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Perspective

K^+ channels as potential targets for the treatment of gastrointestinal motor disorders

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DMP-543 (PubChem CID: 9887884)
E-4031 (PubChem CID: 3185)
Flupirtine (PubChem CID: 53276)
Iberiotoxin (PubChem CID: 16132435)
Linopirdine (PubChem CID: 3932)
Retigabine (PubChem CID: 121892)
Tetraethylammonium (PubChem CID: 5413)
XE-991 (PubChem CID: 656732)

ABSTRACT

K^+ channels play important functional roles in excitable cells, as neurons and muscle cells. The activation or inhibition of K^+ channels hyperpolarizes or depolarizes the cell membrane, respectively. These effects determine in the smooth muscle decrease or increase in Ca^{2+} influx through voltage-gated Ca^{2+} ($Ca_V1.2$) channels and relaxation or contraction, respectively. Recent studies highlight the importance of voltage-dependent type 7 K^+ (K_V7 or KCNQ) channels in regulating muscle tone and contractility in stomach and colon. K_V7 channels, that include 5 subtypes ($K_V7.1$–7.5), are activated at relatively negative potential values, close to those of the resting membrane potential for the smooth muscle cells of some segments of the gastrointestinal tract. Thus, they contribute to set the resting membrane potential and their blockade induces increase in smooth muscle contractility in stomach and colon. In addition, K_V7 channel activation produces profound relaxations of gastric and colonic smooth muscle. Therefore, K_V7 channel activators could be used to relax the smooth muscle and relieve symptoms in diseases such as functional dyspepsia and irritable bowel syndrome with prevalent diarrhea. The discovery of activators selective for the channel subtypes present in the smooth muscle, mainly $K_V7.4$ and 7.5, would allow avoiding adverse cardiac and nervous system effects. A further step forward would be characterizing putative differences among the K_V7 channel subtypes expressed in the various smooth muscles and synthesizing molecules specific for the gastrointestinal smooth muscle.

1. K^+ channels and excitable cells

K^+ channels represent the largest and most heterogeneous family of ion channels. They are the classical examples of channels in which the pore is delimited by more subunits (2 or 4) and are classified into voltage-dependent 6-transmembrane K^+ channels (K_V), Ca^{2+}-activated 6 or 7-transmembrane K^+ channels (K_{Ca}), inwardly rectifying 2-transmembrane K^+ channels (K_{ir}) and two-pore 4-transmembrane K^+ channels (K_{2P}) (Alexander et al., 2013). The number of transmembrane segments refers to each pore-delimiting subunit.

K^+ channels play important roles in excitable cells, as neurons and muscle cells, in which they are involved in several physiological processes, such as action potential firing, neurotransmitter release and smooth muscle contractility. When K^+ channels open, the cell membrane potential hyperpolarizes, as K^+ flows out of the cell due to the large transmembrane electrochemical gradient, and cell excitability decreases. In the smooth muscle, this results in reduction of contractility, that is mainly triggered by Ca^{2+} influx through voltage-gated Ca^{2+} ($Ca_V1.2$) channels following membrane potential depolarization in the different cell types constituting the so called "SIP syncytium" (smooth muscle cells [SMC], interstitial cells of Cajal [ICC] and fibroblast-like cells, that express platelet-derived growth factor receptor α [PDGFRα$^+$ cells]) (Currò, 2010; Sanders, 2008, Sanders et al., 2012). On the other hand, the inhibition of K^+ channels that are open at the resting membrane potential in the SIP syncytium determines membrane depolarization, with increase in $Ca_V1.2$ channel opening probability and consequent muscle contraction (Sanders, 2008). In addition, K^+ channels also contribute to set the resting membrane potential and by this way the different levels of basal muscle tone are observed in the various gut segments (Sanders, 2008).

2. K^+ channels and gastrointestinal tract

Many K^+ channels are expressed in the cells composing the SIP syncytial apparatus, the most important of which are the following: delayed rectifier ($K_V1.1$, $K_V1.2$, $K_V1.5$, $K_V1.6$, $K_V2.2$) channels, A-

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type (K_V4) channels, slowly delayed rectifier (KCNQ or K_V7) channels, HERG ($K_V11.1$) channels, BK ($K_{Ca}1.1$) channels, SK ($K_{Ca}2$) channels, IK ($K_{Ca}3.1$) channels, K_{ATP} ($K_{ir}6$) channels, other K_{ir} (2.1 and 3) channels, TREK ($K_{2P}2.1$) channels (Vogalis, 2000; Sanders, 2008; Koh et al., 2012). Most of these channels are expressed in smooth muscle cells (Table 1). Those functionally more important are $K_V1.2/1.5$, $K_V2.2$, $K_{Ca}1.1$, $K_{Ca}2.3$ and K_{ATP} channels (Sanders, 2008). In particular, the activation of $K_{Ca}2.3$ channels is mainly responsible for the inhibition of gastrointestinal muscle tone caused by the continuous basal release of inhibitory neurotransmitters (Sanders, 2008). K_V4 channels open at low voltage threshold and inactivate rapidly. They conduct A-type K^+ currents that limit the slow wave upstroke. Delayed rectifier K^+ channels activate at higher voltage thresholds than A-type channels and conduct rapid and slow currents (I_{Kr} and I_{Ks}, respectively). They are responsible for plasma membrane repolarization. $K_V1.2/1.5$, $K_V2.2$ and $K_V11.1$ (HERG) channels make most of I_{Kr}, whereas K_V7 (KCNQ) channels make most of I_{Ks}.

3. K_V7 channels

The K_V7 channel subfamily includes 5 channel subtypes ($K_V7.1$–7.5) belonging to the wide group of the "delayed rectifier" K^+ channels (Gutman et al., 2005). $K_V7.1$ channels play important functional roles in cardiomyocytes, where they mediate the late repolarizing I_{Ks} current of the action potential (Peroz et al., 2008). $K_V7.2$, 7.3 and 7.5 play particularly important functional roles in neurons, where their activation generates the "M current" (I_{KM}), a slowly activating and deactivating current inhibited by muscarinic receptors stimulation, that modulates cell excitability and firing pattern (Miceli et al., 2008; Brown and Passmore, 2009). $K_V7.4$ channels have been first described in the inner ear and auditory neurons (Kharkovets et al., 2000) and then in skeletal muscle cells (Iannotti et al., 2010) and in various smooth muscles (Greenwood and Ohya, 2009). These latter express different K_V7 channel subtypes, $K_V7.4$ and 7.5 being generally represented at the highest levels (Jepps et al., 2013).

The molecules most used in pharmacological or electrophysiological studies on K_V7 channels are the activators retigabine and flupirtine and the blockers XE-991, linopirdine and DMP-543. Retigabine is a drug selective for $K_V7.2$–7.5 channels clinically used as an antiepileptic drug (Amabile and Vasudevan, 2013). It has a pharmacological profile similar to that of valproate, but is active at lower doses and has fewer side effects. It is thought that flupirtine is a drug selective for $K_V7.2$–7.5 channels too. It is a molecule in clinical use as a centrally acting non-opioid analgesic in several European countries (Szelenyi, 2013). It also has muscle relaxant and anticonvulsant properties. Linopirdine is a compound that stimulates the release of acetylcholine from central neurons *in vitro*, and improves the performance of experimental tests of learning and memory in laboratory animals (Fontana et al., 1994). However, it has not been effective in clinical trials conducted in patients suffering from Alzheimer's disease (Rockwood et al., 1997). XE-991 and DMP-543 belong to the second generation of linopirdine analogs with an anthracenone structure, are 5–10 times more potent than linopirdine and more resistant to metabolism (Miceli et al., 2008).

K_V7 channels have been shown to regulate the contractility of vascular, gastrointestinal, respiratory and genitourinary smooth muscle, where they are abundantly expressed (Mackie and Byron, 2008; Greenwood and Ohya, 2009; Greenwood and Tribe, 2013; Jepps et al., 2013; Stott et al., 2013). Most studies evaluating the effects of K_V7 channel modulators on smooth muscle contractility were carried out in the blood vessels. Retigabine, flupirtine or S-1, another K_V7 channel activator, relax precontracted segments of various mouse (Yeung et al., 2007; Morecroft et al., 2009) and human (Ng et al., 2011) blood vessels and their effects are blocked by XE-991 (Yeung et al., 2007; Ng et al., 2011). XE-991 and linopirdine induce significant increases in spontaneous contractile activity in the mouse portal vein (Yeung and Greenwood, 2005) and vasoconstriction of different *in vitro* preparations of rat (Joshi et al., 2006, 2009; Mackie et al., 2008), mouse (Joshi et al., 2006; Yeung et al., 2007) and human blood vessels (Ng et al., 2011). As for other smooth muscles, retigabine, flupirtine and other K_V7 channel activators reduce spontaneous or induced contractile activity and muscle tone of rat (Rode et al., 2010), guinea-pig (Afeli et al., 2013; Anderson et al., 2013) and pig (Svalø et al., 2013) urinary bladder and their effects are reversed by XE-991 (Rode et al., 2010; Svalø et al., 2013). K_V7 channel blockers, on the contrary, increase muscle tone and spontaneous or stimulated motor activity of the urinary bladder (Rode et al., 2010; Afeli et al., 2013; Anderson et al., 2013; Svalø et al., 2013). XE-991 increases the spontaneous contractions of mouse and human myometrium, whereas retigabine and flupirtine induce opposite effects (McCallum et al., 2009, 2011). XE-991 and flupirtine contract or relax precontracted human lung slices, respectively (Brueggemann et al., 2012). Flupirtine also relaxes rings of rat and mouse trachea (Evseev et al., 2013).

4. K_V7 channels and the gastrointestinal tract

It has been known for long time that a K^+ current similar to I_{KM} can be activated by membrane depolarization in gastric smooth muscle cells (Sims et al., 1985). This first evidence obtained in the stomach of the toad was then replicated in guinea-pig proximal stomach (Lammel et al., 1991) and in rat gastric antrum (Ohya et al., 2002). The first study on the effects of K_V7 channel modulators on gastrointestinal motor activity was conducted by Jepps et al. (2009), who showed that K_V7 channel blockers (XE-991 and linopirdine) and activators (retigabine) induced excitatory and inhibitory effects on mouse colonic circular muscle spontaneous motor activity, respectively. Afterwards, data produced in our lab showed that K_V7 channels exert important control roles on the muscle tone of rat proximal stomach, since XE-991 and DMP-543 increase basal and precontracted muscle tone and retigabine and flupirtine importantly relax precontracted muscle strips (Ipavec et al., 2011). In addition, K_V7 channels partially mediate the proximal stomach relaxation induced by vasoactive intestinal peptide, one of the most important inhibitory neurotransmitters in the gastrointestinal tract (Ipavec et al., 2011). More recently, we have shown that K_V7 channel activators importantly relax human *taenia coli* preparations under resting conditions or during precontraction (Adduci et al., 2013). All these findings suggest that K_V7 activators might be considered as new possible drugs for the treatment of gastrointestinal motor disorders, in particular of functional dyspepsia and irritable bowel syndrome with prevalent diarrhea (Fig. 1).

Functional dyspepsia is a clinical syndrome frequently found in Western populations (prevalence estimated at 15–20%). It is commonly defined as the presence of symptoms that originate from the gastro-duodenal tract in the absence of any organic, systemic or metabolic diseases that can explain them (Oustamanolakis and Tack, 2012). The typical symptoms of this disease include, in very heterogeneous combinations and intensity, epigastric pain or burning, abdominal bloating, early satiety, postprandial fullness, belching, nausea and vomiting. The most recent classification, based on the Rome III criteria, distinguishes two main forms of functional dyspepsia, the epigastric pain syndrome (EPS), characterized by epigastric pain or burning, and the postprandial distress syndrome (PDS), characterized by early satiety and/or feeling of fullness after meals