Alcohol-induced pancreatic trypsinogen activation depends on calmodulin-sensitive inositol trisphosphate receptors types 2 and 3

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One of the major causes of acute pancreatitis is excessive alcohol intake; however the molecular mechanism of this severe inflammatory disease is not completely understood. Acute pancreatitis is generally initiated by premature trypsinogen activation in pancreatic acinar cells mediated by excessive intracellular calcium release from internal stores. We now show that in two-photon permeabilized mouse pancreatic acinar cells even a relatively low ethanol concentration elicits calcium release from intracellular stores and also induces intracellular trypsin activation. Adding the calcium sensor calmodulin (at a normal intracellular concentration) to the solution surrounding the permeabilized cells markedly reduced ethanol-induced calcium release and trypsin activation. Both ethanol-elicited calcium liberation and trypsin activation were significantly reduced in acinar cells from mice in which type 2 inositol trisphosphate receptors had been knocked out. Double knock out of inositol trisphosphate receptors of both types 2 and 3 further reduced ethanol-induced calcium release and trypsin activation to low levels. Thus the inositol trisphosphate receptor calcium release channels, that are responsible for normal pancreatic stimulus-secretion coupling, also play a major role in the toxic action of ethanol. Calmodulin provides a protective mechanism, regulating the sensitivity of the calcium release process.