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The role of vasopressin in blood pressure control and in experimental hypertension

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Summary

1. The role of vasopressin in blood pressure control and in the pathogenesis of one-kidney Goldblatt hypertension in the conscious dog was investigated.

2. Infusion of synthetic arginine vasopressin to elevate plasma levels approximately five-fold caused bradycardia in normal dogs and increase in mean arterial blood pressure in dogs with pharmacological autonomic blockade.

3. A similar degree of elevation of plasma vasopressin concentration was observed after mild non-hypotensive haemorrhage.

4. Renal artery constriction in unilaterally-nephrectomized dogs caused a rise in plasma renin activity and only a doubling of plasma vasopressin concentration, but a marked rise in mean arterial blood pressure.

5. Vasopressin may play a role in normal cardiovascular homeostatic responses, but its role in the pathogenesis of this form of hypertension is unlikely to be significant.

Key words: blood pressure, haemorrhage, hypertension, vasopressin.

Introduction

Vasopressin is both antidiuretic and vasoconstrictor. However, normal circulating concentrations of vasopressin have been thought not to have a significant pressor effect. More recently, however, Szczepańska-Sadowska (1973) and Cowley, Monos & Guyton (1974) have provided evidence that vasopressin infused at physiological concentrations into conscious dogs has significant vasoconstrictor effects. Furthermore, there have been several recent studies suggesting that vasopressin is important in the pathogenesis of certain forms of hypertension (Khokhar & Slater, 1976; Möhring, Möhring, Petri & Haack, 1977; 1978).

The present study was designed to determine whether the endogenous plasma vasopressin levels achieved during physiological stimulation are similar to those achieved during pressor infusions of exogenous vasopressin and to determine whether there is a role for vasopressin in the pathogenesis of one-kidney Goldblatt hypertension in the dog.

Methods

The experiments were performed on conscious male mongrel dogs. All dogs had a unilateral nephrectomy and those made hypertensive had an inflatable silastic cuff applied to their remaining renal artery. Chronic arterial and venous catheters were inserted into the abdominal aorta, renal artery and vena cava and exteriorized. Mean aortic, central venous and renal arterial pressures were recorded by using Statham P23 DC transducers and a Devices recorder, and blood samples for assay were collected via one of the aortic catheters. Plasma arginine vasopressin (AVP) was measured after extraction by radioimmunoassay (Pullan, Dax, Johnston & Burger, 1977) and plasma renin activity was measured enzymatically by radioimmunoassay of the angiotensin I generated after 2 h incubation at pH 6.5 at 37°C (Johnston, Mendelsohn & Doyle, 1972).

Vasopressin infusions

Synthetic AVP (Ferring) (diluted in 0.9% NaCl) was infused intravenously into 6 dogs at doses of
10, 25 m units min⁻¹ kg⁻¹ for 30 min at each dose and mean arterial blood pressure (MAP) and heart rate were monitored continuously. At the end of each 30 min period a blood sample for plasma AVP measurement was taken. These experiments were then repeated in 5 dogs after total pharmacological autonomic blockade with the following regimen: propranolol hydrochloride 1 mg/kg bolus followed by infusion of 25 µg min⁻¹ kg⁻¹; scopolamine methylbromide 250 µg/kg bolus; phenolamine hydrochloride 4 mg/kg bolus followed by 4 mg h⁻¹ kg⁻¹ infusion; and debrisoquine 1 mg/kg bolus. Complete blockade at the end of the experiments was demonstrated by lack of reflex tachycardia after glyceryl trinitrate-induced hypotension.

Dehydration and haemorrhage

Three dogs were deprived of all fluid but fed normally for 48 h. Body weight, plasma osmolality and plasma AVP were measured after 48 h of dehydration. After several days of recovery these animals were then bled rapidly at 5% of their blood volume every 15 min to a total of 30% of their blood volume. Blood samples for plasma AVP measurement were taken at the end of each 15 min period when central venous pressure, MAP, and heart rate had stabilized. These haemodynamic measurements were made continuously throughout haemorrhage.

Renal hypertension

In six dogs the renal artery was constricted by inflating the cuff over 60 min to lower distal renal arterial pressure to 20 mmHg. After 5 days the cuff was deflated. MAP and plasma volume were measured daily, and blood samples for plasma AVP, plasma renin activity, and creatinine were taken each day. In four further dogs the renal artery was narrowed by inflating the cuff to lower distal renal arterial pressure to 20 mmHg and adjustments were made to the cuff to maintain this pressure over the next 60 min. MAP was measured continuously and blood samples for plasma AVP and plasma renin activity were taken at 0 and 60 min.

Statistics

Control measurements are expressed as means ± SEM and later measurements as means ± SE of the difference from control within animals. Statistical significance was assessed by the paired t-test.

Results

Vasopressin infusions

In normal dogs, basal plasma AVP was 6.7 ± 1.6 pmol/l and the pressure threshold for vasopressin was between 174 ± 44 and 829 ± 179 pmol/l. The pressure response was linearly related to dose and plasma level. However, heart rate fell significantly from 74 ± 6 to 58 ± 2 beats/min ($P < 0.001$) when plasma AVP had risen to only 29 ± 6 pmol/l, suggesting baroreceptor buffering of the blood pressure.

During total autonomic blockade, MAP rose significantly when plasma AVP had risen to only 39 ± 10 pmol/l and the dose–response curve was shifted markedly to the left (Fig. 1). This suggests that there was a change both in the threshold and sensitivity to vasopressin after abolition of autonomic reflexes.

Dehydration and haemorrhage

Water deprivation for 48 h resulted in severe dehydration as shown by a rise in plasma osmolality from 301 ± 1 to 315 ± 3 mosmol/kg and a fall in body weight of 2.9 ± 0.4%. Despite this, plasma AVP only rose from 5.0 ± 0.5 to 6.9 ± 0.9 pmol/l. With haemorrhage, there was a progressive and linear rise in plasma AVP when correlated to the volume of blood removed ($r = 0.73$, $P < 0.001$). When 20% of the blood volume had been

![Fig. 1. Rise in mean arterial blood pressure (mmHg) in a group of normal dogs ($n = 6$, ) compared with the rise in a group of dogs with total pharmacological autonomic blockade ($n = 5$, ) after intravenous infusion of synthetic arginine vasopressin. The plasma levels of vasopressin (AVP) associated with the incremental doses are plotted in pmol/l on the horizontal axis.](image-url)
removed, plasma AVP had risen to 38 ± 23 pmol/l with a fall in central venous pressure of 1.8 ± 0.2 mmHg but without any change in MAP. This plasma AVP level is similar to that achieved at the lowest infusion dose of AVP, and which caused significant bradycardia in normal dogs and rise in MAP in autonomically blocked dogs. After removal of 30% of the blood volume plasma AVP had risen to 364 ± 39 pmol/l and MAP had fallen 22 ± 5 mmHg.

Renal hypertension

After chronic renal artery constriction MAP rose from a control value of 92 ± 2 to 120 ± 5 mmHg on day 1 and rose further to 131 ± 13 mmHg by day 5. Plasma AVP rose significantly from a control value of 5.8 ± 0.6 to 9.4 ± 1.0 pmol/l (P < 0.02) on day 1 and then fell progressively over 5 days. On day 1, when plasma AVP was at its peak, plasma renin activity had risen significantly from 0.4 ± 0.1 to 1.6 ± 0.5 pmol h⁻¹ ml⁻¹ (P < 0.05). Plasma volume and creatinine also rose significantly. After acute renal artery constriction, MAP rose progressively from 90 ± 5 to 118 ± 7 mmHg 60 min after constriction. Plasma AVP did not change significantly (2.9 ± 0.7 pmol/l before constriction to 2.9 ± 0.6 pmol/l 60 min after constriction) while plasma renin activity rose from 0.2 ± 0.1 to 3.0 ± 0.9 pmol h⁻¹ ml⁻¹ (P < 0.05). This suggests that the rise in plasma AVP seen in the chronic study was not due to the increase in renin and angiotensin.

Discussion

Szczepanska-Sadowska (1973) and Cowley et al. (1974) provided evidence for a possible pressor role for vasopressin but before the present report there have been no systematic dose–response studies in conscious animals with measurements of plasma AVP levels.

The demonstration of bradycardia in normal dogs and increase in MAP in autonomically-blocked dogs in response to relatively small elevations of plasma AVP provides evidence for a possible normal regulatory role for vasopressin in cardiovascular homeostasis. Comparable plasma AVP levels were achieved by mild non-hypotensive haemorrhage. Although severe dehydration did not produce plasma AVP levels of this order, dehydration is a relatively weak stimulus to AVP secretion (Moses & Miller, 1974).

Khokhar & Slater (1976) reported increased urinary excretion of AVP in men with benign essential hypertension. Padfield, Brown, Lever, Morton & Robertson (1976) showed that plasma AVP was slightly reduced in men with benign essential hypertension but was elevated in those with malignant hypertension. Möhring et al. (1977; 1978) have shown increased plasma AVP levels in malignant deoxycorticosterone hypertension and malignant 2-kidney Goldblatt hypertension in the rat, and there was also mild elevation in the benign hypertensive rats. In the present study, the rise in plasma AVP during chronic renal artery stenosis in the unilaterally nephrectomized dog raises two questions. Firstly, what caused the rise, and secondly, did it contribute in any way to the pathogenesis of the hypertension?

The rise in plasma AVP occurred despite an increase in blood pressure and plasma volume, both of which are known to suppress AVP secretion (Share, 1974). It is unlikely that a rise in plasma osmolality was responsible since severe dehydration with very high plasma osmolality caused only a very small rise in plasma AVP. It has been suggested (Bonjour & Malvin, 1970) that increased plasma angiotensin II can release AVP from the posterior pituitary and this is a possible explanation. However, this seems unlikely as plasma renin activity (and angiotensin) increased without any change in plasma AVP levels within 60 min after acute renal artery constriction. The most likely explanation for the rise in plasma AVP is that there was decreased clearance of AVP due to decreased renal blood flow induced by renal artery constriction.

MAP during chronic renal artery stenosis rose by 27.8 ± 5.2 mmHg on day 1 when plasma AVP had approximately doubled. This contrasts with the vasopressin infusions in which the lowest infusion dose raised MAP even in the sensitive blocked dogs by only 9.6 ± 4.8 mmHg, but caused a 5-fold increase in plasma vasopressin.

Thus it seems unlikely that vasopressin plays a significant role in the pathogenesis of one-kidney Goldblatt hypertension in the dog, although it probably has a role in the cardiovascular homeostatic response to haemorrhage.

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References


