THE EFFECTS OF PROLONGED ADMINISTRATION OF VASOPRESSIN AND OXYTOCIN ON RENIN, ALDOSTERONE AND SODIUM BALANCE IN NORMAL MAN

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SUMMARY

1. Vasopressin was administered to normal men in metabolic balance for periods of 5–10 days under conditions of water restriction or overhydration. Likewise, oxytocin was administered to two normal men for 10 days.

2. The effects of both neuropeptides on plasma renin activity, aldosterone excretion rate and sodium balance were observed.

3. In the absence of overhydration, vasopressin had no demonstrable effect upon plasma renin activity, aldosterone excretion rate or sodium balance. During overhydration body weight gain and plasma dilution were followed by natriuresis; the associated changes in plasma renin activity and aldosterone excretion, however, were unimpressive.

4. The prolonged administration of oxytocin for 10 days under conditions of normal hydration failed to influence sodium excretion, plasma renin activity or aldosterone excretion.

5. It is concluded that in normal man changes in circulating levels of vasopressin or oxytocin do not play a physiological role in the control of sodium excretion.

The regulation of extracellular fluid volume is complex: both aldosterone and vasopressin have been shown to be important factors in its control. The increased secretion and excretion of aldosterone which follow dietary sodium deprivation (Ulick, Laragh & Lieberman, 1958; Axelrad & Luetscher, 1954) or haemorrhage (Farrell, Rosnagle & Rauschkolb, 1956) are mediated, at least in part, by stimulation of the renin-angiotensin system (Laragh, Angers, Kelly & Lieberman, 1960; Biron, Koiw, Nowaczynski, Brouillet & Genest, 1961; Brown, Davies, Lever & Robertson, 1963). However, aldosterone secretion is also controlled by other factors, including dietary potassium intake (Laragh & Stoerk, 1955, 1957) and ACTH (Liddle, Duncan & Bartter, 1956; Tucci, Espiner, Jagger, Pauk & Lauler, 1967; Newton & Laragh, 1968). Further-

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more, the demonstration that some patients with primary aldosteronism have bilateral adrenal hyperplasia without evidence of stimulation by either angiotensin or ACTH, has suggested the existence of some other, as yet unidentified, trophic stimulus to aldosterone secretion (Laragh, Ledingham & Sommers, 1967; Davis, Newsome, Wright, Hammond, Easton & Bartter, 1967).

Vasopressin release also appears to be governed by multiple factors and is influenced not only by changes in osmolarity of the body fluids (Verney, 1947), but also by changes in blood volume. Ginsburg & Heller (1953) demonstrated that haemorrhage in the rat resulted in an increase in circulating antiuretic material and Weinstein, Berne & Sachs (1960), studying haemorrhage in the dog, showed that this substance was in fact vasopressin. Share (1961) subjected dogs to peritoneal dialysis with hypertonic solutions, thereby producing small gradual decreases in blood volume without affecting mean arterial blood pressure, and demonstrated a six-fold increase in the circulating level of vasopressin. The mechanism whereby the secretion of this hormone is influenced by volume changes is as yet ill-defined, although volume receptors in the left atrium of the heart (Henry, Gauer & Reeves, 1956; Henry, Gupta, Meehan, Sinclair & Share, 1968) and baroreceptors in the region of the carotid arteries have been implicated in the control of its release.

Bartter, Liddle, Duncan, Barber & Delea (1956) produced expansion of body fluid volume in normal man by means of administered vasopressin and water-loading, and caused aldosterone excretion to diminish despite the accompanying dilution of extracellular sodium concentration. However, evidence is lacking about the possibility of a direct effect of prolonged administration of vasopressin on aldosterone secretion in man, occurring in the absence of changes in body fluid volume. By means of direct arterial perfusion of the adrenal gland of the hypophysectomized dog Hilton (1960) showed that lysine vasopressin stimulated hydrocortisone secretion, and that the synthetic analogue acetyl arginine vasopressin stimulated aldosterone; however, the latter finding was demonstrated in one animal only and the effect of arginine vasopressin itself, the naturally occurring hormone in man, was not investigated. Furthermore, vasopressin is known to stimulate ACTH release (McCann, 1957) and, in view of the known transient effect of the latter upon aldosterone secretion, it seemed possible that aldosterone might be stimulated indirectly by vasopressin.

It has been shown in dogs that vasopressin, as well as possessing marked antidiuretic activity, is also markedly natriuretic during water diuresis: conversely, oxytocin is natriuretic during antidiuresis (Brooks & Pickford, 1958; Chan & Sawyer, 1961). A further implication that vasopressin may be involved in sodium metabolism is the report by Bunag, Page & McCubbin (1967) of its action in dogs of suppressing the rise in renal venous plasma renin activity which normally occurs in response to lowering renal perfusion pressure.

In the present experiments, therefore, we have studied in normal man the effects of the prolonged administration of vasopressin, associated with and in the absence of an increase in total body water, and of oxytocin upon aldosterone excretion, peripheral venous plasma renin activity and sodium excretion.

METHODS

The studies were made on seven normal male volunteers, to whom the purpose and nature of the experiment had been fully explained and from whom consent had been obtained. All were maintained in the Metabolic Ward of Presbyterian Hospital, New York, on a constant
diet containing approximately 100 mEq of sodium and 100 mEq of potassium daily. All urine was collected for determination of daily excretion rates of electrolytes, aldosterone, and 17-ketogenic steroids. Normal activity was permitted throughout the studies. Blood was taken at noon, after the subject had been ambulant for at least 4 h, for measurement of plasma electrolyte and cortisol concentrations and plasma renin activity: for the latter 20 ml of venous blood were drawn rapidly into a tube containing either 250 units of thrombin to hasten clotting, or 20 mg of disodium EDTA, and renin activity was determined by a method described previously (Newton & Laragh, 1968). Plasma cortisol was measured by a modification of the method of Silber & Porter (1954), and both urinary and plasma electrolytes by flame photometry. Faecal electrolyte content was not measured. Osmolarity of plasma and urine was measured using a freezing-point osmometer (Advanced Instruments, Inc.). Aldosterone excretion rate was measured by a double isotope dilution technique (Laragh, Sealey & Klein, 1965; Laragh, Sealey & Sommers, 1966), and urinary 17-ketogenic steroids by a modification of the method of Few (1961). In certain of the studies measurements of plasma volume were made using $^{131}$I-labelled serum albumin. Vasopressin was given as Pitressin tannate in oil (PTO) or as aqueous Pitressin (Parke, Davis and Company); oxytocin was given as the synthetic preparation, Pitocin (Parke, Davis and Company): both hormones were given by intramuscular injection. Each subject received the constant diet for 5 days, at the end of which period control observations were made before either hormone was administered.

**Vasopressin studies**

**Water restriction.** In four subjects (D.G., P.K., W.M. and P.W.), following control observations, fluid intake was restricted, usually to less than 1000 ml daily, in order to maintain body weight, measured twice daily, constant, and urine specific gravity, measured at each voiding, above 1.020. In one subject (P.K.) 5 units of aqueous Pitressin were given five times daily, but in the remainder 5 units of PTO and 10 units of aqueous Pitressin were given on the first day and the same dose repeated only when urine specific gravity fell below 1.020. Each of the four subjects was studied for 5 days. It was assumed that this procedure ensured high circulating levels of either endogenous or exogenous vasopressin in each subject throughout the study. Dosage schedules appear in the Figures.

A further two subjects (W.C. and P.J.) were studied in greater detail and for a longer period. After control measurements 5 units of aqueous Pitressin were given 4-hourly for 10 days. During the waking hours body weight was recorded 2-hourly and fluid intake restricted so as to prevent a gain in body weight. In addition, plasma volume was measured on the first, fifth and tenth days of vasopressin administration.

**Water expansion.** In three subjects (D.G., P.K. and W.M.), following control observations, between 10 and 30 units of vasopressin as PTO and aqueous Pitressin were given daily for 5 days, and fluid intake increased such that each subject gained approximately 3 kg in body weight. In two of the subjects mild symptoms of water-intoxication occurred, following which vasopressin was omitted for 1 day.

**Oxytocin studies**

The effect of prolonged and regular administration of oxytocin on plasma renin activity, aldosterone excretion and sodium balance was studied in two subjects (W.C. and P.J.). Following control observations 5 units of Pitocin were given 4-hourly for 10 days, during which
period fluid was allowed *ad libitum*. Measurements of plasma volume were made on the first, fifth and tenth days of oxytocin administration.

**RESULTS**

**Vasopressin**

The metabolic data for the studies in which vasopressin was administered with concurrent restriction of water intake are shown in Figs 1 and 2. In the absence of body fluid expansion, vasopressin had no significant effect upon plasma renin activity, aldosterone excretion or sodium balance. In D.G., body weight rose when vasopressin was given, with an associated increase in urinary sodium excretion: this increase was not associated with any significant change in plasma renin activity or aldosterone excretion. In P.K., W.M. and P.W., weight-gain was satisfactorily prevented by restriction of fluid intake; in these three subjects no significant changes in sodium excretion, plasma renin activity or aldosterone excretion rate occurred.
Fig. 2. Effect of the prolonged administration of vasopressin to normal subjects with restricted fluid intake.

Subjects W.C. and P.J. were studied for 10 days. Both received 30 units of vasopressin daily and body weight gain was satisfactorily prevented in each by water restriction; throughout the studies urinary osmolarity remained above 750 mosmol/l in W.C. and above 500 mosmol/l in P.J., plasma osmolarity remaining unchanged. In P.J. a marked natriuresis occurred on the third to sixth days of vasopressin administration, following which sodium excretion fell considerably. Although in this subject body weight remained fairly constant, plasma volume had expanded by 340 ml at the time of natriuresis; on the tenth day of vasopressin administration, when sodium excretion had fallen below control levels, plasma volume had returned to its
original value. These changes in sodium excretion occurred despite the continued administration of vasopressin throughout the study.

The metabolic data for the three studies in which vasopressin was administered without concurrent restriction of water intake are shown in Fig. 3. In each subject body weight rose by

approximately 3 kg and plasma sodium concentration fell by at least 10 mEq/l. In each a natriuresis occurred during volume expansion: the accompanying changes in plasma renin activity and aldosterone excretion rate were, however, unimpressive. The marked rise in aldosterone excretion rate occurring on the fifth day in P.K., following the withdrawal of vasopressin, was associated with striking falls in both body weight and sodium excretion.

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**Fig. 3.** Effect of the administration of vasopressin to normal subjects with water-loading.
In none of the studies in which vasopressin was given did significant or consistent changes in plasma cortisol or 17-ketogenic steroid excretion occur, thereby excluding any marked effect of vasopressin in the dosages employed upon ACTH release.

**Oxytocin**

The metabolic data for the two studies in which oxytocin was given are shown in Fig. 4. Both subjects were given 30 units of the hormone daily in divided doses for 10 days. In neither were any significant or consistent changes in plasma renin activity, aldosterone excretion rate or sodium excretion observed. Although measurements of plasma cortisol and urinary 17-ketogenic steroids were made in these studies, they failed to show significant changes following oxytocin and have not been presented here.

**DISCUSSION**

In these studies the physiological role of vasopressin in the control of aldosterone, plasma renin activity and sodium metabolism was investigated in normal man. In those subjects to whom vasopressin was given for 5 days only and in whom water intake was restricted, it may be assumed that high circulating levels of vasopressin were present throughout the studies in view
of their persistently high urine specific gravities. The remaining two subjects, W.C. and P.J., who were studied for 10 days, received constant doses of vasopressin which were appreciably above the physiological requirement of normal man. That in each case antidiuretic doses of vasopressin were given was demonstrated by the tendency for water to be retained. When expansion of body fluid volume was prevented, the administration of vasopressin in doses sufficient to produce marked antidiuresis failed significantly to affect aldosterone excretion, plasma renin activity or sodium balance. The absence of changes in plasma cortisol levels or in 17-ketogenic steroid excretion is not surprising, since the dose of vasopressin required to stimulate ACTH release greatly exceeds that necessary for antidiuresis (Nichols & Guillemin, 1959). Furthermore, the role of ACTH in controlling aldosterone secretion in normal man is of doubtful significance, since the rise in aldosterone excretion which follows ACTH administration (Liddle et al., 1956; Tucci et al., 1967; Newton & Laragh, 1968) is only transient and occurs only in response to large unphysiological doses. The latter objection obtains in the acute experiments of Hilton (1960) in which hydrocortisone was released from the isolated perfused adrenal gland of the dog by lysine vasopressin and aldosterone by acetyl arginine vasopressin. In the present studies we have demonstrated in normal man that antidiuretic doses of vasopressin influence neither hydrocortisone nor aldosterone secretion in the absence of changes in body fluid volume.

The studies in which water-retention was permitted during vasopressin administration confirm the observations of Leaf, Bartter, Santos & Wrong (1953) who showed that physiological doses of the hormone produced in normal subjects on unrestricted fluid intakes, prompt water retention with weight gain and serum dilution, followed by a delayed marked increase in sodium and chloride excretion on the second or third day. These changes, like those observed in our own experiments, were prevented by water restriction and led to the conclusion that the increased sodium chloride excretion was a result of water retention and not a direct effect of vasopressin per se. Bartter et al. (1956) expanded normal subjects on low sodium diets with vasopressin and water for several days and observed that the accompanying increase in urinary sodium excretion was associated with a marked fall in aldosterone excretion; it was concluded that the natriuresis was due to the decrease in aldosterone secretion, especially since urinary potassium excretion fell at the same time. In our own studies, however, aldosterone excretion fell only slightly in response to water-retention: when volume expansion was prevented, vasopressin had no consistent effect upon aldosterone secretion. That suppression of mineralocorticoid secretion is not essential for the natriuresis occurring after water-loading has been shown by Jones, Barraclough & Mills (1963), who demonstrated in normal subjects and in patients without functioning adrenal glands that the urinary sodium loss which followed the acute administration of vasopressin and large intravenous loads of 2½% dextrose in water was not prevented by prior administration of large doses of 9α-fluorohydrocortisone, suggesting that in the state of acute volume expansion at least, factors other than aldosterone may be operative in causing sodium rejection. Further evidence suggesting that changes in sodium excretion occurring in response to changes in fluid volume are not related to changes in vasopressin levels was obtained from the study of subject P.J. (Fig. 2) in whom urinary sodium excretion rose with expansion of plasma volume and fell with its contraction, despite the high levels of vasopressin maintained throughout the study.

These studies are also relevant to experiments by Newsome & Bartter (1968) who investigated the relative effects of changes in body fluid volume and serum sodium concentration as stimuli
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for the release of renin. When normal subjects were overhydrated with vasopressin and water, plasma renin activity decreased significantly despite a marked fall in plasma sodium concentration. The possibility that vasopressin had a specific inhibitory effect on renin release, occurring even in the absence of volume expansion, was not investigated by these workers; however, our own studies, which demonstrated no such specific effect of vasopressin on plasma renin activity, exclude this possibility. Furthermore, although Bunag et al. (1967) have demonstrated in dogs that vasopressin, given in larger doses than employed here, inhibits the release of renin normally induced by lowering renal perfusion pressure, the present studies have shown no effect of vasopressin, given in antidiuretic doses, upon renin release in normal man.

The discovery by de Wardener, Mills, Clapham & Hayter (1961) in dogs that the increase in sodium excretion which followed an acute intravenous infusion of saline was largely independent of changes in glomerular filtration rate and mineralocorticoid secretion led to the suggestion that another, as yet unidentified, factor may be involved in the control of sodium excretion. The transmission of the natriuretic response from the saline-infused animal to another by cross-circulation suggested the existence of a humoral agent. The site of production and chemical identity of this postulated factor are therefore of utmost importance, and interest in the former has centred upon the hypothalamus and the pituitary gland. Earlier studies in the dog (Brooks & Pickford, 1958; Chan & Sawyer, 1961) showed that natriuresis could be produced by vasopressin during water diuresis and by oxytocin during water restriction: in the rat, oxytocin caused a marked natriuresis (Chan, 1965). These findings led to the speculation that the two peptides might play a physiological role in the control of sodium excretion. However, the natriuresis during saline loading in dogs occurred in de Wardener's experiments independently of the administration of large doses of exogenous vasopressin. Furthermore, Cort, Hagemann & Lichardus (1965) showed in cats that infusion of vasopressin did not alter the natriuresis occurring after carotid occlusion, a response which these authors believed to be, at least in part, humorally-mediated and independent of changes in steroid secretion. The present experiments in normal man confirm that prolonged administration of vasopressin exerts no significant influence upon sodium excretion, at least under the condition of water restriction. De Wardener, Fabian, Lee, Schrier & Verroust (1968) found no increase in plasma oxytocin levels in dogs undergoing saline infusion: furthermore, a constant infusion of oxytocin had no effect on the associated natriuresis: when the rate of saline infusion was increased, sodium excretion rose despite a fall in plasma oxytocin levels due to dilution of extracellular fluid. Our own studies, in which oxytocin was given for a prolonged period in normal man in a state of moderate hydration, failed to show any significant effect of the hormone upon plasma renin activity, aldosterone excretion rate or sodium balance.

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REFERENCES


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