An RYR1 mutation associated with malignant hyperthermia is also associated with bleeding abnormalities

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Malignant hyperthermia is a potentially fatal hypermetabolic disorder triggered by halogenated anesthetics and the myorelaxant succinylcholine in genetically predisposed individuals. About 50% of susceptible individuals carry dominant, gain-of-function mutations in RYR1 [which encodes ryanodine receptor type 1 (RyR1)], though they have normal muscle function and no overt clinical symptoms. RyR1 is predominantly found in skeletal muscle but also at lower amounts in immune and smooth muscle cells, suggesting that RYR1 mutations may have a wider range of effects than previously suspected. Mild bleeding abnormalities have been described in patients with malignant hyperthermia carrying gain-of-function RYR1 mutations. We sought to determine the frequency and molecular basis for this symptom. We found that some patients with specific RYR1 mutations had abnormally high bleeding scores, whereas their healthy relatives did not. Knock-in mice with the malignant hyperthermia susceptibility RYR1 mutation Y522S (MHS RYR1(Y522S)) had longer bleeding times than their wildtype littermates. Primary vascular smooth muscle cells from RYR1(Y522S) knock-in mice exhibited a higher frequency of subplasmalemmal Ca2+ sparks, leading to a more negative resting membrane potential. The bleeding defect of RYR1(Y522S) mice and of one patient was reversed by treatment with the RYR1 antagonist dantrolene, and Ca2+ sparks in primary vascular smooth muscle cells from the MHS RYR1(Y522S) mice were blocked by ryanodine or dantrolene. Thus, RYR1 mutations may lead to prolonged bleeding by altering vascular smooth muscle cell function. The reversibility of the bleeding phenotype emphasizes the potential therapeutic value of dantrolene in the treatment of such bleeding disorders.
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