Andrew Darkow, Biological Sciences

University: Westminster College
Year in School: Senior
Hometown: Columbia, Missouri
Faculty Mentor: Dr. Kerry McDonald, Medical Pharmacology & Physiology
Funding Source: NIH grant to K.S. McDonald

Role of cardiac troponin I phosphorylation in cardiac function: From molecule to mouse

Andrew G. Darkow, Laurin M Hanft, Aaron C. Hinken, and Kerry S. McDonald

The regulation of cardiac muscle contraction involves the interplay between a variety of molecules on the thick and thin filaments. One important regulatory molecule is troponin, which consists of three subunits, troponin C (TnC) that binds calcium, troponin T (TnT) that binds tropomyosin, and troponin I (TnI) that binds actin and tends to inhibit contraction. Following muscle excitation, cytoplasmic calcium rises and binds TnC, which causes a conformational change in TnI that reduces its affinity for actin; this, in turn, allows TnT and tropomyosin to shift positions revealing myosin binding sites on actin, leading to muscle contraction. Interestingly, cardiac troponin I (cTnI) has several phosphorylation sites, which are known to modulate this regulatory process. For example, phosphorylation of serines 23 and 24 on cTnI by protein kinase A (PKA) is known to decrease the calcium binding affinity of cardiac TnC and, thus, thought to speed muscle relaxation. On the other hand, phosphorylation of cTnI on serines 43 and 45 and threonine 144 by protein kinase C (PKC) decreases both force production and calcium sensitivity of force and is thought to contribute to depressed ventricular function in failing hearts. In this study we investigated the effects of chronic cTnI phosphorylation on cardiac function from transgenic animals in which either PKA phosphorylation sites (Ser-23/Ser-24) (PP) or both the PKA and PKC phosphorylation sites (Ser-23/Ser-24/Ser-43/Ser-45/T-144) (All-P) were replaced with aspartic acid to mimic phosphorylation. Left ventricular cardiac myocytes from PP transgenic mice exhibited less calcium sensitivity of force while myocytes from All-P transgenic mice exhibited decreased maximal force, decreased calcium sensitivity of force, and decreased power output, implicating a dominate role of PKC phosphorylation sites on myofilament function. Consistent with these single myocyte studies, left ventricular power output also was depressed in All-P mice compared to both WT and PP transgenic ventricles. We next tested the hypothesis that PP transgenic mice would engage in greater voluntary running compared to WT and All-P transgenic animals. In contrast to this idea, WT and All-P mice ran ~3- and ~4-fold more than the PP transgenic mouse, respectively. Overall, these results indicate that PKC phosphorylation of cTnI plays a dominant role in depressing contractility and may contribute to the maladaptive behavior.