EFFECT OF LITHIUM AND ANTIDIURETIC HORMONE
ON PLASMA RENIN CONCENTRATION IN DIABETES
INSIPIDUS RATS (BRATTLEBORO RAT MODEL)

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Antidiuretic hormone (ADH) is known to inhibit renin secretion in many
species, but the mechanism of this inhibition and its importance in the control
of renin secretion are unknown. Measurements of plasma renin concentration
(PRC) and plasma renin activity (PRA) in the diabetes insipidus (DI) rat
suggest that physiological levels of ADH may exert a tonic inhibitory effect on
renin release. PRC and PRA are increased in the DI rat and reduced follow­
ing treatment with ADH. Nevertheless it is unclear to what extent these
alterations in renin are due to the presence or absence of ADH per se. In the
absence of ADH, plasma volume, blood pressure, and glomerular filtration
rate are reduced, all of which might stimulate renin secretion. Conversely,
ADH might reduce plasma renin levels in the DI rat indirectly, secondary to
its effects on water balance, as well as by a direct effect on renin secretion.
To differentiate between direct and indirect effects of ADH on renin secretion,
plasma renin concentration was measured in DI rats, before and during ADH
administration, with or without LiCl treatment. Using different doses of ADH,
combined with LiCl treatment, it was possible to raise the titer of antidiuretic
hormone in the plasma of the DI rat while blocking to a varying extent the
action of ADH on tubular water reabsorption. The effect of ADH on PRC
of LiCl-treated and control (NaCl-treated) DI rats was compared.

All rats were maintained in individual metabolism cages for the entire study.
As shown in Table 1, the protocol consisted of pretreatment with 0.1 ml/100 g
BW/day of isotonic saline (N=37) or LiCl (3.0 mEq/kg BW/day) (N=38),
i.p., for 11 days, followed by two weeks of balance study and bleeding for
determination of PRC. Forty-three rats (half LiCl-, half NaCl-treated) were
then injected with 10 mU (N=12), 25 mU (N=11), or 200 mU (N=20)
of ADH (Parke-Davis, Pitressin tannate in oil) per 100 g BW per day, or an
equal volume of sesame oil (N=22), s.c., for one week, followed by two
weeks of balance study and bleeding. Once begun, LiCl, NaCl, ADH, and
oil injections were continued throughout the study. Ten rats received neither
ADH nor oil but only LiCl (N=5) or NaCl (N=5) injections. Blood
samples were obtained by tailcutting in the conscious rat. PRC was determined
by radioimmunoassay (New England Nuclear) of the amount of angiotensin I
generated in the presence of excess substrate. Balance studies consisted of
daily measurement of body weight, water intake, urine volume, osmolality, and
sodium and potassium concentrations. The effects of an intermediate dose of
ADH (20 mU/100 g BW/day) on hematocrit, plasma osmolality, plasma
protein, and sodium and potassium concentrations were also determined in
10 LiCl-treated and 10 NaCl-treated DI rats. Sodium and potassium concentra-
## Table 1

**Protocol for the Study of the Effects of ADH Treatment on Plasma Renin Concentration in LiCl-Treated and Control (NaCl-Treated) DI Rats**

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>1-11</th>
<th>12-18</th>
<th>19-25</th>
<th>26-32</th>
<th>33-39</th>
<th>40-44</th>
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<tbody>
<tr>
<td>Procedures</td>
<td>1. NaCl or LiCl injections</td>
<td>1. NaCl or LiCl injections</td>
<td>1. NaCl or LiCl injections</td>
<td>1. NaCl or LiCl injections</td>
<td>1. NaCl or LiCl injections</td>
<td>1. NaCl or LiCl injections</td>
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<tr>
<td></td>
<td>2. 2-Day balance study (Days 13-15)</td>
<td>2. 2-Day balance study (Days 20-22)</td>
<td>2. ADH or oil injections</td>
<td>2. ADH or oil injections</td>
<td>2. ADH or oil injections</td>
<td>2. ADH or oil injections</td>
</tr>
<tr>
<td></td>
<td>3. Renin (Day 16)</td>
<td>3. Renin (Day 23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 2-Day balance study (Days 13-15)
- 2-Day balance study (Days 20-22)
- 2-Day balance study (Days 34-36)
- 2-Day balance study (Days 41-43)
- Renin (Day 37)
- Renin (Day 44)
tions in urine and plasma were determined by flame photometry; osmolality by freezing-point depression.

The effect of ADH on urine osmolality was greater during the second week of study and only these results have been included in Figures 1 and 2. As shown in Figure 1, ADH had widely differing effects on urine osmolality of LiCl- and NaCl-treated rats. At doses of 10 and 25 mU/100 g BW/day, LiCl-treated rats continued to excrete hypotonic urine while the urine of NaCl-treated rats was hypertonic. At the highest dose of ADH both groups were able to concentrate their urine, although to differing degrees. Despite these disparate effects on water excretion, ADH affected PRC similarly in both groups. As shown in Figure 2, at any dose of ADH, there was no difference in the PRC of LiCl- and NaCl-treated DI rats. These data also suggest that a dose-response relationship may have existed between ADH and renin secretion with maximal effects obtained at 25 mU/100 g BW/day. There was no difference in the effect of this dose and the 200 mU dose on PRC. Although the 10 mU dose of ADH

![Figure 1](image_url)

**Figure 1.** Effect of different doses of ADH or oil (ADH = 0) on urine osmolality (U$_{osm}$) of LiCl-treated and NaCl-treated DI rats. *Significantly different from values prior to ADH or oil treatment, p < 0.05. + Significantly different from NaCl-treated rats, p < 0.05. Values are means ± SEM.
FIGURE 2. Effect of different doses of ADH or oil (ADH = 0) on plasma renin concentration of LiCl-treated and NaCl-treated DI rats. *Significantly different from values prior to ADH or oil treatment, p < 0.05. Values are means ± SEM.

did not alter PRC, oil injections alone (ADH = 0, FIGURE 2) increased PRC, as did multiple bleedings of LiCl- and NaCl-treated rats with neither ADH nor oil injections superimposed. These results suggest that the lowest dose of ADH may have prevented such a rise in PRC.

As shown in FIGURE 3, when all data were pooled, there was no significant correlation between plasma renin concentration and urine osmolality. Moreover, there was no difference in PRC when the urine was hypertonic (78 ± 4 ng AI/ml/h, N = 65) or hypotonic (82 ± 5, N = 84).

As shown in TABLE 2, ADH treatment significantly affected only plasma osmolality, which was decreased by ADH in control (NaCl) rats, but increased in LiCl-treated rats, probably not as a result of, but despite ADH treatment.

These data indicate that the inhibition of renin secretion in the DI rat during ADH treatment is unrelated to effects of ADH on urine concentration. Thus systemic effects on renin release, secondary to changes in water balance, seem an unlikely explanation for the observed inhibition of renin. Rather a direct action of ADH on the renin-producing cell or baroreceptor is suggested.
Figure 3. Linear regression analysis of the relationship between plasma renin concentration and urine osmolality in LiCl-treated and NaCl-treated DI rats. The solid line is the regression line for values during ADH treatment only; the dotted line is the regression line for all values.
<table>
<thead>
<tr>
<th></th>
<th>HCT (%)</th>
<th>Protein (g %)</th>
<th>P_{Osm} (mOsm/L)</th>
<th>P_{Na} (mM)</th>
<th>P_{K} (mM)</th>
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</thead>
<tbody>
<tr>
<td>LiCl</td>
<td>Control</td>
<td>39 ± 0.6</td>
<td>7.5 ± 0.17</td>
<td>294 ± 4</td>
<td>142 ± 0.7</td>
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<td>ADH</td>
<td>40 ± 0.7</td>
<td>7.4 ± 0.09</td>
<td>305 ± 3 †</td>
<td>143 ± 0.8</td>
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<tr>
<td>NaCl</td>
<td>Control</td>
<td>39 ± 0.9</td>
<td>7.7 ± 0.12</td>
<td>313 ± 2</td>
<td>142 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>ADH</td>
<td>41 ± 0.7</td>
<td>7.8 ± 0.17</td>
<td>308 ± 1 *</td>
<td>142 ± 1.4</td>
</tr>
</tbody>
</table>

Values are means ± SEM.
* Significantly different from control, p < 0.05; † p < 0.001.
REFERENCES