REVIEW
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Ion channel mechanism of gastrointestinal motility and gastric hypersensitivity in functional dyspepsia: a review

Terigele Bao[1], Feng Lan[1], Guorui Li[2], Xiyele Mu[1], Ta Na [1], Minghai Fu[1], Yongsheng Chen [1,2*]

[1]School of Mongolian Medicine, Inner Mongolia University for Nationalities, Tongliao 028000, Inner Mongolia Autonomous Region, China. [2]School of Life Sciences, Inner Mongolia University for Nationalities, Tongliao 028000, Inner Mongolia Autonomous Region, China.

[*]**Corresponding to:** YongSheng Chen, School of Mongolian Medicine, Inner Mongolia University for Nationalities, No.536, Huolinhe Street West, Korqin District, Tongliao City, Inner Mongolia Autonomous Region 028000, China. E-mail: Chenys_2000@163.com.

Author contributions

Minghai Fu and Yongsheng Chen were responsible for the conception and design of the manuscript. Terigele Bao, Feng Lan, Xiyele Mu and Ta Na wrote the draft. Yongsheng Chen and Guorui Li performed critical review and revision of the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

FD, functional dyspepsia; SMC, smooth muscle cells; VIP, vasoactive intestinal polypeptide; NO, nitric oxide synthesis; ICC, interstitial cells of Cajal; ATP, adenosine triphosphate; TRP, transient receptor potential.

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Abstract

Functional dyspepsia (FD) is a regularly diagnosed clinical gastrointestinal ailment with a high incidence rate that can considerably impact patients' health and quality of life and impose a substantial financial burden. Modern research on the pathophysiology of functional dyspepsia has not thoroughly explained the underlying reasons. The condition does not manifest any significant organ abnormalities, which raises the disease's difficulty coefficient. Major pathogenic exceptions in FD include gastrointestinal motor dysfunction, gastrointestinal hormone secretion problem, visceral hypersensitivity, and brain-gut axis. Several ion channels have reportedly been implicated in the pathophysiological process of FD. Therefore, it is crucial to comprehend the probable activities of various ion channels in FD. This study focuses on the current state of research on the possible role of several ion channels in the pathogenesis of FD.

Keywords: functional dyspepsia; ion channel; gastrointestinal motility; gastric hypersensitivity; smooth muscle

Introduction

Ion channels are macromolecular protein structures found in organelle plasma membranes or cell endoplasmic membranes capable of displaying distinct selective ion transmembrane transport capabilities and playing a crucial role in maintaining the specific permeability barrier [1]. It has been stated that about 400 linked protein families account for over 1 percent of the human gene pool. Malykhina originally introduced the idea of "channel illnesses" in 2004 and emphasized that several significant clinical symptoms of smooth muscle contraction may be controlled at the level of ion channels [2]. It has been found that ion channel anomalies are strongly associated with gastrointestinal illnesses. Thus, unraveling the molecular basis of gastrointestinal ion channel illnesses can offer a foundation for developing innovative diagnostic, differential diagnostic, and therapeutic techniques for Functional dyspepsia (FD) [3]. The classification of ion channels is based on their specific ion types, gating methods (activation or control), and molecular shapes. The essential ion channels are Na^+, K^+, Ca^{2+}, and Cl^-, as they predominate in smooth muscle cells of the gastrointestinal tract and govern their contraction [4].

FD is a functional gastrointestinal disorder that can present a variety of complicated gastrointestinal symptoms [5]. The most commonly diagnosed symptoms include epigastric distension, discomfort, postprandial fullness, early satiety, epigastric pain, etc. However, its clinical presentations may not be fully explained by organic, systemic, or metabolic illnesses [6]. Comorbidity, acute gastroenteritis, being female, smoking, using nonsteroidal anti-inflammatory medications, and helicobacter pylori infection are risk factors [7]. Rome III diagnostic criteria [8] provide that one or more of the following must be met: 1. early satiety, postprandial fullness, epigastric discomfort, and epigastric burning sensation; 2. no organic condition can explain the aforementioned symptoms; 3. at least six months before to diagnosis and approximately three months following diagnosis. According to a recent study, FD accounts for about one-third of outpatient disorders in the digestive medicine department, with an incidence rate of 18 to 23 percent [9]. In recent years, as a result of the tremendous growth of the economy, societal demand to preserve life has increased dramatically. It has been observed that the incidence rate of FD is growing, which might negatively impact the quality of life and social functions [10, 11]. Currently, the etiology and pathophysiology of FD are unknown; nevertheless, it has been proposed that the incidence and development of FD may be associated with many pathological processes, such as gastrointestinal motility disturbance, gastric hypersensitivity, and impaired stomach compliance [12]. Numerous investigations have demonstrated that ion channels are not only engaged in controlling gastrointestinal motility but also play a significant role in gastric hypersensitivity; these two activities have been identified as key contributors to the incidence and progression of FD [5]. This article will examine the possible roles of several ion channels in the etiology and therapy of FD.

Ion channels can cause gastrointestinal motility disorders

Several related abnormalities are seen in patients with FD, including postprandial hypomotility of the stomach antrum, change in gastric rhythm, poor gastric-duodenal coordination delayed gastric emptying, and so on. The abnormality rate is between 20% and 54%, which has been linked to alterations in the patient's duodenal acid and lipid metabolism, excessive phasic contraction of the proximal stomach after a meal, and gastric dysfunction [12–14]. The cause of delayed gastric emptying is reduced gastric motility, which can severely reduce the motility of the stomach antrum. One of the critical reasons for FD [15, 16] is a failure of the stomach's motility, which can result in antrum overload. In FD, nausea, vomiting, and postprandial satiety are also believed to be associated with stomach emptying [17], and faster gastric emptying has been shown to alleviate these symptoms significantly [18]. In recent years, the successful use of calcium channel antagonists in the treatment of functional gastrointestinal motility disorders has suggested that the occurrence of these diseases may be linked to an imbalance of calcium homeostasis in smooth muscle cells; however, the mechanism of action requires further investigation.

The modulation of gastrointestinal motility has been linked to the incidence, development, and alleviation of functional dyspepsia. As a centrally regulated muscular organ, the gastrointestinal tract is made of multiple layers of smooth muscles. The fast contractions of smooth muscle cells (SMC) accompany intestinal motility. Therefore, it has been shown that the incidence of gastrointestinal motility problems is directly connected to changes in smooth muscle contraction. In the gastrointestinal SMC, there are three distinct ion channels (Figure 1): 1. voltage-gated sodium channels, potassium channels, calcium channels, etc. 2. ligand-gated channels. 3. mechanically-gated channels such as stretch-sensitive channels and volume-sensitive channels, etc. [19]. The fast contraction of smooth muscle cells is mediated by an increase in cytosolic Ca^{2+} concentration [20]. Calcium ions can bind to calmodulin, and the calcium-calmodulin complex can activate myosin light chain kinase and control myosin light chain by phosphorylating 20 kDa (MLC20). This process is the foundation for developing a single bridge between actin and myosin heavy chain and can govern smooth muscle contraction. L-type voltage-dependent calcium channels (L-Ca^{2+}) are the most prevalent and vital calcium channels in the smooth muscle of the digestive tract. It preferentially permits Ca^{2+} to cross the membrane, can participate in smooth muscle excitation and contraction coupling, and can be inhibited by nifedipine medicines. It has a high threshold, large conductance, slow inactivation, and inactivation dependent on intracellular Ca^{2+} concentration, etc. [21].

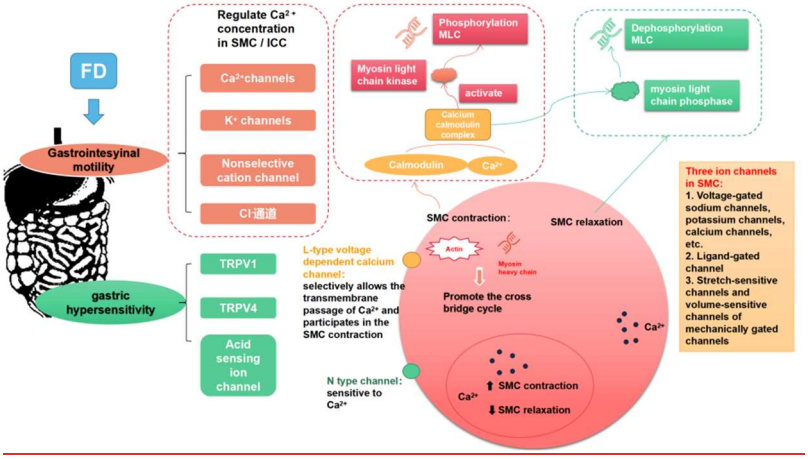

Figure 1: Ion channel and SMC constriction mechanism of gastrointestinal motility and visceral hypersensitivity observed in FD

Calcium ion channels regulate intracellular Ca^{2+} concentration changes

Extracellular calcium influx and intracellular calcium release have been shown as critical factors of SMC contraction. It has been shown that the contractile activity of the gastrointestinal smooth muscle is strongly connected to variations in intracellular Ca^{2+} concentration and that intracellular Ca^{2+} release can also serve as an efficient means of regulating smooth muscle contraction and relaxation [22]. When cells are stimulated externally, the intracytoplasmic Ca^{2+} concentration rises, which can bind to calmodulin and activate myosin light chain Kinase (MLCK). Activated MLCK can then phosphorylate the myosin light chain (MLC), which promotes the formation of cross-bridge cycles between actin and myosin and causes smooth muscle contraction. Myosin light chain phosphatase (MLCP) can dephosphorylate the myosin light chain and promote smooth muscle relaxation [23]. Ca^{2+} is the centra transmitter that may successfully stimulate smooth muscle contraction, and it functions as the cell's ubiquitous secondary messenger. Thus, precise Regulation of intracellular Ca^{2+} release is an efficient means of controlling smooth muscle contraction and relaxation [24].

At present, smooth muscle cell calcium channels are categorized into four main categories: according to their various pharmacological and biophysical features, voltage-dependent calcium channels are classified as L-type, T-type, P-type, and N-type calcium channels. The L-type calcium channel is distinguished by its rapid inactivation, delayed and persistent attenuation, high threshold, large conductance, and intracellular Ca^{2+} concentration-dependent inactivation. It can manifest as a continuous inward current, typically triggered at -40–30 mV and 0–10 mV generates the most inward current. It is the predominant calcium channel found in the smooth muscle of the gastrointestinal tract. It can form action potentials in smooth muscle and can regulate the contraction activity of smooth muscle directly. Kurjak revealed that intestinal synaptosomes could display voltage-dependent Ca^{2+} channel properties and stimulate vasoactive intestinal polypeptide (VIP) release and nitric oxide synthesis (NO). VIP release is predominantly associated with P^{-} and N-type Ca^{2+} channels, but NO synthase-dependent Ca^{2+} can also pass via L-type Ca^{2+} channels. On the contrary, N-type calcium channels have not been cloned on smooth muscle cells of the gastrointestinal tract and interstitial cells of Cajal (ICC). Calcium channels of the T type can exhibit slow inactivation, quick decay, a low threshold, and poor conductance. It can appear as a transient inward current, often triggered around -70–60 mV, predominantly in neurons and myocardium. Receptors can modulate calcium channels, which are subdivided into ligand-gated calcium channels and, second messenger-gated calcium channels, stretch-activated calcium channels; background calcium channels [25].

ICC is mainly situated between the longitudinal and circular muscles of the gastrointestinal tract, near the myenteric plexus, and has been discovered to be strongly connected to gastrointestinal motor neurons and smooth muscle cells. Mesenchymal cells play a crucial part in the conductance of electrical activity and dyskinesia processes in the gastrointestinal tract. A recent article revealed that FD might be coupled with a decrease in the number of ICC or network destruction [26]. Interstitial cells are the primary pacemaker cells among interstitial cells, which can generate rhythmic depolarization and produce slow waves. Pacemaker current refers to the spontaneous inward current produced by these interstitial cells serving as pacemaker cells. The "pacing unit" consists of four parts: inosine triphosphate (IP3), ryanodine-sensitive calcium storage, mitochondria, and calcium-sensitive channels. It is the fundamental component that promotes automatic depolarization. The activation of the receptor causes the IP3 and ryanodine receptor-sensitive drug depots to release calcium, which can then trigger the process of mitochondrial uptake and consumption, which results in a significant decrease in the calcium ion concentration in a specific area of the cell, and can finally trigger the opening of low calcium sensitive channels. Moreover, the ion flow might induce the potential change, resulting in a repetitive electric likely change [27]. It was shown that calcium-activated chloride channels, voltage-dependent calcium channels, and intracellular calcium ion concentration are intimately associated with the formation of ICC pacing potential [28].

Table 1: Ion channels affecting gastrointestinal motility disorders in FD

Name	Type	Expression	
Calcium activated potassium channel	High conductance (BKCa), medium conductance (IKCa), and small conductance (SKCa)	Gastrointestinal smooth muscle, ICC	[28, 29]
Inward rectifier potassium channel	Classical (Kir2.1–2.4) K^+ transport channels (4.2, 5.1, 7.1) g protein gated (kir3.1–3.4) ATP sensitive (Kir6.1–6.2) channels	Some were expressed in smooth muscle cells, kir1.1, 4.1 in gastrointestinal smooth muscle and ICC	[30]
ATP sensitive potassium channel	-	Increase pacing frequency and action potential frequency of muscle cells	[31]
Delay rectifier channel	KV1.1, KV1.2, KV1.5, KV1.6, KV2.2		
Kv4 channel	-		
Slow delay rectifier channel	KCNQ or KV7		
HERG channel（KV11.1）	-	Mostly expressed in SMC	[32, 33]
BK channel（KCa1.1）	-		
SK channel（KCa2）	-		
IK channel（KCa3.1）	-		
Trek channel （K2P2.1）	-		
KV7	-	Rat proximal gastric muscle tension	[34]
Potassium bisphosphate (K2P) channel family	K2P2.1 and K2P5.1	Regulation of gastrointestinal smooth muscle contraction	[35]

K^+ channels and gastrointestinal motility cells

K^+ channels are the most numerous and diverse family of ion channels. All K^+ channels have been discovered to have a role in maintaining the membrane potential. Voltage-gated potassium channels and ligand-gated potassium channels can be distinguished among K^+ channels. Ligand-gated potassium channels include sodium-activated potassium channels, ATP-sensitive potassium channels, adenosine-sensitive potassium channels, muscarinic potassium channels, and phosphatidylcholine-activated potassium channels.

Calcium-activated potassium channels are time-and voltage-dependent and primarily depends on the intracellular Ca^{2+} concentration. There are three different types, which are high-conductance (BKCa), medium-conductance (IKCa), and small-conductance (SKCa) calcium-activated potassium channels. BKCa, the most important of these three, is widely distributed in the

gastrointestinal smooth muscle and ICC because of its maximum conductivity [29, 30]. Moreover, inward rectifier potassium channels (Kir channels) are divided into seven types and 15 subtypes, and some are explicitly expressed in smooth muscle cells. Kir channels can be divided into four different functional groups: classic (Kir2.1–2.4), K^+ transport channels (Kir1.1, 4.1 gastrointestinal smooth muscle and ICC, 4.2, 5.1, and 7.1), G protein gating (Kir3.1–3.4) and ATP-sensitive (Kir6.1–6.2) channels [31].

There are ATP-sensitive potassium channels located in the ICC of the small intestine and colon, which can maintain the resting potential of the ICC at -70 mV by regulating the regular influx of potassium ions. It has been reported that when the ATP-sensitive potassium channel is inhibited, the cell membrane can undergo depolarization, thereby causing ICC calcium influx, increasing the pacing frequency and the action potential frequency of the muscle cells [32]. A number of potassium channels are expressed in the cells that constitute SMC-ICC-PDGFRα^+cell (SIP) syncytium, the most important among which are: delayed rectification (KV1.1, KV1.2, KV1.5, KV1.6, KV2.2) channel, type A (KV4) channel, slow delayed rectification (KCNQ or KV7) channel, HERG (KV11.1) channel, BK (KCa1.1) channel, SK (KCa2) channel, IK (KCa3. 1) channel, TREK (K2P2.1) channel [33, 34]. Most of these channels are expressed in SMC, including the smooth muscle of the gastrointestinal tract. The most important Kir channels in SIP syncytia are Kir2.1, 3, and 6 channels play a pivotal role in the regulation of smooth muscle movement. The former is expressed in ICC, and the latter is expressed in SMC [35].

Other studies have also shown that the KV7 channel can partially mediate the proximal gastric relaxation induced by VIP, which is one of the most important inhibitory neurotransmitters in the gastrointestinal tract [36]. It has been suggested that the KV7 activator might be considered a new possible drug for treating gastrointestinal dyskinesia in functional gastrointestinal diseases. In addition, the K2P channel family includes the K2P2.1 and K2P5.1 channel among 15 channels, which can play important physiological roles in the regulation of gastrointestinal smooth muscle contraction. Their opening probability increases significantly with stretching and in response to NO. These characteristics make them a vital constituent regulating the stability and relaxation of the smooth muscle membrane of the gastrointestinal tract [37].

Other ion channels and gastrointestinal motor cells

Currently, the existence of nonselective cation channels (NSCC) in a variety of smooth muscle cells has been confirmed. NSCC is the most prevalent form of stretch-activated ion channels (SAC channels). These channels display the following attributes: 1. they are primarily permeable to cations and demonstrate low permeability towards anions; 2. the permeability of cation selection is not high, and it can exhibit permeability towards various cations, including K^+, Na^+, Ca^+, and Mg^+; 3. the average value of single ion conductance is between 20 and 40 pS; 4. Gd^{3+} can effectively block it. In addition, investigations have demonstrated that the nonselective cation channel implicated in the pacing activity of gastrointestinal ICC-MY (ICC inside the intermuscular gap between myenteric areas) is a specialized kind of transient receptor potential (TRP) channel [38]. The TRP channel is predominantly a nonselective six-transmembrane cation channel with seven variants, TRPC4 and TRPM7, associated with the gastrointestinal ICC-MY pacing current [39]. It has been discovered that heterologous production of these two channels on HEK293 cells generates an inward current comparable to the ICC pacing current, suggesting that the pacing channel may be a member of the TRP channel family. Another study showed that the TRPV2 ion channel contributes considerably to mouse gastric adaption relaxation and stomach emptying. Mechanism-sensitive TRPV2 is expressed in the inhibitory motor neurons of the mouse stomach and is capable of inducing GAR and GE. Thus, TRPV2 may be a good target for GAR-impaired individuals [40].

The chloride channel is the primary anion channel on the cell membrane and is present in nearly all investigated cells. The chloride ion channels serve various purposes, including transmembrane transport of ions and liquids, modulation of cell volume, and stabilization of cell membrane potential, among others. Many studies have discovered that the gastrointestinal tract contains a specific ANO1 protein (anoctamin 1/TMEM16A), also known as calcium-activated chloride channel protein, which functions as a particular marker protein of gastrointestinal ICC but has also been implicated in the production of slow waves [41–43]. This data suggested that the chloride channel may participate in the pacing processes. In addition, ICC-MY possesses a pKa^- and ATP-activated chloride channel (PacC) that ATP and PKA can activate, produce a tail current, and only actively engage in the post-depolarization process of ICC-MY pacing activity [44]. Consequently, it is possible that these ion channels play a crucial role in FD-associated gastrointestinal motility abnormalities and contribute to the creation and modulation of pacing activity with other channel types.

Abnormal ion channels cause FD gastric hypersensitivity

Gastric hypersensitivity is commonly regarded as an additional significant element in the pathophysiology and development of FD. It has been observed that FD is more responsive than healthy volunteers to mechanical stimulation such as gastric distension [45]. The molecular basis of FD is yet unknown. However, gastric hypersensitivity and aberrant perception of gastrointestinal mechanical strain, temperature, and environmental variables may play a significant role in its formation. It has been demonstrated that sensory neuron-specific targets may be categorized into three distinct groups: receptors and sensors of peripheral nerve terminals, ion channels, and transmitter receptors associated with nerve excitability and conduction. Moreover, targets expressed explicitly by the numerous afferent neurons, such as those linked with transient receptor potential channels TRPV1, acid-sensing ion channels, and anti-tetraketotoxin Na channels [46], have the most significant therapeutic potential.

TRPV4 is a nonselective cation channel family that can be stretched and activated and is one of the drug candidates that can mediate visceral hypersensitivity [47]. TRPV4 was initially identified as a low molar concentration sensitive ion channel, which can be activated by mechanical stimulation, hyperthermia, and epoxyeicosatrienoic acid. It has been found that ATP released by Enterobacteria, activated submucosal basophils, and mast cells can also stimulate inhibitory nerve endings in the intestine. It has been reported that TRPV4 itself is significantly up-regulated in the inflamed gastrointestinal mucosa; therefore, this stretch-activated family of nonselective cation ion channels may interact with the different inflammatory mediators (IL-1β、TNF-α、IL-6) in the intestine and/or the mucosal immune system [48, 49].

The acid-sensing ion channel (ASIC) is a member of the degraded protein/epithelial sodium channel (DEG/ENaC) superfamily. It can actively participate in the process of nociception by sensing protons and is involved in regulating inflammatory chronic visceral hyperalgesia [50, 51]. There is ample evidence to suggest that ASICs, especially ASIC1 and ASIC3, can cause major chemical and mechanical allergies related to inflammatory and non-inflammatory conditions in the gastrointestinal tract [52–55]. Acid-sensitive ion channel 5 (ASIC5) mRNA was expressed in duodenal epithelial cells. It was found that ASIC5 may act as a pain-related chemical receptor or a sensor of bile acid [56]. These results indicated that ASIC5 might be related to the gallbladder and Oddi sphincter disorders in FD. There is also some evidence that TRPV1 might be related to hyperalgesia throughout the digestive tract. TRPV1 can also serve as an important marker in treating upper gastrointestinal pain in FD [57].

Discussion

Mounting evidence indicates that ion channels are attractive targets for FD that can be effective in various pathophysiological conditions. Numerous studies have initiated research tracks to identify the

treatment of FD through ion channel mechanisms. The study on the interventional mechanism of electroacupuncture (EA) of "Zusanli" (ST36) based on the involvement of mast cells/TRPV1 signaling pathway in relieving visceral hypersensitivity in FD rats reveals that gastric compliance was significantly decreased, and the levels of visceral sensitivity increased in the FD rats. TRPV1 immunofluorescence tensity, expression of PAR2 and TRPV1 proteins, and contents of SP and CGRP in the stomach were considerably up-regulated in FD rats, and these symptoms were improved after EA intervention, which may be related to its effects in inhibiting the activation of down-regulating the expression of gastric PAR2 and TRPV1 proteins [58]. Another study on quercetin in the treatment of FD showed that quercetin-induced relaxation of human gastric smooth muscle occurs directly through K^+ channels and suggested that quercetin is a potential nutraceutical in the treatment of functional dyspepsia [59].

Currently, treating FD through ion channels includes endogenous, natural compounds, prescription, and physical intervention. The Ion channel may be a better candidate for the therapy of FD as it is specifically relevant to gastrointestinal motility and gastric hypersensitivity. However, based on the massive family of ion channels, it will not only be a valuable method but also be a challenge for elucidating the pathogenesis and treatment of FD through ion channels.

Conclusion

In conclusion, various distinct ion channels or subtypes can target diverse gastrointestinal cells to regulate some crucial gastrointestinal activities, including functional dyspepsia. It has been discovered that channel blockers such as pinaverium bromide and otilonium bromide can greatly alleviate gastrointestinal smooth muscle spasms and diminish visceral hypersensitivity, albeit with a limited impact. Expanding study is being conducted on the mechanics of ion channels in functional dyspepsia. Therefore, the multi-ion channel modifying components may be considered a viable novel FD medication therapy strategy. Moreover, innovative features or multi-targeted natural medicines should be created to selectively adjust the particular assembly of these channel subunits and their associated accessory proteins. If these strategies are effective, ion channel modulators may become essential medications for treating FD symptoms and may have a substantial role in treating other gastrointestinal tract-related illnesses.

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