasoconstrictor dose-response curves for all three substances to the right: the mean dose-ratios for the doubling in HPVR before and after the α-adrenoceptor antagonist were 32.4 for phenylephrine, 12.1 for noradrenaline and 20.1 for adrenaline, and were not significantly different for any pair of the three substances ($P>0.20$; $n = 4$).

The canine portal venous vascular bed contains α-adrenoceptors which, when stimulated, cause portal vasoconstriction, but β-adrenoceptors are not present in this bed in an adequate population either to mediate a portal vascular response to intraportal injections of isoprenaline, or to modulate the portal vasoconstrictor responses to adrenaline or noradrenaline. This adrenoceptor population contrasts with that of the hepatic arterial bed which possesses both α and β-adrenoceptors (Richardson & Withrington, 1977b).

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Receptors mediating hyperpolarizing responses to catecholamines in rat superior cervical ganglia

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The receptors mediating the hyperpolarizing action of catecholamines on sympathetic ganglion cells have not yet been fully characterized. The present communication describes some attempts to define the receptors responsible for the hyperpolarization of rat sympathetic ganglion cells produced by adrenoceptor stimulants *in vitro*. Potential changes in superfused desheathed rat superior cervical ganglia were recorded extracellularly by the 'air-gap' method of Brown & Marsh (1974), with temperature controlled to 25°C ± 1°C.

The sympathomimetic amines listed in Table 1 produced a rapid, reversible low-amplitude (≥400 μV) hyperpolarization. Clonidine (10^{-9} to 10^{-6} M) and ergometrine (10^{-8} 10^{-5} M) also produced a hyperpolarization which was much more persistent (2–3 h) and had characteristics of partial agonism.