In cholangiocytes, bile salt (BS) uptake via the apical sodium-dependent bile acid transporter (ASBT) may evoke ductular flow by enhancing cAMP-mediated signaling to the cystic fibrosis transmembrane conductance regulator (CFTR) anion channel. We considered that ASBT-mediated BS uptake in the distal ileum might also modulate intestinal fluid secretion. Taurocholate (TC) induced a biphasic rise in the short circuit current across ileal tissue, reflecting transepithelial electrogenic ion transport. This response was sensitive to bumetanide and largely abrogated in Cftr-null mice, indicating that it predominantly reflects CFTR-mediated Cl- secretion. The residual response in Cftr-null mice could be attributed to electrogenic ASBT activity, as it matched the TC-coupled absorptive Na+ flux. TC-evoked Cl- secretion required ASBT-mediated TC uptake, because it was blocked by a selective ASBT inhibitor and was restricted to the distal ileum. Suppression of neurotransmitter or prostaglandin release, blocking of the histamine H1 receptor, or pretreatment with 5-hydroxytryptamine did not abrogate the TC response, suggesting that neurocrine or immune mediators of Cl- secretion are not involved. Responses to TC were retained after carbachol treatment and after permeabilization of the basolateral membrane with nystatin, indicating that BS modulate CFTR channel gating rather than the driving force for Cl- exit. TC-induced
Cl- secretion was maintained in cGMP-dependent protein kinase II-deficient mice and only partially inhibited by the cAMP-dependent protein kinase inhibitor H89, suggesting a mechanism of CFTR activation different from cAMP or cGMP signaling. We conclude that active BS absorption in the ileum triggers CFTR activation and, consequently, local salt and water secretion, which may serve to prevent intestinal obstruction in the postprandial state.