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Review article
Pregledni članak

INHIBITION OF CHOLESTEROL BIOSYNTHESIS IN HYPERCHOLESTEROLEMIA – IS IT THE RIGHT CHOICE?

INHIBICIJA BIOSINTEZE HOLESTEROLA U HIPERHOLESTEROLEMIJI – DA LI JE PRAVI IZBOR?

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Summary: Cholesterol biosynthesis is a complex pathway comprising more than 20 biochemical reactions. Although the final product created in the pathway is cholesterol, the intermediate products, such as ubiquinone and dolichol, also provide vital metabolic functions. Statins are HGM-CoA reductase inhibitors that stop the production of cholesterol by directly inhibiting the mevalonate production. Mevalonate is a precursor of two additional vital molecules, squalene and ubiquinone (coenzyme Q10). We hypothesized that inhibiting the cholesterol biosynthesis with statins for an extended duration may potentiate the oxidative stress, neurodegenerative disease and cancer. Our recommendation was to measure muscle enzymes, antioxidant capacity, and ubiquinone to monitor patients receiving the statins for prolonged periods of time.

Keywords: cholesterol, ubiquinone, statins

Kratak sadržaj: Biosinteza holesterola je kompleksan metabolički put koji obuhvata više od 20 biohemijskih reakcija. Iako je konačan proizvod koji nastaje holesterol, intermedijerni proizvodi, kao što su ubihinon i dolihol, takođe obezbeđuju vitalne metaboličke funkcije. Statini su inhibitori HMG-KoA reduktaze koji zaustavljaju produkciju holesterola direktnom inhibicijom produkcije mevalonata. Mevalonat je prekursor dva dodatna vitalna molekula, skvalena i ubihinona (koenzim Q10). Postavili smo hipotezu da produženo trajanje inhibicije biosinteze holesterola statinima može da potencira oksidativni stres, neurodegenerativne bolesti i kancer. Takođe preporučujemo određivanje mišićnih enzima, antioksidativnog kapaciteta i ubihinona u praćenju pacijenata koji primaju statine u dužem vremenskom periodu.

Ključne reči: holesterol, ubihinon, statini

Introduction

Cholesterol is the principal sterol in the human body and contributes to numerous structural and metabolic functions. Cholesterol is the main component of cell membranes and lipoproteins, and is a precursor for steroid hormones, bile acids, and vitamin D. Similar to other lipids, cholesterol is obtained from food sources. The presence of cholesterol in the human body is essential. Virtually all tissues, but mainly the liver, adrenal cortex, guts, and reproductive tissues, synthesize cholesterol.

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Cholesterol biosynthesis comprises more than 20 enzymatically catalyzed reactions and occurs in four main stages. In the first stage, acetyl-CoA molecules form a six-carbon molecule called mevalonate. In the second stage, mevalonate is converted to activated isoprene units, which are subsequently (stage 3) polymerized to form squalene. In the fourth and final stage, cyclization of squalene forms the steroid nucleus and an additional series of changes leads to formation of cholesterol (1, 2).

The first-stage reaction is clinically relevant, as it the target of certain anti-hyperlipidemia drugs. In the first step, two acetyl-CoA molecules condense to form acetoacetyl-CoA. Subsequently, a third acetyl-CoA condenses with the acetoacetyl-CoA to yield 3-hydroxyl 3-methylglutaryl CoA (HMG-CoA). HMG-CoA is then converted to mevalonate by HMG-CoA reductase. Conversion of HMG-CoA to mevalonate is the

rate-limiting step in the cholesterol biosynthesis, and the primary statin target.

In the second stage, mevalonate is converted to isopentenyl pyrophosphate (IPP). IPP units condense to form geranyl pyrophosphate (GPP) and then farnesyl pyrophosphate (FPP). In addition to cholesterol biosynthesis, the isoprene products perform many vital functions discussed in more details herein.

Despite its numerous beneficial structural and metabolic functions, elevated cholesterol levels are a significant risk factor of coronary artery disease. Thus, inhibiting the cholesterol biosynthesis is widely accepted as a method for treating the hypercholesterolemia, and numerous drugs have been developed to inhibit the enzymes at different steps during cholesterol biosynthesis.

Inhibition of Cholesterol Biosynthesis by Statins

Statins comprise a group of drugs (simvastatin, lovastatin, mevastatin, atorvastatin, pravastatin) that inhibit cholesterol biosynthesis. These drugs selectively inhibit the rate-limiting enzyme of the cholesterol biosynthesis, HGM-CoA reductase, thereby, lowering the blood cholesterol levels. However, statins do not inhibit the enzyme completely. They inhibit roughly 45% to 95% of HGM-CoA reductase activity depending on the dose and the type of statins used (3). HGM-CoA reductase exerts its effects during the first stage of cholesterol biosynthesis, and thus inhibition of HGM-CoA reductase inhibits all of the metabolically active intermediate molecules produced during the stages 2–4 of the cholesterol biosynthesis pathway.

Hypothesis

We hypothesized that HGM-CoA reductase is not the most appropriate inhibitory target for lowering the blood cholesterol levels, particularly for an extended duration. Doing so in a large population which meets the criteria for hypercholesterolemia may trigger serious diseases in many otherwise healthy individuals.

Cholesterol synthesis is a multi-step reaction, requiring 20 different enzymes to complete the pathway. All of these enzymes catalyze intermediate reactions and the resulting products accomplish many other metabolic functions. Two of these intermediate molecules of particular importance are IPP and FPP.

IPP is the precursor of isoprenoids, ubiquinone, and dolichol. Ubiquinone is an essential component of the electron transport chain, which is located within the inner mitochondrial membrane and is responsible for 95% of all human ATP synthesis reactions. Ubiquinone is small and hydrophobic, and thus mobile and freely diffusible within the lipid bilayer of the inner mitochondrial membrane. Ubiquinones accept electrons from $FMNH_2$, which is produced by NADH dehydrogenase (complex I), and from $FADH_2$, which is produced by succinate dehydrogenase (complex II) and acyl CoA dehydrogenase. These steps are absolutely required for subsequent electron transfer to complex III. Ubiquinones carry both electrons and protons and play a central role in coupling the electron flow to proton movement, which is essential for oxidative phosphorylation. A decreased ubiquinone level results in decreased electron transport and subsequently decreased ATP production. Although ubiquinones are concentrated in the inner mitochondrial membrane, they are also widely distributed in other cellular membranes (4) and perform several cell metabolism functions other than ATP production, including the cell signalling and gene expression (5). Oxidative stress causes DNA and protein damage, and plays an important role in the development of cancer, neurodegenerative diseases, cardiovascular disorders, and aging (6, 7). According to the oxidative stress theory, atherosclerosis is the result of the oxidative modification of low-density lipoproteins (LDL) by reactive oxygen species (ROS) in the arterial wall. ROS induce the oxidation of LDL, whose uptake by macrophages is easier than uptake of non-oxidized LDL. Oxidative stress, together with the weakened antioxidative defense system, induces the vascular dysfunction and promotes atherosclerosis. Ubiquinone inhibits atherosclerosis development as described by the oxidative theory (8), and is considered the anti-risk factor of atherosclerosis.

It has been shown that statin therapy decreases circulating and muscle ubiquinone levels (8, 9). Decreased levels of ubiquinone may be responsible for such statin side effects as myotoxicity and rhabdomyolysis (10). Although it is not still clear, some study results indicate that decreased levels of ubiquinone during statin therapy might be associated with the subclinical cardiomyopathy and that this situation is reversible with the ubiquinone supplementation (11).

Oxidative stress and mitochondrial dysfunction have been implicated in many neurodegenerative disorders including the Alzheimer's disease, amyotrophic lateral sclerosis, and Parkinson's disease. For example, studies suggest that, in Parkinson's disease, there is a deficiency of the complex I activity in the mitochondrial electron transport chain. Interestingly, ubiquinone appears to be a promising agent in the treatment of Parkinson's disease. Additionally, in animal models, the experimental studies suggest that ubiquinone protects against many neurodegenerative diseases (12–14).

In addition to ubiquinone, dolichol metabolism and prenylation play important roles in the impact of statins on human metabolism. Dolichol metabolism affects glycoprotein and glycolipid synthesis, which subsequently enables vital cell cycle functions. Glycoproteins and glycolipids comprise a group of structural and functional proteins of major metabolic

importance. Glycoproteins are found in the blood, extracellular matrix, outer surfaces of cell membranes, and organelles such as lysosomes and Golgi complexes. Glycolipids are located in cell membranes, and their polar heads are composed of carbohydrate molecules, which are activated by the attachment of dolichol. Inhibition of dolichol biosynthesis results in the abnormal glycosylation, which in turn has negative effect on many requisite cellular functions and structures. Specifically, it has been shown that the inhibition of dolichol synthesis or function blocks the cell cycle in the late GI phase and if the exposure is prolonged, it induces apoptosis (15–18).

Prenylation is a common mechanism by which the proteins are anchored to the inner cellular membrane surfaces. The attached unit is either a farnesyl or a geranylgeranyl group. Protein prenylation is an important function of the isoprene derivatives, and statins can block prenylation (19). There is strong evidence that statin-induced blocking of the protein prenylation also blocks the cell growth (20).

Statins are approved only for treatment of lipid disorders; however, it is suggested that they may be useful in treating other conditions, such as osteoporosis and Alzheimer's disease (21, 22). Clinical studies have yet to evaluate this assumption. The potential of statins as an anti-cancer treatment has been investigated extensively (20). Despite their benefits in treating the hypercholesterolemia and being studied extensively, statin safety remains unclear. It has been suggested that some statins reduce the risk of developing cancer (23); however, this association has not been validated by other studies (24). Recently, Vinogradova and coworkers (25) conducted a large population-based case control study on 88,125 cases and 362,254 matched controls and found reduced risk of hematological malignancies. More importantly, they found that the prolonged use of statins (> 4 years) was associated with the significantly increased risk of colorectal, bladder, and lung cancers. These cancer types are common in the age group of patients taking anti-hypercholesterolemia drugs. The association between the statins and cancer risk is an important point that warrants further intensive investigation.

When evaluating the metabolic functions of all cholesterol biosynthesis intermediates in hypercholesterolemia patients, physicians may conclude that the inhibition of HMG-CoA reductase with statins may not be the right choice. Rather, physicians may choose to target another inhibitory point in the cholesterol biosynthesis pathway. However, this decision is not straightforward because there are different known target points and associated drugs. For example, triparanol inhibits the final step of cholesterol biosynthesis, the conversion of desmosterol to cholesterol. When triparanol was used to treat hypercholesterolemia patients, it caused an accumulation of desmosterol in tissues, resulting in the development of alopecia, atherosclerosis and cataracts. Triparanol was used in 1960s and its main side effect is known as »Triparanol Disaster« (2).

In conclusion, cholesterol biosynthesis is a complex pathway with many vital intermediate downstream products that serve as potential anti-hypercholesterolemia drug targets. These intermediates are as important to human body function as cholesterol itself. The purpose of the cholesterol biosynthetic pathway is not exclusively to synthesize cholesterol, and mevalonate synthesis does not always result in cholesterol production. Alternatively, the body may utilize mevalonate for synthesizing the ubiquinone, dolichol and other molecules, as well as cholesterol. These molecules are defense against oxidative stress, cancer, neurodegenerative diseases and atherosclerosis. Statin usage over time inhibits cholesterol production, but also compromises the defense system, rendering the patients vulnerable to these diseases. Statins are overprescribed in populations not at risk of cardiovascular disease, and in these patients, the risk of statin use may far outweigh the benefits. Additional studies are required to identify new targets for development of anti-hypercholesterolemia drugs

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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