

Debilitating Leaks

By Alexia Hwang

Despite recent evidence disputing the long-held theory that the burning sensation in muscles is caused by the build-up of lactic acid, speculations on the cause of the common physiological symptom have remained minimal. However, on February 11, Dr. Andrew Marks of the Columbia University Medical Center published a report proposing that muscle fatigue is the result of “leaky” calcium flows into muscle cells (2).

Muscles contract when calcium ions (Ca^{2+}) flow in to muscle cells to catalyze a series of reactions which result in the depolarization of muscle fibers and ATP hydrolysis. In skeletal muscle, ryanodine receptors (RyR1) are the major class of calcium ion release channels required for excitation-contraction coupling (ECC). Structurally, the RyR1 receptor is composed of four 560-kDa subunits and is stabilized in its closed state by a protein called calstabin1. The binding of calstabin1 to RyR1 prevents the channels from “leaking” and improves the efficiency of depolarization-induced contractions. (4)

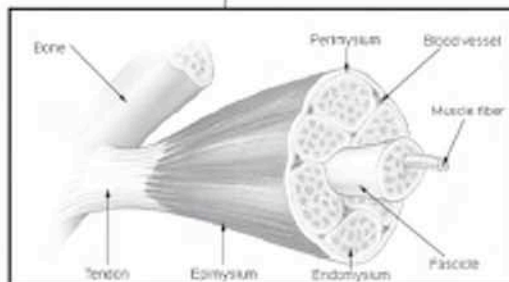
The RyR1 protein complex is remodeled during exercise by phosphorylation and S-nitrosylation, a reaction which converts cysteine residues in proteins to S-nitrosothiols. These reactions progressively decrease the binding affinity of calstabin1 to RyR1. Intense physical activity can lead to the hyperphosphorylation of RyR1 and a depletion of calstabin in muscle cells. The calcium leaks that result reduces the ability of muscles to contract during exercise (1). Furthermore, calcium ions leaked into the cytosol through the faulty channels can activate Ca^{2+} dependent proteins such as calpain, a protease that can cause more damages to muscle cells (4).

Hyperphosphorylation of RyR1 and the depletion of calstabin1 were also observed in the cardiac muscle of patients suffering from heart failure. Since the same calcium channels are present in both skeletal and heart muscle,

these tiny leaks may contribute to the feeling of constant exhaustion that heart failure patients have to endure (5). Although previous research had failed to show a strong correlation between heart function and severe fatigue, patients with weak hearts could still exercise with high intensity. Dr. Mark’s research has introduced a variable that was overlooked – leaks in calcium ion channels (5).

With this new knowledge, the researchers conducted a screen to discover compounds that could enhance the binding affinity of calstabin1 to phosphorylated RyR1. S107 was identified a promising pharmacological agent because it is a chemically stable compound that can be ingested orally and absorbed by the body. This new “anti-fatigue” drug has been tested in mice and was shown to prevent muscle damage and increase the mice’s ability to exercise for longer periods of time. (1). The drug is currently being investigated as a possible therapeutic to help heart patients perform everyday tasks without the accompanying exhaustion (3). ■

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▲ Structure of skeletal muscle

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