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EFFECTS OF LYSINE-VASOPRESSIN AND OXYTOCIN ON CENTRAL CARDIOVASCULAR CONTROL

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1 The cardiovascular effects of intravenous and intracisternal administration of neurohypophysial peptides were compared in dogs anaesthetized with chloralose.

2 Intravenous lysine-vasopressin (0.1 to 100 mu/kg) induced a dose-dependent increase in blood pressure and a decrease in heart rate. In contrast, intracisternal lysine-vasopressin (0.01 to 10 mu/kg) induced a dose-related decrease in blood pressure and did not change heart rate.

3 Intracisternal oxytocin (1 and 10 mu/kg) increased blood pressure and did not change heart rate, whereas the same doses injected intravenously were inactive.

4 Pretreatment with guanethidine (15 mg/kg i.v. 24 h beforehand) abolished the hypotensive responses to intracisternal vasopressin but not the pressor action of intravenous vasopressin.

5 The pressor responses to central injections of oxytocin were not modified by guanethidine.

6 Hypotension elicited by intracisternal vasopressin was probably due to a decrease in sympathetic tone whereas the hypertension induced by intracisternal oxytocin was independent of variations in sympathetic tone.

Introduction

Several neurotransmitters may be involved in the central control of blood pressure or heart rate: monoamines (catecholamines, 5-hydroxytryptamine; for reviews see Chalmers, 1975; Galosy, Clarke, Vasko & Crawford, 1981) acetylcholine (for review see Philippu, 1981) and amino acids (γ-aminobutyric acid: Antonaccio, Kerwin & Taylor, 1978; L-glutamic acid: Chelly, Kouyoumdjian, Mouillé, Huchet & Schmitt, 1979). More recently it has also been suggested that brain peptides (opioid peptides, angiotensin, substance P or kinins) may play an important role in central cardiovascular control (for review see Unger, Ganten, Lang & Rascher, 1981).

Among peptides, little is known of the central cardiovascular effects of neurohypophysial peptides although Varma, Jaju & Bhargava (1969) have shown that the bradycardia produced by the intraventricular injection of vasopressin is due to a central stimulant effect. More recently, Cowley, Munos & Guyton (1974) have found an interaction between vasopressin and the baroreceptor reflex, whereas Liard, Deriaz, Tschopp & Shoun (1981) have shown that intravertebral administration of vasopressin induced an increase in arterial pressure and a decrease in heart rate in conscious dogs.

These results, the hypothesis of Möhring of an involvement of vasopressin in the pathogenesis of experimental arterial hypertension (Möhring, Möhring, Petri & Haack, 1977; Möhring, Kintz & Schoun, 1979) and the recent discovery of pathways originating from vasopressin-containing neurones in the paraventricular nucleus (Sofroniew & Weindl, 1978) led us to compare the central and peripheral effects of neurohypophysial peptides (lysine-vasopressin and oxytocin) on the arterial blood pressure of anaesthetized normotensive dogs.

Methods

General procedure

Mongrel dogs of either sex weighing 7–13 kg were anaesthetized with α-chloralose (100 mg/kg i.v.), intubated and ventilated with an Ideal Palmer respirator in order to suppress a possible effect of these peptides on respiration. The femoral artery and saphenous vein were cannulated for the measurement of arterial blood pressure and the injection of drugs respectively. Systolic and diastolic blood pressures were measured with a Statham P 23 Db transducer connected to a Beckman recorder. Heart rate was counted on the electrocardiogram (lead 2). Intracisternal injections were performed using an 18 gauge needle introduced percutaneously, as previously described (Montastruc & Montastruc, 1980). The minimum time between two successive injections was 15 min.

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Drugs used

Drugs were dissolved in 0.9% w/v NaCl solution (saline) and injected (single injection during 5 s; pH = 6.00) in a volume no larger than 0.5 ml into the cisterna magna. Intracisternal or intravenous saline (pH = 6.00) was administered as a control injection. The following drugs were used: lysine-vasopressin (Ferring), oxytocin (Sandoz). Guanethidine sulphate (Ciba Geigy) was used to deplete the noradrenergic terminals of the sympathetic system.

Statistical evaluation

Groups of 4 to 8 dogs were used. All results are expressed mean ± s.e.mean. The statistical significance was calculated using Student's *t* test for paired comparisons.

Results

Control values

Resting systolic, diastolic blood pressures and heart rate (before injections) were 134 ± 5 mmHg, 76 ± 4 mmHg and 123 ± 5 beats/min respectively.

Intravenous injections

Intravenous administration of lysine-vasopressin (0.01 to 100 mu/kg) induced dose-dependent pressor responses and bradycardia (Figure 1). In contrast, the same doses of intravenous oxytocin did not change blood pressure or heart rate (Figure 2).

Intracisternal injections

Intracisternal injection of saline did not change blood pressure or heart rate.

Intracisternal administration of lysine-vasopressin induced a dose-related decrease in blood pressure up to a dose of 10 mu/kg (Figure 3). This hypotensive effect took about 10 s to apear. Its duration was shorter than the hypertensive response to intravenous vasopressin: 5 to 20 s according to the animals. For the highest dose (100 mu/kg), blood pressure was not significantly changed (Figure 3). In contrast, heart rate was only significantly slowed by a dose of 0.1 mu/kg (Figure 3). Intracisternal administration of oxytocin increased blood pressure for the doses of 1 and 10 mu/kg but did not induce variations for the other doses studied (0.01, 0.1 and 100 mu/kg) (Figure 4). Heart rate was unchanged. The hypertensive response to oxytocin did not begin until 15 s after the injection and its duration was 120 to 160 s according to the animals.

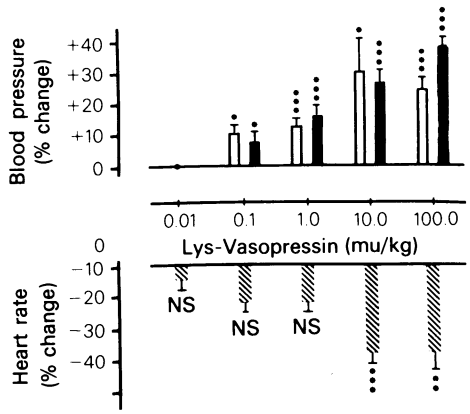

Figure 1 Pressor dose-response curve to intravenous injections of lysine-vasopressin (0.01 to 100 mu/kg) in the anaesthetized dog. The figure shows the increase in systolic (open columns) and diastolic (solid columns) and the decrease in heart rate (hatched columns) induced by vasopressin. Statistical evaluations were made using Student's *t* test for paired comparisons. The means of 8 experiments are given. Vertical lines indicate s.e.mean. $*P<0.05$; $**P<0.02$; $***P<0.01$, NS = not significant.

No tachyphylaxis was observed after each intracisternal injection.

Effects of guanethidine on the intravenous or intracisternal actions of lysine-vasopressin and oxytocin

In dogs pretreated with guanethidine (15 mg/kg i.v. 24 h before the experiment) control blood pressure was significantly lower (systolic value = 113 ± 3 mmHg, $P<0.001$ and diastolic value = 65 ±

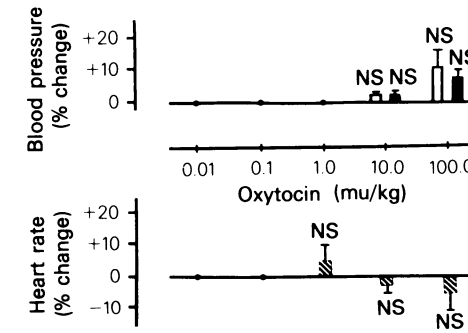

Figure 2 Effect of intravenous oxytocin on blood pressure and heart rate in the anaesthetized dog. $n = 4$. For details see Figure 1.

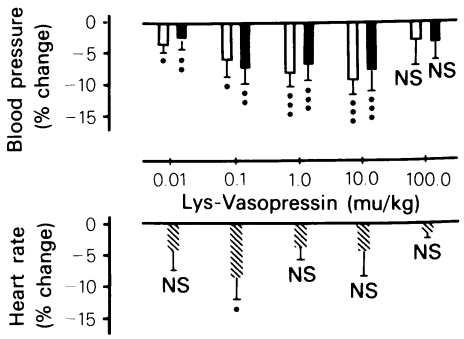

Figure 3 Effect of intracisternal lysine-vasopressin on blood pressure and heart rate in the anaesthetized dog. $n = 8$. For details see Figure 1.

2 mmHg, $P < 0.01$) than the control values. Heart rate was also depressed: 92 ± 4 ($P < 0.01$ when compared with normal dogs). After guanethidine, intravenous vasopressin still increased blood pressure whereas intracisternal vasopressin was without effect (Figure 5). The pressor response to intracisternal oxytocin was not modified (Figure 6).

Discussion

The present paper shows that lysine-vasopressin and oxytocin induced a decrease and an increase respectively in blood pressure when injected into the cisterna magna. However, these doses are very high in physiological terms. These effects are due to central actions since the same doses of neurohypophysial peptides injected intravenously induced either an increase (lysine-vasopressin) or no change (oxytocin) in blood pressure. In contrast to the peripheral actions of lysine-vasopressin, the central effects of vasopressin or oxytocin were not accompanied by important changes in heart rate (except for one dose of lysine-vasopressin).

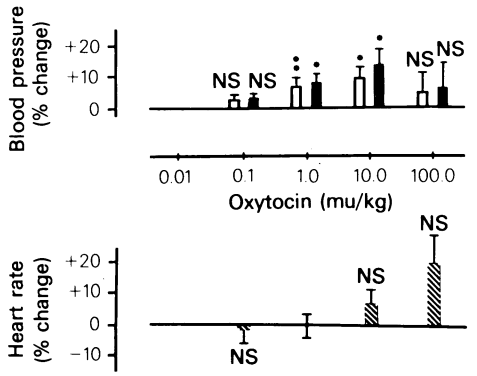

Figure 4 Effect of intracisternal oxytocin on blood pressure and heart rate in the anaesthetized dog. $n = 6$. For details see Figure 1.

The decrease in blood pressure elicited by intracisternal lysine-vasopressin was probably due to a decrease in sympathetic tone since it was prevented by pretreatment with guanethidine. In contrast, the oxytocin-induced hypertensive response was not modified by guanethidine, suggesting that this effect was independent of variations in sympathetic tone or could be due to adrenal medullary discharge since guanethidine has little effect on this gland (Rand & Jurevics, 1977).

It is well known that the amino acid sequences of vasopressin and oxytocin are similar except for two amino acids (phenylalanine and lysine in vasopressin; isoleucine and leucine in oxytocin). Thus a simple variation in two amino acids can change the hypotensive response to intracisternal vasopressin to a hypertensive response to intracisternal oxytocin and also the magnitude of the responses to intravenous hormones. This is another manifestation of the different structure-activity relationships of these peptides.

Möhring *et al.* (1977; 1979) have suggested that plasma vasopressin may play an important role in the pathogenesis of several types of arterial hypertension: DOCA hypertensive rats, spontaneously hypertensive rats, stroke-prone rats. However, similar results were not found in man (Padfield, Brown, Lever, Morton & Robertson 1976; 1981). Our results suggest that the action of vasopressin at some site accessible from the cisterna magna (probably the lower brainstem) is to bring about a reduction in blood pressure. They are consistent with the results of Möhring, Schoun, Kintz & McNeill (1980) who showed that the vasopressin content is decreased in the brainstem of rats with spontaneous hypertension.

Sofroniew & Weindl (1978) have described vasopressin-containing pathways that originate in the area of the paraventricular nucleus and that project down to the brainstem especially into the area of the nucleus of the tractus solitarius (NTS). Matsuguchi, Schmid, Gordon & Johnson (1980) have reported that local injection of vasopressin into the NTS increases arterial pressure in rats. The differences between the results of this work and ours may be due to distinct sites of central injections or interspecies differences. Other central oxytocinergic pathways were recently described (see Brownstein, 1980). These anatomical findings and our present data suggest that neurohypophysial peptides may be factors involved in the central regulation of blood pressure.

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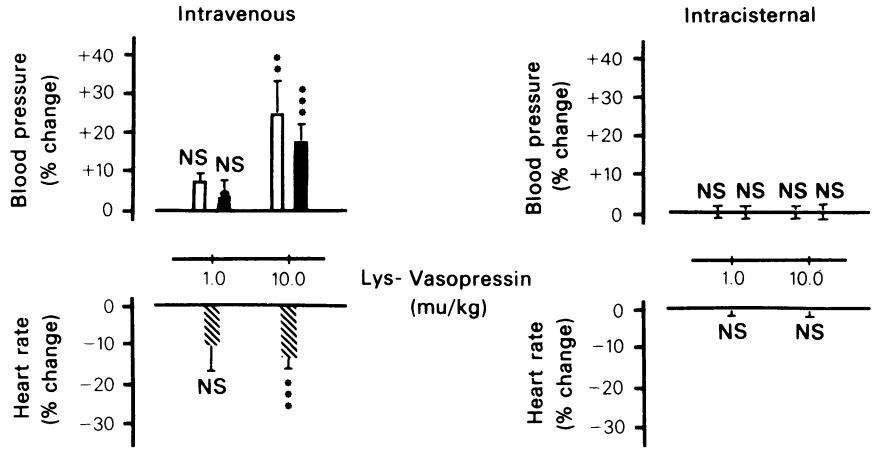

Figure 5 Effect of pretreatment with guanethidine (15 3mg/kg i.v. 24 h beforehand on the responses of arterial blood pressure and heart rate to intravenous ($n = 6$) and intracisternal ($n = 6$) lysine-vasopressin. For details see Figure 1.

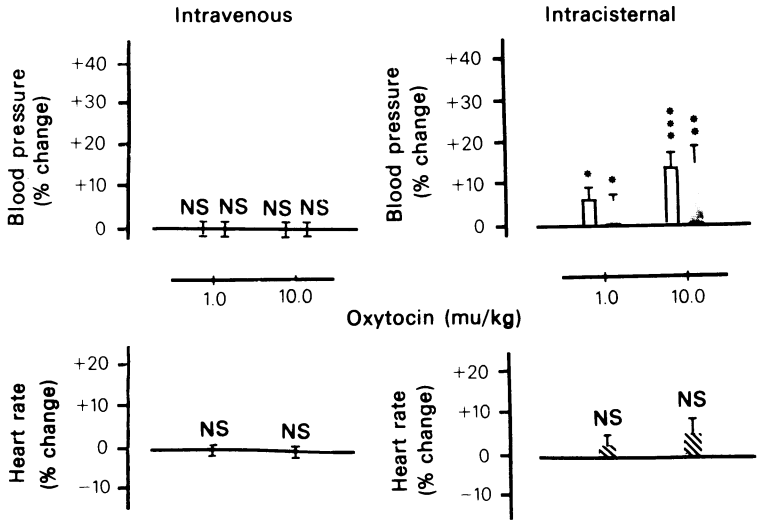

Figure 6 Effect of pretreatment with guanethidine (15 mg/kg i.v. 24 h beforehand) on the responses of arterial blood pressure and heart rate to intravenous ($n = 7$) and intracisternal ($n = 7$) oxytocin. For details see Figure 1.

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