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Full Length Review Article

EFFECTS OF STATINS ON ENDOTHELIAL FUNCTION IN CORONARY ARTERY DISEASE

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ABSTRACT

Cardiovascular Diseases (CVD) are currently the leading cause of death globally for both men and women accounting for 21.9 per cent of total deaths and is projected to increase to 26.3 per cent by 2030. Statins are the treatment of choice for the primary and secondary prevention of cardiovascular disease and in the management of hypercholesterolemia because of their proven efficacy and safety profile. Evidences showed their effectiveness in reduction of cholesterol synthesis and number of pleiotropic effects, which may be cholesterol dependent and cholesterol independent. The present review focus on the origin, properties and effects of statins on endothelial function (non lipid action of statins) through the increase of endogenous production of NO in different pathways.

INTRODUCTION

Coronary artery disease (CAD) is the most common type of multifactorial chronic heart disease. It is a consequence of plaque buildup in coronary arteries. The arterial blood vessels, which begin out smooth and elastic become narrow and rigid, curtailing blood flow resulting in deprived of oxygen and nutrients to the heart (Stoneman *et al*., 2004). CAD is a leading cause of morbidity and mortality throughout the worldwide. The prevalence of biological and metabolic risk factors were also found to be high in development of coronary artery disease. Patients with hypercholesterolemia are at increased risk to experience cardiovascular events and to die from vascular disease (Reilly *et al*., 2008). Statins, among the most commonly prescribed drugs worldwide, are cholesterol let downing agents used to manage cardiovascular and coronary heart diseases and to treat hypercholesterolemia. Statin therapy markedly reduces the relative incidence of acute coronary events in patients with coronary artery disease (Weissert, 2012; Bonettia *et al*., 2003). Although statins are approved only for the treatment of lipid disorders, there is increasing evidence that they may be useful in the treatment of other conditions, such as Alzheimer's disease, osteoporosis, cancer etc. However statins not only lower cholesterol, but also have been reported to exhibit pleiotropic effects (Davignon, 2004).

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Statin Pharmacology

History and Properties of Statins

Dr. Akira Endo and Masao Kuroda of Tokyo, Japan were the pioneers in the discovery of statins. The isolated prototype agent was "compactin" (Mevastatin ML-23613) from the fungus "penicillin citrinum" (in japan 1976) and the first commercially marketed statin was lovastatin (Mevinolin MK 803) extracted from "Aspergillus terreus " by Merck in 1978 (Jeger and Dieterle, 2012). Clinical relevance to Endo's discovery was accomplished by the studies of Joseph Goldstein and Michael Brown, who discovered a cellular receptor for LDL (LDL-R), received the noble prize in 1985 (Villegas *et al*., 2011). Statins can be classified as First, Second and Third generation based on their clinical efficacy. First generation statin drugs include Lovastatin (Fungal derivative), Simvastatin, Pravastatin (Semi synthetic products) have similar chemical structures containing a substituted decalin ring structure. These statins have lowest potency and 40-80 mg doses of (daily) causes 30% reduction in LDL cholesterol levels (Baker and Imtiaz, 2008).

Second-generation statin drugs comprise Fluvastatin, Atorvastatin, Cerivastatin have imporved efficacy are structurally dissimilar synthetic compounds containing fluorophenyl groups linked to the HMG-like moiety and 10-20 mg doses of these statins causes more than 30% reduction in LDL cholesterol levels (Baker and Imtiaz, 2008). Rosuvastatin a single third generation synthetic drug has high potency and its unique chemical characteristics provides the enhanced potency against HMG-COA reductase. The currently six statins approved for prescription are Fluvastatin, Rosuvastatin, Lovastatin, Pravastatin, Simvastatin and Atorvastatin. Cerivastatin was withdrawn from the market in 2001 due to side effects like rhabdomyolysis (Jeger and Dieterle, 2012).

Pharmacokinetic and Pharmacodynamic properties of statins

Statins have differences in pharmacokinetic properties such as absorption, distribution, metabolism and excretion. Some statins (lovastatin, simvastatin) are administered as lactone prodrugs and some are (atorvastatin, rosuvastatin) active at initial and metabolic intermediate stages, while for others, only the parent compound is active (fluvastatin, pravastatin) (Baker and Imtiaz, 2008). All statins undergoes a passive intestinal absorption following administration and subsequently are taken up from the bloodstream into the liver by members of the solute carrier transporter family. Pravastatin and rosuvastatin are hydrophilic and requires active transport to be taken up by the cells. The liver is the site for primary metabolism of statins and also the site for the pharmacodynamic action of statins as it is the organ of primary cholesterol biosynthesis and to some extent statin metabolism also occurs in the kidney.

The cytochrome P450 (CYP) enzyme system of liver plays an important part in the metabolism of the statin (Williams and Feely, 2002). With the exception of pravastatin, all five statins undergo extensive microsomal metabolism by CYP enzymes while Pravastatin is transformed enzymatically in the liver cytosol (Quion and Jones, 1994) . Statins with low systemic bioavailability (i.e., lovastatin and simvastatin) exhibit a greater increase in serum levels when the activity of cytochrome P450 is slowed or inhibited compared with higher bioavailabilities (i.e., fluvastatin). Statins do not differ in their pharmocodynamic property (i.e., their site of action) and all statins function similarly by selectively binding to the active site of hydroxymethylglutaryl co-enzyme A (HMG-CoA) reductase enzyme (Baker and Imtiaz, 2008). Statins also vary in half-life, systemic exposure, maximum plasma concentration, bioavailability, protein binding, lipophilicity, metabolism, and excretion rates. Genetic variation in the genes of statin metabolism and/or of lipid metabolism including cholesterol biosynthesis, may affect the pharmacokinetics and pharmacodynamics of the drug.

Mechanism of Action

Statins mechanism of action is selective, the portion of the statin structure attributed to enzyme inhibition is an HMG mimic specifically competing with HMG-CoA for the catalytic site (HMGCoA-R) and reversibly binds to the enzyme's active site (Weissert, 2012). This competition inhibits the metabolic pathway of HMG-CoA into mevalonate, a precursor molecule for the synthesis of cholesterol and other important lipid moiety molecules such as the isoprenoids, Farnesyl Pyrophosphates (FPP) and Geranyl Pyrophosphates (GPP) which are useful for post-translational modification of a variety of proteins that play a crucial role in the regulation of cell growth and differentiation, gene expression, cytoskeletal assembly and cell motility, protein and lipid trafficking, nuclear transport, inflammation and host defense (Baker and Imtiaz, 2008). Most of the mevalonate pathway products like cholesterol, heme A, dolichols and ubiquinones or coenzyme Q10, prenylated proteins, and geranylgeranylpyrophosphate (GGPP) utilizes Farnesyl pyrophosphate (FPP) as their precursor molecule. Activation of various intracllular proteins require FPP and GGPP. For this activation step farnesyl or geranylgeranyl moieties are coupled to the protein resulting in a farnesylated or geranylgeranylated protein. These reactions are catalyzed by farnesyl transferase and geranylgeranyltransferase. This type of protein activation is referred to as (iso) prenylation.

Signalling proteins (heterotrimeric G proteins & small G proteins) such as Ras, transducin c, rhodopsin kinase and Rho are dependent on prenylation for their activities like cell growth and apoptosis while farnesylated Ras involves in cell growth and differentiation. Statins block the mevalonate pathway leading to disruption of Ras activation, prenylation mediated by Ras, Rho GTPase family proteins, heme A, nuclear lamina, gamma subunit of G-proteins, small guanosine triphopshate (GTP) -binding Ras-like proteins, such as Rab, Rac, Ral and Rap (Mcfarlane *et al*., 2002; Weis *et al*., 2002). Statins with nanomolar concentration can effectively replace the HMG-CoA, a natural substrate for the HMG-CoA reductase enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis which binds at micro molar concentrations (Stancu *et al*., 2001). The resultant reduction in hepatocyte cholesterol concentration triggers increased expression of hepatic LDL receptors, which clear LDL and LDL precursors from the circulation. Statins reduces the cholesterol levels in serum depending on its dosage and it is independent of the hydrophilicity or lipophilicity (Villegas *et al*., 2011). To a lesser extent, statins also lower the levels of very low-density lipoproteins (VLDL) mainly by inhibiting the production of apolipoprotein B in the liver and increase the levels of high-density lipoproteins (HDL) .

Pleiotropic Effects of Statins

Statins prevent the cholesterol biosynthesis and also presents a number of other activities, collectively known as pleiotropic effects in which some are considered as Lipid actions and some are Non lipid actions like reduction activity on platelet activation, coagulation, vascular smooth muscle cell proliferation, endothelin, MMPS, macrophages, inflammation, immunomodulation, reactive oxygen species and improves endothelium function, NO bioactivity and other effects like - decrease in frequency of type II diabetes, blood pressure, allograft rejection, reverting of tumor cells, osteoporosis and risk of fracture which increases the quality life of the patient (Tandon *et al*., 2005; Mason, 2003). The present review is focused on the role of statins in improving the endothelial function.

Endothelial dysfunction and statins (Non-Cholesterol Dependent Effects of Statins)

Endothelium is a single cell layer of simple squamous epithelial cells that lines the heart, the blood and lymph vessels and the serous cavities of the body. It acts as a mechanical barrier between the blood and vessel wall, highly vascular, heals quickly, and is derived from the mesoderm. It serves as an important autocrine and paracrine organ and plays an important role in regulation of various functions of the vasculature such as vasomotion and cell adhesiveness, coagulation, blood flow regulation by producing a number of biochemical mediators with vasodilatory or vasoconstrictive properties. The endothelial cell is responsible for remodeling of the arterial vessel wall in atherosclerosis. It prevents toxic, blood-borne substances from penetrating the smooth muscle of the blood vessel (Schachinger and Zeiher, 2002). To control vasomotor tone the endothelium releases a variety of substances such as prostacyclin, vasoconstrictors-thromboxane, endothelin, hyperpolarizing factor and most importantly, nitric oxide (NO).

No is a small molecule having a molecular weight of 30 Daltons, synthesized from oxidation of L-arginine by a family of nitric oxide synthase (NOS) enzymes in which three isoforms have been identified: two constitutive, the neuronal NOS (nNOS, NOS-1) and endothelial (eNOS, NOS-3), and one inducible NOS (iNOS, NOS-2.). NO has anti platelet, anti-inflammatory and antioxidant properties. It regulates the vascular tone, acts as a neurotransmitter in the brain, and a cytotoxic agent that targets tumor cells. Reduction in the production of nitric oxide is the first step for the occurrence of many diseases**.** Endothelial cells are damaged, if atherogenic factors are unchecked, leading to endothelial dysfunction allowing lipids and toxins to penetrate the endothelial layer, a first sign in the atherosclerosis process (Antoniades *et al*., 2005; Nishevitha *et al*., 2009; Landmesser *et al*., 2004). Endothelial dysfunction is a systemic pathological state of the endothelium in which there is an imbalance between endothelium-derived relaxing factors (e.g. nitric oxide and prostacyclin) and endothelium-derived constricting factors (e.g. thromboxane A2, prostaglandin H2, endothelin-1 and angiotensin II). It is characterized as the decreased synthesis, release, and/or activity of endothelial-derived nitric oxide (Yao *et al*., 2010).

Endothelial nitric oxide synthase (eNOS), plays a key role in vasoregulation as well as in other important physiological processes such as angiogenesis (Nishevitha *et al*., 2009). Statins have beneficial effect on vascular endothelium and improves the endothelial function in patients with hypercholesterolemia and atherosclerosis through cholesterol dependent and independent pathways and also promotes cardioprotective effects via anti-oxidant, anti-inflammatory, anti-thrombotic as well as beneficial plaque-modifying effects and show an immediate inhibition of smooth-muscle cell proliferation and stimulation of re-endothelialisation (Weis *et al*., 2002). Statins could upregulate eNOS in three different mechanisms (Meda *et al*., 2010). The first pathway comprises the Rho/ Rock signaling through which statin increase the stability of eNOS m RNA and subsequent increase in eNOS expression. Based on dose dependent manner statin suppress the pro atherogenic Rho/ ROCK pathway and also blocks the HMG Co. A reductase, resulting in arresting the formation of isoprenoid intermediates such as farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP). These isoprenoid intermediates are important for membrane translocation and activation of small guanosine triphosphate (GTP) binding proteins, including Rho, Ras, and Rac. Small G proteins are monomeric proteins with a low molecular weight of 20-40 Daltons and have intrinsic GTP-hydrolyzing activity along with other functions like regulation on endothelial function, proliferation, contraction and migration of smooth muscle cells as well as cardiomycocyte hypertrophy. More than 100 small G proteins have been identified and comprise a superfamily (Nohriaa *et al*., 2009). They are structurally divided into five subfamilies shown as in (Table 1). Rho and its downstream effector, Rho kinase (ROCK), play an important role in regulating the actin cytoskeleton and thereby affect intracllular transport, gene transcription, messenger RNA expression and stability.

Table 1: Five subfamilies of small 'G' proteins

Sl no	Family	Sub family proteins
1	Ras	Ras,Rap, Rad, Ral, Rin, Rit
2	Rho	Rho, Rac, Cdc42, and Rnd
3	Rab	Rab
4	Sar1/ADP ribosylation factor	Arf, Arl, Ard, and Sarl
5	Ran	Ran

Direct repression of Rho or ROCK is anti-atherogenic by improving e NOS synthesis , decreasing the vascular smooth muscle cell contraction and proliferation, cytokine formation and inflammatory cell trafficking reducing thrombogenicity of the vessel wall. Statins repeats these vascular benefits of selective Rho/Rock inhibitors in vitro via inhibition of Rho. The main targets of statins are Ras and Rho. In endothelial cells, Ras translocation from the cytoplasm to plasma membrane requires farnesylation, whereas gerenalgeranylation is required for Rho translocation. Statins inhibit the isoprenylation leading to accumulation of inactive forms of both these proteins in cytoplasm resulting to eNOS upregulation. Indeed, small G-proteins Rho and Rac influence eNOS expression and NO availability. Rho negatively regulates eNOS expression and Rac contributes to NAD (P) H-oxidase activation and superoxide production, which inactivates NO (Noma *et al*., 2006). The Rho associated Kinases (ROCKs) are important regulators of cell growth, migration, and apoptosis were known to be one of the first downstream targets of Rho A. Statins decrease the synthesis of the Rho A/ ROCK. The indirect inhibition of the Rho/ ROCK pathway by statins as well as the direct inhibition of ROCKs by ROCK inhibitors leads to increased eNOS expression and eNOS activity by stabilization of eNOS m RNA or phosphorylation of eNOS respectively. Thus RhoA/ ROCK inversely regulates eNOS expression through alteration in e NOS m RNA stability. Inhibition of Rho A or ROCK leads to the rapid activation of PI3/Akt and phsophorylation of eNOS (Noma *et al*., 2006).

A second important mechanism by which statin activates NOS is mediated via activation of the pI3/Akt pathway (Bonettia *et al*., 2003; Noma *et al*., 2006). Akt kinase (serine –threonine kinase) plays a central role in control of events like cell proliferation, cell viability. The akt is a part in PI3 kinase

signaling pathway, inhibits proapoptotic factors and is a potential therapeutic target. Phosphotidylinositol 3 kinases (PI3Ks) are hetero dimeric complexes composed of regulatory and catalytic subunits that recruit lipids as second messengers and control a different type of cellular functions including survival, growth and metabolism. Statins rapidly promotes the activation of Akt in endothelial cells leading to eNOS phosphorylation and increased angiogenesis. Statins prevents hypoxia-induced down regulation of eNOS in human endothelial cells by stabilizing eNOS m RNA leads to an increase in NO production by these cells. A third mechanism through which statin regulates eNOS is through their effects on Caveolin 1. The plasma membrane have discrete regions called caveolae consists cholesterol as a major component. Caveolin a structural protein of caveolae plays an important role in organizing the signaling proteins and lipids in microdomains. In cardiovascular system caveolae regulates eNOS by N-Terminal myristolylation, palmitoylation and forms an inhibitory complex with caveolin-1 leads to decrease in activity of enzyme in the cells. Transcription of Cav-1 gene is regulated by cholesterol responsive elements. Exposure of fibroblast and endothelial cells to free cholesterol and LDL Cholesterol was found to up regulate Cav-1 expression. Ca^{+2} mobilizing agents cause disinhibiton of eNOS by promoting Ca^{+2}/ Calmodulin triggered dissociation of Cav-1. Statin down regulates Cav-1 in endothelial cells by blocking the cholesterol synthesis, a favorable effect on vascular function may partly mediated by interruption of the e NOS/ Cav-1 complex (Suciu, 2009).

Conclusion

In summary, accumulating evidence from various research and clinical trials indicates that Statins have pleiotropic effect, and improves the endothelial function through the increase of endogenous production of NO in different pathways.

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