Statin-activation of RyR1 is a class effect but separable from HMG-CoA reductase inhibition

Chris Lindsay[1], Maria Musgaard[2], Angela Russell[1], and Rebecca Sitsapesan[1]

[1]University of Oxford
[2]OMass Therapeutics Ltd

July 26, 2021

Abstract

Background and purpose Statins, inhibitors of HMG-CoA reductase, are mainstay treatment for hypercholesterolemia. However, muscle pain and weakness prevent many patients from benefiting from their cardioprotective effects. We previously demonstrated that simvastatin activates skeletal ryanodine receptors (RyR1), an effect that could be important in initiating myopathy. We therefore investigated if RyR1 activation is a standard property of commonly-prescribed statins. Using a range of structurally-diverse statin analogues we examined structural features associated with RyR1 activation, aiming to identify statins lacking this property. Experimental Approach Compounds were screened for RyR1 activity utilising [^{3}H]ryanodine binding. Mechanistic insight into RyR1 activity was studied by incorporating RyR1 channels from sheep, mouse or rabbit skeletal muscle into bilayers. Key Results All UK-prescribed statins activated RyR1 at nanomolar concentrations. Cerivastatin, withdrawn from the market due to life-threatening muscle-related side effects, was more effective than currently-prescribed statins and possessed the unique ability to open RyR1 channels independently of cytosolic Ca^{2+}. We synthesised the statin pharmacophore and it did not activate RyR1. We also identified five analogues retaining potent HMG-CoA reductase inhibition that inhibited RyR1 and four analogues that lacked the ability to activate RyR1. Conclusion and Implications That cervistatin activates RyR1 most strongly supports the hypothesis that RyR1 activation is implicated in statin-induced myopathy. Demonstrating that statin-regulation of RyR1 and HMG-CoA reductase are separable effects allows the role of RyR1 in statin-induced myopathy to be further elucidated by the tool compounds identified, thus paving the way for the development of effective cardioprotective statins with improved patient tolerance.

Hosted file

`13 July Final Manuscript.pdf` available at https://authorea.com/users/427517/articles/531688-statin-activation-of-ryr1-is-a-class-effect-but-separable-from-hmg-coa-reductase-inhibition

Hosted file

`13 July Final Figures.pdf` available at https://authorea.com/users/427517/articles/531688-statin-activation-of-ryr1-is-a-class-effect-but-separable-from-hmg-coa-reductase-inhibition