Gut Online First, published on July 18, 2013 as 10.1136/gutjnl-2013-305214

New insights into intestinal secretion

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Apart from malabsorption and intestinal barrier dysfunction (via a 'leak-flux' mechanism), diarrhoea may reflect active ion secretion in the small intestine and/or colon. In recent years, our understanding about intestinal secretory mechanisms has increased enormously. Important new findings are (1) chloride, bicarbonate and potassium may be secreted simultaneously, but via independent transport processes and (2) movement of a specific ion across cell membranes may occur via several types of channels selective for that ion, but differing in their molecular structure and intrinsic biophysical properties. Additionally, Linley and coworkers now present evidence that (3) specific types of chloride and potassium channels involved in chloride and potassium secretion are differentially expressed in the apical membrane of enterocytes and goblet cells along the surface cell-crypt cell axis. Thus, we are now in a position to reconsider the ancient concept of exclusively secretory crypt cells and absorptive surface cells.[1]

In general, underlying active intestinal ion secretion is Na^+/K^+-ATPase-dependent primary transport, which results in low intracellular sodium and high intracellular potassium concentrations. The sodium gradient across the basolateral membrane facilitates basolateral chloride or bicarbonate uptake via sodium-coupled cotransport (secondary active transport), as a result of which these anions accumulate intracellularly above their electrochemical equilibrium. As a result of this gradient across the apical membrane, they are subsequently secreted into the intestinal lumen. By contrast, active potassium secretion is the direct result of ATPase-dependent uptake of potassium across the basolateral membrane (primary active transport), resulting in the intracellular accumulation of potassium ions before their movement into the intestinal lumen via apical K^+ channels.

What are the clinical implications of these basic ion transport mechanisms? One has to consider that active ion secretion is a 'temporary' phenomenon in response to a wide variety of triggering factors. Secretion reflects distinct regulatory inputs, usually via activation (opening) of ion channels in response to intracellular messengers like cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), Ca^{2+} or protein kinase C (PKC). In order to transfer these findings into clinics, one has to identify the stimuli for the named pathways. A large number of regulatory events can initiate this as, for example, mineralocorticoids[2] or adenylate/guanylate cyclase activation by pathogens like enterotoxic *Escherichia coli* which—as a result of diarrhoea—spreads from host to host. From a teleological point of view, this was referred to as the 'tears of the gut' against noxious agents.[3] Another example of clinical impact is (deconjugated) bile acid malabsorption secondary to ileal resection or disease, which results in Ca^{2+}-mediated and PKC-mediated colonic anion secretion and diarrhoea.[4] While secretory diarrhoea may be severe and life threatening (eg, cholera), basal secretion ensures an obligatory faecal water content. This is especially apparent in cystic fibrosis, where deficiency of apical cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels and the absence of chloride-driven basal water secretion causes meconium ileus in newborns. Surprisingly, in inflammatory bowel disease, active secretion seems to be of little importance,[5] diarrhoea reflecting malabsorption[6] and/or the 'leak-flux' mechanism.[7]

Thus, over the years, apart from the oral rehydration approach to certain infective diarrhoeas, antidiarrhoeal strategies have focused on the pharmacological control of intestinal ion secretion. As a prerequisite, a detailed analysis of the components and compartmentalisation of different mechanisms of active ion secretion is necessary. In this regard, Linley and coworkers have made an important contribution. Their data strongly suggest that potassium secretion occurs independently from chloride secretion, and that active potassium secretion originates from goblet cells (which make up 25% of the epithelium) via penitrem A-sensitive, high conductance, apical (BK) potassium channels. Thus, from now on, goblet cells should be considered as an important and distinct component of the intestine's secretory capability.

By contrast, active chloride secretion originates from colonocytes making up 75% of the epithelium via apical CFTR channels. Why are potassium channels necessary in this context? For continuing chloride secretion, the cell needs to get rid of potassium which has entered via Na^+/K^+-ATPase or cotransported with chloride via the basolateral $Na^+K^+2Cl^-$ cotransporter NKCC1. This is achieved through clotrimazole-sensitive, intermediate conductance, basolateral (IK) potassium channels. Noteworthy, in line with this concept, the stool is more solid in IK-deficient mice.[8] Molecular details of these transporters are presented in the introduction to Linley and coworkers' paper (2013).

The study from Linley and coworkers is highly significant, in that it provides new insights into the mechanisms of intestinal secretion by identifying different ion channels subtypes in separate cellular compartments, a first step towards selective pharmaceutical targeting of single secretory processes. So far, therapy of diarrhoea is directed towards regulatory inputs from the enteric nervous system (eg, enkephalinase inhibition by racecadotril or δ-opioid receptor activation by loperamide), although adenylate cyclase/intracellular cAMP-dependent chloride secretion is inhibited by Uzara, a traditional African antidiarrheal remedy.[9] Uzara also interferes with Na^+/K^+-ATPase, which energises all active transport processes. It is therefore only useful in secretory-type diarrhoea, and there is an urgent need to discover more selective inhibitors of transporters involved in active ion secretion. However, so far, no specific regulators of single ion channels have come into routine use in gastrointestinal medicine, despite an intensive search (eg, for luminal chloride channel blockers). To some extent, this may reflect the large diversity of channels involved in intestinal ion secretion, which to date has not been explored. Thus, an increased understanding about the individual components of intestinal secretion in different cell types offers the opportunity to overcome these limitations. For example, treatment with two specific ion channel blockers may prevent continued intestinal secretion that might result from inhibiting just one type of ion channel.

However, the reverse is also important. Bisacodyl (a PKC activator) and linaclotide (a guanylate cyclase C agonist) are used to treat constipation by activating ion channels involved in intestinal secretion. Specific activators of the apical BK channels

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described by Linley and coworkers could be very useful too. They could be used to treat idiopathic constipation, and potentially have a key role in the management of cystic fibrosis, where the normal apical CFTR channel-dependent secretory pathway is absent, and activators of an alternative potassium-driven secretory pathway may prove to be clinically effective. Once again, progress in this area will depend on detailed characterisation of ion channels and their regulation within specific types of human intestinal epithelial cells.

Contributors All three authors contributed to the writing of parts of the commentary article.

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Schulzke JD, Siegmund B, Günzel D. *Gut* Published Online First: [*please include* Day Month Year] doi:10.1136/gutjnl-2013-305214

Received 17 June 2013
Revised 25 June 2013
Accepted 29 June 2013

Gut 2013;**0**:1–2. doi:10.1136/gutjnl-2013-305214

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Gut published online July 18, 2013