Simvastatin Alters the RhoA Adaptation to Skeletal Muscle Stress Conditions

Amici DR., Chen D., Chin ER. University of Maryland, College Park, MD

Statin lipid-lowering drugs have been shown to induce muscular stress conditions and increase incidence of myopathy, especially in exercising individuals. RhoA, a GTPase involved in muscle repair and intracellular damage signaling, adapts both acutely (increased activation) and chronically (increased protein expression) to muscular stress conditions. Statins inhibit production of mevalonate, upstream of geranylgeranyl pyrophosphate (GGPP), which anchors newly translated RhoA to the cell membrane. This inhibition may suppress the ability to chronically increase RhoA expression. **Purpose:** To determine if exercise and statin treatment elicit different RhoA adaptations to muscular stress conditions. **Methods:** Mice were randomized into vehicle (Veh) control, one of three simvastatin doses (60, 200, or 400 $mg \cdot kg^{-1}$), or Veh plus intense eccentric exercise (Veh+EX). After two weeks, tibialis anterior muscle was harvested and analyzed via western blot for RhoA activity (percentage activated) and total RhoA expression. **Results:** Both the Veh+EX and all statin groups had elevated RhoA activity ($p<0.05$). RhoA expression increased in the Veh+EX group ($p<0.01$), but was unchanged between Veh and statin groups. There were no significant differences between statin doses. **Conclusion:** The increased RhoA activity with statin treatment and exercise shows a similar acute adaptation to stress, but the expected increase in RhoA expression was suppressed by all doses of simvastatin. This may play a role in the increased myopathy rate observed in exercising statin users. Future study should investigate if other signaling proteins modified by GGPP are also affected.

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	Control (Veh)	Exercise (Veh+EX)	Statin 60 $mg \cdot kg^{-1}$	Statin 200 $mg \cdot kg^{-1}$	Statin 400 $mg \cdot kg^{-1}$
RhoA Expression (AU)	527 ± 12	801 ± 22*	470 ± 73	541 ± 15	497 ± 22
RhoA Activity (%)	14.7 ± 1.1	20.0 ± 1.2*	22.9 + 1.7*	19.5 ± 1.6*	18.5 ± 1.5*