Role of neuronal uptake in the disposition of released [^{3}H]-noradrenaline in the dog's saphenous vein

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The present experiments were designed to obtain more information on the relative importance of neuronal uptake and enzymatic degradation (by monoamine oxidase and catechol-O-methyltransferase) in the disposition of noradrenaline released by nerve impulses.

Helical strips of dogs' saphenous veins were incubated in Krebs-Ringer solution containing [^{3}H]-noradrenaline. They were then mounted for isometric tension recording, and superfusion at constant flow with aerated Krebs-Ringer solution at 37°C (Vanhoutte, Lorenz & Tyce, 1973). The amounts of [^{3}H]-noradrenaline and its major metabolites (3,4-dihydroxyphenylglycol, DOPEG; 3,4-dihydroxymandelic acid, DOMA; normetanephrine, NMN; 3-methoxy-4-hydroxyphenylglycol, MOPEG; and 3-methoxy-4-hydroxymandelic acid, VMA) in the superfusate were determined by column chromatography (Verbeuren, Coen & Vanhoutte, 1977). In certain experiments, the tissue uptake of [^{3}H]-noradrenaline was determined by extraction (Muldoon, Vanhoutte & Tyce, 1978).

Electrical stimulation caused an increase in efflux of [^{3}H]-noradrenaline and its metabolites, except for the VMA fraction which decreased. Cocaine (3×10^{-5}M) given during continuous electrical stimulation significantly augmented all fractions, except for DOPEG which decreased. Desimipramine (DMI; 10^{-6}M) significantly augmented the noradrenaline and VMA fraction, reduced the DOPEG and MOPEG fraction, but did not affect the DOMA and NMN efflux. In strips treated with DMI, cocaine reduced all fractions except VMA which was augmented. In veins treated with phentolamine (3×10^{-5}M), the only significant effect of cocaine and DMI was to augment the overflow of intact [^{3}H]-noradrenaline. At the concentrations used, cocaine, DMI and phentolamine inhibited tissue uptake of [^{3}H]-noradrenaline by 84%, 80% and 34%, respectively.

The present experiments indicate that in the canine saphenous vein: (1) cocaine, besides blocking neuronal uptake, inhibits the evoked release of noradrenaline, and displaces the transmitter and its metabolites from non-neurogenic binding sites; (2) DMI, besides blocking neuronal uptake, has alpha-blocking properties; (3) phentolamine, besides blocking alpha-adrenoceptors, inhibits neuronal uptake; (4) the neuronal uptake process is the rate limiting step in the chain of events leading to intraneuronal deamination of noradrenaline, which leads to the formation of both DOPEG and MOPEG; and (5) blockade of neuronal uptake increases the overflow of [^{3}H]-noradrenaline by less than 50%.

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Effect of profound cooling on adrenergic neuroeffector interaction in the blood vessel wall

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Moderate cooling (from 37° to 20°C) augments the response of cutaneous vessels to sympathetic stimulation and exogenous vasoconstrictor agents (see Vanhoutte, 1979). The present study was performed to investigate the effect of profound cooling (from 37° to 5°C) on the adrenergic neuroeffector interaction in the blood vessel wall. Rings of canine lateral saphenous veins and anterior tibial arteries were mounted for isometric tension recording in an organ chamber filled with Krebs-Ringer bicarbonate solution aerated with 95% O_2 and 5% CO_2. The temperature of the solution could be altered (37, 30, 20, 15, 10 and 5°C) by adjusting the temperature of the water jacket surrounding the organ chamber. Frequency-response curves to electrical stimulation (10V, 2 msec, 0.5 to 16 Hz) or cumulative dose-response curves to either noradrenaline (5×10^{-9} to 10^{-5}M) or potassium ions (K^+) (5.9 to 80 mEq/l) were obtained in different segments of the same vessels, at the different temperatures tested. The responses to K^+ were obtained in solutions containing phentolamine (10^{-6}M), to rule out the evoked release of noradrenaline caused by high concentrations of the ion (Vanhoutte & Verbeuren, 1976).

In unstimulated arteries and veins cooling to 5°C caused a slight decrease in basal tension. The response