Biol Res 26: 397-404 (1993)

Renal vascular and excretory resistance to atrial natriuretic peptide in pre-cirrhotic, bile-duct ligated rats

ANDRES VALDIVIESO[1], MAURICIO P BORIC[2], ANDREA RIQUELME[2] and JUAN ROBLERO[2]

[1] Departamento de Nefrología, Escuela de Medicina;
[2] Unidad de Regulación Neurohumoral, Departamento de Ciencias Fisiológicas, Facultad de Ciencias Biológicas;
Pontificia Universidad Católica de Chile, Santiago, Chile.

Renal response to atrial natriuretic peptide in chronic cholestasis was studied in anaesthetized rats and in their isolated perfused kidneys. Cholestasis was induced by bile duct section after ligature, while controls were sham operated. Three weeks after surgery, cholestatic rats showed moderate arterial hypotension, elevated diuresis and no differences in urinary sodium, glomerular filtration rate (GFR) and fractional sodium excretion (FE_{Na}), when compared to controls. Isolated kidneys of cholestatic rats had equal basal diuresis and less natriuresis than the controls. Cholestatic rats presented blunted natriuretic and diuretic responses to iv injections of atrial natriuretic peptide (ANP 0.5 μg) , associated with reduced increments in GFR and FE_{Na}, when compared with controls. Similarly, the diuretic-natriuretic response of isolated kidneys to ANP ($3.5 \times 10^{-9}M$) was greatly attenuated in this group. ANP did not increase perfusion pressure in cholestatic rats, as it did in controls. These results indicate that animals with chronic cholestasis present refractoriness to ANP, which might be mediated by a direct impairment at the renal vascular and tubular sites for ANP action.

INTRODUCTION

Renal salt and water retention is frequently observed in the clinical course of patients with decompensated Laennec cirrhosis (8). However, this complication is rather unusual in patients with obstructive jaundice (4). Moreover, the tubular handling of sodium in obstructive jaundice presents marked variability, depending on the species studied (4, 26) and the degree of jaundice observed (6). In chronic bile duct ligated (BDL) rats, some authors report the presence of ascites and edema (3,30); in contrast, other communications do not report regular retention of salt and water in this model (1, 2).

Reported circulating plasma levels of atrial natriuretic peptide (ANP) in patients with chronic liver disease are variable, being usually either normal (6,11) or high (20,25).

Interestingly, when plasma levels of ANP are elevated by intravenous infusion in BDL cirrhotic dogs (17) or cirrhotic rats with ascites and urinary sodium retention (14), some animals respond with a significant natriuresis and some do not respond at all. The same phenomenon has been observed in sodium-retaining cirrhotic humans subjected to ANP infusion (23) or to water immersion and subsequent elevation of plasma ANP levels (27). The cause of this natriuretic resistance in sodium-retaining cirrhotics remains unknown.

The present study was undertaken to evaluate the renal response to ANP in anaesthetized, chronic BDL rats, before the

Correspondence to: Dr. Andrés Valdivieso, Depto. de Nefrología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Casilla 114-D, Santiago, Chile. Fax: (56-2) 222-5515.

development of established cirrhosis with sodium retention or ascites. Our results demonstrated a significant resistance to the diuretic and natriuretic effects of ANP in this model. Then, we evaluated their perfused isolated kidney to further study the underlying mechanism of this resistance. This lack of responsiveness is associated with a decreased vascular reactivity to ANP and does not seem to require renal innervation.

MATERIALS AND METHODS

Induction of cholestasis

Adult Sprague-Dawley rats, weighting 200-250 g, were fed with a regular rodent chow. They were randomized into controls and animals destined for induction of chronic cholestasis through bile duct ligation and section (BDL). The experimental rats were anaesthetized with sodium pentobarbital (40 mg/kg ip) and the common hepatic duct was sectioned between ligatures to produce cholestasis. Sectioning was performed near the hepatic hilum to avoid recanalization and excessive bile accumulation in the remnant common duct. Control rats were sham operated (SO).

Female rats were used in whole animal experiments, because of the easiness to cannulate the bladder, and male rats in the studies with isolated kidneys, due to surgical advantages. All the studies were performed 22-28 days after the operation. A subgroup of female rats was adapted to metabolic cages and 24-h urine samples were collected 3 days before the final experiment.

Development of cholestasis was tested by measuring plasma levels of alkaline phosphatase, bilirubin, total protein and serum albumin. A liver biopsy was performed in 6 animals.

All the experiments conformed to the Guiding Principles in the Care and Use of Laboratory Animals, endorsed by the American Physiological Society.

Studies in whole anaesthetized rats

The animals were fasted overnight but had free access to water. They were reanaesthetized with sodium pentobarbital (40 mg/kg ip) and the trachea was cannulated. Catheters (PE-50) were inserted into the left jugular vein, left femoral vein and left carotid artery, for infusion and periodic blood sampling. The arterial catheter was attached to a pressure transducer (Statham F-10) connected to a polygraph (Model 7, Grass Instruments Co., Quincy, MA) for continuous monitoring of mean arterial pressure (MAP). Body temperature was kept at 37° C with a heating lamp. The bladder was cannulated with a silastic catheter via the urethra.

After surgery, an isotonic infusion of 5% dextrose (D5-W; 1.2 ml/h) via jugular vein was maintained along the experiment. After an equilibration period of 45 min, urine was collected for two 20-min basal periods (B1, B2). At the end of the second period, a bolus of synthetic ANP (Atriopeptin II, 5-27 rat form, Sigma Co, St. Louis, MO; 0.5 µg in 100 µl D5-W) was injected via femoral vein, and urine was collected for another two periods of equal length (E1, E2).

Glomerular filtration rate (GFR) was estimated from the urinary clearance of radioactive inulin (Inulin-carboxyl-^{14}C; specific activity 2.1 mCi/g, New England Nuclear, Boston, MA) in a subgroup of seven BDL and six SO animals. A priming dose (0.3 µCi in 0.15 ml D5-W per 100 g) was followed by a sustained addition of the isotope (0.02 µCi/min/100 g) to the infusion fluid for the rest of the experiment. Blood samples (*ca* 120 µl) were obtained just before B2 and E2 periods to measure serum sodium and ^{14}C-inulin. To maintain isovolemia, the removed blood was immediately replaced by an equal volume of heparinized blood obtained from a matched group donor rat. Volume, sodium and radioactive inulin were determined in each urine sample.

Isolated kidney studies

The kidney was perfused according to a modification of the technique described by Roblero *et al.* (5,21). The renal circulation was isolated and after administration of heparin (1200 IU/kg), a PE-240 catheter was introduced into the inferior vena cava and a

metallic needle (BD-20) was placed into the right renal artery through the superior mesenteric artery. The ureter was ligated and canulated with a PE-10 catheter.

The kidney was immediately perfused with Krebs-Henseleit-Bicarbonate solution, pH 7.4, modified with the addition of 7% bovine albumin (Calbiochem, San Diego, CA), 2 mM sodium pyruvate, 6 mM glucose and 6 mM urea. The fluid was passed through a silastic coil (1.5 m length, 1 mm ID) exposed to a mixture of 95% O_2, 5% CO_2 immediately before the entrance to the kidney. After a brief open circuit perfusion, the kidney was placed in a perfusion camera and a closed circuit perfusion (100 ml) was started for equilibration and washing during 20 min.

The perfusion flow was set and maintained with a peristaltic pump at approximately 35 ml/min (Masterflex, Cole Palmer, Chicago Ill). The temperature was maintained at 37° C by a water bath. Mean arterial perfusion pressure (MPP) was measured with a strain gauge transducer (Statham F-10) and recorded on a Grass polygraph.

The experiment was started by connecting a second closed circuit perfusion reservoir with fresh medium (total volume 60 ml). Urine was collected for two 15 min basal periods (B1, B2); then 0.5 µg ANP was injected into the perfusate (final concentration 3.5×10^{-9} M) and urine was collected for another two 15-min periods (E1, E2). Urinary volume and sodium were determined in all samples.

Analytical techniques

Urine was collected into pre-weighed plastic tubes and its volume was measured gravimetrically. Sodium was determined by an ion selective electrode (NOVA-6, Biomedical). Hematocrit was measured in blood collected directly into microhematocrit tubes. Serum alkaline phosphatase, bilirubin, total protein and albumin concentrations were determined by standard SMA12 techniques. For GFR determinations, samples of plasma and urine (10 µl) were pipetted into glass vials containing 10 ml Aquasol (New England Nuclear Co, Boston, MA) and ^{14}C-Inulin was determined using a liquid scintillation counter (Radiac Beta Nuclear, Chicago Inc.). GFR (µl/g/min) and fractional excretion of sodium (FE_{Na}) were calculated using standard methods.

All data are expressed as means ± se. Baseline data represent the average of B1 and B2 periods. Statistical significances were determined using Analysis of Variance (ANOVA) for repeated measurements. Intragroup differences were assessed by Newman-Keuls test for multiple comparisons. Unpaired t-tests were used to compare differences between both groups.

RESULTS

Characterization of BDL rats

Body weights of rats with chronic BDL (224 ± 4.2 g; n = 27) were not different from those of SO controls (224 ± 5.7 g; n = 17). There were no ascites in the BDL rats. Liver biopsy (n = 6) showed chronic cholestasis, fibrosis and extensive bile duct proliferation. Early changes consistent with hepatic cirrhosis were found in two of them. Serum alkaline phosphatase (BDL: 437.0 ± 35.4 *vs* SO: 166 ± 16.2 U/l; $p < 0.0005$) and bilirubin (BDL: 9.80 ± 0.60 *vs* SO: 0.30 ± 0.02 mg/dl; $p < 0.0005$) were significantly higher in BDL rats. Serum albumin was significantly lower (BDL: 2.2 ± 0.1 *vs* SO: 3.2 ± 0.1 g/dl $p < 0.0005$) in BDL rats, whereas total protein (BDL:7.4 ± 0.4 *vs* SO: 7.0 ± 0.2 g/dl $p > 0.05$) and hematocrit (BDL: 47.5 ± 0.1 *vs* SO: 48.2 ± 0.4 %; $p > 0.05$) were not significantly different for both groups. Results of 24-h urine collection in experimental (n = 19) and control (n = 9) animals showed that unanaesthetized cholestatic rats excreted significantly more urine (5.6 ± 0.7 *vs* 3.4 ± 0.9 ml/24h, $p < 0.05$) and sodium (287.6 ± 39.1 *vs* 156.2 ± 16.1 mM/24 h; $p < 0.025$) than sham operated controls.

Observations in anaesthetized rats

Compared with controls, cholestatic rats had a lower baseline mean arterial pressure and a higher urinary flow rate. On the other hand, there were no significant differences in

baseline urinary sodium excretion, glomerular filtration rate and FE_{Na} between both groups (Figs 1 and 2).

Administration of ANP in SO animals produced a slight reduction in arterial pressure and marked transient increments in diuresis, natriuresis, GFR and FE_{Na} (Figs 1 and 2). In contrast, it was noteworthy that the diuretic and natriuretic responses to ANP were markedly attenuated in cholestatic rats (Fig 1). Moreover, BDL rats also showed no change in GFR and a lower increment in FE_{Na} when compared with SO rats responses to ANP (Fig 2). This blunted natriuretic response does not seem to be a consequence of a larger drop in arterial pressure after ANP; the drop in MAP in BDL rats only reached statistical significance during E2 (Fig 1).

In fact, the influence of arterial pressure on natriuresis was further studied by correlation analysis between MAP and natriuresis. Analysis within groups showed that there was a significant negative correlation between changes in urinary sodium and MAP in control rats ($r = -0.506$; $n = 17$; $p < 0.05$) but not in cholestatic rats ($r = -0.36$; $n = 27$; $p > 0.05$).

Observations in isolated perfused kidneys

There were no differences in perfusion flow rates between the kidneys of SO and BDL rats (36.9 ± 0.5 and 35.2 ± 1.9 ml/min, respectively; $p > 0.05$). The same was true for the initial perfusion pressure (78.6 ± 2.5 *vs* 76.3 ± 4.7 mmHg). Addition of ANP produced a significant and sustained increase in perfusion pressure in control kidneys, whereas this increase was undetectable in the BDL group (Fig 3).

Baseline urine flow rates were also similar in the SO and BDL groups. In contrast, baseline urinary sodium excretion was significantly lower in kidneys from cholestatic rats (Fig 3). Both groups of rats responded to the addition of ANP with sustained increases in UV and U_{Na}; however, these increments were significantly lower in the experimental group than in the controls (Fig 3).

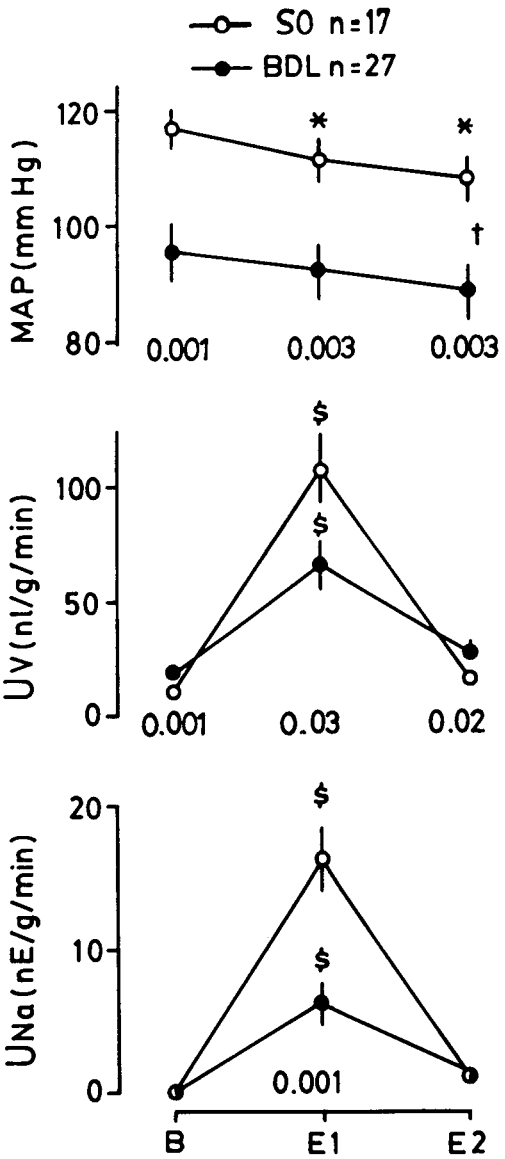

Fig. 1: Mean arterial pressure (MAP), urinary volume (U_v), and urinary sodium (U_{Na}) excretion in sham operated (SO) and bile duct sectioned-ligated (BDL) rats, prior and after an intravenous bolus dosis of ANP (0.5 μg). Mean ± SE. When not shown, SE bars lay within symbols.

Baseline U_v : SO = 11.2 ± 1.2; BDL = 20.4 ± 2.2 (nl/g/min)

E2 Uv : SO = 17.8 ± 1.2; BDL = 28.9 ± 4.1 (nl/g/min)

Baseline U_{Na} : SO = 0.20 ± 0.05; BDL = 0.28 ± 0.08 (nE/g/min)

E2 U_{Na} : SO = 1.27 ± 0.18; BDL = 1.38 ± 0.52 (nE/g/min).

* = $p < 0.01$ *vs* Baseline; † = $p < 0.05$ *vs* Baseline; $ = $p < 0.001$ *vs* Baseline and E2 (ANOVA and Newman-Keuls test).

Numbers at bottom show statistical significance of differences between BDL and SO at each time point (Unpaired t test, one tail).

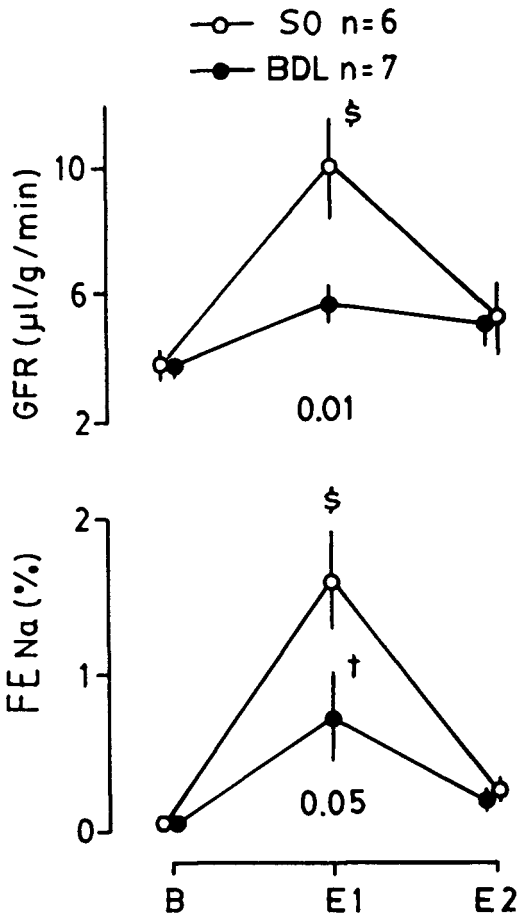

Fig. 2: Glomerular filtration rate (GFR) and fractional sodium excretion (FE_{Na}) in sham operated (SO) and bile duct sectioned-ligated (BDL) rats, prior and after an intravenous bolus dosis of ANP (0.5 µg). These rats represent a subgroup of those depicted in Fig. 1. Mean ± SE. When not shown, SE bars lay within symbols.
Statistical analysis for FE_{Na} (%) was performed after the Arc-Sin transformation of the data. Baseline FE_{Na}: SO = 0.057 ± 0.014; BDL = 0.061 ± 0.020 (%).
$ = $p < 0.001$ *vs* Baseline and E2; † = $p < 0.05$ *vs* Baseline and E2 (ANOVA and Newman-Keuls test).
Numbers at bottom show statistical significance of differences between BDL and SO at each time point (Unpaired *t* test, one tail).

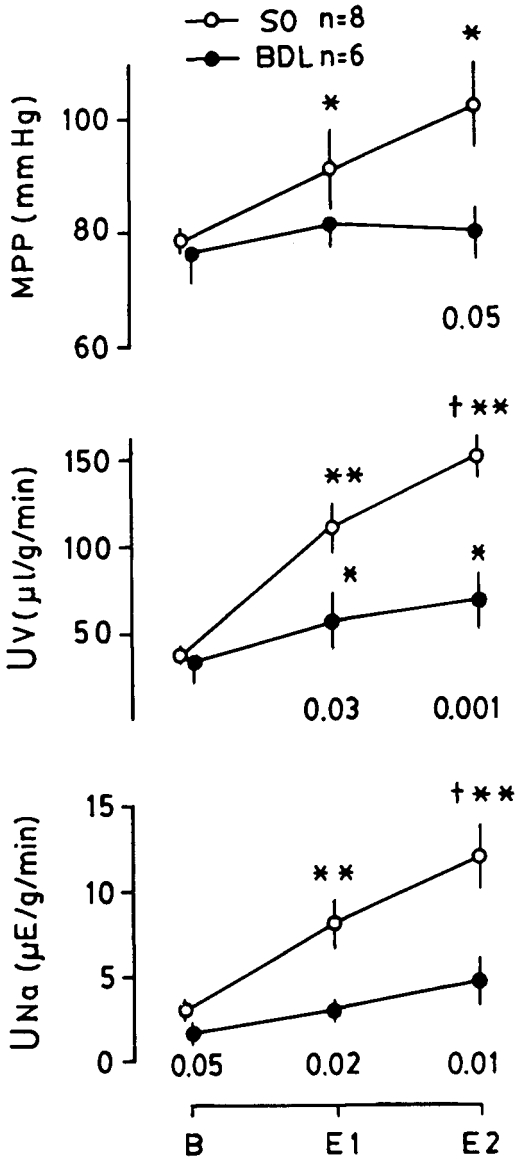

Fig. 3: Mean perfussion pressure (MPP), diuresis (U_v) and urinary sodium excretion (U_{Na}) in isolated kidneys obtained from sham operated (SO) and bile duct sectioned-ligated (BDL) rats, prior and after addition of ANP (10 ng/ml) to the perfusion fluid. Mean ± SE.
* $p < 0.05$ *vs* Baseline; ** $p < 0.01$ *vs* Baseline; † $p < 0.05$ *vs* E1 (ANOVA and Newman-Keuls test).
Numbers at bottom show statistical significance of differences between BDL and SO at each time point (Unpaired *t* test, one tail).

DISCUSSION

Ligature and section of the common bile duct is accompanied by irreversible biochemical and pathological changes leading to death within five weeks (29). Our experimental animals presented clear histological and biochemical evidences of cholestasia after three weeks; thus this period was chosen to assess the response to ANP.

Unanaesthetized BDL rats showed elevated 24 hour urine and sodium excretion. Similar findings have been described in BDL

dogs and rats (4) and they have been attributed to a natriuretic effect of biliary salts (9). The day of the experiment, anaesthetized BDL rats presented arterial hypotension and increased basal diuresis, without differences in natriuresis when compared to controls. Early arterial hypotension and reduced peripheral resistance had also been reported in BDL rats (22) and they were attributed to hypovolemia (30) and/or to a blunted pressure response to vasoconstrictors (22).

Our data demonstrate a significant refractoriness to the diuretic and natriuretic effects of ANP in pre-cirrhotic rats with chronic cholestasia, without ascites. This resistance was observed both in the whole anaesthetized animals and in their isolated perfused kidneys.

The mechanisms for the natriuretic action of ANP are complex and still under debate. Current knowledge points to a combination of renal hemodynamic effects leading to an increased filtered load and a direct inhibition of tubular sodium reabsorption (16). ANP-induced rise in GFR seems to be due to elevations in both the glomerular hydrostatic pressure and the glomerular ultrafiltration coefficient (10). On the other hand, inhibition of sodium reabsorption by ANP takes place in the medullary collecting duct (28). Reduced tubular reabsorption can also be a consequence of an increased blood flow and hydrostatic pressure in vasa recta (19).

It is well known that in cirrhotic patients and animals with ascites and sodium retention there is renal resistance to the diuretic and natriuretic effects of ANP (14,17, 23,27). In our study, refractoriness to ANP in pre-cirrhotic animals was expressed as a lack of a GFR peak, but also as a reduction in FE_{Na}. This suggests that our rats presented simultaneous inhibitions of glomerular and medullary ANP actions. These data do not allow us to discern a specific alteration among the mechanisms involved in this response.

Theoretically, several mechanisms can explain this blunted response to ANP: changes in renal perfusion pressure, activation of anti-natriuretic factors or variations in the number of specific biological or clearance ANP receptors.

Natriuresis induced by ANP is strongly dependent on renal perfusion pressure (15, 24). Thus, it is likely that the moderate hypotension observed in our anaesthetized BDL rats contributed to their weak GFR response to ANP. Lopez *et al.* (14), studying CCl_4-induced cirrhotic rats with ascites, observed that their resistance to ANP disappeared upon normalization of arterial pressure with vasoconstrictors. Moreover, the striking parallelism between changes in perfusion pressure and natriuresis detected in our isolated kidneys seems to explain the resistance to ANP in the experimental group. The changes in perfusion pressure observed in our control group confirm earlier reports in isolated rat kidneys, showing that hemodynamic changes induced by ANP are required for diuresis and natriuresis.

Camargo *et al.* (7) demonstrated lack of natriuresis when ANP-induced vasoconstriction was prevented by using either a low Ca^{++} buffer or verapamil. These authors postulated that ANP produced a preferential efferent arteriolar vasoconstriction in vasodilated perfused kidneys, increasing renal vascular resistance and filtration fraction. In this regard, our results suggest that lack of vascular (efferent) responsiveness to ANP mediates resistance in BDL rats. In spite of the above, we found no correlation between natriuresis and MAP in our BDL rats, whereas such correlation was found in the control animals. Likewise, in BDL cirrhotic dogs with ascites, there was no relationship between ANP-induced drop in blood pressure and natriuresis (18).

The above findings support the concept of an additional independent mechanism causing refractoriness to sodium excretion in animals with chronic cholestasia.

The blunted natriuresis observed in our anaesthetized BDL rats, may also be explained by activation of the renal sympathetic nervous system. Koepke *et al.* (13), have reported that resistance to ANP administration in BDL cirrhotic rats with ascites was reversed with renal denervation. They also postulated that adrenergic hyperactivity could explain renal sodium retention in several sodium retaining disorders (12). It is difficult to propose a higher renal sympathetic traffic in response to ANP in our

acutely denervated isolated kidneys, although we cannot exclude a direct action of ANP upon their adrenergic nerve terminals.

Moreover, this hypothesis was not confirmed in BDL dogs where renal denervation did not reverse sodium retention (18). On the other hand, we have shown that the isolated kidney maintains the excretory pattern characteristic to its previous *in vivo* physiological status (5). Thus, it is possible that other antinatriuretic circulating factors, present in BDL rats, could still be acting during the perfusion period. Our findings can also result from a reduced number of specific ANP receptors, an increased number of clearance receptors or a decreased efficiency in the intracellular signal transduction process for GMP production. It is possible that elevated circulating ANP levels (20) could lead to a down regulation of active ANP receptors. However, refractoriness to elevated serum ANP, induced by water immersion (27) or infusion of ANP (18), is not associated with a lower urinary excretion of cGMP. Resistance to ANP may occur at post-transductional level or may be due to a decreased number of receptors at some particular nephron segments. However, new studies are required to support these assumptions.

ACKNOWLEDGMENTS

We thank Drs Ignacio Duarte and Sergio González for their help in the histological studies; Mrs Maricarmen Tobar and Mrs Cecilia Chacon for their handling of analytical samples; Mrs Judith Gengler and Mrs Eliana Lira for their excellent technical assistance in the experiments, and Drs Soffa Salas and Flavio Nervi for reviewing the manuscript. This work was partially financed by grant 642/89 from FONDECYT.

REFERENCES

1. AARSETH S, BERGEN A, AARSETH P (1979) Circulatory homeostasis in rats after bile duct ligation. Scand J Clin Lab Invest 39: 93-97.
2. ALLISON ME, MOSS NG, FRASER MN, DOBBIE JW, RYAN CJ, KENNEDY AC, BLUMGART LH (1978) Renal function in chronic obstructive jaundice: a micropuncture study in rats. Clin Sci Mol Med 54: 649-659.
3. BANK N, AYNEDJIAN HS (1975) A micropuncture study of renal salt and water retention in chronic bile duct obstruction. J Clin Invest 55: 994-1002.
4. BETTER OS (1983) Bile duct ligation: An experimental model of renal dysfunction secondary to liver disease. In: EPSTEIN M (ed) The Kidney in Liver Disease. 2nd Ed. Amsterdam: Elsevier. p 295-311.
5. BORIC MP, CORTHON J, SILVA R, ROBLERO J (1990) Polarity of kallikrein release and activation in isolated rat kidneys. Am J Physiol 259: F752-F757.
6. BURGHARDT W, WERNZE H, DIEHL KL (1986) Atrial natriuretic peptide in cirrhosis: relation to the stage of disease, sympathoadrenal system and renin-aldosterone axis. Klin Wochenschrift 64 (S6): 103-107.
7. CAMARGO MJF, KLEINERT HD, ATLAS SA, SEALEY JE, LARAGH JH , MAACK T (1984) Ca-dependent hemodynamic and natriuretic effects of atrial extract in isolated rat kidney. Am J Physiol 246: F447-F456.
8. EPSTEIN M (1988) Renal sodium handling in liver disease. In: EPSTEIN M (ed) The Kidney in Liver Disease. 3rd Ed. Baltimore: Williams & Wilkins. p 3.
9. FINESTONE H, FECHNER CM, LEVY M (1984) Effects of bile and bile salts infusions on renal function in dogs. Can J Physiol Pharmacol 62: 762-768.
10. FRIED T, McCOY RN, OSGOOD RW, STEIN JH. (1986) Effect of atriopeptine II on determinants of glomerular filtration rate in the in vitro perfused dog glomerulus. Am J Physiol 250: F1119-F1122.
11. GERBES AL, WERNZE H, ARENDT RM, RIEDEL A, SAUERBRUCH T, PAUMGARTEN G (1989) Atrial natriuretic factor and renin-aldosterone in volume regulation in patients with cirrhosis. Hepatology 9: 417-422.
12. KOEPKE JP, DI BONA GF (1987) Blunted natriuresis to atrial natriuretic peptide in chronic sodium-retaining disorders. Am J Physiol 252: F865-F871.
13. KOEPKE JP, JONES S, DI BONA GF (1987) Renal nerves mediate blunted natriuresis to atrial natriuretic peptide in cirrhotic rats. Am J Physiol 252: R1019-R1023.
14. LOPEZ C, JIMENEZ W, ARROYO V, LA VILLA G, GAYA J, CLARIA J, RIVERA F, RODES J (1989) Role of altered systemic hemodynamics in the blunted renal response to atrial natriuretic peptide in rats with cirrhosis and ascites. J Hepatol 9: 217-226.
15. MAACK T, ATLAS S, CAMARGO MJ, COGAN MG (1986) Renal hemodynamic and natriuretic effects of atrial natriuretic factor. Fed Proc 45: 2128-2132.
16. MAACK T, MARION DN, CAMARGO MJ, KLEINERT HD, LARAGH JH, VAUGHAN ED JR, ATLAS SA (1984) Effect of auriculin (ANF) on blood pressure, renal function and the renin-aldosterone system in dogs. Am J Med 77: 1069-1075.
17. MAHER E, CERNACEK P, LEVY M (1989) Heterogenous renal responses to atrial natriuretic peptide. II. Cirrhotic dogs. Am J Physiol 257: R1068-R1074.
18. MAHER E, CERNACEK P, LEVY M (1990) Physiological features of edematous dogs unresponsive to atrial natriuretic peptide. Am J Physiol 258:F1490-1496.
19. MENDEZ RE, DUNN BR, TROY JL, BRENNER BM (1986) Modulation of the natriuretic response to atrial natriuretic peptide by alterations in peritubular Starling forces in the rat. Circ Res 59: 605-611.
20. OLIVERA A, GUTKOWSKA J, RODRIGUEZ-PUYOL D, FERNANDEZ-CRUZ A, LOPEZ-NOVOA JM (1988) Atrial natriuretic peptide in rats with experimental cirrhosis of the liver without ascites. Endocrinology 122: 840-846.

21. ROBLERO J, CROXATTO H, GARCIA R, CORTHORN J, DE VITO E (1976) Kallikrein-like activiy in perfusates and urine of isolated rat kidneys. Am J Physiol 231:1383-1389.
22. SAITO S. (1981) Clinical and experimental studies on the hyperdynamic states in obstructive jaundice. J Jap Surg Soc 82: 483-497.
23. SALERNO F, BADALAMENTI S, INCERTI P, CAPOZZA L, MAINARDI L (1988) Renal response to atrial natriuretic peptide in patients with advanced liver cirrhosis. Hepatology 8: 21-26.
24. SEYMOUR AA, BLAINE EH, MAZACK EK, SMITH SG, STABILITO IL, HALEY AB, NAPIER MA, WHINNERY MA, NUTT RF (1985) Renal and systemic effects of synthetic atrial natriuretic factor. Life Sci 36: 33-44.
25. SHENKER Y, SIDER RS, OSTAFIN EA, GREKIN RJ (1985) Plasma levels of immunoreactive atrial natriuretic factor in healthy subjects and in patients with edema. J Clin Invest 76:1684-1687.
26. SITPRIJA V, KASHEMSANT U, SRIRATANABAN A, ARTHACHINTA S, POSHYACHINDA V (1990) Renal function in obstructive jaundice in man: Cholangiocarcinoma model. Kidn Intl 38: 948-955.
27. SKORECKI KL, LEUNG WM, CAMPBELL P, WARNER LC, WONG PY, BULL S, LOGAN AG, BLENDIS LM (1988) Role of atrial natriuretic peptide in the natriuretic response to central volume expansion induced by head-out water immersion in sodium-retaining cirrhotic subjects. Am J Med 85: 375-382.
28. SONNENBERG H, HONRATH U, CHONG CK, WILSON DR (1986) Atrial natriuretic factor inhibits sodium transport in medullary collecting duct. Am J Physiol 250: F963-F966.
29. TRAMS EG, SYMEONIDES A (1957) Morphologic and functional changes in the livers of rats after ligation or excision of the common bile duct. Am J Pathol 33:13-25.
30. YARGER WE (1976) Intrarenal mechanism of salt retention after bile duct ligation in rats. J Clin Invest 57: 408-418.