($3{\cdot}5 \times 10^{-7}$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

those to isoprenaline, a sympathomimetic amine not transported by the neuronal uptake system (Burgen & Iversen, 1965).

Male guinea-pigs weighing 300–350 g were injected intravenously with 6-OHDA, 2×25 mg/kg on day 1 and 2×50 mg/kg on day 7. The trachae were removed on days 8–10. Denervation of the tracheae was judged to have been effective as no formaldehyde-induced fluorescence could be detected by histochemical examination and responses to tyramine were abolished.

Isolated, intact tracheae from control or 6-OHDA treated guinea-pigs were set up as described by Coleman & Farmer (1971). In untreated preparations a maximally effective concentration of cocaine (10 μg/ml—Coleman & Levy unpublished) produced a 3·77-fold ($P<0·001$) increase in sensitivity to NA but no significant change in sensitivity to isoprenaline ($P>0·05$). In preparations taken from animals pretreated with 6-OHDA, NA was 6·25 times ($P<0·001$) more potent and isoprenaline 2·7 times ($P<0·001$) more potent than in normal tracheae. Cocaine failed to increase further the sensitivity to either NA or isoprenaline in preparations from animals pretreated with 6-OHDA.

The results suggest that the supersensitivity caused by chemical denervation with 6-OHDA resembles that caused by surgical denervation. A post-synaptic component is indicated by (a) the potentiation of responses to isoprenaline in chemically denervated tracheae and (b) the greater potentiation of responses to NA in chemically denervated tracheae than in normal tracheae in the presence of cocaine. A pre-synaptic component is indicated by the greater potentiation of responses to NA than isoprenaline in chemically denervated tracheae.

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The effect of N^6,$O^{2'}$-dibutyryl adenosine 3′:5′-cyclic monophosphate on noradrenaline synthesis in isolated superior cervical ganglia

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Levels of noradrenaline (NA) and its associated enzymes in adrenergic neurones are affected by the activity of the preganglionic fibres (Molinoff & Axelrod, 1971). Pre-ganglionic stimulation causes a several-fold increase in the adenosine 3′: 5′-cyclic