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Responses of the mouse vas deferens to dopamine and some related drugs

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There is increasing interest in the possibility that dopamine (DA) may be an important neurotransmitter in the peripheral nervous system (Thorner, 1975). Recently, Tayo (1977) has suggested that DA may exert a dual influence on the vas deferens of several species, acting on both pre- and post-junctional DA receptors. In the present study we have examined the possibility of there being specific post-junctional DA receptors in the mouse vas deferens, a tissue in which the nature of the motor transmitter is in dispute (Jones & Spriggs, 1975; Jenkins, Marshall & Nasmyth, 1977).

Vas deferens preparations were dissected and mounted in organ baths containing Krebs' bicarbonate solution (Mg^{2+}-free) which was gassed continuously with 95% O_2:5% CO_2 and maintained at 37°C. Responses to agonist drugs were recorded isometrically, a resting tension of 500 mg being placed on the tissue. Antagonists were added to the Krebs' reservoir and were left in contact with the tissue for 30 min prior to addition of agonist. pD_2, pA_2 and pD'_2 values were calculated from the resultant dose-response curves.

Initially, a comparison was made of the sensitivity of the tissue to noradrenaline (NA) and DA. Although the muscle contracted to increasing doses of DA, it was much less sensitive to DA than it was to NA, there being differences both in the pD_2 values (NA = 5.14 ± 0.03; n = 10; DA = 3.83 ± 0.11, n = 7) and in the maximum responses (NA = 1.22 ± 0.08 g; DA = 0.59 ± 0.05 g). These experiments were carried out in the presence of cocaine (2 μM) in order to remove the influence of neuronal uptake from the results.

The responses to both NA and DA were antagonized competitively by phentolamine (pA_2 against NA = 7.76 ± 0.05; pA_2 against DA = 7.94 ± 0.13).

The DA agonist bromocriptine did not contract the muscle, but antagonized the responses to both NA and DA. In both cases the antagonism was non-competitive (pD'_2 against NA = 7.62 ± 0.05; pD'_2 against DA = 7.99 ± 0.12). The specificity of this antagonism was determined by observing the effect of bromocriptine on the dose-response curve to carbachol, which was unaltered.

Apomorphine, also considered to be a DA agonist, neither contracted the muscle nor antagonized the responses to NA or DA in low concentrations. However, apomorphine did alter the characteristics of the response to these agonists, producing large oscillations in tone during the contractions.

The results suggest that it is unlikely that specific post-junctional DA receptors exist in the mouse vas deferens. Further, they confirm that the 'DA agonist' bromocriptine is a potent α-adrenoceptor antagonist (Gibson, James, Shaw & Tracey, 1977). The observed differences between bromocriptine and apomorphine on α-adrenoceptor systems may explain some of the differences between these two drugs on CNS activity (Johnson, Loew & Vigouret, 1976).

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Vascular effects of bromocriptine in the hindlimb of the dog

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Intra-arterial injection of apomorphine into the canine femoral vasculature produces an immediate and short-lasting vasodilatation (Buylaert, Willems & Bogaert, 1977). This apomorphine effect is mimicked by a number of dopamine receptor agonists and is antagonized by haloperidol and other neuroleptic drugs, suggesting that a dopamine receptor is involved (Buylaert, Willems & Bogaert, 1978). Bromocriptine is an agonist for central dopamine receptors which is used in man. Its effects on the vasculature of the dog hindlimb are reported here.

In mongrel dogs (14–28 kg) anaesthetized with sodium pentobarbitone (30 mg/kg i.v.), blood pressure was measured in the left brachial artery and blood flow was monitored in both femoral arteries (Buylaert *et al.*, 1977). In some animals the sympathetic nerve supply to the right hindlimb was interrupted by transecting the lumbar sympathetic chain (L4–L5). Injections of the drugs were given into the femoral artery through a catheter introduced via the arteria profunda femoris; with the doses chosen, no changes in blood pressure occurred.

Low doses of bromocriptine ($\leq 0.5 \times 10^{-8}$ mol) had no effect on femoral flow when injected into the hindlimb. A higher dose of bromocriptine (4×10^{-8} mol) produced an increase in femoral flow in 26 out of 29 dogs. This increase in flow was slower in onset and of a smaller degree, but longer lasting (>10 min) than the increase seen with apomorphine (0.25×10^{-8} mol); bromocriptine (8×10^{-8} mol) did not further increase the dilatation present after a dose of 4×10^{-8} mol. In 6 dogs, a decrease preceded the increase with 4×10^{-8} mol. In 3 out of 29 animals, only a transient decrease of flow was observed.

Injection of the same dose of bromocriptine (4×10^{-8} mol) into a denervated hindlimb in 5 dogs produced only a transient decrease of femoral flow; this decrease was antagonized by phentolamine (1 mg/kg i.v.; $n = 4$).

Bromocriptine (4×10^{-8} mol) was also injected into the hindlimb 5 to 7 min after local administration of haloperidol (30 μg) or haloperidol (100 μg) (7 animals for each treatment) and the increase in flow was compared to that seen with the same dose of bromocriptine in the contralateral, untreated limb. Haloperidol had no lasting effect on femoral flow and caused a dose-dependent inhibition of the increase in flow by bromocriptine. Lactic acid, the solvent for