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Ion Channels under the Sun

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IN LATE JUNE 2013, scientists from all corners of the globe gathered in Nassau, Bahamas, for the Sixth Biennial FASEB Science Research Conference (SRC) on Ion Channel Regulation. Afternoons were spent enjoying snorkeling, diving, sailing, or relaxing amid palm trees swayed by the gentle trade winds; mornings and evenings were all business, as the latest research in the burgeoning field of ion channel regulation was debated.

Ion-conducting proteins are thought to account for 1% of human genes, are essential for the function of all living cells and for electrical activity in living organisms, and underlie such diverse processes as fluid homeostasis, volume regulation, muscular contraction, nervous signaling, gastric acidification, and endocrine function. Although ion channels have historically been underrepresented as therapeutic targets, ion channel dysregulation is a key feature in some of the most pervasive threats to 21st century public health, including diabetes and other metabolic disorders, and neurodegenerative diseases.

In an era in which the study of membrane proteins is arguably defined and dominated by atomic-level insights into structure and the molecular correlates of function, regulatory processes might, at first, seem a side-note not worthy of an entire conference. However, as the speakers and attendees at the FASEB SRC on Ion Channel Regulation demonstrated, nothing could be further from the truth. High-resolution, structural studies have afforded us an unprecedented understanding of how ion channels and transporters operate, answering some long-standing questions and fleshing out hypotheses and theories generated by earlier functional studies. Yet, in an era when our tools allow us to address the biomedical relevance and translational ramifications of basic research, as physiologists and channelologists, we are, more than ever before, seeking to discover how ion channels function in native systems and how they misbehave with consequences for human health.

As physiologists, we have historically always broken things to help understand how they work. This naturally yields information as to what happens in ion channelopathies (diseases involving disruption of ion channel function) and consequent therapeutic options. When Hodgkin and Huxley (1) analyzed sodium and potassium ion fluxes in the squid giant axon, eliminating the sodium influx by removing external bath sodium, as they pieced together the ionic ele-



FASEB SRC on Ion Channel Regulation, June 23–28, 2013, Nassau, Bahamas. Conference logo, depicting an ion channel selectivity filter in the form of twin coconut palms (designed by G. W. Abbott). Image Copyright Federation of American Societies for Experimental Biology.

ments of action potentials, they set the groundwork for manipulation of ionic currents to stem abnormal electrical activity to prevent or treat disorders, including epilepsy and chronic pain. Their work inspired use of pharmacologic agents to inhibit specific sodium or potassium channels to probe their contribution to the axonal action potential (2, 3), experiments that mirrored what is now known to occur unintentionally in drug-induced cardiac arrhythmias, in which drug-induced ion channel blockade predisposes to life-threatening ventricular arrhythmias (4). Similarly, any scien-

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tist who has generated and studied knockout mice has broken the system to understand it and has potentially modeled a human disease state.

As channelologists, we are now in the exciting position in which we can harness an enormous range of techniques, including transcriptomics, proteomics, single-molecule fluorescence, a cornucopia of transgenic manipulations, optogenetics, and high-throughput or high-resolution (low noise) patch-clamping, to study ion channels within the context of physiological systems and disease. In addition, protein chemists and molecular biologists (including some who started life as traditional physiologists) have advanced the study of membrane proteins to provide atomic-level views of channels in complexes with their regulatory partners, thus providing insight into disease-causing mutations and mechanisms underlying small-molecule regulation of channels, at high resolution. This has been achieved by scientists sharing both a passion for understanding ion channels and a drive for pushing the boundaries of what can be achieved with high-resolution structural biology techniques, ranging from the relatively static (*e.g.*, crystallography, in which mutagenesis or environmental manipulations can be used to study different channel gating states and conformations) to the dynamic (including electron paramagnetic resonance and other spectroscopic techniques).

Happily, the delegates of the 2013 FASEB SRC on Ion Channel Regulation brought all of these elements together, making for an eye-opening exhibition, not just of how much we understand about ion channel physiology but also, of how far the field of physiology has progressed and expanded and how much channelologists have embraced new techniques to overcome previous obstacles. In this context, a major and ongoing step forward in our understanding of channels and channelopathies has been the understanding that most channels are anchors for large macromolecular complexes. When associated regulatory proteins that modulate ion channel function are mutated in inherited disorders, they disrupt native ionic currents and underlie a range of pathologies that mimic the effect of mutations within the channels themselves. The conference, with its theme of ion channel regulation, naturally encompassed this topic, which is an increasingly studied aspect in the field of inherited channelopathies. The pathophysiological consequences of ion channel disruption, together with the aforementioned surge in discovery of inherited ion channelopathies and development of new technologies to study ion channels and their regulatory proteins, contribute to the current, rapid growth of our understanding of ion channel regulation and to the interest in a conference centered on this topic. Incorporating sessions covering a range of organ systems and diseases and describing approaches from the molecular level to whole-animal or computer-simulation, the conference attracted neurobiologists, cardiovascular researchers, systems biologists, biophysicists, structural biologists, pharmacologists, and physiologists.

Overview of the scientific sessions

In the first session—**Ion channels coregulating heart and brain**—the main emphasis was on the intersection between two devastating families of disorders: epilepsy and cardiac arrhythmias, in which ion channel dysfunction plays major roles. Naoto Hoshi (5, 6) and Daniel Neverisky (both at University of California, Irvine, CA, USA) and Mark Shapiro (The University of Texas Health Science Center at San Antonio, TX, USA) (7, 8) discussed their work on the regulation of the potassium channel, voltage-gated, KQT-like (KCNQ) sub-family of voltage-gated potassium (Kv) channels by proteins, including A-kinase anchor proteins (AKAPs), calmodulin, and potassium voltage-gated channel subfamily E, member 2 (KCNE2), and how this helps yield native currents, including the muscarinic-regulated M-current, essential for mammalian brain function and dysfunction, which underlies some forms of epilepsy. After a talk by Henrik Sindal Jensen (H. Lundbeck A/S, Copenhagen, Denmark) (9), covering novel sodium channel activators, Jeff Noebels (Baylor College of Medicine, Houston, TX, USA) (10) and Lori Isom (University of Michigan Medical School, Ann Arbor, MI, USA) (11) examined mechanistic links between seizures and cardiac arrhythmias that can culminate fatally in sudden unexplained death in epilepsy (SUDEP).

In the session **Ion channels and transporters in cancer**, Annarosa Arcangeli (University of Florence, Italy) (12) discussed her pioneering work on an increasingly recognized link between the human ether-à-go-go-related gene (hERG) Kv channel and cancer, and Saverio Gentile (Loyola University Medical Center, Chicago, IL, USA) (13) examined ways to exploit Kv channels to elicit senescence in cancer cells. Rajjini Rao (Johns Hopkins University, Baltimore, MD, USA) (14) and William Brackenbury (University of York, UK) (15) illuminated roles for the calcium release-activated calcium channel protein 1 (Orai1) and voltage-gated sodium channels, respectively, in breast cancer. Nancy Carrasco (Yale University, New Haven, CT, USA) (16, 17) described the sodium/iodide symporter (NIS) and how it can be exploited to deliver radioiodide therapeutically to kill tumors, and Heather Pinkett (Northwestern University, Evanston, IL, USA) (18) talked about her structural studies on ATP-binding cassette (ABC) importers and how this can shed light on mechanisms of resistance to chemotherapy.

The next session, titled **Crosstalk**, was dominated by a channel system that is the *sine qua non* of crosstalk: the store-operated calcium entry system, controlled by Orai/stromal interaction molecule 1 (Stim1), in which endoplasmic reticulum (ER) membrane-located Stim1 communicates to plasma membrane-located Orai channels to tell them that the ER calcium store has been depleted, and thus, Orai1 opens to let in calcium from outside of the cell. This topic was covered by established leaders in this field, Michael Cahalan (University of California, Irvine,

CA, USA) (19) and Richard Lewis (Stanford University, CA, USA) (20), and by newcomer Changfeng Zhang (University of the Pacific, Stockton, CA, USA). Peter Mohler (The Ohio State University, Columbus, OH, USA) (21) discussed his work uncovering the contribution of ion channel regulatory proteins to human diseases, with a focus on ankyrins and spectrins, and Mark Anderson (University of Iowa, Iowa City, IA, USA) (22) ended the session with a description of his tour de force on Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) signaling in mitochondria.

In an eclectic session encompassing **Contrasting modes of ion channel regulation**, Amy Lee (University of Iowa) (23) and Daniela Pietrobon (University of Padova, Italy) (24) described their work on the role of voltage-gated calcium channels in neuropsychiatric disease and cortical spreading depression, respectively. Erika Piedras-Renteria (Loyola University Medical Center) (25) talked about how Kelch-like 1 proteins regulate neuronal calcium channels, and Geoffrey Pitt (Duke University Medical Center, Durham, NC, USA) (26) described unexpected regulation of cardiac and neuronal calcium channels by fibroblast growth factor homologous factors. Federico Sesti (Rutgers, The State University of New Jersey, New Brunswick, NJ, USA) (27) described his recent work, showing that oxidation of Kv2.1 can contribute to aging-associated neurodegeneration by virtue of a defect in endocytosis, leading to accumulation of Kv2.1 oligomers in lipid rafts. Lea Sanford (Weill Cornell Medical College, New York, NY, USA) (28) discussed a novel screening methodology, in which plasma membrane deformation is exploited to screen compounds for ion channel activity.

As mentioned earlier, a giant leap in the ion channel world has been the advent of crystallographic analysis of channel proteins, leading to an atomic resolution picture of many of the main classes of ion channel proteins, starting with the structure of the *Streptomyces lividans* potassium channel (KcsA), reported in 1998 by Roderick Mackinnon (29). In the conference's keynote address, William Catterall (30) described the **Structure and function of voltage-gated sodium channels at atomic resolution**, drawing on his recent forays into crystallography and his life's work into ion channel pharmacology and physiology. Tasked with the unenviable job of following this, David Christini (Weill-Cornell Medical College) (31, 32) chaired the session on **Ion channels in cardiac arrhythmias** and presented his trail-blazing, multiscale modeling of atrial arrhythmias, and Al George Jr. (Vanderbilt University, Nashville, TN, USA; now Northwestern University) (33, 34) discussed mechanisms of sodium channel-linked extreme congenital arrhythmias—again, drawing from both his decades of work in this field and his recent insights into arrhythmia mutations in an unexpected channel regulator, the calcium-binding protein calmodulin, and the impact of splicing events on severity of channelopathies in the fetal heart. Rounding off the session, Torsten

Roepke (Charité-Universitätsmedizin Berlin, Germany) (35, 36) talked about mechanisms of cardiac arrhythmia linked to the KCNE family of Kv channel regulatory subunits, emphasizing his studies using *Kcne* gene-targeted mouse models.

In the **New and notable ion channel and transporter structures session**, a group of relatively young investigators, who have already contributed enormously to the membrane protein-structure field, discussed high-resolution insights into channel structure-function. Ning Zheng (University of Washington, Seattle, WA, USA) (37) discussed the structural basis for Ca²⁺ selectivity of a voltage-gated channel based on a prokaryotic sodium channel, but engineered to be Ca²⁺-selective. Christopher Johnson (Vanderbilt University) (34) described spectroscopic studies of the molecular basis for calmodulin-linked arrhythmias, and Seok Yong Lee (Duke University) (38) described structural and function studies of the ternary complex of the C-terminal domain from a human voltage-gated sodium channel, a fibroblast growth factor homologous factor, and calmodulin. Both of these topics were timely examples of the inroads being made into our understanding of ion channel regulation and disease using structural techniques. Session Chair Crina Nimigean (Weill-Cornell Medical College) (39) and Ming Zhou (Baylor College of Medicine) (40) taught us how crystallography can be used to dissect out the finer points of ion-channel gating and its regulation by membrane potential or regulatory proteins. Illustrating the importance of bringing together leading investigators from disparate fields, Simon Scheuring (Aix Marseille Université, Provence, France) (41) captured the imagination of the audience, as we reveled in his work examining the motion of membrane proteins, using high-speed atomic force microscopy, and each imagined our favorite ion channels starring in the stunning animations that he and his colleagues generated using unlabeled proteins.

In **Ion channels in metabolism and development**, Paul Rosenberg (Duke University) (42) revisited store-sensor Stim1 and discussed its role in long-term Ca²⁺ signaling and glucose and lipid metabolism, and Colin Nichols (Washington University) (43) updated us on the latest findings in his extensive body of work encompassing inward rectifier potassium channels, focusing on the K_{ATP} channels, which play a central role in pancreatic function and diabetes. Ita O'Kelly (University of Southampton, UK) (44) discussed how acid-sensitive, two-pore domain potassium (K2P) channels are retrieved from the plasma membrane, and Tracey Hermansteyne (Washington University) ruled out a role for A-type (fast-inactivating) Kv channels in contributing to the daily changes observed in neuronal excitability within the suprachiasmatic nucleus and linked to circadian rhythms. With the use of genetically altered zebrafish and mice, Kapil Ramachandran (Johns Hopkins University) (45) showed us work performed in the Geoffrey S. Pitt lab, demonstrating and explaining why

L-type calcium channels are essential for normal mandibular development. David Clapham (Harvard University) (46, 47) wowed conference attendees with his images of mice in which cilia were genetically encoded to fluoresce, and described how this modification enabled never-before-seen glimpses into ciliary ion channel physiology.

The penultimate session focused on a different aspect to ion channel regulation, *i.e.*, channel manipulation by **Small molecules**, both natural and man-made. Neil Harrison (Columbia University, New York, NY, USA) (48) revealed novel roles for glycine in controlling neuronal excitability in unexpected places and for GABA in directing motility of axonal growth cones. Min Li (Johns Hopkins University) (49) discussed his work in developing and understanding the mechanisms of allosteric modulation of KCNQ family potassium channels by small molecules. Margaret Lee (Zalicus, Cambridge, MA, USA) (50) described development of novel, small molecules that state-dependently target calcium channels to treat pain, and the role of metabotropic glutamate receptor 1 (mGluR1)/GluR δ 2 (GluRd2) complexes in cerebellar signaling was presented by David Brecht (Johnson & Johnson, San Diego, CA, USA) (51). Session Chair Colleen Clancy (University of California, Davis, CA, USA) (52) rounded off the morning with a demonstration of the power of computational modeling in predicting and understanding drug-channel interactions and their role in treating cardiac arrhythmias.

In the final session the life history of channels—from the cradle to the grave—was covered. Tom McDonald (Albert Einstein College of Medicine, Bronx, NY, USA) (53, 54) kicked off **The life and death of ion channels** with new insights into a novel regulatory mechanism in which noncoding data in the hERG channel messenger RNA sequence controls channel synthesis and trafficking efficiency, and Dierk Thomas (University of Heidelberg, Germany) (55, 56) discussed how alternative mRNA translation initiation regulates ion selectivity, intersubunit interactions, and drug sensitivity of K2P channels. Nicole Schmitt (University of Copenhagen, Denmark) (57) reported new mutations in the Tandem of p domains in a Weak Inward rectifying K⁺ channel (TWIK)-related acid-sensitive 1 K2P channel (TASK-1) that predispose to atrial fibrillation, a novel link between this channel and a disease highly prevalent in the aging population. Guiscard Seebohm (University of Münster, Germany) (58) described how coxsackievirus B3 infection can cause sudden cardiac death by, among other mechanisms, altering cardiac myocyte Kv and L-type calcium channel protein membrane density and cellular distribution. In the conference-closing talk, Steve Goldstein (Brandeis University, Waltham, MA, USA) (59, 60) covered his groundbreaking work on non-nuclear small ubiquitin-like modifier (SUMO) pathways, in which ion channels are regulated by direct, covalent modification in the form of SUMOylation.

Other conference highlights

The FASEB SRC on Ion Channel Regulation has developed a cult following over the years, as it brings together, in a concentrated and intense week, investigators with common but broad goals but disparate expertise and specific interests. In addition, it has provided a forum for workshops in which issues outside of the meeting's main scientific focus are discussed. In the 2013 conference, Drs. Colleen Clancy, Lori Isom, Margaret Lee, Colin Nichols, and Crina Nimigean chaired a panel-mentoring session, entitled **Challenges and opportunities for women in science**. Attended by a large number of female attendees, in particular junior investigators and trainees, the panel members gave their insights into the ups and downs of scientific careers. The emphasis was not just on the challenges posed by being a woman in science but also on the now-universal challenge of carving out a career path in a time of science-funding austerity. Attendees received perspectives both from academia and from industry and from those juggling other challenges, including families and administrative responsibilities. An often-posed conundrum, and one discussed at length in the panel session, is that although women are represented healthily at the predoctoral stage and are competitive with their male counterparts in terms of graduating with doctoral degrees, the further one looks up the ladder in academia or industry, the more male-dominated it becomes. From the feedback received, this session was adjudged a resounding success and proved to be inspiring for several of the trainees who attended.

At the conclusion of the conference, an awards ceremony followed the final talks, which were themselves preceded by an afternoon sailing and snorkeling trip, during which delegates, ranging from technicians and undergraduates to thought leaders in the ion channel world, rubbed shoulders and reflected on the constant ability of the natural world to astound and captivate us. A panel of judges from academia, scientific publishing, and industry voted for the best talks and posters given by trainees, who were presented with awards generously provided by the National Institutes of Health and *The Journal of General Physiology*. Ten trainees were awarded travel awards, with three in particular—Tracey Hermanstynne, Kapil Ramachandran, and overall winner Lea Sanford—receiving additional recognition. Of the 10, six were women; the awardees came from diverse backgrounds and ethnicities and studied in geographically diverse institutions.

Aside from the obvious dissemination of knowledge that conferences such as the FASEB SRC deliver, other goals were achieved. Trainees presented their data in the same sessions as their scientific heroes and received recognition for their hard work and achievements. In bustling poster sessions, students from countries all around the world mingled with one another, made new friends, and presented their findings to some of the most accomplished scientists in their discipline. And not insignificantly, amid the funding-related doom and

gloom that is putting off many talented junior scientists from pursuing what was once the career of their dreams, something else was achieved. Trainees were able to spend an evening or two in the *Daiquiri Shack* across the road from the conference hotel, discussing the day's scientific revelations over a freshly made piña colada with their peers, mentors, and mentors' mentors, realizing that there may be light at the end of the tunnel. FJ

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