for 60 min and the effect of perfusion with normal and modified Krebs solutions on the spontaneous release of ^{3}H-(−)-noradrenaline was then measured over a further 60 min period. The effect of changes in ion composition of the perfusing solution on the release of ^{3}H-(−)-noradrenaline caused by injection of noradrenaline 200 ng, metaraminol 20 μg, octopamine 50 μg and tyramine 100 μg, were studied and the results are summarized in Table 1.

TABLE 1

Perfusate composition	Mean spontaneous release D.P.M./ml	Mean increase in ^{3}H-noradrenaline outflow (D.P.M./ml)±S.E. on injection of Noradrenaline 200 ng	Octopamine 50 μg	Metaraminol 20 μg	Tyramine 100 μg
Normal	1,849	950±135	2,127±202	3,807±320	2,516±231
Mg^{2+} FREE	1,976	969±129	2,793±256	3,961±301	2,807±276
Ca^{2+} FREE	2,618	1,009±145	6,271±481	4,921±384	10,031±641
Ca^{2+} and Mg^{2+} FREE	3,549	1,117±172	10,098±836	9,551±522	16,728±1,062

These results indicate that the potentiation of the pressor response to sympathomimetic amines in the rat mesentery preparation is at least partly attributable to an increased release of noradrenaline under these conditions. It would also seem that the presence of Ca^{2+} in the bathing medium is not essential for the release of noradrenaline by sympathomimetic amines, and that Ca^{2+} exerts some influence on the potency of sympathomimetic amines in isolated preparations. Perfusion of the mesenteric arteries with Ca^{2+} and Mg^{2+} free solutions does not interfere with the uptake process for tyramine, octopamine and metaraminol.

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Effects of acetylcholine on vasoconstriction and release of ^{3}H-noradrenaline in response to sympathetic nerve stimulation in the isolated artery of the rabbit ear

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Vasoconstrictor responses of the isolated artery from the rabbit ear to sympathetic nerve stimulation at low frequencies (1–5 Hz) were increased in the presence of low concentrations of acetylcholine (ACh) ($<1\times10^{-9}$M) and were decreased by higher concentrations of acetylcholine ($>1\times10^{-8}$M). These findings are in accord with those of Malik & Ling (1969), who used rat mesenteric artery. To determine whether the effect of ACh on responses was due to alterations in transmitter release, observations were made on the efflux of tritium from arteries previously incubated with ^{3}H-noradrenaline (^{3}H-NA). Tritium release was increased by a low concentration (1×10^{-10}) of ACh but was decreased by higher concentrations of ACh ($>1\times10^{-7}$M).

Atropine antagonized the effects of ACh in decreasing vasoconstriction and tritium efflux in response to sympathetic nerve stimulation. In a series of experiments with stimulation at 2 Hz, a decrease of 50% or more in the contractile response was obtained with concentrations of ACh ranging from 5×10^{-8} to 1×10^{-6}M, then atropine

($3{\cdot}5 \times 10^{-7}$M) was added. In one-third of these experiments, not only did atropine antagonize the effects of ACh, but the contractile responses exceeded the control level. Using arteries labelled with ^{3}H-NA, atropine partly antagonized the reduction in tritium efflux caused by ACh (1×10^{-7} to 1×10^{-6}M). When a higher concentration of ACh was used (1×10^{-5}M) the efflux in response to stimulation at 5 Hz was increased above control levels by atropine in two experiments but was only partly restored in three. Atropine alone had no effect on tritium efflux in response to sympathetic nerve stimulation.

The results show that ACh inhibits release in response to sympathetic nerve stimulation in the rabbit ear artery and that the inhibitory effect is abolished by atropine. These findings agree with those of Löffelholz & Muscholl (1969) who used rabbit heart.

In some experiments, the contractile responses and transmitter efflux were facilitated by ACh in the presence of atropine. Another muscarinically acting cholinomimetic drug, McN-A-343, decreased transmitter efflux as did ACh, but regularly facilitated efflux and contractile responses in the presence of atropine.

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Mechanisms of 6-hydroxydopamine-induced supersensitivity in guinea-pig isolated intact trachea

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Surgical sympathetic denervation of the nictitating membrane of the cat causes the development of a supersensitivity to noradrenaline (NA) that consists of two distinct components (Trendelenburg, 1963). One component is similar to the supersensitivity produced by pre-ganglionic nerve section (decentralization); it is of moderate degree and non-specific. It appears to develop whenever the influence of central impulses on the effector organ is excluded for periods of 7 to 14 days and is probably of post-synaptic origin. The second component of denervation supersensitivity is very like that caused by cocaine; it is specific for those amines removed by the neuronal uptake process and is probably of pre-synaptic origin.

6-Hydroxydopamine (6-OHDA) destroys sympathetic nerve endings producing, in effect, a 'chemical denervation' (Tranzer & Thoenen, 1967; Malmfors & Sachs, 1968). Subsequent development of supersensitivity to NA has been demonstrated in several tissues (Haeusler, Haefely & Thoenen, 1969; Haeusler, 1971; Finch & Leach, 1970). We have investigated whether treatment with 6-OHDA produces supersensitivity to sympathomimetic amines in guinea-pig tracheal preparations and whether such supersensitivity is similar to that produced by surgical denervation of cat nictitating membrane. Responses to NA, a sympathomimetic amine effectively transported by the neuronal uptake system, are compared with