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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References

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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