

Pharmacological role of atorvastatin in myocardium and smooth muscle progenitor cells

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ABSTRACT

Atorvastatin is a synthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor with a great potency in the reduction of lipids and it has been well documented in both primary and secondary prevention studies. It exhibits pleiotropic properties in both in-vitro and in vivo conditions. Conversely, atorvastatin remain under-utilized in several situations. The main objective of this review is to focuses the pharmacological benefits, pleiotropic properties of the atorvastatin related to smooth muscle proliferation and myocardium.

Keywords: Atorvastatin, Smooth muscle cells, Angiotensin, Myocardium

INTRODUCTION

Smooth muscle cells are essential for the function of vasculature and myocardium. By contraction and relaxation, they modify the luminal diameter, which enables blood vessels to maintain a proper blood pressure. The increased growth potential of vascular smooth muscle cells represents one of the crucial

anomalies responsible for the development of hypertension and atherosclerosis, which leads to cardiovascular disease (CVD).¹ Although effective statins are available, however the prevalence of CVD remains higher.² Atorvastatin therapy is an effective way for reducing cholesterol level, thus could reduce the development of cardiovascular events by decreasing both inflammatory activity and atherogenic lipoprotein.³ Statin

mediated anti-inflammatory effects may contribute to the ability of the atorvastatin could reduce risk of CVD. This review focuses the benefits of atorvastatin related to smooth muscle proliferation and myocardium.

Vascular smooth muscle cells (VSMCs)

Vascular smooth muscle cells (VSMCs) are the cellular components of the normal blood vessel wall that gives structural integrity and manage the diameter by contracting and relaxing dynamically in response to vasoactive stimuli.⁴ VSMCs also involved in the function during vessel remodeling in physiological conditions such as pregnancy, exercise or after vascular injury.⁵

Atorvastatin and smooth muscle proliferation

VSMC are essential for maintaining vasculature homeostasis and function. Several studies have shown that statins attenuate vascular proliferative disease, for example, transplant-associated arteriosclerosis.⁶ Chronic treatment with atorvastatin directly decreases mitogen-induced nuclear Ca²⁺ mobilization.⁷ In aortic smooth muscle cell atorvastatin and mevastatin notably inhibits the mRNA expression of endothelial ET (A) and ET (B) receptors. Furthermore, the specific antagonists of ET (A) and ET (B) receptors significantly inhibited smooth muscle cell proliferation. It has been suggested that endothelial receptors and the mevalonate pathway are involved smooth muscle cell proliferation induced by bFGF.⁸

Bruemmer et al findings revealed that minichromosome maintenance (MCM) proteins play a vital role during the proliferation of vascular smooth muscle cell.⁹ Inhibition of MCM6 and MCM7 expression through the blocking of E2F function may contribute importantly to the inhibition of vascular smooth muscle cell DNA synthesis by atorvastatin. Chandrasekar et al results indicate that the proatherogenic cytokine such as, interleukin-18 (IL-18) induces human coronary artery smooth muscle cell migration in matrix metalloproteinase (MMP-9) dependent manner.¹⁰ Atorvastatin suppress IL-18 mediated aortic smooth muscle cell migration and has therapeutic benefits for attenuating the development of atherosclerosis and restenosis.

Erythropoietin directly stimulates the proliferation of vascular smooth muscle cell. Erythropoietin-induced proliferation in rat VSMCs was inhibited by statins through their inhibition of HMG-CoA reductase activity.¹¹ Lipophilic statins exert direct effects on distal human pulmonary artery smooth muscle cell and are likely to involve inhibition of Rho GTPase signaling.¹² Atorvastatin inhibition of periostin expression induced by transforming growth factor- β (TGF- β 1) in VSMCs may be exerted by inhibition of the production of mevalonate and other isoprene compounds and by blocking the Rho/Rho kinase signaling pathway.¹³

Leptin contributes to the pathogenesis of atherosclerosis. Angiotensin II increases leptin synthesis in cultured adipocytes. Statin decreases the leptin expression in adipocytes and human coronary artery endothelial cells. Angiotensin II induces leptin expression in human VSMCs and atorvastatin can suppress the leptin expression induced by angiotensin II. Rac, reactive oxygen species (ROS) and JNK pathways mediate the inhibitory effect of atorvastatin on angiotensin II-induced leptin expression.¹⁴

Recently, it has been suggested that statins may also modulate VSMC activation by their influence on the rennin-angiotensin system. Ang-(1-7) was identified as a major product of Ang I metabolism in VSMC culture. In this setting tumor necrosis factor alpha (TNF- α) decreases the conversion of Ang I to Ang-(1-7). Interestingly, atorvastatin attenuated the effects of TNF- α on Ang-(1-7) production as well as reversed the influence of TNF- α on angiotensin converting enzyme and angiotensin converting enzyme 2 expressions. Atorvastatin enhancement of ACE2/Ang-(1-7) axis in VSMCs could signify a new and favourable mechanism on cardiovascular action.¹⁵

Atorvastatin and its effects on the myocardium

Cardiac hypertrophy is an adaptive response of the heart to pressure excess. In the myocardium, the small GTP-binding proteins, Rho, Rac, Ras and oxidative stress are concerned in the hypertrophic response.¹⁶ Animal studies have emphasized that a phagocyte-type NADPH oxidase may be a significant basis of ROS in the myocardium.^{17,18} NADPH oxidase-dependent ROS production appears to be involved in cardiac hypertrophy in response to pressure excess, stretch, angiotensin II-infusion and α -adrenergic stimulus.¹⁹⁻²²

Certainly, statins inhibit oxidative stress and cardiac hypertrophy in angiotensin II-induced rodents.²³ This has also been demonstrated in clinical studies where statins inhibit cardiac hypertrophy in hypercholesterolemic patients.²⁴ ROS mediated by NADPH-oxidase are increased in left ventricular myocardium from individuals with heart failure and correlate with an increased activity of Rac1 GTPase and treatment with statin decreases the Rac1 function of the human heart.²⁵ Atorvastatin attenuate lethal reperfusion-induced injury by contingent on the activities of PI3K and Akt as well as the presence and activity of eNOS.²⁶

The Scandinavian Simvastatin Survival Study (4S) suggests that statins reduce the incidence and morbidity of heart failure.²⁷ Patients with heart failure are illustrated by augmented vascular tone as well as endothelial dysfunction, which may be enhanced by statin therapy. Statins have proven to maintain the cardiac function in animal model's heart failure of and myocardial hypertrophy.^{28,29} Chen et al results provide novel in vivo evidence for the key role of Connexin43 gap junctions in

left ventricular hypertrophy and the possible mechanism in the anti-hypertrophic effect of statins.³⁰ These findings recommend that statins have therapeutic benefits in heart failure patients or atherosclerotic heart disease.

CONCLUSION

Atorvastatin exert positive effects through restoring of smooth muscle cells, thus promoting normal vasculature homeostasis. It also improves cardiac function and involved in the enhancement of myocardium, which helps in decreasing the risk of CVD.

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