

## EDITORIAL—A LATIN AMERICAN PERSPECTIVE ON ION CHANNELS

# A Latin American Perspective on Ion Channels

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### ABSTRACT

Ion channels, both ligand- and voltage-gated, play fundamental roles in many physiologic processes. Alteration in ion channel function underlies numerous pathologies, including hypertension, diabetes, chronic pain, epilepsy, certain cancers, and

neuromuscular diseases. In addition, an increasing number of inherited and de novo ion channel mutations have been shown to contribute to disease states. Ion channels are thus a major class of pharmacotherapeutic targets.

Enormous advances have been made since the early notion that the cell membrane lipid bilayer is a barrier to ion flux. These advances include the development of patch-clamp and other electrophysiologic techniques, the cloning of the genes coding for a myriad of different types of ion channels, and the crystallization of ion channels in different conformational states bound to various pharmacologic agents. Historically speaking, the development of drugs that target ion channels was based not on a deep understanding of the pharmacophore but rather on empirical results from the screening of drugs for effective actions in model systems. This gave way to high-throughput screening efforts using new technologies and large, diverse chemical libraries, thereby partially relieving the bottleneck in the discovery of drugs targeting ion channels. More recently, the emergence of high-resolution structures of ion channels has paved the way for structure-based design that relies on *in silico* approaches, including molecular modeling together with structure-functional analysis and virtual screening of drug databases.

Both at home and abroad, Latin American scientists have made many key contributions to the field of ion channels. Although the days of dictatorships in the region are gone, social, political, and economic turmoil are still a menace, and investment in Latin American science (both in manpower and infrastructure) lags behind that of other countries with a similar gross domestic product. In spite of this, Latin American scientists have developed many innovative ideas, driven by a strong Latin passion for life and nature and a desire for knowledge.

Dating back many decades, Latin America has a long tradition of excellence in biophysics. A large number of the key findings that underlie our understanding of electrical

signaling in the nervous system have important roots in Latin American laboratories. One such example is the University of Santiago in Chile, which ran a marine biology laboratory in Montemar. The Laboratory of Cell Physiology was established in 1962 in a former brothel on the coast. Funds were limited, and equipment was rudimentary; however, the jumbo Humboldt squid of the Pacific coast was a valuable local source of giant axons, similar to those used by Nobel Prize winners Alan Hodgkin and Andrew Huxley to make their discoveries on the generation of action potentials. It was in Montemar that Chileans Mario Luxoro and Eduardo Rojas provided the first evidence to support the idea that proteins embedded in the lipid bilayer, rather than the lipids themselves, are responsible for the transport of ions across the cell membrane (Rojas and Luxoro, 1963). Internationally recognized electrophysiologists, such as Francis Otto Schmidt (Massachusetts Institute of Technology) and Clay Armstrong (University of Pennsylvania, Philadelphia), visited Montemar during the Southern Hemisphere summers. Armstrong, Rojas, and Francisco Bezanilla went on to demonstrate that the sodium and potassium flux underlying the action potential occurs through different proteins (Armstrong et al., 1973). Bezanilla, a renowned Chilean physiologist (now at the University of Chicago), and Armstrong first measured the gating currents in sodium channels (Armstrong and Bezanilla, 1973). Ramón Latorre, who is contributing to this special issue (and is now at the University of Valparaiso, Chile), also began his career at Montemar.

Meanwhile, in 1955, in Argentina, recent graduate from the University of Buenos Aires, School of Medicine, Hersch "Coco" Gerschenfeld joined the Institute of Anatomy and Embryology to work with Eduardo de Robertis, one of the fathers of cellular biology, who had returned from exile in Montevideo, Uruguay. In 1959, Coco moved to the Centre d'Etudes de Physiologie Nerveuse in Paris to work with Ladislav Tauc. They were

pioneers in the use of the mollusk *Aplysia* and showed that acetylcholine can activate two types of receptors, an excitatory and an inhibitory one, with different pharmacologic properties (Tauc and Gerschenfeld, 1961). These were the foundations for Eric Kandel's and JacSue Kehoe's later work, which showed that a given presynaptic neuron can excite, inhibit, or have mixed effects on its postsynaptic targets, depending on the expression pattern of postsynaptic receptors. After training with Tauc, Coco returned to Buenos Aires to produce a series of landmark publications characterizing the ionic selectivity of the various channels opened by acetylcholine, providing the first description of excitatory serotonin receptors (Gerschenfeld, 1964; Gerschenfeld and Stefani, 1965; Chiarandini et al., 1967). Because of the political instability in Argentina, he left the country in 1966 and finally joined Phillippe Ascher at the Laboratoire de Neurobiologie at the Ecole Normale Supérieure in Paris, where he played a major role in the development of cellular neurobiology in France and collaborated very effectively with Colombian scientist Isabel Llano. During his time in Buenos Aires, Gerschenfeld worked with many talented students, including Dante Chiarandini and Enrico Stefani. Gerschenfeld and Stefani would have been the founders of a school of channel biophysics in Argentina, a project truncated for political reasons and exile, to be resumed by Osvaldo Uchitel (on his return from Ricardo Miledi's laboratory at University College London) in Buenos Aires and by Francisco Barrantes in Bahía Blanca in the 1980s.

In parallel to these events in Chile and Argentina, a new research center, The Center for Research and Advanced Studies of the National Polytechnic Institute, was established in México under the leadership of Arturo Rosenblueth in 1961. He was known for his work with Walter Cannon on the chemical mediation of homeostasis and with Norbert Wiener on the basis of cybernetics. CINVESTAV hosted influential researchers working on various aspects of ion channels. Around 1960, Ricardo Miledi, a former student of Arturo Rosenblueth, joined Bernard Katz at the Department of Biophysics, University College London. Miledi and Katz discovered the major role of  $\text{Ca}^{2+}$  in the release of acetylcholine at the neuromuscular junction (Katz and Miledi, 1965). Furthermore, they realized that stochastic fluctuations in membrane potential, so-called acetylcholine noise at the endplate, represented fluctuations in the number of individual ion channels that were open. By using spectral analysis, their work provided the first estimate of the conductance of a synaptic channel (Katz and Miledi, 1970). Today, several of Miledi's students have formed a strong group working on ligand-gated channels at the Institute of Neurobiology of the Autonomous University of México.

Prominent scientists in other countries have also contributed to the development of Latin American biophysics: Carlo Caputo, with his work on muscle excitation-contraction coupling, and Reinaldo Di Polo, with his contributions to calcium homeostasis at the Venezuelan Institute for Scientific Research in Caracas. In Uruguay, Eduardo Ríos and his trainees Gustavo Brum and Gonzalo Pizarro at the Department of Biophysics, University of the Republic, School of Medicine, are also contributing to muscle calcium homeostasis and excitation-contraction coupling. Although all his work was performed away from Colombia, his home country, Rodolfo

Llinás's classic work with the squid giant axon and calcium channels is a hallmark in biophysics.

Latin American scientists continue to provide many important advances in the field of ion channel structure, function, pharmacology, and pathophysiology. The present special issue broadcasts a series of minireviews provided by only a subset of the outstanding scientists working in Latin America. It includes the structure, function, and/or modulation of the transient receptor potential channel vanilloid 1 (Diaz-Franulic et al., 2016),  $\text{K}^+$  channels (Moreno-Galindo et al., 2016; Niemeyer et al., 2016) and ligand-gated ion channels (Burgos et al., 2016; Calvo and Beltrán González, 2016; Corradi and Bouzat, 2016). The participation of ion channels in pathophysiology-like cell volume regulation (Pasantes-Morales, 2016), pancreatic  $\beta$ -cell function (Velasco et al., 2016), autophagy (Filippi-Chiela et al., 2016), and cancer (Morrone et al., 2016; Fernandez et al., 2016) is also highlighted.

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