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Identification of molecular targets of fropofol-induced cardiac depression with the novel photoaffinity label ortho-azi-fropofol.

Abstract

Anesthetic molecules have unique pharmacology that makes them incredibly interesting but challenging to study. The decades long debate about the mechanisms of anesthetic action continues to this day, but anesthetic actions extend far beyond sedation and hypnosis. The “non-anesthetic” pharmacologic actions of anesthetics have received little attention outside of their annoyance to the clinician. However, were it not for its sedative effects, the negative inotropy of propofol could be viewed instead for its therapeutic potential in diseases such as hypertrophic cardiomyopathy (HCM). Fropofol is an analogue of propofol that exhibits the same negative inotropy of propofol, but lacks all other anesthetic endpoints. This MRTG proposal seeks to understand the molecular mechanisms of cardiac depression of propofol and fropofol utilizing photoaffinity labels (PALs) to identify protein targets and binding sites in cardiac myofibrils. Zebrafish with genetically engineered mutations that eliminate these binding sites can then be used to correlate functional relevance of these sites and confirm their mechanistic role in cardiac depression. The negative inotropic effects of any mutations with or without propofol and fropofol will be characterized via a newly described technique that uses a simple light microscope, widely available software, and a high-speed camera. These findings will be confirmed via direct measurements of contractile force in ex-vivo ventricular tissue of adult zebrafish. Together, these studies will provide further understanding of propofol and fropofol’s mechanism of cardiac depression that could generate a novel pharmacologic therapeutic for HCM.