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Short communication

NORADRENALINE: CENTRAL INHIBITORY CONTROL OF BLOOD PRESSURE AND HEART RATE

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Noradrenaline injected bilaterally into the brainstem in the area of the nucleus tractus solitarii decreased systemic arterial blood pressure and heart rate of anesthetized rats. The effect of noradrenaline was prevented by a preceding injection of the α-adrenergic blocking agent phentolamine, at the same site. The results suggest an inhibitory role of an α-adrenoceptor in the area of the nucleus tractus solitarii in the central control of blood pressure.

α-Adrenoceptor and central inhibitory blood pressure control
Nucleus tractus solitarii
Phentolamine
Noradrenaline

1. Introduction

Noradrenaline probably has an important inhibitory role in the central control of arterial blood pressure. Although its systemic administration elevates blood pressure, intraventricular administration of noradrenaline may decrease blood pressure and heart rate (Bhargava et al., 1972; Baum and Shropshire, 1973). The same action is exerted by the intraventricular administration of the amino acid precursor of noradrenaline, L-dopa (Baum and Shropshire, 1973). Hypotension and bradycardia caused by the systemic administration of L-dopa is in particular pronounced when extracerebral dopa decarboxylase is inhibited to prevent the conversion of L-dopa in catecholamines in peripheral tissues (Henning and Rubenson, 1970; Yamori et al., 1972; Baum and Shropshire, 1973). The central inhibitory cardiovascular action of L-dopa is blocked by inhibition of cerebral dopa decarboxylase (Henning and Rubenson, 1970; Yamori et al., 1972). These inhibitory effects may be caused by noradrenergic receptor stimulation since central α-adrenoceptor blockade inhibits the hypotension and bradycardia of noradrenaline and L-dopa (Bhargava et al., 1972; Schmitt et al., 1972; Van Zwieten, 1973). The location of the receptors mediating the inhibitory effect has not been determined precisely. One possibility is the carotid sinus afferent pathway at the level of the obex of the medulla oblongata (Van Zwieten, 1973). Ablation of the area of the nucleus tractus solitarii, an area of primary termination of carotid sinus fibres, produces hypertension in rats (Doba and Reis, 1973), while electrical stimulation of this region causes hypotension and bradycardia (De Jong et al., 1975). It is of interest therefore to study the effect of microinjection of noradrenaline into this area on blood pressure and heart rate. This report describes such studies in anesthetized rats and will show that noradrenaline decreases systemic arterial blood pressure and heart rate.

2. Materials and methods

Male rats, weighing 210–250 g, of an inbred Wistar strain (TNO, Zeist, The Netherlands) were

used in these studies. The animals were anesthetized with ether and placed in a David Kopf Stereotaxic apparatus with the head flexed to 45° to facilitate exposure of the obex. The caudal tip of the obex was used as the stereotaxic zero. Bilateral microinjections in a volume of 0.8 μl were given at 0.5 mm lateral and a depth of 1.0 mm of the obex. Injections were given through a stainless steel cannula (0.3 mm o.d.) 20–30 min after the onsett of the anesthesia. The 0.8 μl volume was delivered in 30 sec with an Agla micrometer syringe and a Sharlow micrometer. All the injection sites were verified histologically. From the total number of 46 rats data of 39 were evaluated (table 1). Data of 6 rats could not be used due to incorrect injection site and the results of one rat were not included due to blood loss during the experiment.

Blood pressure and heart rate were monitored continuously using a Grass polygraph with a strain gauge (Statham P-23 AC) and a cardiotachometer (Narco biosystems). For this purpose an indwelling iliac cannula (Buñag et al., 1971) was implanted under ether anesthesia 20–24 hr before the experiment.

Noradrenaline bitartrate (OPG, Ltd) and phentolamine methane sulphonate (Regitine®, CIBA) were used. Injection of vehicle (0.9% NaCl) served as control procedure.

3. Results

Administration of noradrenaline in doses of 1–5 nmoles decreased blood pressure as well as heart rate (table 1). The effect was noticable within a min and reached a maximum within 5 min. The effect on blood pressure and heart rate with the higher dose of noradrenaline was more pronounced and longer-lasting but the effect of both doses had disappeared within 30 min. The administration of noradrenaline (5.0 nmoles) 10 min after the administration of an α-adrenergic blocking agent, phentolamine (10 nmoles), was without effect. Phentolamine alone, had no effect on blood pressure and heart rate (table 1).

In subsequent experiments (unpublished data) it was found that bilateral injections of noradrenaline

Table 1
Hypotension and bradycardia after noradrenaline administration into the area of the nucleus tractus solitarii of the brainstem in anesthetized rats, and inhibition of these responses by the preceding administration of phentolamine. Mean blood pressure and heart rate and the changes in these cardiovascular parameters are given in mm of mercury (mm Hg) and in beats per min (bpm). The means ± S.E.M. are listed. The numbers in parentheses indicate the number of animals used in each group.

Microinjection of	(*n*)	Blood pressure and heart rate				
		Initial value (control period)	Change after			
			5 min	10 min	30 min	
Vehicle	(7)	110 ± 3	+ 7 ± 2	+ 8 ± 3	+ 5 ± 5	(mm Hg)
		387 ± 8	−11 ± 8	− 4 ± 8	+ 3 ± 14	(bpm)
Noradrenaline, 1.0 nmoles	(7)	111 ± 3	−17 ± 3*	−14 ± 1*	+ 3 ± 4	(mm Hg)
		380 ± 11	−49 ± 14	−39 ± 19	+ 5 ± 12	(bpm)
Noradrenaline, 5.0 nmoles	(6)	115 ± 4	−39 ± 4*	−11 ± 9	+ 5 ± 5	(mm Hg)
		396 ± 9	−117 ± 12*	−62 ± 18	− 3 ± 14	(bpm)
Phentolamine, 10.0 nmoles + vehicle	(7)	118 ± 7	+ 4 ± 2	+ 3 ± 1	− 1 ± 2	(mm Hg)
		346 ± 17	− 3 ± 5	+ 3 ± 5	−13 ± 7	(bpm)
Phentolamine, 10.0 nmoles + noradrenaline, 5.0 nmoles	(6)	124 ± 6	+10 ± 3	− 1 ± 1	0 ± 3	(mm Hg)
		340 ± 17	−12 ± 8	−15 ± 8	− 5 ± 8	(bpm)
Vehicle + noradrenaline, 5.0 nmoles	(6)	120 ± 4	−34 ± 6*	−17 ± 3*	− 8 ± 3	(mm Hg)
		377 ± 18	−99 ± 22*	−56 ± 13*	−27 ± 12	(bpm)

* Noradrenaline-induced changes that are significantly different ($p < 0.01$) from the control value observed after the administration of vehicle.

(5.0 nmoles) given 0.5 mm more lateral or 1.0 mm more rostral or caudal had no effect on blood pressure and heart rate. This may indicate that the distribution of the receptor sites is restricted to a rather small area in the middle part of the nucleus tractus solitarii.

4. Discussion

The present observations lend further support to the existence of a central inhibitory noradrenergic control mechanism of blood pressure and offers more direct evidence for the involvement of the area of the nucleus tractus solitarii herein. This area through the primary termination of afferent carotid sinus baroreceptor fibres is intimately linked to cardiovascular control (Doba and Reis, 1973; De Jong et al., 1975). Interestingly, this area has a very high density of noradrenergic terminals, as visualized histochemically (Fuxe, 1965). It has been suggested that the centrally acting hypotensive drugs clonidine and α-methyldopa act through α-adrenoceptor stimulation in the area of the nucleus tractus solitarii mimicking activation of the depressor baroreceptor reflex pathways (Schmitt et al., 1971; Haeusler, 1973; Henning, 1973; Sinha et al., 1973; Van Zwieten, 1973). Although this suggestion needs experimental verification the present findings underline the likelihood of such a postulate.

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