Research Article

Simvastatin: A Hopeful Promise for Treatment of Retinopathy and Neuropathy in Diabetic Patients

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ABSTRACT

Diabetes, a metabolic disorder diagnosed by hyperglycemia, is as a result of defects in insulin secretion, insulin action, or both. The most common complication of diabetes is neuropathy, which happened for more than 50% of diabetic patients. Diabetic peripheral neuropathy (DPN) is a disorder diagnosed by demyelination, axonal atrophy, blunted regenerative potential, and loss of peripheral nerve fibers. The exact mechanism of this disorder is still unknown. Diabetic retinopathy (DR) is another major complication of diabetes which eventually causes blindness. The exact mechanism of this disorder has not been understood yet. According to past studies, activation of ERK in MAPK signaling pathway increases in DPN. As well as it was shown that increased expression of JNK leads to DR. Simvastatin as a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor has showed a beneficial effect on both DPN and DR. In this hypothesis, we propose that mechanism of simvastatin in DPN is decreasing phosphorylated ERK (pERK) via different ways and in DR is decreasing JNK via WNT signaling pathway.

Keywords: Diabetic peripheral neuropathy, Diabetic retinopathy, Simvastatin

INTRODUCTION

Nowadays one of the fastest growing epidemics is diabetes. Diabetes, a metabolic disorder diagnosed by hyperglycemia, is as a result of defects in insulin secretion, insulin action, or both[1]. Type 1 diabetes mellitus (T1DM) is an autoimmune disease in which β cells of pancreas destroy and leads to insulin deficiency. In the other types of diabetes mellitus, type 2, (T2DM) cells cannot uptake insulin, leads to insulin resistance. As well as insulin deficiency could be seen in T2DM. T1DM would be happened in earlier age but the onset of T2DM is usually in older age, although this type of diabetes could be happened in young adults. About 90% of diabetic patients have type 2[2]. This disease can lead to several complications like hypertension, neuropathy, proliferative retinopathy and diabetic nephropathy[3]. The most common complication of diabetes is neuropathy, which happened for more than 50% of diabetic patients[4]. Diabetic peripheral neuropathy (DPN) is a disorder diagnosed by demyelination, axonal atrophy, blunted regenerative potential, and loss of peripheral nerve fibers. DPN increased morbidity and mortality. The exact mechanism of this disorder is still unknown. Some studies suggested that the reason of DPN is hyperglycemia. Enhanced polyol pathway, increased oxidative stress, increased nonenzymatic glycation of structural proteins, altered protein kinase C activity as well as poly ADP-ribose polymerase activation are some mechanisms suggested as a mechanisms of hyperglycemia leads to DPN[5]. Diabetic retinopathy (DR) is another major complication of diabetes which eventually causes blindness. The exact mechanism of this disorder has not been understood yet[6]. Formation of microaneurysms, thickening of capillary basement membrane, and loss of microvascular pericytes are the pathogenesis of DR. The other complications of DR include progressive microvascular permeability and increased microvascular closures which lead to ischemia and tissue hypoxia[7]. Recently, the most important treatment to prevent onset or progression of DR is controlling glycemia, blood pressure, and serum lipid levels[8]. Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors that have been widely used as cholesterol-lowering agents especially for prevention of cardiovascular diseases[9]. Some studies have shown simvastatin (SIM) improves diabetic peripheral neuropathy[10, 11] and diabetic retinopathy[7, 12, 13] via different mechanisms. According to past studies, activation of ERK in MAPK signaling pathway increases in DPN[5, 14]. As well as Oshitari *et al.* had shown that increased expression of JNK leads to DR(6). SIM has showed a beneficial effect on both DPN and DR[10, 12, 13]. In this hypothesis, we propose that mechanism of SIM in DPN is decreasing phosphorylated ERK (pERK) via different ways and in DR is decreasing JNK via WNT signaling pathway.

Detailed Hypothesis

Figs. 1 and 2 show our detailed hypothesis. SIM can decrease pERK in three ways of MAPK signaling pathways: 1) inhibits conversion of Mevalonic acid to isoprenoids, which is needed for RAS to anchorage in membranes[15] Thereby signaling of RAS disturbs and leads
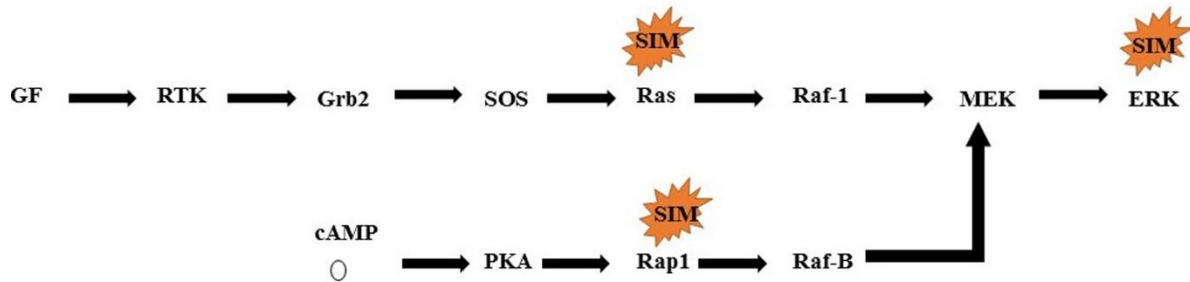
Figure 1: Simvastatin mechanism of action on diabetic peripheral neuropathy.

Figure 2: Simvastatin mechanism of action on diabetic peripheral retinopathy.

Figure 3: Simvastatin mechanism of action on diabetic peripheral neuropathy as for Ohsawa et al study (11)

to cascading decreases in Raf-1, MEK, and pERK. 2) As well as, SIM decreases geranylgeranylation of RAP1[16] which leads to decrease in activated Rap1 and then decrease in Raf-B, MEK, and activated ERK. 3) Beside, SIM itself can directly decrease pERK[9]. Several studies showed that "the activation of RhoA proteins appears to be a common component of the pathogenesis of diabetic complications"[11]. RhoA is one of the WNT signaling pathway members. WNT proteins induce morphological changes in responding cells. There are three different WNT pathways, the canonical pathway, the planar cell polarity pathway and the Wnt/Ca2+ pathway[17, 18]. By inhibiting of RhoH activity[19] in planar cell polarity, JNK decreases. Hereon SIM can be used to treat DR.

DISCUSSION
One of the classes of lipid-lowering agents is statins which have been used in coronary heart disease to reduce morbidity and mortality. Statins also showed pleiotropic effects. Their pleiotropic effect is in translocation of small GTP-binding proteins like Ras, Rho, Rab, Rac, Ral, and Rap from cytosol to plasma membrane[11, 16, 20]. Some studies have shown a beneficial effect of SIM in DPN and DR[10, 12, 13]. Ohsawa *et al.* demonstrated the beneficial effect of SIM on DPN via RhoA/ROCK pathway. They believed that while the spinal expression of eNOS (endothelial nitric oxide synthetase) was decreased in diabetic mouse, inhibiting of RhoA by SIM leads to increasing amount of eNOS up to normal range (Fig. 3)[11].

Kowluru *et al.* showed activation of H-RAS can lead to increasing in apoptosis of retinal endothelial cells in diabetic patients' eyes. They believed that SIM is good for DR via inhibiting membrane translocation of H-Ras[13]. Conversely, Sen *et al.* believed one of the risk factors of DR is hypercholesterolemia. Hence, SIM can be used for treatment of DR[12]. Another study demonstrated SIM prevents progression of DR. because of its increasing effect on endothelial progenitor cells. Endothelial progenitor cells are lineage-specific stem cells which play

a biomarker role for retina cells. They also showed that the other mechanism in which SIM could prevent progression of DR is its effect on amount of blood NO. The level of NO serum decreased in rat with DR. SIM treatment increased it[7].

CONFLICT OF INTEREST STATEMENT
There is no conflict of interest.

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