Calcium handling by human skeletal muscle fibres with ryanodine receptor variants

R.H. Choi and B.S. Launikonis , School of Biomedical Sciences, The Univeristy of Queensland, St Lucia, QLD 4072, Australia.

Malignant hyperthermia (MH) is a clinical syndrome of skeletal muscle that presents as a hypermetabolic response to volatile anaesthetic gases, where susceptible persons may develop lethally high body temperatures. Genetic predisposition mainly arises from mutations on the skeletal muscle ryanodine receptor (RyR). Dantrolene is administered to alleviate MH symptoms but its mechanism of action and its influence on the Ca^{2+} transients elicited by MH triggers are unknown. Here we show that Ca^{2+} release in the absence of Mg^{2+} is unaffected by the presence of dantrolene but that dantrolene becomes increasingly effective as cytoplasmic free [Mg^{2+}] (free $[Mg^{2+}]_{cyto}$) passes mM levels. Furthermore, we found in human muscle susceptible to MH that dantrolene was ineffective at reducing halothane-induced repetitive Ca^{2+} waves in the presence of resting levels of free [Mg^{2+}]cyto (1 mM). However, an increase of free $[Mg^{2+}]_{cyto}$ to 1.5 mM could depress the period between Ca^{2+} waves. These results reconcile previous contradictory reports in muscle fibres and isolated RyRs, where Mg^{2+} is present or absent, respectively, and defines the mechanism of action of dantrolene is to increase the Mg^{2+} affinity of the RyR (or ‘stabilize’ the resting state of the channel); and suggests that the accumulation of the metabolite Mg^{2+} from MgATP hydrolysis is required to make dantrolene administration effective in arresting an MH episode.