Kv7 channels are involved in human malignant hyperthermia

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Malignant hyperthermia (MH) is a rare pharmacogenetic syndrome of skeletal muscle characterized by muscle rigidity (hyper-contractility), rhabdomyolisis and rapid increase in body temperature associated to hypermetabolism, hypercapnis, tachycardia, hypoxia that can lead in death rapidly. This syndrome is triggered by volatile anaestetics and depolarizing muscle relaxants.Despite genetic studies have identified RyR1 gene as primary locus, with more than 300 of RYR1 mutations associated to MH, less than 50% of MH susceptible subjects have mutations in the RYR1 gene (Girard et al., 2009; McCarty et al., 1990). Therefore the diagnostic gold standard to detect MH susceptibility relies on the In Vitro Contracture Test(IVCT). This is an invasive procedure since a biopsy from the quadriceps muscle must be harvested. IVCT assesses the SKM contractile response to exogenous addition of halothane and caffeine in vitro, and it allows to diagnose MH negative response (MHN, non susceptible to MH syndrome) in which no contraction is observed following addition of halothane and/or caffeine, and MH susceptible (MHS) in which, following halothane and/or caffeine exposure, an increased resting tension over 2mN occurs. Recently it has been demonstrated that hydrogen sulphide (H2S) is involved in the MH syndrome, in particular it has been observed that in skeletal muscle of MHS subjects there is an increase in CBS mRNA and protein expression, coupled to higher levels of H2S, compared to MHN subjects (Vellecco et al., 2016). Among the molecular targets involved in H2S actions, recently it has been proposed that H2S can also activate vascular Kv7 voltage-gated potassium channels (Martelli et al., 2013). Aim of this study is to evaluate the possible involvement of Kv7 channels in the MH syndrome. Primary skeletal muscle cell culture of MHN and MHS subjects have been used and the involvement of three different type of potassium channels have been tested by using selective activators and inhibitors. Exposure of MHN skeletal muscle cells to potassium channel activators, such as cromakalim (KATP channel activator), NS1619 (BK channel activator) and retigabine (Kv7 channel activator), induced hyperpolarization of the membrane potential, although with different levels of efficacy. Accordingly, selective potassium channels blockers, such as glibenclamide (KATP blocker), iberiotoxin (BK blocker), and XE991 (Kv7 blocker), induced membrane depolarization. In MHS skeletal muscle cells, the effects of potassium channel blockers were poorly influenced. In contrast, the hyperpolarizing effects of cromakalim and NS1619 were significantly increased, if compared to those observed in MHN skeletal muscle cells. Interestingly, in MHS cells, retigabine (activator of Kv7 channels) induced a paradoxical depolarizing response (effect opposite to that observed in MHN cells). These findings provide interesting insights to improve the knowledge of MH syndrome and to focus on Kv7 channels as a novel target for MH syndrome.

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