clonidine. HR was consistently depressed 3 h after each dose. Following withdrawal of ICI 106270 both BP and HR returned to control with no significant overshoot in either during the subsequent 2–3 days.

The tachycardia on withdrawal of clonidine in dogs occurred in every animal treated and may represent a useful model for assessing the likelihood of centrally acting antihypertensives to produce rebound in man. In this model ICI 106270 did not produce rebound tachycardia.

References

CAVERO, I., FENARD, S., FINCH, L., LEFEVRE, F. & ROACH, A. (1977). Studies on the rebound hypertension after clonidine withdrawal in conscious hypertensive cats, rats and dogs. *Br. J. Pharmac.*, **60**, 288–289P.

CLOUGH, D.P., HATTON, R., PETTINGER, S.J., SAMUELS, GILLIAN M.R. & SHAW, A. (1978). Substituted aryl-tetrahydro-pyrrolo imidazoles: a new class of centrally acting antihypertensives. *Br. J. Pharmac.*, **62**, 385–386P.

DIX, R.K. & JOHNSTON, E.M. (1977). Withdrawal syndrome upon cessation of chronic clonidine treatment in rats. *Eur. J. Pharmac.*, **44**, 153–159.

OATES, HELEN F., STOKER, LYNETTE M., MONAGAHAN, JUDITH C. & STOKES, G.S. (1978). Withdrawal of clonidine: effects of varying dosage or duration of treatment on subsequent blood pressure and heart rate responses. *J. Pharmac. exp. Ther.*, **206**, 268–273.

The effects of mianserine, amitriptyline, ciclazindol and viloxazine on presynaptic α-receptors in isolated rat atria

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Presynaptic α-receptor antagonists evoke increases in stimulus-induced noradrenaline release in cardiac tissue which possess few, if any, postsynaptic α-receptors (Starke, 1972). According to Schildkraut's (1965) hypothesis of depression, elevation of the synaptic concentration of noradrenaline (NA) leads to an antidepressant effect. Presynaptic α-receptor blockade has been proposed as a mode of action of some antidepressants (Baumann & Maitre, 1975).

Low frequency field stimulation of isolated rat atria (three trains of 4 s duration, consisting of square wave pulses, 0.5 ms pulse width, 10–25 V, not exceeding 2.5 Hz, delivered at 30 s intervals) in the presence of atropine sulphate (5 μM) evoked increases in rate which were sensitive to modulation of presynaptic α-receptors. The presynaptic α-agonist clonidine (3.2×10^{-9}–3.2×10^{-8} M) inhibited stimulus induced rate increases without affecting submaximal responses to exogenous NA.

The presynaptic α-antagonist piperoxan (3.2×10^{-6} M) did not affect the intrinsic atrial rate or the response to NA. However, the response to stimulation was enhanced and the action of clonidine was blocked. Mianserine (2.9×10^{-6} M) similarly enhanced responses to stimulation and blocked the action of clonidine, but was more potent than piperoxan. The intrinsic atrial rate and responses to NA were not affected.

Amitriptyline (1.4×10^{-6} M) and desmethylimipramine (2.9×10^{-7} M) increased the intrinsic rate (mean 10/min and 17/min respectively, $n = 6$) without modifying the response to NA. Responses to stimulation were weakly enhanced. Amitriptyline evoked a partial block of the action of clonidine. These agents induced arrhythmia which limited further studies in this system. Ciclazindol (2.7×10^{-6} M) produced a larger increase in intrinsic rate (34/min, $n = 6$), but did not affect the response to NA. There was a weak, non significant increase in responses to stimulation, and a partial block of the response to clonidine. Viloxazine (1.1×10^{-5} M) also increased the intrinsic rate (67/min, $n = 2$) precluding observation of other parameters. A lower concentration (1.1×10^{-6} M) which had a minimal effect on basal rate (15/min, $n = 7$) did not affect the response to stimulation but reduced the response to NA. The response to clonidine was not significantly affected.

The increase in intrinsic rate observed with these antidepressants could result from block of reuptake or from release of NA (Tessel, Smith, Russ & Hough, 1978), whereas antagonism of the action of clonidine probably results from presynaptic α-receptor antagonism. On this basis, mianserine and piperoxan are potent presynaptic α-receptor antagonists, the other antidepressants are less potent, particularly viloxazine which shows no activity.

References

BAUMANN, P.A. & MAITRE, L. (1975). Blockade of the presynaptic α-receptor in rat cortex by antidepressants. *Experentia*, **31**, 726.

SCHILDKRAUT, J.J. (1965). The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am. J. Psychiat.*, **122**, 509–522.

STARKE, K. (1972). Influence of extracellular noradrenaline on the stimulation evoked secretion of noradrenaline from sympathetic nerves: evidence for an α-receptor mediated feed-back inhibition of noradrenaline release. *Naunyn Schmiedebergs. Arch. Pharmac.*, **275**, 11-23.

TESSEL, R.F., SMITH, C.B., RUSS, D.N. & HOUGH, I.B. (1978). The effect of cocaine HCl and a quarternary derivative of cocaine, cocaine methiodide, on isolated guinea pig and rat atria. *J. Pharmac. exp. Ther.*, **205**, 569-576.

Investigations into the role of spinal α-adrenoceptors in cardiovascular modulation in rats

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Bulbospinal adrenergic pathways may modulate sympathetic preganglionic neuronal activity and therefore influence sympathetic outflow (Dahlström & Fuxe, 1965). These spinal integrative systems are influenced by several centrally acting hypotensive agents (Chalmers, 1975; Franz, Hare & Neumayr, 1978).

Using a range of agents with preferential α_1, or α_2-receptor activity, we have examined the contention that α-adrenoceptors located in the spinal cord might exert differential modulation of heart rate or blood pressure at various levels along the neuroaxis.

Groups of 5-7 female normotensive rats (200-250 g) were anaesthetized with urethane (1.25 g/kg i.p.). The trachea was cannulated and arterial blood pressure measured from the carotid artery. The spinal subarachnoid space was cannulated according to the method of Yaksh & Rudy (1976) allowing injection of drugs (total volume 7-10 μl) at the C_7-T_1 level, in the region of the outflow of the cardiac nerves, or at T_5-T_6, the outflow to the adrenals and vascular resistance areas in the viscera. Respiration was measured using a thermistor probe implanted in the tracheal cannula.

Intrathecal (i.t.) administration of clonidine (0.1-2 μg) at level C_7-T_1 or T_5-T_6 caused dose dependent falls in mean blood pressure and heart rate. These effects were immediate in onset and maximal for 40-60 minutes. Neither the cannulation procedure nor the administration of clonidine (i.t.) had any significant effects on respiration. Administration of adrenaline (C_7-T_1 or T_5-T_6; 2 μg, i.t.) induced similar effects to clonidine. Phenylephrine (2-10 μg, C_7-T_1) or saline vehicle (C_7-T_1 or T_5-T_6) failed to lower blood pressure or heart rate over 40 minutes. The bradycardia (31 ± 4%) evoked by a submaximal dose of clonidine (1 μg, C_7-T_1) was significantly ($P < 0.05$) greater than the effects elicited from area T_5-T_6 (21 ± 2%). However, similar falls in blood pressure (33 ± 5%) were evoked from both areas. Bilateral vagotomy reduced only the bradycardia elicited by a low dose of clonidine (1 μg, i.t., $P < 0.05$) and had no influence on the hypotensive effect, indicating a sympathetic nervous involvement in these cardiovascular responses.

Pretreatment with the preferential α_2-receptor antagonists yohimbine or piperoxane, or the preferential α_1-receptor antagonists prazosin or thymoxamine (1-50 μg, i.t., 30 min) decreased basal blood pressure with less effect on the resting heart rate; α_1-receptor antagonists were the more active cardiodepressor agents. The bradycardia elicited by clonidine (1 μg, i.t.) was significantly antagonised by pretreatment with piperoxane, or thymoxamine (10 μg, i.t., 30 min, $P < 0.01$) and abolished by a larger dose of piperoxane (50 μg, i.t., 30 min). Prazosin at lower doses (1-10 μg, i.t., 30 min) also significantly antagonised this clonidine-induced bradycardia in a dose dependent manner. The hypotensive effect induced by clonidine (1 μg, i.t.) was significantly antagonised only by pretreatment with prazosin (10 μg, i.t., 30 min; $P < 0.01$).

These results indicate that intrathecal administration of clonidine or adrenaline can induce differential bradycardic and hypotensive effects from different levels in the spinal cord. At the preganglionic outflow of the cardiac nerves, both prazosin and piperoxane were potent antagonists of the clonidine-induced bradycardia. Prazosin was also an effective antagonist of the clonidine-induced hypotension at this level.

Since phenylephrine failed to modify blood pressure or heart rate after i.t. injection and no preferential antagonism of the clonidine-induced effects could be demonstrated by either α_1 or α_2-receptor antagonists, it remains unclear whether a single predominant α-receptor system is involved in these responses.

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References

CHALMERS, J.P. (1975). Brain amines and models of experimental hypertension. *Circ. Res.*, **36**, 469-480.

DAHLSTRÖM, A. & FUXE, K. (1965). Experimentally induced changes in the intraneuronal amine levels of bulbospinal neurone systems. *Acta Physiol. Scand.*, **64** (suppl.) 247.