FAER
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Anesthetic interactions with ryanodine receptor 1 in malignant hyperthermia

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Malignant hyperthermia is a disease, triggered by several anesthetic agents in the presence of any of a number of mutations, that can be fatal (incidence 1:15000-30000, 70-80% mortality without treatment). The calcium channel ryanodine receptor 1 (RYR1) is held open, allowing uncontrolled calcium ion efflux from the sarcoplasmic reticulum, which must then be evacuated, generating overwhelming metabolic activity. Interestingly, this effect persists even after the otherwise low-affinity agent is discontinued. The mechanism for this is not yet known. We hypothesize that MH-causative mutations on RYR1 increase the binding affinity of anesthetic agents to RYR1, but the binding sites and affinity in these sites is also not known. Using computational molecular dynamics simulation (MD) methods in conjunction with experimental photoaffinity labeling, we will 1) identify anesthetic binding sites on RYR1 and 2) evaluate how MH-causative mutations modulate anesthetic binding affinity. The overall result of this project will be a mechanistic understanding of how anesthetic binding to RYR1 is modified in the setting of disease-inducing mutations; this can then inform further studies of MH and RYR1 as well as therapeutic development.