Periodic paralysis as a paradigm for channelopathies of neuromuscular apparatus: from drug discovery to clinical use

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The periodic paralysis (PP) are rare autosomal-dominant disorders associated to mutations in the skeletal muscle ion channel genes characterized by fiber depolarization with un-excitability, episodes of weakness with variations in serum potassium concentrations. The PP are classified as hyperkalemic PP(hyperPP), hypokalemic PP(hypoPP), Andersen's syndrome(AS) and thyrotoxic PP(TPP).

In AS, the patients have loss-of-function mutations in the KCNJ2 gene which encodes the inward rectifier potassium channel, Kir2.1. These mutations suppress the muscle and cardiac outward K^+ currents and/or enhanced the inward currents leading to prolonged cardiac Q-T interval, arrhythmia and PP. The mutants Kir2.1 is expressed in myoblast and osteoclasts and contributes to the facial and skeletal malformations.

In TPP, the muscle PP has been linked to mutations of KCNJ18 gene encoding for the Kir2.6. TPP mutants show decreased current density during thyrotoxicosis or lack the modulation by second messengers. Abnormal K^+ channel genes transcription during thyrotoxicosis cause drastic changes in resting potential and weakness.

In hyperPP, the pathomechanism is explained by the gain-of-function mutations in the α-subunit of the muscle voltage-gated Na^+ channel, Nav1.4. The mutant channels show failure of the inactivation process which results in continual Na^+ influx and depolarization which leads to inactivation of Na^+ channels, activation of the voltage-dependent K^+ channels that elevate the serum K^+ ions levels and paralysis.

HypoPP has been associated with mutations in both the α1-subunit of the muscle Cav1.1 and Nav1.4 channels. The mutants carry a depolarizing gating pore currents (*I*gp). Abnormal activation of the *I*gp or deficiency in the Kir/KATP channels predispose to fiber depolarization and paralysis.

Drug therapies of PP can be separated into two categories, treatments used for acute attacks and prophylactic treatments. In hyperPP, acute attacks may respond to salbutamol or glucose/insulin therapy that exert their repolarizing actions by activating the $3Na^+/2K^+$-ATPase and restoring the serum K^+ levels. In hypoPP, acute attacks are treated with oral KCl glucose-free. The treatment of the hyperkalemia and hypokalemia is achieved with the administration of the benzothiazide and K^+ sparing diuretics, respectively. But the most effective medications for the prevention of attacks of paralysis remain the use of the carbonic anhydrase inhibitors (CAI) such as acetazolamide (ACTZ) and dichlorphenamide (DCP). These drugs repolarize the fibers and prevent the paralysis and weakness in animal models and in human hypoPP patients induced by insulin/ glucose injection by activating the calcium-activated K^+ (BK) channels. ACTZ prevents vacuolar myopathy in the muscle of K-depleted rats which implies that it may averts the progressive myopathy seen in hypoPP as well as the inter-attack of weakness in humans. However, none of the patients with glycine substitutions had benefit by ACTZ treatment. The treatment of AS is complicated by the necessity of treating skeletal and cardiac muscle symptoms. For the muscle weakness, therapy involves the use of CAI drugs while the treatment of the cardiac symptoms of AS is based on the use of β-blockers, calcium and sodium channel blockers. Treatment of TPP is based on the surgical and iodine 131 treatments, while adrenergic symptoms are cured by beta blockers. No specific treatments for the weakness are available in TPP.

In conclusion, it remains safe and effective in the treatment of PP the proposal of targeting the K^+channels by drugs capable to modulate at nanomolar concentrations the skeletal muscle subtypes with less side effects. No *I*gp blockers are available for clinical use and the drug discovery failed to identify high affinity ligands for these mutant subunits. Supported by Telethon grants, GGP10101.