Renal sodium retention in cirrhosis: relation to aldosterone and nephron site

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Summary

1. In a group of patients with cirrhosis who showed a wide range of values for the rate of renal sodium excretion, the latter was found to be inversely related to both the plasma concentration and rate of renal excretion of aldosterone. However, for a given sodium excretion the values for aldosterone were significantly lower in the patients than for a group of healthy control subjects. These findings suggest either an increased renal tubular sensitivity to aldosterone or the participation of other factors in the pathogenesis of the sodium retention.

2. Based on measurements of the rate of urine flow and the clearances of free water and inulin during a maximal water diuresis, the fractional reabsorption of sodium by the 'proximal', 'diluting segment' and 'distal' segments of the nephron was estimated. For patients retaining sodium the enhanced reabsorption occurred at both proximal and distal sites, the latter being quantitatively more important. There was no significantly enhanced sodium reabsorption in the diluting segment.

Key words: aldosterone, cirrhosis, nephron, sodium.

Introduction

One of the most striking characteristics of patients with severe cirrhosis of the liver is a profound reduction in the rate of renal sodium excretion. In some this can readily be explained because renal blood flow is severely reduced (Baldus, Summerskill, Hunt & Maher, 1964b; Tristani & Cohn, 1967; Epstein, Berk, Hollenberg, Adams, Chalmers, Abrams & Merrill, 1970), but in many others, with an equally reduced capacity to excrete sodium, renal blood flow is normal or even increased (Epstein, Lesser & Berger, 1950; Baldus, Feichter, Summerskill, Hunt & Wakim, 1964a; Klinger, Vaamonde, Vaamonde, Lancestremere, Morosi, Frisch & Papper, 1970; Wilkinson, Smith, Clarke, Arroyo, Richardson, Moodie & Williams, 1977).

Hormonal factors might be particularly important in mediating the sodium retention in the patients without renal impairment and increased values for both the rate of renal excretion and plasma concentrations of aldosterone may occur (Chart & Shipley, 1953; Leutscher & Johnson, 1954; Peterson, 1959; Wolff, Bette, Blaise, Düsterdieck, Jahnecke, Kobayashi, Krück, Lommer & Schieffer, 1966). Although an inverse relationship between the rates of sodium and aldosterone excretion has been described (Wolff, Koczorek & Buchborn, 1958), the relationship between sodium excretion and the plasma aldosterone concentration has not been reported. We have now studied a group of patients with cirrhosis in whom renal function was not markedly impaired. The rate of renal sodium excretion has been related to both the plasma concentration and the rate of renal excretion of aldosterone, the former more accurately reflecting the concentration at the renal tubule, but at one point in time only, whereas the latter gives an integrated estimate over 24 h.
We have also attempted to delineate the major nephron site for the increased sodium reabsorption, utilizing data obtained during a maximal water diuresis, since results from previous studies are discrepant. In one study it was suggested that the enhanced sodium reabsorption occurred proximally (Schedl & Bartter, 1960), whereas results from another point to the diluting segment of the nephron (Chaimovitz, Szylman, Alroy & Better, 1972).

Methods
The 40 patients were selected from 68 consecutive patients with cirrhosis whose renal function had been investigated in detail. The patients included did not have markedly impaired renal function (inulin clearance >60 ml/min; p-aminohippurate clearance >300 ml/min). Cirrhosis had been proven histologically in all cases and was due to alcohol (27 patients), active chronic hepatitis (four), primary biliary cirrhosis (four) and the remaining five were grouped as cryptogenic. Ages ranged from 33 to 68 years. Thirty-four of the 40 patients were male. No patient had received diuretics or other drugs (except vitamin supplements) for at least 2 weeks before the time of study, and those with a history of recent encephalopathy, sepsis or gastrointestinal haemorrhage had also been excluded. Systolic arterial pressure ranged from 110 to 125 mmHg and none had evidence of cardiac or renal disease.

Each patient received a sodium intake of 40–50 mmol/day for 5 days (30 took 10–20 mmol in the diet and 30 mmol as a wax-based slow-release preparation (Slow Sodium, Ciba), and ten received their sodium in the diet alone). Potassium intake varied between 40 and 70 mmol/day. At approximately 09.00 hours on day 5, after an overnight fast, an oral water load of 20 ml/kg body weight was taken over 1 h. This was immediately followed by intravenous loading doses of inulin and p-aminohippurate followed by constant infusions. After allowing 30 min for equilibration, three 30 min urine collections were made by voluntary voiding and plasma was taken for inulin, p-aminohippurate and osmolality determinations at the mid-point of each period. The clearances of inulin (\( C_{\text{inulin}} \)) and p-aminohippurate are expressed as the mean values obtained. The amounts of inulin and p-aminohippurate infused were calculated so as to give expected steady plasma concentrations of 20–30 mg (0.004–0.006 mmol)/100 ml and 2–3 mg (0.009–0.014 mmol)/100 ml respectively, the latter being well below the tubular maximum for p-aminohippurate in cirrhosis (Schroeder, Shear, Sancetta & Gabuzda, 1967). The blood sample for aldosterone estimation was taken immediately before the water load, the patient having been supine for at least 60 min.

Analytical methods
The plasma concentration of aldosterone and the rate of renal excretion for aldosterone 18-glucuronide were determined by radioimmunoassay as previously described, the dichloromethane extraction method for the plasma determinations being used (Jowett & Slater, 1977; Jowett, Smith & Slater, 1975; Jowett, Slater, Piyasena & Ekins, 1973). Normal ranges were determined in healthy laboratory staff under identical conditions of sodium intake and posture. For these subjects the plasma concentration ranged from 136 to 528 pmol/l (mean 294 pmol/l ± SEM 35, \( n = 17 \)). The renal excretion ranged from 30 to 109 nmol/24 h (mean 60 nmol/24 h ± 6, \( n = 18 \)), values very similar to those obtained by others for a similar rate of sodium excretion (Laragh, Sealey & Sommers, 1966).

Inulin and p-aminohippurate were determined colorimetrically (Varley, 1967), sodium by flame photometry and osmolality by depression of the freezing point.

Estimation of segmental sodium reabsorption
Free water clearance (\( C_{\text{water}} \)) was calculated as the difference between urine flow rate (\( V \)) and osmolal clearance (\( C_{\text{osm}} \)) for the period of maximal diuresis. For patients in whom the minimal urine osmolality (\( U_{\text{osm}} \)) was <75 mosmol/kg, the data derived from the clearance studies were used to estimate segmental sodium reabsorption (Alexander, Doner, Auld & Levinsky, 1972). Under the conditions of maximal water diuresis it is assumed that water is not absorbed at or beyond the diluting site (thick segment of the ascending limb of the loop of Henle) and \( V \) is therefore equal to the rate of delivery of fluid to this point. Since sodium reabsorption is isotonic up to that point \( V/C_{\text{inulin}} \) is a measure of the fractional delivery of sodium to the diluting segment. The fractional reabsorption of sodium before this point (referred to hereafter as 'proximal') is therefore given by \( 1 - V/C_{\text{inulin}} \). Sodium reabsorption by the thick segment of the ascending limb of the loop generates free water and so the value for \( C_{\text{water}} \) corrected for delivery, \( C_{\text{water}}/V \), is a measure of fractional diluting segment sodium reabsorption. From these two derived
TABLE 1. Summary of renal, electrolyte and aldosterone data for complete series of patients

A detailed Table (Clinical Science Table no. 78/10) has been deposited with the Librarian, the Royal Society of Medicine, 1 Wimpole Street, London, W1M 8AE, from whom copies are obtainable on request. PAH, p-aminohippurate.

<table>
<thead>
<tr>
<th></th>
<th>Plasma sodium (mmol/l)</th>
<th>Clearance (ml/min)</th>
<th>Maximum urine flow (ml/min)</th>
<th>Minimum urine osmolality (mosmol/kg)</th>
<th>Clearance (ml/min)</th>
<th>Calc. segmental sodium reabsorption (%)</th>
<th>Renal sodium excretion</th>
<th>Aldosterone</th>
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<td></td>
<td>Inulin</td>
<td>PAH</td>
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<td>Osmolal</td>
<td>Free water</td>
<td>Proximal</td>
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<td>10-0</td>
<td>72</td>
<td>2-2</td>
<td>89.7</td>
<td>80-5</td>
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<tr>
<td>SEM</td>
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<td>8</td>
<td>37</td>
<td>0.7</td>
<td>7</td>
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* Determined in healthy subjects receiving sodium intake 40–50 mmol/day (n = 8–18).
values and the filtered sodium load \((C_{\text{inulin}} \times \text{plasma sodium concentration})\), the absolute sodium delivery to the part of the nephron beyond the diluting segment ('distal') can be calculated. The fractional distal sodium reabsorption was calculated from the latter value and the simultaneously determined rate of renal sodium excretion.

**Statistical methods**

Group comparisons were made by using an unpaired t-test, and correlation coefficients with standard methods. Sodium excretion–aldosterone relationships were expressed logarithmically (Rosei, Brown, Cumming, Fraser, Semple, Lever, Morton, Robertson, Robertson & Tree, 1978). Values are given as mean ± SEM, unless otherwise stated.

**Results** (Table 1)

Despite a similar sodium intake in all patients (40–50 mmol/24 h) the rate of renal sodium excretion on the day of investigation showed a wide range from 1 to 84 mmol. Eighteen of the patients were in positive sodium balance with weight gain and increasing ascites during the 5 days of controlled intake and had a renal sodium excretion of between 1 and 38 mmol/24 h (mean 9). Of the other 22 patients, three were in negative balance with weight loss and were spontaneously losing ascites (renal sodium excretion 66–84 mmol/24 h, mean 74). The remaining 19, of whom four had ascites, were in sodium equilibrium with constant body weight and a renal sodium excretion on the day of investigations of 27–60 mmol (mean 44).

During the 30 min period of maximal water diuresis the rate of renal sodium excretion ranged from 2 to 196 μmol/min and this measurement showed a good correlation with the rate of sodium excretion over the whole 24 h \((r = +0.722, P < 0.001)\).

A wide range of values was also found for the other measurements made, namely inulin clearance 63–254 ml/min, \(p\)-aminohippurate clearance 312–1533 ml/min, plasma sodium concentration 122–142 mmol/l, filtered sodium load \(10^3 \times 8.9–10^3 \times 34.0 \mu\text{mol/min, maximal urine flow 1.7–21.3 ml/min, minimum urine osmolality 40–289 mosmol/kg, osmolal clearance 0.9–3.7 ml/min and free water clearance −0.2–17.6 ml/min. The rate of renal sodium excretion was unrelated to the filtered sodium load \((r = −0.154, P \text{ N.S.}),\) inulin

![Graph](image_url)

**Fig. 1.** Relationship of the rate of renal sodium excretion to the supine plasma aldosterone concentration. ●, Patients without ascites; ○, patients with ascites. \(r = −0.794; P < 0.001\).
clearance ($r = +0.088$, $P$ N.S.), or $p$-aminohippurate clearance ($r = +0.089$, $P$ N.S.).

**Relationship between the rate of renal sodium excretion and the plasma aldosterone concentration**

The plasma aldosterone concentration was below the normal range of 136–528 pmol/l in 15 patients, normal in 11, and raised up to 15 401 pmol/l in 11.

The rate of renal sodium excretion during the clearance study was inversely related to the plasma aldosterone concentration ($r = -0.794$, $P < 0.001$; Fig. 1). However, for a given rate of sodium excretion the plasma aldosterone concentration in the patients appeared to be lower than found in the control subjects, and normal values for aldosterone were found in five patients who were actually in positive sodium balance. In order to further define the relationship between the plasma aldosterone concentration and the sodium reabsorption in the distal part of the nephron, the site at which aldosterone has its greatest effect, the aldosterone values from the patients were compared with values from control subjects in whom both the calculated delivery of sodium to the distal nephron and the rate of renal sodium excretion were similar. In eight control subjects the ranges for these values were 300–464 μmol/min and 60–125 μmol/min respectively. Nine of the patients had both values within these ranges and their mean plasma aldosterone concentration was significantly lower than in the comparable control group (104 pmol/l ± 24, 296 pmol/l ± 44 respectively; $P < 0.005$).

**Relationship between the 24 h renal excretions of sodium and aldosterone**

In 12 patients the rate of renal excretion of aldosterone was below the normal range of 30–109 nmol/24 h, normal in 18 and raised up to 1377 nmol/24 h in eight. Nine of the patients in positive sodium balance had normal values. Overall, sodium excretion was inversely related to the aldosterone excretion ($r = -0.857$, $P < 0.001$; Fig. 2). Comparing the aldosterone excretion rates in control subjects and patients who had an identical range of sodium excretion (30–65 nmol/24 h), the values for the patients were significantly lower (33 nmol/24 h ± 4, 60 nmol/24 h ± 6 respectively, $P < 0.005$).

**Inferred site of enhanced sodium reabsorption in the nephron**

Twenty-eight patients were able to dilute their urine to a minimum $U_{\text{osm}}$ of <75 mosmol/kg, thus enabling an assessment of segmental sodium reabsorption. The ranges of values were: proximal sodium reabsorption 80.1–96.3%, diluting segment 73.0–85.4% and distal 54.2–98.0%. The relative roles of the different nephron segments in the pathogenesis of the abnormal sodium retention is illustrated by comparing the mean values of fractional reabsorption between the patients who were

**Fig. 2.** Relationship of the rate of renal sodium excretion to the rate of renal excretion of aldosterone 18-glucuronide in patients without ascites (●) and patients with ascites (○). $r = -0.857$; $P < 0.001$. 
in sodium equilibrium with those in positive sodium balance (Fig. 3). For these two groups respectively the values were: proximal 88.3 ± 1.2% and 92.1 ± 0.7%, P < 0.0125; diluting segment 80.0 ± 0.7% and 81.9 ± 1.0%, P N.S.; distal 71.3 ± 2.4% and 90.7 ± 2.1%, P < 0.001. The difference between these two groups for the distal part of the nephron was significantly greater than for the proximal part (P < 0.001).

**Effect of spironolactone**

Thirteen of the 16 patients in positive sodium balance were later given spironolactone alone as diuretic treatment. Doses of 50–600 mg/day were used and all 16 patients went into negative sodium balance and eventually lost their ascites.

**Discussion**

The range of values for the different renal function variables, including the very high clearances of inulin and p-aminohippurate in some patients, is similar to those reported by others (Epstein et al., 1950; Papper & Saxon, 1959; Baldus et al., 1964a; Shear, Hall & Gabuzda, 1965; Klinger et al., 1970). The lack of relationship of the rate of renal sodium excretion to the filtered sodium load, or to the clearances of inulin or p-aminohippurate, would be consistent with the participation of a hormonal factor in the regulation of sodium excretion in these patients. The statistically significant inverse correlations between the rate of sodium excretion and both measurements of aldosterone suggest an important role for the latter. In fact the correlation coefficient relating sodium excretion and plasma aldosterone concentration (r = −0.794) is almost identical with that found by Rosei et al. (1978) in normal subjects. Other evidence suggesting a major role for aldosterone includes: (a) the effect of spironolactone in reversing the sodium retention in both the present study and as reported by others (Eggert, 1970; Vesin, 1975); (b) the effect of adrenalectomy in reversing the sodium retention provided that large amounts of corticosteroids are not given as replacement therapy (Marson, 1954; Giuseffi, Werk, Larson, Schiff & Elliott, 1957; Henley, Streeten & Pollard, 1960); (c) in an investigation into the effect of β-adrenoreceptor blockade in cirrhosis the sodium excretion changed exactly as would have been predicted by the changes in aldosterone (Wilkinson, Bernardi, Smith, Jowett, Slater & Williams, 1977). However, the normal values for aldosterone in some of the patients actively retaining sodium immediately suggests the participation of other factors. Two other studies have also shown that the plasma aldosterone concentration is not necessarily elevated in patients accumulating ascites (Epstein, Levinson, Sancho, Haber & Re, 1977; Wernze, Speech & Müller, 1978), and a dissociation between the changes in the plasma aldosterone concentration and rate of sodium excretion after oral sodium loading (Chonko, Bay, Stein & Ferris, 1977) is also in keeping with a role for other factors.

The reduced values for aldosterone in the patients in sodium equilibrium must also be explained. If the non-aldosterone factors determining sodium excretion were dominant the retained sodium would suppress aldosterone secretion. However, in view of the evidence cited above for the importance of aldosterone this seems unlikely. An alternative explanation is that there might be an increased renal tubular sensitivity to the effects of aldosterone in cirrhosis. Davis, Holman, Carpenter, Urquart & Higgins (1964) found that very small amounts of aldosterone caused sodium retention in adrenalectomized dogs with constriction of the thoracic segment of the
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inferior vena cava, a model with many similarities to human cirrhosis with ascites, and proposed an increased renal tubular sensitivity. Altered sensitivity to aldosterone has been described in other states, including starvation in the obese (Kolanowski, Desmecht & Crabbe, 1976) and in the presence of excesses of other adrenocortical hormones (Uete & Venning, 1960). The reactivity of the kidney may also change according to previous sodium balance, e.g. prior sodium depletion may result in a greater degree of collecting duct sodium reabsorption after an infusion of Ringer’s solution (Stein & Reineck, 1975); since the kidney retaining sodium in cirrhosis ‘behaves’ as though the patient were sodium depleted, a related mechanism is possible. An increased renal tubular ‘sensitivity’ could conceivably be due to the reduced plasma albumin concentration characteristic of cirrhosis. Aldosterone is about 50% albumin bound (Baxter, Schambelan, Matulich, Spindler, Taylor & Barter, 1976) and so, for a given total plasma aldosterone concentration (which is what the immunoassay measures), the amount of free or biologically active hormone may be increased in the patient with cirrhosis and hypoaalbuminaemia, but considering the high affinity of receptors for aldosterone (Fanestil & Edelman, 1968; Vyzantiades, Ekins & Slater, 1970) this seems unlikely.

Two recent studies have questioned the importance of aldosterone in cirrhosis. Rosoff, Zia, Reynolds & Horton (1975) administered amino-glutethamide, a drug which interferes with steroid synthesis, to three patients with avid sodium retention. Although previously elevated plasma concentrations of aldosterone fell markedly, there was no increase in sodium excretion. However, these patients were reported to have ‘long-standing diuretic-resistant ascites’ and, in our experience and that of others (Baldus et al., 1964a; Arroyo & Rodes, 1975), such patients invariably have a reduced level of renal perfusion, which would be expected to be associated with sodium retention independently of the action of aldosterone (Thompson & Pitts, 1952). Epstein, Pins, Schneider & Levinson (1976) suggested that aldosterone was unlikely to be of major importance in the pathogenesis of the sodium retention since spironolactone caused only a ‘modest’ rise in sodium excretion, yet they reported an increase from a mean value of 2.2 to 25.9 µmol/min, associated with a weight loss of 5.7 kg. They also found that isothermic water immersion to the thoracic region and is therefore similar to the effect of acutely administering a saline load, increased sodium excretion whether mineralocorticoid activity was blocked with spironolactone or enhanced with DOCA. They also considered this to be evidence against an important role for aldosterone in mediating sodium retention. Although this study demonstrates that the natriuresis of acute volume expansion is independent of suppression of aldosterone, a fact established by others (De Wardener, Mills, Clapham & Hayter, 1961; Levinsky & Lalone, 1963), their conclusion is based on the presumption that the mechanism for natriuresis to an acute volume load is closely related to the mechanism for chronic sodium retention in cirrhosis.

The validity of measurements made during a water diuresis to infer the extent of sodium reabsorption in the different parts of the nephron has been investigated, and extensively discussed by others (Eknoyan, Suki, Rector & Seldin, 1967; Alexander et al., 1972; Levinsky & Levy, 1973; Danovitch & Bricker, 1976). Although it is unlikely that the values obtained are quantitatively exact, they appear to be qualitatively valid, especially if restricted, as in the present study, to instances in which the urine osmolality has fallen to <75 mosmol/kg. Thus the present results suggest, within the limitations of the method, that the enhanced sodium reabsorption in cirrhosis occurs at both proximal and distal sites, with the latter being quantitatively more important, which is also in keeping with a major role for aldosterone in promoting the sodium retention. Results of treatment with other ‘distal’ diuretics also suggest an increased distal sodium reabsorption in that both amiloride and triamterene have been shown to reverse the sodium retention (Vesin, Roberti & Viguie, 1969; Sanchez-Tapias, 1973). Whether the increased ‘distal’ reabsorption occurs in the distal convoluted tubule or collecting duct cannot be defined, but many studies in laboratory animals now implicate the collecting duct as the most important nephron site for the regulation of sodium excretion in a variety of physiological states (Stein & Reineck, 1975).

Schedl & Barter (1960) concluded that the enhanced sodium reabsorption occurred proximally, since it was found that a reduced free water clearance could be corrected by mannitol infusion, a procedure that inhibits proximal sodium reabsorption, but sodium reabsorption at more distal sites was not evaluated. Chaimovitz et al. (1972) found that free water clearance, corrected for
sodium delivery to the diluting segment, was higher for four cirrhotic patients retaining sodium, suggesting enhanced reabsorption by the diluting segment. This is in contrast to our findings, but may be due to different conditions of study since Chaimovitz et al. investigated their patients during volume expansion with hypotonic saline.

It is to be stressed that segmental sodium reabsorption could not be evaluated in 12 of the 40 patients in the present study because of failure to dilute the urine sufficiently. Whether this was due to a more enhanced proximal sodium reabsorption, so limiting the amount delivered to the diluting segment for the generation of free water, or to other mechanisms, such as 'inappropriate antidiuretic hormone', is uncertain.

It is also to be emphasized that the present patients are a selected group in that such patients has not been investigated but when renal blood flow is markedly reduced it is unlikely that aldosterone is of major pathogenic importance (Thompson & Pitts, 1952).

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References


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