Aldosterone Receptor Blockade Inhibits Increased Furosemide-Sensitive Sodium Reabsorption in Rats with Liver Cirrhosis

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ABSTRACT

We examined the role of chronic aldosterone receptor blockade on the altered furosemide-sensitive sodium reabsorption in rats with liver cirrhosis induced by common bile duct ligation. CBL and sham-operated control animals were treated with the aldosterone receptor antagonist canrenoate (20 mg/day i.v.) for 4 weeks. Untreated CBL and sham-CBL served as control groups. The plasma concentration of aldosterone was within the normal range in all groups. Sodium balance studies showed that aldosterone receptor blockade prevented sodium retention in cirrhotic rats. Clearance studies showed that the glomerular filtration rate was unchanged, whereas the renal plasma flow was increased in CBL rats. A test dose of furosemide (7.5 mg/kg b.wt. i.v.) produced significantly greater diuretic (+56%) and natriuretic (+56%) responses in CBL rats than in sham-operated controls. The urinary furosemide excretion rate \( (U_{\text{FURV}}) \) reflects delivery of furosemide to the thick ascending limb. When the natriuresis was expressed relative to \( U_{\text{FURV}} \) (i.e., the natriuretic efficiency), we found that natriuretic efficiency of furosemide was significantly increased in untreated CBL rats (+59%). However, the natriuretic efficiency of furosemide was normalized in CBL rats treated with canrenoate. The urinary excretion of furosemide was unchanged in untreated CBL rats, but it was significantly increased in cirrhotic rats treated with canrenoate (+43%). This suggests that in CBL rats, chronic canrenoate treatment increases the renal elimination of furosemide as a consequence of reduced metabolism. These data suggest that chronic aldosterone receptor blockade with canrenoate prevents sodium retention in cirrhotic rats partly by inhibition of increased sodium reabsorption in the thick ascending limb.

Liver cirrhosis is a chronic disease with marked progressive changes in systemic and renal hemodynamics. Initially, liver cirrhotic patients have peripheral vasodilation and increased cardiac output but do not have clinical signs of fluid retention (the compensated state). During the late decompensated state, liver cirrhosis is associated with sodium retention, edema and ascites. The renal mechanisms that initiate sodium retention during the early compensated stage of liver cirrhosis are still unknown. Experimental studies have demonstrated that the sodium retention that initiates edema and ascites formation in cirrhosis occurs 1 to 2 weeks before ascites become detectable (Jiménez et al., 1985; Levy and Wexler, 1987). The early sodium retention seems to be mediated by an increased tubular NaCl reabsorption because the GFR is unaltered at this stage of the disease (Levy, 1977; Wood et al., 1988; Wong et al., 1993, 1994). In rats with secondary biliary cirrhosis induced by CBL, we recently reported that rats with sodium retention but without ascites (i.e., compensated liver cirrhosis), had an exaggerated natriuretic response to furosemide and an increased volume of the TAL epithelium in the inner stripe of the outer medulla (Jonassen et al., 1997). These functional and structural changes suggest that increased NaCl reabsorption in the TAL may be involved in the early sodium retention observed during liver cirrhosis.

An increased plasma aldosterone level is considered to be among the most important mechanisms involved in the avid sodium retention in patients with decompensated liver cirrhosis. This provides the rationale for the use of aldosterone receptor antagonists in the management of edema and ascites in decompensated cirrhotic liver disease (Bernardi et al., 1994), and it was recently shown that aldosterone receptor blockade with spironolactone prevents the reformation of ascites become detectable (Jimez et al., 1985; Levy and Wexler, 1987).
ascites after paracentesis in patients with decompensated cirrhosis (Fernandez-Esparrach et al., 1997). However, the plasma aldosterone level is unchanged in the early compensated stage of liver cirrhosis in both rats and humans, which supports the notion that increased plasma aldosterone level does not mediate the early sodium retention that precedes edema and ascites formation.

In addition to the well known stimulatory effect of aldosterone on sodium reabsorption in the collecting duct, studies using in vitro microperfusion of Henle’s loop and in vivo studies on isolated tubules have shown that aldosterone also stimulates sodium transport in rat medullary TAL (Stanton, 1986; Work and Jamison, 1987). However, the physiological and pathophysiological significance of this action of aldosterone in unknown.

Therefore, the aim of this study was to examine the long-term effects of aldosterone receptor blockade on sodium balance, renal hemodynamics and renal tubular sodium handling in normal rats and in rats with sodium retention due to compensated liver cirrhosis. Sham-operated animals and rats with liver cirrhosis induced by CBL were treated with the aldosterone receptor antagonist canrenoate administered as a constant i.v. infusion for 4 weeks. Untreated CBL and sham-CBL served as control groups. Renal hemodynamics and tubular function were assessed in chronically instrumented, conscious animals by clearance technique, and sodium reabsorption in TAL was evaluated from the natriuretic response to a test dose of furosemide.

**Methods**

**Materials.** Barrier-bred and specific pathogen-free female Wistar rats (210–230 g) were obtained from the Department of Experimental Medicine, Panum Institute, University of Copenhagen, Denmark. The animals were housed in a temperature (22–24°C) and moisture (40–70%) controlled room with a 12-hr light-dark cycle (light on from 6:00 A.M. to 6:00 P.M.). All animals were given free access to tap water and pelleted rat diet containing 14% protein (Altromin catalog no. 1314; Altromin International, Lage, Germany) and 6.00 A.M. to 6:00 P.M.). All animals were given free access to tap water after every urine collection. During housing in metabolic cages, the diet was changed to a granulated standard diet (Altromin catalog no. 1310, Altromin International, Lage, Germany) to which was added lithium citrate, 12 mmol of lithium/kg dry diet. This dose of lithium given in the diet produced plasma lithium concentrations in the range of 0.1 to 0.2 mmol/l without influencing renal function (Leyssac et al., 1994). After 2 days of adaptation, daily sodium balance was measured during the last 3 days before the renal function study.

Renal function was examined by clearance techniques 4 to 5 weeks after CBL or sham-CBL. The animal was transferred to a restraining cage, and intravenous infusion (150 mM glucose, 13 mM sodium chloride, 3 mM lithium chloride; 2.5 ml/hr) with [3H]inulin (batch no. 147 and 151; Amersham; Buckinghamshire, UK; specific activity, 43 and 23 GBq/mmol, respectively; infusion rate, 2.5 μCi/hr) and [14C]tetraethylammonium bromide (New England Nuclear, Boston, MA; lot no. 2967-517; specific activity, 0.10 GBq/mmol; infusion rate, 1.5 μCi/hr) was started. After a 90-min equilibration period, urine was collected during two 30-min control periods. Then furosemide (Demex Ltd., Copenhagen, Denmark) at 7.5 mg/kg b.wt. was given as an i.v. bolus injection (37.5 μg furosemide/sec), and urine was collected in four periods of 10 min each. Arterial blood samples of 300 μl each were collected into ammonium-heparinized capillary tubes at the end of the equilibration period, at the end of the control periods and at the end of the experiment. For measurements of the plasma aldosterone concentration, an 800-μl sample was drawn into a prechilled test tube during the equilibration period. The blood sample was centrifuged immediately at 4°C, and plasma was transferred to a prechilled test tube and stored at −20°C until analysis. An additional 0.1-ml arterial blood sample was drawn for analysis of plasma bilirubin and ALAT. All blood samples were replaced immediately with heparinized blood from a normal donor rat.

During the clearance experiment, MAP and HR were measured continuously using Baxter Uniflow pressure transducers (Bentley Laboratories, Uden, Holland) connected to pressure and HR couplers (Hugo Sachs GmbH, Hugstetten, Germany). Signals were displayed on a Watanabe Instruments WR 3101 Linearorder Mark VII (Watanabe Instruments, Tokyo, Japan) and sampled on-line using a data acquisition program written in LabView (National Instruments, Austin, TX) and developed in collaboration with Bie Data (Copenhagen, Denmark). After the clearance experiment, all catheters were sealed, the bladder was flushed with ampicillin (0.6 mg/ml), and the animals were returned to their home cages. To replace furosemide-induced sodium losses, rats were given free access to 1.5% sodium chloride solution in addition to tap water for 24 hours after the renal function study.

**Experimental groups.** The following groups of animals were studied: sham (n = 7), sham-operated control rats without canrenoate treatment; sham-CAN (n = 8): sham-operated rats chronically treated with canrenoate (20 mg/24 hr); CBL (n = 8), CBL control rats without canrenoate treatment; and CBL-CAN (n = 8), CBL rats chronically treated with canrenoate (20 mg/24 hr).

**Analytical procedures.** Urine volume was determined gravimetrically. Concentrations of sodium, potassium and lithium in plasma and urine were determined by atomic absorption spectrophotometry using a Perkin-Elmer (Allered, Denmark) model 2380 atomic absorption spectrophotometer. [3H]Inulin and [14C]tetraethylammonium bromide in plasma and urine were determined by dual-label liquid scintillation counting on a Packard Tri-Carb liquid
scintillation analyser, model 2250CA (Packard Instruments, Greve, Denmark). The concentration of furosemide in urine was determined by a high-pressure liquid chromatographic method (Andreasen et al., 1981). Plasma concentrations of bilirubin and ALAT were measured by reflowmetry using a Reffotron (Boehringer-Mannheim GmbH, Mannheim, Germany). The plasma concentration of aldosterone was measured by radioimmunoassay using a commercial kit (Coat-A-Count Aldosterone; DPC, Los Angeles, CA).

**Calculations.** Renal clearances (C) and fractional excretions (FE) were calculated by the standard formula:

\[
C = \frac{U \cdot V}{P}; \quad FE = \frac{C}{GFR}
\]

Where U is concentration in urine, V is urine flow rate and P is plasma concentration. Inulin clearance was used as a marker for GFR, and tetraethylammonium clearance was used as a marker for the ERPF. As opposed to the renal clearance of p-aminohippurate, renal handling of tetraethylammonium is not affected by infusion of furosemide (Petersen and Christensen, 1987). Tetraethylammonium has ganglionic blocking properties, but when administered in tracer amounts as used in this study, tetraethylammonium does not affect effluent renal sympathetic nerve activity in rats (Petersen and DiBona, 1992a).

The EFF was calculated as \( EFF = GFR/ERPF \). Lithium clearance (\( C_{Li} \)) was used as a marker for the outflow of tubular fluid from the proximal tubules (Thomsen and Shirley, 1997). Thus, \( C_{Li}/GFR \) is an estimate of the fractional delivery of fluid and sodium from the proximal tubules, and \( C_{Na}/C_{Li} \) is an estimate of the fractional excretion of sodium from the distal nephron (i.e., nephron segments beyond the proximal tubules). Micropuncture studies on the effect of furosemide on tubular lithium handling suggest that during control conditions, 2% to 5% of filtered lithium may be reabsorbed in the TAL, and therefore only changes of \( FE_{Li} \) in excess of 2% to 5% can be attributed to changes in proximal tubular sodium reabsorption (Shirley et al., 1992; Frandsen et al., 1993). However, when comparisons are performed between groups in which all animals are treated with furosemide, any difference among groups can be ascribed to changes in proximal tubular sodium reabsorption because there is no evidence for lithium reabsorption beyond the early distal convoluted tubules in sodium replete rats (Petersen and DiBona, 1992b; Shirley et al., 1992; Frandsen et al., 1993). Like most other clearance markers, the validity of the use of lithium clearance as a marker for proximal tubular sodium transport has not been examined in cirrhotic animals, but in animal models with normal plasma levels of vasopressin there is no evidence for increased lithium reabsorption (Shirley et al., 1992; Frandsen et al., 1993).

Furosemide is secreted in the proximal tubules and is delivered to its site of action in the TAL by the tubule fluid. Because furosemide is not reabsorbed in nephron segments further downstream, the \( U_{NaV} / U_{FURV} \) reflects the amount of furosemide delivered to the Na-K-2Cl cotransporter at the luminal site of the TAL (Brater, 1983). Thus, the natriuretic efficiency of furosemide is calculated as:

\[
U_{NaV} / U_{FURV}
\]

This measure is considered the most accurate parameter for comparisons of the natriuretic action of furosemide between different treatment groups.

**Statistics.** Data are presented as mean ± S.E. Within-group comparisons were analyzed with Student’s paired t test. Between-group comparisons were performed by one-way analysis of variance followed by Fisher’s Least Significant Difference test. Differences were considered significant at the .05 level.

**Results**

**Organ weights, sodium balance, diuresis and plasma biochemistry.** Table 1 shows body weight, liver and kidney weights at the end of the study 5 weeks after CBL or sham-CBL. There were no statistical difference between the body weight in the four experimental groups. However, compared with the sham-operated control rats, the average daily weight gain during the 5-week experimental period was significantly increased in the untreated CBL rats. This increased daily weight gain was not observed in canrenoate-treated CBL rats. Despite increased daily weight gain in untreated CBL rats, these animals had no signs of ascites at the time of necropsy.

The liver-to-body weight ratio was about twice as high in CBL than in sham-operated control rats. Livers from CBL animals had a micronodular, yellow surface and a firm consistency. The kidney-to-body weight ratio was significantly increased in CBL rats, and chronic aldosterone receptor blockade did not change the kidney-to-body weight ratio in neither CBL rats nor sham-operated controls.

In cirrhotic rats, plasma concentrations of bilirubin and ALAT were significantly increased, whereas plasma aldosterone levels were within the normal range and similar to plasma levels found in control animals (table 2). Chronic aldosterone receptor blockade did not change the plasma aldosterone concentration neither in cirrhotic or in sham-operated animals. Plasma sodium and potassium levels were similar in all four groups.

Figure 1 shows daily sodium balance during the last 3 days before the renal clearance experiments. All rats were in a positive sodium balance, which is in accordance with the positive weight gain found in all four groups. The daily sodium intake was similar in all four groups suggesting that neither CBL nor chronic canrenoate treatment affected the rats’ appetite. However, daily sodium excretion was significantly decreased in untreated cirrhotic rats, which caused sodium retention relative to control animals. Aldosterone receptor blockade had no effect on sodium balance in sham-operated control rats, but it prevented sodium retention in cirrhotic rats.

### Table 1

**Effect of chronic canrenoate treatment on body, liver and kidney weight 5 weeks after common bile duct ligation (CBL) or sham-CBL (sham)**

<table>
<thead>
<tr>
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<tr>
<td></td>
<td>g</td>
<td>g/day</td>
<td>g</td>
<td>%</td>
<td>g</td>
<td>%</td>
</tr>
<tr>
<td>Sham (n = 7)</td>
<td>246 ± 3</td>
<td>0.45 ± 0.12</td>
<td>10.91 ± 0.44</td>
<td>4.44 ± 0.20</td>
<td>2.26 ± 0.04</td>
<td>0.92 ± 0.01</td>
</tr>
<tr>
<td>Sham-CAN (n = 8)</td>
<td>247 ± 6</td>
<td>0.23 ± 0.13</td>
<td>13.08 ± 0.41</td>
<td>5.32 ± 0.22</td>
<td>2.28 ± 0.06</td>
<td>0.92 ± 0.02</td>
</tr>
<tr>
<td>CBL (n = 8)</td>
<td>260 ± 10</td>
<td>1.02 ± 0.16(^a)</td>
<td>25.54 ± 1.49</td>
<td>9.88 ± 0.61(^a)</td>
<td>2.52 ± 0.19(^a)</td>
<td>1.08 ± 0.06(^a)</td>
</tr>
<tr>
<td>CBL-CAN (n = 8)</td>
<td>243 ± 7</td>
<td>0.49 ± 0.10(^b)</td>
<td>22.11 ± 1.02</td>
<td>9.15 ± 0.47(^b)</td>
<td>2.51 ± 0.09</td>
<td>1.04 ± 0.04(^b)</td>
</tr>
</tbody>
</table>

\(^a\) P < .05 vs. sham.

\(^b\) P < .05 vs. CBL.

Values are mean ± S.E.M.
TABLE 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>P-aldosterone</th>
<th>P-bilirubin</th>
<th>P-ALAT</th>
<th>P-sodium</th>
<th>P-potassium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n = 7)</td>
<td>2.15 ± 0.29</td>
<td>b</td>
<td>33.1 ± 2.6</td>
<td>152.3 ± 2.0</td>
<td>5.40 ± 0.20</td>
</tr>
<tr>
<td>Sham-CAN (n = 8)</td>
<td>2.88 ± 1.20</td>
<td>b</td>
<td>30.6 ± 1.6</td>
<td>148.8 ± 1.5</td>
<td>5.10 ± 0.11</td>
</tr>
<tr>
<td>CBL (n = 8)</td>
<td>3.09 ± 1.74</td>
<td>127 ± 5</td>
<td>64.2 ± 6.0a</td>
<td>146.3 ± 3.9</td>
<td>5.51 ± 0.15</td>
</tr>
<tr>
<td>CBL-CAN (n = 8)</td>
<td>2.29 ± 0.77</td>
<td>102 ± 17</td>
<td>50.0 ± 6.8a</td>
<td>150.0 ± 2.1</td>
<td>5.38 ± 0.12</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.M.
* P < .05 vs. sham-CAN.
* Value below detection limit (8.55 μM).

Fig. 1. Sodium balance 4 to 5 weeks after common bile duct ligation (CBL) or sham ligation in untreated rats and in rats chronically treated with the aldosterone receptor antagonist canrenoate (CAN) (20 mg/day i.v.). Daily sodium balance was calculated as sodium intake minus urinary sodium excretion. Mean ± S.E., n = 7 or 8 per group. * P < .05 vs. Sham. # P < .05 vs. CBL.

Systemic and renal hemodynamics. Table 3 shows systemic and renal hemodynamics before and during the diuretic peak response to i.v. furosemide in the four groups. During base-line conditions, MAP and HR (not shown) were similar in all four groups. However, untreated cirrhotic rats had a significantly increased ERPF and a significantly decreased EFF in absence of changes in GFR. Chronic aldosterone receptor blockade did not affect systemic and renal hemodynamics in control rats. However, in cirrhotic rats, aldosterone receptor blockade tended to decrease ERPF, which was associated to a significant increase in EFF. In all four groups, systemic and renal hemodynamic parameters were unchanged during the furosemide-induced diuretic peak response.

Renal tubular water and electrolyte handling. Data on urine flow rate and renal sodium handling during base-line conditions and during the diuretic peak response (0–10 min after furosemide administration) are shown in figure 2. Before furosemide administration V, U_NaV and FE_Na were similar in all four groups. However, the diuretic and the natriuretic responses to furosemide were significantly increased in cirrhotic rats compared with sham-operated control animals. Thus, the diuretic response to furosemide was increased by 59% (ΔV: 177.2 ± 4.0 vs. 111.6 ± 7.4 μl/min/100 g b.wt.; P < .001) and the natriuretic response by 56% (ΔU_NaV: 19.8 ± 0.9 vs. 12.7 ± 0.6 μmol/min/100 g b.wt.; P < .001). During the furosemide peak diuresis, the fractional sodium excretion was 80% higher in untreated cirrhotic rats than in control animals (FE_Na 16.6 ± 1.2 vs. 9.2 ± 0.3%; P < .001). Chronic aldosterone receptor blockade significantly inhibited the increased natriuretic response to furosemide in cirrhotic rats (FE_Na: 13.5 ± 1.1 vs. 16.6 ± 1.2%; P < .05). In control rats, aldosterone receptor blockade did not change the natriuretic response to furosemide, but the diuretic response was increased by 27% in canrenoate-treated control rats (ΔV: 142.1 ± 7.0 vs. 111.6 ± 7.4 μl/min/100 g b.wt.; P < .01).

During control conditions, the renal handling of lithium and potassium (not shown) was similar among groups and i.v. furosemide produced similar increases in C_Li, FE_Li and FE_K in all groups.

Furosemide excretion rate and natriuretic efficiency of furosemide. As shown in figure 3, the furosemide excretion rate was similar in cirrhotic and sham-operated control rats, but the natriuretic efficiency of furosemide (U_NaV/U_FURV) was 59% higher in untreated cirrhotic rats than in control rats (0.89 ± 0.13 vs. 0.55 ± 0.04 μmol sodium/mg furosemide; P < .01). The furosemide excretion rate as well as the natriuretic efficiency of furosemide was unaffected by canrenoate treatment in control rats. However, in cirrhotic rats, canrenoate treatment caused a significant increase in the furosemide excretion rate (33.3 ± 1.8 vs. 24.6 ± 2.6 μg/min/100 g; P < .01), and the urinary recovery of furosemide during the first 40 min after i.v. furosemide administration was significantly increased in canrenoate treated cirrhotic rats compared to canrenoate-treated controls (73.6 ± 5.4% vs. 51.3 ± 2.0%; P < .001). Thus, when the natriuretic response to furosemide was expressed in terms of natriuretic efficiency, chronic aldosterone receptor blockade with canrenoate caused a complete normalization of the exaggerated natriuresis in the cirrhotic rats.

Discussion

The present results demonstrate that chronic aldosterone receptor blockade with canrenoate prevents sodium retention in cirrhotic rats. Moreover, as a reflection of increased tubular NaCl reabsorption in the TAL, cirrhotic rats with Na retention had an increased natriuretic efficiency (U_NaV/U_FURV) of furosemide. This increased efficiency was normalized by chronic canrenoate treatment. Our data suggest that chronic aldosterone receptor blockade with canrenoate prevents sodium retention in cirrhotic rats partly by inhibition of the increased NaCl reabsorption in the TAL.

 Increased plasma aldosterone levels is considered among the most important mechanisms involved in the avid sodium retention in patients with decompensated liver cirrhosis. This provides the rationale for the use of spironolactone in the management of edema and ascites in decompensated cirrhotic liver disease (Bernardi et al., 1994). However, several experimental and clinical studies support the notion that
aldosterone is not involved in the early NaCl retention that precedes edema and ascites formation. Levy (1977) found that the plasma aldosterone concentration was normal in dogs with compensated liver cirrhosis and NaCl retention. The present study confirms our previous finding that plasma aldosterone is unchanged in CBL rats with compensated liver cirrhosis and NaCl retention.

Thus, an increase in plasma aldosterone concentration cannot explain the early NaCl retention that precedes ascites formation in liver cirrhosis. However, the present study confirmed the findings that aldosterone receptor blockade prevents NaCl retention in cirrhotic rats (Jiménez et al., 1985). Furthermore, the present study points to the TAL as a possible major site of action of canrenoate in cirrhotic rats. In vivo perfusion of Henle’s loop of superficial nephrons (Stanton, 1986) and in vitro perfusion of isolated TAL (Work and Jamison, 1987) have shown that aldosterone replacement therapy normalizes the decreased TAL NaCl reabsorption in adrenalectomized rats. However, several studies have demonstrated that concentrations of mineralocorticoids that stimulate Na-K-ATPase activity in the collecting duct do not affect Na-K-ATPase activity in the TAL in rats and rabbits (El Menissi and Doucet, 1983; Mujais et al., 1985; Doucet et al., 1990), which suggest that aldosterone does not stimulate NaCl reabsorption in the TAL by a direct action on the Na-K-ATPase.

The urinary excretion rate of furosemide was similar in sham-operated and cirrhotic rats. However, in cirrhotic rats, canrenoate treatment increased the amount of furosemide excreted in the urine by 35% relative to controls. The renal plasma flow tended to be decreased by canrenoate treatment in cirrhotic rats that excludes increased renal delivery of furosemide as a mechanism for the increased urinary furosemide excretion rate. Therefore, the increased urinary excretion of furosemide observed during chronic canrenoate treatment in cirrhotic rats suggests that canrenoate may impair the metabolic degradation of furosemide in this animal model.

When the natriuretic efficiency of furosemide (\(U_{Na}/U_{FURV}\)) was compared in the four treatment groups, we found that canrenoate treatment normalized the increased natriuretic efficiency in cirrhotic rats without affecting the natriuretic efficiency of furosemide in rats with normal liver function. This suggests that the presence of aldosterone is
required for the expression of increased tubular NaCl reabsorption in the TAL in cirrhotic rats. We recently reported that the adaptive functional and structural changes in the TAL in cirrhotic rats were also completely absent in vasoressin deficient Brattleboro rats with liver cirrhosis (Jonassen et al., 1997). Together with the present findings, these data suggest that both aldosterone and vasopressin have permissive actions on the adaptive changes observed in the TAL in cirrhotic rats. Little is known about the regulation of NaCl reabsorption in the TAL, but our findings suggest that there may be important interaction between the actions of aldosterone and vasopressin in the TAL like it has been demonstrated in the collecting duct (Coutry et al., 1995; Hawk et al., 1996).

In conclusion, these results showed that chronic treatment with the aldosterone receptor antagonist canrenoate, inhibits the NaCl retention that precedes ascites formation in cirrhotic rats without significant changes in the plasma concentration of aldosterone. In addition, chronic treatment with canrenoate normalizes the increased furosemide-sensitive sodium reabsorption observed in the TAL in rats with liver cirrhosis. Therefore, these data suggest that aldosterone receptor blockade with canrenoate prevents the NaCl retention in cirrhotic rats, partly by inhibition of the exaggerated NaCl reabsorption in the TAL.

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