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Short communication

α-METHYLNORADRENALINE INDUCED HYPOTENSION AND BRADYCARDIA AFTER ADMINISTRATION INTO THE AREA OF THE NUCLEUS TRACTUS SOLITARII

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Bilateral injections of α-methylnoradrenaline into the area of the nucleus tractus solitarii of the brain stem caused a dose-dependent decrease of systemic arterial blood pressure and heart rate of anesthetized rats. The effects were prevented and even reversed by a preceding injection of the α-adrenoceptor blocking agent phentolamine. Pressor doses of angiotensin II and of arginine-vasopressin at the same site failed to decrease blood pressure and heart rate.

Nucleus tractus solitarii | α-Methylnoradrenaline | Angiotensin II | Heart rate
Arginine-vasopressin | Blood pressure

1. Introduction

The central blood pressure lowering effect of α-methyldopa may be mediated by its metabolite α-methylnoradrenaline (Henning and Rubenson, 1971). The brain structures at which this action is exerted so far remain to be identified. Experiments in cats in which α-methyldopa was infused into the vertebral artery indicate that the main site may be located in the medulla oblongata (Henning and Van Zwieten, 1968). Administration of noradrenaline into the medulla oblongata in the area of the nucleus tractus solitarii in the rat decreased blood pressure and heart rate (De Jong, 1974). The present report describes the effect of local administration of α-methylnoradrenaline at the same medullary site on blood pressure and heart rate of anesthetized rats.

2. Materials and methods

The experiments were performed on male Wistar rats (outbred stock, Wi/Cpb, TNO, Zeist), weighing 200—250 g. The rats were anesthetized with urethane (1.25 g/kg i.p.). After fixation of the rat in a stereotaxic apparatus (David Kopf) with the head flexed to 45°, the dorsal surface of the lower brainstem was exposed by a limited occipital craniotomy. Bilateral injections into the nucleus tractus solitarii (0.5 mm lateral of the obex and at a depth of 1.0 mm) were carried out with a stainless steel needle (outer diameter 0.2 mm) connected via a polyethylene cannula with an Agla micrometer syringe and a Shardlow micrometer. Various doses of α-methylnoradrenaline dissolved in 0.9% NaCl solution were administered bilaterally in a volume of 0.6 μl over

a period of 30 sec. Control rats received 0.6 μl of vehicle only.

Blood pressure was continuously recorded from a permanent indwelling iliac cannula (Nijkamp et al., 1975) with a Statham transducer (Model P23-AC) connected to a Grass polygraph. The iliac cannula had been implanted under ether anesthesia at least 24 hr prior to the experiment. Heart rate was computed from the blood pressure pulse wave by a cardiotachometer (Narco Bio-systems, Model BT 1200). Drugs given i.v. were dissolved in 0.2 ml 0.9% NaCl solution and administered into the right jugular vein. Control rats received 0.2 ml vehicle only. After termination of the experiments, the brains were fixed in 5% formalin. Frozen sections of 100 μ were cut and stained with 0.1% thionine. The injection sites were controlled microscopically.

The following drugs were used: (±)-erythro-α-methylnoradrenaline · HCl (Cobrefin®, Winthrop Laboratories), phentolamine methane sulphonate (Regitine®, Ciba); 1-asp-5-val-angiotensin II amide (Hypertensin®, Ciba); arginine-vasopressin (232 U/mg, Organon).

3. Results and discussion

Local injection of α-methylnoradrenaline (5.8, 23.0, 92.0 nmol) into the area of the nucleus tractus solitarii at the level of the obex caused a dose-dependent decrease in mean blood pressure and heart rate (table 1). Blood pressure started to fall immediately after completion of the bilateral injections. The lowest dose (5.8 nmol) caused a short lasting decrease in blood pressure which reached a maximum after 5 min. The higher doses (23.0 and 92.0 nmol) decreased blood pressure and heart rate for over 30 min. Maximal effects were observed after 5—10 min. Compared to the effect of noradrenaline injected at the same site in doses causing a similar degree of hypotensin (De Jong, 1974), the effect of α-methylnoradrenaline appears to be of longer duration.

Heise and Kroneberg (1972), showed that the central inhibitory action on blood pressure and heart rate of intraventricularly administered α-methylnoradrenaline was blocked by phentolamine given by the same route. In this study, phentolamine in a dose of 23 nmol ad-

TABLE 1

Effect of graded doses of α-methylnoradrenaline on mean blood pressure and heart rate after local administration into the area of the nucleus tractus solitarii of the brain stem of anesthetized rats. Blood pressure and heart rate, and the changes in these 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 in mm Hg (heart rate in bpm)				
		Basal values	Changes after			
			5 min	10 min	20 min	30 min
Vehicle	9	123 ± 5	+6 ± 6	+5 ± 6	+1 ± 4	-2 ± 3
		391 ± 18	-4 ± 9	+12 ± 4	+39 ± 15	+39 ± 17
α-Methylnoradrenaline 5.8 nmol	7	122 ± 5	-16 ± 2*	-13 ± 2	-3 ± 2	+1 ± 26
		386 ± 18	-27 ± 11	-12 ± 14	+13 ± 21	+42 ± 26
α-Methylnoradrenaline 23.0 nmol	6	117 ± 4	-33 ± 6*	-33 ± 6*	-23 ± 5*	-15 ± 4*
		423 ± 5	-56 ± 14*	-66 ± 7*	-43 ± 7*	-28 ± 9*
α-Methylnoradrenaline 92.0 nmol	6	126 ± 6	-39 ± 5*	-43 ± 4*	-32 ± 3*	-20 ± 3*
		421 ± 12	-38 ± 7	-75 ± 11*	-86 ± 11*	-74 ± 14*

* α-Methylnoradrenaline-induced changes that are significantly different ($p < 0.01$) from the respective control values after the administration of vehicle (1 nmol of α-methylnoradrenaline corresponds to 219.5 ng).

ministered into the area of the nucleus tractus solitarii followed after 10 min by a dose of 23 nmol of α-methylnoradrenaline applied at the same site completely prevented and even reversed the fall in blood pressure and heart rate, with a maximum reached within approximately 2 min. The mean changes (± S.E.M.) observed in 6 rats at this time were +31 ± 6 mm Hg and +27 ± 9 bpm in the phentolamine-treated rats compared to −14 ± 5 mm Hg and −28 ± 15 bpm for the controls which had received 0.9% NaCl 10 min prior to α-methylnoradrenaline. In the control group a maximal decrease in blood pressure and heart rate of the same magnitude as that shown in table 1 was reached within 10 min. In the phentolamine-treated animals no secondary decrease in blood pressure and heart rate occurred. Phentolamine by itself caused no significant change in blood pressure but reduced heart rate by 20% within 2—3 min.

In order to establish the specificity of the structures in the medulla oblongata for α-methylnoradrenaline, the effect of the 2 pressor peptides angiotensin II and arginine-vasopressin was studied in equipressor amounts. I.v. administration of the 3 different doses of α-methylnoradrenaline used caused a dose-dependent increase in mean blood pressure of urethanized rats of 20—60 mm Hg (unpublished data). Basal values of blood pressure and heart rate in these groups of rats (table 2) did not differ from those reported in table 1. I.v. administration of the 2 peptides caused a dose-dependent increase in blood pressure. Only the highest dose of vasopressin (480 pmol) decreased heart rate. However, bilateral application of these doses into the area of the nucleus tractus solitarii in another group of rats failed to cause cardiovascular changes (table 2). These observations suggest therefore that the observed inhibitory cardiovascular action of α-methylnoradrenaline cannot be explained by local vasoconstriction.

α-Methylnoradrenaline presumably is the metabolite which mediates the blood pressure lowering effect of α-methyldopa (Henning and Rubenson, 1971). Central α-adrenoceptor blockade by intraventricularly administered phentolamine prevented the fall in blood pressure caused by α-methyldopa (Finch and Hauesler, 1973). In the present study injection of phentolamine into the area of the nucleus tractus solitarii inhibited both the hypotension and bradycardia induced by α-methylnoradrenaline. The present findings thus support the hypothesis that α-methyldopa acts through

TABLE 2

Effect of graded doses of angiotensin II and of arginine-vasopressin on mean blood pressure and heart rate after local administration into the area of the nucleus tractus solitarii and after i.v. administration. Maximal changes in blood pressure and heart rate which were observed within 5 min are given in mm of mercury (mm Hg) and in beats per min (bpm). The means ± S.E.M. of 4—5 anesthetized rats are listed.

Treatment	Blood pressure in mm Hg Heart rate in bpm	
	Nucleus tractus solitarii	Intravenous
Vehicle	−5 ± 4 −16 ± 6	+2 ± 2 −31 ± 11
Angiotensin II 39 pmol	−6 ± 8 −13 ± 13	+18 ± 3** −33 ± 10
Angiotensin II 117 pmol	+5 ± 5 −28 ± 7	+41 ± 7** −31 ± 8
Angiotensin II 351 pmol	+17 ± 7 −31 ± 6	+68 ± 5** −38 ± 13
Arg-vasopressin 41 pmol	0 ± 12 −30 ± 14	+22 ± 5** −38 ± 4
Arg-vasopressin 164 pmol	−1 ± 5 −21 ± 11	+47 ± 11** −52 ± 18
Arg-vasopressin 656 pmol	0 ± 11 −20 ± 8	+54 ± 3** −128 ± 32*

* $p < 0.05$
** $p < 0.01$
} compared to the control values after the administration of vehicle (1 pmol of angiotensin II corresponds to 1030 pg and 1 pmol of arg-vasopressin corresponds to 1051 pg = 0.244 mU).

α-adrenoceptor stimulation in this particular region of the medulla oblongata (Van Zwieten, 1973).

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