Effect of vasopressin on plasma volume and renin release in man

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Summary

1. Arginine vasopressin was infused into seven healthy young male volunteers at 12.5 and 25 units/min for 1 h at each dose. Plasma renin activity fell sharply and progressively in each subject. The mean fall was 47% and 66% of the initial value at the end of the lower and higher rates of arginine vasopressin infusion respectively; over 70% of the observed fall in plasma renin activity occurred at the end of the first infusion period.

2. The majority of the plasma arginine vasopressin concentrations achieved were within the physiological range observed after fluid deprivation and orthostatic stress in man, particularly at the lower rate of infusion.

3. There was no change of arterial pressure, despite a slight bradycardia at the lower rate of infusion; at the higher rate of infusion, there was only a very slight pressor response.

4. There was a concomitant and significant fall of plasma protein concentration and peripheral venous packed cell volume without any significant change of plasma sodium concentration or plasma osmolality, implying an expansion of plasma volume.

5. The results indicate that, in man, physiologically relevant amounts of arginine vasopressin suppress the rate of renin secretion indirectly by increasing the plasma volume at the expense of the extravascular fluid volume.

Key words: arginine vasopressin, extracellular fluid volume, interstitial fluid volume, plasma osmolality, plasma protein, plasma renin activity, plasma renin concentration, plasma sodium, plasma volume.

Introduction

It is axiomatic that the renin–aldosterone system and vasopressin are important in the regulation of plasma volume. In dogs, a reduction of blood volume induced by slow haemorrhage increases the plasma concentration of both angiotensin (Scornick & Paladini, 1961; Hodge, Lowe & Vane, 1966; Regoli & Vane, 1964) and vasopressin (Baratz & Ingraham, 1960; Weinstein, Berne & Sachs, 1960; Henry, Gupta, Meehan, Sinclair & Share, 1968). In man, also, postural hypovolaemia has been shown to increase the plasma concentration or 'activity' of both renin (Conn, Rovner & Cohen, 1965; Brown, Davies, Lever, McPherson & Robertson, 1966) and vasopressin (Segar & Moore, 1968; Moore, 1971; Davies & Forsling, 1975). These observations suggest a close physiological relationship between the two endocrine systems which must be central to the control of plasma volume.

In dogs, vasopressin infused at near physiological rates suppresses plasma renin activity (Bunag, Page & McCubbin, 1967; Vander, 1968; Tagawa, Vander, Bonjour & Malvin, 1971), even when the filtration function of the kidney is destroyed (Shade, Davis, Johnson, Gotshall & Spielman, 1973). Conversely, it has been suggested that angiotensin infusions increase vasopressin secretion (Bonjour & Malvin, 1970), although the report of Claybaugh, Share & Shimizu (1972) does not support this. We have
therefore set out to determine the effect of infusing arginine vasopressin in physiologically relevant amounts on plasma renin activity in man. We have also made measurements which indicate that the suppression of plasma renin activity which we have observed is due to the effect of vasopressin on the distribution of extracellular fluid between its intravascular and extravascular compartments.

**Materials and methods**

**Subjects and experimental protocol**

The studies were performed on twelve male volunteers, aged 19–23 years. They all took an unrestricted diet but ethanol and tobacco were disallowed for at least 12 h before the study began. On the morning of the study they ate a light breakfast with a glass of milk and then they rested, fully recumbent, for 2 h (from 07.00 to 09.00 hours). Small indwelling catheters (Butterfly R-19, Abbott Laboratories, Chicago, Ill., U.S.A.) were placed in both antecubital veins under local anaesthesia. Blood samples were collected from one of these catheters and the other catheter was used for infusion. After obtaining two control blood samples (at −10 and 0 min), glucose (50 g/l) was infused at 09.00 hours by an infusion pump (Palmer, England) at a constant rate of 0.8 ml/min for 240 min. Blood samples were collected at 15 min intervals between 09.00 and 10.00 hours (pre-infusion period, 0–60 min), 12.00 and 13.00 hours (recovery period, 180–240 min) and at 10 min intervals between 10.00 and 12.00 hours (vasopressin infusion period, 60–180 min). During the pre-infusion and recovery periods only glucose was infused and during the arginine vasopressin infusion period seven of the subjects were infused with synthetic arginine vasopressin at a constant rate of 12.5 munits/min and 25 munits/min for 60 min at each dose. Arginine vasopressin was standardized by pressor bioassay, with USP posterior lobe reference standard, and was estimated to contain 170 i.u./ml (Sigma Chemical Co., St Louis, Mo., U.S.A.). This solution was diluted with glucose (50 g/l) to obtain the required concentrations of arginine vasopressin for infusion. In order to provide a proper control for the study, five subjects were infused with glucose only throughout the study period. In these subjects the amount of blood removed and the frequency of sampling was identical with those who were infused with arginine vasopressin.

The effect of infusion on arterial blood pressure and heart rate was determined by infusing arginine vasopressin in six other male volunteers (aged 19–24 years) at the same rate (12.5 munits/min and 25 munits/min) for 40 min at each dose. Blood pressure and heart rate were recorded every 10 min, but the slow glucose (50 g/l) infusion (0.8 ml/min) given in the main study was not used.

**Collection of blood**

Blood samples were collected into plastic syringes, transferred into heparinized polystyrene tubes, precooled to 4°C, and the plasma was separated immediately by centrifugation at 4°C. The plasma was then decanted into plastic tubes, ‘snap-frozen’ and stored at −20°C. All samples were analysed within 2 weeks of collection.

**Analytical procedures**

Arginine vasopressin was estimated, in 5–10 ml plasma samples, after adsorption on to glass beads and elution with aqueous acetone (Forsling, 1974), in rats anaesthetized with ethanol (Forsling, Jones & Lee, 1968). The design of the assay and the assessment of its error limits were carried out according to the description given by Errington & Rocha e Silva (1972). Losses on storage and extraction were allowed for in each plasma sample, and the values reported have been corrected accordingly; overall losses for this study were 34% ± 7 (mean ± sd). A cautious assessment of the detection limit of the actual assay runs used in producing the values reported was 0.5 μunit/ml of plasma.

Plasma renin activity was determined by estimating the rate of generation of angiotensin I, which was measured in 1 ml of plasma by the precise radioimmunoassay technique of Ménard & Catt (1972), with angiotensin I antibody kindly donated by Dr J. Ménard. Their method was modified only in that dimercaprol was omitted from the mixture of angiotensin inhibitors. A realistic estimate for the limit of detection was 0.1 pmol h⁻¹ ml⁻¹. The use of plasma renin activity to index changes of plasma renin concentration was validated by the addition of three increments of MRC Standard Human Renin (batch no. 68/356; Medical Research Council, Division of Biological Standards, National Institute for Medical Research, London) to plasma obtained from the same subject during pre-infusion, arginine vaso-
Vasopressin, plasma volume and renin release

Effects of vasopressin infusion

Effect on plasma renin activity and plasma vasopressin concentration. In Fig. 1 the mean plasma renin activity and arginine vasopressin concentrations have been plotted against time. During the pre-infusion period, when only glucose was infused, plasma renin activity and concentration of arginine vasopressin remained stable. Arginine vasopressin, infused at 12.5 munits/min, lowered renin activity sharply and progressively in all the subjects: mean activity fell from 1.73 pmol h⁻¹ ml⁻¹ ± 0.10 to 0.92 pmol h⁻¹ ml⁻¹ ± 0.08 or by 45% (P < 0.001) at the end of the first hour. The corresponding mean plasma arginine vasopressin rose from 1.61 munits/ml ± 0.21 to 9.71 munits/ml ± 1.42. Doubling the rate of infusion to 25 munits/min lowered plasma renin activity further to a mean value of 0.59 pmol h⁻¹ ml⁻¹ ± 0.06 or by 65%, and the mean plasma arginine vasopressin concentration rose to 14.46 munits/ml ± 3.64. The plasma arginine vasopressin concentrations achieved during the second infusion period varied (maximum coefficient of variation = 67%). In one subject the plasma concentration rose only from 1.1 to 8.4 munits/ml, but, despite this moderate increase, the corresponding plasma renin activity fell from 1.65 pmol h⁻¹ ml⁻¹ to 0.37 pmol h⁻¹ ml⁻¹ or 77%.

After termination of the infusion of arginine vasopressin (recovery period) plasma renin activity increased progressively in all subjects as the plasma arginine vasopressin concentration fell. At the end of the recovery period, the mean renin activity was 1.49 pmol h⁻¹ ml⁻¹ ± 0.1, or very nearly the same as, but rather lower than, the mean pre-infusion value. However, the mean plasma arginine vasopressin concentration was also higher than the mean pre-infusion value, at 3.17 munits/ml ± 0.4.

Effect on plasma protein concentration and plasma renin activity. The percentage change (from the mean pre-infusion value in each subject) in plasma protein concentration and renin activity in response to infusion of arginine vasopressin is shown in Fig. 2. There was a progressive and highly significant (P < 0.001) decrease of plasma protein concentration, which
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Fig. 1. Effect of arginine vasopressin (AVP) infusion on plasma AVP concentration and renin activity, expressed as mean values ± SEM. Note that the mean plasma renin activity falls progressively; over 70% of the observed suppression occurs at the end of first AVP infusion period when the mean plasma AVP concentration is still well within the physiological range. The concentration of infused glucose was 50 g/l. A1 = angiotensin I.

**Effect on plasma osmolality and plasma sodium concentration.** Fig. 3 shows the percentage change of plasma osmolality and plasma sodium concentration plotted against time. There was no significant change either of plasma osmolality or plasma sodium concentration during infusion of vasopressin.

**Effect on heart rate and arterial blood pressure.** The response of the blood pressure and heart rate to infusion of arginine vasopressin is shown in Fig. 4. The percentage change has been calculated from the mean pre-infusion values and is plotted against time. The mean heart rate fell significantly (P < 0.05, \( n = 6 \)) from 68 beats/min ± 5.0 to 63 beats/min ± 4.3 or 6% within 10 min of starting the infusion at 12.5 munits/min. Slight but significant bradycardia was maintained throughout the study and doubling the rate of infusion to 25 munits/min did not further lower the heart rate (62 beats/min ± 3.7 or a fall of 7% from the mean pre-infusion value). Although the mean arterial pressure did not change significantly, a moderate but significant (P < 0.025) increase was recorded in the mean diastolic blood pressure from 75 mmHg ± 2.2 to 79 mmHg ± 2.2 or 5% at the end of the higher rate of infusion. However, at the lower
Fig. 2. Effect of arginine vasopressin (AVP) infusion on plasma protein concentration (mean ± SEM) and plasma renin activity (individual results), expressed as a percentage change (Δ) from the mean pre-infusion value. Both variables remain stable before infusion and both fall and subsequently rise concomitantly as AVP is infused and then stopped. The concentration of infused glucose was 50 g/l.

Fig. 3. Effect of arginine vasopressin (AVP) infusion on plasma sodium concentration and plasma osmolality, expressed as the percentage change (Δ) from the mean pre-infusion value (± SEM). Note the absence of any significant change. The concentration of infused glucose was 50 g/l.
FIG. 4. Effect of arginine vasopressin (AVP) infusion on heart rate and mean arterial pressure, expressed as the percentage change (Δ) from the mean pre-infusion value. There is no significant change of mean arterial blood pressure (BP), although a slight but significant bradycardia is maintained during the AVP infusion. Results are shown as mean values ± SEM.

Mean heart rate (beats/min) = 67 68 63 65 62 65 64 67 62 62
Mean systolic BP (mmHg) = 117 120 118 118 118 118 120 118 120
Mean diastolic BP (mmHg) = 72 75 74 76 75 78 77 79 76 79

FIG. 5. Effect of a glucose (50 g/l) infusion (0.8 ml/min) alone on the plasma protein concentration (mean ± SEM) and plasma renin activity (individual data), expressed as the percentage change (Δ) from the mean pre-infusion value. Both variables remain unchanged throughout the 4 h period of the study.
rate of infusion there was no significant change of blood pressure despite a significant fall of the mean heart rate. The systolic blood pressure did not change significantly throughout the study.

**Effects of glucose infusion**

**Effect on plasma protein concentration and plasma renin activity.** The mean percentage change of plasma protein concentration and renin activity in the five subjects infused with glucose only is shown in Fig. 5. There was no significant change either of the mean plasma protein concentration or the plasma renin activity throughout the experimental period. The mean plasma protein concentration changed by $+0.3\% \pm 0.5$ and $-0.7\% \pm 1.1$ at the end of the second and third hours, corresponding to the end of the lower and higher rates of arginine vasopressin infusion respectively. The corresponding change of plasma renin activity was $-1.6\% \pm 0.6$ and $-1.2\% \pm 1.0$ from the mean pre-infusion values. In accordance with the lack of change in the plasma protein concentration, the mean percentage change of plasma volume ($0.9\% \pm 1.8$), estimated from the peripheral venous PCV at the end of the third hour, also did not change significantly. Thus in these studies there was no change of either the estimated mean plasma volume or of renin activity, despite the removal of the same amount of blood, as in the vasopressin infusion studies.

**Effect on plasma sodium concentration and plasma osmolality.** When glucose (50 g/l) alone was infused, there was no significant change of plasma osmolality or plasma sodium concentration, nor was there any trend throughout the period of study, despite measurements being made every 10–15 min. The variation was less than 1% throughout for both, well within the error of their respective estimations.

**Discussion**

Our results confirm the findings of animal experiments that plasma renin activity is reduced sharply by vasopressin infused at rates which have no effect on arterial pressure. We suggest that this indicates a reduction in the rate of renin release. This interpretation assumes first, that changes of plasma renin activity parallel those of renin concentration and, secondly, that changes of renin concentration, under the conditions of our study, reflect the rate of renin release. We have confirmed that changes of plasma renin activity reflect those of renin concentration but it is more difficult to exclude the possibility that changes of concentration may not reflect changes of renin secretion. Renin is metabolized mainly, if not completely, by the liver (Heacox, Harvey & Vander, 1967; Schneider, Davis, Baumber & Johnson, 1970). The hepatic extraction ratio is not altered by severe haemorrhage in dogs (Johnson, Davis, Baumber & Schneider, 1971) or by an 80° tilt in hypertensive men (Kokot, Kuska & Czekala, 1968), so that renin clearance should be proportional to hepatic blood flow. Pitressin (a mixture of arginine vasopressin and lysine vasopressin) increases hepatic arteriolar resistance in man (Tsakiris & Buehllmann, 1961) and decreases hepatic blood flow (Bearn, Billing, Edholm & Sherlock, 1951; Davis, Gorlin, Reichman & Storaasli, 1957; Shaldon, Dolle, Guevara, Iber & Sherlock, 1961; Ericsson, 1972). Thus a reduction of total hepatic blood flow induced by vasopressin will, if anything, reduce the hepatic clearance of renin and therefore increase rather than decrease the plasma renin concentration. These considerations lead us to conclude that, under the present experimental conditions, the observed fall of plasma renin activity is mainly, if not completely, due to a reduction in the rate of release of renin from the juxtaglomerular cells. Similar conclusions have been drawn from animal experiments reported by Vander (1968) and, more recently, by Tagawa et al. (1971) and Vandongen (1975).

The plasma concentrations of arginine vasopressin seen in this study (2.6–16.9 µunits/ml) are quite modest physiologically, although they are probably maximally antidiuretic. They are clearly within the range seen after surgical trauma (Moran, Miltenberger, Shu’ayb & Zimmermann, 1964; Moran & Zimmermann, 1967) as well as after a standardized 85° head-up tilt (Davies & Foraling, 1975). They are also well within the range reported by Czaczkes, Kleeman & Koenig (1964) after fluid deprivation (2.7–22.0 µunits/ml) although, in this context, others have usually reported slightly lower values (Yoshida, Motohashi, Ibayashi & Okinaka, 1963; Robertson, Mahr, Athar & Sinha, 1973; Morton, Padfield & Forsling, 1975).

Thus it is reasonable to conclude that the rate of renin secretion can be sharply reduced in man by plasma concentrations of vasopressin which are within the physiological range. This agrees with the animal studies quoted above.

Our studies go further in that they suggest a
mechanism for the effect of arginine vasopressin on plasma renin activity. Previous theories to explain the mechanism by which vasopressin reduces renin secretion include changes in the macula densa sodium concentration, the renal afferent arteriolar pressure and a direct effect on the juxtaglomerular cells. The macula densa hypothesis is based on the observation that vasopressin induces natriuresis in the water-loaded dog (Sartorius & Roberts, 1949; Anslow & Wesson, 1955; Brooks & Pickford, 1958; Chan & Sawyer, 1961), rat (Ogle, 1968) and ruminants (MacFarlane, Kinne, Walmsley, Siebert & Peters, 1967). However, Shade et al. (1973) have demonstrated that vasopressin can inhibit renin release in the absence of a functioning macula densa in dogs.

As no consistent changes have been observed in renal haemodynamics by doses of arginine vasopressin which markedly inhibit the release of renin in dogs, previous workers (Vander, 1968; Tagawa et al., 1971; Shade et al., 1973) have drawn an indirect conclusion that the inhibition of renin release is due to a direct effect of vasopressin on the juxtaglomerular cells.

However, from an analysis of the changes of plasma protein concentration and haematocrit that we have observed, we suggest that arginine vasopressin, infused at a rate which has little cardiovascular effect, increases plasma volume at the expense of the extravascular fluid. Since the inverse relationship between plasma volume and renin secretion is well established, the increase of plasma volume which we have observed may well explain the fall of plasma renin activity.

This conclusion assumes that the changes of plasma protein concentration and the changes of PCV reflect changes of plasma volume during the period of the study. Both variables changed in the same direction, but the interpretation of the fall of PCV is complicated by the fact that about 190 ml of blood was removed during the course of the study. Adjusting for this, the PCV would still appear to have fallen in such a way as to imply an increase in plasma volume of about 200 ml. This observation, by its magnitude alone, can hardly be ascribed to sequestration of erythrocytes, although a small component may possibly be due to a change of small vessel/large vessel PCV ratio (Chacalos, 1967). It is also possible that arginine vasopressin, in amounts which do not change perfusion pressure, provokes a subtle increase in the rate of protein loss across capillaries. However, this would lead to an increase of peripheral PCV rather than the reduction we have observed. A significant increase of plasma volume when vasopressin is infused into trained conscious dogs for 1 h has been demonstrated by Szczepanska-Sadowska (1973). The mean increase of plasma volume (estimated by dye-dilution technique) was 120 ml when the mean plasma vasopressin concentration was 22 μunits/ml, or similar to that which is observed after a non-hypotensive haemorrhage in the dog (Szczepanska-Sadowska, 1972).

Our studies are short-term; in the longer term different results may be obtained. Goodwin, Ledingham & Laragh (1970) gave large amounts of vasopressin daily for 5 days to normal people and suggested that, when fluid intake was restricted, plasma renin activity did not change. However, although they claim that the changes of activity were 'unimpressive', two subjects did show a fall of renin activity and a rise of plasma volume. Indeed, Newsome & Bartter (1968) had already shown that chronic administration of vasopressin lowers plasma renin activity only when accompanied by an increase of plasma volume. Our results are consonant, but it is still possible that the changes of plasma volume and renin activity that we observed may not be causally related. The fall of plasma renin activity in our study is equivalent to that seen when sodium chloride (150 mmol/l) is infused into normal humans so as to produce a comparable increase of plasma volume in the same period of time (Tuck, Dluhy & Williams, 1974). Thus even kinetic considerations are compatible with our hypothesis but the possibility that there is also a direct effect of arginine vasopressin on the juxtaglomerular apparatus, as has been suggested in animal studies, cannot be excluded.

None the less, we suggest that the evidence best fits with the idea that, in man, physiologically relevant amounts of vasopressin suppress the rate of renin secretion indirectly by increasing plasma volume at the expense of the extravascular fluid.

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