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Direct effect of lithium on active and inactive renin secretion

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Rabbit kidney cortex slices were used to investigate the effect of lithium chloride (0 to 20 mM) on renin release. Secretion of active renin was increased in the presence of lithium but inactive (acid-activatable) renin secretion was unchanged. Increased plasma renin activity in patients receiving lithium therapy may be the result of direct effects of lithium on renin secretion mechanisms rather than being secondary to altered renal sodium handling.

Introduction Patients receiving lithium therapy for psychiatric disorders initially have an elevated plasma renin activity (PRA) (Demers, Hendler, Allen & Boyd, 1972; Shopsin, Sathananthan & Gershon, 1973; Altamura & Morganti, 1975). Acute elevation of PRA has also been demonstrated in rats (Gutman, Benzakein & Liveh, 1971) and dogs (Nally, Rutecki & Ferris, 1980) following infusion of lithium chloride. It is not clear whether lithium ions act directly on the juxtaglomerular cells or if the altered renin release is secondary to concurrent changes in renal function (Myers, Morgan, Carney & Ray, 1980). In addition, previous studies have only considered the active form of renin. The kidney also secretes an inactive, but activatable, renin and certain stimuli have differential effects on active and inactive renin release. We have therefore investigated release of both forms of renin *in vitro* using a kidney cortex slice preparation.

Methods Cortex slices were prepared from the kidneys of New Zealand White rabbits and incubated for 90 min in modified Krebs-Ringer bicarbonate buffer (pH 7.4). Renin release into the incubation buffer was investigated. Inactive renin was measured after activation during dialysis to pH 2.8. Active and activated renins were determined by radioimmunoassay of angiotensin I formed during incubation with excess sheep renin substrate at 37°C. Experimental details and the evaluation of all these methods has been published elsewhere (Munday, Noble & Richards, 1982).

Pairs of slices were incubated in each of a series of Krebs buffers in which lithium chloride replaced part of the sodium chloride, up to a maximum [Li^+] of 20 mM. In order to confirm that the results obtained did not merely reflect the effect of a decrease in [Na^+], a further pair of slices from each kidney was incubated in buffer in which 20 mM choline was substituted for an equivalent part of the sodium chloride. Osmolarity of all solutions remained between 245 and 260 mosmol/l.

The Wilcoxon signed-rank test was used to analyse results for renin estimation. For each experiment, the percentage of total renin release which was in the inactive form was calculated and a paired Student's *t* test used to analyse these data.

Results The means ± s.e.mean from 8 experiments investigating renin release by kidney cortex slices during a 90 min incubation are shown in Table 1.

Lithium chloride, in the concentration range 0 to 20 mM, caused a dose-related increase in the secretion of active renin and, at the highest concentration, an increase of 113% was recorded ($P < 0.01$). No significant changes in inactive renin were found. As a consequence inactive renin, which formed 24.8 ± 8.9% of total renin released under control conditions, only formed 11.3 ± 3.9% of total renin in the presence of 20 mM lithium chloride. These changes could not be attributed to the effect of reducing incubation buffer [Na^+]. Replacing an equivalent amount of sodium in the buffer by 20 mM choline chloride did not alter the secretion of either form of renin. Active renin release was 7.6 ± 1.6 ng Ang I. mg tissue^{-1} h^{-1} compared to a control of 6.8 ± 1.7 ng Ang I. mg tissue^{-1} h^{-1} and inactive renin released in the presence of 20 mM choline chloride was 2.2 ± 0.2 ng Ang I. mg tissue^{-1} h^{-1} compared to control figures of 2.0 ± 0.3 ng Ang I. mg tissue^{-1} h^{-1}.

It is concluded that lithium ions act directly on the juxtaglomerular cells to increase the release of active renin. Inactive renin secretion appears to be unaffected by the presence of lithium ions.

Discussion Lithium therapy is accompanied by complex changes in renal function which have been

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Table 1 Effect of lithium chloride on the release of active and inactive renin by rabbit kidney cortex slices

[*LiCl*] (mM)	0	1	5	10	20
Total renin†	8.7±1.6	11.1±1.8	10.9±2.2	13.3±2.4*	17.8±2.9**
Active renin†	6.8±1.7	8.4±1.5	8.9±2.1	10.5±2.2*	13.9±3.5**
Inactive renin†	2.0±0.3	2.6±0.5	2.2±0.3	2.8±0.4	3.1±1.2
Inactive renin as % total renin	24.8±8.9	22.3±6.1	14.4±4.4	15.6±3.9	11.1±3.9*

Results are shown as mean ± s.e.mean of data from 8 experiments.
†units: ng Angiotensin I generated. mg wet weight tissue^{-1} h^{-1}.
*$P<0.05$; **$P<0.01$ for paired comparison with controls.

reviewed by Myers *et al.* (1980). Changes include polyuria and, initially at least, natriuresis. Micropuncture studies provide a possible mechanism for this since lithium ions inhibit sodium reabsorption in the proximal tubule of the nephron (Hecht, Kashgarian, Forrest & Hayslett, 1978). In their review of the literature on renin release, Keeton & Campbell (1980) concluded that lithium-induced alterations in proximal tubule sodium handling also provided the trigger to increase renin secretion. Data reported here do not support this concept. Lithium ions stimulate the release of active renin by rabbit kidney cortex slices and this effect is clearly not secondary to altered renal function. Furthermore, our previous studies with rabbit kidney cortex slices (Munday *et al.*, 1982) have shown that this preparation responds to a decrease in [Na^+] with increased release of active renin. Inhibition of proximal tubular sodium reabsorption by lithium ions would lead to increased [Na^+] at the macula densa, the site at the start of the distal tubule which is presumed to act as a sodium load or concentration detector in the control of renin release.

Inactive renin release was not significantly changed by the presence of lithium ions despite the increase in active renin secretion. This is in contrast to the effect of changes in [Na^+]. Reducing [Na^+] bathing rabbit kidney cortex slices inhibited the secretion of inactive renin whilst increasing secretion of the active form (Munday *et al.*, 1982).

We conclude that lithium ions act directly on the kidney to increase active renin release. The study also provides further evidence that situations which have previously been reported to modify renin secretion do not necessarily have a parallel effect on the release of active and inactive renins.

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