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THE EFFECTS AND INTERACTIONS OF ANGIOTENSIN AND VASOPRESSIN ON THE HEART OF UNANAESTHETIZED SHEEP

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SUMMARY

1. The effects of infusions of angiotensin and vasopressin, in stepwise concentrations, on the cardiac baroreflex and on cardiac output were studied in seven adult unanaesthetized sheep and compared with those obtained with infusions of phenylephrine. Six animals were treated with the β-adrenoceptor blocking drug, propranolol (in order to inhibit the effects of the sympathetic nervous system on the heart). One animal was not treated with propranolol.

2. In those animals in which arterial pressure increased during infusion of vasopressin, the slope of the systolic pressure–pulse interval relation was greater than that seen when phenylephrine was used to increase arterial pressure. Compared with the cardiac response to pressor doses of phenylephrine, infusions of angiotensin were associated with a lesser degree of cardiac slowing and a lesser reduction in cardiac output.

3. The effects of combined infusions of angiotensin and vasopressin on the cardiac baroreflex were studied. In five sheep which were infused with a pressor dose of angiotensin (1·1 μg/min), the stimulatory effect of vasopressin (1·0 u./min) on pulse interval and its depressant effect on cardiac output were attenuated.

4. In seven sheep infused with 0·5 u./min of vasopressin, I.V. infusions of angiotensin (0·2–5·0 μg/min), produced a progressive decrease in pulse interval and increase in cardiac output as the dose was increased.

5. Therefore, angiotensin can offset the cardioinhibitory effects of vasopressin. Since cardiac sympathetic activity was blocked and neither drug has any direct chronotropic effect on the heart, it would appear that these interactions between the two drugs affect the cardiac vagus either at a peripheral or central level.

INTRODUCTION

Previous studies have shown that the reflex slowing of the heart that occurred in response to a transient rise in arterial pressure is inhibited when angiotensin II or III are used to raise the blood pressure of unanaesthetized sheep (Ismay, Lumbers & Stevens, 1979; Lumbers & Potter, 1983). This may occur because of an inhibitory

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effect of angiotensin on efferent cardiac vagal discharge (Lumbers, McCloskey & Potter, 1979), and an effect of angiotensin on the cardiac vagus at the level of the heart (Potter, 1982).

On the other hand, vasopressin depresses heart rate (Montani, Liard, Schoun & Mohring, 1980; Heyndrickx, Boettcher & Vatner, 1976). A significant component of this cardioinhibitory effect of vasopressin is due to its ability to enhance efferent cardiac vagal activity. There was no direct inhibitory effect of I.V. injections of vasopressin on heart rate (Courtice, Kwong, Lumbers & Potter, 1984).

The inhibitory effects of angiotensin on the cardiac baroreflex and the ability of vasopressin to enhance the baroreflex are unaffected by β-adrenoceptor blockade (Ismay *et al.* 1979; Courtice *et al.* 1984). Thus, although they are both powerful vasoconstrictor agents, angiotensin and vasopressin have opposing effects on heart rate; a significant component of which is mediated through the vagus.

Often, the two peptides are released together, e.g. in haemorrhage and in other forms of volume depletion (Hall & Hodge, 1971; Szczepanska-Sadowska, 1973; Schwartz & Reid, 1981). Since both peptides are vasoconstrictor agents, it can be predicted that their effects on peripheral resistance when they are released together would be synergistic, while their actions on heart rate and cardiac output would be antagonistic.

To study the combined effects of the two hormones on heart rate and cardiac output, experiments were carried out in chronically catheterized adult sheep. First, the effects of infusions of angiotensin and vasopressin were studied separately and their effects on the cardiac baroreflex and cardiac output compared with the effects of pressor infusions of phenylephrine. Then the effects of combined infusions of the two peptides on the cardiac response to their pressor effect was investigated. So that the interactions of the two peptides on the vagal component of the cardiac baroreflex could be studied, all but one of these experiments were carried out in animals in which cardiac sympathetic activity was blocked by continuous infusion of propranolol.

METHODS

Experiments were carried out in eleven chronically catheterized castrated male sheep. Under anaesthesia induced by sodium thiopentone (1 g Pentothal, Abbott) and maintained with 1–2·5% halothane in oxygen, polyvinyl catheters were inserted a distance of 0·25 m into two femoral veins and one femoral artery. To measure cardiac output by thermodilution a Swan–Ganz catheter (model 93A-131-7F) was inserted into a jugular vein and passed through the right side of the heart so that the thermistor was located in the pulmonary artery. The position of the tip of the Swan–Ganz catheter was determined from the pressure-wave profile. The sheep were treated with a single dose of penicillin (600 mg, daily by I.M. or I.V. injection, Crystapen) and streptomycin (1 g, daily by I.M. or I.V. injection, Glaxo) for 3 days after surgery. They were housed in metabolic cages, allowed free access to lucerne chaff and water, and not used in experiments for 5 days. Catheters were flushed daily with heparin saline 50 u./ml and arterial catheters were loaded with heparin saline (1000 u./ml (Heparin, CSL Australia; see also Ismay *et al.* 1979).

Experiments were carried out over an 8 h period. Blood pressure was recorded continuously via the femoral artery polyvinyl catheter (2·7 mm o.d.; 1·5 mm i.d.; length 1·36 m) using Bell and Howell pressure transducers connected to either a Devices or Grass recorder. The pressure transducers were calibrated with a mercury manometer. Pressure transducers were placed on the animal's back so that on all occasions the same reference level was used. Pulse interval was determined from the blood pressure record (paper speed, 5–25 mm/s). Instantaneous changes in pressure occasionally produced an oscillation in this system equivalent to a heart rate of 600

beats/min. Measurements of cardiac output were made by injecting 10 ml 0·15 M-sterile saline (Abbott), equilibrated with the ambient temperature (20–22 °C), into the right atrium via the Swan–Ganz catheter. An Edwards cardiac output computer (model 9500) was used to calculate cardiac output. Three to five measurements of cardiac output were made for each dose of peptide infused. All dilutions of drugs were made using 0·15 M-sterile saline (Abbott). In all but one sheep, cardiac β-adrenoceptor activity was blocked using propranolol (Inderal, 15 mg I.V. followed by a continuous infusion of 0·5 mg/min; see also Ismay *et al.* 1979).

Seven sheep were given infusions of angiotensin (0·2–5·0 μg/min Hypertensin, Ciba), of phenylephrine (12–600 μg/min, Neosynephrine, Winthrop) and vasopressin (0·1–2·0 u./min, Pitressin, Parke Davis). In one animal this experiment was repeated, so that cardiac output could be determined, that is, in six of these eight experiments cardiac output was measured. Each dose of each drug was infused for 6 min and then the dose was increased, i.e. the doses were increased in stepwise increments. When a dose–response curve had been obtained for a particular drug, the infusion was stopped and after 10–20 min the next drug was infused. By this time blood pressure, heart rate and cardiac output had returned to control levels. 2 h after these infusions were finished, vasopressin was infused at a fixed rate of 0·5 u./min. While the vasopressin was infused, the effects of infusions of increasing doses of angiotensin, given in stepwise increments, on the vasopressin-induced bradycardia were determined.

In three of five other experiments, carried out in four other sheep and in one animal used in the experimental protocol described above, vasopressin was infused at 1·0 u./min. When arterial pressure and heart rate had returned to control levels after this infusion of vasopressin was stopped, angiotensin was infused at 1·1 μg/min. After 10 min and while this infusion was continued, vasopressin was again infused at 1·0 u./min. In the two other experiments, the order of the infusions was reversed, i.e. the effects of angiotensin alone and in combination with vasopressin were determined and then the effects of vasopressin alone.

Analysis of data

Four to five estimates of systolic pressure, diastolic pressure and heart rate were made during the last 1–2 min of infusion of a dose of a drug, i.e. at a time when the response of the animal was steady. Cardiac output was measured at the same time. The mean of these observations was obtained. The relation between systolic pressure and pulse interval was studied, because pulse interval is linearly related to cardiac vagal activity during β-adrenoceptor blockade, while heart rate has a reciprocal relation to vagal activity under the same conditions (Parker, Celler, Potter & McCloskey, 1984). No data in which the systolic pressure was 200 mmHg or more were used in analysis of systolic pressure–pulse interval relations.

Data were analysed using regression analysis using a statistical package (SPSS, Nie, Hadlai-Hull, Jenkins, Steinbrenner & Bent, 1974) and analysis of variance together with a Neuman–Kreuls test for the differences of means (Zar, 1974) or Student's t test where appropriate. One of the animals (17) did not receive propranolol. In this animal, the effects of angiotensin and vasopressin on the cardiac baroreflex and the effects of increasing doses of angiotensin on the actions of vasopressin on the heart were not qualitatively different from those observed in animals treated with propranolol, so it has been included. Data are expressed as mean ± S.E. of mean.

RESULTS

The effects of pressor infusions of phenylephrine, angiotensin and vasopressin on pulse interval

Fig. 1 shows the effects of infusions of phenylephrine, angiotensin and vasopressin on systolic and diastolic pressure, pulse interval and cardiac output. The data were obtained from eight experiments done in seven sheep. Vasopressin had a lesser effect on blood pressure than did either angiotensin or phenylephrine. However, it had a similar effect on pulse interval and cardiac output to that seen with infusions of phenylephrine, i.e. pulse interval increased and cardiac output decreased (Fig. 1). Angiotensin and phenylephrine in the doses infused had similar effects on arterial

pressure, but phenylephrine produced a progressive increase in pulse interval and a fall in cardiac output, while infusions of angiotensin produced only a small increase in pulse interval and cardiac output did not change (Fig. 1).

The relation between pulse interval and systolic pressure was determined in each experiment for each of the three vasoactive drugs (Fig. 2) and the significance of the relation analysed by regression analysis. Table 1 shows the slopes, correlation coefficients and significance values from those experiments in which the relation between systolic pressure and pulse interval was significant ($P < 0.05$).

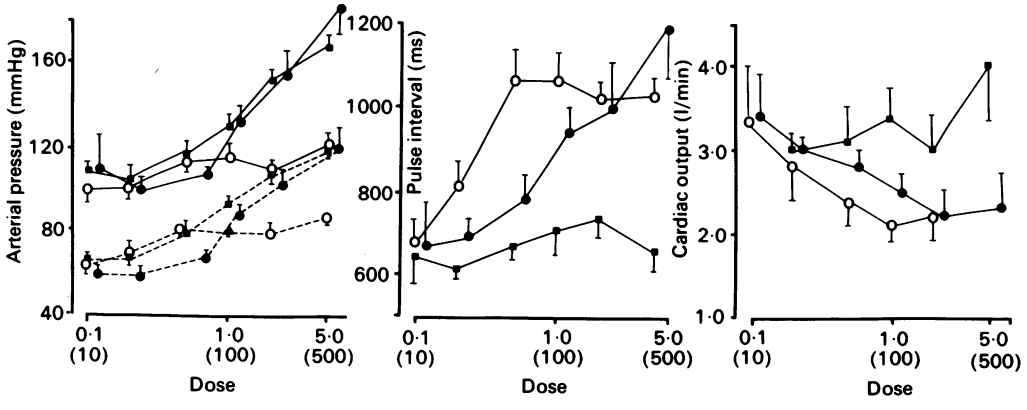

Fig. 1. Dose–response curves to angiotensin (■), phenylephrine (●) and vasopressin (○). Abscissa: logarithmic scale; numbers not in parentheses = doses of angiotensin (μg/min) or vasopressin (u./min) infused into the sheep; numbers in parentheses = doses of phenylephrine infused into sheep (μg/min). Left panel, systolic (—) and diastolic pressure (--- mmHg; mean ± S.E. of mean). Middle panel, pulse interval (ms). Right panel, cardiac output (l/min). Vasopressin had a lesser effect on arterial pressure than either phenylephrine or angiotensin, but its cardioinhibitory effect was more pronounced. Angiotensin and phenylephrine had similar effects on arterial pressure, but angiotensin only had a minimal effect on pulse interval and cardiac output.

When phenylephrine was used to raise arterial pressure, there was a significant linear relation ($P < 0.05$) between pulse interval and systolic pressure, in all but one case. In six of the eight experiments, there was a significant relation ($P < 0.05$) between pulse interval and systolic pressure when vasopressin was infused. The slopes of the relations between systolic pressure and pulse interval obtained when vasopressin was used to raise pressure were compared with the slopes obtained when phenylephrine was used to raise arterial pressure. The slope was greater (Table 1, Fig. 2) when vasopressin was used to increase arterial pressure.

In the two experiments in which there was no relation between systolic pressure and pulse interval when vasopressin was infused, increasing doses of vasopressin did not cause a rise in arterial pressure. In one of these two animals in which the arterial pressure was 139/69 mmHg before infusion of vasopressin and 129/87 when 5·0 u./min of vasopressin was infused, pulse interval increased from 377 to a maximum of 1111 ms and cardiac output fell from 5·4 to 3·4 l/min. In the other animal in which the arterial pressure was 109/80 mmHg before infusion of vasopressin and

111/87 at the maximum dose infused (2·0 u./min), pulse interval increased from 645 to 927 ms and cardiac output fell from 2·97 to 2·2 l/min.

Fig. 2 shows that angiotensin had less effect on pulse interval at a given level of systolic pressure, than phenylephrine. Furthermore, the relation between systolic pressure and pulse interval was not always linear (see Fig. 2) so that in only four of

TABLE 1. The slopes (ms/mmHg) of the relations between systolic pressure and pulse interval

Expt.	ANG	PHE	VP
17	2·1 (0·97, 0·003)	7·5 (0·97, 0·01)	19·2 (0·93, 0·003)
20	3·6 (0·98, 0·001)	10·5 (0·99, 0·001)	17·9 (0·89, 0·05)
201	N.s.	3·2 (0·89, 0·05)	16·5 (0·83, 0·05)
22	N.s.	5·0 (0·96, 0·003)	84·8 (0·97, 0·003)
23	N.s.	N.s.	14·8 (0·99, 0·005)
24	1·1 (0·84, 0·05)	5·5 (0·99, 0·005)	N.s.
25	4·5 (0·85, 0·05)	14·8 (0·99, 0·005)	61·9 (0·91, 0·05)
41	N.s.	4·2 (0·91, 0·05)	N.s.

Expt. = experiment number, ANG = slopes obtained when arterial pressure was increased by the stepwise infusion of angiotensin (0·1–5·0 μg/min), PHE = slopes obtained when arterial pressure was increased by infusions of phenylephrine (12–600 μg/min), VP = slopes obtained when arterial pressure was increased by infusions of vasopressin (0·1–5·0 u./min). Only those slopes in which there was a significant relation between pulse interval ($P < 0·05$) and systolic pressure are shown. Values in parentheses are the correlation coefficients and significance levels, N.s. = non-significant correlation between systolic pressure and pulse interval. Expt. 17 did not receive propranolol.

the eight experiments was a significant linear relation ($P < 0·05$) obtained between systolic pressure and pulse interval when angiotensin was used to elevate arterial pressure. In these four cases the slope of the relation was less than when phenylephrine was used to raise pressure (Table 1). In six experiments in six of the animals cardiac output was measured. Cardiac output fell when arterial pressure was increased. The rate of decrease in cardiac output was greatest when vasopressin was used to increase pressure, while infusions of angiotensin were associated with the smallest reductions in cardiac output (Fig. 3).

To see the effect of combined infusions of angiotensin and vasopressin on the control of heart rate, two series of experiments were carried out. In the first of these experiments, the effects of vasopressin 1·0 u./min on arterial pressure, pulse interval, heart rate and cardiac output were determined in five sheep. Arterial pressure increased from a mean value of $(103 \pm 2·4)/(66 \pm 2)$ to $(121 \pm 7)/(86 \pm 6)$ mmHg. Pulse interval rose from 759 ± 95 to 1284 ± 87 ms and cardiac output fell (control: from $4·49 \pm 0·2$ to $2·77 \pm 0·22$ l/min, Fig. 4). The effects of angiotensin 1·1 μg/min were then investigated. Arterial pressure rose from $(103 \pm 5·3)/(65 \pm 4)$ mmHg to

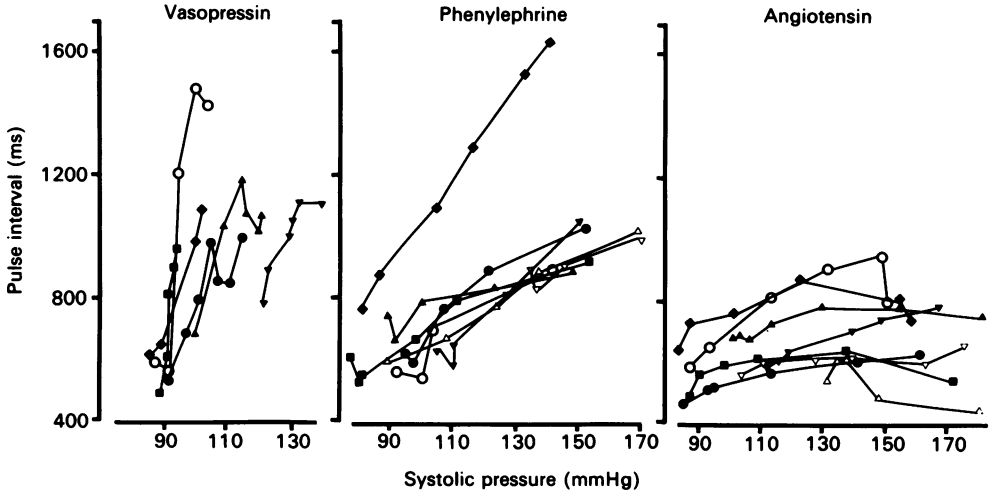

Fig. 2. The relation between systolic pressure and pulse interval when the arterial pressure of unanaesthetized sheep was increased by infusions of vasopressin (left-hand panel), phenylephrine (12–240 μg/min, middle panel) and angiotensin (0·5–5·0 μg/min, right-hand panel). When arterial pressure was increased by vasopressin (0·1–2·0 u./min) the greatest increments in pulse interval were observed. When arterial pressure was increased by angiotensin the smallest increments in pulse interval were observed. Symbols designate individual experiments. (●) did not receive propranolol.

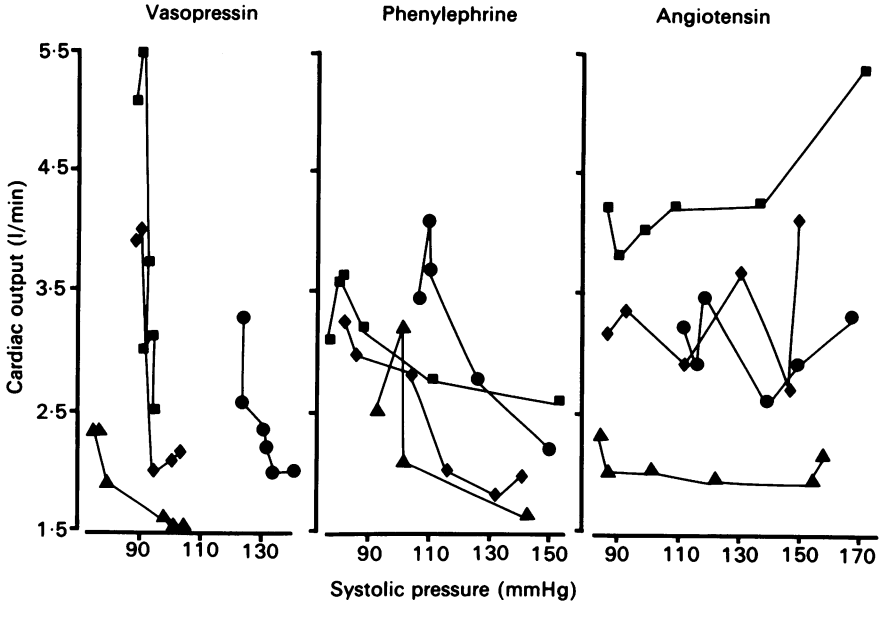

Fig. 3. The relation between cardiac output (ordinate) and systolic pressure in four sheep in which vasopressin (0·1–2·0 u./min) caused a rise in arterial pressure and in which cardiac output was measured. Vasopressin (left-hand panel) produced a marked fall in cardiac output over a small range of arterial pressure, whilst angiotensin infusions (0·5–5·0 μg/min) had no effect on cardiac output despite a marked pressor effect. The effect of pressor infusions (12–240 μg/min) of phenylephrine are shown in the middle panel.

(146±5)/(96±4) mmHg. Pulse interval increased slightly (control: from 896±110 to 979±74 ms) but cardiac output did not change (control: from 4·41±0·27 to 3·99±0·34 l/min, Fig. 4). 10 min after the infusion of angiotensin had started and when its effects on cardiovascular function had been determined, vasopressin was infused as the infusion of angiotensin continued. Arterial pressure increased further,

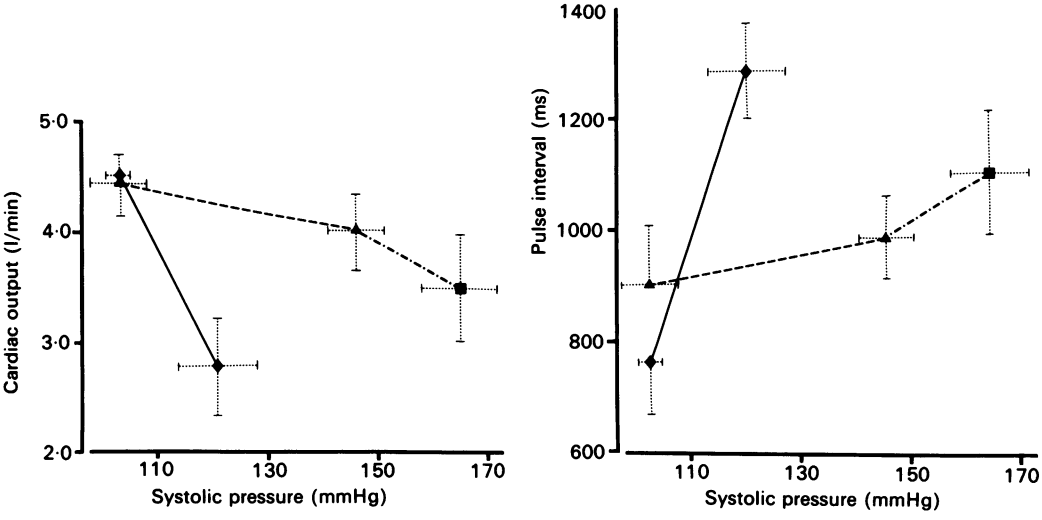

Fig. 4. The effect of vasopressin 1·0 u./min (◆) on pulse interval (left-hand panel) and cardiac output (right-hand panel, mean±S.E. of mean), and angiotensin 1·1 μg/min (▲) relative to their effects on systolic pressure. When the infusion of vasopressin (■) was repeated together with the infusion of angiotensin, pulse interval did not fall and cardiac output did not fall to the levels observed when vasopressin was infused alone.

to (165±7)/(111±9) mmHg, but pulse interval only increased slightly to 1096±113 ms, and cardiac output decreased only slightly to 3·46±0·46 l/min. Fig. 4 shows that the effects of vasopressin on heart rate and cardiac output were attenuated in the presence of infusion of 1·1 μg/min of angiotensin.

In this experiment the effects of vasopressin were compared at two very different levels of arterial pressure (103/66 mmHg and 146/96 mmHg). Thus it was difficult to be certain that the reduction in the cardioinhibitory effects of vasopressin in the presence of angiotensin was due to an interaction of the two peptides or simply the result of the elevated arterial pressure. Since infusions of vasopressin 0·5 u./min only caused a rise in arterial pressure of 10 mmHg (Fig. 1) it was possible to superimpose infusions of angiotension (0·2–5·0 μg/min) and examine the effects of these doses of angiotensin on the bradycardia caused by the concomitant infusion of vasopressin, over a wider range of arterial pressures.

In eight experiments in seven sheep vasopressin was infused at 0·5 u./min. In six of these seven animals cardiac output was measured. The arterial pressure increased from (98±7)/(61·4±5·1) to (104±4·2)/(74·8±3·3) mmHg, $n = 8$; pulse interval rose from 644±41 to 999±57 ms, $n = 8$, $P < 0·005$. Cardiac output fell from 3·73±0·5 to 2·52±0·3 l/min, $n = 6$, $P < 0·05$. When the infusion of vasopressin was continued and

angiotensin II was infused in stepwise increments, the maximum pulse interval (1035 ± 39 ms) and minimum cardiac output (2·33 ± 0·3 l/min) occurred during infusion of vasopressin 0·5 u./min and a dose of angiotensin of 0·2 μg/min, when the arterial pressure was only 113/84 mmHg. As the dose of angiotensin was increased, arterial pressure increased, but pulse interval fell and cardiac output increased, so that when the arterial pressure was 170/118 mmHg, the pulse interval was 841 ± 60 ms and the cardiac output was 3·48 ± 0·6 l/min (Fig. 5).

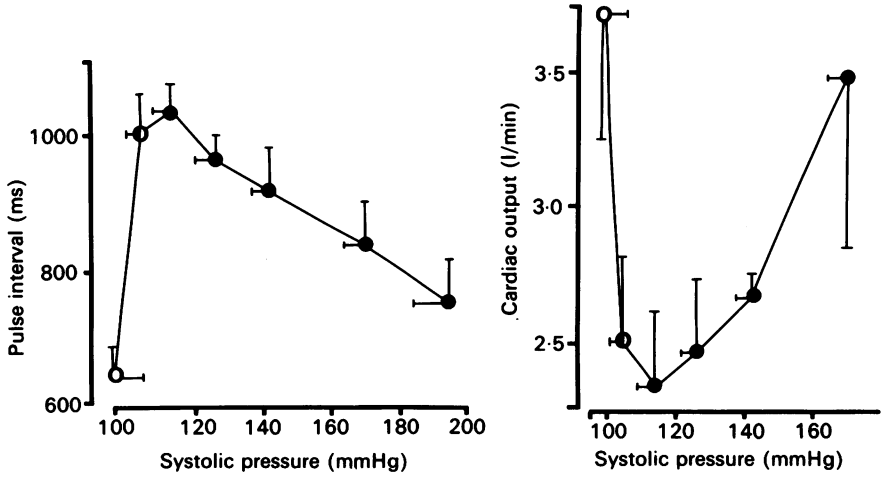

Fig. 5. In order to test further the effects of combined infusions of angiotensin and vasopressin on the heart, the effect of vasopressin 0·5 u./min (◐) on pulse interval (left-hand panel) and cardiac output (right-hand panel) relative to systolic pressure was measured (abscissa). Increasing doses of angiotensin (0·2–5·0 μg/min, ●) were then infused. Open symbols represent control values before any infusion. Increasing doses of angiotensin antagonized the cardioinhibitory effects of vasopressin, despite the increase in arterial pressure.

Thus increasing doses of angiotensin offset the cardioinhibitory effects of infusions of vasopressin of 0·5 u./min.

DISCUSSION

Phenylephrine was used to test the cardiac baroreflex because it has no direct cardiac effects (Varma, Johnson, Sherman & Youmans, 1960), except in high doses (Tung, Drummer, Louis & Rand, 1982) and it has been used previously (Smyth, Sleight & Pickering, 1969; Ismay *et al.* 1979).

In previous experiments we have shown that both angiotensin and vasopressin have effects on efferent cardiac vagal activity (Lumbers *et al.* 1979; Courtice *et al.* 1984). Angiotensin inhibits efferent cardiac vagal activity and vasopressin stimulates it. The present series of experiments show that when the two peptides are infused separately into adult unanaesthetized sheep it is possible to show that infusions of vasopressin enhance the cardiac baroreflex while infusions of angiotensin inhibit it. Since the doses of angiotensin and phenylephrine which were infused produced

comparable rises in arterial pressure, it is unlikely that the inhibitory effects of angiotensin are due to the sigmoid nature of the cardiac baroreflex. Fig. 2 shows that at comparable pressures, pulse interval is lowest when angiotensin is infused. It could be claimed that in part the marked cardioinhibitory effects of vasopressin, which seem to offset its vasoconstrictor action (see Fig. 1) could be due to a direct effect of vasopressin at the level of the heart. However, neither I.V. injections of vasopressin (Courtice *et al.* 1984) nor infusions of vasopressin (E. R. Lumbers, unpublished observations) have any negative chronotropic effect on the heart rate of sheep treated with atropine and propranolol to block cardiac sympathetic and parasympathetic pathways. Furthermore, Montani *et al.* (1980) showed that in the unanaesthetized dog, vasopressin had no effect on heart rate when efferent autonomic pathways to the heart were destroyed. In addition, cardiac sympathetic activity was blocked in all but one animal, so vasopressin enhances that part of the cardiac baroreflex dependent upon the integrity of the cardiac vagus. It is not possible from the experiments described to suggest a site for this action of vasopressin.

On the other hand, the site at which angiotensin inhibits the cardiac baroreflex is better characterized. Angiotensin has no effect on the baroreceptors themselves (Lumbers *et al.* 1979), it enhances efferent cardiac vagal activity (Lumbers *et al.* 1979) and also enhances the activity of the vagus at a peripheral level, i.e. at the heart (Potter, 1982). Also angiotensin affects cardiac vagal activity by a central action on the area postrema (see Severs & Daniels-Severs, 1973). Thus, intravertebral infusions of low doses of angiotensin are pressor because they increase cardiac output (Lumbers & Reid, 1981). Angiotensin, like vasopressin has no effect on the heart rates of sheep in which cardiac vagal activity has been blocked by combined blockade with atropine and propranolol, and β-adrenoceptor blockade on its own has no effect on the inhibitory action of angiotensin on the cardiac baroreflex. Therefore, angiotensin inhibits the cardiac baroreflex by acting on the cardiac vagus both centrally and peripherally (Ismay *et al.* 1979; Lee, Ismay & Lumbers, 1980).

The effects of vasopressin and angiotensin on the pulse interval determined their effects on cardiac output. Thus, the most rapid fall in cardiac output was seen when vasopressin was infused and the pressor response to angiotensin was not accompanied by any change in cardiac output (Fig. 3).

Angiotensin and vasopressin are both released in those situations where maintenance of arterial pressure is threatened (e.g. haemorrhage, Hall & Hodge, 1971; Szczepanska-Sadowska, 1973). While both peptides cause vasoconstriction, their opposing effects on the vagal component of the cardiac baroreflex would appear to be antagonistic. However, the results described in Figs. 4 and 5, suggest that angiotensin in sufficient doses can offset the cardioinhibitory actions of vasopressin on the vagal component of the cardiac baroreflex, since all but one experiment was carried out in animals in which cardiac sympathetic activity was blocked. Although we have used pharmacological doses of both vasopressin and angiotensin to demonstrate the interactions between the two peptides on the vagus, it is possible that such interactions occur with physiological levels of these peptides. It has been shown for example, that vasopressin in concentrations similar to those measured in dehydration is vasoconstrictor but not pressor presumably because of its cardioinhibitory effects (Montani *et al.* 1980). The ability of angiotensin to block the cardioinhibitory effects of vasopressin might

therefore provide a useful mechanism in maintaining arterial pressure in pathophysiological situations. Thus, in circumstances such as mild dehydration, the vasoconstrictor effects of vasopressin are overcome because baroreflex pathways are enhanced, and so arterial pressure does not rise. The relative difficulty in obtaining a pressor response to vasopressin in the sheep (Fig. 1) because of its marked effects on cardiac output (Fig. 3) tends to support this hypothesis. However, in those situations where the release of vasopressin is secondary to a severe reduction in blood volume and where the production of angiotensin is enhanced, the depressant effects of vasopressin on cardiac output would be disadvantageous. Angiotensin, because it blocks the effects of vasopressin on the heart, would therefore play an essential role in maintenance of tissue perfusion, when the circulating blood volume is reduced.

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