# Effects of a novel RyR1 inhibitor on malignant hyperthermia model mice

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Type 1 ryanodine receptor (RyR1) is a $Ca^{2+}$ release channel in the sarcoplasmic reticulum and plays an important role in excitation-contraction coupling. Genetic mutations in RyR1 cause various skeletal muscle diseases including malignant hyperthermia (MH). Since the main underlying mechanism of MH is hyperactive $Ca^{2+}$ release by gain-of-function of the RyR1 channel, inhibition of RyR1 is a promising treatment for the disease. We have recently developed an efficient high-throughput screening platform for the RyR1 inhibitor and identified oxolinic acid as a novel RyR1 inhibitor (Murayama et al., Mol Pharmacol, 94: 722-730, 2018). Structure development study has resulted in the acquisition of several oxolinic acid derivatives (OAD) with greater potency (Mori et al., Eur J Med Chem, 179: 837-848, 2019). In this study, we tested therapeutic effects of OAD on MH model mice carrying mutation in the *RYR1* gene. OAD reduced resting intracellular $Ca^{2+}$ and suppressed caffeine-induced contracture in skeletal muscle from heterozygous MH mice. The heterozygous mice died with an increased body temperature when they were anesthetized by isoflurane. Pre-administration of OAD completely prevented rise in the body temperature and death. In addition, OAD rescued the mice after they developed MH episodes. Similar results were also obtained with MH model mice carrying different RyR1 mutation. These results suggest that OAD are a promising candidate for effective treatment of MH.