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Evidence for a dopaminergic mechanism for modulation of adrenergic transmission in the rabbit ear artery

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Much of the evidence for a pre-junctional α-adrenoreceptor through which noradrenaline (NA) release from adrenergic nerves is inhibited is based on the increased release in the presence of α-adrenoreceptor antagonists (Hotta, 1969; Häggendal, 1970; Kirpekar & Puig, 1971; Enero, Langer, Rothlin & Stefano, 1972; McCulloch, Rand & Story, 1972). In guinea-pig atria, phenoxybenzamine (1×10^{-5}M) increased NA release in response to sympathetic stimulation by about six-fold (McCulloch *et al.*, 1972); however, in rabbit ear artery the increase was only about two-fold.

We have now investigated the effects of a number of sympathomimetic amines on stimulation-induced efflux of radioactivity from arteries previously incubated with (^{3}H)-(-)-NA, using the method of Allen, Rand & Story (1973). Cocaine (1×10^{-4}M) was present in the perfusion fluid to prevent displacement of labelled NA by exogenous amines.

As with atria (McCulloch *et al.*, 1972), (—)-NA (5×10^{-7}M) inhibited stimulation-induced release of radioactivity from the artery by about 40%. Dopamine (5×10^{-8}, (5×10^{-7} and 5×10^{-6}M) also inhibited release by about 25%, 40% and 50%, respectively. Tyramine (5×10^{-7}M) and (+)-NA (5×10^{-7}M) had no effect.

The effect of dopamine (5×10^{-7}M) on the vasoconstrictor responses to sympathetic stimulation depended on the regime of stimulation. With 10 s periods every 2 min (1 ms pulses at 2 or 5 Hz), responses were at first reduced. However, in the continued presence of dopamine, responses tended to recover and even to exceed the control level, and there was a parallel increase in responses to exogenous NA. With 30 s periods every 30 min, responses were generally enhanced by dopamine (in the presence of cocaine), although transmitter release was markedly reduced, as mentioned above. The slowly developing increase in responsiveness of the effector cells may possibly be due to the formation of an inhibitor of extraneuronal uptake, such as the 3-methoxy metabolite of dopamine.

The observations that dopamine inhibits release of transmitter NA and at the same time potentiates vasoconstrictor responses to NA can be fitted into a unified concept of transmission economy. If axonal reserves of NA should run down because of excessive sympathetic activity, dopamine may accumulate in the transmitter pool. Continued sympathetic activity would then release a larger proportion of dopamine than usual. This dopamine may act back on pre-junctional dopamine receptors to inhibit transmitter release and thereby enable the synthetic mechanism to make good the deficit of trans-

mitter NA. At the same time, the released dopamine acts post-junctionally to increase the sensitivity of the effector cells. Thus, despite a reduction in transmitter release, there is a compensatory effect which tends to maintain transmission.

Although there is evidence in accord with this hypothesis for adrenergic transmission in the rabbit ear artery, the mechanism does not appear to operate in the guinea-pig atria or vas deferens.

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Effect of tricyclic antidepressants on the cardiovascular responses of the rat

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Moir, Crooks, Cornwell, O'Malley, Dingwall-Fordyce, Turnbull & Weir (1972), using a hospital-based drug information system, confirmed a possible correlation between the administration of amitriptyline and the incidence of sudden and unexpected death in patients with a diagnosis of cardiac disease. They found the incidence to be 13 such cases in 119 amitriptyline treated patients compared with only 3 in a matched control group. There were only 4 such deaths in a group of 87 patients receiving imipramine compared with 2 in the control group.

One or more of the following factors, acting alone or in combination, could contribute to the cardiotoxic effect of this group of drugs: potentiation of the effects of catecholamines by inhibition of their uptake; an atropine-like effect, or a direct effect on the myocardium.

This investigation was designed to compare the catecholamine potentiating and anticholinergic activity of 5 tricyclic antidepressant drugs (imipramine, desmethylimipramine, amitriptyline, nortriptyline and chlorimipramine) in the rat. This was done by determining the cardiovascular response to intravenously injected noradrenaline, isoprenaline, carbachol and to vagal stimulation in urethane anaesthetized rats after acute or chronic pretreatment with one of the above antidepressants. Chronic treatment with all 5 drugs was at the rate 10 (mg/kg)/day for 14 days via the drinking water; acute administration of 20 mg/kg or 40 mg/kg by intraperitoneal injection 1 h before the start of the experiment was carried out with 2 compounds only, amitriptyline and desmethylimipramine. Blood pressure, ECG and heart rate were monitored throughout the experiment.

After chronic administration, the pressor effect of noradrenaline was potentiated and was of longer duration; the carbachol depressor effect was slightly reduced but the effect of vagal stimulation on blood pressure was almost completely abolished compared with the control group. Imipramine and desmethylimipramine antagonized the increase in heart rate caused by isoprenaline.

After acute administration the pressor effect of noradrenaline was potentiated though the smaller of the two doses had the greater potentiating effect, possibly due to the α-adrenoceptor blocking action of high doses of tricyclic compounds (Asberg, Cronholm,