S107 Mitigates RyR2-Mediated Cardiac Dysfunction in COVID-19-Infected Rodents

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Cardiac complications associated with SARS-CoV-2 infection include arrhythmias, myocarditis, and heart failure. However, the pathogenesis underlying COVID-19-induced cardiac dysfunction remains poorly understood. The current investigation characterized the role of the ryanodine receptor (RyR2), an intracellular calcium release channel on cardiomyocytes' sarcoplasmic reticulum, in the pathophysiology of COVID-19-induced cardiac dysfunction. Rycal s107, a RyR2 stabilizer, was evaluated as a therapeutic to mitigate the RyR2-mediated calcium leak and restore cardiac function in COVID-19-infected rodents. Biochemical analyses of immunoprecipitated RyR2 from infected mouse and Syrian hamster cardiac tissue revealed pronounced phosphorylation and oxidation of RyR2 and depletion of its stabilizing subunit, calstabin2, hallmarks of a pathological calcium leak. In situ s107 treatment increased binding of calstabin2 to RyR2, likely stabilizing the channel. Calcium spark imaging corroborated these findings, demonstrating a significant increase in calcium spark frequency in cardiomyocytes treated with cytokines identified to be upregulated in COVID-19 cardiac tissue ($P<.0001$). Calcium spark frequency normalized following ex vivo s107 treatment. Echocardiograms revealed a 0.73-fold decrease in ejection fraction in infected hamsters compared to controls ($P<.001$). In vivo s107 treatment significantly improved cardiac function ($P=.02$). These findings confirm the role of RyR2 in cardiac pathophysiology associated with COVID-19 and highlight the therapeutic potential of s107 in improving cardiac function by reducing the RyR2 $Ca2+$ leak. This study sets the stage for future in vivo investigations and clinical trials, employing s107 to reduce COVID-19 morbidity and mortality.

Awards Won: