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COMMENTARY

Statin therapy and myocardial no-reflow

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HMG-CoA reductase inhibitors (statins) have now become one of the most powerful pharmacological strategies in the treatment of cardiovascular diseases. Originally, the cardioprotective effects of statins were thought to be mediated through lipid lowering actions. However, it has now become increasingly clear that the beneficial effects of statins are not related to the lipid lowering effects, but rather to a number of pleiotropic actions. Of particular interest, statins have been shown to increase bioavailability of nitric oxide and protect against vascular inflammation and cardiac cell death in a number of cardiovascular disease states. In this present issue of the *British Journal of Pharmacology*, Zhao and colleagues provide a novel mechanism of action for statins with the observation that simvastatin reduces myocardial 'no-reflow' after ischemia and reperfusion by activating the mitochondrial K_{ATP} channel. The findings of the present study have very profound implications for the treatment of cardiovascular disease. This commentary discusses the implications of these findings and how they relate to the established cardioprotective actions of statins.
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3-Hydroxyl-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (known commonly as the statins) have now become one of the most powerful pharmacological strategies in the treatment of cardiovascular diseases. Originally, the cardioprotective effects of statins were thought to be mediated through the inhibition of the liver enzyme HMG-CoA reductase, which results in the lowering of serum cholesterol levels. By reducing the severity of atherosclerosis in this manner, statins reduce the incidence of acute myocardial infarction, stroke and other cardiovascular diseases. However, it has now become increasingly clear through both clinical and experimental studies that the cardioprotective actions of statins are not limited to the prevention of cardiovascular disease, but include acute protection and these effects have been shown to be mediated by mechanisms independent of cholesterol-lowering actions (Lefer, 2002).

Zhao *et al*. (2006) now demonstrate in this issue of the *British Journal of Pharmacology* that simvastatin reduces myocardial no-reflow following ischemia and reperfusion by activation of the mitochondrial K_{ATP} channel in the myocardium. The 'no-reflow' phenomenon is characterized by the absence of tissue perfusion despite both epicardial coronary artery patency and flow. Although the underlying mechanisms of this phenomenon have not been fully elucidated, the end result is microvascular damage produced by vasoconstriction and obstruction associated with reperfusion injury. Therefore, the recognition of the 'no-reflow' phenomenon affords an opportunity for therapeutic intervention designed to augment tissue perfusion and maintain the viability of myocardium at risk for infarction (Alfayoumi *et al*., 2005). In this current experimental study, simvastatin ($2\,mg\,kg^{-1}\,day^{-1}$) was administered to mini-pigs for 2 days before occlusion of the left anterior descending coronary artery (3 h) and reperfusion (2 h). Simvastatin therapy increased coronary blood flow after reperfusion, decreased the area of no-reflow of the ischemic zone by 57%, preserved endothelial junctions and reduced myocardial necrosis. The authors also very elegantly demonstrate the preservation of post-ischemic left ventricular function in simvastatin-treated animals. Yet, the most interesting aspect of this study was the observation that the specific mitochondrial K_{ATP} channel blocker, 5HD, but not the selective sarcolemmal K_{ATP} channel blocker, HMR 1883, abolished all of the observed beneficial effects of simvastatin. Therefore, this novel finding suggests that pretreatment with simvastatin may precondition the myocardium against ischemia and reperfusion by signaling through the mitochondrial K_{ATP} channel.

Exposing tissue to various drugs has been shown to mimic the protective effects of brief ischemic insults (i.e., pharmacological preconditioning). Some of the drugs that have been reported to have preconditioning effects include K^+ channel openers and nitric oxide (NO) donors (Hanley and Daut, 2005). The exact mechanism(s) by which preconditioning exerts its protective effects is incomplete, although several signaling molecules, including NO, have been implicated. It has also been suggested that the key signaling pathways of preconditioning ultimately converge on the mitochondria

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to safeguard its function (Honda *et al.*, 2005). Specifically, numerous studies have implicated mitochondrial K_{ATP} channels as a major trigger and/or end effector of preconditioning (Hanley and Daut, 2005). Statins are potent modulators of endothelial cell nitric oxide synthase (eNOS) function and have been shown to upregulate eNOS enzyme levels and NO synthesis (Laufs *et al.*, 1997, 1998) (Figure 1). Likewise, NO, either endogenous or exogenous, has been shown to mediate the opening of mitochondrial K_{ATP} channels in the setting of preconditioning (Dawn and Bolli, 2002). Furthermore, statins have been shown to attenuate oxidant-induced mitochondrial dysfunction in cardiac myocytes (Jones *et al.*, 2003). Therefore, the activation of the mitochondrial K_{ATP} channel by simvastatin in this current study by Zhao *et al.* (2006) could be mediated by the actions of NO. Opening of these channels will shift the balance between K^+ uniport and K^+/H^+ antiport, causing a transient net K^+ uptake and matrix swelling, resulting in a higher steady-state volume (Garlid *et al.*, 1996). This opening increases the mitochondrial matrix volume over a fairly narrow range and greatly activates electron transport at the point where electrons feed into ubiquinone. Extensive research efforts (Honda *et al.*, 2005) have led to the postulation of three mechanisms to explain the protective effects of mitochondrial K_{ATP} channel opening during preconditioning. These include (1) depolarization of the mitochondrial membrane potential, decreasing the electrochemical gradient for Ca^{2+} entry during reperfusion; (2) mitochondrial matrix swelling that helps to maintain outer and inner mitochondrial membrane contact sites and matrix integrity required for efficient electron transport; and (3) the generation of very low levels of reactive oxygen species (ROS) that triggers protection by limiting the production of higher levels of ROS following ischemia and reperfusion, thus aiding in the prevention of mitochondrial permeability transition. It is also well established that statins mediate anti-inflammatory actions by inhibiting the upregulation of adhesion glycoproteins involved in leukocyte–endothelial cell interactions (Lefer *et al.*, 2001; Scalia *et al.*, 2001) (Figure 1). In the current study by Zhao *et al.* (2006), simvastatin could exert the observed beneficial effects through the upregulation of eNOS, which would provide NO to precondition both endothelial cells and cardiac myocytes against ischemia and reperfusion (Figure 1). NO-mediated anti-inflammatory actions serve to attenuate capillary plugging by both platelets and leukocytes. Both of these actions could then protect the heart against ischemia and reperfusion injury, thus attenuating no-reflow and cell death.

In summary, numerous preclinical studies have demonstrated statin-mediated cardioprotection in the setting of myocardial infarction and congestive heart failure (Jones *et al.*, 2001, 2002; Yamakuchi *et al.*, 2005; Folkeringa *et al.*, 2006). The beneficial effects of statins are not entirely related to the lipid-lowering effects of these drugs, but rather to a number of diverse actions (Lefer, 2002). Of particular interest, the increased bioavailability of NO has been shown to mediate the cardioprotective actions of statins by inhibiting vascular inflammation and cardiac cell death. Zhao *et al.* (2006) provide a new mechanism of action for statins with

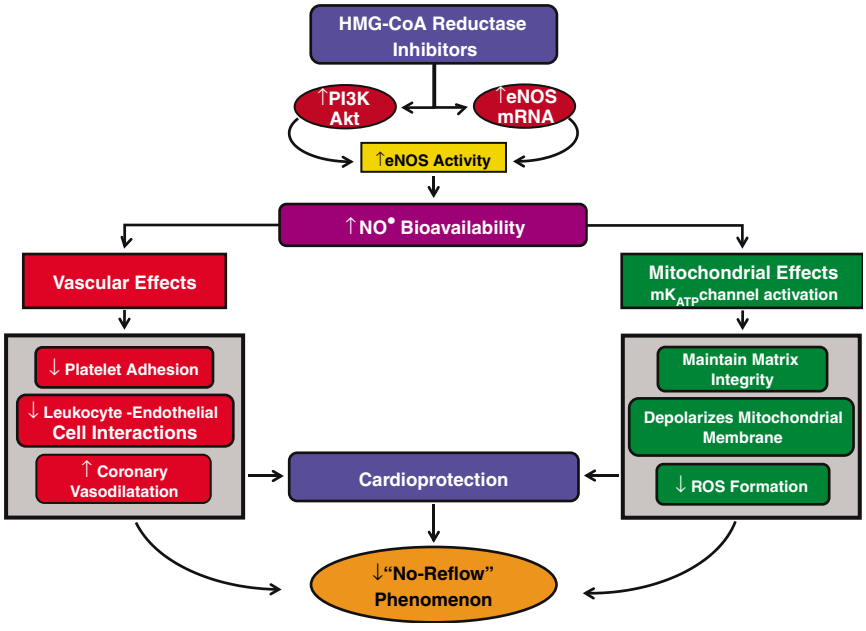

Figure 1 Cardioprotective actions of statins. Statins increase NO bioavailability through PI3K/Akt- and Rho-mediated signaling. NO can then mediate cytoprotection in the setting of myocardial ischemia and reperfusion through effects on the coronary vasculature and at the level of the mitochondria within cardiac myocytes. The vascular effects of increased NO bioavailability include the attenuation of both platelet and leukocyte adhesion and plugging within the coronary microcirculation and coronary vasodilatation. Statin-mediated generation of NO can also result in protection of the mitochondria through the activation of mitochondrial K_{ATP} channels (mK_{ATP}). The opening of these channels serves to depolarize the mitochondrial membrane, maintain the integrity of the mitochondrial matrix and decrease ROS generation by the mitochondria following ischemia and reperfusion.

the observation that simvastatin reduces myocardial no-reflow after ischemia and reperfusion by activating the mitochondrial K_{ATP} channel. This new observation reinforces the already strong case for the use of statins as a therapeutic strategy for cardiovascular diseases by introducing evidence that statins can exert cardioprotective effects through classical mitochondria-mediated preconditioning mechanisms. However, more experimental evidence is certainly warranted to elucidate fully the possibility of statins acting via these established pathways.

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