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Renal sodium retention in pre-ascitic cirrhosis: The more we know about the puzzle, the more it becomes intricate

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Ascites develops in 5–10% of patients with compensated cirrhosis per year and carries an ominous prognosis [1]. The appropriate management and possible prevention of this complication obviously depends on an in-depth knowledge of ascites pathophysiology, which remains somewhat elusive despite many studies that have addressed the topic over decades. There is no doubt that post-sinusoidal portal hypertension is the main "local" pathogenetic factor, and renal sodium retention is the main "systemic" event leading to a positive fluid balance and, ultimately, ascites formation. However, uncertainties surround both the efferent (that is the factors/systems promoting renal sodium retention) and afferent (that is the factors that activate efferent mechanisms) factors associated with renal sodium handling abnormalities [2]. Sodium balance has been demonstrated to become positive before ascites formation both in animal models of cirrhosis and humans [3–6]. Study of the early mechanisms leading to ascites would help unveil its pathophysiology in a stage of the disease where further complications involving systemic hemodynamics and renal function may act as confounding factors. In this issue of the Journal of Hepatology, Sansoè and co-workers present a fine study on an efferent mechanism potentially leading to renal sodium retention in pre-ascitic cirrhosis [7].

It has been convincingly demonstrated, both in animal models of cirrhosis and patients, that pre-ascitic renal sodium retention occurs while the glomerular filtration rate is well-preserved, indicating that sodium handling abnormalities reside at the tubular level [3–6]. Micropuncture studies performed in dogs with dimethylnitrosamine-induced cirrhosis showed that sodium resorption by the proximal convoluted tubule and hence sodium delivery to the more distal nephron segments are not impaired [3]. This demonstrates that sodium retention occurs beyond the proximal convoluted tubule, and implies that both Henle's loop and the collecting duct could be involved.

In line with the hypothesis that the collecting duct, the aldosterone-sensitive portion of the nephron, is the main site of sodium retention, is the demonstration that a progressive increase in positive sodium balance paralleled an increase in urinary aldosterone excretion in rats with pre-ascitic CCl_4-induced cirrhosis [4]. Even more compelling evidence in favour of a central role of hyperaldosteronism was provided by fully preventing renal sodium retention and ascites formation with the administration of the aldosterone antagonist spironolactone [4]. Data from humans appear to agree with these findings. The distal fractional tubular resorption of sodium was found to be increased and critical in regulating both central fluid volume and sodium excretion [8]. It is noteworthy that sodium retention in patients only occurs in the erect posture, whereas natriuresis ensues while supine [5,9]. In standing patients, renal sodium excretion is inversely correlated with plasma aldosterone concentration, which is only slightly increased [5]. Given the hyperbolic relationship between these variables, even subtle changes in aldosterone secretion can induce substantial changes in natriuresis. Moreover, the supine-induced increase in renal sodium excretion was exactly predictable, based on the parallel changes in plasma aldosterone concentration [5]. The role of aldosterone in promoting positive sodium balance and, hence, plasma volume expansion in patients with pre-ascitic cirrhosis is also supported by the effect of aldosterone antagonists: spironolactone lowers plasma volume [10] and chronic K-canrenoate administration reduces the occurrence of a combined end-point such as progression of esophageal varices and/or onset of ascites in compensated patients [11]. Further studies in human cirrhosis confirmed that erect posture-related renal sodium retention occurs at the distal nephron. However, they indicated that the proximal tubule is also involved, likely because of the selective activation of the intrarenal renin-angiotensin system [6,12]. In fact, the systemic renin-angiotensin system was not activated and low-dose Losartan, an angiotensin II receptor antagonist, prevented the upright-induced renal sodium retention.

Taken together, these studies appear to indicate that distal, aldosterone-dependent, and proximal, angiotensin II-dependent sodium retention are the main mechanisms leading to extracellular volume expansion in patients with pre-ascitic cirrhosis. This scenario, however, is not devoid of shadows. The main criticism of the role of aldosterone derives from the finding that, in certain experimental conditions, sodium balance can be positive even with normal plasma aldosterone concentration. The striking effect of posture on the renin-aldosterone axis explains why supine patients with pre-ascitic cirrhosis exhibit normal or even

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depressed plasma aldosterone concentrations [5]. However, this cannot apply to quadrupeds like dogs [3]. Thus, attention shifted to a hitherto neglected portion of the nephron: the loop of Henle. By assaying the natriuretic efficiency of Furosemide in rats with bile-duct ligation, Jonassen et al. [13] provided indirect evidence for an increased activity of the bumetanide-sensitive $Na^+K^+2Cl^-$ symporter (BSC-1) located in the luminal membrane of epithelial cells lining the thick ascending limb (TAL) of Henle's loop, which appeared to be hypertrophic. These findings were confirmed in CCl_4-induced cirrhosis [14], suggesting that increased sodium chloride resorption at the loop of Henle contributes to the early sodium retention that precedes ascites formation. Consistently, immunoblotting of renal sodium transporters or channels in cirrhotic rats revealed an increase in many of them, including BSC-1 [15]. However, the abundance of aldosterone-sensitive transport proteins was also markedly increased.

Sansoè et al. adopted a different approach to evaluate Henle's loop function in pre-ascitic cirrhosis [16]. They employed calcium infusion as a tool to gauge sodium handling in the TAL of Henle's loop, since hypercalcemia lowers sodium resorption through the inhibition of BSC-1 with an effect resembling that of loop diuretics. This effect is mediated by the activation of calcium-sensing receptors (CaRs), whose molecular structure was identified in 1993 [17]. These members of family C of the G protein-coupled receptors are expressed in many human tissues, namely the parathyroid glands, where they regulate PTH synthesis and secretion, and kidney, where they influence electrolyte and water resorption [18]. All nephron segments express CaRs, with the possible exception of glomeruli, but the effect of their stimulation is mainly evident in the TAL of Henle's loop, where it reduces BSC-1 content, and the distal convoluted tubule, where it suppresses water channel expression [17,18]. The role of CaRs in renal sodium handling in health and disease is not fully understood. However, there are conditions where changes in CaRs structure or function could play a role, such as type 5 Bartter syndrome and essential hypertension [18].

In patients with pre-ascitic cirrhosis, intravenous calcium load decreased the fractional sodium resorption beyond the proximal tubule, resulting in greater diuresis, natriuresis, and free water clearance with respect to healthy controls [16]. As aldosterone-driven potassium secretion was similar in patients and controls and unaffected by calcium loading, the authors concluded that sodium retention in cirrhotic patients had to occur in Henle's loop. In our view, however, the fact that the subjects were studied during prolonged supine posture, which is known to suppress aldosterone and promote natriuresis in pre-ascitic cirrhosis [5], likely influenced these results.

Sansoè et al. further assessed the activity of the calcium-dependent diuretic system in experimental cirrhosis [7], evaluating renal function, hormonal status, renal prostaglandin E_2 (PGE_2) excretion, and renal tissue concentrations of BSC-1 and CaRs in rats with CCl_4-induced cirrhosis in the pre-ascitic stage. They found that the renal content of BSC-1 was increased, confirming previous findings [15], whereas that of CaRs was reduced. Then, by administering the calcimimetic molecule poly-L-arginine they found that diuresis, renal sodium excretion, and free water clearance, which were reduced in cirrhotic rats, returned to normal. Such an effect occurred without any change in the renin-aldosterone axis or arginine-vasopressin levels and was associated with an increase in renal blood flow, likely promoted by an enhanced PGE_2 synthesis. Unfortunately, the calcimimetic drug was not given to normal rats, so we cannot know whether the renal responses seen in cirrhotic animals were enhanced, an effect that would have strengthened the hypothesis that the CaRs/BSC-1 system plays a major role in pre-ascitic renal sodium retention. In addition, the causes/mechanisms leading to CaRs downregulation remain unexplained.

In conclusion, the mechanisms leading to extracellular fluid expansion in pre-ascitic cirrhosis are further complicated by the addition of a new player: the BSC-1 at the ascending limb of Henle's loop. Like many other pathophysiological backgrounds of disease, early renal sodium handling abnormalities of cirrhosis appear to result from the interplay of several factors/systems, including aldosterone, angiotensin II and still undefined factors influencing CaRs and BSC-1 expression, without forgetting the potential roles of the sympathoadrenergic system [19] and prostaglandins [20]. As a consequence, almost all nephron segments participate in sodium retention, even though a hierarchy between them, if any, cannot be defined as yet. Nevertheless, the new findings on the role of BSC-1 and the possibility to suppress its activity with poly-L-arginine is particularly appealing as this molecule, besides natriuresis, also improved renal perfusion and did not activate vasoconstrictor systems. On the other hand, caution is required before translating the results obtained in experimental animals to patients, also taking into account that posture has a substantial influence on sodium retaining systems and renal function.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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