New territory opened by periodic paralysis associated with mitochondrial DNA mutation

Science is an exploration of knowledge. Early world maps did not recognize large land masses until someone first observed them. The report by Auré et al. describes new territory in the field of periodic paralysis and other disorders of skeletal muscle membrane excitability. The muscle membrane has to balance on a knife edge between excessive excitability manifest by conditions such as myotonia, and inexcitability, as occurs intermittently in periodic paralysis. Understanding disorders of altered muscle membrane excitability is important because the knowledge gained leads to increased understanding of how excitable membranes function and may suggest ways of treating membrane disorders that can involve many tissues, including brain, peripheral nerve, and skeletal and cardiac muscle.

Pathophysiologic investigations have focused on the roles of specific ion channels in maintaining normal skeletal muscle membrane excitability. Chloride channels enhance membrane stability, and the first identified channelopathies producing myotonia were loss-of-function chloride channel mutations. Gain-of-function sodium channel mutations disturbing the normal balance of channel opening (activation), closing, and inactivation can also produce myotonia. Paralytic episodes in periodic paralysis are associated with membrane depolarization that activates sodium channels leading to membrane inexcitability. The channels associated with periodic paralysis include $CAGN1 S$ (calcium), $SC N A 4 A$ (sodium), and $K C N J 2$ (inward rectifier potassium channel). That similar phenotypes can result from mutations of genes encoding different ion channels emphasizes the important interplay among ion channels involved with membrane excitability. Mutations of sodium and calcium channels associated with hypokalemic periodic paralysis share a common mechanistic pathway because the mutations permit an alternative current pathway through the mutant channels that can depolarize the membrane.

The new pathophysiologic territory defined by Auré et al. was that membrane excitability could be indirectly altered. In the previously discussed disorders of skeletal membrane excitability, including periodic paralysis, the pathophysiology could be explained by direct alterations of the operations of mutated ion channels. Episodes of periodic paralysis resulted from membrane depolarization that was a direct consequence of altered channel function. Auré et al. did not find any of the previously recognized channelopathy mutations associated with periodic paralysis. Instead, they found consistent mutations of mitochondrial DNA. They identified the $M T - A T P 6$ m.9185T>C p.Leu220Pro mutation that was previously associated with Leigh syndrome. In addition, they also discovered the $M T - T L 1$ m.3271T>C mutation that caused MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes) syndrome in the one subject who had MELAS. They studied the effect of these mitochondrial DNA mutations in cultured fibroblasts and observed defects of complexes V and I as well as oxidative stress. The precise pathophysiologic connection between the altered intracellular metabolism and periodic paralysis phenotype is not clear; in patient-derived fibroblasts, however, the mitochondrial mutations resulted in altered potassium ion permeability associated with plasma membrane depolarization.

The possibility of indirect effects on channel function was suggested by prior studies of hypokalemic periodic paralysis. Type 1 hypokalemic periodic paralysis, which is associated with mutations involving $C A G N 1 S$, and a related disorder, thyrotoxic periodic paralysis, are associated with reduction in the outward current component of a specific potassium channel and reduced voltage-gated sodium channel current. Reductions in these currents may be epiphenomena, although an expected consequence of reduced voltage-gated sodium current, reduced membrane excitability, is observed in type 1 hypokalemic periodic paralysis.

A causative role for these anomalous currents in the susceptibility to periodic paralysis is supported by the observation of analogous functional changes in conventional channelopathies of skeletal muscle.
In type 2 hypokalemic periodic paralysis, the sodium channel mutations increase resting-state inactivation, which would be expected to reduce the baseline sodium channel current.\textsuperscript{2–4} There is also evidence that reduced inward rectifier potassium current contributes to the hypokalemic periodic paralysis phenotype. Inward rectifier potassium channel mutations occur in both thyrotoxic periodic paralysis\textsuperscript{8} and Andersen-Tawil syndrome,\textsuperscript{9} which includes a periodic paralysis phenotype. In an animal model of hypokalemic periodic paralysis, partial block of inward rectifier potassium channels leads to hypokalemia-induced depolarization.\textsuperscript{10} Altered action of insulin on the inward rectifier potassium channel contributes to insulin-induced paralysis in type 1 hypokalemic periodic paralysis.\textsuperscript{11} Additionally, increasing inward rectifier potassium channel current may be the mechanism of action of acetazolamide-induced improvement of symptoms in hypokalemic periodic paralysis.\textsuperscript{12} All of these changes would be exacerbated by the inward current conducted by an alternative pathway in both type 1 (calcium) and type 2 (sodium) hypokalemic periodic paralysis.\textsuperscript{5}

In contrast to the possibility that altered function of inward rectifier potassium channels and reduced voltage-gated sodium channel current contribute to the membrane depolarization in type 1 hypokalemic periodic paralysis, the work of Auré et al.\textsuperscript{1} leaves little doubt that altered mitochondrial function contributed to the periodic paralysis phenotype in their subjects. The challenge for future explorers is to determine how oxidative stress alters membrane function.

**AUTHOR CONTRIBUTIONS**

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Stephen Cannon: drafting/revising the manuscript.

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**REFERENCES**