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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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Effect of dihydroergotamine on the arteriovenous oxygen content difference and shunting of 15 μM microspheres over the cranial circulation of the cat

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Dihydroergotamine (DHE) is a potent antimigraine drug used for treatment of the acute attack as well as in migraine prophylaxis. The beneficial effect of DHE in migraine is generally attributed to its vasoconstrictor action. Vascular changes, dilatation of the cranial arteries in particular, have been strongly implicated in the pathogenesis of the migraine headache (Dalessio, 1972). Opening up of arteriovenous anastomoses or shunts, which are normally occurring precapillary communications between the arteriolar and venular side of the circulation, has been proposed by Heyck (1969) as the basic derangement underlying the migraine attack. In order to support this hypothesis, Heyck measured in 7 migraine patients the arteriovenous oxygen content difference ($CavO_2$) over the cranial circulation by sampling blood from the external jugular vein assuming it to be an index of fractional shunting. The $CavO_2$ amounted to significantly less on the side of the headache (0.76 ± 0.44 mmol/l) as compared to the non-diseased side (1.78 ± 0.76 mmol/l). Furthermore, administration of DHE followed by subsidence of headache resulted in a significant increase in $CavO_2$ (from 0.64 ± 0.58 to 2.26 ± 0.74 mmol/l).

We studied the effect of DHE on the $CavO_2$ over the cranial circulation of the cat and were able to confirm Heyck's observation (Table 1). Although DHE also decreased the shunting of 15 μm microspheres (Table 1), the changes in the above two parameters were not correlated which suggested that the $CavO_2$ is not an index of the proportion of carotid blood flow shunted through the arteriovenous anastomoses (PSFr). This notion was further supported by the observation that no correlation existed between the base-line values of the two parameters ($r_s = -0.14$, $n = 8$).

The mode of action of DHE as demonstrated by the use of 15 μm microspheres, which by their size become trapped in the tissue capillaries but pass through most arteriovenous anastomoses to enter the venous circulation, supports the concept of a primary involvement of arteriovenous anastomoses in the hemodynamic changes underlying the migraine headache. However, the lack of correlation between the shunting of microspheres and the $CavO_2$ sheds doubt on the validity of Heyck's assumption that the $CavO_2$ is an index of PSFr.

Table 1 The effect of dihydroergotamine on the arteriovenous oxygen content difference ($CavO_2$) and shunting of 15 μm microspheres (PSFr) over the cranial circulation of the cat

	Base-line Values ($n = 16$)	*Saline* ($n = 24$)	*Dihydroergotamine* ($n = 8$) 5	*10*	*20 μg/kg*
$CavO_2$ (mmol/l)	0.81 ± 0.09	0.89 ± 0.07	1.07 ± 0.10	1.37 ± 0.12*	1.73 ± 0.20*
PSFr (%)	35.1 ± 4.9	31.8 ± 1.8	27.5 ± 5.3	22.3 ± 4.2	16.2 ± 3.1*

Mean ± s.e. mean; * $P \leq 0.05$, two-tailed Wilcoxon rank sum test vs. saline.

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