MOLECULAR BASIS OF SKELETAL MUSCLE DISORDERS IN HORSES

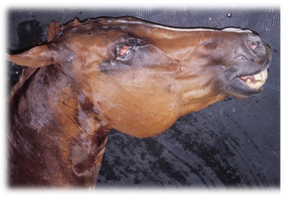
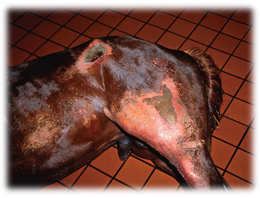
Malignant hyperthermia and Hyperkalemic periodic paralysis

Alba Castellà Planes, June 2017

Universitat Autònoma de Barcelona

1. Objectives

- To know at which point is the study of two of the main hereditary equine muscle pathologies: malignant hyperthermia (MH) and hyperkalemic periodic paralysis (HYPP).
- To collect bibliography related to these disorders and their triggering agents.
- To try to establish a link between the different characteristics of each of them.

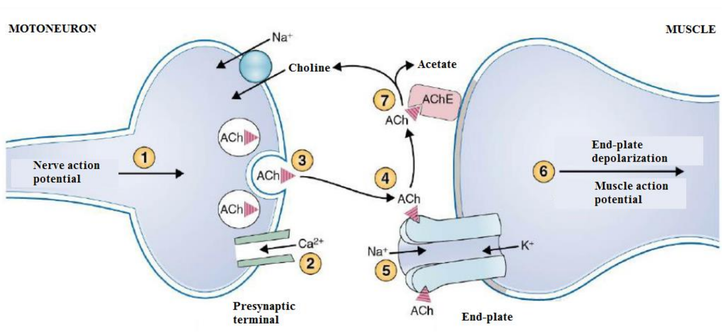




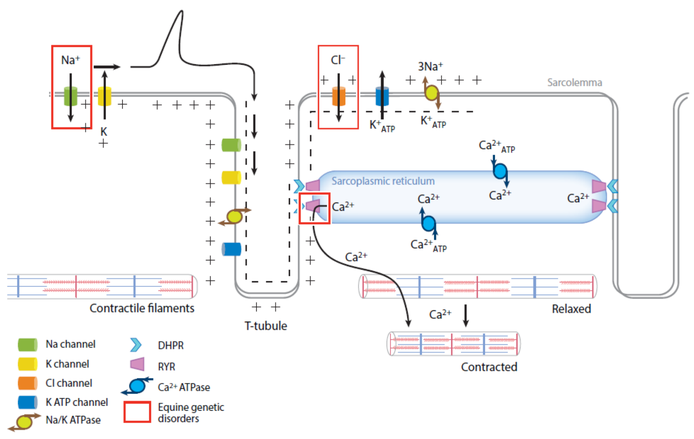
2. Introduction

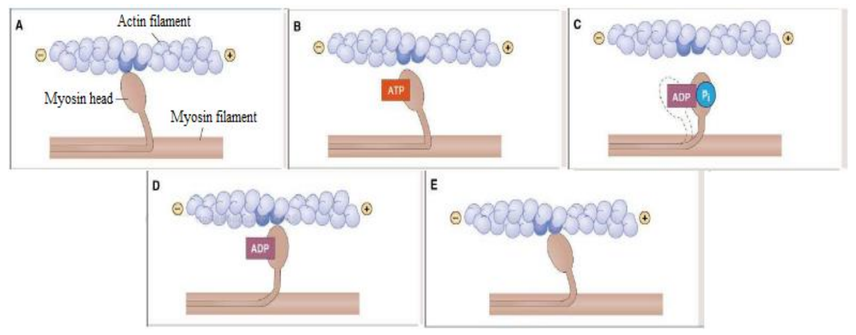
MH is a syndrome in which a high body temperature and muscular rigidity are the most characteristic clinical signs. In most cases it is caused by an autosomal dominant mutation in the exon 46 that codifies for de type 1 ryanodine receptor (RyR1) of the sarcoplasmic reticulum. This modification causes an uncontrolled release of calcium into the sarcoplasm and persistent muscle contraction, and it is often triggered by inhalant anesthesia, depolarizing muscle relaxants and, in some cases, stress.

HYPP is a disorder that is mostly seen in Quarter Horses, Paints, Appaloosas and crossbreeds. It is caused by a codominant autosomal mutation in the SCN4A gene, that codifies for the α-subunit of the voltage-gated sodium channel ($Na_v1.4$) of the skeletal muscle. This mutation leads to a failure to the channel inactivation mechanism.

3. Excitation-contraction coupling







4. Malignant hyperthermia

4.1. Clinical signs

The most characteristic feature, as the pathology name denotes, is the elevation of the body temperature. Other common clinical signs are muscle rigidity, rhabdomyolysis, fasciculations, ocular globe retraction, protrusion of the third eyelid, sweating, tachycardia and tachypnea. Analytical changes include lactic acidosis, elevation of the CK activity, hyperkalemia, high levels of P_i and myoglobinuria.

4.2. RyR1

The RyR1 is a calcium release channel localized in the terminal cisternae membrane of the sarcoplasmic reticulum and its function is essential for the muscular contraction.

It is regulated by numerous molecules, such as ATP, caffeine, calcium (Fig. 1), magnesium and potassium. From all of these, calcium plays a basic regulatory role and increases the channel activity when its sarcoplasmic concentration is between 10 to 100 μM.

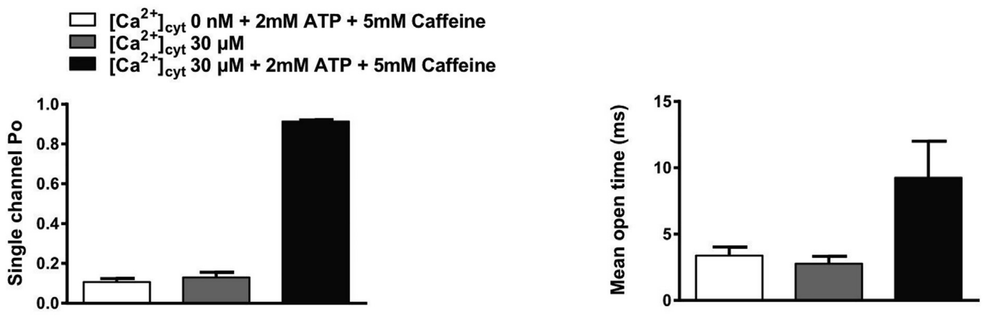


Fig 1. SR calcium release triggered with KCl, caffeine and 4-C*m*C in wild type RyR1 channels (des Georges et al. 2016).

4.3. RyR1 HM

The HM mutation causes a R2454G (arginine for glycine) substitution in the exon 46 from the chromosome 10. In some cases, this change induces an exacerbated calcium release from the SR when the animal is exposed to halothane, succinylcholine or stress.

To date, several abnormalities of this channel have been described: a higher sensitivity to caffeine, potassium and 4-chloro-*m*-chresol (4-C*m*C) (Fig. 2) and a minor inhibition capacity from magnesium and calcium at basal concentrations (Fig. 3).

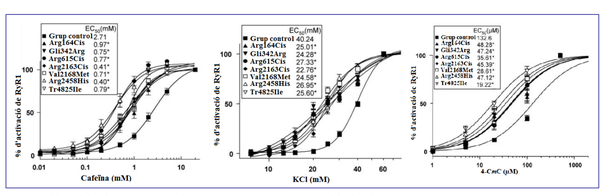


Fig 2. Calcium release from de SR triggered by increasing concentrations of caffeine, KCl and 4-C*m*C in RyR1 channels with and without de MH mutation (Yang et al. 2003).

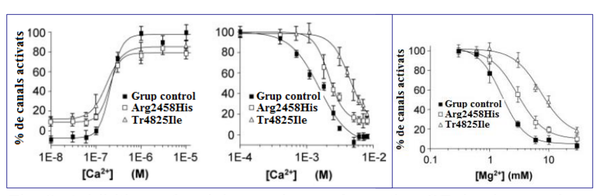


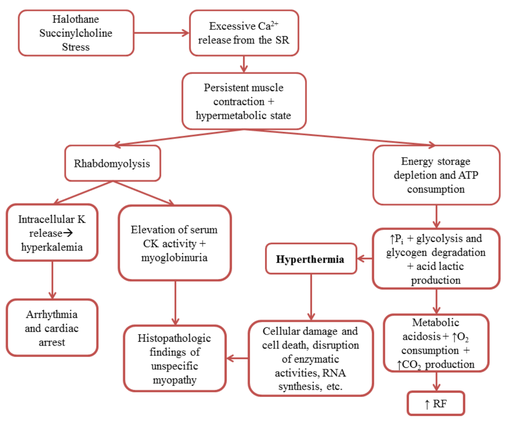
Fig 3. Inhibition of calcium release from the SR by increasing concentrations of calcium (Ca^{2+}) and magnesium (Mg^{2+}) in RyR1 channels with and without de MH mutation (Yang et al. 2003).

4.4. Treatment and prevention

Treatment: immediate discontinuation of inhalatory anesthetic, cooling therapy with alcohol, cold water and cold fluid therapy compensated with sodium bicarbonate.

Prevention: premedication with dantrolene PO 30-60 min. before anesthetic induction.

4.5. Pathogenesis



5. Hyperkalemic periodic paralysis

5.1. Clinical signs

The most common clinical signs are: facial myotonia, fasciculations in the flanks, neck and shoulders, sweating and, in some cases, protrusion of the third eyelid. Occasionally, these episodes can lead to generalized weakness, dorsal displacement of the soft palate, laryngeal paralysis, dyspnea and dysphagia. Some of the most typical analytical changes are hyperkalemia, higher total protein, and elevation of the CK and AST serum activities.

5.2. SCN4A

The SCN4A gene codifies for the voltage-gated sodium channel of the sarcolemma and T tubules, which is formed by two subunits, α and β. The α-subunit is composed of four domains, each of them with six transmembrane helixes, and only with this structure the channel could be functional. The β-subunit is responsible for the kinetics and activation (Fig. 4).

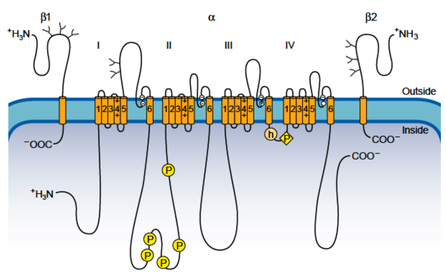


Fig. 4. Structure of the voltage-gated sodium channel (Hille and Catterall 2012).

In the rest state, the $Na_v1.4$ channel remains closed, and it opens when a membrane potential reaches the threshold for contraction. The fast influx of sodium toward the sarcoplasm induces the depolarization of the sarcolemma and thus the beginning of the action potential in the myocyte. Once the membrane is depolarized, the sodium channels close and the potassium channels open to return to the polarized state.

5.3. SCN4A HYPP

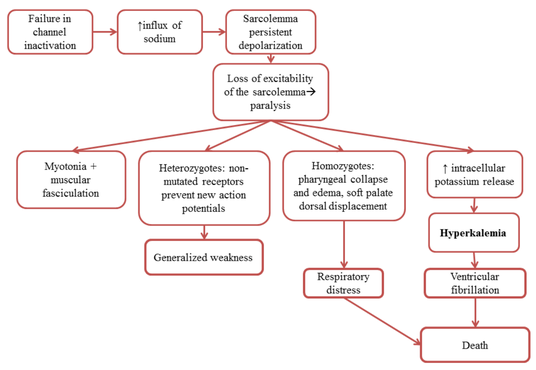
This mutation is located in the third segment of the domain IV, near the inactivation site. Therefore, it causes a failure in the inactivation process of the channel. The abnormal influx of sodium makes the membrane to become less polarized, and thus more susceptible to reach the activation threshold and persistent depolarization. The hyperkalemia is due to the release of intracellular potassium to try to repolarize the cell.

5.4. Treatment and prevention

Treatment: dextrose and calcium gluconate as a cardioprotective, glucose and insulin, calcium bicarbonate or β-adrenergic agonists to promote the influx of potassium toward the intracellular fluid. In cases of severe dyspnea it may be necessary a tracheotomy.

Prevention: low potassium diets, regular light exercise and/or chronic administration of acetazolamide or thiazides.

5.5. Pathogenesis



6. Conclusions

- These two pathologies have been widely studied due to the fact that both of them have also been described in human medicine.
- However, it has not yet been described the reason why the triggering agents, under the same conditions, sometimes produce a clinical episode and sometimes not.
- The genetic testing may be necessary in some cases to allow registration, mainly of the Quarter Horses, to compete in some categories. The variability on the clinical signs, in HYPP, and in the mutation gene, in MH, highlights the need to make an effort to collect more information and better understand the pathogenesis.