marked reduction in the isoprenaline tachycardia without affecting the increase in hind limb blood flow on intra-arterial injection of isoprenaline. The effects of butoxamine were not as clearly defined.

These results are compatible with the concept of β_1- and β_2-adrenoceptors.

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The potentiation of the cardiovascular responses of the dog to noradrenaline by desmethylimipramine

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The systemic pressor effects of noradrenaline injected intravenously are potentiated by desmethylimipramine (DMI). The mechanism of potentiation may be one or more of several, including an action on the heart, or increases in the effective concentration of noradrenaline either in the circulating blood or at a local level.

Dogs were anaesthetized with pentobarbitone sodium (32 mg/kg intravenously) and one hind leg was perfused at a constant rate by a Sigmamotor pump. Arterial blood was supplied to the pump from a cannula in the lower aorta and delivered to the leg through a cannula in the femoral artery. The femoral and sciatic nerves were cut and mass ligatures tied around the leg passing under the femoral artery and vein.

DMI (3 mg/kg intravenously) potentiated the blood pressure and perfusion pressure responses to noradrenaline. However, the increases in hind leg resistance induced by intravenous noradrenaline (0·5–2 μg/kg) were potentiated to a much greater degree than were the increases induced by noradrenaline injected directly into the leg. These experiments suggested that the potentiation was not simply due to an increase in noradrenaline concentration locally in vessels of the perfused hind leg or to a change in receptor sensitivity.

In other anaesthetized dogs, arterial blood concentrations of noradrenaline were estimated by the blood-bathed organ technique (Vane, 1964). Rat stomach strips were superfused with arterial blood at 10 ml/min. Noradrenaline, which relaxed the strips, was injected either directly into the bathing blood to calibrate the assay tissues or intravenously into the dog. DMI did not substantially alter the relaxations of the rat stomach strips induced by direct injections of noradrenaline, either in degree or duration. The peak concentrations of noradrenaline in the arterial blood following intravenous injections (0·5–2 μg/kg) were no greater after treatment with DMI (3 mg/kg intravenously) than before. However, the relaxation of the rat stomach strip after intravenously injected noradrenaline was prolonged.

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.

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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