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Chemical Sensing and Its Contribution to Ion Transport in the Colon

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Abstract: The primary function of the gastrointestinal (GI) tract is to extract dietary nutrients. Therefore, the GI tract must have an effective surveillance system that continuously monitors the luminal contents for beneficial or harmful compounds. Recent studies have shown that specialized cells in the intestinal mucosa can sense changes in the luminal contents. These changes directly influence fundamental GI functions such as ion transport, motility, and local blood flow via hormonal and/or neuronal pathways. Recently, the gut chemosensory system on the regulation of ion transport has received increasing attention, as failure of this system causes dysfunction in host homeostasis, as well as GI disorders. Moreover, regulation of ion transport in the colon is critical for host defense and for electrolytes balance. This review summarizes the role of the gut chemosensoy system, focusing on epithelial ion transport in the colon.

Key Words: Gut chemosensory system, Anion secretion, Colon, Host defense.

Introduction

The gastrointestinal (GI) tract is designed primarily to obtaining energy sources from the diet. During the enzymatic digestion of food molecules known as hydrolysis, water is needed to split large molecules into smaller ones. Under physiological conditions, approximately 8 L of fluid is secreted into the small intestine per day. However, 85 to 90% of the secreted fluid is reabsorbed in the small intestine, with approximately 10-15% of remaining fluid normally passing through the ileocecal valve into the large intestine daily[1]. The remnants of digestion that enter the large intestine include water, some nutrients, and indigestible dietary fibers. The main functions of the colon are to salvage the remaining fluid and electrolytes from the small intestine, as well as to dehydrate and store feces. Moreover, colonic epithelia are able to secrete fluid as a host defense mechanism.

In the colon, approximately 100 trillion enteric bacteria (gut microbiota) are present in the lumen and the gut microbiota is composed of over 400 different species[2]. Indeed, within this vast ecosystem, the gut microbiota continuously produces large quantities of bioactive chemicals as suggested by their

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genome sequences and confirmed by an analysis using Basic Local Alignment Search Tool (BLASTP)[3]. These bioactive chemicals have a profound influence on many aspects of human health because the gut microbiota is able to produce both beneficial and harmful substances, which must be distinguished by the host colon.

One of the most important host-defense mechanisms of the colon is to flush out harmful materials by fluid secretion, mainly through Cl^- secretion. In fact, large intestine has a large capacity for secretion; large amounts of fluids are handled by the colon in the case of secretory diarrheas or reabsorptive states on a daily basis[1)4)].

Regulation of colonic ion transport is regulated by various regulatory factors which are derived from enteric nervous system (ENS) and enteric endocrine cells (EEC) and via remote pathways that originate in the central nervous system, including neural and endocrine mediators[5)6)]. In addition to these regulatory systems, recent studies have shown that bioactive substances produced by the gut microbiota contribute to the regulation of epithelial ion transport through the gut chemosensory system[7)].

This review aims to summarize recent findings on colonic anion secretion in response to gut chemosensory system.

Colonic chemosensing - an overview

The presence of a gut chemosensory system is evident because the same taste transduction molecules in the taste buds of lingual papillae, such as α-gustducin, are also present in human and rodent intestinal mucosa[8)9)]. Several types of receptors have been identified in the intestinal epithelia, including olfactory receptors (ORs), sweet and umami receptors, bitter taste receptors (T2Rs), metabolic glutamate receptors, calcium sensing receptor, and free fatty acid receptors (FFARs)[7)]. The chemical sensor of the gut chemosensory system consists mainly of G protein coupled receptors (GPCRs). Many of the GPCRs are expressed on ECC although brush cells and enterocytes sense luminal contents as well.

Short-chain fatty acid receptors

Short-chain fatty acids (SCFAs) are predominant free fatty acids in the content of the large intestine, present at ~100 mM and mainly consist of acetate, propionate, and butyrate. They are produced as a result of bacterial fermentation of specific dietary fibers indigestible by the upper GI tract. SCFAs are not only important nutrients, but also act as signaling molecules that affect various functions in the host depending on their carbon chain lengths.

In 2003, two orphan GPCRs, FFAR2 (GPR43) and FFAR3 (GPR41), were discovered to be receptors for SCFA[10-12)]. They differ in their specificity for SCFAs of different carbon chain lengths. We have previously reported that FFAR2 or FFAR3 is expressed in colonic epithelia, particularly peptide YY (PYY) and glucagon-like peptide 1 (GLP-1)-containing L-type enteroendocrine cells in human[13)], guinea-pigs[14)], and rats[15)].

Luminal application of SCFAs, propionate or butyrate but not acetate induces Cl^-/HCO_3^- secretion in the middle and distal colon and rectum[16)17)]. On the other hand, propionate and butyrate do not evoke Cl^-/HCO_3^- secretion in the proximal colon. Pretreatment of the mucosal surface with procaine or superficial mucosal damage with hypertonic sodium sulfate or xylose inhibits the propionate-induced

secretion by 90%[16)17)]. Thus, propionate-induced Cl^-/HCO_3^- secretion is caused by the activation of SCFAs receptors located on mucosal epithelial cells. With respect to the involvement of SCFA receptors, FFAR3 may be involved in the secretory process since acetate, the preferred ligand of FFAR2, has no effect on mucosal Cl^-/HCO_3^- secretion in distal colon of rats[16)].

Bitter taste receptors (T2R)

The five basic tastes recognized by humans and many other animals are bitter, sweet, sour, salty and umami[18)]. Bitter chemicals are detected by a small family of receptors (T2R) that are structurally related to rhodopsin - the number ranges from 3 to 49, depending on the species[19)]. The ability to sense bitter taste has evolved to allow animals to detect toxins in the environment that are primarily produced by plants. Thus, a bitter taste signals the presence of toxic substances, allowing the host to avoid harmful materials[20)]. The mRNA expression of human *T2R-1*, *T2R-4*, *T2R-38* as well as their rat orthologs *T2R-1*, *T2R-16* and *T2R-26*, is detected in the colonic mucosa by real-time PCR (RT-PCR)[21)]. However, unlike FFAR2- and FFAR3-expressing cells, cell type(s) expressing bitter taste receptors have not been identified.

Recently, we have shown that the introduction of a bitter compound, 6-n-propyl-2-thiouracil (6-PTU) at concentrations greater than 10^{-4} M to the mucosa increased short-circuit current (*Isc*) in both human and rat colons in a concentration-dependent manner[21)]. Multiple T2R family members (at least T2R-1, -4, and -38) in humans are known to detect 6-PTU[22)23)]. Human taste tests and brief-access mouse studies have shown that the minimal effective concentration of 6-PTU is～10^{-4} M[21)24)25)]. Therefore, human and rat T2R-expressing cells in the colon are activated by a similar concentration of 6-PTU, suggesting that they have a similar ability to sense bitterness. Based on these findings, it is speculated that the physiological function of bitter taste receptors located in the colon is to detect chemical compounds derived from bacterial metabolism to distinguish between beneficial or harmful substances to host. The increase in *Isc* induced by 6-PTU was reduced by basolateral Na^+-K^+-$2Cl^-$ cotransporter (NKCC1) inhibitor, bumetanide, and luminal cystic fibrosis transmembrane conductance regulator (CFTR) inhibitor, NPPB. NPPB-sensitive Cl^- channel, CFTR located at the apical membrane, also secretes HCO_3^-. Thus, the 6-PTU-induced increase in *Isc* is due to the secretion of Cl^- and HCO_3^- in the colon.

With respect to the physiological significance of bitter receptors, bitter tastant-induced anion secretion in the colon is an important mechanism to flush out noxious agents from the colonic lumen. Normally, bitter compounds in the large intestine are most frequently bile acids and metabolites derived from the bile acids utilized by gut microbiota. As secondary bile acids promote tumors[26)], bitter sensing in the large intestine may be a necessary mechanism for host defense.

Odorant Receptors (OR)

The colonic mucosa of both humans and rats express *OR* mRNA, and luminal odorants induce 5-hydroxytriptamine (5-HT) secretion in isolated duodenal enterochromaffin (EC) cells and cell lines[27)28)]. Volatile odorants, such as terpenoids derived from five carbon isoprene units, are widely produced by plants, insects, and bacteria, including members of the gut microbiota[29)]. Indeed, various volatile compounds are detected in human feces[30)]. Therefore, it is likely that odorants are synthesized in the colonic lumen and monitored by mucosal chemosensors.

Recently, we have shown that luminal application of thymol, a major odorant component in edible herbs, induces Cl^-/HCO_3^- secretion in a concentration-dependent manner in both human and rat colons[31]. As pretreatment of the tissues with a neural blockade, tetrodotoxin (TTX) or non-selective cyclooxygenease inhibitor, piroxicam did not inhibit this response, it is suggested that thymol-induced anion secretion is independent of the neural and prostaglandins (PG) synthesis pathways.

Thymol-induced anion secretion in the distal colon is reduced by a transient receptor potential A1 (TRPA1) blocker, HC-030031[31]. Furthermore, *TRPA1 mRNA* is detected in the isolated mucosa of humans and rats[31)32)]. Several odor molecules are known ligands of not only GPCRs, but also the TRP channel. Thymol activates TRP vanilloid 3 (TRPV3) and TRPA1 in a cell expression system[33)34)]. In the GI tract it has been reported that TRPA1 activity is involved in the control of small intestinal motility through the release of 5-HT from EC cells[35]. Therefore, it is reasonable to speculate that thymol-induced electrogenic anion secretion is mediated by the TRPA1 channels in the colon as well.

As bacteria can synthesize isoprene unit[36], production of active odor molecules similar to thymol may be possible in the mammalian colon. Thus, colonic mucosa is potentially exposed to high concentrations of various volatile odorants. Because irritant odors, similar to bitter tastants, are danger signals for the host, ORs can play an important role in host defense on the colonic luminal surface. For OR-expressing cells, Braun et al. have recently shown that EC cells in human ileum express 4 olfactory receptors (*OR73*, *hOR17-7/11*, *OR1G1*, and *hOR17-210*) by laser microdissection and RT-PCR[27]. However, little is known about OR localization or OR-expressing cell types in the colon, though *OR1G1* and *TRPA1* are present in both human and rat colonic mucosa by RT-PCR[31]. Therefore, further studies should be carried out to identify the specific sensor cells expressing ORs and TRPA1. Currently, it is unclear whether OR1G1 is directly involved in thymol-induced anion secretion and whether ORs are linked to TRPA1.

TRP channels

The TRP channel member, TRPA1 (also known as ANKTM1), was first identified as a cold-sensitive cation channel in murine sensory neurons and is thought to have a role in nociception[37]. Since multiple environmental irritants can activate TRPA1, TRPA1 may function as a chemosensor in the GI tract as well.

To date, 28 mammalian TRP channels have been cloned and characterized. *TRPA1* expression in the colon has been demonstrated in humans, mice, rats and dogs by northern blot analysis and RT-PCR[37-39]. As described in the section Odorant Receptors, luminal thymol-induced anion secretion involves TRPA1. The function of TRPA1 in the transepithelial ion transport system was examined using a potent TRPA1 agonist allyl isothiocyanate (AITC)[31].

In human and rat large intestines, the addition of AITC to the luminal side induced an increase in *Isc*[31]. Increases in *Isc* induced by the activation of TRPA1 are dependent on Cl^- uptake by NKCC1 and on excretion of Cl^-/HCO_3^- by Cl^- channels at the apical membrane.

The function of prostaglandin E_2 (PGE_2) in the GI tract has been well studied, especially in relation to its receptors, EP_1, EP_2, EP_3 and EP_4. A selective EP4 agonist (ONO-AE3-208) significantly reduced AITC-induced anion secretion, whereas the $EP_{1/2}$ antagonist AH6809 did not affect the response to AITC, indicating that EP4 is involved in AITC-induced anion secretion in both human and rat colons[31].

It has been reported that the activation of TRPA1 inhibits spontaneous contractions and transit by direct activation of myenteric neurons[40]. Therefore TRPA1 agonist induced colonic Cl^- secretion with inhibition of colonic transit seems to physiologically regulate the movement of luminal content in the colon. In addition, TRPA1 may also play a role in flushing out noxious chemicals via inducing massive fluid secretion.

Conclusion

As colonic mucosa is continuously exposed to noxious chemicals, including toxic compounds such as bacterial metabolites and products of oxidative stress, in addition to food derivatives, the chemosensory system in the gut is critical for distinguishing beneficial and harmful substances in the gut lumen. Therefore, proper fluid secretion in the colon is important to flush away noxious chemicals, while maintaining host homeostasis. A variety of sensory receptors expressed in the colonic mucosa serve important functions, at least in anion secretion. However, specific mechanisms involved in anion secretion induced by the gut chemosensory system are largely unknown. Therefore, more studies are required to define the involvement of the gut chemosensory system in colonic ion transport.

The author declares no conflicts of interest.

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〈和文抄録〉

大腸での化学物質受容とイオン輸送制御

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消化管の基本的な役割は食物から栄養素を吸収することである．従って，消化管内には，管腔内に存在する化学物質を生体にとり有用なものと有害なものとを取捨選択して取り込むための化学物質受容機構が存在する．最近の研究から粘膜上皮に存在する特殊な細胞群がこの受容機構に関与していることが明らかとなってきた．消化管管腔内の化学物質の組成や濃度の変化は直ちに消化管の基本的機能である運動や分泌あるいは血流に影響する．さらに，このような消化管に存在する化学物質受容機構の破たんは局所的な消化管の機能障害ばかりでなく宿主の基本的な恒常性維持機構にも影響する．消化管でのイオン輸送を伴う水分泌は電解質の制御や生体防御機構にとっても極めて重要である．本総説では，大腸での化学物質受容機構に焦点を当て，この受容機構がどのようにイオン輸送制御に関与しているかについて，我々の最近の知見を交えて解説した．

キーワード：化学物質受容機構，イオン分泌，大腸，生体防御．

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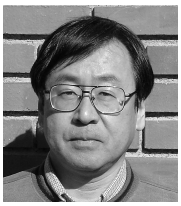

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