Advances in Ca^{2+} modulation of gastrointestinal anion secretion and its dysregulation in digestive disorders (Review)

WEIXI SHAN[1*], YANXIA HU[1*], JIANHONG DING[1], XIAOXU YANG[1], JUN LOU[1], QIAN DU[1], QIUSHI LIAO[1], LIHONG LUO[2], JINGYU XU[1] and RUI XIE[1]

[1]Department of Gastroenterology, The Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563003; [2]Department of Oncology and Geriatrics, Traditional Chinese Medicine Hospital of Chishui City, Guizhou 564700, P.R. China

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Abstract. Intracellular calcium (Ca^{2+}) is a critical cell signaling component in gastrointestinal (GI) physiology. Cytosolic calcium ($[Ca^{2+}]_{cyt}$), as a secondary messenger, controls GI epithelial fluid and ion transport, mucus and neuropeptide secretion, as well as synaptic transmission and motility. The key roles of Ca^{2+} signaling in other types of secretory cell (including those in the airways and salivary glands) are well known. However, its action in GI epithelial secretion and the underlying molecular mechanisms have remained to be fully elucidated. The present review focused on the role of $[Ca^{2+}]_{cyt}$ in GI epithelial anion secretion. Ca^{2+} signaling regulates the activities of ion channels and transporters involved in GI epithelial ion and fluid transport, including Cl^- channels, Ca^{2+}-activated K^+ channels, cystic fibrosis (CF) transmembrane conductance regulator and anion/HCO_3^- exchangers. Previous studies by the current researchers have focused on this field over several years, providing solid evidence that Ca^{2+} signaling has an important role in the regulation of GI epithelial anion secretion and uncovering underlying molecular mechanisms. The present review is largely based on previous studies by the current researchers and provides an overview of the currently known molecular mechanisms of GI epithelial anion secretion with an emphasis on Ca^{2+}-mediated ion secretion and its dysregulation in GI disorders. In addition, previous studies by the current researchers demonstrated that different regulatory mechanisms are in place for GI epithelial HCO_3^- and Cl^- secretion. An increased understanding of the roles of Ca^{2+} signaling and its targets in GI anion secretion may lead to the development of novel strategies to inhibit GI diseases, including the enhancement of fluid secretion in CF and protection of the GI mucosa in ulcer diseases.

Correspondence to: Professor Jingyu Xu or Professor Rui Xie, Department of Gastroenterology, The Affiliated Hospital of Zunyi Medical University, 149 Dalian Road, Zunyi, Guizhou 563003, P.R. China
E-mail: xujingyu_gzzy@126.com
E-mail: xr19841029@aliyun.com

*Contributed equally

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Contents

1. Introduction

It is well known that $[Ca^{2+}]_{cyt}$ has an essential role in numerous important mammalian cell functions, including neurotransmitter release, gene regulation, muscle contraction, cell proliferation, differentiation and apoptosis (1). Since the function of $[Ca^{2+}]_{cyt}$ as the cell's secondary messenger is based on the presence of a concentration gradient between $[Ca^{2+}]_{cyt}$ and external Ca^{2+} ($[Ca^{2+}]_{ext}$) (2), normal $[Ca^{2+}]_{cyt}$ homeostasis is important. Under normal physiological conditions, the concentration of $[Ca^{2+}]_{cyt}$ is <100 nM, which is ~10,000 times lower than $[Ca^{2+}]_{ext}$ (>1 mM) (3,4). Furthermore, the membrane potential of ~-60 mV adds to the large electrochemical gradient and this huge concentration gradient favors the entry of Ca^{2+} into cells (5). Therefore, when cells are activated, Ca^{2+} is transported down this electrochemical gradient into the cells through the specific transmembrane Ca^{2+} channels, leading to increases in the $[Ca^{2+}]_{cyt}$ (5).

To restore the resting levels of $[Ca^{2+}]_{cyt}$, Ca^{2+} is transported back to the extracellular space or stored in intracellular Ca^{2+} pools by Ca^{2+} pumps and transporters (6,7). Furthermore, $[Ca^{2+}]_{cyt}$ exhibits differences functions in different type of cells (8). These are key factors that determine different specific Ca^{2+}-dependent cellular responses affected by complex, spatiotemporal variations in $[Ca^{2+}]_{cyt}$ (Fig. 1). A major determinant of these variations are different functionally distinct membrane calcium channels and exchangers, such as the receptor-operated calcium channels, voltage-gated channels, Na^+/Ca^{2+} exchangers (NCX) and calcium pumps (9). In addition, the intracellular stores are an important determinant

for Ca^{2+} release (10). To date, the ryanodine receptor (RyR) and inositol triphosphate receptor (IP_3R) channels on the endoplasmic reticulum (ER), have been identified, which lead to Ca^{2+}-induced Ca^{2+} release (CICR) or release of IP_3, respectively, to mediate the release of Ca^{2+} from intracellular stores and increasing the $[Ca^{2+}]_{cyt}$ (11).

In the digestive system, $[Ca^{2+}]_{cyt}$ also has critical roles in the regulation of digestive functions (12,13). This includes GI motility and ion transport, food digestion and nutrient absorption (14). In the epithelial cells of the GI tract, ion secretion and absorption of electrolytes and fluid are two essential functions and ion transport is also a critical physiological process in the human GI tract (15). GI epithelium secretes anions (Cl^- and HCO_3^-), providing the driving force for fluid transport to maintain fluid homeostasis in the human body (16). GI epithelial anion secretion is controlled by several neuro-humoral factors, including prostaglandin E2 (PGE2), acetylcholine (ACh) and 5-hydroxytryptamine (5-HT) (17). These factors mediate epithelial anion secretion mainly through Ca2+, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) signaling pathways (17).

The physiological roles and molecular mechanisms of cAMP- and cGMP-dependent regulation of GI epithelial anion secretion have been extensively defined (18). Since certain adenylyl cyclase subtypes are Ca^{2+}-dependent and multiple interactions between Ca^{2+} and cAMP signaling pathways exist in mammalian cells, it was previously thought that Ca^{2+} may mediate epithelial anion secretion indirectly through cAMP signaling (19).

However, various lines of evidence indicate that Ca^{2+} signaling is able to mediate epithelial anion secretion in a cAMP-independent manner (19,20). Although the critical role of Ca^{2+}-dependent regulation has been verified, the underlying regulatory mechanisms remain to be fully elucidated. The current researchers have been investigating the Ca^{2+}-mediated regulation of anion secretion by GI epithelium and provided solid evidence for a regulatory role of Ca^{2+} signaling in a cAMP-independent manner, as well as the underlying molecular mechanisms (19).

While the critical role of Ca^{2+} signaling in other types of secretory cell (such as those of the airways and salivary gland) is well known (21), the roles of Ca^{2+} signaling in GI epithelial secretion and its molecular mechanisms have remained to be fully elucidated. Further research is required to molecularly identify the Ca^{2+}-activated ion transporters in GI epithelial cells. In addition, the application of muscarinic agonists was observed to lead to an increase in $[Ca^{2+}]_{cyt}$ in secretory cells and promote GI anion secretion (22). However, this phenomenon has been extensively studied in other types secretory cells, such as the secretory cells in the avian basal gland (21).

Overall, the Ca^{2+} signaling and anion secretion mechanisms are of important clinical relevance and need to be further elucidated. In cystic fibrosis (CF), certain calcium agonists stimulate Ca^{2+}-activated Cl^- channel (CaCC)-dependent and CF transmembrane conductance regulator (CFTR)-independent secretion and agents that stimulate Ca^{2+} signaling may be used therapeutically to restore ion and fluid secretion defects (23). Conversely, in certain other types of GI disease, such as intestinal inflammation and diarrhea, inhibition of intracellular Ca^{2+} signaling may have therapeutic potential to ameliorate excessive fluid secretion (24,25) (Table I). Therefore, in the present review, the current state of knowledge regarding Ca^{2+} signaling in the regulation of GI epithelial anion secretion and the associated GI disorders was summarized.

2. General aspects of GI epithelial anion secretion

GI epithelial HCO_3^- secretion. GI epithelial bicarbonate (HCO_3^-) is produced on the surface GI epithelial cells and secreted to the luminal side of the epithelium; it isinvolved in the formation of gastrointestinal mucus with a slightly alkaline pH (12). The basolateral side of electroneutral Na^+-coupled HCO_3^- cotransporter is one of the important transporters for HCO_3^- absorption (12). With the help of the carbonic anhydrase, the HCO_3^- is taken up and it is also generated inside the cells (26).

To date, several pathways for the export ofHCO_3^- into the luminal side of the GI mucosa have been elucidated: i) The CFTR or the CaCC is able to promote electrogenic HCO_3^- efflux, ii) luminal electroneutral anion/HCO_3^- exchangers have been confirmed to contribute to the transport of HCO_3^- and iii) HCO_3^- may betransported via the short-chain fatty acids (SCFA)/HCO_3^- exchanger in the colon (27,28). Electroneutral secretion of HCO_3^- is paralleled by the activity of Na^+/H^+ exchanger-3 (29). Furthermore, the luminal Cl^- channels, as a recycling pathway for Cl^-, are important for HCO_3^- secretion and they may serve in the electrogenic secretion of HCO_3^- via the luminal Cl^-/HCO_3^- antiporters (27). One of the Cl^- channels, CFTR, which is located on the apical side, was clearly demonstrated to be involved in the response of HCO_3^- secretion in the intestine a pancreatic duct (30). Besides the CFTR, Ca^{2+}, cAMP and cGMP were indicated to induce HCO_3^- secretion in the small intestine (31). Current data has also demonstrated that the CFTR is involved in the regulation of the intracellular pH and that the expression and function of Cl^-/HCO_3^- exchangers and down-regulated in adenoma were regulated by the CFTR (32). Of note, CFTR is necessary for HCO_3^- secretion in numerous other epithelial tissues as well (33). Thus, it is likely that the CFTR contributes to anion secretion and control of the luminal pH in the entire GI tract, but in the mammalian colon, the SCFA-dependent HCO_3^- secretion is the primary mechanism of HCO_3^- secretion (34). Well-regulated HCO_3^- secretion is critical for the mucosal defense against luminal acid due to its neutralization effect in the upper GI tract and against bacteria in the lower GI tract due to its stimulation of mucus secretion and maintenance of the intestinal barrier function (35). Aside from mechanisms of mucosal protection, normal HCO_3^- secretion in the small intestine is assumed to establish and maintain an optimal pH for the activity of luminal digestive enzymes (35). The small intestine is in an alkaline range of pH 6.7-8.0, which is the best pH value for the optimal activity of pancreatic enzymes (36). The duodenum in particular is an important organ exerting pH control for enzymatic digestion (37).

Defective intestinal HCO_3^- secretion has been indicated to be a risk factor for intestinal inflammation and peptic ulcer diseases (38). Furthermore, intestinal HCO_3^- secretion has been critically involved in the pathophysiology of acute infectious diarrhea (39). Cholera and numerous other acute diarrheal illnesses may increase the intestinal secretion and

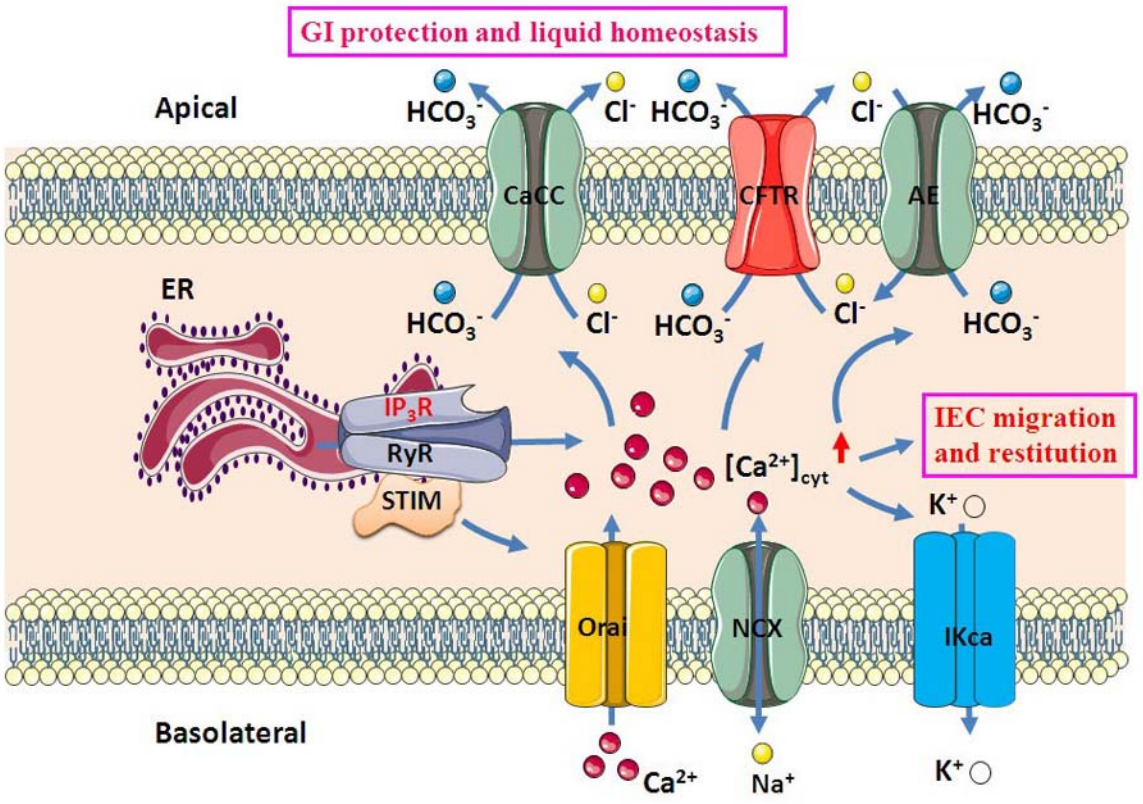

Figure 1. Ca^{2+}-mediated GI epithelial anion secretion. An increase in $[Ca^{2+}]$cyt resulted from intracellular Ca^{2+} release through IP3R or RyR on the ER and extracellular Ca^{2+} entry through Orai and NCX on the plasma membrane stimulates apical CaCC, AE and CFTR, as well as basolateral IKCa. Ca^{2+} signaling activates IEC migration and restitution and stimulates HCO_3^- and Cl^- secretion, which induces epithelial protection and liquid homeostasis, respectively. CaCC, Ca^{2+}-activated Cl^- channel; AE, anion exchange; CFTR, cystic fibrosis transmembrane conductance regulator; IKCa, intermediate-conductance Ca^{2+}-activated K^+ channel; ER, endoplasmic reticulum; RyR, ryanodine receptor; IP3R, inositol triphosphate receptor; STIM, stromal interaction molecule; Orai, ORAI calcium release-activated calcium modulators; NCX, Na^+/Ca^{2+} exchangers; IEC, intestinal epithelial cell; GI, gastrointestinal.

loss of HCO_3^-, which may result in a severe HCO_3^- deficit and metabolic acidosis (40). Defective GI epithelial HCO_3^- secretion has been critically implicated in the pathogenesis of CF (30). A previous study examining the human duodenum indicated a CFTR-dependent alkaline transport in subjects without CF, which was absent in patients with CF (41). Furthermore, electrogenic HCO_3^- secretion was detected in the colon of mice without CF, while it was absent in mice with CF (42). The defective HCO_3^- transport in CF may be crucial for the severity of the symptoms of CF (43). Defective HCO_3^- transport probably causes obstruction of the pancreatic duct and exocrine pancreatic insufficiency (44). Impaired duodenal HCO_3^- production and failure to buffer gastric acid is responsible for an increased incidence of epigastric pain and morphological changes in the duodenum of patients with CF (45).

GI epithelial Cl^- secretion. In GI physiology, fluid secretion has a critical role and is driven by active Cl^- transport from the basolateral to the apical side of enterocytes (46). The basolateral Na^+-K^+-2Cl^-cotransporter (NKCC1) is one of the important transporters for Cl^- secretion (47). The rate secretion of Cl^- is regulated by the activity of NKCC1, which is dependent on the intracellular Cl^- concentration, cell swelling and probably phosphorylation (47). It has also been confirmed that the cAMP-activated KVLQT1/KCNE3 and Ca^{2+}-activated K^+ channels are able to maintain Cl^- transport (48). The basolateral Cl^- is taken up by NKCC; however, its exit is primarily via the apical CFTR. Channels such as CaCC and other Cl^- channels may also take part in apical Cl^- secretion (49). Na^+ and water follow via a paracellular route (50). These ion and fluid transports initiated by pathogens (e.g., cholera toxin and rotavirus) involve multiple factors, such as 5-HT, substance P, ACh and vasoactive intestinal peptide, as well as the release of inflammatory mediators from mast cells and neutrophils [e.g. interleukins (ILs) and prostaglandins] (51). Ion and fluid secretion may be activated by different mechanisms that involve second messengers (cAMP, cGMP or Ca^{2+}) to activate membrane ion channels (20).

Differences between GI epithelial secretion of Cl^- and HCO_3^-. It is generally assumed that the GI epithelial HCO_3^- and Cl^- secretion have the same regulatory mechanisms (52). However, this notion requires to be confirmed through a systematic comparison between them (52). As mentioned earlier, GI epithelial Cl^- and HCO_3^- secretion is mainly controlled by cAMP and Ca^{2+} signaling, which may interact and cross-talk to regulate epithelial ion transport (13,27). Previous studies have demonstrated that most well-known secretagogues, including 5-HT, ACh, forskolin and PGE_2, stimulate intestinal HCO_3^- and Cl^- secretion in parallel (53-55). However, whether epithelial HCO_3^- and Cl^- secretion occur in parallel and whether they are regulated by the same or different signaling/mechanisms currently

Table I. Ca^{2+}-mediated GI epithelial anion secretion and the membrane ion channels involved.

Ion channel	Mechanism	Expression	Related diseases	Author (refs)
HCO_3^-	Maintenance of intestinal barrier function. Mechanisms of mucosal protection. Establishes and maintains optimal pH for the activity of luminal digestive enzymes	GI epithelial cells	Intestinal inflammation, peptic ulcers, acute infectious diarrhea, metabolic acidosis, CF, obstruction of the pancreatic duct, exocrine pancreatic insufficiency, CLD, IBD	Chen *et al* (26) Fei *et al* (36) Kuna *et al* (38) Gennari *et al* (40) Ramos *et al* (45)
Cl^-	Transports the secreted fluid from the lateral base to the apical side of intestinal cells	Basolateral GI epithelial cells	Acute infectious diarrhea, metabolic acidosis, CLD, IBD	Frizzell *et al* (27) Mohammad-Panah *et al* (49)
CFTR	Contributes to the secretion of anions and fluids in enterotoxin-induced secretory diarrhea	Pancreas, epithelial cells in airways, intestinal tract	CF	Goodman *et al* (66) Deachapunya *et al* (67)
CaCC	May participate in anion secretion in the mammalian GI epithelium	Intestinal tract	CF	Caputo *et al* (76) Yang *et al* (17) Morris *et al* (79) Kunzelmann *et al* (83)
Anion/ HCO_3^- exchangers	Protects gastric mucosa by combating aggressive factors	Apical membrane of intestinal epithelial cells	Acute infectious diarrhea, metabolic acidosis, IBD, CLD, CF	Singh *et al* (92) Tang *et al* (59) Smith *et al* (94)
SOC and STIM/Orai channels	Gene expression, cell growth and organ development	Intestinal epithelial cells	CF	Rao *et al* (105) Onodera *et al* (106)
K_{Ca}	Contributes to the stabilization of membrane voltage and provides the driving force for electrogenic anion transport	Intestinal epithelium	CLD, IBD, secretory diarrhea, CF	Julio-Kalajzić *et al* (114) Dong *et al* (121,127) Xie *et al* (13) Assaha *et al* (115) Wang *et al* (116)
NCX	Maintenance of Ca^{2+} homeostasis in a variety of tissues. Involved in the Ca^{2+}-dependent anion secretion	Cardiomyocytes, vascular cells, neurons, small intestinal epithelial cells	Intestinal inflammation, acute infectious diarrhea, metabolic acidosis, CF, CLD, IBD	Lee *et al* (124) Seip*et al* (126) Dong *et al* (121,127) Kocks *et al* (110)

GI, gastrointestinal; HCO_3^-, bicarbonate; CF, cystic fibrosis; CLD, congenital chloride diarrhea; IBD, inflammatory bowel disease; Cl^-, chloride; CFTR, cystic fibrosis transmembrane conductance regulator; CaCC, Ca^{2+}-activated Cl^- channel; SOC, store-operated calcium channels; STIM, stromal interaction molecule; Orai, ORAI calcium release-activated calcium modulators; K_{Ca}, Ca^{2+}-activated K^+ channel; NCX, Na^+/Ca^{2+} exchangers.

remains elusive. Notably, it has been indicated that both forskolin- and carbachol (CCh)-induced rat colonic Cl^- secretion was inhibited by estrogen (56) and further studies by the current researchers revealed that estrogen stimulates duodenal bicarbonate secretion (DBS) in humans and mice without altering basal duodenal short-circuit current (*Isc*), an index primarily of epithelial Cl^- secretion (57,58). These results demonstrated that estrogen may have different roles in regulating intestinal HCO_3^- and Cl^- secretion. These findings also suggest that GI epithelial HCO_3^- and Cl^- secretion may not be necessarily triggered in the same way or by identical signaling/mechanisms. Furthermore, a previous study by the current researchers revealed that calcium-sensing receptor (CaSR) activation raises $[Ca^{2+}]_{cyt}$; however, it reduces cAMP-induced exclusive duodenal HCO_3^- secretion without simultaneously altering duodenal Cl^- secretion (13). Similarly, Tang *et al* (59) demonstrated that CaSR activation stimulated colonic HCO_3^- secretion via SCFA/HCO_3^- and Cl^-/HCO_3^- exchangers; however, it inhibited Cl^-secretion via the cAMP/CFTR pathway. It may, therefore, be proposed that a different regulatory mechanism likely exists for GI epithelial HCO_3^- and Cl^- secretion. While cAMP may have a critical role in CFTR-mediated Cl^- secretion, Ca^{2+} signaling may be critical in anion/HCO_3^--mediated HCO_3^- secretion.

3. Ca^{2+} modulation of GI epithelial anion secretion

Evidence for Ca^{2+}-mediated anion secretion. Although Ca^{2+} may mediate epithelial anion secretion through the cAMP signaling pathway, growing lines of evidence indicate that Ca^{2+} signaling is able to mediate epithelial anion secretion in a cAMP-independent manner (19). The evidence is as follows: i) The increase in $[Ca^{2+}]_{cyt}$ induced by stimulation of cholinergic muscarinic type 3 receptor (M3R) were indicated to be due to activation of basolateral K^+ channels, which enhanced the driving force for luminal anion exit (60); ii) Ca^{2+}/calmodulin and protein kinase C (PKC) was demonstrated to be involved in the CCh-mediated regulation of luminal and basolateral K^+ channels (61); iii) several previous studies suggested a contribution of Ca^{2+}/PKC to CFTR activation (62,63); and iv) activation of muscarinic receptors resulted in an increase in $[Ca^{2+}]_{cyt}$; however, it decreased cAMP levels, which indeed triggered Ca^{2+}-dependent duodenal transepithelial HCO_3^- secretion (13). Since cAMP-mediated ion transport has been extensively reviewed (64), the present study focused on Ca^{2+}-mediated GI epithelial anion secretion and the membrane ion channels involved.

Apical CFTR. CFTR is expressed in different tissue types, including the pancreas, epithelial cells in the airways, GI tract and other fluid-transporting tissues (30). CF is caused by mutations in the CFTR gene, resulting in impaired Cl^- and HCO_3^- transport and plasma membrane targeting (65). CFTR is mainly located in the luminal membrane of enterocytes and has a major role to contribute to the secretion of anions and fluid in enterotoxin-induced secretory diarrheas such as cholera (66). Numerous lines of solid evidence suggest a pivotal role for CFTR in GI anion and fluid secretion (27,30,65,66).

Numerous *in vitro* studies have indicated that the application of glibenclamide and 5-nitro-2-(3-phenylpropylamino) benzoic acid further inhibited the PGE_2 and cAMP-mediated increase in I_{sc} and anion secretion in GI epithelial sheets and cell lines (67,68). Mice with gene ablation of CFTR developed intestinal obstruction (69,70). The resultant characteristic ion transport impairment resulted in defective intestinal anion and fluid secretion and increased fluid absorption (71). In CFTR-null mice, increased expression of alternative Cl^- channels was present and the development of mild intestinal symptoms was observed (72). Furthermore, in CFTR-knockout mice, cholera toxin failed to cause massive fluid secretion through CFTR-dependent protein (72). CFTR has long been considered a primarily cAMP-activated Cl^- channel to activate GI epithelial anion secretion (30). The majority of studies have confirmed that CFTR also responds to Ca^{2+}-mobilizing secretagogues and contributes substantially to cholinergic and purinergic responses in native tissues (30,62).

CFTR channels may be stimulated by the G protein-coupled receptor-mediated signal via Gq protein α subunit, further activating Ca^{2+}-dependent adenylyl cyclase and tyrosine kinases, and by inhibition of protein phosphatase type 2A (PP2A) (72). For instance, the M3R couples strongly to $G_{\alpha q}$. Stimulation of M3R produces diacylglycerol and IP_3 to activate PKC and mobilize intracellular Ca^{2+}, which in turn activates the proline-rich tyrosine kinase 2/Src complex (62). Src stimulates CFTR activity by phosphorylating it directly and inhibiting its dephosphorylation through the inactivation of PP2A (62). Under basal conditions, constitutive Ca^{2+} entry through store-operated Ca^{2+} channels partially activates adenylyl cyclase and induces tonic CFTR activity (62).

A recent *in vitro* study by the current researchers revealed that the stimulation of mouse duodenal I_{sc} by CCh was significantly inhibited in a Ca^{2+}-free solution (17). After the application of CCh, the intracellular calcium was significantly increased; however, there was no increase cAMP and compared to the CFTR-knockout mice. CCh-induced Ca^{2+} was involved in the duodenal Cl^- and HCO_3^- secretion in wild-type mice. The CCh-induced intracellular calcium signaling also stimulated the phosphorylation of CFTR and promoted the CFTR transport to the plasma membrane of duodenal epithelial cells. Furthermore, CCh induced duodenal ion secretion and stimulated PI3K/Akt signaling pathway in duodenal epithelium and all of these effects were attenuated by selective PI3K inhibitors. Therefore, a novel molecular mechanism of Ca^{2+} signaling in CFTR-mediated ion secretion via PI3K/Akt was indicated.

Rasmussen *et al* (73), revealed that cigarette smoking increased $[Ca^{2+}]_{cyt}$-induced CFTR internalization, which was prevented by chelation of cytoplasmic Ca^{2+}. Furthermore, this phenomenon was inhibited by the macrolide antibiotic bafilomycin A1, which inhibited cigarette smoking-induced Ca^{2+} release and prevented CFTR clearance from the plasma membrane, further linking cytoplasmic Ca^{2+} and CFTR internalization. Patel *et al* (74), also indicated that an increase in $[Ca^{2+}]_{cyt}$ induced a reduction of cell surface CFTR expression. Therefore, CFTR appears to be the channel that is in charge of not cAMP-activated, Ca^{2+}-activated Cl^- and HCO_3^- secretion in human GI mucosa (30).

Apical CaCC. There is currently evidence that the CaCC are a further class of important Cl^- channels that may participate in anion secretion in the mammalian GI epithelium (75). In luminal membranes of GI epithelia of subjects with and without CF, CaCC are stimulated by Ca^{2+} ionophores and Ca^{2+}-mobilizing secretagogues (76), including acetylcholine, bradykinin, histamine, CCh and extracellular nucleotides adenosine triphosphate (ATP) and uridine triphosphate (UTP) (77,78). In mice with CF, the expression of Ca^{2+}-dependent Cl^- channels was detectable in the intestine and was age-dependent. In young mice (age, 2-3 weeks), Cl^- secretion was induced by carbachol in the small intestine (17). Furthermore, it was indicated that in non-CF and CF mouse pup crypts, the application of nonstructural protein 4 (NSP4) caused severe diarrhea (79). However, compared to the young CF mice, the NSP4-induced Cl^- secretion was largely reduced in adult CF mice. These data further support that the expression and function of CaCC are age-dependent. Indeed, it was also revealed that the adult CF mice (age, 6-12 weeks) did not exhibit CFTR-dependent Cl^-secretion; however, they did have a partial CFTR-independent duodenal HCO_3^- secretion in response to CCh (17). Therefore, CaCC may have an important role in the regulation of intestinal Cl^-secretion in young CF mice and may be important for duodenal HCO_3^- secretion in adult CF mice.

The Ca^{2+}-activated TMEM16A anion channel (or anoctamin 1) was reported to be able to conduct HCO_3^- upon a

significant increase in cytosolic Ca^{2+} levels (80). However, the role of anoctamin 1 in GI epithelial anion secretion remains under debate (81). More recently, a study by the current researchers indicated that caffeine-stimulated Ca^{2+}-dependent duodenal anion secretion was attenuated by niflumic acid and T16Ainh-A01, two selective CaCC blockers with different chemical structures, suggesting that the TMEM16A anion channel is likely one of the downstream effectors of Ca^{2+} signaling (82).

It has been demonstrated that a residual cholinergic Cl^- secretion was preserved in a subset of patients with CF with a mild phenotype (83). In T84 colonic carcinoma cells, the role of CaCC has also been characterized and it was indicated to be responsible for Ca^{2+}-mediated Cl^-secretion in these cells (83). However, other studies suggested that the integrated function of CFTR is important for CaCC (84), as Ca^{2+}-dependent cholinergic Cl^- secretion was able to be completely inhibited by the deactivation of CFTR (85). All those results suggest that residual cholinergic Cl^-secretion in CF tissues depends on the residual function of mutant CFTR. Therefore, although there is evidence for an alternative CaCC in the mouse colon and human colonic carcinoma cell lines, the promotion by CaCC is probably limited (86).

Apical anion/HCO_3^- exchangers. It has been generally accepted that HCO_3^- secretion from the upper GI tract is important for the protection of normal mucosa (87). There are three anion/HCO_3^- exchangers: Solute carrier family 26 member 6 [SLC26A6; also known as putative anion transporter 1 (PAT1)], DAR and SLC4A9 (also known as anion exchange protein 4); all those channels contribute to the DBS to resist various aggressive factors, such as the acidic gastric output (88,89). However, at least three distinct mechanisms of HCO_3^- secretion have been described in the distal colon of rats (90,91): i) Cl-dependent: The HCO_3^- secretion mediated by a brush-border Cl^-/HCO_3^- exchange; ii) SCFA-dependent: HCO_3^- secretion as a result of activation of SCFA/HCO_3^- exchange; and iii) cAMP-induced: HCO_3^- secretion associated with a CFTR (91).

As Cl^-/HCO_3^- exchanger was expressed on the apical membrane of the small intestinal epithelium and likely has a role in secretagogue-stimulated DBS (92,93), its possible involvement in estrogen-stimulated DBS was assessed in a study by the current researchers (94). The results suggested that estradiol (E_2) indeed stimulated murine DBS, which was attenuated by 4,4'-diisothiocyanostilbene-2-2'-disulfonic acid, a commonly used inhibitor of Cl^-/HCO_3^- exchanger. E_2 was also able to increase $[Ca^{2+}]_{cyt}$ in duodenal epithelial cells expressing estrogen receptor, whereas 1,2-*Bis*(2-aminophenoxy) ethane-*N*,*N*,*N*',*N*'-tetraacetic acid tetrakis (acetoxymethyl ester) (BAPTA-AM) one of an intracellular calcium chelator inhibited the E_2-stimulated murine DBS. It was therefore suggested that the activation of estrogen receptor stimulates the Ca^{2+}-dependent DBS via Cl^-/HCO_3^- exchanger.

Colonic bicarbonate secretion (CBS) is closely linked to electrolyte movement and overall fluid in the colon (59). As mentioned earlier, CaSR activation increases $[Ca^{2+}]_{cyt}$; however, it decreases intracellular cAMP production. Consistently, Tang *et al* (59) reported that CaSR activation inhibited cAMP-activated CBS; however, it increased the lumen Cl^-- and SCFA-dependent CBS. Consequently, upon activation of electroneutral Cl^-/HCO_3^- and SCFA/HCO_3^- exchangers, CaSR stimulated CBS; by contrast, if forskolin-stimulated electrogenic CFTR-mediated HCO_3^- conductance dominated, CaSR inhibited CBS. Consistently with the results on the Ca^{2+}-mediated regulation of Cl^-/HCO_3^- exchanger-mediated DBS reported by the current researchers (13), these results further suggest a critical role of Ca^{2+} signaling in the regulation of Cl^-/HCO_3^- and SCFA/HCO_3^- exchanger-mediated CBS (59). Therefore, modulation of CaSR activity may provide a new therapeutic approach to correct HCO_3^- deficits and metabolic acidosis, a primary cause of morbidity and mortality in acute infectious diarrheal illnesses (59). However, Lamprecht *et al* (95) reported on Ca^{2+}-mediated inhibition of colonic DRA. Both the calcium ionophore A23187 and UTP that increased Ca^{2+} were able to inhibit DRA in these cells.

Basolateral store-operated channels and stromal interaction molecule (STIM)/Orai calcium release-activated calcium modulators. Store-operated calcium channels (SOC) are a major pathway for calcium signaling in virtually all mammalian cells and involved a variety of functions, including gene expression, cell growth and organ development (96-98). The SOC is stimulated by the diverse set of surface receptors via depletion of the Ca^{2+} concentration from the ER (99). The stromal interaction molecule (STIM) proteins were identified as the ER Ca^{2+} sensors and the Orai proteins as store-operated channels and since then, rapid progress has been made in the elucidation of the unique mechanisms of store-operated calcium entry (SOCE) (99). The role of STIM1/Orai signaling was previously studied mostly in nonpolarized cells, such as lymphocytes (100,101) or nonconfluent 293 cells (102,103). However, only a few studies have assessed the function of STIM1/Orai signaling in polarized GI epithelia (104-106). In the human colonic tumor cell line NCM460, STIM1 stimulated by the emptying of intracellular Ca^{2+} stores after the production of cAMP (104). In addition, in the intestinal epithelial cell (IEC)-6 cell line from rat intestinal crypts, STIM1/Orai was indicated to have a role in wound healing (105). In the rat colonic epithelium, STIM1/Orai was identified as a key component of intracellular Ca^{2+} signaling involved in the regulation of both apical and basolateral Ca^{2+} influx (106).

Although the critical role of Ca^{2+} signaling in GI epithelial anion secretion is well-known (13), the mechanisms by which $[Ca^{2+}]_{cyt}$ homeostasis in GI epithelial cells is controlled remain to be fully elucidated (11). Under normal physiological conditions, in non-excitable epithelial cells, the occurrence of Ca^{2+} entry mainly depends on the SOC (99). In non-excitable cells, agonists induce Ca^{2+} signaling mostly depending on the intracellular Ca^{2+} release mainly from the ER and Ca^{2+} influx from the extracellular medium (107). IP_3-sensitive and ryanodine-sensitive Ca^{2+} stores have been identified within the ER (108,109). The former is activated by the binding of IP_3 to IP_3R, while the latter is activated by the binding of ryanodine to RyR to induce ER Ca^{2+} release into the cytosol (110).

The IP_3R-mediated Ca^{2+} influx pathway was reported to have a role in the regulation of GI epithelial anion secretion (109,111). Similarly, a study by the current researchers indicated that muscarinic receptors were activated after the application of CCh and induced mouse intestinal Cl^- secretion, which was significantly inhibited by selective SOC blockers added to the serosal side of duodenal tissues in a Ca^{2+}-free

serosal solution (82). Furthermore, the study revealed that calcium release-activated calcium/Orai channels may represent the molecular candidate of SOC involved in the CCh-induced increase of intracellular Ca^{2+} in GI epithelium. As the underlying mechanisms of RyR-mediated ER Ca^{2+} release as an important component of SOCE to contribute to GI epithelial anion secretion had remained elusive, the role of RyR/Ca^{2+} storage was also further investigated by Dong *et al* (82). The results suggested that caffeine, a selective RyR activator, markedly increased mouse intestinal Cl^- and HCO_3^- secretion. However, this process was suppressed by Ca^{2+}-free serosal solutions and selective blockers of SOC/Ca^{2+} and knockdown of the protein expression of Orai1 channels also inhibited the Cl^- and HCO_3^- secretion on the serosal side of duodenal tissue. Furthermore, the caffeine-induced anion secretion was inhibited by ER Ca^{2+} chelator and RyR blockers (82). In addition, the protein expression of STIM1 and Orai1 was detected. In IEC cells, the caffeine-induced SOCE was attenuated by selective SOC inhibitor (82).

It was therefore concluded that the RyR/Orai1/Ca^{2+} signaling on the basolateral side has a critical role in the regulation of GI epithelial anion secretion (67). Lefkimmiatis *et al* (112) indicated that in a newly identified type of SOC termed 'store-operated cAMP signaling' (SOcAMPS), the luminal ER Ca^{2+} sensor STIM1 does not depend on changes in $[Ca^{2+}]_{cyt}$. The decreasing free Ca^{2+} concentration within the ER lumen induces a rise in intracellular cAMP. Therefore, they proposed the SOcAMPS, in which the content of internal Ca^{2+} stores is directly connected to cAMP signaling through a process that involves STIM1. Subsequently, Nichols *et al* (113) determined that in T84 colonic cells, the I_{sc}, cAMP and PKA activity was increased under Ca^{2+}-free conditions after treatment with Ca^{2+}-releasing agonist CCh and Ca^{2+} ionophore and suppressed by pre-treatment with BAPTA-AM. Furthermore, the effects of ER Ca^{2+} store depletion on cAMP/PKA activity were attenuated by Ca^{2+} entering from the extracellular space, indicating that the production of cAMP decreased after Ca^{2+} influx. They proposed that a discrete component of the 'Ca^{2+}-dependent' secretory activity in the colon is derived from cAMP generated through SOcAMPS. These studies further support the notion that Ca^{2+} and cAMP signaling may independently trigger epithelial ion transport.

Basolateral Ca^{2+}-activated K^+ channels (K_{ca}). In GI epithelial cells, K^+ channels are important in the intestinal epithelium, contribute to the stabilization of membrane voltage and provide the driving force for electrogenic anion transport (114). The concept that cholinergic agents promote the intestinal Cl^- secretion via the activation of membrane K^+ conductance and maintain the cellular Cl^- transport has been widely accepted (115). Certain cholinergic agents, such as CCh, activate muscarinic receptors or acetylcholine raises the $[Ca^{2+}]_{cyt}$, which activates K_{Ca} conductance and secondarily stimulates Cl^- secretion via the apical CFTR (116). Therefore, basolateral K^+ channels hyperpolarize apical membrane potential and increase the electrical driving force for anion (Cl^- and HCO_3^-) secretion to maintain electroneutrality.

To date, three different subtypes of K_{Ca} channels expressed on colonic surface and crypt cells have been identified: Large-conductance K_{Ca} channels, intermediate-conductance K_{Ca} channels (IK_{Ca}) and small-conductance K_{Ca} channels (117,118). Among them, IK_{Ca} channels have an important role in epithelial Cl^- secretion. A selective blocker of IK_{Ca} channels, clotrimazole, inhibited the Cl^- secretion in intact colonic epithelium and human colonic T84 cells (119). In addition, it has been demonstrated that activation of CFTR alone is insufficient to evoke transepithelial Cl^- secretion and that basolateral membrane K^+ channels are also necessary components of the secretory response (30). Therefore, basolateral membrane K_{Ca} channels represent an important potential therapeutic target to increase Cl^- secretion in patients with CF.

While the expression and function of K_{Ca} channels and their role in the regulation of duodenal epithelial ion transport and DBS in the duodenal epithelium have remained elusive, it is well known that $[Ca^{2+}]_{cyt}$ has an important role in epithelial ion transport (2,11); however, the underlying mechanisms of $[Ca^{2+}]_{cyt}$ to induce duodenal HCO_3^- secretion, or indeed other ion transport systems, had not been explored in detail. Therefore, the functionality of K_{ca} and their role in the regulation of duodenal mucosal ion transport were explored. A previous review by the current researchers provided evidence that IK_{Ca} or intermediate conductance calcium-activated potassium channel protein 4/SK4 channels are located on the basolateral side of duodenal epithelial cells and are involved in the regulation of Ca^{2+}-mediated duodenal Cl- and HCO_3^- secretion (120). Furthermore, it was indicated that clotrimazole, a selective blocker of basolateral IK_{Ca}, was able to inhibit Ca^{2+}-mediated duodenal Cl^- and HCO_3^- secretion, suggesting its potential utility as an anti-diarrheal drug for the treatment of secretory diarrhea (13,121).

NCX. The plasma membrane NCX is an important membrane transporter and has a critical role in the maintenance of Ca^{2+} homeostasis in a variety of tissue types (122).

NCX is a bidirectional plasma membrane transporter and in each cycle, three Na^+ for one Ca^{2+} are transported in the opposite direction and this process depends on electrochemical gradients (123). The expression and function of NCX have been demonstrated in cardiomyocytes, vascular cells and neurons (124). They are able to function in a forward mode to excrete intracellular Ca^{2+} and in reverse mode to induce extracellular Ca^{2+} entry and various associated signal transduction pathways (124). NCX was previously reported to be expressed in small intestinal epithelial cells and to function in the forward mode that is involved in the absorption of Ca^{2+} into the bloodstream. However, NCX also has a role in GI epithelial anion secretion (125).

Seip *et al* (126), demonstrated an interaction between SOC and NCX in the rat colon, where the influx of Na^+ across SOC serves to reduce the driving force for Ca^{2+} extrusion via the NCX and thereby maintains the increase in $[Ca^{2+}]_{cyt}$ during the induction of rat colonic anion secretion. Consistently, Kocks *et al* (110) reported a cross-talk between the depletion of intracellular Ca^{2+} stores and NCX, which may maintain a long-lasting increase in $[Ca^{2+}]_{cyt}$ to amplify Ca^{2+}-dependent colonic Cl^- secretion. While it was demonstrated that muscarinic receptor induced the activation of $[Ca^{2+}]_{cyt}$ increases, which regulates anion secretion, the underlying mechanisms of Ca^{2+} remained largely elusive. A previous study by the current researchers determined whether NCX has a role in the regulation of duodenal mucosal anion secretion by controlling

Ca^{2+} homeostasis (127). The results indicated that activation of muscarinic receptors stimulated NCX activity in a reverse mode to increase $[Ca^{2+}]_{cyt}$ in epithelial cells, leading to Ca^{2+}-dependent HCO_3^- and Cl^- secretion (127). In conclusion, NCX has an important role in Ca^{2+}-dependent anion secretion by controlling Ca^{2+} homeostasis in GI epithelial cells.

4. Associated GI diseases

Ulcers. Ulcers refer to mucosal injury reaching the submucosa in the GI tract (128). Peptic ulcers may develop in the stomach or proximal duodenum and at the margin of a gastroenterostomy, Meckel's diverticulum or the esophagus (128). *Helicobacter pylori* (*H. pylori*) infection, non-steroidal anti-inflammatory drugs and stress cause a large proportion of peptic ulcers (129). Since patients with ulcers usually have hyperchlorhydria, proton-pump inhibitors are used to inhibit gastric acid secretion, besides eradication of *H. pylori* infection with antibiotics (130). It is well established that GI epithelial HCO_3^- secretion is critical for defending the vulnerable epithelium against various aggressive factors (87). The mucus secreted on the surface of GI mucosa and the bicarbonate ions secreted by the GI epithelium form a mucous bicarbonate barrier (87). When H^+ in gastric acid diffuses to the stomach wall, it is neutralized by HCO_3^- secreted by epithelial cells (87). In this way, the surface of the gastric mucosa remains in a neutral or partially alkaline state, preventing gastric acid and pepsin from attacking the mucosa (131). The esophagus also requires HCO_3^- secretion to protect the epithelial surface from acid reflux (132). Furthermore, normal mucus release from GI epithelium requires concurrent HCO_3^- secretion, which is essential for the release of mucin molecules and their proper expansion on the surface of epithelium as well (133). As a matter of fact, DBS, as an important protector, has been confirmed in patients with duodenal ulcer whose acid-stimulated DBS is only 41% of that of healthy subjects (94). The defect in intestinal HCO_3^- secretion has further been indicated to be a risk factor for peptic ulcer diseases (134).

Additionally, normal colonic HCO_3^- secretion is critical for the mucosal defense against bacteria in the lower GI tract (87). The luminal pH was indicated to be acidic in the colon of patients with ulcerative colitis (UC), which may be caused at least in part by disturbances in the ion transport in the inflamed colon (135). Therefore, it appears important to recover normal GI epithelial HCO_3^- secretion in patients with peptic ulcers and inflamed colon to prevent their recurrence. It is of growing interest to discover novel drugs to stimulate sufficient GI epithelial HCO_3^- secretion for mucosal protection as a potential adjuvant therapy for ulcer diseases or prevention of their recurrence.

CF. Epithelial HCO_3^- secretion is impaired in the GI tract of patients with CF, suggesting a pivotal role of the CFTR in mediating epithelial HCO_3^- secretion (64). Patients with CF usually have an epithelial HCO_3^- deficit. As discussed earlier, while the CFTR is mainly triggered by the cAMP/PKA pathway, most of the channels involved in GI epithelial anion secretion, including CaCC, anion exchangers, K_{Ca} and even CFTR, may be generally triggered by Ca^{2+} signaling (136). For instance, the CaCC is stimulated by Ca^{2+} ionophores and Ca^{2+}-mobilizing secretagogues in luminal membranes of GI epithelia from subjects with or without CF (136), including ACh, CCh, histamine, bradykinin, ATP and UTP (77,78). Furthermore, a previous study by the current researchers demonstrated that adult CF mice exhibited a partial CFTR-independent duodenal HCO_3^- secretion in response to CCh, although they did not display CFTR-dependent Cl^-secretion (58). More recently, a study by the current researchers demonstrated that caffeine stimulated Ca^{2+}-dependent duodenal anion secretion, which was able to be attenuated by selective CaCC blockers, suggesting that the CaCC is one of the downstream effectors of Ca^{2+} signaling (82). Therefore, after the cAMP-activated CFTR is impaired in CF, targeting the Ca^{2+}-mediated pathway may be a potential adjuvant for CF therapy. Calcium ions have a critical role in the normal functioning of the gastrointestinal system (137). Certain calcium channel blockers were used to affect all of the organs of the gastrointestinal tract and may have therapeutic efficacy against esophageal spasm, mesenteric vascular insufficiency, irritable bowel syndrome, dyskinesis of the Sphincter of Oddi and insulinoma (137); however, this requires further intensive investigation.

Inflammatory bowel disease (IBD). IBD, including Crohn's disease and UC, is a group of chronic inflammatory disorders of the GI tract. Diarrhea is the most highly prevalent and debilitating symptom of IBD (138). The pathogenesis of IBD is multifactorial and involves variations in patients' genome, immune response, the intestinal microbiome and environmental factors to result in an excessive and abnormal host immune response (139). However, the change of expression and/or function of epithelial ion channels and transporters may result in electrolyte retention and water accumulation in the intestinal lumen, leading to diarrhea in IBD (139). IBD is a chronic inflammatory disorder with high complex endogenous inflammatory meditators, including IL-1β, tumor necrosis factor-α, interferon-γ, IL-6, monochloramine and nitric oxide (140). They may act on intestinal epithelial ion transport and smooth muscle (141). Furthermore, the colon of patients with UC has an acidic luminal pH, which impairs the ion transport in the inflamed colon (142). Consistently, the expression of Cl^-/HCO_3^- exchanger SLC26A3 (DRA) was reported to be markedly decreased in the inflamed colon (143). The expression of DRA was also indicated to be absent exclusively in UC patients, indicating inadequate membrane trafficking events (144,145). Furthermore, in a recent genome-wide association study, a single-nucleotide polymorphism in the SLC26A3 gene was identified as a risk factor for UC development (146). A strong reduction in Cl^- absorption was identified in parallel with a low expression of DRA in UC colonic crypts (147). Therefore, decreased DRA expression may lead to a deficient Cl^- absorption in UC, which emphasizes the important role of DRA in UC-associated diarrhea (148).

Congenital chloride diarrhea (CLD). It is well established that DRA and PAT-1 are the two major transporters involved in apical Cl^-/HCO_3^- exchange in the GI tract (88,90). As mentioned above, loss of the expression and function of DRA may induce diarrheal disorders (143). However, mutations in the DRA gene that encode Cl^-/HCO_3^- exchange cause a rare diarrheal disorder named CLD, which is associated with a high stool concentration of Cl^-, metabolic alkalosis and physiologic

evidence of an absence of Cl^-/HCO_3^- exchange in the colon and ileum (149). Therefore, the characteristics of patients with CLD include voluminous diarrhea, massive loss of Cl^- via the stool and metabolic alkalosis. Furthermore, the pH of the ileocolonic lumen in patients with IBD has been reported to be reduced due to limited HCO_3^- secretion (146). Since DRA serves as the major luminal intestinal Cl^-/HCO_3^- exchanger responsible for bulk intestinal Cl^- absorption and HCO_3^- secretion, DRA deficiency is one of the important factors in the pathogenesis CLD and IBD (147). Therefore, based on the reported Ca^{2+}-mediated inhibition of colonic DRA, it may be speculated that inhibition of intracellular Ca^{2+} signaling may have therapeutic potential to improve excessive fluid secretion, thereby providing a novel research direction for the treatment of CLD and IBD.

5. Conclusion

GI epithelial anion and fluid transport have critical roles in maintaining normal physiological functions in the GI tract. Defective GI epithelial anion secretion has been critically implicated in the pathophysiology of ulcer diseases, CF, intestinal inflammation, diarrhea/constipation and even metabolic acidosis. Similarly, $[Ca^{2+}]_{cyt}$ also has a critical role in the regulation of digestive functions. GI epithelial anion secretion is known to be controlled by several neuro-humoral factors, including PGE_2, ACh and 5-HT. These factors mediate epithelial anion secretion mainly through Ca^{2+}, cAMP and cGMP signaling pathways. Although multiple interactions exist between Ca^{2+} signaling and the cAMP pathway to trigger GI epithelial anion secretion, growing lines of evidence indicated that Ca^{2+} signaling may mediate epithelial anion secretion in a cAMP-independent manner. Ca^{2+} signaling modulates GI epithelial anion secretion through acting on CFTR, CaCC, Cl^-/HCO_3^- exchanger, SOC, K_{ca} and NCX. It was previously assumed that those channels and transporters involved in GI epithelial secretion of Cl^- and HCO_3^- are identical; however, emerging evidence suggests they are different. While cAMP may be a critical factor in CFTR-mediated Cl^- secretion, Ca^{2+} signaling may have a critical role in Cl^-/HCO_3^--mediated HCO_3^- secretion. Elucidation of the precise regulatory mechanisms of Ca^{2+}-mediated GI epithelial Cl^- and HCO_3^- secretion will markedly enhance the current knowledge of ion and fluid transport in the GI tract. Further investigation on the differences between GI epithelial secretion of Cl^- and HCO_3^- may provide novel potential drug targets to protect the upper GI tract against ulcer diseases and promote epithelial HCO_3^- secretion.

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Authors' contributions

WS, YH, JD, XY, JL, QD, QL and LL conceived the current review article. JX and RX were responsible for the collection and assembly of the articles/published data for inclusion and interpretation in this review. All authors were involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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