Effect of denervation and cocaine on the response of isolated rat vas deferens to noradrenaline and methoxamine

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In the rat vas deferens, cocaine increases the maximum response and shifts the dose-response curve for noradrenaline (NA) to the left (Barnett, Greenhouse & Taber, 1968). The former has been ascribed to a postjunctional effect and the latter to the prevention of neuronal NA uptake by cocaine (Trendelenburg, 1972). To provide evidence for the site of action we used methoxamine, an alpha-adrenoceptor agonist, whose neuronal uptake is negligible (Trendelenburg, Maxwell & Pluchino, 1970).

Vasa deferentia of rats were placed in oxygenated Tyrode solution at 37°C, and the isotonic contractions were recorded on a kymograph and developed tension on Grass polygraph. Denervation of tissue was carried out by desheathing (Birmingham, 1970) 24 h before experiment. Reserpinization was achieved by reserpine (5 mg/kg and 2.5 mg/kg, 48 and 24 h before experiment respectively).

Cocaine (2.94 μM), potentiated the effect of NA 12-fold and increased the maximum response by $75 \pm 12.4\%$. Denervation potentiated the response to NA ten-fold. Cocaine had no significant effect on the dose-response curve and maximum response to NA in denervated vasa deferentia.

ED_{50} of methoxamine was 1.49 ± 0.36 μM in intact tissue and 2.83 ± 0.81 μM in reserpinized tissue. Devervation did not alter ED_{50} of methoxamine significantly (4.32 ± 0.77 μM in reserpinized tissue) and phentolamine shifted the dose-response curve to the right in a parallel fashion.

ED_{50} for methoxamine after pretreatment with cocaine was 1.49 ± 0.40 μM in intact tissue and 4.36 ± 1.01 μM in reserpinized tissue. Cocaine increased the maximum response to methoxamine by $3.5 \pm 5.3\%$ and $13 \pm 2.7\%$ in intact and reserpinized tissue respectively. This was significantly lower than that observed for NA.

These results support the idea that cocaine potentiates the response to NA by inhibiting the neuronal uptake of NA. They also suggest that the increase in maximum response to NA in intact rat vasa deferentia is at least partly due to prejunctional effects of cocaine.

References

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The effects of AH 5158 on metabolism of ^{3}H(–)noradrenaline released from the cat spleen by nerve stimulation

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In the isolated blood perfused cat spleen AH 5158, 5-(1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl) salicylamide, acts as a selective post-synaptic α-adrenoceptor antagonist. The drug elevates transmitter overflow but the mechanism involves inhibition of uptake rather than inhibition of pre-synaptic α-adrenoceptors (Blakeley & Summers, 1976). The present experiments investigate whether the site of uptake inhibition is neuronal or extraneuronal and whether AH 5158 affects degradative enzymes.

Isolated blood perfused cat spleens were labelled with [^{3}H]-(–)-noradrenaline (0.5 nM/min for 10 min; blood flow 6.0 ± 0.3 ml/min, $n = 9$). Loosely bound label was washed out by perfusion with Krebs bicarbonate saline for 30 minutes. Blood perfusion was re-established and the spleen perfused for 30 minutes. After stimulation of the splenic nerves with 200 impulses at 10 Hz, venous blood was collected in four 1 min fractions, chilled and centrifuged. One aliquot of plasma was counted directly and another was taken for the separation of [^{3}H]-(–)-noradrenaline