

Every day normal adults put  $\sim 30$  g of conjugated bile salts into their intestines. Most are incorporated into micelles and large vesicles that also contain cholesterol and lecithin, but a small fraction are present as monomers in solution. In the gut lumen, these micelles and vesicles also take up fatty acids and monoglycerides. The chemical activity of the free bile salt monomers is far less in the presence of lipid-rich mixed micelles than in the presence of pure bile salt micelles. As these lipid-rich micelles and vesicles travel down the small intestine, the contained lipids are absorbed, increasing the activity of the dissolved bile salt monomers. The distal ileum keeps this activity low by quickly absorbing the monomers via a sodium-dependent active transport process that is so efficient that normally almost no bile acids reach the colon. If the ileum is diseased or has been resected, however, significant quantities of bile acids do reach the colon, and there, in the absence of protective lipids, the chemical activities of the dissolved bile acid anions reach levels that affect colonic ion transport. Specifically, they stimulate the secretion of electrolytes and water, causing diarrhea (1). Not all bile acids have this effect. Dihydroxy bile acids with both hydroxy groups in the alpha configuration (this does not include ursodeoxycholic acid, which has one of its hydroxys in the beta configuration) do; the more hydrophilic trihydroxy bile acids do not. Deconjugation of the bile acids by colonic bacteria further enhances their secretory potency.

What is the mechanism for this effect? Some years ago, dihydroxy bile salts were shown to increase colonic mucosal cAMP levels and adenylyl cyclase activity (2). Subsequent studies suggest, however, that this is an indirect effect of bile salts mediated by prostaglandins and other compounds released from affected leukocytes and fibroblasts in the lamina propria.

In 1989 Dharmasathaphorn et al. (3) identified  $\text{Ca}^{2+}$  as the intracellular mediator for the action of bile salts on colonic epithelial cells. They showed that taurodeoxycholate (TDC), when applied to confluent monolayers of T84 cells (a colon cancer cell line that actively secretes  $\text{Cl}^-$  in response to a variety of stimuli), stimulates net  $\text{Cl}^-$  secretion, increases cytosolic  $\text{Ca}^{2+}$ , but does not alter the level of cAMP or cGMP. They also found that TDC was more potent on the basolateral side of the monolayer than on the apical side. Apical TDC stimulated secretion only at concentrations that markedly increased the

conductance of the monolayer, suggesting bile salt-induced leakage of bile salts to the basolateral side.

How do bile salts increase cytosolic  $\text{Ca}^{2+}$  in colonic epithelial cells, and is the  $\text{Ca}^{2+}$  responsible for the associated secretion? In this issue of the journal, Devor et al. (4) show that application of TDC to isolated T84 cells activates three conductances, one for  $\text{K}^+$ , one for  $\text{Cl}^-$  (both are necessary for secretion), and a nonselective cation conductance, and causes both a 10-fold increase in cytosolic  $\text{Ca}^{2+}$  and an accumulation of inositol monophosphate, reflecting production of inositol 1,4,5-triphosphate ( $\text{IP}_3$ ). In clever and persuasive ways, they show that the increase in  $\text{Ca}^{2+}$  is responsible for the activation of  $\text{K}^+$  and  $\text{Cl}^-$  conductances (but not the nonspecific cation conductance) and that  $\text{IP}_3$  is responsible for the increase in  $\text{Ca}^{2+}$ . TDC's effect on the T84 cell plasma membrane is quite subtle: in the time intervals between discrete channel openings, the membrane resistance is as high as ever. Its effects are strikingly similar to those of the muscarinic cholinergic agonist, carbachol (5).

How does TDC stimulate polyphosphoinositide turnover in the basolateral membrane of T84 cells? Is there a specific receptor for TDC coupled to a G protein that, in turn, activates phospholipase C (PLC)? Does TDC more directly activate PLC? Or does TDC disrupt the membrane structure sufficiently to make otherwise unavailable polyphosphoinositides available for degradation by PLC? The authors raise these interesting questions but have no answers. This is a fruitful area for future research.

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