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Pharmacological inhibition of ENaC or NCX can attenuate hepatic ischemia-reperfusion injury exacerbated by hypernatremia

Key words: Liver transplantation; Epithelial sodium channel (ENaC); Na^+/Ca^{2+} exchanger (NCX); Hypernatremia

Research Summary

Background: Donors with serum sodium concentration >155 mmol/L are extended criteria donors for liver transplantation (LT). Elevated serum sodium of donors leads to an increased incidence of hepatic dysfunction in the early postoperative period of LT; the exact mechanism has not been reported.

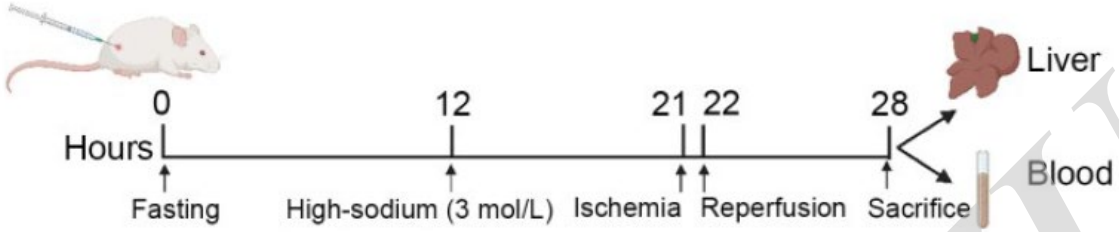
Methods: We constructed a Lewis rat model of 70% hepatic ischemia-reperfusion (I/R) with hypernatremia and a BRL-3A cell model of hypoxia-reoxygenation (H/R) with high sodium concentration (HS) culture medium precondition. To determine the degree of injury, biochemical analysis, histological analysis, and oxidative stress and apoptosis detection were performed. We applied specific inhibitors of the epithelial sodium channel (ENaC) and Na^+/Ca^{2+} exchanger (NCX) in vivo and in vitro to verify their role in injury.

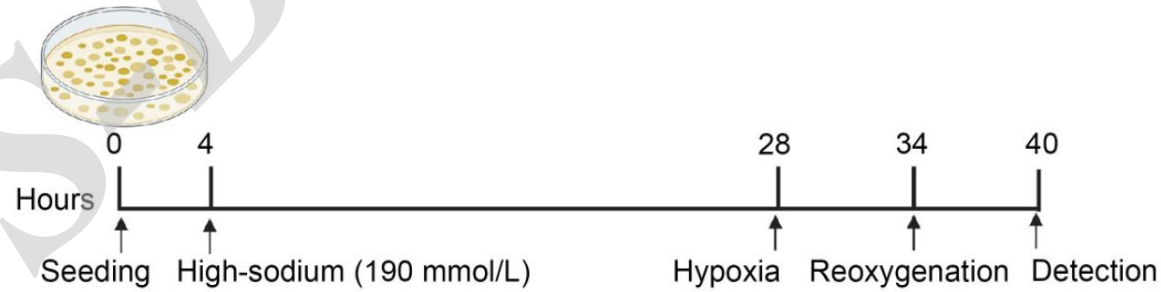
Results: Serum alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase levels and the area of hepatic necrosis were significantly elevated in the HS + I/R group. Increased reactive oxygen species (ROS) production, MPO-positive cells, and aggravated cellular apoptosis were seen in the HS + I/R group. The HS + H/R group of BRL-3A cells showed significantly increased cellular apoptosis and ROS production compared to the H/R group. The application of Amiloride (Amil), a specific inhibitor of ENaC, reduced ischemia-reperfusion injury (IRI) aggravated by HS both in vivo and in vitro, evidenced by decreased serum transaminases, inflammatory cytokines, apoptosis, and oxidative stress. SN-6, a specific inhibitor of NCX, had a similar effect.

Innovation points

1. We applied original animal and cellular models of HS.

Our experiments verified that a stable 190 mmol/L serum sodium concentration rat model could be established by applying a 3 mol/L NaCl solution pumped through the tail vein.





2. We proved hypernatremia aggravates hepatic ischemia-reperfusion injury.

3.The application of Amiloride and SN-6, specific inhibitors of ENaC and NCX, reduced ischemia-reperfusion injury aggravated by HS both in vivo and in vitro

Schematic diagram of the mechanism by which hypernatremia aggravates hepatic IRI.

Elevated extracellular Na^+ leads to the increase of the entry of Na^+ into the cell via ENaC. Increased intracellular Na^+ promotes the exchange of intracellular Na^+ with extracellular Ca^{2+} via NCX. Intracellular Ca^{2+} overload leads to increased production of ROS and NLRP3, which ultimately enhances cellular apoptosis and inflammation. The inhibitors of ENaC and NCX, Amil and SN-6, can reduce hypernatremia-aggravated hepatic IRI.