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THE ROLE OF ATRIAL NATRIURETIC PEPTIDE (ANP) IN CHRONIC LIVER DISEASE

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Abstract—The role of atrial natriuretic peptide (ANP) and potential defects of ANP in liver disease are reviewed. Patients with cirrhosis of the liver show no decrease of ANP plasma concentrations nor changes in the pattern of ANP immunoreactivity nor changes of splanchnic ANP clearance. The renal effects of exogenously administered as well as endogenously released ANP are blunted in cirrhosis, in particular in patients with ascites. This seems due to increased activity of sodium-retaining hormonal systems and changes of the renal ANP receptor status. Pharmacological inhibition of ANP-degradation or clearance may yield therapeutic potential.

CONTENTS

1. FEATURES OF ANP

The atrial natriuretic factor was identified in 1984 as a peptide hormone (hence the name atrial natriuretic peptide, ANP) with particular importance in the regulation of intravascular volume and blood vessel tonus (Cantin and Genest, 1986; Inagami, 1989; Lang *et al.*, 1987; Larose *et al.*, 1985; Needleman and Greenwald, 1986). Since little is known about the physiological role or pathophysiological importance of brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), the other recently discovered members of the natriuretic peptide family, this review will concentrate on ANP. Following appropriate stimulation, such as atrial distention (Gerbes *et al.*, 1986, 1988; Gerbes and Vollmar, 1988; Lang *et al.*, 1985), a 126 amino acid prohormone is released from the secretory granules of atrial myocytes and cleaved. This is followed by an increase of both clearance products, the C-terminal 28 amino acid as well as the N-terminal fragment in the plasma. The C-terminal fragment has been identified as a biologically active hormone, whereas a biological action of the N-terminal fragment is not generally accepted. While the heart is the major source of circulating ANP, synthesis of ANP has also been found in various extracardiac organs such as intestine, lung and thymus and organs of the reproductive system (Gerbes *et al.*, 1991a; Gutkowska and Nemer, 1989; Vollmar, 1990). Elimination of ANP from the circulation occurs by enzymatic degradation or binding to clearance receptors in several organs such as kidney, lung or liver (Gerbes

Dedicated to Professor Dr G. Paumgartner on the occasion of his 60th birthday.

Abbreviations—ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; B-receptor, biological-active-receptor; cGMP, cyclic guanosine-mono-phosphate; CNP, C-type natriuretic peptide; C-receptor, clearance receptor.

and Vollmar, 1990). Liver and intestinal circulation contribute significantly to the extraction of ANP with arterio-venous extraction ratios found between 28 and 75% (Gerbes and Vollmar, 1990; Gerbes *et al.*, 1992). There are two different types of ANP receptors: two kinds of biological-active (B)-receptors, coupled to guanylate cyclase, exhibiting a high affinity for C-terminal ANP and a clearance-receptor (C-receptor) binding C-terminal ANP with lower affinity but also binding truncated ANP analogs (Almeida *et al.*, 1989; Chinkers *et al.*, 1989; Kollenda *et al.*, 1991; Maack *et al.*, 1987; Wilcox *et al.*, 1991). The two B-receptor types exhibit different affinity to the members of the natriuretic peptide family ANP, BNP and CNP. Physiological changes of the intravascular volume, e.g. dehydration or sodium loading, can affect the density of B- and C-receptors for ANP to a different extent (Kollenda *et al.*, 1990). Thus, changes of ANP receptor status may constitute a way of regulating the ANP system.

Major effects of ANP affect intravascular volume and pressure. Several of these biological activities are rather well described: relaxation of smooth muscle cells, suppression of renin and aldosterone synthesis and release, as well as various renal effects mediated by glomerular and tubular receptors resulting in natriuresis and diuresis. Recently, evidence has accumulated for biological actions in the reproductive and immune systems (Gutkowska and Nemer, 1989; Vollmar, 1990). A physiological role of ANP in the regulation of intravascular volume and pressure is supported by various investigations employing blockade of ANP release, administration of specific antibodies or very low dose infusions of ANP. Transgenic mice overexpressing ANP and constantly exhibiting 10-fold elevated plasma concentrations show a markedly lower arterial blood pressure (Field *et al.*, 1991).

2. ACTIONS OF ANP ON THE LIVER AND HEPATIC CIRCULATION

In the anesthetized dog, intraarterial bolus injections of ANP caused graded increases in hepatic arterial blood flow representing a vasodilation, comparable to the effects of isoprenaline. In contrast, there was no obvious effect on portal venous inflow resistance. The action of ANP, discernable at concentrations of at least 0.1 nM, would suggest a change of total liver blood flow in favor of the arterial component (Withrington *et al.*, 1990). Liver perfusion of rats with ANP 40 nM, but not with a truncated ANP analog, inhibited hepatic glycolysis and stimulated glucose production modestly (Rashed *et al.*, 1992). These effects seem to be mediated by the B-receptor. In rat liver regenerating after partial hepatectomy, the density of ANP binding sites was increased 2-fold, due to an increase of B- and C-receptors (Nair *et al.*, 1991). Finally, there is increasing evidence for a protective effect of ANP against ischemia/reperfusion damage of perfused rat livers (Witthaut *et al.*, 1992). These effects were observed at 200 nM concentrations of ANP, but not at 20 nM concentrations, and thus reflect a pharmacological phenomenon rather than a physiological action of circulating peptide.

3. HEMODYNAMIC CHANGES AND PATHOPHYSIOLOGY OF ASCITES FORMATION IN LIVER CIRRHOSIS

Recently, new concepts have been introduced in the complex pathophysiology of renal sodium retention, hemodynamic alterations and ascites formation in liver cirrhosis (Gerbes, 1991). There is general acceptance of the pathophysiological importance of the cirrhotic changes in the liver, reducing centrally effective blood volume (Henriksen *et al.*, 1992) by a decrease of the colloid osmotic and an increase of the hydrostatic pressure, thus changing Starling forces in the splanchnic circulation. This, together with a peripheral vasodilation (Schrier *et al.*, 1988) activates sodium retaining neurohumoral systems, such as the renin–angiotensin–aldosterone and the symphatico-adrenergic systems contributing to renal sodium retention. There has been an intense search for humoral factors involved in vasodilation, sodium retention and, finally, ascites formation in chronic liver disease. Years ago, it was postulated that the deficiency of some natriuretic hormone was involved in the pathophysiological changes of cirrhosis (Buckalew and Gruber, 1983; Epstein, 1981; Kramer, 1975; Naccarato *et al.*, 1981; De Wardener and Clarkson, 1985). Unfortunately, this putative hormone with digoxine-like immunoreactivity has not been identified yet. These unsuccess-

ful efforts may explain the excitement following the identification of ANP. Therefore, many investigations aimed at finding a defect of the ANP system, compatible with a deficiency of natriuretic activity and resulting in sodium retention. In this respect, interest has focused on determination of plasma concentrations and their dependence on various factors, relation to other volume-regulating hormones and to renal function, release into and clearance from the circulation, renal and vascular responses to ANP and, finally, the therapeutic potential of ANP. The results suggest ANP as another clue to the puzzle, rather than the solution to the problems of understanding the pathophysiology of hemodynamic changes and sodium retention in chronic liver disease.

4. ANP IN LIVER DISEASE

4.1. Plasma Concentration

The first communication on ANP in patients with cirrhosis of the liver found slightly elevated concentrations compared to controls (Gerbes *et al.*, 1985). Ever since, numerous investigations have found mainly normal or elevated plasma concentrations (Gerbes *et al.*, 1987; Epstein, 1989). Recently, it was shown that plasma concentrations of BNP in patients with cirrhosis were elevated (La Villa *et al.*, 1992). Thus, there is no deficiency of circulating natriuretic peptides in patients with cirrhosis with or without ascites. In view of the wide range of ANP concentrations reported, methodological aspects, as well as the influence of various patient-related factors, are worth mentioning. Validation of the radioimmunoassays by recovery experiments, by parallelity of dilution curves to the standard curve, by intra- and interassay variation, as well as by characterization of the immunoreactivity, seem mandatory for reliable detection. Extraction of plasma prior to the radioimmunoassay is indispensable. This can be clearly judged from the results of the International Collaborative Study of the proposed international standard for atrial natriuretic factor on behalf of the American Heart Association/International Society of Hypertension/World Health Organisation.* Unfortunately, this comparison of assays from many laboratories all over the world has never been published, due to the lack of consent from some participants. At the present time, however, most assays seem suitably standardized and the importance of plasma extraction is generally agreed upon.

Several communications have shown a significant influence of posture, circadian rhythms, diet, diuretics, paracentesis or albumin infusion on ANP plasma concentrations. Most investigations of neurohumoral systems are performed with the subjects in supine position. While this should allow for standardization, it reflects the posture of man during only one-third of the day. Most of the time is spent in the sitting and standing positions, which, therefore, should also be considered. In our initial observation, we found elevated ANP plasma concentrations in supine patients with cirrhosis, but later no significant difference to controls in patients maintaining a sitting position (Gerbes *et al.*, 1985, 1989). Most recently, no difference of ANP plasma concentration was found between cirrhotic patients without ascites and controls while standing (Bernardi *et al.*, 1992). Following the assumption of supine position, ANP concentrations increased at 30 min in the patients with cirrhosis and at 60 min in the controls, with mean values at 120 min of supine position in cirrhosis almost 2-fold those of controls. This was paralleled by a greater decrease of peripheral vascular resistance and a greater increase of cardiac output in the group of patients in the horizontal posture. Renal sodium excretion, which was reduced in the standing position, increased 3-fold, no longer differing from supine controls (Bernardi *et al.*, 1993).

These data do not only provide clear evidence for the posture dependence of ANP plasma concentrations, but may also suggest an influence of the peptide on peripheral vascular resistance and renal sodium excretion of patients with preascitic cirrhosis. Inverse correlations of ANP plasma concentration to plasma volume and cardiac output were described by one group (Vinel *et al.*, 1989), but others observed linear correlations to plasma volume and atrial volume (Rector *et al.*, 1990) and showed increased natriuresis together with a trend towards increased ANP concen-

*National Institute for Biological Standards and Control, Holly Hill, Hampstead, London, NW3 6RB, U.K. (1986) Invitation letter.

trations (Panos *et al.*, 1992). While these authors, as well as another group (Colantonio *et al.*, 1989), failed to detect a significant circadian rhythm of ANP in patients with compensated or decompensated cirrhosis, plasma renin activity and plasma aldosterone concentrations showed more marked circadian profiles in patients with cirrhosis than in controls with highest elevations during day time. These observations support earlier findings (Trevisani *et al.*, 1989) of alterations of circadian rhythm in patients with hyperaldosteronism correlating to the pattern of renal sodium excretion. Thus, both ANP and renin–aldosterone seem to be involved in renal sodium handling of patients with cirrhosis. We have, therefore, proposed a ratio of ANP/aldosterone, possibly reflecting natriuretic hormonal activities, and found a correlation to baseline as well as to water immersion stimulated sodium excretion in patients with and without ascites (Gerbes *et al.*, 1989). This has been confirmed by recent observations (Bernardi *et al.*, 1993; Angeli *et al.*, 1992), showing that patients with ascites undergoing spontaneous diuresis had higher ANP/plasma renin activity ratios than controls. This ratio was also higher in patients responding to diuretic therapy than in non-responders (Angeli *et al.*, 1992).

ANP plasma concentrations in patients with chronic liver disease are influenced by short-term changes of sodium intake. On a 100 mmol, as compared to 20 mmol, per day sodium diet, patients with cirrhosis and a history of volume retention showed a more marked increase of plasma ANP concentration than patients without ascites or controls (Warner *et al.*, 1990). Furthermore, diuretic therapy influences plasma concentrations in patients with ascites. Our preliminary observation (Gerbes *et al.*, 1985) of a decrease of plasma ANP following diuretic therapy was confirmed by different groups (Uemura *et al.*, 1989; Salerno *et al.*, 1990b). The latter investigators found higher than normal ANP plasma concentrations only in patients with ascites not subjected to diuretic therapy. Decreases of plasma ANP following hemodialysis and increases following albumin infusion were observed in patients with fulminant hepatic failure (Panos *et al.*, 1991).

These findings underline the importance of standardizing conditions for determination of neurohumoral systems, and especially of ANP, and may explain quite a few discrepancies and variations of results obtained by different investigators. Altogether, ANP plasma concentrations in cirrhosis are normal or elevated.

4.2. Characterization of ANP Immunoreactivity

Despite increased ANP plasma concentrations in cirrhosis, biological activity could be reduced with precursor forms or degradation products of ANP, recognized by the immunoassay but exhibiting less biologic activity (Arendt *et al.*, 1987). In a preliminary observation (Arendt *et al.*, 1986), the HPLC molecular weight pattern of immunoreactive ANP of patients with cirrhosis did not differ significantly from controls. This was confirmed recently (Jiménez *et al.*, 1991): about two-thirds of the ANP immunoreactivity analyzed by chromatography in both cirrhotic patients with ascites and healthy subjects coeluted with synthetic ANP 99–126. Moreover, cirrhotic ANP displayed the same ability to inhibit the binding of ^{125}I-labelled ANP to rat glomerular and bovine adrenal membrane ANP receptors as did synthetic human ANP. Thus, there is no evidence for dysregulation of the ANP maturation process in cirrhosis.

4.3. Release Into and Clearance From the Circulation

ANP plasma concentrations in chronic liver disease different from controls could be due to alterations of release and/or clearance. There are discrepant findings in this respect.

Following central volume expansion by head-out water immersion, healthy subjects showed a 2-fold increase of ANP plasma concentrations (Gerbes *et al.*, 1988); this was blunted to about half in patients with cirrhosis and ascites (Gerbes *et al.*, 1989). Similarly, ANP increase upon infusion of 500 mL saline solution was smaller in patients with ascites. In contrast, patients with ascites and peripheral edema exhibited an exaggerated ANP increase following water immersion (Epstein, 1989). Increased ANP plasma concentrations in the coronary sinus and higher coronary sinus blood flow in patients with cirrhosis and ascites as compared to healthy volunteers, unfortunately not matched for age, lead to the estimation of a strikingly increased cardiac release of ANP in cirrhosis (Ginès *et al.*, 1988). Several investigations have demonstrated a marked increase of circulating ANP

in patients with cirrhosis and ascites following massive central volume expansion, e.g. following the implantation of a peritoneo-venous shunt (Klepetko *et al.*, 1988). For obvious reasons, however, this response cannot be compared to that of healthy controls. Altogether, there is no clear evidence for alterations of ANP release in patients with cirrhosis.

Obviously, plasma concentrations of endogenous substances are determined by both release and clearance (Gerbes and Vollmar, 1990; Henriksen, 1991). Interestingly, the liver with an arterio-venous extraction ratio of about 40% for C-terminal ANP in rats contributes significantly to the overall splanchnic ANP extraction (Gerbes *et al.*, 1992). Thus, liver disease might affect hepatic ANP clearance and influence peripheral plasma concentrations. However, splanchnic ANP extraction ratio in patients with cirrhosis with or without ascites as well as hepatic-intestinal clearance were found to be similar as in controls (Henriksen *et al.*, 1990, 1993; Tesar *et al.*, 1990). Recently, a negative correlation of serum bilirubin concentration and splanchnic ANP extraction was found in patients with cirrhosis (Moreau *et al.*, 1991). Interestingly, 3 of these 11 subjects exhibiting a very low indocyanine green clearance and presumably very poor splanchnic clearance also showed very low peripheral venous as well as arterial ANP concentrations. This would allow the conclusion, that some patients with severe cirrhosis and a decreased ANP clearance show an even more striking decrease of ANP synthesis, resulting in low peripheral venous concentrations. Thus, there is no convincing evidence for changes of splanchnic ANP clearance in cirrhosis.

4.4. Renal and Vascular Response to ANP

A number of investigations have demonstrated a blunted renal response to ANP in both animal models of cirrhosis as well as in patients (Badalamenti *et al.*, 1992; Brenard *et al.*, 1992; Firth *et al.*, 1988; Ginès *et al.*, 1992; Laffi *et al.*, 1989; López *et al.*, 1989; Maher *et al.*, 1990; Panos *et al.*, 1990; Salerno *et al.*, 1990a; Tesar *et al.*, 1989; Tulassey *et al.*, 1990). Several hypotheses have been offered to explain the reduced renal response to ANP: increased activity of the counteracting renin–aldosterone and sympathico-adrenergic systems, ANP-induced reduction of renal perfusion pressure, activation of sodium retaining neurohumoral systems upon lowering of arterial pressure by ANP, changes of renal ANP receptor status and signal transduction.

Regarding the response to endogenous ANP elevations, the infusion of 2 L of saline solution lead to comparable increases of plasma ANP concentrations in 6 controls, 6 patients with and 6 patients without ascites (Tesar *et al.*, 1989). This was accompanied by a significant increase in urinary flow and sodium excretion in both controls and non-ascitic cirrhotics, but not in patients with ascites. Similarly, during head-out water immersion with an increase of plasma ANP concentration, patients with cirrhosis and ascites did not show an increase of renal excretion of the second messenger cyclic guanosine-mono-phospate (cGMP) (Gerbes *et al.*, 1989). Following the end of immersion, these patients exhibited a decrease of natriuresis despite persistant elevation of plasma ANP.

The response to exogenously administrated ANP seems to be clearly heterogeneous in patients with decompensated cirrhosis. An infusion of 100 ng/min/kg body weight for 45 min following an initial bolus of 50 μg of ANP elicited a remarkable increase in natriuresis in 5 patients with cirrhosis and ascites, induced an intermediate response in 4 patients and showed no effect in 6 patients (Laffi *et al.*, 1989). Both responders and non-responders showed a significant decrease in mean blood pressure, which in the non-responders was followed by a significant increase of plasma renin activity and heart rate. The authors, therefore, hypothesized that the natriuretic effect of ANP in non-responders was blunted by the hemodynamic and hormonal changes triggered by the concommitant ANP induced hypotension. A similar heterogenous response to ANP was observed in preascitic bile duct-ligated dogs (Maher *et al.*, 1990). ANP administration at 175 ng/kg/min induced an increase of sodium excretion in 5 dogs but not in another 4. These observations suggest some defect of ANP signal transduction in cirrhosis.

In several investigations, patients with cirrhosis, following even low dose infusions of ANP, showed a marked decrease of mean arterial pressure, e.g. by 18% after 25 ng/kg/min ANP

(Brenard *et al.*, 1992). Therefore, it has been speculated that this further reduction of a lower than normal basal blood pressure (Beutler *et al.*, 1989) in cirrhosis, by reducing renal perfusion pressure and stimulating the activity of sodium retaining hormonal systems, could counteract the natriuretic effect of ANP (Gerbes *et al.*, 1989). Furthermore, it could be possible that patients with cirrhosis exhibit an exaggerated vascular reactivity that could enhance peripheral vasodilation and further reduce the renal response (Salerno *et al.*, 1990b). To elucidate this question, ANP was combined with norepinephrine administration (Badalamenti *et al.*, 1992; Ginès *et al.*, 1992; López *et al.*, 1989). While urinary flow rate was markedly improved by the coadministration of ANP (1 mg/kg as bolus) and norepinephrine, dosed to raise baseline blood pressure by 15–20 mm Hg, there was no improvement of sodium excretion (Badalamenti *et al.*, 1992). In another study, the infusion of 15 ng/kg/min of ANP prompted no increase of urinary volume nor sodium excretion in 11 of 16 patients with cirrhosis and ascites (Ginès *et al.*, 1992). In seven of these patients, an infusion of norepinephrine that raised their arterial pressure to the levels of responders did not reverse the blunted renal response. These observations point towards a blunted response of the kidney, irrespective of systemic blood pressure or renal perfusion pressure. This contention is supported by the observation of impaired natriuretic response in the isolated kidneys of rats with experimental cirrhosis (Panos *et al.*, 1990). It seems to be an ANP-specific phenomenon, since isolated kidneys from cirrhotic animals showed a normal natriuretic response to stepwise increases in perfusion pressure. In normal subjects, a bolus injection (33 μg) of ANP evokes an increase in cGMP plasma levels (Heim *et al.*, 1990) and renal cGMP excretion. Patients with cirrhosis and ascites, however, with increased basal plasma cGMP concentrations showed less increase of humoral cGMP following endogenous ANP elevations (Pilz, 1991) or following a 30 min infusion of 0.5 μg/kg ANP (Miyase *et al.*, 1990).

In order to further elucidate the blunted response of the kidney in cirrhosis, the glomerular ANP receptor status was investigated. On isolated glomeruli of bile duct ligated rats without ascites, density of ANP-binding sites was found to be increased in comparison to sham-operated controls (Morgan *et al.*, 1992). These authors found just one single type of ANP-binding site, which was not characterized further. Given the totally different function of the B- and C-receptors for ANP, however, quantitative discrimination seems mandatory when searching for functional changes. Therefore, we had developed a displacement-binding assay employing ANP, as well as a truncated analog binding to C-receptors only for the quantitative discrimination of B- and C-receptors (Kollenda *et al.*, 1991). This was particularly important to resolve the seeming contradiction of previous reports (Ballermann *et al.*, 1985; Cachofeiro *et al.*, 1989), namely a blunted biological response and reduced cGMP generation despite an increase of total glomerular ANP receptor density in various conditions. We found a doubling of ANP receptor density following water deprivation in rats, entirely due to an increase of C-receptors with no change of B-receptors (Kollenda *et al.*, 1990). Thus, it would seem that changes of the density of the C-receptors, involved in the clearance of ANP rather than of the guanylate cyclase coupled B-receptors were important in physiologic regulations of the ANP system. We then investigated the glomerular receptor status of bile duct ligated rats with cirrhosis and ascites, exhibiting no difference in ANP plasma concentrations compared to sham-operated controls. Total glomerular ANP receptor density in cirrhotic animals was about twice that of controls, and quantitative discrimination showed that this increase was solely due to a doubling of the C-receptor density. The reduction of B-receptor density did not reach significance (Gerbes *et al.*, 1991b). The change of ANP receptor status in this model of cirrhosis could thus result in an increased binding of ANP to glomerular clearance receptors and in a smaller portion of ANP remaining to bind a slightly reduced number of guanylate cyclase coupled receptors. This could contribute to the blunted renal effect of ANP in cirrhosis.

The other component most likely involved in the reduced renal response to ANP is the increased activity of sodium retaining neurohumoral systems, as mentioned above. The combination of mannitol and ANP infusion could significantly increase renal sodium excretion in patients with cirrhosis and ascites not responding to ANP alone (Morali *et al.*, 1992). Thus, it seems that an increased proximal tubular reabsorption of sodium and an increased activity of the renin–aldosterone and symphatico-adrenergic systems as seen in these patients might contribute to the ANP unresponsiveness in patients with cirrhosis and ascites.

4.5. Therapeutic Potential

Notwithstanding the above mentioned blunted response to ANP administration, pharmacological interventions leading to a minor increase of endogenous ANP in the kidney might have therapeutic potential in patients with liver disease and sodium retention. As mentioned before, inactivation of ANP is mainly due to two mechanisms: binding to clearance receptors, resulting in internalization and catabolism or hydrolysis by ecto-enzymes, in particular enkephalinase (E.C. 3.4.24.11) (Gerbes and Vollmar, 1990). This ANP-degrading enzyme has been characterized in renal tissue. Therefore, enkephalinase inhibition might result in augmented renal ANP effects. A single oral dose of Sinorphan, an enkephalinase inhibitor, caused a small increase of plasma ANP and cGMP levels in patients with cirrhosis and ascites (Dussaule *et al.*, 1991). This was followed by a slight and transient increase in humoral sodium excretion during a 2 hr period after drug administration. Interestingly, plasma aldosterone concentrations decreased significantly. Thus, enkephalinase inhibitors would seem an interesting diuretic substance, supressing the renin–aldosterone axis by raised endogenous ANP levels rather than activating it as other diuretics do. It has been shown, that infusion of the vasopressin analog ornipressin via hemodynamic effects significantly improved renal function in patients with hepato-renal syndrome (Lenz *et al.*, 1991). Possibly the coadministration of enkephalinase inhibitors might be of further benefit for these patients with liver disease and severely impaired renal function.

5. SUMMARY

Following the identification and characterization of ANP, its role in liver disease has been laboriously investigated. In particular, potential defects of ANP have been looked for. In patients with cirrhosis of the liver with or without ascites, no difference or even an increase of ANP plasma concentrations were detected. There is no evidence for circulation of immunoreactive ANP products with reduced biological activity in cirrhosis. Following volume stimulation, patients with ascites may exhibit a smaller plasma ANP increase than healthy controls. ANP clearance in the splanchnic circulation seems not to be affected in cirrhosis. It is widely accepted that the renal effect of endogenous and exogenously administered ANP is blunted in cirrhosis. This may be due to the increased activity of counteracting sodium retaining hormonal systems, such as the renin–aldosterone and the sympathico-adrenergic systems, as well as to changes of the renal receptor status with increased density of clearance receptors. Further investigations will show, whether pharmacological inhibition of ANP degradation or clearance may yield a therapeutic potential.

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