Bench to patient side development of precision medicine in skeletal muscle ion channelopathies

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Skeletal muscle ion channelopathies encompass a number of rare diseases characterized by episodic muscle stiffness and/or muscle weakness (Imbrici et al., 2016). Severity of symptoms ranges from mild disturbance of movements to life-threatening conditions. Flaccid paralysis is due to loss of muscle fiber excitability resulting from mutations in sodium (SCN4A gene), calcium (CACN1A4), and potassium (KCNJ2) channels. Muscle stiffness is due to muscle fiber over-excitability resulting from mutations in sodium, calcium, and chloride (CLCN1) channels. When needed, available pharmacotherapy is symptomatic. In flaccid paralysis, drugs are used to maintain K+ homeostasis and repolarize muscle fiber plasma membrane. In myotonia (stiffness), sodium channel blockers are used to reduce action potential firing in muscle fibers. Among the latter, the class I antiarrhythmic mexiletine has recently received orphan drug designation for myotonic syndromes. A retrospective study showed that mexiletine is usually well tolerated, with dyspepsia, headache, and cardiac palpitations as common adverse events. Yet a number of patients (about 25 %) are intolerant or report unsatisfactory response to mexiletine. In addition, mexiletine is contraindicated in cardiomyopathic conditions. Alternative drugs to mexiletine are absolutely needed. We thus developed a rat model of pharmacologically-induced myotonia to test repurposing drugs and new derivatives of known sodium channel blockers. We identified new promising antimyotonic drugs, including riluzole and a potent, use-dependent tocainide derivative (Desaphy et al., 2014; De Bellis et al., 2017). We also wondered whether SCN4A mutations causing myotonia may modify hNav1.4 channel sensitivity to mexiletine. We found that the mutation G1306E is indeed less sensitive to mexiletine but conserves sensitivity to flecainide, another antiarrhythmic sodium channel blocker (Desaphy et al., 2001; 2004). Based on this result, at least five myotonic patients carrying G1306E, who were unsatisfied with mexiletine, obtained great improvement by shifting to flecainide (Desaphy et al., 2013). A similar approach allowed a successful mexiletine-to-flecainide shift in a young girl carrying another mutation, P1158L, that evokes molecular biophysical defects in hNav1.4 channel similar to G1306E (Desaphy et al., 2016). The pharmacological characterization of SCN4A mutations found in the myotonic patients cohort identified by the Italian Network of Skeletal Muscle Channelopathies is undergoing, with the aim to identify the best drug for each mutation. Nondystrophic myotonias are also caused by mutations in CLCN1 encoding ClC-1 chloride channels (Imbrici et al., 2015). Loss of function of ClC-1 channels stems from alteration of gating or impairment of intracellular trafficking toward the plasma membrane. To date, no ClC-1 channel activator is available. We currently use potent and reversible inhibitors of ClC-1 channels as pharmacological tools to define the drug binding sites and better understand effects of drugs on channel gating. In parallel, we use these drugs in proof-of-concept studies to verify the ability of pharmacological chaperones to restore sarcolemma expression of trafficking-deficient ClC-1 mutants. Altogether, these studies define a pharmacogenetics strategy to address precision medicine in myotonic individuals carrying sodium or chloride channels mutations, stratified as a function of the molecular defect (supported by

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