A review of two equine channelopathies: hyperkalemic periodic paralysis and malignant hyperthermia

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Introduction and objectives

Beyond the positive traits, a side-effect of human-driven selective breeding is the inadvertently concentration of heritable muscle diseases among others, for which mutations impact on electrical conduction, muscle contraction, and energy metabolism. Two of these genetic diseases, hyperkalemic periodic paralysis and malignant hyperthermia, are reviewed in this project, which emphasizes the understanding of the molecular bases and pathophysiology, as well as aims to present the current state of knowledge of the prevalence, clinical signs, diagnosis and treatment for each disease.

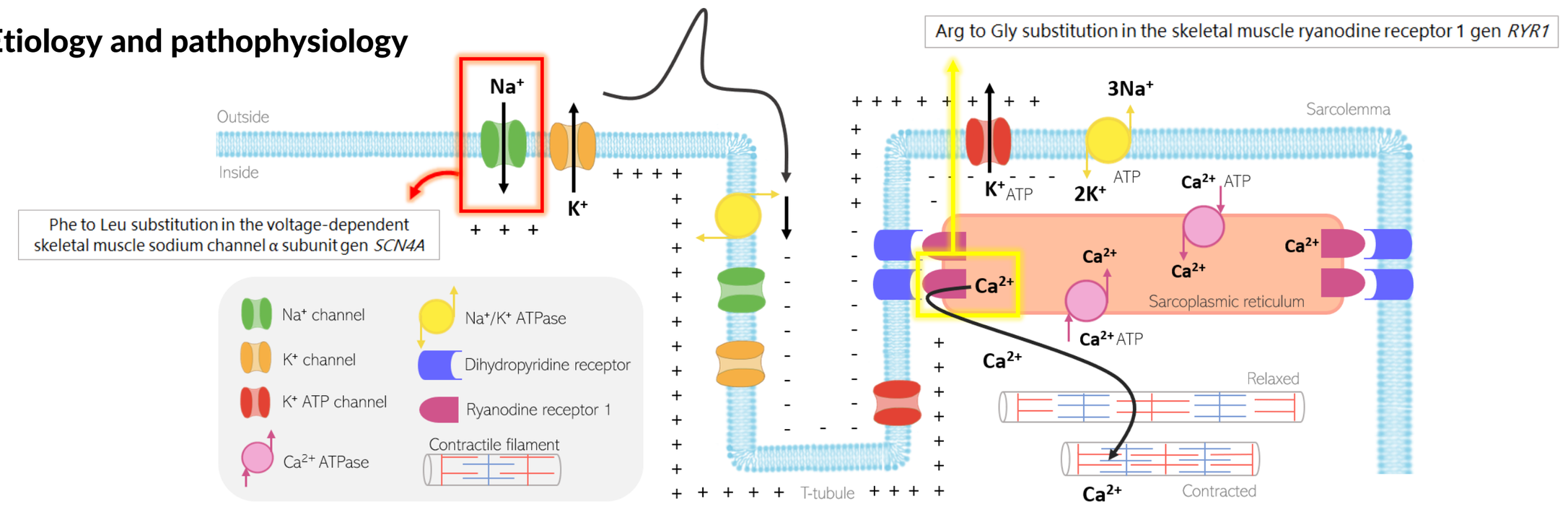
Hyperkalemic periodic paralysis

Hyperkalemic periodic paralysis (HYPP) is a muscle disorder that affects approximately 1.5% of the Quarter Horse and 4.5% of the Paint Horse breeds descendants of the popular Quarter Horse stallion Impressive. Clinical signs consist in episodes of myotonia and muscle fasciculations that can evolve to severe weakness, recumbency and occasional death, usually coincident with elevated serum potassium concentrations.

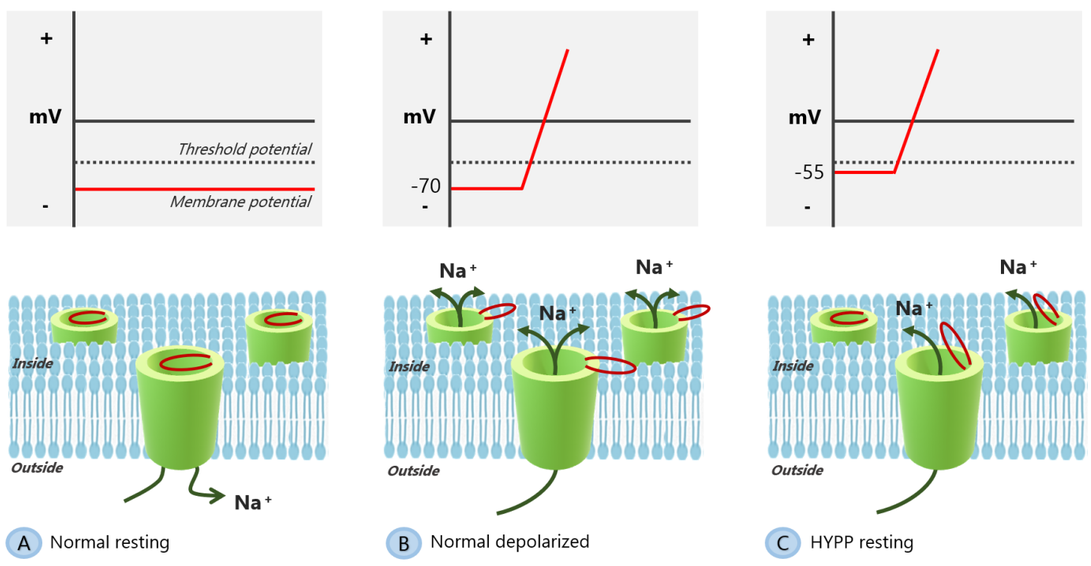
Malignant hyperthermia

Malignant hyperthermia (MH) is a pharmacogenetic fatal disorder arised by the disproportionate elevation of muscle activity induced by exposure to inhalation anesthetics, succinylcholine or in some cases stress or excitement. Under anesthesia, the clinical and laboratory findings are hyperthermia, tachycardia, tachypnea, acidosis, muscle rigidity, rhabdomyolysis and electrolyte derangements. Prevalence is estimated at 1.3% and mortalilty rate at 34%.

Etiology and pathophysiology

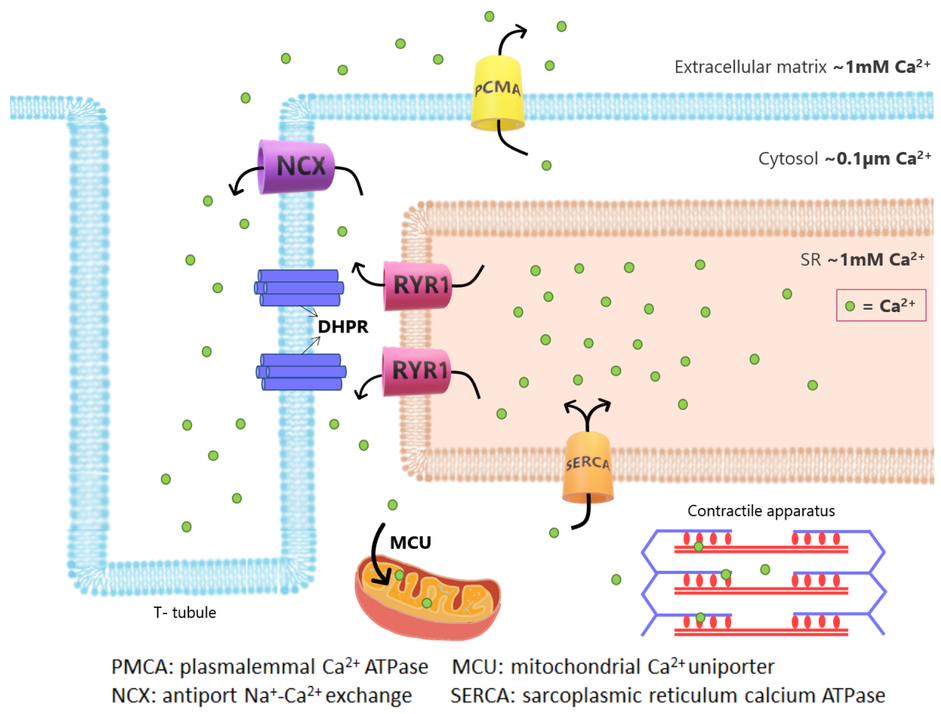


The **HYPP** mutation occurs in a highly conserved region of the α subunit of the skeletal muscle voltage-dependent sodium channel. The defective channel presents a destabilisation of its inactivated state, resulting in decreased rates of entry into and increased rates of exit from the inactivated state. Thus, an excessive inward flux of sodium followed by an outward flux of potassium (hyperkalemia) result in the fiber's resting potential being close to the threshold potential and hence more readily to elicit action potentials.



At the beginning of an attack, the inward current causes mild depolarization leading to myotonia and muscle fasciculations. As the attack progresses more and more muscle fibers become paralyzed as the more profound depolarization of the muscle membrane causes inactivation of both mutant and wildtype channels, thus rendering the muscle fiber inexcitable.

In **MH**, the probabilities of RYR1 channel for the open state is increased and for the close state is reduced. Halothane act directly to overcome the inhibition in sensitized channels, resulting in an efflux of calcium from the sarcoplasmic reticulum (SR) into cytosol and consequent activation of the contractile machinery. Soon, the normal mechanisms of cytosolic calcium extrusion become overwhelmed:



PMCA: plasmalemmal Ca^{2+} ATPase
NCX: antiport Na^{+}-Ca^{2+} exchange
MCU: mitochondrial Ca^{2+} uniporter
SERCA: sarcoplasmic reticulum calcium ATPase

These processes consume large amounts of ATP, the main cellular energy carrier, and generates excessive heat (hyperthermia). The muscle cell is damaged by the depletion of ATP and cellular constituents leak into the circulation, including potassium, myoglobin, creatine, phosphate and creatine kinase.

Diagnosis

Family history, clinical signs, laboratory evaluation and electromyography have been used in the diagnose of HYPP, however, definitive diagnosis can only be achieved by the DNA test, which determines an animal as heterozygous or homozygous.

Therapy

Tretament is principally focused on the reduction of hyperkalemia. An oncoming episode of HYPP can sometimes be aborted with mild exercise or feeding grain. In severe cases, administration of calcium gluconate (0.2– 0.4 ml/kg of a 23% solution diluted in 2 L of 5% dextrose) will provide immediate improvement. Prevention of HYPP attacks is based on regular exercise and dietary manage (<1.1% potassium concentration) or administration of acetazolamide (2–4mg/kg q 12–14 h p.o.).

Diagnosis

Early recognition of a MH reaction with immediate discontinuation of inhalated anesthesia is decisive. While under anesthesia, the diagnose is based on classic clinical signs. There is a rapid DNA test available to determine whether the individual carries the mutation that confer susceptibility to MH.

Therapy

If a horse is suspected with MH susceptibility, pretreatment with oral dantrolene (4mg/kg) 30 to 60 min prior to anesthesia is recommended. Dantrolene inhibits the calcium efflux from RYR1 receptors. However, caution must be taken, specially in horses with hyperkalemic periodic paralysis, as dantrolene administration induces hyperkalemia and adverse cardiovascular effects.

Conclusions

Progress in understanding the genetic and molecular bases of equine muscle diseases such as hyperkalemic periodic paralysis and malignant hyperthermia, has enabled its fair characterization and the development of DNA-based diagnostic tests to reduce or eliminate these genes from the populations. Currently, there are many inherited disorders for which a genetic mutation is not yet known, so the research in this field still must grow to stop unknowing transmission of diseases to future generations and allow the development of more targeted evidence-based treatments.