Targeting Ion Channels: An Important Therapeutic Implication in Gastrointestinal Dysmotility in Patients With Spinal Cord Injury

Miroslav Radulovic,1,2 Preeti Anand,3 Mark A Korsten,1,2 and Bing Gong1,3*

Departments of 1Medicine and 2Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; and 3National Center of Excellence for the Medical Consequences of SCI, James J Peters Veteran Affairs Medical Center, Bronx, NY, USA

Gastrointestinal (GI) dysmotility is a severe, and common complication in patients with spinal cord injury (SCI). Current therapeutic methods using acetylcholine analogs or laxative agents have unwanted side effects, besides often fail to have desired effect. Various ion channels such as ATP-sensitive potassium (KATP) channel, calcium ions (Ca$^{2+}$)-activated potassium ions (K$^+$) channels, voltage-sensitive Ca$^{2+}$ channels and chloride ion (Cl$^-$) channels are abundantly expressed in GI tissues, and play an important role in regulating GI motility. The release of neurotransmitters from the enteric nerve terminal, innervating GI interstitial cells of Cajal (ICC), and smooth muscle cells (SMC), causes inactivation of K$^+$ and Cl$^-$ channels, increasing Ca$^{2+}$ influx into cytoplasm, resulting in membrane depolarization and smooth muscle contraction. Thus, agents directly regulating ion channels activity either in ICC or in SMC may affect GI peristalsis and would be potential therapeutic target for the treatment of GI dysmotility with SCI. (J Neurogastroenterol Motil 2015;21:494-502)

Key Words
Dysmotility; Gastrointestinal; Interstitial cells of Cajal; Ion channels; Myocytes, smooth muscle

Introduction

Gastrointestinal (GI) dysmotility is one of the most common medical complications following spinal cord injury (SCI). Both acute and chronic SCI cause loss of the excitatory neural input to enteric neurons, causing overall lack of neural excitability to the gut, result in constipation, abdominal pain, nausea, bloating, and fecal incontinence, which has significant negative impact on quality of life and increases long-term morbidity.1 Currently conventional therapeutic strategies are laxatives, high-fiber diet, cholinergic agonists, mechanical removal of fecal matter.2 These methods have obvious inadequacies, although combination therapies are often employed but may fail to have desired effect while causing an increase in adverse effects. For example, chronically using laxatives has been found to be associated with laxative colon

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*Correspondence: Bing Gong, MD
Department of Medicine, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Placc, New York, NY 10029-6574, USA
Fax: +1-201-658-3148, E-mail: bing.gong@va.gov
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or colon cancer; chronic mechanical fecal removal is an ordeal for the patient and inconvenient for healthcare workers. Moreover, cholinergic agonists could result in bronchospasm, bronchorrhea, thereby limiting its use in patients who have chronic obstructive pulmonary disease or suffer from respiratory insufficiency in addition to SCI. Thus studies aimed at finding effective and convenient therapeutic regimens with better adverse effect profile are essential.

Several mechanisms are involved in the causation of GI dysmotility after SCI. These include possible injury to parasympathetic nerve system or motor neuron of enteric nervous system which causes the dysfunctional release of the major regulatory neurotransmitters such as acetylcholine, substance P, etc. This results in a decrease in interstitial cells of Cajal (ICC) activity and diminishes contraction of smooth muscle cells (SMCs) of GI tract, causing the reduction in both nonpropulsive segmental contractions and high amplitude propagating contractions in large intestine.

Ion channels play important roles in the GI motility. Under physiological condition, the release of acetylcholine or substance P from the parasympathetic post-ganglionic nerve terminal innervating GI smooth muscle inactivates potassium ion (K⁺) channels causing membrane depolarization, and then increasing calcium ions (Ca²⁺) influx into cytoplasm. The Ca²⁺ release causes contraction of circular muscle layer, followed by shortening of the longitudinal muscle, thus pushes the bolus of food forward, forming peristaltic wave. ICC are central to the generation and propagation of the cyclical electrical activity while SMCs are responsible for electromechanical coupling. Recent, evidence shows that abnormal ion channel activities are related to the human GI dysmotility. For example people with mutations in SCN5A have higher prevalence of Brugada syndrome and functional dyspepsia, as well as irritable bowel syndrome (IBS). Thus agents directly regulating ion channel activities either in ICC or in SMCs may affect the GI peristalsis. For example, certain potassium channel blockers and compounds increasing Ca²⁺ release or Ca²⁺ sensitivity specifically acting on GI tract would be potentially effective therapeutic agents for GI dysmotility. In this review, we will discuss main groups of ion channels distributed in the GI tract and their potential therapeutic roles in the treatment of GI dysmotility after SCI.

**General Electrophysiological Properties of Interstitial Cells of Cajal and Smooth Muscle Cell**

ICC are pacemaker-cells abundantly distributed in stomach, small intestine and colon. ICC are mainly found in the mesenteric plexus which is located deep to muscular plexus close to smooth muscle forming synapse like junctions with enteric nerve and forming gap junctions with smooth muscle cells. They generate, and transmit signals from enteric neurons to smooth muscles through the gap junctions (Fig. 1). Dysfunction of ICC caused by inflammation, mechanich damage or SCI induced enteric nervous dysfunction may result GI paralysis. The ICC set the basic electric rhythm (slow wave) through establishing the electrochemical equilibrium between the spontaneous depolarizing pacemaker currents and hyperpolarizing K⁺ outward current.
The inward pacemaker currents in ICC of colon tract have been identified to be Ca^{2+}-activated chloride channels (CaCC) and non-selective cation channels (NSCC).^{14-16} The membrane depolarization caused by the pacemaker currents turns on the T-type Ca^{2+} channels in the ICC, resulting Ca^{2+} influx and formation of train action potential. The ICC action potential complex propagates to SMC through the gap junction of interstitial network and initiates the voltage-sensitive calcium (CaV) channels including L-type (CaV1) and T-type (CaV3) L-type Ca^{2+} channel in SMC to initiate the excitation-contraction process and causing smooth muscle contraction.^{17-19} The ICC physically closely contact with the varicosities of the enteric nerve, and are sensitive to stretch in addition to a number of enteric neurotransmitters including acetylcholine, adenosine triphosphate, nitric oxide.^{6}

Enteric nerve when stimulated by mechanical stretch or chemical signal via afferent neurons, causes GI parasympathetic and motor neurons to release acetylcholine triggering train of action potentials and smooth muscle contraction (Fig. 2).^{20} The frequency of slow-wave sets the rate of muscle movement, while the degree of membrane depolarization or the amount of Ca^{2+} influx of ICC determines the ionotropicity and contractility of SMC. In patients with SCI, the enteric parasympathetic system is disturbed causing dysregulation of neurotransmitter release, thus resulting GI dysmotility. A wide variety of ion channels has been identified in ICC and SM according their electrophysiological properties, some of these channels play crucial role in the GI motility, thus, we may regulate the GI motility through directly acting on ion channels, the down-stream site of acetylcholine.

Targeting ATP-sensitive Potassium Channel in Interstitial Cells of Cajal

ATP-sensitive potassium (K_{ATP}) channels are found in a variety of tissues including nervous system, smooth muscles in GI system and pancreatic β cells and play crucial physiological roles in these systems.^{21,22} Classical K_{ATP} channels are comprised of 2 types of subunits: the pore-forming inwardly rectifying K⁺ channel subunit (Kir6.x), members of Kir channel gene family and regulatory sulfonylurea receptors (SUR1, SUR2A, and SUR2B) members of the ATP-binding cassette superfamily. Genetic disruption of either subunit will lead to dysregulation of smooth muscle, nerve through a heterotrimeric G protein subunit activated protein kinase C (PKC) regulated signaling pathway resulting an abnormal activation of L-type Ca^{2+} channel.^{23} K_{ATP} channel has been identified in ICCs in intestine and colon which is consisted of Kir6.2 and SUR 2B. Its inward rectifying K⁺ current sets the resting membrane potential about −70 mv.^{24} Experiments have showed that one of the mechanisms of acetylcholine promoting GI motility is through an inhibition of K_{ATP} channel activity, causing membrane depolarization thus increasing Ca^{2+} influx in ICC, and increasing the ICC firing frequency.^{25} K_{ATP} channels blockers such as glibenclamide and tolbutamide currently used for the treatment of diabetes through an increase in insulin release have also been shown to increase the rhythm of slow waves and to increase the frequency of the generation of train action potentials of smooth muscles in GI tract. On the other hand, phentolamine, hydrogen sulfide (H₂S), and adenosine, decreases the GI motility by activating K_{ATP} channels causing a decrease of intracellular Ca^{2+} oscillation in ICC and...
has been used to treat IBS related diarrhea and this effect was abolished by glibenclamide. Similar to the effects of KATP channel in smooth muscle in GI tract, pinacidil, a specific KATP channel opener has therapeutic effects on mild essential hypertension by relaxing arterial smooth muscle. Interestingly experiments have showed that activation of KATP channels by prostaglandin E2 (PGE2) through EP2 receptor in cultured ICC from murine small intestine causes smooth muscle relaxation reducing GI motility, hence has been used for the treatment of inflammatory bowel syndrome. These evidences, although from other systems, support the idea that regulating the activity of KATP channels in ICC could be used to treat the GI dysmotility especially in patients with SCI.

#### Targeting ATP-sensitive Potassium Channel in Smooth Muscle Cell

The expression of KATP channel in SMC of GI tract has been identified as co-expression of SUR2B/Kir6.1 or Kir6.2. Increased expression of KATP channel due to inflammation is related to decreased colon motility due to the SMC hyperpolarization. While SUR2B/Kir6.1 is mainly expressed at plasma membrane, the SUR2B/Kir6.2 is mainly located at cytosol of SMC. The regulation of KATP channel is cAMP-PKA/PKC cascade pathway dependent. Certain inhibitory neurotransmitters activate KATP channel through G-protein coupled receptor, by binding with Gα subunit, activate adenylyl cyclase, increase cAMP and cause PKA dependent phosphorylation, this results in SMC membrane hyperpolarization, thus reducing GI motility. Thus agents which increase the adenylyl cyclase, elevating cyclic AMP including calcitonin gene-related peptide, adenosine and prostacyclin, and specific KATP channel openers (pinacidil and diazoxide); activation of KATP channel in SMC of GI and could be used to reduce the GI motility to treat the IBS related diarrhea. For example, in antral smooth muscle of guinea-pig cromakalim, diazoxide, and nicardipine cause membrane hyperpolarization by opening KATP channels therefore, reduce the first component and abolish the second component of slow waves. It may be associated with the opening of mitochondrial KATP channel in SMC thus affecting the regulation of Ca^{2+} handling. Thus evidence suggests that pinacidil and nicardipine may prove useful in providing relief from gastric spasm, while KATP channel inhibitors such as glibenclamide or 5-hydroxydecanoic acid may have therapeutic potential in delayed gastric emptying, as a new type of prokinetic agent.

In the contrary, excitatory neurotransmitters such as acetylcholine, PKC activator phorbol esters (phorbol 12, 13-dibutyrate) which block KATP channels in GI SMC, cause membrane depolarization, increasing colon/intestinal motility through an activation of PKC. Thus KATP channels blockers such as glibenclamide, tolbutamide, 5-hydroxydecanoic acid, and HMR-1098 specifically acting on the subtype of channels in SMC may mimic acetylcholine’s effects on GI tract while have less non-specific effects on other organs.

#### CI^− Channel Facilitates ATP-sensitive Potassium Channel Mediated Gastrointestinal Motility

It has been shown that the spontaneous transient depolarization and spontaneous slow wave in isolated ICC cells can be blocked by niflumic acid, a molecule that specifically inhibits Cl^− channels suggesting that the Cl^− channel contributes to the membrane depolarization of ICC. The major Cl^− channel expressed in colon ICC and SMC is a CaCC. It is abundantly expressed in GI smooth muscles; it can be activated by increased intracellular Ca^{2+} levels and enteric neurotransmitters. The Anoctamin-1 (ANO1) subtype of CaCC is mainly expressed in ICC, which plays important role in the slow wave generation. Neurokinin-1 has potent effects on the colon contraction could be blocked by the CaCC blockers such as tamoxifen or chlorotoxin, possibly indicating that effects of Neurokinin-1 on colon are through activation of Cl^− channel, and it may have therapeutic potential in the treatment of constipation after SCI. Currently, novel CaCC opener phenanthroline is being extensively studied, especially in treatment for cystic fibrosis caused by abnormal function of cystic fibrosis transmembrane conductance regulator (CFTR) due to decreased secretion of the Cl^− and sodium ion (Na^+) through the Cl^− channel of the CFTR in the epithelium. Phenanthroline does not affect the cAMP or intracellular Ca^{2+} levels, while it activates the Cl^− channel, suggesting that it may act directly on the Cl^− channels and not through an indirect regulation. Another Cl^− channel activator, lubiprostone which is bicyclic fatty acid derived from PGE1 currently used for the treatment of chronic constipation and constipation predominant IBS. The underlying mechanism is to increase Cl^− secretion through Cl^− channel increasing Ca^{2+} influx in gastrointestinal SMC in addition to activating prostaglandin E receptors (EP1 or EP4), thus causing smooth muscle contractions. Hence both lubiprostone and phenanthroline act by activating Cl^− channel, causing an increase in Cl^− secretion and intestinal fluid or directly enhancing the GI motility in smooth muscle.
Small-conductance Ca$^{2+}$-activated K$^+$ (SK) channels play a role in the regulation of smooth muscle tone in GI tract. SK channels are abundantly distributed in murine proximal colon, three isoforms of SK channels have been identified (SK1, SK2, and SK3). This channel is responsive to inhibitory neurotransmitters in colonic smooth muscles such as ATP which opens SK channel and causes smooth muscle cell hyperpolarization, mechanistically, reducing the smooth muscle contraction. In human, mutations in the gene encoding the Ca$_2$.1α1 subunit of the P/Q-type voltage-gated calcium channel causes episodic ataxia, a type of inherited movement disorder caused by the reduction in the activity of SK channels. SK channels are activated under basal conditions in colonic smooth muscles contributing to regulation of resting membrane potential, open SK channels maintain membrane hyperpolarization, preventing the activation of Ca$^{2+}$ channels, causing smooth muscle relaxation. On the other hand, apamin, a peptide neurotoxin extracted from bee venom, blocks SK channels expressed in the GI smooth muscles and causes membrane depolarization (10 mV) and an augmentation of action potentials, thus increases the contractions in colonic muscles. Clotrimazole, an antifungal agent acts by blocking SK channels expressed in the GI smooth muscles and has been used to treat myotonic muscular dystrophy. Clotrimazole, an antifungal agent acts by blocking SK channels expressed in the GI smooth muscles and has been used to treat myotonic muscular dystrophy.

Voltage-sensitive Ca$^{2+}$ Channels

Two major Ca$^{2+}$ channels: voltage-sensitive calcium channels L-type and T-type have been found in GI SMCs and ICC. T-type Ca$^{2+}$ channel is sensitive to mibebradil and low depolarization voltage but resistant to dihydropyridine (DHP) and nefidipine. T-type Ca$^{2+}$ channel plays important role in the ICCs, causing slow spontaneous depolarization, thus activating pacemaker cells. L-type Ca$^{2+}$ channel mainly sensitive to DHP and high voltage stimuli, provides bulk Ca$^{2+}$ required for the excitation-contraction coupling. L-type Ca$^{2+}$ channels cause colon dysmotility, resulting in constipation, a common adverse effect observed in patients on DHP calcium channel blockers which are being investigated may be a potential therapeutic target for the treatment of GI dysmotility after SCI.
channel blocker therapy for hypertension. On the contrary, activating Ca\(^{2+}\)-activated K\(^+\) channels by trimebutine increases gastric emptying, intestinal and colonic contractility via activation of T-type Ca\(^{2+}\) channel at lower dosage (1-10 \(\mu\)M). On the other hand, it has been used for irritable bowel disorders at higher concentration (100-300 \(\mu\)M) causing inhibition of L-type Ca\(^{2+}\) channels thus reducing colon peristalsis.\(^{56}\) The voltage-sensitive Ca\(^{2+}\) channels in ICC and SMC can be activated by K\(^+\) channel blockers such as reported potent novel fluoro-oxindoles BMS-204352 and racemic compound 1 which are sensitive to the intracellular Ca\(^{2+}\) levels,\(^{57}\) or agents activating Cl\(^-\) channels as described early in the K\(^+\) channel section. Moreover, Ca\(^{2+}\) channel openers such as amylin or ryanodine increases Ca\(^{2+}\) influx into the cytosol from sarcoplasmic reticulum, resulting in positive inotropic effect in muscle, which could be a potential target for the treatment of GI dysmotility.

### Stretch-dependent K\(^+\) Channel

Stretch-dependent K\(^+\) (SDK) channels abundantly expressed in colonic smooth muscle cells, which encode TWIK-related K\(^+\) channel (TREK) and TWIK-related arachidonic acid stimulated K\(^+\) channel (TRAAB) subunits, are sensitive to mechanical stretch, thus causing relaxation in response to smooth muscle elongation produced by contents filling colonic lumen. These are activated by the enteric inhibitory neurotransmitter, nitric oxide mediated cGMP-dependent pathway.\(^{58}\) Its major function is to increase the colonic proximal luminal diameter by relaxing GI smooth muscle, during filling to conserve water and electrolytes. This is probably mechanism of action and functionally important for other visceral organs such as uterus and bladder that could be expanded extensively without causing irritable contractions. It has been reported that methionine and its de-

| Ion channels                      | Antagonists                  | Agonists                      | Clinical application                          | Clinical application                          |
|----------------------------------|------------------------------|-------------------------------|-----------------------------------------------|-----------------------------------------------|
| **K\(_{ATP}\)** channels         | Glibenclamide                | Diabetes (increasing insulin release) | Phobol-dibutyrate                              | IBD and diarrhea                              |
|                                  | Tolbutamide                  | GI dysmotility and constipation (increasing SMC and ICC pulse frequency) | Cromakalim                                    | GI track spasm (reducing GI SMC and ICC pulse frequency) |
|                                  | 5-HAD                        |                               | Nicorandil                                      |                                               |
|                                  | HMR-1098                     |                               | Pinacidil                                       |                                               |
| **Ca\(^{2+}\)** activated K\(^+\) channel** | Aamin                        | Increase the contractions in colonic smooth muscles (treat constipation) | Neurokinin-1                                   | Increase GI motility                          |
|                                  | Clotrimazole                 |                               | Phenanthroline                                  | Treat cystic fibrosis and constipation         |
|                                  | Verapamil                    |                               | Lubiprostone                                    | Chronic constipation                           |
|                                  | Hydrogen sulfide             | Treat myotonic muscle dystrophy |                                               | Increase GI motility                          |
|                                  | Trimebutine                  |                               |                                               | (same as above)                               |
| **Ca\(^{2+}\)** activated Cl\(^-\) channels** | Tamoxifen                    | IBD and diarrhea               | Amylin                                         |                                               |
|                                  | Chlorotoxin                  |                               | Fluoro-oxindoles                               |                                               |
|                                  |                               |                               | BMS-204352                                      |                                               |
| **Voltage-sensitive Ca\(^{2+}\)** channels** | Mibebradil                   | Esophageal spasm               |                                               |                                               |
|                                  | Nedipine                     | IBS                            | Amylin                                         |                                               |
|                                  | Nimodipine                   | Mesenteric vascular insufficiency | Fluoro-oxindoles                               |                                               |
|                                  | Prandipine                   | Dyskinesis of the Sphincter of Oddi | BMS-204352                                    |                                               |
|                                  | Bepridil                     | Insulinoma                     | Racemic compound 1 (same as above)             |                                               |
| **Stretch-dependent K\(^+\)** channel** | Methionine                   | Increase the bladder contractility |                                               |                                               |
|                                  | L-cysteine                   | Increase GI motility           |                                               |                                               |
|                                  | L-methionine                 |                               |                                               |                                               |
|                                  | DL-homocystine               |                               |                                               |                                               |
|                                  | Caffeine                     |                               |                                               |                                               |
|                                  | Cyclopiazonic acid           |                               |                                               |                                               |
|                                  | Ryanodine                    |                               |                                               |                                               |

GI, gastrointestinal; ICC, interstitial cells of Cajal; IBD, inflammatory bowel disorders; IBS, irritable bowel syndrome.
derivatives increases the bladder contractility by inhibiting stretch-dependent K+ channel.59 The electrophysiological property of the activation of the SDK channel causes membrane hyperpolarization, prevent the activation of the L-type Ca2+ channels in SMC causing GI relaxation.60 Pharmacologically, sulfur-containing amino acids, such as L-cysteine, L-methionine, or DL-homocysteine block the SDK channel, cause SMC depolarization and muscle contraction.61 Other compounds such as caffeine, ryanodine, and cyclopiazonic acid may also have similar effects. Thus the SDK channel is a another possible target for the treatment of GI dysmotility. Above mentioned compounds effecting on ion channels in GI tract were summarized in Table.

Summary

GI tract dysmotility is a severe complication after SCI. Currently, treatment for the GI dysmotility mainly consists of acetylcholine agonists which has undesirable side effects, especially among the SCI patients with compromised pulmonary function or bronchial diseases such as asthma and chronic bronchitis. Ion channels have been found to be abundantly distributed in ICC and SMCs of GI tract and play an important physiological role in the regulation of ICC activity and SMC contractility. K+ channel blockers (glibenclamide, tolbutamide, H2S, nitroblue tetrazolium, fluoro-oxindoles BMS-204352, and 5-HAD), Cl− channel (Neurokinin-1, phenanthroline) and Calcium channel (trimebutine) openers specially act on the GI SMC and ICC could cause membrane depolarization, increasing Ca2+ influx both in ICCs and SMCs, increasing the frequency of excitatory impulses onto smooth muscle, triggering the smooth muscle contraction. The increase in Ca2+ influx, into the cytosol of SMC also directly increases, the smooth muscle contractility, thus promoting bowel movements, and preventing complications caused by constipation. Several drugs targeting ion channels have been applied clinically to treat other diseases, which may have beneficial effects on the GI dysmotility. For example, KATP channel blockers glibenclamide and tolbutamide used in the treatment of Diabetes Mellitus and CaCC opener phenanthroline used to treat cystic fibrosis cause potent GI smooth muscle contraction and, could be used for the treatment of GI dysmotility. Comparing with the traditional acetylcholine agonists, selective ion channel blockers/openers have specific local effect on the GI tract, thus may serve as potential treatment modality for GI dysmotility with better side effect profile. These compounds acting on various ion channels with specificity for GI tract could be important tools in regulating GI motility and may be answer to complex and distressing problem of GI dysmotility after SCI.

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