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Recent developments in ion channel pharmacology

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The human genome contains a total of 247 ion channel genes: 140 voltage-gated ion channels, 60 ligand-gated ion channels and 47 "other" channels such as chloride, aquaporin and connexion/pannexin channels (see the UPHAR/BPS Guide to Pharmacology at http://www.guidetopharmacology.org/). This makes ion channels the third largest group of signaling molecules after protein kinases and G-protein coupled receptors. While many of the classic voltage-gated Na_V, Ca_V and K_V channels open in response to changes in membrane voltage, ligand-gated ion channels are opened by the binding of a neurotransmitter to orthosteric sites. However, there is some blurring of the boundaries with K_{ATP} and TRP channels or ryanodine receptor channels, which are gated by second messengers and other intracellular and/or extracellular mediators and have been grouped either with voltage-gated or ligand-gated channels based on their structure and sequence.

Ion channels are crucial to all aspects of life by regulating neuronal and cardiac excitability, muscle contraction, hormone secretion, fluid movement, and immune cell activation. Ion channel modulation accordingly offers tremendous opportunities for drug development. However, with 7% of clinically used drugs targeting ligand-gated ion channels and only 5% targeting voltage-gated ion channels, ion channels are currently somewhat "underrepresented" in comparison to GPCRs as drug targets. This paucity of drugs targeting voltage-gated ion channels has often been blamed on a combination of several circumstances including (1) the technical difficulties associated with high-throughput ion channel screens, (2) the very high sequence homology between related channels, particularly between Na_V and Ca_V channels, making it extremely difficult to develop subtype specific small molecule modulators, and (3) the lack of crystal structures that could assist with structure based drug design and which for a long time has made ion channels very unpopular with medicinal chemists.

This thematic issue of "Channels" provides an update on ion channel drug development by experts in the field. In the first paper, Aaron Gerlach and Brett Antonio examine the validation of ion channel targets and discuss that the weighting of efficacy, safety, preferred mechanism of action and translatability can differ based on the role of the particular channel in normal physiology and disease. In the second paper, Alison Obergrussberger and colleagues review advances in ion channel screening techniques. In the next paper Palle Christophersen and Heike Wulff discuss pharmacological gating modulation of calcium-activated K^+ channels and highlight potential therapeutic uses for both positive and negative gating modulators of small-conductance $K_{Ca}2$ and intermediate conductance $K_{Ca}3.1$ channels. In the following paper, Sharan Bagal and colleagues briefly review Na_V channels as drug targets and then give an update on the recent advances from several major pharmaceutical companies in discovering and moving Na_V subtype-specific small molecules into clinical trials, primarily for pain indications. In the fifth paper, Sarah E. Skerratt and Christopher West carry on with the topic of pain and review advances in targeting various Na_V, TRP, TRV, Ca_V, P_2X_7 and ionotropic glutamate receptor channels for the treatment of pain. In the final paper, Birgit T. Priest and Jeff S. McDermott provide an overview of ion channels in the heart and then highlight recent developments for each of the major cardiac channels both as drug targets and from a safety perspective. It is our hope that these selected industrial expert updates will stimulate further exploration of the huge potential of ion channels as drug targets.

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