# Statin therapy makes things worse for alcohol drinkers

High cholesterol levels in humans represent a risk factor for life-threatening cardio/cerebrovascular conditions, including heart attack and stroke. It is estimated that nearly 94.6 million, or 40 % of American adults, have total blood cholesterol levels above 200 mg/dL, with approximately 12 % of such population reaching over 240 mg/dL. The latter is recognized as one of the criteria for clinically defined hypercholesterolemia. Statins constitute the most commonly prescribed drugs in the US to decrease cholesterol levels in humans. Statins inhibit the enzyme HMG-CoA (or 3-hydroxy-3-methylglutaryl-coenzyme A) reductase which plays a central role in the production of cholesterol. Remarkably, the overall health benefits observed with statins include effects beyond cholesterol lowering, which are known as cholesterol-independent or “pleiotropic” effects. Thus, it is difficult to predict a final effect of statin therapy on cholesterol-dependent physiological or pathological processes.

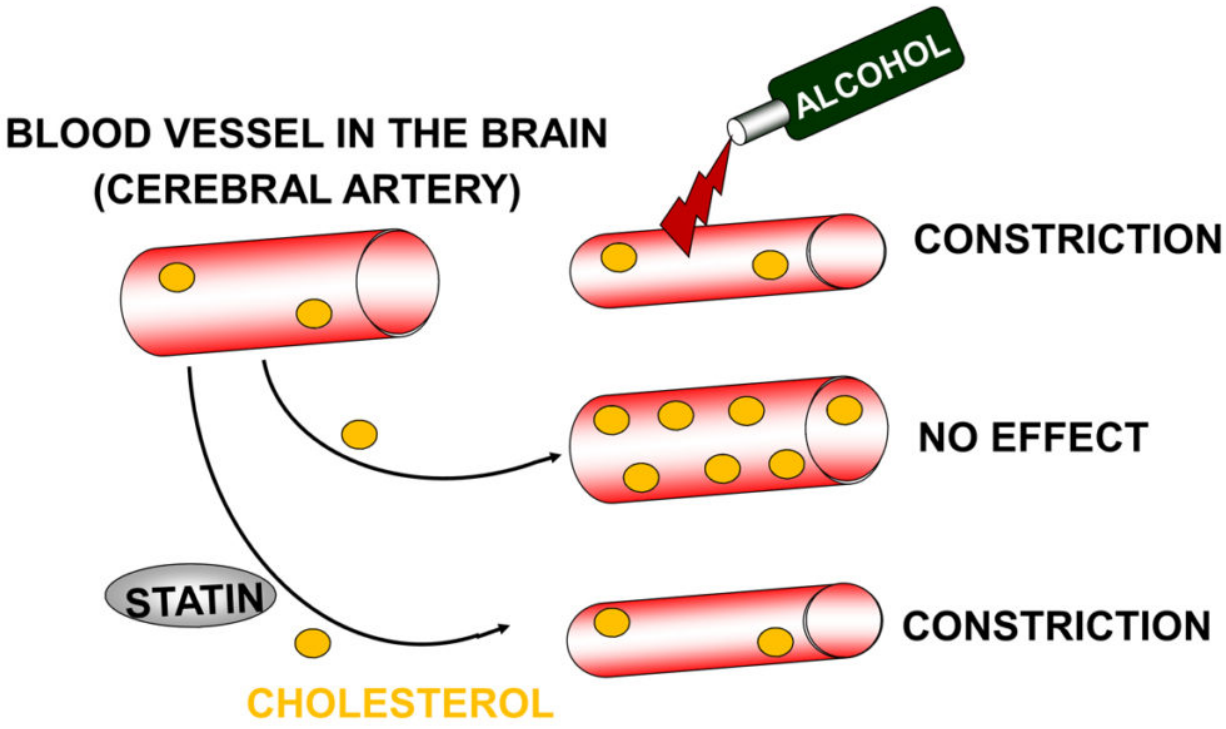


Fig. 1. Modification of a cerebral artery diameter by alcohol. Alcohol at concentrations that are reached in the blood during a moderate-to-heavy drinking episode decreases diameter of blood vessels in the brain (cerebral arteries). Increase in a cholesterol level in the blood leads to a buildup of cholesterol in the artery and protects against effect of alcohol on an artery diameter. Cholesterol lowering therapy by atorvastatin prevents cholesterol accumulation and restores vulnerability of cerebral arteries to alcohol-induced decrease of a diameter (constriction).

Episodic moderate-to-heavy alcohol (ethanol) intake that results in blood alcohol levels of 18-80 mM is associated with an increased risk for cerebral ischemia, stroke and death from cerebrovascular disease. These pathologies may result from, or be exacerbated by, an enhanced constriction of cerebral arteries. It has been demonstrated that alcohol-induced cerebral artery constriction (AICAC) is caused by ethanol inhibition of voltage/$Ca^{2+}$-gated $K^+$ (BK) channels of large conductance in vascular smooth muscle. Smooth muscle BK channel complexes include the channel-forming alpha and small, accessory beta 1 subunits. The latter represents one of the major protein targets for ethanol. However, several factors beyond the presence of the BK beta 1 subunit promote ethanol-induced BK channel inhibition and resulting AICAC. Cholesterol levels represent a major regulator of BK channels sensitivity to ethanol. Moreover, high cholesterol food intake *in vivo* protects against AICAC by the cholesterol buildup in cerebral artery tissue. The consequences of statin therapy on AICAC and underlying mechanisms remain unknown.

In the present work, we set to discover effects of statin therapy on AICAC and identify the mechanisms that would enable statin-driven modification of AICAC. We used atorvastatin administration (10 mg/kg daily for 18-23 weeks) to rats on a high cholesterol (2%) diet, evaluation of a cerebral artery diameter, fluorescence imaging of the vascular smooth muscle BK channel subunit proteins and a cholesterol level, and patch-clamp electrophysiology on native vascular smooth muscle BK channels in cerebral artery myocytes. Middle cerebral arteries were pressurized *in vitro* at 60 mmHg and AICAC was evoked by 50 mM ethanol that is the equivalent to blood alcohol detected in humans following moderate-to-heavy drinking. Using these methodologies, we tested the hypothesis that atorvastatin exacerbated AICAC by preventing cholesterol buildup in cerebral artery tissue and shifting vascular smooth muscle cholesterol to an optimal level that enables ethanol inhibition of BK channels.

Our work reports for the first time a novel effect of atorvastatin, i.e., exacerbation of AICAC and underlying ethanol-induced inhibition of the vascular smooth muscle BK channel. The newly discovered effect is caused by the statin-driven removal of an excessive cholesterol level in cerebral artery vascular smooth muscle. Notably, while the decrease in a cholesterol level of cerebral artery myocytes by atorvastatin was mild, AICAC and ethanol-induced inhibition of BK channels were robust when compared to cerebral artery myocytes from rats on a high-cholesterol diet without atorvastatin therapy. In light of our findings, it may be advisable to give special considerations to the risk of excessive alcohol drinking after cholesterol-lowering atorvastatin therapy.

***Maria N. Simakova, Shivantika Bisen, Alex M. Dopico, Anna N. Bukiya***
*Dept. Pharmacology, University of Tennessee HSC, Memphis TN, USA*

## Publication

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