Ion channels as targets for treatment of gastrointestinal motility disorders

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Ion channels are found in every cell type. Ion channels are membrane proteins that allow regulated transfer of ions across the membrane. As a result, they often produce electrical signals that regulate cellular function and transduce signals into electrical events. Ion channels can be broadly classified into voltage-gated ion channels, ligand-gated ion channels and mechanosensitive ion channels according to their primary gating modality. Most ion channel gating is regulated by more than one mechanism, and therefore there is considerable overlap between the three classes. Due to the highly regulated nature of the opening and closing of most ion channels and the number of small molecules that have been shown to both activate (open) and inhibit (close or inactivate) ion channels, ion channels are often considered as attractive targets for drugs.

There are over 400 ion channel genes representing over 1.5% of the human genome, yet less than 10 ion channels are currently the target of available drugs. This presents a potential opportunity. Classes of ion channels expressed in the gastrointestinal tract that are known targets for drugs include:

1. Ca²⁺ channels (e.g. nifedipine, diltiazem, otilonium bromide)
2. Na⁺ channels (e.g. lidocaine, ranolazine)
3. Potassium channels (e.g. glipizide, amiodarone)
4. Chloride channels (e.g. lubiprostone)

Advantages to targeting ion channels include:

1. They are convergence points for integrated cellular communication
2. They allow high throughput passage of ions and therefore modulation can have significant effects
3. There are several subtypes allowing targeting
4. Most channels have discrete ligand binding sites making them very sensitive to chemical modulation

However, the relative lack of current drugs targeting ion channels suggests that there are also disadvantages to targeting ion channels. This is indeed the case. Disadvantages include:

1. Most ion channels are expressed in more than one cell type decreasing the ability to target organs
2. Given their critical role in cellular homeostasis, modulation can have significant side effects
3. A specific disadvantage to ion channel targeting for motility disorders in that no ion channels are known to be only expressed in the key cell types involved in the control of gastrointestinal motility

One mechanism to select potential ion channels as gastrointestinal drug targets is to determine the electrophysiological effects of spontaneous mutations in ion channels that result in development of gastrointestinal side effects. Another is to examine the side-effect profile of known ion channel modulators. This talk will focus on both these methods, on an overview of the ion channels expressed in the gastrointestinal tract and on the benefits and potential risks involved in targeting them to treat motility disorders.

References


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