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Pathogenesis of solute-free water retention in experimental ascitic cirrhosis: Is vasopressin (ADH) the only agent to blame?

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Background: Catecolamines and angiotensin II overproduction reduces fluid delivery to the Henle's loop and renal excretion of solute-free water. In ascitic cirrhosis, hypersecretion of vasopressin (ADH) is thought to rule tubular free-water reabsorption (TFWR), but ADH V2-receptor antagonists are not beneficial in the long-term treatment of hyponatremic ascites.

Aim: We explore the hypothesis that excess TFWR in ascitic cirrhosis could depend on proximal tubular fluid retention rather than on ADH hypersecretion.

Methods: 60 ascitic cirrhotic rats were carefully assessed: rats receiving 13-week CCl4 administration only (group G1), cirrhotic rats receiving daily diuretics (0.5 mg/kg furosemide + 2 mg/kg K+-canrenoate during the 11th-13th weeks of CCl4) (G2), cirrhotic rats treated with diuretics + daily oral guanfacine, α2-adrenergic receptor agonist and sympatholytic agent, 2 (G3), 7 (G4), or 10 mg/kg (G5); ascitic rats treated with diuretics + SSP-004240F1, vasopressin V2-receptor antagonist, 1 mg/kg (G6).

Results: Diuretics + V2 antagonists (in G6) and diuretics + guanfacine 2 mg/kg (in G3) reduced TFWR from 32±11 (in G1) to 21±9 and to 20±8 microL/min, respectively (P<0.03). Compared to G2, the addition of guanfacine (2 mg/kg) (in G3) to diuretics reduced serum norepinephrine from 423±122 to 211±111 ng/L (P<0.01), plasma renin activity from 25±12 to 9±7 ng/mL/h (P<0.03), and TFWR from 45±18 to 20±8 microL/min (P<0.01). In the population of 60 rats, TFWR did not correlate with ADH levels (r=0.12, P: n.s.), but showed correlations with plasma aldosterone (r=0.51, P<0.01), urinary potassium excretion rate (r=0.90, P<0.001), and osmolar clearance (r=0.93, P<0.001).

Conclusions: Increased distal delivery of fluid, achieved through a reduction in adrenergic function and renin levels, is as effective as ADH V2-receptor blockade to blunt excess TFWR in ascitic cirrhosis.

Biography

Giovanni Sansoè graduated in Medicine (University of Torino, Italy) in 1990 and specialized in Gastroenterology and Digestive Endoscopy (University of Modena, Italy) in 1996. He completed a Fellowship in Hepatology (University of Toronto, Canada) in 2005. He worked as Clinical Associate Professor for a few months (University of Calgary, Canada) in 2008. He is a Clinical Hepatologist of the Gradenigo Hospital, University of Torino, Italy. He has published more than 30 papers in reputed journals dealing with the renal complications of portal hypertension. He serves as invited reviewer for the following medical journals: Gut, J Hepatol, Am J Kidney Dis, and others.

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