These results suggest that although the peak concentrations of noradrenaline in the blood stream after an intravenous injection are not increased by DMI, the noradrenaline may circulate for a longer time, thus contributing to the potentiation of the pressor effects. Alternatively, the increase in pressor response may be due to the release of another vasoactive substance by noradrenaline after DMI treatment.

REFERENCE

VANE, J. R. (1964). The use of isolated organs for detecting active substances in the circulating blood. *Br. J. Pharmac. Chemother.*, **23**, 360–373.

Evidence that guanethidine does not block adrenergic nerves by acting as a false transmitter

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Although guanethidine fulfils the criteria for a false transmitter substance in adrenergic nerves recently reviewed by Kopin (1968), there is some doubt that guanethidine blocks adrenergic transmission in this way, for block develops before significant depletion of noradrenaline (Cass & Spriggs, 1961).

If adrenergic neurone blockade is to be attributed to the release of an inactive false transmitter, then it must be shown that the release of the false transmitter by nerve stimulation can quantitatively account for blockade. The present study, therefore, was designed quantitatively to define the relationship between simultaneously released guanethidine and noradrenaline following splenic nerve stimulation during recovery from block produced by guanethidine.

The isolated cat spleen was perfused with oxygenated Krebs solution, containing ^{3}H-guanethidine (specific activity 132 μCi/mg) for 20 min, after which the perfusate was replaced with drug-free solution. After 10 min the splenic nerves were stimulated at 30 Hz for 10 s every 30 min. Two minute collections of the effluent perfusate were assayed for noradrenaline by the method of Haggendal (1963) and for ^{3}H-guanethidine by liquid scintillation spectrometry. Two concentrations of guanethidine were used; 10^{-6} g/ml, which produced just-complete block of the splenic response during the first stimulation, and 3×10^{-7} g/ml.

It was found that the guanethidine released by nerve stimulation was directly proportional to the noradrenaline released during recovery for up to 3 h. Furthermore, the guanethidine released was inversely proportional to the degree of block present. Blockade of the splenic response to nerve stimulation was a function of the concentration of guanethidine in the effluent perfusate just before stimulation. The ratio of noradrenaline to guanethidine released by nerve stimulation remained relatively constant for up to 3 h during recovery from guanethidine block. This ratio was 0·7 after exposure to guanethidine (10^{-6} g/ml) and 1·7 following guanethidine (3×10^{-7} g/ml).

It was concluded that guanethidine did not produce adrenergic neurone blockade by functioning simply as an inactive false transmitter. Its primary effect during these subacute experiments was to block the process leading to release of transmitter substance from the synaptic vesicles. The results, however, suggest that the partial

replacement of noradrenaline in the vesicles by guanethidine might contribute to the lesser degree of blockade during a later phase of recovery.

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REFERENCES

CASS, R. & SPRIGGS, T. L. B. (1961). Tissue amine levels and sympathetic blockade after guanethidine and bretylium. *Br. J. Pharmac. Chemother.*, **17**, 442–450.

HAGGENDAL, J. (1963). An improved method for fluorimetric determination of small amounts of adrenaline and noradrenaline in plasma and tissues. *Acta physiol. scand.*, **59**, 242–254.

KOPIN, I. J. (1968). False adrenergic transmitters. *Ann. Rev. Pharmac.*, **8**, 377–394.

Uterine response to adrenergic nerve stimulation in the guinea-pig

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Although there are many published reports which indicate that under certain experimental conditions stimulation of the sympathetic nerves can induce uterine contractions, the physiological importance of the adrenergic innervation of the myometrium is still unclear. In most animals, the uterus can function in the apparent absence of sympathetic innervation. However, it has been suggested that adrenergic nerves may exert a modifying influence on the myometrium, perhaps by changing its sensitivity to circulating hormones (Abrahams, Langworthy & Theobald, 1964). The present experiments were designed to study the effects of hypogastric nerve stimulation on uterine motility in the anaesthetized guinea-pig. The study had two objectives; one, to determine the effects of various frequencies of nerve stimulation on uterine motility *per se*, and two, to determine whether nerve stimulation could influence uterine sensitivity to oxytocin.

Guinea-pigs either in oestrus or immediately post partum were anaesthetized with urethane. After laparotomy the hypogastric nerves were cut below the inferior mesenteric ganglion and threaded through platinum electrodes. Intra-uterine pressure was recorded with a saline-filled catheter. Heart rate was monitored with a cardiotachometer and in some animals blood pressure was registered from the carotid artery. Nerve stimulation at frequencies between 1 and 20 Hz with rectangular pulses of 1·5 ms duration and 1·5 mA intensity for periods of 5 min caused uterine contractions. These contractions were abolished by phentolamine (5 μg/kg, intravenously). Nerve stimulation at frequencies between 1 and 6 Hz and at lower intensity, 1·0 mA, although not causing a contraction of the uterus, increased the uterine sensitivity to injected oxytocin (4 mu./kg, intravenously). This increase in sensitivity was abolished by phentolamine (5 μg/kg, intravenously) and by hexamethonium (5 mg/kg) and potentiated by propranolol (5 μg/kg). It was not accompanied by any observable changes in blood pressure or heart rate and was reproducible for many hours. Furthermore, it was much more pronounced in oestrus than after delivery (oestrus, mean increase=55%; post partum, mean increase=35%).

The frequencies of nerve stimulation at which the increase in oxytocin sensitivity was observed are within the same physiological frequency range as those thought to occur in other autonomic neuro-effector systems (Folkow, 1952). We suggest that