BILE ACIDS DIFFERENTIALLY REGULATE SMOOTH MUSCLE CONTRACTILITY IN MOUSE ILEUM

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Background: Bile acids stimulate propulsive gastrointestinal (GI) transit and regulate motility through multiple receptor-mediated signaling pathways. Bile acid receptors, including the transmembrane G-protein-coupled receptor (TGR5) and the nuclear farnesoid-X-receptor (FXR), are prominently expressed in the GI tract. Mechanisms by which different bile acid receptors mediate intestinal motor functions are not well understood. In this study, we aimed to determine whether different bile acids differentially influence longitudinal smooth muscle contractions in the mouse ileum.

Materials/Methods: Ileal ileum was isolated from healthy adult C57BL/6 female mice. Intestinal segments were everted over a metal rod to expose the mucosal surface containing bile acid transporters and receptors. The everted segments were suspended in organ baths for isometric force measurements. Ileal segments were treated with 0.1, 1, 10 and 100 μM of ursodeoxycholic acid (UDCA), chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), lithocholic acid (LCA), or glycocholic acid (GCA). To understand potential roles of the cell surface bile acid receptors, ileal segments were treated with 0.1, 1, 10 and 100 μM of agonists to TGR5 (INT-777), muscarinic M1/M3 receptors (cevimeline), or epidermal growth factor receptor (EGF). To understand potential roles of the nuclear bile acid receptors, ileal segments were treated with 0.1, 1, 10 and 100 μM of agonists to FXR (fexaramine), pregnane X receptor (rifampicin), vitamin D receptor (calcitriol), or glucocorticoid receptor (methylprednisolone). Delta-force responses to each stimulus were recorded with a force-transducer.

Results: Intestinal smooth muscle contractility was increased in a dose-dependent manner by UDCA and by agonists to both TGR5 and muscarinic receptors. Conversely, 100 μM of DCA inhibited contractility. CDCA, LCA, GCA, and agonists the nuclear bile acid receptors had no net effect on ileal contractility. The stimulatory effect of UDCA was dependent on tissue eversion; UDCA had no effect when applied to non-everted ileum.

Conclusions: Individual bile acids differentially influence intestinal smooth muscle contractility in a dose-dependent manner. The stimulatory effect of UDCA is dependent upon direct access to the mucosal surface. Understanding how specific bile acids influence intestinal motor functions may facilitate the development of targeted therapies for GI disorders characterized by intestinal dysmotility or altered bile acid homeostasis.

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