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Plugging the leaks– New drug discovery based on leak current channels

The resting membrane potential and thus the threshold for neuronal responsiveness to incoming signals are determined, in part, by various leak currents. Major types of channels that conduct these currents include the Na⁺ leak current channel (NALCN) and two pore-domain K⁺ channels (K2Ps). Presently, little is known about the neuropharmacology of these important channels. There are no known inhibitors or modulators of the NALCN and only a few examples of agents that affect K2Ps. Genetic defects in these channels in man are associated with dystonias, developmental delay and schizophrenia, in the case of the NALCN, and cardiac abnormalities and migraine, in the case of K2Ps. In addition, there are striking movement deficits in model organisms, such as *Caenorhabditis elegans*, bearing mutations in the nematode orthologues of these genes. Our group is using mutant strains of *C. elegans* with gain-of-function mutations in NALCN and K2Ps to identify pharmacologic agents that modulate the function of these proteins. Furthermore, these studies are providing novel insights into the connections between the leak current channels and other channels that regulate neuronal excitability. We have already identified a number of drugs that directly or indirectly correct the movement deficits caused by the gain-of-function mutations. This line of research may have therapeutic implications for Parkinson's disease, dystonias and even schizophrenia.

Biography

Donard S Dwyer received his PhD from the University of Alabama at Birmingham. After receiving a Post-doctoral fellowship, he worked as a Staff Scientist at the Max-Planck-Society Laboratories in Würzburg, Germany. He then joined the faculty at the University of Alabama at Birmingham for six years before becoming department head at a start-up biotechnology company in Cambridge, MA. For the past 20 years, he has been a member of the faculty in the Departments of Psychiatry and Pharmacology, Toxicology and Neuroscience at LSU Health Sciences Center in Shreveport, LA. He is currently Professor and Vice-Chair for Research in Psychiatry. His research focuses on understanding and treating neuropsychiatric illnesses, including schizophrenia, and movement disorders.

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