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Calcium-Dependent Cell Damage Induced by Bile Acid

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The mechanism of how cholelithiasis increases the risk of acute pancreatitis remains obscure. When gallstones obstruct the lower biliary tract, bile acids can enter the pancreas either by luminal diffusion or by interstitial leakage. Here we provide the first evidence that bile acids can be transported into pancreatic acinar cells through the membrane transporters and induce cell death by impairing intracellular Ca^{2+} signals. A comprehensive molecular and functional study demonstrated that pancreatic acinar cells express the Na^{+}-coupled bile acid transporter Ntcp1 in the luminal membrane and the HCO_3^{-}-coupled bile acid transporter Oatp1 in the basolateral membrane. Measurements in intact and permeable pancreatic acini and in isolated skeletal muscle microsomes showed that bile acids specifically inhibit the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) pump to chronically deplete parts of the Ca^{2+} stored in the ER. This, in turn, leads to activation of capacitative Ca^{2+} entry and a chronic $[Ca^{2+}]_i$ load. The increase in $[Ca^{2+}]_i$ activates the inflammation-associated JNK pathway and the NF- B transcription factors, leading to cell damage and death. Notably, activation of the inflammatory signals and cell death were inhibited by buffering $[Ca^{2+}]_i$ by loading the cells with BAPTA. These findings suggest an underlying mechanism for bile acid-induced cell injuries and provide therapeutic targets for the treatment.