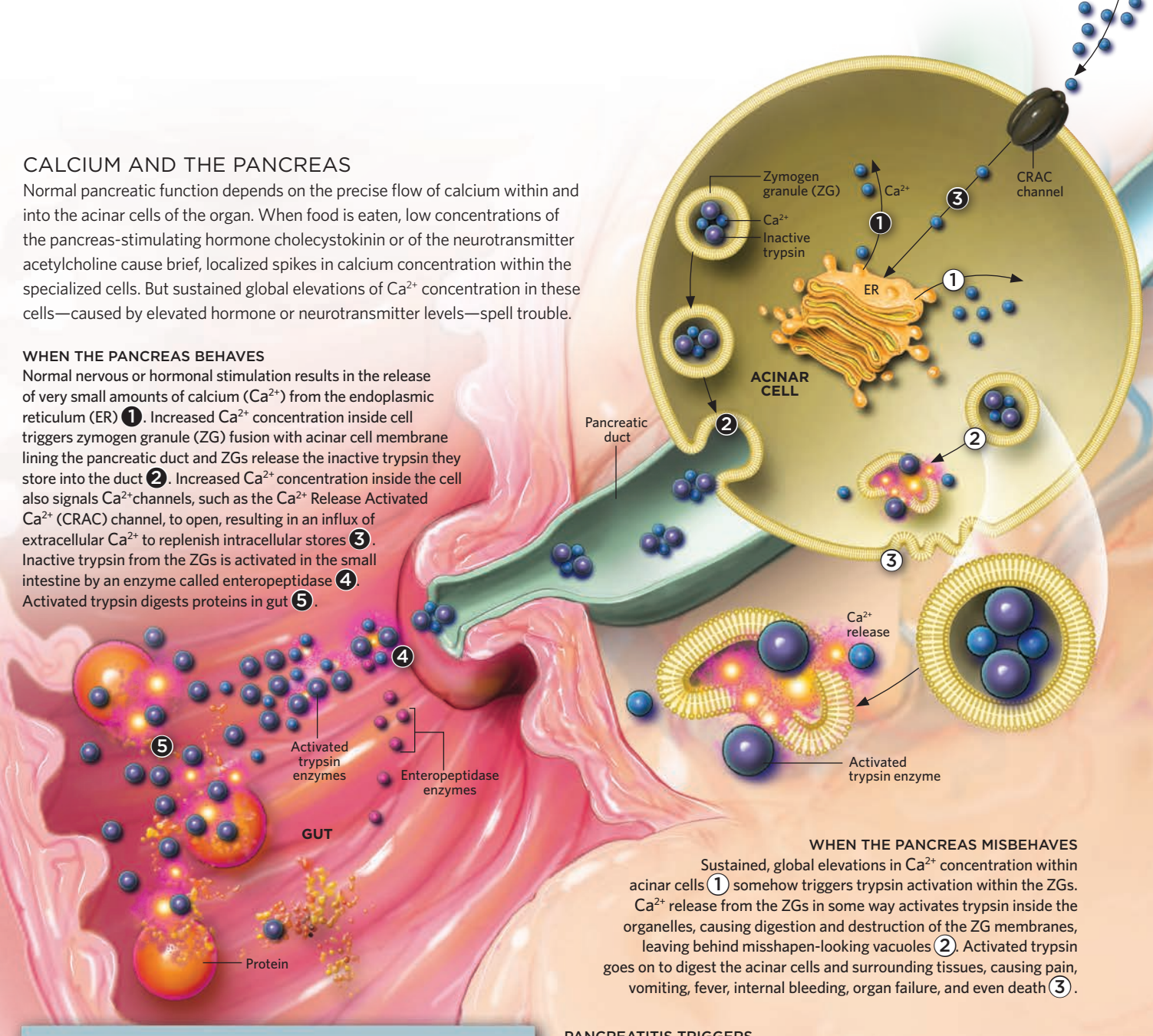
CALCIUM AND THE PANCREAS

Normal pancreatic function depends on the precise flow of calcium within and into the acinar cells of the organ. When food is eaten, low concentrations of the pancreas-stimulating hormone cholecystokinin or of the neurotransmitter acetylcholine cause brief, localized spikes in calcium concentration within the specialized cells. But sustained global elevations of Ca^{2+} concentration in these cells—caused by elevated hormone or neurotransmitter levels—spell trouble.

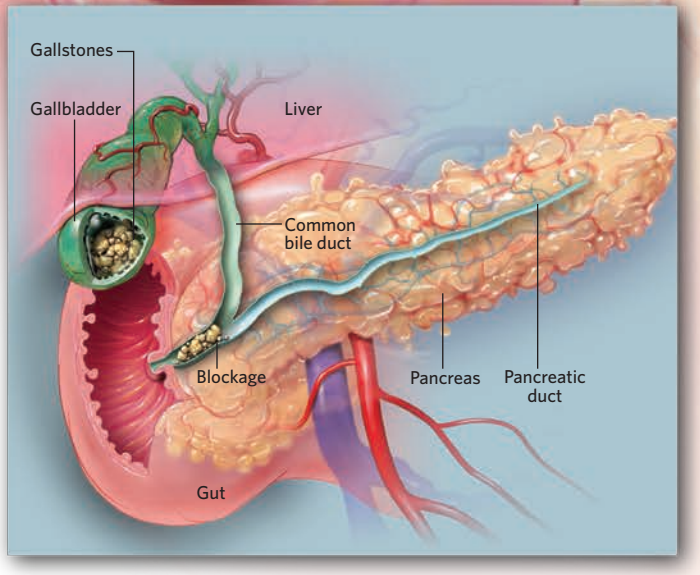
WHEN THE PANCREAS BEHAVES

Normal nervous or hormonal stimulation results in the release of very small amounts of calcium (Ca^{2+}) from the endoplasmic reticulum (ER) (1). Increased Ca^{2+} concentration inside cell triggers zymogen granule (ZG) fusion with acinar cell membrane lining the pancreatic duct and ZGs release the inactive trypsin they store into the duct (2). Increased Ca^{2+} concentration inside the cell also signals Ca^{2+}channels, such as the Ca^{2+} Release Activated Ca^{2+} (CRAC) channel, to open, resulting in an influx of extracellular Ca^{2+} to replenish intracellular stores (3). Inactive trypsin from the ZGs is activated in the small intestine by an enzyme called enteropeptidase (4). Activated trypsin digests proteins in gut (5).



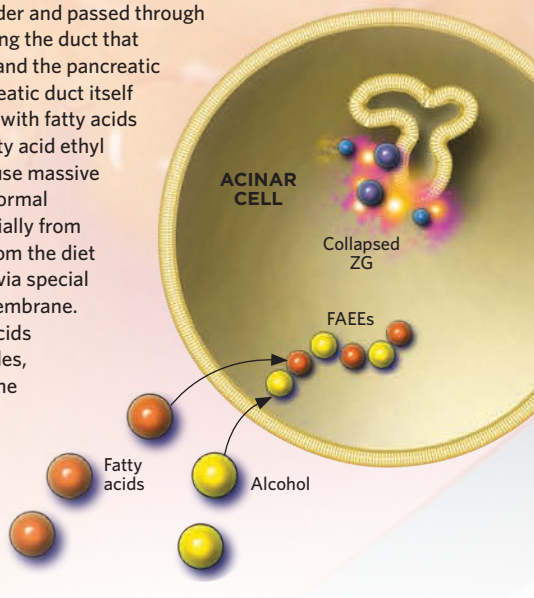
WHEN THE PANCREAS MISBEHAVES

Sustained, global elevations in Ca^{2+} concentration within acinar cells (1) somehow triggers trypsin activation within the ZGs. Ca^{2+} release from the ZGs in some way activates trypsin inside the organelles, causing digestion and destruction of the ZG membranes, leaving behind misshapen-looking vacuoles (2). Activated trypsin goes on to digest the acinar cells and surrounding tissues, causing pain, vomiting, fever, internal bleeding, organ failure, and even death (3).



PANCREATITIS TRIGGERS

Acute pancreatitis can be brought on in two ways. Jagged accretions of cholesterol called gallstones can be formed in the gallbladder and passed through ducts until they end up blocking the duct that unites the common bile duct and the pancreatic duct or obstructing the pancreatic duct itself (left). Or alcohol can interact with fatty acids within acinar cells to form fatty acid ethyl esters (FAEEs), which can cause massive intracellular Ca^{2+} release in normal pancreatic acinar cells, especially from the ZGs (right). Fatty acids from the diet are taken up into acinar cells via special transporter proteins in the membrane. Inside the acinar cells, fatty acids combine with alcohol molecules, which diffuse readily across the membrane, to form FAEEs.



ANDREW SWIFT FOR THE SCIENTIST MAGAZINE, FEBRUARY 2012