The physiological basis of muscle-generated motor activity revolves around the precise regulation of intracellular Ca²⁺ ions. Central to this process is a special organelle found in muscle cells called the sarcoplasmic reticulum (SR), which is responsible for the storage, release, and reuptake of the Ca²⁺. When appropriately signaled by a motor neuron, high-conductance channels in the SR, known as ryanodine receptors (RyRs), release a great volume of Ca²⁺ ions into the muscle cell lumen, to produce muscle contraction; conversely, SERCA ATPase pumps in the SR return the free Ca²⁺ ions from the muscle cell lumen back into the SR, to produce muscle relaxation (Bers, 2002; Carafoli, 2002; Fill et al., 2002).

The new experimental heart drug S107 has been associated with improved muscle performance, though it is still unclear if it directly affects the binding activity of either FKBP or calmodulin (CaM) RyR accessory proteins. The purpose of my research was to investigate whether S107 does in fact directly increase the binding affinity of FKBP12.6, as originally proposed by Dr. Andrew Marks of Columbia University. In addition, I also investigated if S107 affects the binding affinity of CaM as a possible supplementary mechanism of action, or in the case of a negative result for FKBP, as a primary mechanism of action.

Effect of S107 on FKBP – We found that S107 induced no significant increase (or any other change) in the binding affinity of FKBP12.6 or 12.0 for RyR2. This suggests that any increase in the binding of FKBP12 to RyR that correlates with S107 treatment under in vivo conditions is a product of an indirect, and yet uncharacterized, mechanism. This idea also lends support to the work of other researchers who have instead proposed that FKBP binding to RyR insignificantly reduces Ca²⁺ leak through the channel, and that S107 must therefore elicit its therapeutic mechanism of action through an indirect manner that completely circumvents FKBP (Blayney et al., 2010; Cornea et al., 2010).

Effect of S107 on CaM – Our results show that S107 produced a slight decrease in the binding affinity of CaM for RyR2 (but only in the presence of GSG6). This decrease in binding affinity is significant, but seen only in mM Ca²⁺ concentrations (as in diastole), suggesting that RyR2 channels that have undergone pathological oxidation due to disease, age, or stress bind CaM with reduced affinity if treated with S107. As a result, Ca²⁺ leak through the channel would increase, because S107 would partially negate CaM binding that would otherwise help stabilize the RyR2 and inhibit leak. Based on these results, increased binding affinity of CaM for RyR2 due to S107 is an unsupported explanation for the drug’s therapeutic mechanism of action used to improve muscle function.

References


