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AMINERGIC CONTROL OF VASOPRESSIN SECRETION IN THE CONSCIOUS RAT

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The influence of aminergic pathways on basal and stimulated vasopressin (AVP) release was studied in conscious rats, the stimulus for hormone release being an intracerebroventricular (ICV) injection of 5 μl 0.85M sodium chloride. The animals were treated with either phenoxybenzamine, propranolol or haloperidol prior to administration of the central hypertonic stimulus. Phenoxybenzamine elevated basal plasma vasopressin concentrations, while propranolol and haloperidol had no effect. The secretion of AVP in response to the hypertonic stimulus was potentiated by phenoxybenzamine and haloperidol, but the effect of propranolol was equivocal. The antagonists had no effect on basal arterial pressure at the time of hypertonic saline administration or the pressor response to ICV sodium chloride.

Key words: *Vasopressin; Noradrenaline; Dopamine; Osmoreceptors.*

INTRODUCTION

There is a considerable body of evidence implicating aminergic pathways in the control of neurohypophysial hormone secretion (1, 2) Furthermore the concentrations of noradrenaline and dopamine in the hypothalamus are higher than the average brain content (3). The noradrenaline is of extrahypothalamic origin, the largest contribution being from the A1 cell group which projects from the hypothalamus through the ventral noradrenergic bundle, terminating on the cell bodies in the magnocellular nuclei (4). There are two intrahypothalamic dopamine containing pathways, the tuberoinfundibular pathway and the incerto-hypothalamic axons which terminate in the paraventricular nucleus (5).

The nature of the effects of catecholamines on AVP secretion is not clearly established. Both noradrenaline and dopamine have been reported to increase

(6, 7) and decrease (9) AVP secretion depending on the experimental preparation employed. Dopamine has been shown to decrease the AVP response to a peripheral osmotic stimulis in the rat (10), whilst the influence of noradrenaline is unclear. A series of studies on the effects of peripheral administration of hypertonic saline revealed the nature of the response depended on the route of administration. Elevation of peripheral osmolality may also evoke AVP secretion by a number of routes including stimulation of putative peripheral osmoreceptors (11). The studies have therefore been extended to investigate the effect of aminergic antagonists on central osmotic stimulation of AVP secretion in the conscious rat. The stimulus chosen was an ICV injection of 5μl 0.85M sodium chloride, a commonly employed challenge which has been shown to produce an increase of AVP concentrations in the physiological range without stimulation of ACTH Secretion (12).

METHODS

Animal Preparation

The observations were obtained from male Sprague-Dawley rats (250—290 g) maintained in constant temperature and humidity, with a 12 h light/12 h dark cycle (lights on at 06.00 h). Food (R & M No. 1 Maintenance Diet, Special Diet Services, Witham, Essex. U. K.) and water were available ad libitum. Initially a 21 gauge guide cannula was implanted stereotaxically into the dorsal third ventricle under fentanyl citrate, fluanisone and diazepam anaesthesia (0.32 10.0 and 2.5 mg/kg: IM/IP, respectively) and sealed with a capped stylet. After at least three days recovery, polythene cannulae (OD 0.96 mm; ID 0.58 mm) were introduced into the left jugular vein and carotid artery as described by Forsling and Wells, (13).

Experimental Procedure

After 24 hours recovery food and wàter were removed, and the carotid cannula was connected to a pressure transducer (Bell and Howell, Basingstoke, U. K.) to record arterial pressure and the jugular cannula via an extension to an infusion pump set to deliver sterile (0.15 M) NaCl at 0.1 ml/min. This infusion minimises the impact of blood sampling. The extension lines were sufficiently long to permit unrestrained movement of the rat within the cage. The stylet was removed from the guide cannula and replaced with a small rubber slice for locating the intracerebroventricular (ICV) injection needle. After 7 min infusion a control blood sample of 1.0 ml was collected on ice from the arterial cannula, the plasma was removed and the cells returned in sterile saline (total volume 0.6 ml). After 15 min infusion, 5μl 0.85 M NaCl were injected into the dorsal third ventricle and further blood samples collected after 2 and 10, or 5 and 20 min. Packed cell volume was determined in the first and last samples and the separated plasma stored at 20°C for subsequent determination of plasma AVP concentration by radioimmunoassay (10). The standard employed was the first International Standard for AVP (77/501) and the intra and inter assay coefficients of variation were 7.7 and 11.9% respectively for 1.25 μu/ml.

Administration of aminergic antagonists.

Further groups of animals were treated with aminergic antagonists in doses shown to be effective in modulating AVP secretion (10). Phenoxybenzamine hydrochloride (Dibenyline; Smith, Kline & French Laboratories Ltd., Welwyn Garden City, U. K.) was administered via the jugular cannula at a dose of 1.5 mg/kg, 90 min prior to the ICV osmotic stimulus. Propranolol (Inderal; ICI plc.; Pharmaceuticals Division, Macclesfield, U. K.), or haloperidol (Serenace; Searle Pharmaceuticals, High Wycombe, U. K.), were administered intravenously 15 min prior to the ICV osmotic stimulus in doses of 1.0 and 0.25 mg/kg respectively.

Statistics

All results are presented as means $\pm$SEM and comparisons performed using two and one way analysis of variance or Student's t-test for unpaired data.

RESULTS

There was no significant change in packed cell volume between the first and last sample the values being 38.3 ± 0.7 and $37.0 \pm 0.8\%$ respectively ($n = 60$) indicating blood volume was unaltered. Mean arterial blood pressure remained

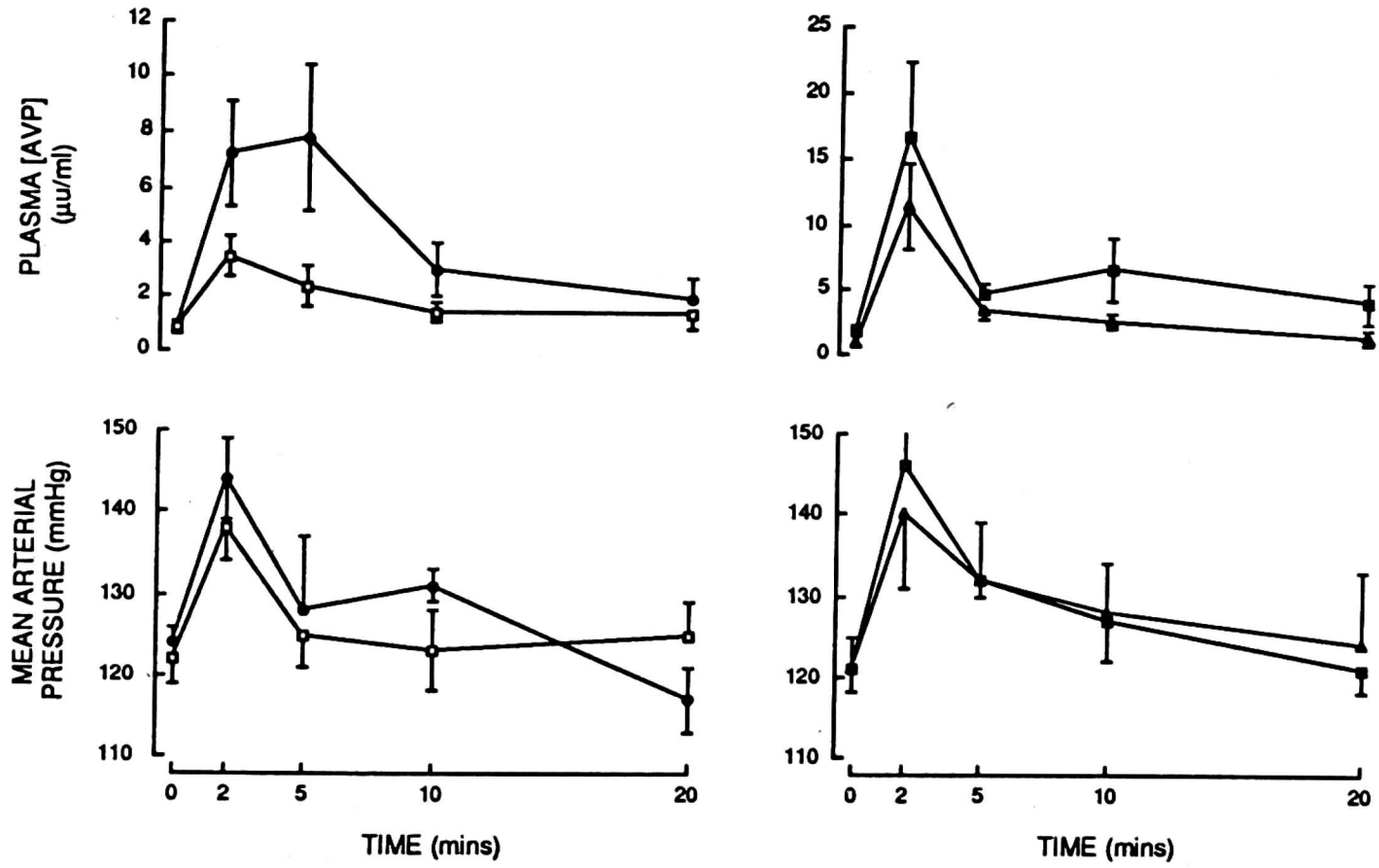

Fig. 1 The effect on plasma AVP concentration and mean arterial pressure of ICV administration of 5 μl 0.85 M NaCl alone (○) and in the presence of propranolol (●), (left hand panel) phenoxybenzamine (■) or, haloperidol (▲) (right hand panel)

relatively constant from the start of the in infusion until administration of the ICV injection. At the time of the observations, the blood pressure in those animals receiving i. v. injections of antagonists was stable and not significantly

different from that in the untreated animals; although fluctuations were noted after the injection of phenoxybenzamine. As shown in *Fig. 1* administration of the osmotic stimulus evoked a transient elevation in mean arterial pressure from 122 ± 3 to 138 ± 4 mmHg ($n = 14\&7$; $p < 0.05$) at 2 minutes. This response was unaffected by prior treatment with the aminergic antagonists.

The basal plasma AVP concentration of 0.85 ± 0.23 μu/ml ($n = 14$) was unaffected by prior treatment with propranolol, or haloperidol (0.80 ± 0.20 and 0.80 ± 0.21 μu/ml respectively) but elevated by phenoxybenzamine to 1.85 ± 0.40 μu/ml ($n = 14$; $F = 4.63$). The plasma AVP concentration 2 min after administration of the osmotic stimulus was significantly increased being 3.49 ± 0.75 μu/ml whereas that in the group receiving 0.15 M NaCl remained unchanged at $0.89 + 0.2$ μu/ml ($n = 7$). The increase in plasma AVP seen on ICV injection of hypertonic saline was potentiated by phenoxybenzamine and haloperidol, concentrations reaching 16.74 ± 5.62 μu/ml ($n = 7$, $F = 5.46$) and 11.40 ± 3.24 μu/ml ($n = 6$, $F = 6.58$ $p < 0.05$). The plasma AVP concentration 2 minutes following administration of the osmotic stimulus in the presence of propranolol was 7.24 ± 1.89 μu/ml ($n = 10$) but this was not significantly higher ($F = 2.51$) than that following treatment with the osmotic stimulus alone. However, propranolol appeared to prolong the elevation in AVP secretion resulting in plasma AVP concentrations of 7.79 ± 2.63 μu/ml ($n = 7$) at 5 minutes as compared to $2.5 + 0.74$ μu/ml ($n = 7$) in the control group.

DISCUSSION

Many different types of preparation have been employed to determine the role of aminergic pathways in the control of AVP release. Peripherally administered hypertonic saline is commonly employed to stimulate AVP secretion by elevation of extracellular fluid osmolality (10, 11). However the induced alterations in blood volume and pressure may also contribute to the final plasma AVP concentrations achieved. In the present study hypertonic saline was administered into the third ventricle in amounts sufficient to produce a small increase in plasma vasopressin similar to that seen on dehydration (14).

The results obtained indicate that in the rat the aminergic pathways influence AVP secretion under basal and stimulated conditions, but do not mediate the blood pressure response to ICV hypertonic saline. This is consistent with the suggestion that the elevated AVP concentrations do not contribute to the rise in blood pressure (12). The elevation in basal AVP concentrations produced by phenoxybenzamine reveals that noradrenaline exerts a tonic inhibition on basal AVP secretion mediated by the α-adrenoceptors. The ICV administration of more specific antagonists indicates that this inhibition is produced by the action of noradrenaline at the pre-synaptic

α_2-adrenoceptors (6). In contrast noradrenaline does not appear to alter basal AVP secretion via the β-adrenoceptors.

The potentiation by phenoxybenzamine of AVP secretion in response to injection of sodium chloride, demonstrates that the a-adrenoceptors also mediate the tonic inhibitory influence of noradrenaline on osmotically stimulated release. Noradrenergic inhibition of AVP secretion can be removed by acid lesioning of the A1 region of the brainstem (15) and a model for the role of these fibres has been proposed by Blessing (16). In this model the noradrenergic neurones make excitatory synaptic connections with the magnocellular neurones α_1 adrenergic receptors probably being involved. However, it appears that the predominant action of noradrenaline in the rat is inhibitory. The ascending noradrenergic neurones form a crucial connection in the baroreceptor pathway to AVP secretion and their activity may determine the threshold and magnitude of the AVP response to osmotic stimulation. They may act to set a 'window' permitting the osmotic stimulation of AVP secretion to be superimposed upon the release profile caused by baroreceptor activity. There is also evidence for a noradrenergic projection from the A2 brainstem region to the neural lobe (17) which may contribute to the noradrenergic control of basal AVP secretion.

The results achieved with haloperidol indicate that dopaminergic innervation has no influence on basal AVP secretion but exerts an inhibitory influence on osmotically stimulated AVP secretion. Although dopamine appears to have an inhibitory influence on osmotically stimulated AVP secretion, haloperidol has been shown to have no effect on the AVP release evoked by ICV injection of angiotensin II (18). A similar distinction has been found for dipsogenesis in the minipig, with dopamine attenuating sodium induced, but not angiotensin II induced drinking (19). The connection of AVP secretion and drinking with the dopaminergic innervation of the hypothalamus may indicate a physiological role for dopamine in this system.

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