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Editorial

Advances in voltage-gated calcium channel structure, function and physiology

It is well established that calcium ions are important signalling molecules that mediate a wide range of physiological functions, including muscle contraction, enzyme activation, and secretion. Excitable cells contain numerous pathways by which intracellular calcium concentration can be elevated. Voltage-gated calcium channels are the primary mechanism of depolarization evoked calcium entry into heart, muscle and brain cells. The mammalian genome expresses multiple calcium channel subtypes that fulfill specific cellular functions. These calcium channels can either be monomers (as is the case with low voltage- activated T-type calcium channels), or multimeric protein complexes that are formed through the assembly of multiple calcium channels subunits (as for the high voltage-activated calcium channels). This special issue of BBA Biomembranes, focuses on some of the key roles of calcium channels, as well as aspects of calcium channel structure and modulation.

In the lead off article, Dr. Diane Lipscombe discusses the role of alternate splicing in calcium channel function. Most calcium channel subtypes are subject to regulation by alternate splicing mechanisms, and the resulting splice variants support specific cellular functions. Dr. Jiang Yang then describes the regulation of high voltage-activated calcium channels by the ancillary Cavβ subunit. This subunit associates with the pore forming Cavα1 subunit of the channel complex to not only regulate plasma membrane expression, but also channel function and modulation. Along these lines, Dr. Annette Dolphin discusses the role of the other major high voltage-activated calcium channel ancillary subunit – Cavα2δ – in membrane trafficking of the channel complex, and as a target for the gabapentinoid pain therapeutics. Dr. Jin Tao then focuses on low voltage activated T-type calcium channels and their modulation by second messengers. T-type calcium channels play major roles in network synchrony and epilepsy as discussed by Drs. Hee-Sup Shin and Snutch in two articles in this issue. In addition, there is growing evidence that T-type channels mal also control low threshold exocytosis, as described by Drs. Norbert Weiss and Zamponi.

Dr. Kurt Beam leads off a series of articles concerning the Cav1 (L-type) calcium channel family. Dr. Beam summarizes the unique functioning of the skeletal muscle Cav1.1L-type channel. Dr. Alexandra Koschak then discusses how naturally occurring mutation in the Cav1 family provides novel insights into calcium channel structure and function. Rounding out the L-type channel segment, Dr. Emilio Carbone focuses on the roles of Cav1.2 and Cav1.3 calcium channels in chromaffin cells. The issue then moves towards N-type (Cav2.2) calcium channels. Dr. Adams provides a detailed overview of modulation of N-type calcium channels by peptide toxins isolated from fish hunting cone snails, and their therapeutic potential for chronic pain. Drs. Kevin Currie and Zamponi then provide a detailed account concerning the modulation of N-type calcium channels by G proteins and G protein coupled receptors, a field of long history and an example of deep insights into molecular mechanisms of channel modulation. Dr. Henry Colecraft takes a broader view of high voltage activated calcium channel modulation by RGK proteins, a family of small G proteins that mediate a complex regulation of calcium channel activity. Finally, Dr. Daniela Pietrobon completes the issue by highlighting the role of Cav2.1 (P/Q-type) calcium channels in familial forms of migraine. In patients with this disorder naturally occurring mutations in the P/Q-type gene give rise to migraine phenotypes with varying degrees of severity.

Clearly, this collection of reviews is only a snapshot of the many exciting findings in the calcium channel field. However, it provides a topical overview of pertinent topics in this area by some of the world's leading calcium channel researchers.

Dr. Zamponi is one of the leading experts in the field of voltage gated calcium channels, with a specific interest in the role of calcium channels in the development of chronic pain. Dr. Zamponi has published close to 200 peer reviewed articles and holds numerous US patents on new pain therapeutics. He is an Alberta Innovates-Health Solutions Scientist and Canada Research Chair, and he is currently the Senior Associate dean for Research in the Faculty of Medicine at the University of Calgary.

Dr. Snutch is a Professor and Canada Research Chair in the Michael Smith Laboratories, Departments of Psychiatry and Zoology, and the Brain Research Centre at the University of British Columbia. He is best known for his seminal work on the family of voltage-gated calcium channels as it relates to their molecular cloning, modulation and pharmacology. Dr. Snutch has also designed and developed novel small organic calcium channel blockers aimed at the treatment of pain and epilepsy and which are currently in human clinical trials.

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