Blunted Pressure Natriuresis in the Brattleboro Diabetes Insipidus Rat


Antidiuretic hormone is known to stimulate the renal synthesis of prostaglandins. These autacoids, in turn, modulate the pressure natriuresis phenomenon. Accordingly, the present study was done to test the hypothesis that, in the absence of antidiuretic hormone and antidiuretic hormone-dependent prostaglandin synthesis, the pressure natriuresis response is blunted. Experiments were performed on Brattleboro diabetes insipidus rats (n=7) and Long Evans control rats (n=14). A change in perfusion pressure in the Long Evans rats from 89.3±1.0 to 108.7±1.1 mm Hg (p<0.05) was associated with significant increases in the fractional excretion of sodium (1.1±0.2 to 2.3±0.3%) and the urinary prostaglandin excretion (32.6±6.8 to 56.6±10.0 pg/min). In contrast, a similar change in perfusion pressure in the diabetes insipidus rat from 88.6±1.4 to 106.2±1.5 mm Hg (p<0.05) resulted in no significant increases in either sodium or prostaglandin excretions. Treatment of a third group of diabetes insipidus rats (n=9) with 1-desamino-8-D-arginine vasopressin (1 μg/day) restored the natriuretic response to increases in renal perfusion pressure. Treated diabetes insipidus and Long Evans control rats had comparable natriuretic responses to increases in renal perfusion pressure. Untreated diabetes insipidus rats, on the other hand, had blunted responses. In summary, the pressure natriuresis response in diabetes insipidus rats is blunted compared with Long Evans control rats. We conclude that antidiuretic hormone is necessary for the complete expression of the pressure natriuresis response. (Hypertension 1989; 13:322–326)

Increases in renal perfusion pressure result in increases in urinary sodium excretion, a phenomenon known as pressure natriuresis. Since pressure natriuresis occurs in the absence of changes in glomerular filtration rate, renal plasma flow, or the filtered sodium load, it is likely to result from a direct inhibition of tubular sodium transport. Pressure natriuresis may be due, at least in part, to the renal prostaglandins. Prostaglandin synthesis inhibition blunts the effect of changes in perfusion pressure on sodium excretion. Brattleboro diabetes insipidus rats lack antidiuretic hormone. These rats also have a decreased prostaglandin synthesizing ability compared with the parent stock, Long Evans rats. Treating diabetes insipidus rats with antidiuretic hormone restores prostaglandin production, which suggests that prostaglandin synthesis is enhanced by antidiuretic hormone. For the above reasons, the diabetes insipidus rat offers a unique model for studying the pressure natriuresis phenomenon in the absence of antidiuretic hormone-dependent prostaglandin synthesis.

Accordingly, the present study was designed to test the hypothesis that the absence of antidiuretic hormone and the resulting decreased prostaglandin synthesis lead to a blunted pressure natriuresis in the diabetes insipidus rat.

Materials and Methods

Experiments were performed on male homozygous Brattleboro diabetes insipidus (n=7) and Long Evans (n=14) rats (200–320 g body weight, Blue Spruce Farms, Inc., Altamont, New York). All rats were fed normal Purina chow that contained 0.1 meq sodium/g of chow. All rats had free access to water.

A third group consisting of diabetes insipidus rats (n=9) was treated with 1-desamino-8-D-arginine vasopressin (dDAVP) (USB Laboratories, Tarrytown, New York) at 1 μg/day. Treated diabetes insipidus rats were compared with Long Evans control rats. We conclude that antidiuretic hormone is necessary for the complete expression of the pressure natriuresis response.
Two weeks before the experiment, osmotic minipumps were implanted intraperitoneally under pentobarbital anesthesia. The minipumps delivered doAVP at a rate of 1 μg/day.

On the day of the experiment, the rats were anesthetized with Inactin (Byk-Gulden, Konstanz, FRG) (100 mg/kg body wt i.p.) and placed on a heated table to maintain the body temperature at 36–38° C. A tracheostomy was performed, and all rats were allowed to breathe spontaneously. Catheters were placed into a jugular vein for infusions and a carotid artery for blood pressure monitoring and blood sampling. All rats were infused with a solution that contained 5% inulin and 6.25% albumin in isotonic saline at a rate of 1 ml/hr for the duration of the experiment. The dome of the bladder was catheterized for urine collection. An inflatable silastic cuff was placed around the aorta cephalad to the renal arteries. Inflation of the cuff resulted in a decrease in renal perfusion pressure. The cuff was connected to an electric servo-controlling system that allowed for precise control of the perfusion pressure. A catheter tip was placed in the aorta caudal to the renal arteries through a common iliac artery and served to confirm changes in renal perfusion pressure.

A 3% body weight volume expansion with isoncotic albumin was given over an hour to replace surgical losses of fluid. Subsequently, diabetes insipidus rats were infused with a solution of 10 mM sodium chloride in 1.4% glucose, and Long Evans and treated diabetes insipidus rats were infused with isotonic saline at rates adjusted to equal the urine flow (approximately 6 ml/hr and 1.5 ml/hr, respectively). A 120-150-minute equilibration period was allowed.

After the equilibration period, a 30-minute clearance period was begun. A 0.5 ml blood sample was taken at the midpoint of the clearance period. Plasma was removed, the packed cells were resuspended in isotonic saline and infused into the rat. Renal perfusion pressure was then reduced approximately 20 mm Hg by inflation of the aortic cuff. A 20-minute equilibration period at the new perfusion pressure was allowed; and then another 30-minute clearance period was started. In half of the animals in each group the order was reversed. A clearance period was begun at a low renal perfusion pressure and again after the perfusion pressure was allowed to return to normal. Since the initial mean arterial pressure in Long Evans rats (126±3 mm Hg) was higher than in diabetes insipidus (114±2 mm Hg) and treated diabetes insipidus rats (115±3 mm Hg), renal perfusion pressure was first reduced to a comparable level.

**Analyses**

Inulin concentrations in plasma and urine were determined by the anthrone method. Sodium concentrations in urine and plasma were measured with a Beckman E2A electrolyte analyzer (Beckman Instr., Inc., Fullerton, California). Plasma and urine osmolalities were determined with a vapor pressure osmometer (model 5100, Wescor Inc., Logan, Utah).

**Results**

The data are summarized in Figure 1 and Table 1. A change in perfusion pressure in the Long Evans rat from 89.3±1 to 108.7±1 mm Hg (p<0.05) is associated with significant increases in urinary flow rate (34.4±5.8 to 61.0±8.5 μl/min), urinary sodium excretion (3.6±0.7 to 8.2±1.2 μeq/min), fractional excretion of sodium (1.1±0.2 to 2.3±0.3%), and urinary prostaglandin excretion (32.6±6.8 to 56.6±10.0 pg/
The urinary prostaglandin levels. It is also possible, as has been previously suggested, that the excreted prostaglandins represent a variable fraction of the total prostaglandin synthesis. Therefore, the urinary prostaglandin data are expressed as a percent of control, control being the urinary prostaglandin excretion at the lower perfusion pressure. Both the Long Evans control rats and the treated diabetes insipidus rats showed a large increase in prostaglandin excretion with increases in perfusion pressure. Untreated diabetes insipidus rats, on the other hand, showed only a slight increase in urinary prostaglandin excretion when the renal perfusion pressure was increased. These data are summarized in Figure 2.

**Discussion**

The present study demonstrates that the pressure natriuresis phenomenon is blunted in the Brattleboro diabetes insipidus rat. Since the natriuretic response to increases in perfusion pressure is

All values are expressed as mean±SEM. LE, Long Evans rats; DI, diabetes insipidus rats; RPP, renal perfusion pressure; UOsm, urine osmolality; UV, urinary flow rate; GFR, glomerular filtration rate; FENo, fractional excretion of sodium; UoV, urinary sodium excretion; UPGE2, urinary prostaglandin E2 concentration; UPGE2V, urinary prostaglandin E2 excretion.

*p<0.05 vs. lower perfusion pressure value.

†p<0.05 vs. Long Evans control value at similar perfusion pressure.

**Table 1. Kidney Function at Low and High Renal Perfusion Pressures**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LE control rats (n=14)</th>
<th>DI rats (n=7)</th>
<th>Treated DI rats (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPP (mm Hg)</td>
<td>89.29±1.03</td>
<td>108.71±1.08*</td>
<td>106.24±1.47*</td>
</tr>
<tr>
<td>UOsm (mosm/l)</td>
<td>708.99±65.12</td>
<td>625.21±65.11*</td>
<td>712.14±34.20</td>
</tr>
<tr>
<td>UV (ol/min)</td>
<td>34.42±5.80</td>
<td>60.99±8.50*</td>
<td>104.77±6.87</td>
</tr>
<tr>
<td>GFR (ml/min/100 g body wt)</td>
<td>0.83±0.05</td>
<td>0.85±0.04</td>
<td>0.76±0.08</td>
</tr>
<tr>
<td>FENo (%)</td>
<td>1.09±0.23</td>
<td>2.32±0.34*</td>
<td>1.32±0.30</td>
</tr>
<tr>
<td>UoV (ol/min)</td>
<td>3.63±0.74</td>
<td>8.15±1.21*</td>
<td>3.41±0.90</td>
</tr>
<tr>
<td>UPGE2 (pg/ml)</td>
<td>841.2±139.1</td>
<td>1464.8±597.2*</td>
<td>525.6±124.0t</td>
</tr>
<tr>
<td>UPGE2V (pg/min)</td>
<td>32.57±6.81</td>
<td>56.64±9.96*</td>
<td>48.25±17.75</td>
</tr>
<tr>
<td>UOsm, (%)</td>
<td>197.40±43.35</td>
<td>104.39±11.331</td>
<td>165.94±18.71</td>
</tr>
</tbody>
</table>

In contrast, a similar change in perfusion pressure in the Brattleboro diabetes insipidus rat from 88.6±1.4 to 106.2±1.5 mm Hg (p<0.05) resulted in no significant increases in the urinary flow rate, the fractional and absolute excretions of sodium, and the urinary prostaglandin excretion. The urinary flow rate (92.1±15.6 vs. 34.4±5.8 µl/min) was elevated, and the urine osmolality (201.9±39.2 vs. 709±65.1 mosm/l) and urinary sodium excretion (1.82±0.32 vs. 3.41±0.90) decreased in this group compared with the Long Evans control rats at the lower renal perfusion pressure (Figure 1, Table 1).

Changes in renal perfusion pressure in the Long Evans rats were not associated with significant changes in the glomerular filtration rate, but the natriuresis phenomenon is blunted in the Brattleboro diabetes insipidus rat. Since the natriuretic response to increases in perfusion pressure is...
restored by dDAVP, this study establishes that antidiuretic hormone is necessary for the complete expression of a normal pressure natriuresis in the diabetes insipidus rat.

One mechanism for pressure natriuresis may involve the renal prostaglandins, since blockade of these autacoids leads to a blunted natriuresis in response to increases in renal perfusion pressure. It is known that antidiuretic hormone stimulates prostaglandin synthesis in renal medullary tissue. Brattleboro rats lack antidiuretic hormone, and their renal synthesis of prostaglandin E2 and prostaglandin F2α is known to be decreased. Treatment with antidiuretic hormone or the nonpressor analogue dDAVP restores the synthesis of prostaglandins, a response mostly due to interstitial cells and not tubular elements in the kidney. The present study confirms that treatment with dDAVP increases renal prostaglandin synthesis and suggests that this synthesis is necessary for a normal pressure natriuresis. Thus, the inability of the diabetes insipidus rat to increase prostaglandin synthesis may account for the blunted natriuretic response to increasing perfusion pressure.

It is possible that prostaglandins directly inhibit the tubular reabsorption of sodium, leading to a natriuresis. The proximal tubule may be a site of action of these autacoids. This has been suggested by earlier micropuncture studies that point to the proximal tubule as a site reactive to increases in perfusion pressure. The renal prostaglandins may also affect sodium reabsorption at sites distal to the proximal tubule since previous studies have shown that the medullary collecting duct contributes to the increased sodium reabsorption that follows prostaglandin synthesis inhibition.

Another mechanism whereby pressure natriuresis could be blunted in the diabetes insipidus rat is a medullary washout. Increases in renal perfusion pressure not only cause a natriuresis but also decrease urine osmolality and medullary solute concentrations. Medullary plasma flow in the diabetes insipidus rat is high, and the medullary salt gradient is decreased. Therefore, it is possible that the preexistent medullary washout in these animals prevents further changes in water and sodium reabsorption. As a result, pressure natriuresis becomes blunted. These observations may be attributed to a lack of autoregulation of medullary blood flow in response to changes in renal perfusion pressure. However, previous findings that pressure diuresis is preserved in animals with diabetes insipidus and in water diuresis do not support this hypothesis.

In these conditions a medullary washout would be expected to be already present, and changes in perfusion pressure should cause little or no change in diuresis and natriuresis. Nonetheless, some of the previous studies were incomplete because they did not measure sodium excretion and comparisons with normal rats were not made.

Finally, a blunted pressure natriuresis in the diabetes insipidus rat may be the result of the chronic extracellular fluid volume contraction attributable to the absence of antidiuretic hormone. This chronic change in extracellular volume has been suggested as the cause of increased activity in antinatriuretic systems that have been documented in the diabetes insipidus rat. This possibility is not supported by the more recent observations that water-replete Brattleboro rats are not hypovolemic and that their plasma volumes are not different from Long Evans control rats. Nonetheless, the antinatriuretic activity of angiotensin and the sympathetic nerves may antagonize the natriuretic effect of increases in perfusion pressure in these rats.

In summary, increases in renal perfusion pressure in the Long Evans rat were associated with an increased prostaglandin synthesis and a decreased tubular sodium reabsorption. In contrast, similar increases in renal perfusion pressure were associated with an inability to increase renal prostaglandin synthesis and a diminished natriuretic response in the Brattleboro diabetes insipidus rat. Treatment with dDAVP for 2 weeks restored the ability to increase prostaglandin synthesis and sodium excretion in response to increases in renal perfusion pressure. Therefore, we conclude that antidiuretic hormone is necessary for the complete expression of the pressure natriuresis response.

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References

KEY WORDS • prostaglandins • antidiuretic hormone • kidney • natriuresis • sodium excretion
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