Multiple roles for transient receptor potential (TRP) non-selective cation channels in liver function

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The liver plays a central role in whole body homeostasis by mediating the metabolism of carbohydrates, fats, proteins, drugs and xenobiotic compounds, and the secretion of bile acids and proteins. The liver is perfused with blood from two sources. The portal vein conveys blood from the gastrointestinal and splenic vascular beds and accounts for about 80-90% of the blood flow. The hepatic artery delivers oxygenated blood. The components of bile fluid are secreted from hepatocytes into the bile cannaliculus then *via* the biliary tree to the terminal bile duct. The liver (considered as a composite organ) is composed of many cell types. These are principally the hepatocytes, endothelial cells, Kupffer cells, smooth muscle cells, stellate and oval cells, neuronal cells and the cholangiocytes lining the bile ducts. Hepatocytes account for about 70% of the mass of the liver.

The nature and physiological functions of transient receptor potential (TRP) non-selective cation channels expressed in the liver will depend on the cell type being considered. Most studies on the roles of liver TRP channels have investigated hepatocytes. Many members of the TRP non-selective cation channel family are expressed in hepatocytes but only a few have been studied in any depth (Rychkov & Barritt, 2011). The level of expression and precise intracellular functions of a given hepatocyte TRP channel may vary between species. It is likely that TRP channels in hepatocytes mediate the entry of Ca^{2+} and Na^{+} in response to specific hormonal and neuronal stimuli and deliver Ca^{2+} to specific intracellular locations. While there is some evidence that in a number of other animal cell types, some TRP proteins, including TRPC1 (canonical) and some other members of the TRPC family, can interact with STIM1 and are involved in store-operated Ca^{2+} entry (SOCE), there is no evidence for such a role in rat hepatocytes. However, a role for TRP proteins in hepatocyte SOCE cannot be excluded. There is evidence that in hepatocytes TRPC1 is involved in the control of cell volume, and for roles of TRPV1 (vanilloid) and TRPV4 in cell migration, TRPC6 and TRPM7 (melastatin) in the regulation of hepatocyte proliferation and for TRPM1 in lysosomal Ca^{2+} release. It is likely that TRPM6 and TRPM7 are involved in the regulation of Mg^{2+} homeostasis in hepatocytes, but this has not been well studied. TRP channels, especially TRPM2, TRPM7, TRPC5 as well as store-operated Ca^{2+} channels are likely involved in Ca^{2+} entry to hepatocytes in pathological conditions such as liver toxicity, hepatitis, and ischemia reperfusion injury. Studies of the expression of TRP proteins in liver tumor cell lines suggest that altered expression of TRPC6, TRPM2, TRPM7 and TRPV1 may play a role in the development and progression of hepatocellular carcinoma and of metastatic liver cancers. Recent results obtained in our laboratory have shown that in steatotic hepatocytes Ca^{2+} entry is greatly impaired compared with that in normal hepatocytes. While much of this impairment involves SOCE, some may be due to altered TRP channel function. The activity of TRPP2 (PKD2L1), which associates with PKD1, a member of the polycystin family, to form functional ion channels, is altered in hepatocytes and cholangiocytes in patients with autosomal dominant polycystic kidney disease. While there are no reports of the nature of TRP channels expressed in liver sinusoidal endothelial cells, on the basis of recent results obtained with endothelial cells from other blood vessels such as bovine aorta, it is likely that members of the TRPC family play an important role in the functions of endothelial cells in liver sinusoids. Moreover, other studies have shown that the expression of some endothelial TRP proteins is regulated by the blood glucose concentration and may be altered in insulin resistance and type 2 diabetes (Bishara and Ding 2010). It can be concluded that: (i) TRP channels have a wide variety of physiological functions in the liver; (ii) expression and function of a given TRP protein depend on cell type; and (iii) much is still to be discovered about liver TRP channels.

Bishara NB, Ding H. (2010) *American Journal of Physiology Heart Circulation Physiology* **298**: H171-H178.
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