HEPATOPORTAL BUMETANIDE-SENSITIVE Na^+- and K^+-SENSOR MECHANISMS

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Summary

We have demonstrated that Na^+ receptor exists in the hepatoportal region plays an important role in regulating body fluid homeostasis. The afferent pathway is the periarterial hepatic nerve, the efferent pathway is the renal sympathetic nerve, and the central pathway involves nucleus solitary tract, area postrema, periventricular hypothalamic nucleus, and supraoptic nucleus. However, sensing mechanism of Na^+ has been unclear. To investigate mechanisms involved in hepatoportal Na^+ sensing, responses of hepatic afferent nerve activity (HANA) to intraportal hypertonic NaCl injection were measured before, and after, intraportal infusion of inhibitors of Na^+ transport systems. HANA increased in response to the intraportal injection of 0.75 M NaCl in a dose-dependent manner. The HANA response was not affected by amiloride or SITS, but was suppressed in a dose-dependent manner by intraportal infusion of ouabain, furosemide, or bumetanide. These results indicate that the hepatoportal Na^+ receptor senses the Na^+ concentration via the bumetanide-sensitive Na^+ K^+ $2Cl^-$ cotransporter. Although the linkage between the Na^+ K^+ $2Cl^-$ cotransporter and the increased HANA is unclear, two possibilities can be considered. Firstly, an increase in hepatocellular volume, induced by Na^+ influx via the Na^+ K^+ $2Cl^-$ cotransporter, might stimulate the connected nerve terminal. Secondly, the nerve terminal itself might bear the Na^+ K^+ $2Cl^-$ cotransporter and the increasing Na^+ concentration might depolarize the nerve terminal. If either of these is true, the possibility exists that the bumetanide-sensitive Na^+ K^+ $2Cl^-$ cotransporter also senses the K^+ concentration in the portal vein. Accordingly, to determine whether a K^+-sensor mechanism exists in the hepatoportal region, HANA responses to intraportal injection of KCl were examined in anesthetized rats. Hepatic afferent nerve activity increased in response to intraportal injection in a K^+ concentration-dependent manner and the increase was attenuated by inhibition of the Na^+ K^+ $2Cl^-$ cotransporter by bumetanide in a dose-dependent manner. These results suggest that a bumetanide-sensitive K^+-sensor mechanism exists in the hepatoportal region. Stimulation of this mechanism by intraportal KCl infusion elicited an immediate and powerful kaliuresis with no significant change in the plasma K^+ concentration; this was significantly greater than the kaliuresis induced by intravenous KCl infusion and was attenuated by severing the periarterial hepatic nervous plexus. These results indicate that a hepatoportal bumetanide-sensitive K^+-sensor mechanism senses the portal venous K^+ concentration and that stimulation of this sensor mechanism causes kaliuresis, which is mainly mediated by the periarterial hepatic nervous plexus.