

the present study, high enkephalin levels were restricted to patients with ascites. Finally, most other peptides and amines found in increased circulating levels in patients with advanced cirrhosis (*e.g.* insulin, renin, catecholamines) have an enhanced release rate—and not an impaired hepatic inactivation—as the main cause of the increased plasma levels (5, 6). However, in my opinion, an enhanced release of methionine enkephalin would be equally interesting.

As admitted by the authors, there is experimental evidence of the co-release of methionine enkephalin and epinephrine from the adrenal glands during sympathetic activation, which is in accord with the positive correlation between plasma methionine enkephalin and epinephrine demonstrated in their study. Thus, the increased methionine enkephalin might simply follow the sympathoadrenal overactivity in the same way as neuropeptide Y follows the release of norepinephrine.

Like most previous reports on endogenous vasodilators, Thornton and coworkers did not find any relationship between the circulating level of the potential vasodilator and the decreased arterial blood pressure. This may be due to the fact that at least three powerful vasoconstrictor systems (renin-angiotensin-aldosterone, sympathoadrenal and vasopressin) may compensate for the fall in arterial blood pressure (1).

The authors propose that increased plasma opioid peptide activity increases histamine release, which in turn leads to increased lymphatic permeability in the liver, lymph leakage and ascites formation. However, available evidence suggests that microvascular permeability is *decreased* in the cirrhotic liver, with defenestration and appearance of a basement membrane (6). More likely, in my opinion, would be an effect of histamine on sinusoidal pressure (7). Moreover, these patients do not show signs of general edema due to lymphatic leakage, as one would expect if a blood-borne substance had increased the lymphatic permeability.

Although some aspects of Thornton and coworkers' interpretation may be questioned, the essential finding of a highly increased endogenous, vasodilator peptide is very important, and future longitudinal studies during development of hepatic ascites are anticipated with interest.

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AUGMENTATION OF THE NATRIURETIC RESPONSE TO ATRIAL NATRIURETIC FACTOR IN CIRRHOSIS

Ganger DR, Gottstein J, Blei AT. Hemodynamic and renal effects of atrial natriuretic factor in portal hypertensive rats. Potentiation by Phe-Ile-Orn-vasopressin. *J Pharmacol Exp Ther* 1988; 246:941-945.

ABSTRACT

The effects of atrial natriuretic factor (ANF) on splanchnic hemodynamics and renal function in portal hypertensive models are described incompletely. Furthermore, ANF-induced vasodilatation and hypotension may limit the assessment of its own renal physiological effects. We infused ANF (human ANF 102-126) to anesthetized portal vein-ligated rats, a model with prehepatic portal hypertension. Arterial pressure was reduced by 17%, but portal pressure was unaffected. Diuresis and natriuresis were explained in part by an increase in glomerular filtration rate; in addition, renal vascular resistance was significantly decreased. The natriuretic response to ANF was slightly, but significantly, decreased in portal hypertensive rats as compared to controls (fractional excretion of sodium, 1.8 ± 0.4 vs. 2.9 ± 0.3 ; $P < .05$). The addition of Phe-Ile-Orn-vasopressin, a V1 receptor agonist, normalized arterial pressure but induced a significant decrease in the portal pressure (15 ± 0.9 mm Hg base line vs. 12.8 ± 0.7 combination group; $P < .01$). Furthermore, the combination of both drugs markedly potentiated the natriuretic effects (0.4 ± 0.1 μ Eq/min of control vs. 10.0 ± 2.3 ANF vs. 32.2 ± 3.3 combination group; $P < .001$). The natriuretic potentiation resulted from increments in glomerular filtration rate and renal blood flow. Normalization of arterial pressure may enhance the renal physiological effects of ANF, in this portal hypertensive model.

COMMENTS

Identification, characterization and synthesis of atrial natriuretic factor (ANF) has raised considerable interest regarding volume regulation in cirrhosis (1). The natri-

uresis observed subsequent to administration of ANF is due to several factors, *e.g.* increase in glomerular filtration rate (GFR), inhibition of tubuloglomerular feedback, induction of medullary "washout" and direct inhibition of tubular sodium reabsorption, the relative effects of which are difficult to determine. In addition, ANF suppresses plasma concentrations of renin and aldosterone by inhibiting the synthesis of aldosterone and by blocking the release of renin and aldosterone (1). ANF is of considerable therapeutic interest in cirrhosis with its proximal and distal tubular sodium retention and activation of the renin-aldosterone system due to decreased, centrally effective, intravascular volume.

In patients with cirrhosis, particularly those with ascites, response to stimulation of endogenous release of ANF (2) as well as to low-dose infusion of synthetic ANF seems to be blunted (3). The reduced response might be due to alterations in the status of renal ANF receptors and/or to systemic and renal hemodynamic abnormalities. Several investigations support the contention that the decrease in mean arterial pressure following ANF administration in cirrhosis mediates the blunted natriuresis (4-6). Following a bolus administration of 1 μ g per kg ANF, mean arterial pressure decreased by 18 ± 3 mmHg in cirrhotic patients compared to 9 ± 2 mmHg in control subjects (4). Thus, cirrhotic subjects with an activated renin-angiotensin-aldosterone system seem particularly sensitive to the vasodilatory effects of ANF. Natriuretic response of ANF (50 μ g bolus followed by 50 ng per kg·min infusion) in cirrhosis with ascites was more pronounced in those patients with lower basal plasma renin activity and plasma aldosterone concentrations (5). In contrast, patients with an activated renin-aldosterone system show further increase of plasma renin activity after ANF, concomitant with a decrease of renal plasma flow and of GFR, and no increase of natriuresis. In another study, the increase of natriuresis was inversely related to changes in plasma renin activity, blood pressure and heart rate induced by ANF (6). Therefore, in cirrhotic patients with ascites, low-dose infusions of ANF (50 or 60 ng per kg·min) of ANF may induce greater natriuresis than high-dose infusions (75 or 300 ng per kg·min) (6). Thus, renal response to ANF administration may be optimized by a dosage large enough to induce natriuresis but small enough to avoid systemic hemodynamic alterations that activate compensatory responses. Alternatively, ANF-induced hypotension might be prevented by coadministration of vasoconstrictor substances. Vasopressin (VP) would seem a suitable candidate with considerable natriuretic potential in patients with ascites and impaired renal function (7).

In the study of Ganger et al. under comment, the effects of ANF were investigated in rats with portal hypertension induced by portal vein constriction. Infusion of ANF in high dose (500 ng per kg·min) induced a similar decrease of mean arterial pressure to that seen in control rats and only a small decrease in natriuresis. Interpretation of these data is somewhat difficult since no baseline renal perfusion and function values for the control group were provided. The second part of this paper provides fascinating data. The investigators com-

pared the effects of an infusion of ANF (500 ng per kg·min) and of VP (5 ng per kg·min) individually and together. Indeed, the ANF-induced decrease in mean arterial pressure was prevented by the co-infusion of VP. Renal blood flow and GFR, which were only slightly affected by either agent alone, were increased significantly by the combination. The most remarkable findings were the potentiation of natriuresis and of diuresis by the combined infusion. Thus, in this model of portal hypertension, coadministration of VP with ANF overcame hypotension, the limiting factor for ANF administration, and potentiated the natriuresis and diuresis. If further studies in animal models confirm these findings, clinical trials of ANF together with vasopressin should be undertaken.

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HEPATOLOGY *Elsewhere* CORRESPONDENCE

ANIMAL MODELS FOR ALCOHOLIC LIVER DISEASE

To the Editor:

We agree with most of the comments made in Dr. Mezey's review of the paper of Ainley et al. in *HEPATOLOGY Elsewhere* (*Hepatology* 1989; 9:904). However, we disagree when Dr. Mezey writes that the intragastric tube feeding rat model of experimental liver disease does