Hereditary ion channelopathies: from gene to disease to precision medicine

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Ion channels are transmembrane proteins dedicated to the passive flux of selected ions across membranes. More than 400 human genes encoded ion channel subunits, which are involved in many physiological processes, including neurotransmission, contraction, exocrine and endocrine secretion, immune response, and cell proliferation and differentiation. It is thus not surprising that mutations in these genes are responsible for hereditary human diseases, the so-called ion channelopathies, which can be debilitating or life-threatening (Conte Camerino et al., 2007; 2008). The discovery of channelopathies, some three decades ago, coincides with the achievement of electrophysiological and molecular biology techniques and their combination. The possibility to study the dysfunction of a mutated channel in an heterologous system of expression and to correlate it with the clinical phenotype have tremendously increased our knowledge about the structure/function relationship of ion channels and their role in physiology and pathology. Importantly the ion channelopathies can also serve as paradigms to understand the more complex and frequent multifactorial diseases. Altogether these progresses have underscored the therapeutic potential of ion channel modulators. Drugs acting on ion channels were already in use before the channelopathies were known, but most of these drugs were used empirically and were found to act on ion channels afterward. Now our knowledge about their role in diseases have validated ion channels as very promising druggable targets (Desaphy and Conte Camerino, 2010).

Mutations in ion channel genes can cause either a gain or a loss of channel function by altering gating or ion permeation; others can change expression levels of channel proteins by altering transcription, intracellular trafficking, or degradation. Recently, some mutations were also shown to create an aberrant gating pore conducting the so-called omega currents, parallel to the normal ion permeant pathway. The therapy of channelopathies is usually based on the empiric use, most often off-label, of symptomatic drugs. Ion channelopathies are very rare diseases, which challenge the completion of randomized clinical trials to demonstrate the efficacy of drugs. Nevertheless, some RCT were recently performed, which eventually allowed marketing authorisation (e.g. ivacaftor for the treatment of cystic fibrosis due to mutations in the CFTR chloride channel gene) or orphan drug designation (e.g. mexiletine for the treatment of nondystrophic myotonias due to mutations in chloride or sodium channel genes). Importantly, the drugs may be designed to correct specifically the defect of ion channel mutant. For instance, ivacaftor works as a gating modifier and is expected to work only in a subset of CFTR mutations, which account for 4-5 % of cystic fibrosis cases (Ramsey et al., 2011). We also demonstrated that some sodium channel mutations may impair mexiletine antimyotonic activity, while showing a better response to flecainide both in vitro and in patients (Desaphy et al., 2001; 2004; 2013). The later consideration highlights the critical need to achieve precision medicine through a deep disease genotyping and phenotyping and the search for drugs acting selectively on ion channel mutants displaying similar behaviour.

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