J. Physiol. (1984). **354**, *pp.* 547–556
With 4 text-figures
Printed in Great Britain

EXCITATION OF THE CARDIAC VAGUS BY VASOPRESSIN IN MAMMALS

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(*Received 4 November 1983*)

SUMMARY

1. In unanaesthetized sheep, the sensitivity of the baroreceptor–cardio-inhibitory reflex was greater when intravenous vasopressin was used to raise blood pressure, than when intravenous phenylephrine was used to raise blood pressure. This difference was still evident in animals in which β-adrenergic blockade had been carried out using propranolol.

2. In the presence of combined β-adrenergic and muscarinic blockade, a direct negative chronotropic effect of intravenous vasopressin could not be demonstrated. It was concluded, therefore, that intravenous vasopressin enhanced cardiac vagal tone.

3. This effect of vasopressin on efferent cardiac vagal tone was confirmed directly in anaesthetized dogs by recording from single cardiac vagal efferent fibres. Furthermore, recordings from single carotid sinus baroreceptor fibres did not demonstrate a direct action of vasopressin on the sensitivity of the baroreceptors. However, the pressor effect of vasopressin is associated with a greater increase in efferent cardiac vagal discharge than that seen when equipressor doses of phenylephrine are given, or when blood pressure is raised by a similar amount by inflation of an intra-aortic balloon.

4. Studies in isolated guinea-pig atrial preparations and in anaesthetized rabbits and dogs, revealed no consistent peripheral action of vasopressin on the action of the vagus at the heart.

INTRODUCTION

Vasopressin seems to be important in maintenance of blood pressure in haemorrhage, chronic adrenal insufficiency and water restriction (Schwartz & Reid, 1981; Schwartz, Keil, Maselli & Reid, 1983; Schwartz & Reid, 1983). Paradoxically, however, it is not a particularly potent pressor agent, because intravenous infusions of it cause marked falls in heart rate and therefore cardiac output (Hendrickx, Boettcher & Vatner, 1976; Montani, Liard, Schoun & Mohring, 1980). There are several possible mechanisms by which pressor doses of intravenous vasopressin could reduce heart rate and some of these were investigated in the present study. These include a sensitization of the baroreceptor nerve endings, a central facilitation of the arterial baroreceptor reflex, or a peripheral effect on the heart.

METHODS

Three series of experiments were carried out using different animal species in order to take advantage of methods developed for particular purposes in each. In unanaesthetized sheep, the sensitivity of the baroreceptor cardio-inhibitory reflex was measured by the change in pulse interval that occurred in response to changes in arterial pressure. In anaesthetized dogs, recordings from carotid sinus baroreceptor afferent fibres and cardiac vagal efferent fibres were made. Peripheral effects of the vagus at the heart were studied in anaesthetized rabbits and dogs and in an isolated spontaneously beating guinea-pig atrial preparation.

Cardiac baroreflex sensitivity in unanaesthetized sheep

Experiments were carried out using eight chronically catheterized sheep, prepared using methods previously described (Ismay, Lumbers & Stevens, 1979). The effects on heart rate of the pressor effects of intravenous injections of 2–4 u. vasopressin (Pitressin, Parke Davis) were compared with the effects on heart rate of the pressor response to intravenous injections of 0·25–0·5 mg intravenous phenylephrine (Neosynephrine, Winthrop). In some experiments, propranolol (Inderal, ICI) was given as a 15 mg loading dose followed by an infusion of 0·5 mg/min to block cardiac β-adrenoceptors. Combined cardiac sympathetic and parasympathetic blockade was obtained by intravenous administration of 15 mg propranolol and 2–4 mg atropine, followed by an infusion of propranolol 0·5 mg/min and atropine 0·4 mg/min (Ismay *et al.* 1979). The slope of the systolic pressure–pulse interval relation, derived from data obtained during the rise of arterial pressure from its control to peak levels in these conditions, has been used as a measure of the sensitivity of the cardiac baroreflex (Smythe, Sleight & Pickering, 1969; Ismay *et al.* 1979). Since phenylephrine has no direct cardiac effects (Varma, Johnson, Sherman & Youmans, 1960) except in very high doses (Tung, Drummer, Louis & Rand, 1982) it has been used to quantitate baroreflex sensitivity. By comparing the effects of other agents on baroreflex sensitivity with that determined when phenylephrine is used to raise blood pressure it has been possible to demonstrate which of these substances alter the gain of the cardiac baroreflex (see Ismay *et al.* 1979; Lumbers & Potter, 1982). Such comparisons have been made here, using vasopressin. Student's *t* test was used to compare these relations.

In the experiments which were carried out in unanaesthetized sheep, the animals were on occasions restless, and a significant positive correlation between systolic pressure and pulse interval (Nie, Hadlai Hull, Jenkins, Steinbrenner & Bent, 1975) was not always obtained. Only when a significant positive correlation existed for a particular set of data points were slopes calculated by linear-regression analysis of those points, and included in the results. Ten out of twenty-five tests of the cardiac baroreflex using phenylephrine to raise arterial pressure and three out of sixteen tests using vasopressin were excluded because of the lack of a significant direct relation between systolic pressure and pulse interval.

Nerve fibre recordings

Experiments were performed on fourteen dogs weighing 4·5–14 kg. The animals were anaesthetized with intravenous thiopentone (15 mg/kg; Pentothal, Abbott) followed by intravenous chloralose (80–100 mg/kg; α-chloralose, Sigma). Each animal was pre-medicated with morphine sulphate (1 mg/kg). The trachea was cannulated low in the neck and a nylon catheter was inserted into an external carotid artery to measure blood pressure. Another cannula was inserted into a femoral vein for administration of anaesthetic and drugs. A balloon-tipped catheter was inserted into a femoral artery and advanced so that the inflatable balloon lay in the upper abdominal aorta. Rectal temperature was kept between 37 and 39 °C. The dogs breathed spontaneously throughout all experiments. Animals were prepared for nerve recording as described previously (Lumbers, McCloskey & Potter, 1979) and vagal and baroreceptor fibres were dissected and identified as they described. Vagal recordings were made from the central end of the cut nerve on the right; the left vagus was intact. Vasopressin (0·05 u./kg), phenylephrine (25–50 μg), or inflation of the intra-aortic balloon were used to raise blood pressure. Propranolol (1 mg/kg) was used to block β-adrenoceptors (Davis, McCloskey & Potter, 1977).

Effects of vasopressin on the action of the vagus at the heart

In another series of experiments in four dogs anaesthetized with chloralose and four rabbits anaesthetized with pentobarbitone and urethane, both vagi were exposed in the neck and cut, and

sympathetic β-blockade was carried out by intravenous injection of propranolol (1 mg/kg; Courtice, Potter & McCloskey, 1983). The peripheral end of the right vagus nerve was stimulated supramaximally every 10 s with four to six shocks, 300 ms apart (each shock 1 ms duration, ~5 V). Arterial blood pressure, electrocardiogram (e.c.g.) and beat-by-beat heart rate, triggered from the e.c.g. were monitored continuously. A bolus dose of vasopressin (0·03–0·10 u./kg) was injected intravenously and the effect on heart rate during vagal stimulation was recorded.

In addition, a series of experiments was carried out on isolated, spontaneously beating atria of the guinea-pig ($n = 8$). In these preparations, the right vagus nerve was located and cut in the neck, then dissected free in continuity with the atria (Potter, 1982). The atria were placed in Krebs solution which was bubbled with oxygen and maintained at 30 ± 1 °C, and the atria were connected to an isometric force transducer (Grass FT03). In some experiments, adrenergic β-blockade was achieved by addition of practolol (Eraldin, ICI; final concentration 2 μg/ml) to the bath. Practolol was used in the organ bath preparation instead of propranolol as it causes less depression of myocardial contractility. Isometric tension and heart rate (registered beat by beat, triggered from the tension signal) were recorded on a Grass polygraph. The cut end of the right vagus nerve was drawn by suction into a glass pipette containing a pair of Ag–AgCl electrodes. Through these electrodes the vagus was stimulated every 10 s, as in the intact animals. The effect of the vagus on heart rate was recorded in the presence and absence of vasopressin (0·1–0·3 u. was added to 25 ml bath).

A brief account of some of this work has already been made (Lumbers & Potter, 1982).

RESULTS

Cardiac baroreflex sensitivity in unanaesthetized sheep

The resting systolic pressures and pulse intervals in six of the sheep ranged from 91 to 122 mmHg and from 880 to 1520 ms. The magnitude of the rise in systolic pressure caused by phenylephrine and vasopressin varied according to the doses used. For purposes of comparisons, we attempted to adjust these doses to produce equal rises in pressure with the two agents in any one animal. Because the relation between pulse interval and systolic pressure is linear in the range of pressures studied here (Ismay *et al.* 1979), failure to achieve equipressor responses with the two pressor agents will not have affected the results. From animal to animal the range of pressor responses was 14–77 mmHg for vasopressin and 27–72 mmHg for phenylephrine. No data are reported for trials in which systolic pressure was elevated to 200 mmHg or more. After a pressor response to an intravenous injection of phenylephrine or vasopressin had been elicited, no further tests were carried out until the arterial pressure and heart rate had returned to resting levels. The time interval between injections ranged from 15 to 45 min.

The mean baroreflex sensitivity obtained when vasopressin was used to raise pressure was $31·5 \pm 2·71$ (S.E. of mean) ms/mmHg. Where phenylephrine was used to raise arterial pressure it was $21·5 \pm 1·54$ (S.E. of mean) ms/mmHg. Thus, the sensitivity of the cardiac baroreflex elicited by intravenous vasopressin was significantly greater than the sensitivity of the cardiac baroreflex elicited by intravenous phenylephrine ($t = 6·69$, $P < 0·005$, Fig. 1, closed circles).

In three of the sheep, it was observed that β-adrenoceptor blockade with propranolol did not reduce the sensitivity of the cardiac baroreflex response to intravenous vasopressin. The sensitivity of the cardiac baroreflex was still greater, when induced with vasopressin rather than with phenylephrine, after β-adrenoceptor blockade (Fig. 1, open circles).

It seemed possible that the greater degree of cardiac slowing elicited in response to the pressor effect of vasopressin was due to a direct negative chronotropic effect, perhaps as a result of myocardial ischaemia. To test this, the effects on heart rate in response to injections of 2–4 u. vasopressin were studied in four of the sheep in the presence of combined β-adrenergic and cholinergic, muscarinic blockade. No slowing of the heart was observed in any of these experiments, (Fig. 2) thereby excluding this possibility.

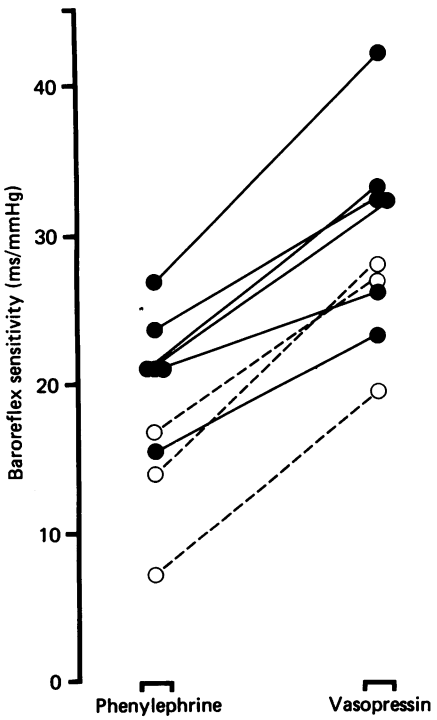

Fig. 1. Mean baroreflex sensitivities (ms/mmHg) of six ewes measured when systolic pressure was increased by intravenous injections of phenylephrine and vasopressin, ●. The baroreflex sensitivities of one of these six ewes and another two ewes were measured during β-adrenergic blockade with propranolol: systolic pressure was increased by intravenous injections of phenylephrine and vasopressin, ○. The baroreflex sensitivity measured during vasopressin-induced hypertension was greater than when phenylephrine was used to raise arterial pressure.

Nerve fibre recordings

Responses of baroreceptor fibres. Six single baroreceptor fibres dissected from the carotid sinus nerve were studied. Blood pressure was raised from its resting level in steps by 50–70 mmHg in each dog. This gave a range of blood pressure levels with a corresponding level of baroreceptor discharge. Baroreceptor discharge was plotted against systolic pressure and in no fibre could we demonstrate a significant difference between the discharge at comparable blood pressure levels when vasopressin or phenylephrine were used as the pressor agent. Therefore, like angiotensin II and

angiotensin III (Lumbers *et al.* 1979; Lumbers & Potter, 1983) intravenous vasopressin had no specific effect on baroreceptor endings, in the anaesthetized dog.

Responses of cardiac vagal efferent fibres. Single cardiac vagal fibres dissected from the right cervical vagus were studied in detail in fourteen anaesthetized dogs (see Lumbers *et al.* 1979). Increases in blood pressure of 20–75 mmHg from resting level caused by inflation of an intra-aortic balloon, intravenous injection of phenylephrine and

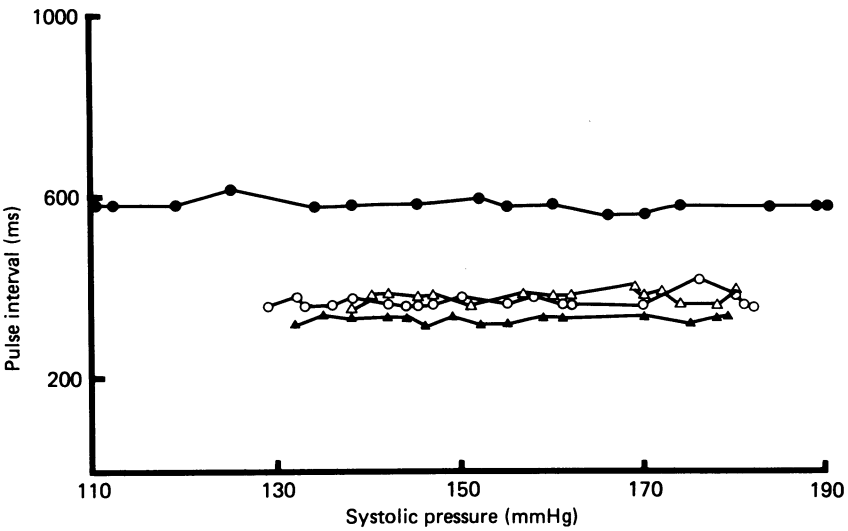

Fig. 2. Systolic pressure and pulse interval relations in four ewes after injection of 2 u. vasopressin during adrenergic and cholinergic blockade with propranolol and atropine.

intravenous injection of vasopressin, caused an increase in cardiac vagal efferent discharge as blood pressure rose (Fig. 3). However, the discharge was greater when intravenous injection of vasopressin was used to raise blood pressure despite the fact that the rise in blood pressure evoked by vasopressin was always less than that when phenylephrine or inflation of an intra-aortic balloon was used (Fig. 3). The increase in cardiac vagal activity was maintained over several minutes even after the blood pressure had returned to its resting value (Fig. 4).

Effects of vasopressin on the action of the vagus at the heart

No potentiation of vagal action by vasopressin could be demonstrated in the eight isolated guinea-pig atrial preparations studied. The addition of vasopressin to the bath did not affect the action of the vagus on the heart, nor was any direct negative chronotropic effect observed. The influence of vasopressin on vagal action on the heart was also tested in four anaesthetized rabbits and four dogs. In two of the four rabbits studied, vasopressin caused a marked increase in the effect of vagal stimulation on heart rate. This effect lasted for more than 1 min on each test in these two rabbits, and occasionally as long as 8 min. Administration of 20 or 30 μg phenylephrine, which produced changes in blood pressure similar to those seen with vasopressin, did not

change the effect of the vagus on heart rate. There was usually a slight fall in heart rate in the periods between vagal stimuli throughout these experiments.

The effect of vasopressin on vagally stimulated changes in heart rate in the dog was not so marked. In one dog, heart rate slowed more in response to vagal stimulation during vasopressin administration, but in the other three, there was no effect. There were no consistent changes in heart rate in the absence of vagal stimulation in the dogs.

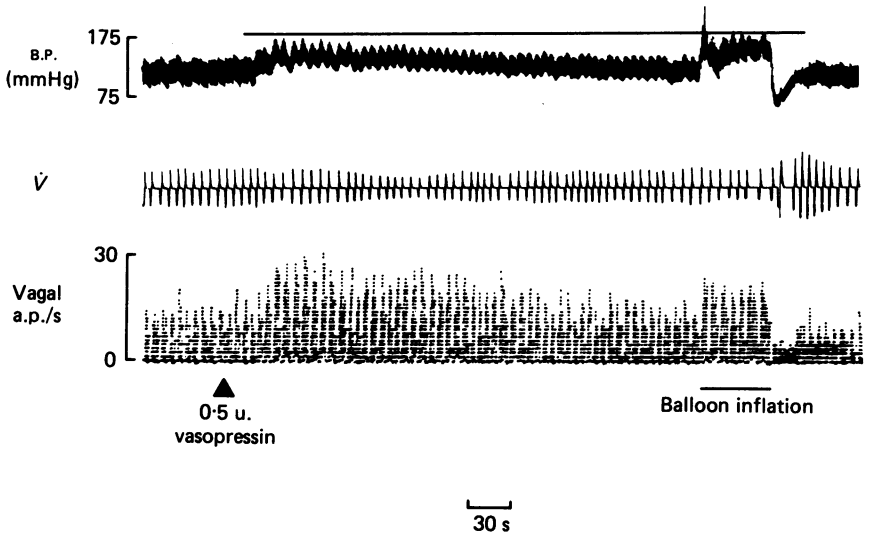

Fig. 3. Records of blood pressure, tracheal air flow ($\dot{V}$: inspiration upwards) and cardiac vagal efferent discharge (vagal a.p./s) from an anaesthetized dog are shown. At the arrow, vasopressin was injected intravenously, blood pressure was raised and cardiac vagal efferent activity increased. Note the prolonged rise in vagal discharge. When blood pressure was raised mechanically, by inflation of an intra-aortic balloon, vagal discharge was lower than when vasopressin was used to raise blood pressure. Note the vagal discharge was lower despite the higher blood pressure level during balloon inflation.

DISCUSSION

Imai, Nolan & Johnston (1983) showed that endogenous vasopressin levels can modulate the arterial baroreflex sensitivity in rats. The present series of experiments showed that vasopressin enhanced baroreflex sensitivity in unanaesthetized sheep, so that for any given rise in systolic pressure there was a greater increase in pulse interval when vasopressin was used to increase peripheral resistance, rather than the β-adrenergic vasoconstrictor, phenylephrine. Furthermore, after β-adrenoceptor blockade the sensitivity of the vasopressin-induced baroreflex was still greater. However, no reflex or direct cardiodepressor effects were demonstrable after vagal blockade. It follows that the enhanced baroreflex sensitivity seen in the presence of vasopressin is vagally mediated. Experiments in anaesthetized dogs gave more direct evidence on this. These showed that vasopressin caused an increase in cardiac vagal efferent activity, greater than that seen when phenylephrine or an intra-aortic

balloon were used to increase arterial pressure. In both sets of experiments the enhancement of cardiac vagal efferent activity may have occurred through stimulation of baroreceptor afferent discharge, a direct stimulatory effect of vasopressin on cardio-inhibitory neurones within the central nervous system, or perhaps even by direct stimulation of other sensory nerve endings which can cause bradycardia reflexly. These could include the ventricular chemosensitive fibres described by Coleridge & Coleridge (1980).

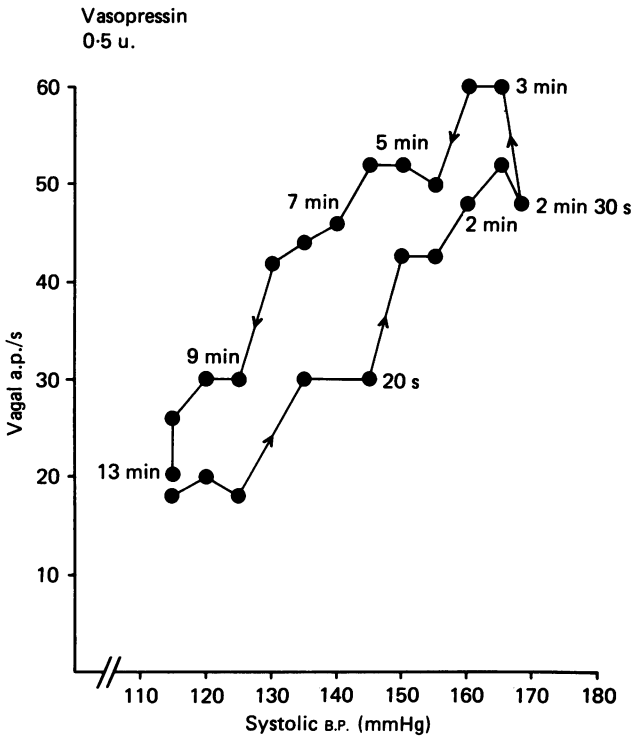

Fig. 4. Results from an anaesthetized dog are shown. Cardiac vagal efferent discharge (vagal a.p./s) is plotted against systolic blood pressure, at the various intervals of time indicated, after intravenous injection of vasopressin. In this animal it took 13 min for blood pressure to return to its resting value. Vagal discharge increased as blood pressure rose (lower curve; increasing time indicated by →) and this increase in discharge was prolonged as blood pressure returned to resting values (upper curve). Vagal discharge was greater at any blood pressure as pressure returned to resting values than when blood pressure was rising.

Our experiments have shown that there was no significant difference in baroreceptor discharge whether blood pressure was raised by either vasopressin or phenylephrine. However, these experiments were carried out in anaesthetized dogs and it is well known that in this situation endogenous vasopressin levels are raised (Bonjour & Malvin, 1970). Therefore, it is possible that baroreceptor discharge had already been increased to a maximum by direct action of vasopressin on the baroreceptor nerve endings. Nevertheless, in the present experiments, baroreceptor discharge was not

significantly altered by vasopressin, and so the action of vasopressin in increasing cardiac vagal efferent discharge in similar preparations in the series cannot be attributed to baroreceptor activation.

Varma, Bhuwaneshwar & Bhargava (1969) showed that injections of vasopressin into the lateral or fourth ventricle produced a profound bradycardia associated with an insignificant rise in blood pressure. However, they concluded that a 'direct stimulating action of vasopressin' on central cardio-inhibitory neurones played only a minor role in the production of the bradycardia produced by intravenous vasopressin. This conclusion was based on the finding that there was a direct negative chronotropic effect of vasopressin. However, Varma *et al.* (1969) used very high doses of vasopressin. In our series of experiments there was no consistent direct negative chronotropic effect of vasopressin in sheep and dogs and only a slight effect in rabbits. In the isolated atrial preparation, no direct negative chronotropic effect of vasopressin was seen, as found also by Nakashima, Angus & Johnston (1982). Thus, it is likely that in our experiments a direct central action of vasopressin on cardiodepressor pathways accounts for the increased cardiac vagal efferent activity. This hypothesis is supported by Liard, Deriaz, Tschopp & Schoun (1981) who found that intravertebral infusions of vasopressin caused a small but significantly greater effect on heart rate than did intravenous infusions of vasopressin.

When intravenous angiotensin II is used to raise arterial pressure, it acts on central neural pathways of the arterial baroreflex to inhibit efferent cardiac vagal discharge (Lumbers *et al.* 1979). It also acts on the peripheral end of the vagus, inhibiting vagal action at the heart (Potter, 1982). The latter effect is not a direct positive chronotropic effect but depends on the ability of angiotensin to block cardiac vagal action peripherally. The action of angiotensin at both the central and peripheral ends of the cardiac vagus suggested to us the possibility of similar sites for the opposite effects of vasopressin. To test this, the effects of vasopressin on the fall in heart rate produced by stimulation of the cut end of the peripheral vagus were studied. In isolated guinea-pig atrial preparations no effect was observed. In only three of eight whole-animal experiments was there evidence of any stimulatory effect of vasopressin on the ability of the vagus to slow the heart. To reconcile these findings, we postulate that vasopressin has no direct effect on peripheral vagal transmission or action, but that the occasional potentiation of vagal action by vasopressin seen in the rabbit is the result of intense coronary vasoconstriction leading to local ischaemic hypoxia (Varma *et al.* 1969). Hypoxia has been shown to be a potent stimulus of the peripheral vagus (Courtice *et al.* 1983).

The cardio-inhibitory actions of vasopressin could be important in the regulation of arterial pressure because vasopressin has two major actions: one through its effect on the kidney which is important in the control of the composition of body fluids; the other action relates to maintenance of arterial pressure through its vasoconstrictor effect. Montani *et al.* (1980) have shown that when endogenous vasopressin release is stimulated by intravenous infusions of hypertonic saline, the changes in heart rate, cardiac output and peripheral resistance are identical to those seen when exogenous vasopressin is infused. This would suggest that the facilitatory effects of vasopressin on the baroreflex control of heart rate prevents undue fluctuations in blood pressure when the hormone is required for maintenance of osmolality. On the other hand, in

situations where maintenance of blood pressure is of importance – e.g. haemorrhage, and severe volume depletion – the profound effects of vasopressin on heart rate and hence cardiac output would be disadvantageous. It is interesting to speculate that as angiotensin II and III have effects on the baroreflex opposite to those produced by vasopressin, and that as the three peptides are released in volume deplete states (e.g. haemorrhage), the angiotensins may block the effects of vasopressin on the cardiac baroreflex in such states so that its pressor action is potentiated.

We thank D. I. McCloskey for helpful advice, D. Condie and A. D. Stevens for technical assistance, and Y. M. Hoban for preparation of the typescript. This work was supported by the National Heart Foundation of Australia which also supported T.E.K. as a Vacation Scholar. E.K.P. is supported by an N.H. & M.R.C. Australian Postdoctoral Fellowship.

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