Opening CFTR in the Intestine: Flushing on Demand

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EDITORIAL

Opening CFTR in the Intestine: Flushing on Demand

A new paper by Cil et al[1] has described the discovery and characterization of a small molecule capable of opening the Cl^- channel cystic fibrosis transmembrane regulator (CFTR). CFTR accounts for the majority of salt and water secretion across mucosal surfaces and into the ducts of secretory glands, and it is important for mucosal hydration in the intestine, lung, and cornea. The new channel opener was identified from a library of 120,000 drug-like synthetic compounds by using a high-throughput, single-cell screen for agonists of Cl^- transport. It is a phenylquinoxalinone named $CFTR_{act}J027$.

The investigators tested the idea that $CFTR_{act}J027$ may be applied clinically as a possible therapy for constipation. Constipation remains a significant and widespread clinical problem. The mainstays of management for decades have been various types of osmotic agents to hydrate the stool, or gut motility–stimulating drugs. More recently, new drugs have emerged that have sought to harness the natural flushing and lubrication mechanism in the intestine by promoting transepithelial fluid secretion. Prosecretory drugs currently approved include linaclotide, a peptide agonist of the guanylate cyclase C receptor, which activates CFTR. The drug also activates the other cyclic-nucleotide gated transporters responsible for the secretory response (basolateral K^+ channels and the $Na^+/K^+/2Cl^-$ cotransporter NKCC1). Lubiprostone is a prostaglandin analog that is thought to increase intracellular cyclic adenosine monophosphate and activate CFTR along with the other cyclic-nucleotide gated transporters in a similar way.

Unlike linaclotidea and lubiprostone, however, $CFTR_{act}J027$ appears to act on CFTR alone, without affecting other transporters, and without affecting intracellular signaling intermediates such as the cyclic nucleotides. The benefit of direct action on the CFTR channel is clear: a defined mechanism of action, lower likelihood of side effects, and the possibility of mucosal targeting without systemic absorption. However, there are some disadvantages related to such a narrow scope of action. Cyclic guanosine monophosphate agonists such as linaclotide and plecanatide also modulate ascending sensory nerve pathways and colonic motor pathways to inhibit visceral pain proprioception and to promote motility. Both effects likely contribute to the clinical efficacy of these compounds in the treatment of patients with irritable bowel syndrome or other functional gastrointestinal disorders.

Still, the article by Cil et al[1] outlines a number of properties that make $CFTR_{act}J027$ a promising candidate for clinical applications. The investigators used a classic opioid mouse model of constipation and showed that $CFTR_{act}J027$ is both highly specific and effective at improving constipation. Strikingly, they showed that head-to-head, at least in this mouse model, $CFTR_{act}J027$ is more effective than both linaclotide and lubiprostone despite much higher equivalent doses for these drugs than would be used clinically. The study also described some initial pharmacology and toxicity for $CFTR_{act}J027$, suggesting that the compound may undergo rapid first-pass metabolism, which likely would limit (unwanted) systemic accumulation. The flip side of CFTR function is that prolonged and irreversible activation of CFTR in the intestine causes the massive secretory diarrhea seen in *Vibrio cholerae* and toxigenic *Escherichia coli* infections. Fortunately, and perhaps because of $CFTR_{act}J027$'s lack of action on the other pathways that regulate and drive fluid secretion, cholera-like diarrhea does not occur after administration. In fact, by directly targeting and opening CFTR, the compound primarily may potentiate the normal physiological regulation of intestinal fluid secretion, although this remains to be proven.

Constipation-associated conditions such as constipation-predominant irritable bowel syndrome and opioid-induced constipation affect a large and growing proportion of the US population. This study is therefore an important and timely advance toward increasing the therapeutic options for these disorders. There are still many hurdles to overcome before application clinically. However, perhaps $CFTR_{act}J027$, or another more refined compound that opens CFTR, will be found effective in treating constipation in human beings. This would have a big impact.

WAYNE I. LENCER, MD
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts

Reference

1. Cil O, Phuan P-W, Lee S, et al. CFTR activator increases intestinal fluid secretion and normalizes stool output in a mouse model of constipation. Cell Mol Gastroenterol Hepatol 2016;2:317–327.

Correspondence
Address correspondence to: Wayne I. Lencer, MD, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, Massachusetts 02115. e-mail: Wayne.Lencer@childrens.harvard.edu.

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