Increased renal excretion of arginine-vasopressin during mild hydropenia in young men with mild essential benign hypertension

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Summary

1. The rate of renal excretion of arginine-vasopressin was determined during unrestricted fluid intake for 24 h and in response to fluid deprivation for 18 h in nine young men with very mild essential hypertension and compared with that in sixteen normotensive men of similar age.

2. Despite an equivalent osmolar stimulus, excretion of arginine-vasopressin was significantly greater in the hypertensive group than in the reference group. This difference increased progressively with increasing dehydration.

3. We suggest that these findings are mainly due to an increased rate of secretion of arginine-vasopressin in response to mild hydropenia in hypertensive patients and that a moderate increase of release of arginine-vasopressin during periods of fluid deprivation may exert vascular effects and thus influence the perpetuation of hypertension.

Key words: arginine-vasopressin, extracellular fluid volume, interstitial fluid volume, plasma volume, renal tubular free water reabsorption.

Introduction

In recent years there has been much interest in potential abnormalities of extracellular fluid volume in hypertension. However, there has been no general agreement. For instance, extracellular fluid volume or plasma volume has been shown to be normal (Walser, Duffy & Griffith, 1956; Hollander, Chobanian & Burrows, 1961; Cranston & Brown, 1963; Eisenberg & Wolf, 1965), increased (Grollman & Shapiro, 1953; Teng, Shapiro & Grollman, 1954; de Graeff, 1957) or decreased (Rochlin, Shohl & Blakemore, 1961; Tibblin, Bergentz, Bjure & Wilhelmsen, 1966; Tarazi, Fröhlich & Dustan, 1968; Tarazi, Dustan & Fröhlich, 1969) in essential hypertension. It is axiomatic that vasopressin is important in the sensitive regulation of plasma volume and, since it is also a pressor agent, we have set out to reveal an abnormality of vasopressin control in uncomplicated mild essential hypertension by studying the rate of excretion of arginine-vasopressin as an index of changes of its plasma concentration. Since the mean biological half-life of exogenous vasopressin in man is 5.6 min (Fabian, Forsling, Jones & Pryor, 1969), the rate of renal excretion of AVP, rather than its plasma concentration, probably provides a better index of AVP secretion integrated over a period of time. Therefore we have studied urine rather than plasma. Our results indicate that, during mild hydropenia, AVP excretion rate is significantly raised in hypertensive patients.

Methods

Subjects and experimental protocol

Nine male hypertensive patients under 45 years of age (range 27–45 years) were compared with sixteen normotensive male volunteers of similar age (range 20–40 years). All were in good health and uncomplaining. The hypertensive group consisted of a consecutive series of patients who had untreated, mild (usually labile) essential hypertension (average recumbent blood pressure at 10.00 hours was 148 ± 7 mmHg systolic and 94 ± 4 mmHg diastolic). Cardiac and renal function was assessed by chest X-ray, elec-
trocardiography, rapid-sequence intravenous pyelography and the estimation of the 24 h endogenous creatinine clearance. Other estimations to exclude secondary hypertension included plasma concentrations of sodium, potassium, bicarbonate, urea and cortisol, plasma renin activity (recumbent and erect) and the rate of renal excretion of aldosterone 18-glucuronide and vanillylmandelic acid. All subjects took an unrestricted diet and were encouraged to continue their usual activities. Alcohol and tobacco were disallowed for at least 24 h before the study began. Timed urine samples were collected by voluntary voiding into plain plastic containers every 8 h for 24 h, while the subjects were on unrestricted food and fluid intake. During fluid deprivation for 18 h, two samples at 4 h interval, one 8 h (overnight) sample and one 2 h (08.00 to 10.00 hours) sample were collected. Venous blood samples were obtained at the end of each collection period into heparinized polystyrene tubes and the plasma was separated by centrifugation. Two aliquots from each sample were stored at -20°C until assayed. The study was approved by the Clinical Investigation Panel of The Middlesex Hospital.

Analytical techniques

AVP was extracted from 5 ml aliquots of urine and estimated by employing a sensitive and highly specific radioimmunoassay, as reported previously (Khokhar, Ramage & Slater, 1975a). The method has an estimated detection limit of 5.2 fmol of AVP/ml. The intra-assay and inter-assay coefficient of variation is 3.5–7% and 2.5–10% respectively, depending upon the magnitude of response. By infusing AVP in healthy volunteers to achieve plasma concentrations within the physiological range, we have shown that there is a good correlation (r = 0.93, P < 0.001) between plasma AVP concentration and the rate of renal AVP excretion (Khokhar, Slater, Forsling & Ramage, 1975b). Thus changes of the rate of renal excretion of AVP can be taken to reflect changes of plasma AVP concentration.

The osmolality of each plasma and urine sample was determined by freezing-point depression (Osmometer model 3L, Advanced Instruments Inc., Mass., U.S.A.). The renal clearance of solutes (C_{osm}) and the rate of renal tubular generation (C_{water}) or reabsorption (T^{water}) of solute free water was calculated for each collection period, as described by Smith (1956).

Statistics

The significance of the difference between results was tested by Student's t-test. Mean values are given, followed by 1 SEM. Non-parametric statistical assessment was also made by the use of the x^2-test.

Results

During unrestricted fluid intake, as well as in response to dehydration, plasma osmolality was similar in both groups. After hydropenia for 18 h, mean plasma osmolality rose from 278 ± 1.3 to 282 ± 1.5 mosmol/kg (P < 0.02), or +4 mosmol/kg, in the reference group and from 277 ± 2.6 to 281 ± 3.1 mosmol/kg (P < 0.01), or +4 mosmol/kg, in the hypertensive group. However, despite a similar

![Graph](image-url)

**FIG. 1.** Relationship between the rate of AVP excretion and free water clearance within the osmolality ranges 0–400, 400–800 and 800–1200 mosmol/kg of water. The hypertensive group (open columns; n = 9) shows an abnormally high rate of AVP excretion within the urine osmolality range 400–1200 mosmol/kg of water despite a normal rate of water reabsorption. Results for normal subjects (n = 16) are given as solid columns. Vertical bars indicate SEM. Significance: *P < 0.01; **P < 0.001.
osmolar stimulus, the response of vasopressin excretion was different in the two groups. Fig. 1 shows the relationship between the rate of renal AVP excretion, urine osmolality and the rate of renal tubular clearance of free water. In the osmolality range 0–400 mosmol/kg the mean rate of AVP excretion was $55 \pm 5$ fmol/min in the reference group and $54 \pm 9$ fmol/min in the hypertensive group; mean $C_{\text{water}}$, was $2.9 \pm 1.1$ ml/min and $2.8 \pm 0.9$ ml/min respectively. During the initial stages of hydropenia (osmolality range 400–800 mosmol/kg) the mean rate of AVP excretion rose to $64 \pm 5$ fmol/min, or +18%, in the reference group and to $89 \pm 7$ fmol/min, or +66%, in the hypertensive group. The response of the two groups was significantly different ($P < 0.01$). With progressive dehydration (osmolality range 800–1200 mosmol/kg) this difference became even more significant ($P < 0.001$); the mean rate of AVP excretion increased by 59% to 102+6 fmol/min in the reference group and by 86%, to 167+12 fmol/min in the hypertensive group. Despite a significantly higher AVP excretion rate in the hypertensive group, mean $T_{\text{water}}$ was similar to that achieved in the reference group.

Discussion

Our results show that in young men with mild essential hypertension the rate of renal AVP excretion was significantly greater during mild hydropenia than in the reference group, despite a similar osmolar stimulus. We have shown a good correlation between the rate of renal AVP excretion and plasma AVP concentration over the physiological range (Khokhar et al., 1975b) and since, in most circumstances, plasma concentrations of AVP are determined primarily by the rate of its release rather than its rate of metabolic clearance (Share, 1967; Moore, 1971), we suggest that the changes which we have observed in hypertensive patients are mainly due to a higher rate of AVP release; since the groups were so similar in other respects, any abnormality of AVP clearance within the narrow range relevant to this study is unlikely.

The mechanism by which a mild osmotic stress induces a greater rate of AVP release in hypertensive patients is necessarily complex. One interpretation would presuppose that the kidney of mildly hypertensive patients is relatively resistant to the antidiuretic action of vasopressin, and this is reasonable since we have shown that, despite a greater rate of renal AVP excretion, hypertensive patients do not show a greater rate of renal tubular water reabsorption. If this were so, we might expect a marginally raised plasma osmolality in hypertensive people, as in patients with nephrogenic diabetes insipidus. Since this is not the case, a rather more elegant but more speculative interpretation presents itself. This involves the assumption that the plasma volume in mild essential hypertension is indeed lower than normal (Rochlin et al., 1961; Tibblin et al., 1966; Tarazi et al., 1968, 1969) and links this idea with the interesting observations of Moses & Miller (1971), which suggest that, in man, a decrease of plasma volume lowers the osmotic threshold of AVP release. This concept fits well with our data, but it does not take into account the fact that both in man (Khokhar, Slater, Forsling & Payne, 1976) and in dogs (Szczepanska-Sadowska, 1972), infusions of AVP, to achieve plasma concentrations within the physiological range, tend to increase plasma volume at the expense of the interstitial fluid volume rather than decrease it. Notwithstanding these apparent contradictions, which clearly demand further study, we suggest that an increased rate of AVP release during mild hydropenia may exert considerable vascular effects and so influence the perpetuation of hypertension.

References


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