The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are potent inhibitors of cholesterol biosynthesis. Statins slow the progression, and foster the regression, of atherosclerosis, resulting in an improvement of cardiovascular outcomes in humans with elevated serum cholesterol levels.\(^1\) In addition, statins improve endothelial function as a pleiotropic effect.\(^2\) Interestingly, a recent study suggests that statins reduce blood pressure in patients with hypertension.\(^3\) However, the mechanisms involved in the depressor response to statins may not be because of improved endothelial dysfunction alone, because other mechanisms, such as effects on the sympathetic nervous system (SNS), have not been fully evaluated in humans.

**Figure.** Atorvastatin inhibits the activation of the sympathetic nervous system through inhibition of reactive oxygen species (ROS) and upregulation of nitric oxide (NO) in the rostral ventrolateral medulla (RVLM). In the RVLM, ROS are mainly produced by the AT\(_1\) receptor and nicotinamide adenine dinucleotide phosphate [NAD(P)]H oxidase, and reduced by manganese (Mn)-superoxide dismutase (SOD) and copper/zinc-SOD. Atorvastatin decreases NAD(P)H oxidase activity through inhibition of Rac1 membrane translocation, and activates Mn-SOD in the RVLM. Furthermore, atorvastatin also increases neural NO synthase (nNOS) and endothelial NOS (eNOS), which cause the increase in NO production in the RVLM.
in the RVLM of SHRSP, thereby reducing the activation of the SNS. Another previous study demonstrated that simvastatin normalized autonomic function in rabbits with heart failure by inhibiting central angiotensin II mechanisms. Those authors suggested that superoxide via nicotinamide adenine dinucleotide phosphate [NAD(P)H] oxidase activation in the RVLM is involved in this mechanism. Recently, we also examined the effects of atorvastatin administered directly into the brain on changes in blood pressure and activation of the SNS in SHRSP, and demonstrated that atorvastatin administered chronically into the brain inhibits the activation of the SNS in SHRSP. This is associated with reduced oxidative stress because of inhibition of NAD(P)H oxidase in the RVLM of these rats. Another intriguing finding is that the increased sympathetic neural effects, and the changes in oxidative stress in the RVLM were comparable between oral administration (50 mg·kg⁻¹·day⁻¹) and intracerebroventricular injection (2 mg·kg⁻¹·day⁻¹) of atorvastatin. The blood–brain barrier in SHRSP might be disrupted and therefore orally administered atorvastatin would be able to affect the brain directly. Another important property of atorvastatin is that it is a lipophilic statin, which makes it easier to cross the blood–brain barrier compared with other cardiovascular drugs, such as some of the β-blockers.

In this issue of the Journal, Gomes et al describe how, by measuring the postganglionic muscle sympathetic nerve activity (MSNA) directly, which is a gold standard method of evaluating SNS activity in humans, they were able to reduce MSNA in mild to moderate hypertensive patients. Whereas the lower MSNA levels did not translate into lower venous plasma norepinephrine levels, lower blood pressure levels or a change in heart rate variability, their report is the first randomized, placebo-controlled, double-blind, cross-over designed study to demonstrate the sympathoinhibitory effect of atorvastatin in hypertensive humans. Although it is necessary to confirm the longer term clinical outcomes and mechanisms, their message has significant clinical implications.

In conclusion, the results from the report described by Gomes et al are consistent with our studies in animal experiments. The oral administration of atorvastatin might inhibit activation of SNS via a reduction of ROS in the brain (Figure). Abnormal activation of the SNS causes hypertension, heart failure, and ischemic heart disease, and we consider that oral administration of atorvastatin has the potential to treat cardiovascular diseases by sympathoinhibition via its antioxidant effect in the RVLM.

References