Pharmacological role of atorvastatin in myocardium and smooth muscle progenitor cells

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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). Although effective statins are available, however the prevalence of CVD remains higher. 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.

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
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. VSMCs also involved in the function during vessel remodeling in physiological conditions such as pregnancy, exercise or after vascular injury.

**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. Chronic treatment with atorvastatin directly decreases mitogen-induced nuclear Ca2+ mobilization. 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.

Bruemmer et al findings revealed that minichromosome maintenance (MCM) proteins play a vital role during the proliferation of vascular smooth muscle cell. Inhibition of MCM6 and MCM7 expression through the blocking of E2F function may contribute importantly to the inhibition of vascular smooth muscle cellDNA 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 matrixmetalloprotease (MMP-9) dependent manner. 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. Lipophilic statins exert direct effects on distal human pulmonary artery smooth muscle celllare are likely to involve inhibition of Rho GTPase signaling. Atorvastatin inhibition of peristin expression induced by transforming growth factor-β (TGF-β1) 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. 

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.

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.

**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. Animal studies have emphasized that a phagocyte-type NADPH oxidase may be a significant basis of ROS in the myocardium. NADPH oxidase-dependent ROS production appears to be involved in cardiac hypertrophy in response to pressure excess, stretch, angiotensin II-infusion and adrenergic stimulus.

Certainly, statins inhibit oxidative stress and cardiac hypertrophy in angiotensin II-induced rodents. This has also been demonstrated in clinical studies where statins inhibit cardiac hypertrophy in hypercholesterolemic patients. 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. Atorvastatin attenuate lethal reperfusion-induced injury by contingent on the activities of PI3K and Akt as well as the presence and activity of eNOS.

The Scandinavian Simvastatin Survival Study (4S) suggests that statins reduce the incidence and morbidity of heart failure. 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. 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. 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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REFERENCES

1. Hadrava V, Kruppa U, Russro RC, Lacourciere Y, Tremblay J, Hamlet P. Vascular smooth muscle cell proliferation and its therapeutic modulation in hypertension. Am Heart J. 1991;122(4):1198-203.
2. Anand VA, Muneeb M, Divya N, Senthil R, Abdul Kapoor MM, Gowri J, et al. Clinical significance of hypertension, diabetes and inflammation, as predictor of cardiovascular disease. Int J Biol Med Res. 2011;2(1):369-73.
3. Anand VA, Cheniappan M, Kalavathy S, Uma K, Saravanan MP, Kumar SP. Redeeming measures of atorvastatin in the risk factors of cardiovascular diseases. International Journal of Pharmacology. 2008;4(4):305-9.
4. Metz RP, Patterson JL, Wilsn E. Vascular smooth muscle cells: isolation, culture, and characterization. Methods Mol Bio. 2012;843:169-76.
5. Keyes LE, Moore LG, Walchak SJ, Dempsey EC. Pregnancy stimulated growth of vascular smooth muscle cells: importance of protein kinase C-dependent synergy between estrogen and patelet-derived growth factor. J cell physiol. 1996;166(1):22-32.
6. Braun-Dullaeus RC, Mann MJ, Dzau VJ. Cell cycle progression: new therapeutic target for vascular proliferative disease. Circulation. 1998;98:82-9.
7. Wamhoff BR, Dixon JL, Sturek M. Atorvastatin treatment prevents alterations in coronary smooth muscle nuclear Ca2+ signaling in diabetic dyslipidemia. J Vasc Res. 2002;39(3):208-20.
8. Xu CB, Stenman E, Edvinsson L. Reduction of bFGF-induced smooth muscle cell proliferation and endothelin receptor mRNA expression by mevastatin and atorvastatin. Biochem Pharmacol. 2002;64(3):497-505.
9. Bruemmer D, Yin F, Liu J, Kiyono T, Fleck E, Van Herle A, Graf K, Law RE. Atorvastatin inhibits expression of minichromosome maintenance proteins in vascular smooth muscle cells. Eur J Pharmacol. 2003;462(1-3):15-23.
10. Chandrasekar B, Mummidii S, Mahimainathan L, Patel DN, Bailey SR, Imam SZ, et al. Interleukin-18-induced human coronary artery smooth muscle cell migration is dependent on NF-κappaB and AP-1-mediated matrix metalloproteinase-9 expression and is inhibited by atorvastatin. J Biol Chem. 2006;281(22):15099-109.
11. Kaneda T, Tsuruoka S, Fujimura A. Statins inhibited erythropoietin-induced proliferation of rat vascular smooth muscle cells. Eur J Pharmacol. 2010;649(1-3):38-43.
12. Ali OF, Gowercott EJ, Butrous GS, Wharton J. Pleiotropic effects of statins in distal human pulmonary artery smooth muscle cells. Respir Res. 2011;12:137.
13. Li J, Yan W, Wang J, Tan W, Zhou Y, Yang K. Roles of periostin in proliferation and migration of vascular smooth muscle cells and the effect of atorvastatin on them. Zhong Nan Da XueXueBao Yi Xue Ban. 2012;37(7):689-94.
14. Shyu KG, Chen SC, Wang BW, Cheng WP, Hung HF. Mechanism of the inhibitory effect of atorvastatin on leptin expression induced by angiotensin II in cultured human coronary artery smooth muscle cells. Clin Sci (Lond). 2012;122(1):33-42.
15. Suski M, Gebksa A, Olszanecki R, Stachowicz A, Uraz D, Madej J, et al. Influence of atorvastatin on angiotensin I metabolism in resting and TNF-α-activated rat vascular smooth muscle cells. J Renin Angiotensin Aldosterone Syst. 2013;15(4):378-83.
16. Thorburn J, Xu S, Thorburn A. MAP kinase-and Rho-dependent signals interact to regulate gene expression but not actin morphology in cardiac muscle cells. EMBO J. 1997;16:1888-900.
17. Aikawa M, Rabkin E, Sugiyama S, Voglic SJ, Fukumoto Y. An HMG-Co-A reductase inhibitor, cerivastatin, suppresses growth of macrophages expressing matrix metalloproteinases and tissue factor in vivo and in vitro. Circulation. 2001;103:276-83.
18. Bendall JK, Cave AC, Heymes C, Gall N, Shah AM. Pivotal role of a gp91 (phox)-containing NADPH oxidase in angiotensin II-induced cardiac hypertrophy in mice. Circulation. 2002;105:293-6.
19. Li JM, Gall NP, Grieve DJ, Chen M, Shah AM. Activation of NADPH oxidase during progression of cardiac hypertrophy to failure. Hypertension. 2002;40:477-84.
20. Aikawa R, Komuro I, Yamazaki T, Zou Y, Kudoh S, Zhu W, et al. Rho family small G proteins play critical roles in mechanical stress-induced hypertrophic responses in cardiac myocytes. Circ Res. 1999;84:458-66.
21. Nakagami H, Jensen KS, Liao JK. A novel pleiotropic effect of statins: prevention of cardiac hypertrophy by cholesterol-independent mechanisms. Ann Med. 2003;35:398-403.
22. Xiao L, Pimentel DR, Wang J, Singh K, Colucci WS, Sawyer DB. Role of reactive oxygen species and
NAD (P) H oxidase in alpha (1)-adrenoceptor signaling in adult rat cardiac myocytes. Am J Physiol Cell Physiol. 2002;282:C926-34.

23. Node K, Nakagami H, Liao Y, Grimm M, Takemoto Y, Kitakaze M, et al. Statins as antioxidant therapy for preventing cardiac myocyte hypertrophy. J Clin Invest. 2001;108:1429-37.

24. Lee TM, Chou TF, Tsai CH. Association of pravastatin and left ventricular mass in hypercholesterolemic patients: role of 8-iso-prostaglandin f2alpha formation. J Cardiovasc Pharmacol. 2002;40:868-74.

25. Maack C, Kartes T, Kilter H, Schafers HJ, Nickenig G, Bohm M, Laufs U. Oxygen free radical release in human failing myocardium is associated with increased activity of rac1-GTPase and represents a target for statin treatment. Circulation 2003;108:1567-74.

26. Bell RM, Yellon DM. Atorvastatin, administered at the onset of reperfusion, and independent of lipid lowering, protects the myocardium by up-regulating a pro-survival pathway. J Am Coll Cardiol. 2003;41(3):508-15.

27. Kjekshus J, Pedersen TR, Olsson AG, Faergeman O, Pyorala K. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. J Card Fail. 1997;3:249-54.

28. Drexler H. Endothelium as a therapeutic target in heart failure. Circulation. 1998;98:2652-5.

29. Laufs U, Kilter H, Konkol C, Wassmann S, Bohm M, Nickenig G. Impact of HMG CoA reductase inhibition on small GTPases in the heart. Cardiovasc Res. 2002;53:911-20.

30. Chen HJ, Yao L, Chen TG, Yu M, Wang LH, Chen JZ. Atorvastatin prevents connexin43 remodeling in hypertrophied left ventricular myocardium of spontaneously hypertensive rats. Chin Med J (Engl). 2007;120(21):1902-7.

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