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Statins and cardioprotection — More than just lipid lowering?

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ABSTRACT

Lipid-lowering using HMG-CoA reductase inhibitors or statin therapy forms the cornerstone of medical therapy in the primary and secondary prevention of cardiovascular disease. In addition, to the improvements in lipid profile, the beneficial effects elicited by this class of drugs may be attributed to their diverse variety of non-lipid lowering pleiotropic effects, including improved endothelial function, reduced oxidative stress, less platelet adhesion, and increased atherosclerotic plaque stability. A less appreciated effect of statin therapy that has been reported in experimental studies is its cardioprotective effect with respect to its ability to directly protect the myocardium from the detrimental effects of acute ischaemia–reperfusion injury. In the current article we review the cardioprotective effects of statin therapy beyond serum lipid lowering, the underlying mechanisms involved and the potential implications for patients with coronary heart disease.

Contents

1. Introduction

Coronary heart disease (CHD) is the leading cause of morbidity and mortality worldwide. HMG-CoA reductase inhibitors (henceforth referred to as 'statins') have become standard medical therapy in the armamentarium available for the prevention and treatment of cardiovascular disease. Large randomised controlled clinical trials have established their role as effective medical therapy for the primary (Shepherd et al., 1995; Downs et al., 1998) and secondary (Pedersen et al., 2005; Heart Protection Study Collaborative Group, 2002) prevention of cardiovascular events. HMG-CoA reductase inhibitors competitively inhibit the conversion of acetyl coenzyme A and acetoacetyl coenzyme A to mevalonate in the formation of cholesterol and prevent the formation of the isoprenoids (Istvan, 2002) (see Fig. 1). Statins were first developed in order to lower total serum cholesterol and improve the lipid profile but have subsequently been shown to exert a variety of beneficial, 'pleiotropic' effects, particularly relevant to cardiovascular disease, including improved endothelial function, reduced oxidative stress, less platelet adhesion, and atherosclerotic plaque stabilisation (Ray & Cannon, 2005).

It is well-established that statin therapy offers widespread beneficial effects on the cardiovascular system through both its lipid lowering and non-lipid lowering effects described above. However, in this article, we will focus on a less appreciated non-lipid lowering effect of statin therapy, namely its potential to directly protect the myocardium from the detrimental effects of acute ischaemia–

Abbreviations: AAR, Area at risk; AR, Adenosine receptor; CK, Creatine Kinase; CK-MB, Creatine Kinase (MB isoform); eNOS, Endothelial nitric oxide synthase; GGPP, Geranyl geranyl pyrophosphate; I, Ischaemia; IPC, Ischaemic pre-conditioning; IPost, Ischaemic post-conditioning; iNOS, Inducible nitric oxide synthase; I/R, Ischaemia-Reperfusion; IRI, Ischaemia- Reperfusion Injury; KO, Knock out; L-NAME, Nitro-L-arginine methyl ester; MACE, Major adverse cardiac events; mPTP, Mitochondrial permeability transition pore; MPO, Myeloperoxidase; NO, Nitric Oxide; 8-OHdG, 8-Hydroxydeoxyguanosine; PCI, Percutaneous coronary intervention; PI3K, Phosphoinositide-3 Kinase; PMI, Peri-operative myocardial infarction; PMN, Polymorphonuclear leukocyte; PTEN, Phosphatase and tensin homolog deleted on chromosome ten; R, Reperfusion; RISK, Reperfusion Injury Salvage Kinase; 8-SPT, 8-Sulfophenyl theophylline; Trop-T, Troponin- T; ULN, Upper limit of normal; WT, Wild type.

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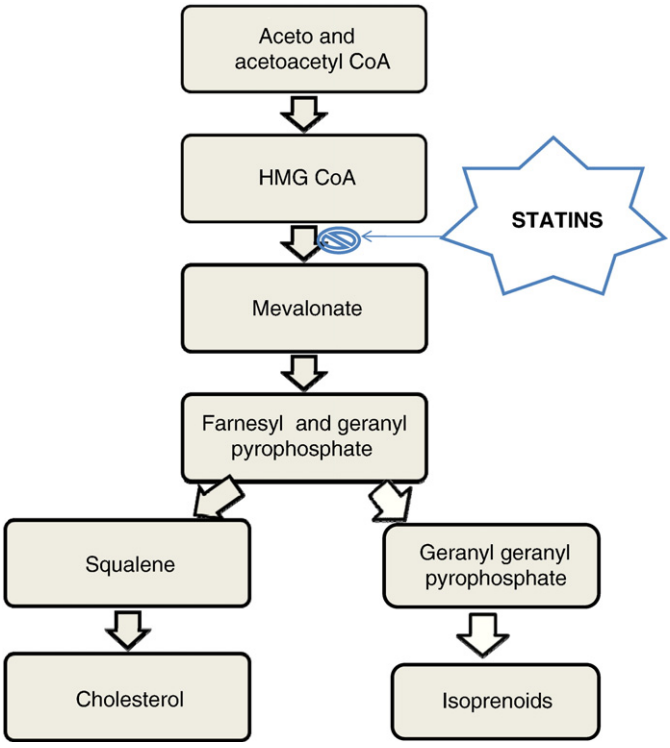

Fig. 1. The HMG-CoA reductase inhibitors or 'statins' prevent the formation of mevalonate and the isoprenoids.

reperfusion injury, a feature which has been widely documented in the experimental literature. The mechanisms underlying this cardioprotective effect and the implications for clinical therapy of patients with CHD will be covered.

2. Experimental cardioprotection using statin therapy

In the late 1990s, the finding that statin therapy was beneficial in terms of improving cardiovascular outcomes resulted in a search for the mechanisms underlying this cardioprotective effect. Using experimental animal models of acute myocardial ischaemia–reperfusion injury, it is possible to examine the effects of statin therapy at different time-points in the course of the acute ischaemia–reperfusion insult. In this section we review the experimental evidence for acute cardioprotection elicited by statin therapy administered prior to the index ischaemic insult. Clearly, the time-point at which the statin treatment is administered has a direct bearing on its potential for clinical application. For example, pre-ischaemic statin treatment would be limited to the clinical settings of planned cardiac surgery and elective PCI procedures in which the timing of the ischaemia can be readily anticipated.

2.1. Statin therapy administered prior to myocardial ischaemia

Initial studies in 1998 suggested that statin therapy may be able to exert direct cytoprotective effects through the upregulation of endothelial nitric oxide synthase (eNOS), a critical non-lipid lowering effect of statin therapy (Laufs et al., 1998). On this background, in 1999, the first experimental animal studies were published demonstrating direct cardioprotective effects elicited by statin treatment. Ueda and colleagues (Ueda et al., 1999) investigated the effects of pravastatin pre-treatment on the response of the hypercholesterolaemic rabbit heart to the endogenous cardioprotective effects of ischemic preconditioning (IPC). Crucially this important study found that the presence of hypercholesterolaemia blunted the cardioprotective benefits of IPC. These authors were able to demonstrate that pravastatin could restore the infarct-limiting effects of IPC in hypercholesterolaemic hearts, and the mechanism underlying this effect was not associated with lipid-lowering and was attributed to the activation of ecto-5'-nucleotidase, an adenosine producing enzyme. Interestingly, in this study, pravastatin given alone without the added stimulus of IPC did not reduce infarct size, suggesting perhaps that a sub-threshold dose of pravastatin had been used. Lefer and colleagues (Lefer et al., 1999) demonstrated that pre-treatment with simvastatin was able to protect isolated perfused normocholesterolaemic rat hearts against acute ischemia–reperfusion injury. The authors reported that the cardioprotective effect was dependent on the presence of neutrophils and resulted from the reduction of the inflammatory response provoked by acute ischaemia–reperfusion injury (see Table 1 for a summary of the experimental studies demonstrating pre-ischaemic cardioprotection with statin therapy).

Subsequent experimental studies have demonstrated pre-ischaemic cardioprotection in the absence of cholesterol-lowering using other statins including rosuvastatin (Ikeda et al., 2003), atorvastatin (Lazar et al., 2003), pitavastatin and cerivastatin (Sanada et al., 2004) and lovastatin (Kocsis et al., 2008). Interestingly, lovastatin has been reported as being protective when given chronically but not when perfused acutely in isolated rat hearts. The acute regime abolished protection from IPC but IPost remained protective, whilst with chronic use lovastatin abolished protection from IPost but IPC was unaffected (Kocsis et al., 2008). The authors postulate that in these scenarios lovastatin reduces coenzyme Q9 and reduces the ability of the myocardium to adapt to ischaemic stress. Simvastatin-induced cardioprotection has been reported in other clinically relevant animal models of disease including atherosclerosis (using the ApoE−/− mice) (Scalia et al., 2001) and type II diabetes (using the Db/Db mice) (Lefer et al., 2001). Many of these studies have also investigated the effect of pre-ischaemic statin therapy when administered in vivo for 1–21 days, exploring a number of different types of cardioprotective mechanisms, and therefore a direct protective effect on the myocardium or at the level of the cardiomyocyte could not be inferred. In this respect, experimental studies have made progress by demonstrating acute cardioprotective effects with statin therapy when administered 20–60 min before or immediately prior to acute myocardial ischaemia–reperfusion injury insult (Kawabata et al., 2001; Tiefenbacher et al., 2003; Sanada et al., 2004). However, other experimental studies have demonstrated cardioprotection in the absence of endothelial cells and systemic factors such as neutrophils in the isolated buffer-perfused heart as well as in cultured human ventricular cardiomyocytes subjected to simulated ischaemia–reperfusion injury (Verma et al., 2004), confirming that statin therapy is able to exert direct cardioprotective effects on the heart at the level of the cardiomyocyte.

An interesting finding by our research group concerning the pre-ischaemic cardioprotective effect elicited by atorvastatin pre-treatment in the rat heart was that chronic treatment with 2 weeks therapy failed to limit-infarct size, although the cardioprotective effect could be re-captured by administering an acute high-dose of atorvastatin immediately prior to IRI (Mensah et al., 2005). This finding was attributed to the down-regulation of the PI3K-Akt signal transduction pathway, a critical cellular protective pathway (see later section). This important finding has clinical implications for CHD patients most of whom are already on chronic statin therapy — the implication being that their current statin treatment regime may not confer cardioprotection against an episode of acute myocardial ischaemia–reperfusion injury, although the beneficial cardioprotective effect may be recaptured by administering an additional high-dose of statin immediately prior to IRI (see later section). However, it must be appreciated that other experimental studies have failed to observe loss of cardioprotection with chronic statin therapy, which may be due to the use of different animal models and experimental technique