Pre- and post-synaptic activities of some dopamine analogues and related compounds

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Structural requirements for peripherally acting dopamine receptor agonists have been reviewed by Goldberg, Volkman & Kohli (1978). We have extended these studies and compared the effects of 10 compounds on the rabbit isolated perfused ear artery preparation and the renal vasculature of the anaesthetised dog.

Rabbit central ear arteries were isolated and perfused with Krebs-Henseleit solution (3 ml/min, 37°C, 95% O_2/5%CO_2) containing cocaine HCl (5×10^{-5} M) and yohimbine HCl (2×10^{-7} M). Vascular sympathetic nerves were stimulated via bipolar platinum ring electrodes for 10 s every 2.5 min (0.5–1 Hz, supramaximal voltage, 0.5 ms pulse width) and compounds were injected intraluminally. Activity at pre-synaptic dopamine receptors was measured as inhibition of stimulation-induced vasoconstriction sensitive to antagonism by metoclopramide (2.5×10^{-6} M).

Renal arterial blood flow measurements were made in pentobarbitone-anaesthetised beagles (McNay & Goldberg, 1966). Renal vascular resistance was also measured. Each animal received phenoxybenzamine HCl (5–10 mg/kg i.v. and 0.1 mg/min i.v.). Compounds were injected (max dose 3×10^{-7} mol/kg) into an intra-renal arterial saline infusion and post-synaptic (vascular) dopamine receptor activity was measured as increases of renal blood flow or falls in renal vascular resistance susceptible to antagonism by haloperidol (0.13 μmol kg^{-1} min^{-1} i.a.).

Compounds were tested in at least 4 ear artery preparations and 2 anaesthetised dogs. Negative log ED_{50} values were estimated from the appropriate dose-response curves. Results obtained are summarised in Table 1.

Our results confirm the potent dopamine receptor activities of certain semi-rigid dopamine analogues, but suggest that structural requirements for pre- and post-synaptic peripheral receptors may differ less than has been previously indicated.

The extended β-rotameric form (V) was a potent agonist in both systems, while pre-synaptic agonists (α-rotamers, II and VI) also show some post-synaptic activity (as measured by vascular resistance changes), a property not previously reported. *N*-alkyl substitution (IV, VI) imparts both potency and relative selectivity for pre-synaptic sites.

DPI (VIII) a potent agonist at dopamine receptors on snail neurones (Struyker-Boudier, Teppema, Cools & Van Rossum, 1975) inhibited neuronal vasoconstriction in the ear artery, but was not dopamine in either test system. Inactivity of VII, IX & X suggests that their central effects may not involve direct interaction with dopamine-like receptors.

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Further sub-classification of α-adrenoceptors in the cardiovascular system, vas deferens and anococcygeus of the rat

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Observations on pressor effects of agonist drugs in the pithed rat by Bentley, Drew & Whiting (1977) are indicative of two types of post-junctional α-adrenoceptors, one of which is activated by noradrenaline but not by phenylephrine and is resistant to prazosin suggesting similarities with the α_2 receptors previously found only pre-junctionally (Langer, 1974).

We have tested this hypothesis by comparing the pre-junctional and post-junctional effects of 5 α-adrenoceptor agonists i.e. clonidine, guanabenz, oxymetazoline, phenylephrine and xylazine, on four different organ systems in the rat. Arterial blood pressure, heart rate and longitudinal isometric tension of anococcygeus were monitored *in situ* in the pithed rat (Gillespie & McGrath, 1973; Docherty & McGrath, 1979). The longitudinal isometric tension of isolated transversely bisected portions of vas deferens was monitored in Krebs' bicarbonate solution at 37°C (McGrath, 1978). Pre-junctional effects were assessed as percent inhibition of (a) the cardioaccelerator response to a single supramaximal stimulus (0.05 ms) to the sympathetic outflow at Tl (Gillespie, MacLaren & Pollock, 1970) or (b) the contractile response of the prostatic portion of vas deferens to a single field stimulus (0.5 ms) (McGrath, 1978). Post-junctional effects were assessed as (c) the increase in diastolic pressure (d) the contraction of anococcygeus and (e) the potentiation of the contractile response to a single field stimulus (0.5 ms) of the epididymal portion of the vas deferens.

(a) and (b) The order of potency for pre-junctional effects was similar in the heart and vas deferens. Dose/response curves were parallel; oxymetazoline, guanabenz and clonidine were approximately equipotent and xylazine was $\times 10$ less potent. Phenylephrine had no detectable inhibitory effect.

(c) The order of potency for the pressor effect was different from that in (a) and (b). Xylazine was $10\times$ less potent than guanabenz but the curves for clonidine and oxymetazoline lay to the left of that of guanabenz. Phenylephrine lay between xylazine and guanabenz. After prazosin (1 mg/kg) the effect of phenylephrine was abolished, guanabenz, oxymetazoline and clonidine became equipotent and xylazine was unaffected, i.e. the pattern in (a) and (b) was repeated. After yohimbine (1 mg/kg) the dose/response curve for each drug was moved to the right but the effect was greatest for guanabenz and xylazine.

(d) For contraction of anococcygeus oxymetazoline, clonidine and phenylephrine were approximately equipotent and prazosin sensitive, while guanabenz and xylazine were prazosin resistant and $100–1000\times$ less potent.

(e) For potentiation of responses in vas deferens clonidine and oxymetazoline were equipotent, phenylephrine $10\times$ less potent (all prazosin sensitive) and neither guanabenz nor xylazine produced any detected potentiation.

These results suggest that (1) phenylephrine acts on α_1, guanabenz and xylazine on α_2 and clonidine and oxymetazoline on both α_1 and α_2-adrenoceptors (2) the post-junctional effects in the vas deferens were α_1, in anococcygeus mainly α_1 with a small α_2 component and in blood vessels had a significant component from both α_1 and α_2-adrenoceptors.

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The effect of amitriptyline on presynaptic receptors in the dog saphenous vein

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According to the catecholamine hypothesis of affective disorders, antidepressant drugs should increase the concentration of noradrenaline in the synaptic cleft (Schildkraut, 1965). This could be achieved by the blockade of neuronal uptake, however, the potency of antidepressant drugs to inhibit uptake and their clinical effectiveness correlate poorly (Ghose & Coppen, 1977). Since the release of noradrenaline from the adrenergic nerves is modulated by a number of inhibitory presynaptic receptors (Langer, 1977), blockade of these receptors could also be an important mode of action for antidepressant drugs.

We have examined the effects of amitriptyline on presynaptic receptors in the dog isolated saphenous vein. Spiral strips of vein were mounted in organ baths for isometric tension recording. Other strips were incubated with [^{3}H]-noradrenaline and mounted for superfusion, isometric tension recording and the measurement of radioactivity and of [^{3}H]-noradrenaline in the superfusate (McGrath, 1977).

In the presence of cocaine (3×10^{-5} M), amitripty-