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КРАТКОЕ СООБЩЕНИЕ

THE PROBABLE BIOINORGANIC MECHANISM OF SIDE-EFFECTS OF STATINS

ВОЗМОЖНЫЙ БИОНЕОРГАНИЧЕСКИЙ МЕХАНИЗМ ПОБОЧНЫХ ЭФФЕКТОВ СТАТИНОВ

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КЛЮЧЕВЫЕ СЛОВА: статины, бионеорганический механизм, побочные эффект.

ABSTRACT: About 25 million people obtain statins to treat hypercholesterolemia. However, several thousand patients experience side-effects, for instance, myopathy, rhabdomyolisis and idiopathic polyneuropathy. This is caused by inhibition of mevalonatic pathway of cholesterol synthesis, mediated by 3-hydroxy-3-methyl-glutaryl-CoA-reductase (HMG-CoA-reductase) by statins. They block formation of restored isopentenylpyrophosphate (Δ^2IPP), substrate of synthesis of selenoproteins (glutathione peroxidase, deiodinase, thioredoxin reductase, and selenoprotein N), responsible for thyroxin homeostasis, antioxidant defence, myocyte regeneration and antiviral defence. There are also other hypotheses. Statins contain complex forming atoms, and, according to laws of element interaction, induce pathomorphosis of I, Se, Ca, Fe, Cu, Zn, Mn, Mg polymicroelementoses.

РЕЗЮМЕ: Для лечения гиперхолестеринемии около 25 млн. человек применяют лекарственные препараты статины. Однако у нескольких тысяч больных наблюдаются побочные эффекты в виде миопатии, рабдомиолиза и полинейропатии. Этот феномен объясняют ингибированием статинами в мевалонатном цикле синтеза холестерина оксиметилглутарил-КоА-редуктазы (HMG-CoA-reductase). В результате прекращается образование восстановленного изопентенилпирофосфата (d=Δ^2IPP). Последний является субстратом для синтеза селенопротеинов (глутатионпероксидазы, дейодиназы, тиоредоксинредуктазы и селенопротеина N), ответственных за гомеостаз тироксина, антиокислительной системы, регенерацию миоцитов и противовирусную защиту. Но эта гипотеза — не единственная. Исходя из наличия в статинах атомов-комплексообразователей и законов межэлементного взаимодействия, механизм побочных эффектов объясняется статининдуцированным патоморфозом полимикроэлементоза I, Se, Ca, Fe, Cu, Zn, Mn, Mg.

Currently a new group of medicines — statins — are widely applied to correct hypercholesterolemia (Betteridge, Khan, 2001). All over the world statins are used by about 25 million patients. However, development of undesirable phenomena — myopathy (2—3 cases on 10 thousand cases), rhabdomyolisis, and polyneuropathy (4—5 cases) is found. As a whole, each year side-effects of application of statins are observed in several thousand patients.

The mechanism of action of statins is well investigated. Cholesterol is synthesized from Acetyl-CoA through mevalonatic pathway by isoprenoids transformation to acetoacetyl-CoA (AACoA). AACoA by the appropriate synthase turns in 3-hydrooxi-3-methyl-glutaryl-CoA (HMG-CoA), then to mevalonic acid, further to mevalonat-5-phosphat → mevalonat-5-pyrophosphat → Δ^3-isopenthenylpyrophosphat → Δ^2-isopenthenylpyrophosphat. That is converted by farnesyl pyrophosphate synthase through geranylpyrophosphate, farnesylpyrophosphate and squalene to cholesterol. Statins inhibit HMG-CoA-reductase, breaking off synthesis of cholesterol.

To explain mechanism of undesirable effects formation, B. Moosman and Ch. Behl (2004) assumed that statins break a pathway of selenoproteins biosynthesis. They are synthesized in enzyme-linked isopenthylation of selenocystein-tRNA (sec-tRNA) by tRNA-isopenthenyl-transferase. The substrate of this enzyme is Δ^2-isopenthenyl pyrophosphate (Δ^2IPP).

The normal way of biosynthesis of selenoproteins is perverted. Damage of cellular biomembranes by free radicals and the infringement connected to metal-ligand homeostasis causes myopathy and polyneuropathy.

However, this hypothesis doesn't completely explain causes of side-effects of statins development.

Considering formulas of some statins (Fig. 1), one can note, that they contain reaction groups.

Natural statins contain groups =O, capable to provide electrons to the present metals with formation of coordination connections. Synthetic statins contain also more active groups =NH and ?N. Long action of these ligands induce deficiency of I, Se, Mn, Mg, and, possibly, other metals (Zn, Cu, Fe), that results in suppression of activity of coordinated enzymes, in particular, polymerases, and also nonhaemic Fe-and Cu-containing components of a respiratory circuit.

At the 1st Congress of Russian Society of Trace Elements in Medicine (Moscow, 2004) Mukhin et al. (2005) presented the circuit of interaction of elements (Fig. 2).

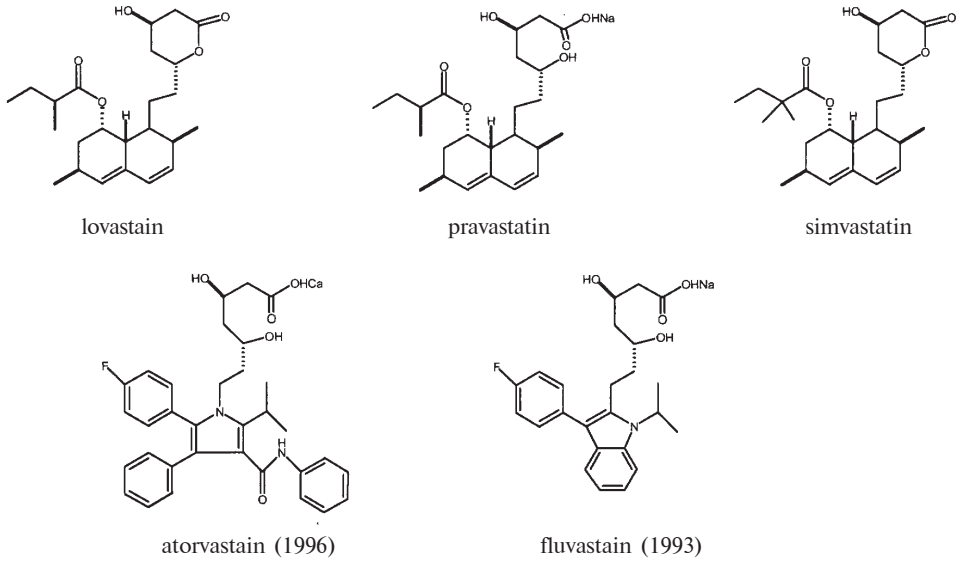

Fig. 1. *Some statins (natural— lovastatin, pravastatin, simvastatin, synthetic— atorvastatin, fluvastatin)*

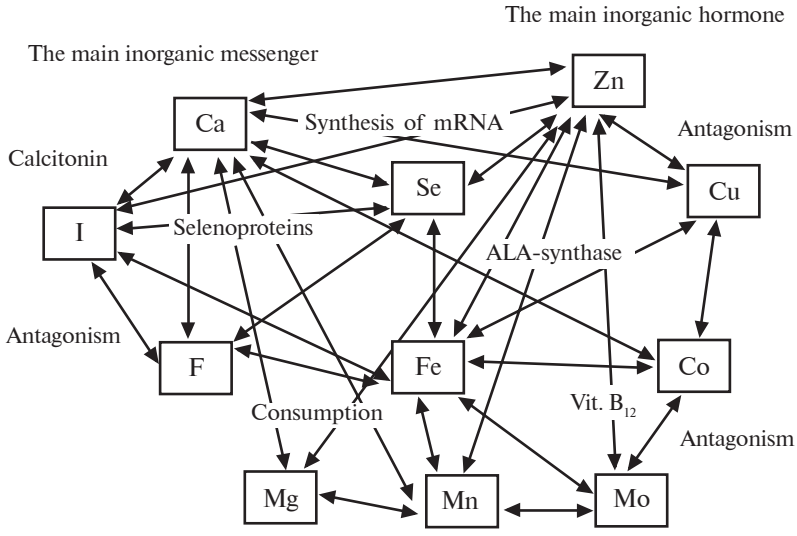

Fig. 2. *Metabolic interrelations of important elements*

Note: Se-proteins are synthesized with the help Zn-containing DNA- and RNA-polymerases (it is not specified on the circuit); F, Co, Cu, Ca, Se, Zn supervise mastering Fe; Antagonists: Zn — Cu, F — Se, Ca — Mg, I — Se, 3d-metals are antagonists among themselves and with alkaline-ground metals, halogens are antagonists among themselves.

Major elements in metabolism work according to the principle of feedback. Actually interaction of elements in metabolism is more complex. Trying to correct deficiency of one element can cause difficultly predicted consequences for some other elements. Except for endemic factors, deficiency of selenoproteins, including glutathione peroxidase, can be provoked by long ingestion of drugs that act as active ligands of these selenoproteins.

Deficiency of selenoproteins results in deficiency of iodine I, and, therefore, infringements of Ca homeostasis («the main inorganic messenger»); that is, statin-induced pathomorphosis of polymicroelementosis develops. These undesirable effects are weak, because statin-containing complexes have low stability constants.

Addition of selenium-containing preparations to diet of statin-treated patients without the appropriate control can provoke undesirable effects, because «free» (unbound to organic molecules) selenium is highly toxic. For example, H_2Se is on the order more toxic than HCN.

Thus, treatment of hypercholesterolemia by statins must be controlled by the contents and ratio of microelements in blood.

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