West Virginia University

C. EUGENE BENNETT
DEPARTMENT OF CHEMISTRY

Investigation of Mechanism of Calcium Sensitivity Modulation of Cardiac Troponin C by Small Molecules

Steffen Lindert, PhD
Department of Chemistry and Biochemistry
Ohio State University

Cardiac troponin C (cTnC) binds intracellular calcium and subsequently cardiac troponin I (cTnI), initiating cardiac muscle contraction. Structural studies have shown the binding location of small molecules to be a hydrophobic pocket in the regulatory domain of cTnC (cNTnC) but have not shown the influence of these small molecules on the dynamics of opening this domain. Here we describe an application of an umbrella sampling method used to elucidate the impact these calcium sensitivity modulators have on the free energy of cNTnC hydrophobic patch opening. We found that all molecules lowered the free energy of opening in the absence of the cTnI, with bepridil facilitating the least endergonic transformation. In the presence of cTnI, however, we saw a stabilization of the open configuration due to DPA and dfbp-o binding, and a destabilization of the open configuration imparted by bepridil and W7. Additionally, differences in the free energy of hydrophobic patch opening of hypertrophic (HCM) and dilated cardiomyopathy (DCM) cTnC systems were investigated. Molecular dynamics and umbrella sampling simulations revealed a lower free energy of opening for the HCM mutations. The DCM mutations all exhibited a higher free energy of opening. Our developed simulation protocol presents a novel approach to study calcium sensitivity modulation by small molecules. Additionally, we identified several novel drug candidates for heart failure, using a structure-based drug discovery protocol.

Students, meet the speaker after the seminar in a student/postdoc session from 4:45-5:15 pm

Date: Mon, Oct. 7, 2024
Time: 3:30-4:30 pm
Location: Clark Hall 312