Statins and mitochondria

ABSTRACT

The aim of this review is to report on the influence of statins on mitochondrial function. Statins are serum cholesterol-lowering drugs. They act by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the first committed enzyme of the mevalonate pathway. In this way, statins inhibit endogenous cholesterol synthesis. Emerging evidence suggests that statins impair mitochondria, demonstrated by abnormal mitochondrial morphology, decreased oxidative phosphorylation capacity and yield, decreased mitochondrial membrane potential, and activation of the intrinsic apoptotic pathway. The mechanisms of statin-induced mitochondrial dysfunction are not fully understood. The following causes are proposed: (i) deficiency of coenzyme Q10, an important electron carrier of the mitochondrial respiratory chain; (ii) inhibition of respiratory chain complexes; (iii) diminution of protein prenylation resulting from inhibition of the mevalonate pathway; and (iv) induction of the mitochondrial apoptosis pathway. These phenomena could play a significant role in the etiology of statin-induced diseases, especially myopathy. Studies on statin-induced mitochondrial apoptosis could be useful in developing a new cancer therapy.

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Abbreviations: COX – cytochrom *c* oxidase; FPP – farnesyl pyrophosphate; GGPP – geranylgeranyl pyrophosphate; HMG-CoA – 3-hydroxy-3-methylglutaryl-coenzyme A; ROS – reactive oxygen species

INTRODUCTION

Civilization diseases are one of the main health problems occurring in developed or rapidly developing countries. They include cardiovascular diseases, e.g., atherosclerosis, myocardial infarction, or hypertension [1,2]. Cardiovascular disease risk factors include conditions of elevated cholesterol levels in the blood, which can be reduced by an appropriate diet or by means of statins. Due to the well-documented positive effects on the cardiovascular system, statins are commonly applied drugs. They stabilize atherosclerotic plaques, reduce the inflammatory response, and improve the functioning of vascular endothelium.

The popularity of statins has been confirmed by statistics. Statins are the most commonly used cholesterol-lowering drugs, as they are used by every fourth US citizen over the age of 40 [3]. In addition, in 2001, statins held the first two places in the ranking for the best-selling prescription drugs in the world [4].

The first statin - mevastatin - was isolated from *Penicillium citrinium* in 1976 by a team led by the Japanese biochemist, Akira Endo [5]. Two years later, Brown and colleagues published a study that described the mechanism of mevastatin action on human fibroblasts and adrenal gland cells [6]. These studies have led to the development of new methods for the treatment of hypercholesterolemia, i.e., high levels of cholesterol in the blood plasma [7-10]. After years of research, in 1987, Merck introduced the first pharmaceutical statin, lovastatin. Since then, more compounds have been added to the group of statins, both of natural (lovastatin) and synthetic (rosuvastatin, pitavastatin, atorvastatin, fluvastatin) origin (Fig. 1). Statins are divided into two groups. In the first group, the statins are in the form of an inactive prodrug (simvastatin). Their structure contains a β-lactone ring, which is hydrolyzed into the active form. The second group includes statins in the hydroxy acid form, which do not require activation (pravastatin and atorvastatin). In terms of properties, statins can be divided into those that are hydrophilic (pravastatin and rosuvastatin) and hydrophobic (atorvastatin, cerivastatin, fluvastatin, and simvastatin). Statins represent a class of compounds that differs in their structure and properties (Table 1) but has a similar biological activity. These compounds are structural analogs of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase. They work by blocking the endogenous synthesis of cholesterol through reversible inhibition of a key enzyme of the mevalonate pathway, i.e., HMG-CoA reductase (EC 1.1.1.88) (Fig. 2). In addition to blocking cholesterol synthesis, statins also inhibit the production of other intermediates of the mevalonate pathway, e.g., isoprenoids such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). FPP and GGPP are involved in protein prenylation. Prenylation is a post-translational

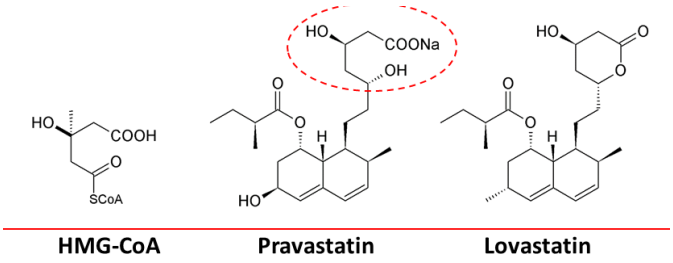

Figure 1. Chemical structure of HMG-CoA reductase and two selected statins: pravastatin and lovastatin. The open conformation of the β-lactone ring (dashed line) is responsible for the biological activity of statins due to its similarity to HMG-CoA - the natural substrate of HMG-CoA reductase [9,10].

modification of proteins involving the covalent addition of hydrophobic isoprene units (farnesyl or geranylgeranyl) to a polypeptide chain that enables the protein to anchor to the cell membrane. Another effect of hampering HMG-CoA reductase by statins is the inhibition of synthesis of the coenzyme Q10 (ubiquinone), an essential non-protein electron carrier of the mitochondrial respiratory chain in the inner mitochondrial membrane.

Mitochondria are organelles that play key roles in cell metabolism. They are involved in important steps of cellular respiration, such as the Krebs cycle (the TCA cycle), fatty acid β-oxidation, and oxidative phosphorylation. The role of mitochondria extends far beyond the production of energy in the form of ATP [11]. They are an important source of reactive oxygen species (ROS), which, apart from contributing to oxidative stress and cell death, participate in cell signaling [12]. Therefore, mitochondrial disorders contribute to the development of many diseases. Mitochondrial dysfunction may be determined genetically (e.g., in **Leber's hereditary optic neuropathy, LHON,** and Leigh syndrome) or may be caused by exogenous factors. It seems that such factors may include statins. More and more studies have revealed the harmful effects of these popular cholesterol-lowering drugs on mitochondria [13]. The reported symptoms of such damage include, among others, inhibition of mitochondrial respiratory chain complexes, a drop in the mitochondrial membrane potential, uncoupling of oxidative phosphorylation, induction of apoptosis, a decrease in mitochondrial DNA (mtDNA) in a cell, abnormal ion homeostasis, mor-

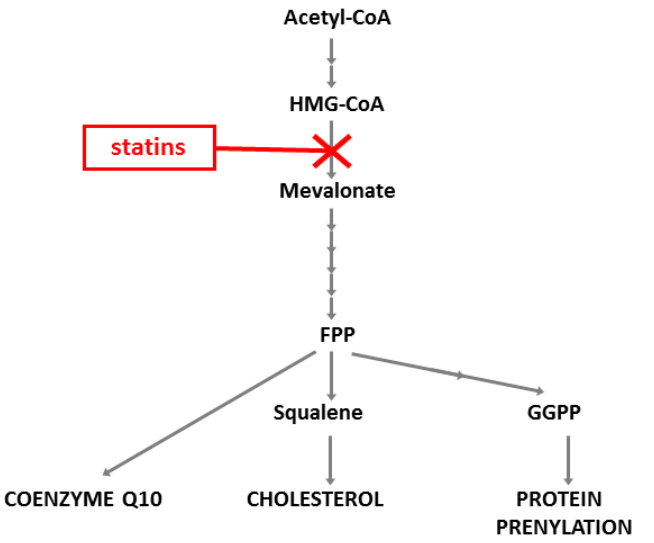

Figure 2. The cholesterol synthesis pathway and the site of action of statins. Abbreviations: acetyl-CoA - acetyl-coenzyme A; HMG-CoA - 3-hydroxy-3-methyl-glutaryl coenzyme A; FPP - farnesyl pyrophosphate; GGPP - geranylgeranyl pyrophosphate.

phological changes of the mitochondria [14], and inhibition of β-oxidation [13]. Most of these disorders have been observed in patients with statin-associated myopathies. The side effects of statins include disorders of skeletal muscle, such as myopathies and myalgia. Muscle pain of a varying severity affects even 7% of patients treated with statins [15]. A rare but extreme reaction to statins is rhabdomyolysis, a severe damage to muscle tissue. It occurs in every 3.4 per 100,000 patients [16]. In recent years, the consequences of statin therapy associated with myopathies have been intensively studied. Therefore, the vast majority of publications on the effect of statins on mitochondria relate to muscles.

The studies on the influence of statins on cells and mitochondria have utilized biological material derived from patients treated with statins or from animals, e.g., mice [17]. Some of the studies have been performed on cell lines. It should be mentioned, though, that the concentrations of statins applied in experiments may be controversial [18]. The average concentration of statins in the serum depends

Tabela 1. Właściwości wybranych statyn [8,9,65].

	hydrophilic	llipophilic	lactone form (prodrug)	hydroxy acid form	natural origin	synthetic origin
Atorvastatin		+		+		+
Cerivastatin *		+		+		+
Fluvastatin		+		+		+
Lovastatin		+	+		+	
Pitavastatin		+		+		+
Pravastatin	+			+	+	
Rosuvastatin	+			+		+
Simvastatin		+	+		+**	

*Cerivastatin was withdrawn from the market in 2001 [8]. ** Semi-synthetic derivative of lovastatin [65].

on the type and applied dose of a particular statin (1-15 nM). In varying tissue types, the statin concentration may significantly differ. For example, as a result of accumulation, the statin concentration can be three times higher in the liver, while in the muscle, it can reach a third of the concentration in the serum. In many studies, cells were treated with statins at a concentration several times greater than the values observed under physiological conditions.

The aim of this review is to summarize the current state of knowledge on the effects of statins on mitochondrial function.

MITOCHONDRIAL MORPHOLOGY

Histochemical staining of skeletal muscle biopsies from patients with statin-associated myopathies reveal features of mitochondrial dysfunctions, such as an increase in the lipid amount stored in mitochondria or the presence of ragged red fibers (RRF) [19,20]. RRF reveal a subsarcolemmal accumulation of abnormal mitochondria, which can be visualized by Gömöri staining. Another abnormality observed in patients with statin-associated myopathies are fibers, which do not contain one of the complexes of the mitochondrial respiratory chain (cytochrome *c* oxidase), that disturbs the transport of electrons during oxidative phosphorylation [19-21]. The relationship between statins and the described changes has been confirmed by Philips and colleagues [20]. They have noted that these morphological abnormalities disappear when patients stop taking statins.

POTENTIAL DISORDERS OF THE MITOCHONDRIAL RESPIRATORY CHAIN

COENZYME Q10

Coenzyme Q10, called also ubiquinone, is essential in mitochondrial oxidative phosphorylation. In this last stage of cellular respiration, the oxidation of reduced nucleotides (NADH and FADH) results in energy release and storage in the form of ATP. Coenzyme Q, as a small non-protein electron carrier of the mitochondrial electron transport chain, freely moves across the inner mitochondrial membrane transferring electrons from substrate dehydrogenases to complex III. The main enzymes that reduce coenzyme Q are NADH-ubiquinone oxidoreductase (complex I) and succinate-ubiquinone oxidoreductase (complex II). When the homeostasis of living organisms is maintained, coenzyme Q10 is synthesized in all animal cells and tissues in sufficient levels to perform its physiological function [22]. The biosynthesis of coenzyme Q10 is initiated in the endoplasmic reticulum and ends in the Golgi apparatus membranes, from where it is transported to other organelles, including the inner mitochondrial membrane [23]. The main compounds required for the synthesis of coenzyme Q10 are 4-hydroxybenzoate and the polyprenyl chain. By inhibiting HMG-CoA reductase, statins prevent the endogenous synthesis of coenzyme Q10, which can lead to disturbances in the process of mitochondrial oxidative phosphorylation and an increase in mitochondrial production of ROS. Regardless of its prooxidative properties promoting the formation of ROS, coenzyme Q10 is one of the most important lipophilic antioxidants that prevents the formation of free radicals, oxidative modifications of proteins, lipids and nucleic acids, and contributes to the regeneration of other potent lipophilic antioxidant, α-tocopherol [24]. Reduced forms of coenzyme Q10, ubiquinol ($CoQH_2$) and ubisemiquinone radical ($CoQH^{\cdot}$), exhibit antioxidant properties. The ubisemiquinone anion intermediate ($CoQ\text{-}^{\cdot}$), resulting from the one-electron reduction of hydroquinone, exhibits prooxidative properties. Therefore, the reduced level of cellular and mitochondrial coenzyme Q10, caused by the inhibition of HMG-CoA reductase, may strengthen the adverse effects of increased level of ROS due to a decrease in antioxidant protection and an increase in the prooxidative production of free radicals.

Many studies have confirmed a diminution in the level of coenzyme Q10 in the serum of patients undergoing statin therapy. Publications devoted to this subject show that this diminution can range from 16% to 49% [25]. Notably, coenzyme Q10 is transported by lipoproteins, e.g., LDL (low-density lipoprotein). Therefore, the statin-induced reduction of the coenzyme Q10 level in the blood is caused not only by a decreased synthesis of endogenous coenzyme Q10 but also by a reduction in the LDL level [26]. This may explain why the level of coenzyme Q10 in the blood does not reflect its cellular level, e.g., in muscle cells [25]. While a pronounced majority of studies confirm the decrease in the coenzyme Q10 level in the blood of patients taking statins [25], the analyses performed on muscles are not so evident, because they reveal no significant changes [27,28], a strong decline [29,30], or an increase in the coenzyme Q10 level [31].

In many disease states (including heart diseases, circulatory insufficiency, neurodegenerative diseases, and diseases associated with decreased immunity or cancer), that are associated with an increased formation and action of ROS, the coenzyme Q10 level is lowered. In cells, ROS are produced mainly in mitochondria. Therefore, a deficiency of mitochondrial coenzyme Q10, which disturbs oxidative phosphorylation and increases the mitochondrial ROS production, may be one of the major causes of diseases associated with a deficiency of coenzyme Q in the organism.

A deficiency of coenzyme Q10 may contribute to the abnormal functioning of mitochondria, which may be indirectly revealed by symptoms observed in patients with a deficiency of coenzyme Q10 such as the increased ratio of the lactate/pyruvate levels in the blood [32], decreased activity of the mitochondrial respiratory chain, decreased ATP production, or increased ROS production in the muscle [2,30,33]. Similar effects of the reduced cellular content of coenzyme Q10 were observed in experiments carried out on animal models [34]. It is postulated that a shortage of coenzyme Q10 that disables mitochondria underlies statin-induced myopathy and the damage to skeletal muscle [25]. Therefore, supplementation of coenzyme Q10 or compounds supporting its synthesis is recommended (e.g., folic acid or vitamin B) in the form of pharmaceutical preparations or with a diet rich in coenzyme Q10 (meat, fish, or oils). Approximately 50% of coenzyme Q10 is supplied by food [35]. It is slowly absorbed in the gastrointestinal tract and has a relatively long plasma half-life (34 h) [36]. Reports on

the effectiveness of coenzyme Q10 supplementation in patients with statin-associated myopathies are contradictory. Some studies indicate that oral supplementation effectively raises the level of coenzyme Q10 in the blood [37-40] and reduces the symptoms of myopathy [41,42]. Other reports indicate that, despite the increase in the level of coenzyme Q10, the statin tolerance does not increase, and muscle pain is not reduced in patients [43]. Despite intensive research, there is still no conclusive evidence that the deficit of coenzyme Q10 in mitochondria may be caused by the use of statins in the treatment of hypercholesterolemia and cardiovascular diseases, or that it may be a direct cause of myopathy [44].

RESPIRATORY CHAIN AND OXIDATIVE PHOSPHORYLATION

Proper coupling of electron transport in the respiratory chain with the activity of ATP synthase is essential for efficient oxidative phosphorylation and, thereby, the ATP synthesis in mitochondria. Studies performed on muscle biopsies from statin-treated patients and on myocyte cell lines show that statins reduce oxygen consumption in the mitochondria by reducing the rate of electron transport in the respiratory chain and decreasing the efficiency of oxidative phosphorylation [30,45]. The correlation between the use of statins and mitochondrial dysfunction through the reduced levels of coenzyme Q10 is not clear. Larsen and colleagues reported that in biopsy samples of muscle fibers from healthy volunteers and patients taking simvastatin, mitochondrial coenzyme Q10 levels were comparable [28]. Nevertheless, in the permeabilized muscle fibers from statin-treated patients, a reduction in the maximal respiratory activity was observed together with a reduced efficiency of oxidative phosphorylation. This effect was observed only when substrates of respiratory complex I and complex II were applied together. These results suggest another negative influence of statins on mitochondria in addition to blocking the endogenous synthesis of coenzyme Q10. Other studies performed both on cell lines and cells derived from biopsies indicate that the respiratory chain is inhibited by statins not only through reduction of the availability of coenzyme Q10 but also through effect on the individual electron transferring complexes [29,46]. For example, inhibition of complex IV by lovastatin was observed in astrocytes, and complex I was inhibited by simvastatin in rat cardiomyocytes. Moreover, interesting conclusions have been provided by the research performed on isolated mitochondria. A direct statin treatment of mitochondria isolated from cells that had not been previously exposed to these drugs excludes the effect of coenzyme Q10 deficiency. Under such conditions, inhibition of the mevalonate pathway does not occur because the pathway is located in the cytoplasm.

Studies by Nadanaciva and colleagues included the comparison of the effect of six types of statins on mitochondria isolated from a rat liver [47]. Simvastatin and lovastatin exhibited the greatest toxicity towards mitochondria. Both of these statins most efficiently inhibited the non-phosphorylating respiratory state of mitochondria, whereas fluvastatin and cerivastatin worked less effectively, and atorvastatin and pravastatin were the least efficient. Analysis of the effect caused by each of the statins on the particular complexes demonstrated that lovastatin and simvastatin inhibit complex III, complex IV, and ATP synthase. None of the studied statins inhibit complex II. In addition, cerivastatin, the statin withdrawn from the market because of the side effects occurring in treated patients, moderately interferes with mitochondrial functioning. The observed 40% inhibition of ATP synthase and the slight inhibition of the respiratory complexes do not seem to be significant enough to explain these side effects. In the study performed on mitochondria isolated from rat skeletal muscle, only cerivastatin, among all tested statins (cerivastatin, fluvastatin, atorvastatin, simvastatin, and pravastatin) showed the uncoupling effect [25]. According to the authors, this effect may explain the more toxic effect of cerivastatin on the muscle when compared to that of the other statins. Additionally, after treatment of mitochondria isolated from rat muscle with cerivastatin, fluvastatin, or atorvastatin, a 50-65% decrease in the membrane potential of non-phosphorylating mitochondria has been observed, which is the result of an impairment of proton-pumping respiratory complexes, i.e., complexes I, III, and IV. These studies report the greater toxicity of lipophilic statins (cerivastatin, fluvastatin, atorvastatin, and simvastatin) on mitochondria when compared to that of the hydrophilic statins (pravastatin).

The majority of statins are transported in a pharmacologically active form, i.e., in the form of hydroxy acid. However, statins can be converted by uridine diphosphate glucuronosyltransferase (UDP glucuronosyltransferase, UDPGT) to lactone, i.e., to the form of a β-lactone ring [48]. This form is three times more cytotoxic than the acid form. Studies on a myoblast cell line treated with statins in the lactone form showed a decrease in the efficiency of oxidative phosphorylation and a significant inhibition of complex III (approximately 80%). These results were confirmed by studies performed on muscle cells obtained from patients with statin-associated myopathies. They showed a reduced activity of the complex III. *In silico* analysis and functional studies led to the identification of a lactone binding site on the Q_o binding site of complex III [48].

APOPTOSIS

Mitochondria play an important role in apoptosis, i.e., a programmed cell death. They are involved in internal factor-induced apoptotic signaling, which is known as the mitochondrial pathway [49]. Studies have revealed statin-induced proapoptotic effects, which are closely related to mitochondria. In mitochondria, statins (especially lipophilic statins) inhibit respiratory chain functioning, uncouple oxidative phosphorylation, causing a reduction in the membrane potential [25,50]. The decrease in the mitochondrial membrane potential may result in increased permeability of the inner mitochondrial membrane, which is believed to initiate programmed cell death [51,52]. This increased membrane permeability may lead to leakage of the outer mitochondrial membrane and then to an increase in the volume of the mitochondrial matrix (mitochondrial swelling) and the outflow of cytochrome *c* from the intermembrane space [25]. The release of cytochrome *c* from mitochondria is a key factor for the activation of caspase-9, which triggers the

proteolytic cascade of caspases. Similar changes have been observed in mitochondria of rat myoblasts treated with lipophilic statins.

The initiation and execution of apoptosis is also related to the excessive production of ROS by mitochondria. In the muscle cells of patients with statin-associated myopathies, the increase in the level of hydrogen peroxide of mitochondrial origin has been shown together with the increase in the proportion of BAX protein (Bcl-2-associated X protein) to Bcl-2 (B-cell lymphoma 2), which confirms the induction of apoptosis [53]. Interestingly, atorvastatin applied to rats induces apoptosis only in muscles, in which most of the energy is obtained via glycolysis (e.g., in the plantaris muscle containing mostly fast-twitch fibers) [53]. In muscles, that obtain energy mainly from oxidative phosphorylation (e.g., in the soleus muscle with mainly slow-twitch fibers) such effects have not been observed. This observation indicates a greater sensitivity of the glycolysis-dependent muscle cells to statins, probably due to their lower antioxidant potential.

Glycolysis is also a major source of energy in tumor cells (Warburg effect). Numerous studies confirm that statins induce programmed cell death in various tumor lines [54-59]. Some of them report that this response is often associated with activation of the mitochondrial apoptotic pathway [59,60], accompanied by the release of the second activator of caspase (Smac/Diablo) from the mitochondria into the cytosol, leading to activation of caspase-9 [25]. Studies on lymphoma cell lines also indicate the triggering of the inner, mitochondrial apoptotic pathway by statins [50]. In these cells, the statin-induced apoptotic response comprises a decline in the mitochondrial membrane potential, increased production of ROS by mitochondria, activation of the pro-apoptotic BAX protein, suppression of anti-apoptotic Bcl-2, and activation of the Akt kinase pathway. The cytotoxic effect of statins has been blocked when the mevalonate pathway products (FPP and GGPP) are provided to cells [50]. This suggests that the shortage of these compounds is the cause of apoptosis in the examined cells due to the lack of prenylation of proteins regulating apoptosis. These findings were also confirmed by studies performed on other cell lines [54,59,61,62]. It has also been suggested that the reduction in protein prenylation involved in the process of autophagy can prevent the removal of damaged mitochondria, which, in turn, can lead to cell death [63].

SUMMARY

Statins are drugs used not only due to the effective reduction of cholesterol level in the blood but also for their positive pleiotropic effect on the cardiovascular system. However, statins may have side effects that are related to mitochondria. Numerous studies mentioned above prove that statins cause mitochondrial pathway-induced apoptosis and mitochondrial dysfunction manifested by morphological changes, inhibition of the mitochondrial respiratory rate, a decrease in the efficiency of oxidative phosphorylation, and a decrease in the mitochondrial membrane potential. Possible effects of statins on mitochondria are summarized in Figure 3.

Not all statins impair mitochondrial functioning in the same way. The effects depend on the type of statins applied, including the dose [25,47], form (lactone or hydroxy acid) [48], and degree of hydrophobicity/hydrophilicity of the statin molecule [25,54,64]. It is worth noting that a significant number of publications describing the effect of statins on mitochondria is based on *in vitro* studies. Björkhem-Bergman and colleagues have emphasized that often in studies on cell lines, the applied statin concentrations do not reflect the physiological conditions in human organisms; thus, the data should be treated cautiously [18].

In conclusion, the analysis of the literature describing the influence of statins on mitochondria indicates three possible mechanisms by which statins adversely affect mitochondrial functions, such as coenzyme Q10 deficiency (including mitochondrial coenzyme Q10 deficiency), the direct effect of statins on the components of the mitochondrial respiratory chain, and the reduction in prenylated proteins as a result of the insufficient availability of FPP and GGPP. Studies verifying the concept of coenzyme Q10 deficiency as a cause of mitochondrial dysfunction are vague. This concept has been undermined by studies carried out on statin-treated isolated mitochondria, in which the absent mevalonate pathway cannot be inhibited by statins. Studies on the effect of statins on isolated mitochondria indicate a change in both the functioning of the entire respiratory chain (reduction in mitochondrial respiratory rate) and the activity of its particular complexes. The concept of lowering the level of protein prenylation has been confirmed mainly in the studies on the induction of the mitochondrial apoptosis pathway by statins. In recent years, the mechanism of statin-induced programmed cell death in tumor cells has been extensively studied. It is believed that this mechanism will be beneficial in developing a new anti-cancer therapy with the use of statins. The mechanism by which statins affect mitochondria is still not fully understood. Therefore, it is important to conduct further studies on the effects of statins on human cells, with particular emphasis on mitochondria. These studies may significantly contribute to the development of medicine in the treatment of cardiovascular and cancer diseases.

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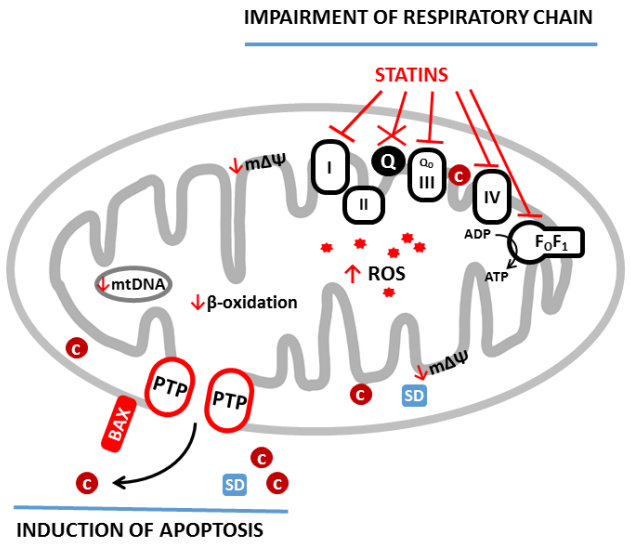

Figure 3. Scheme illustrating the possible effects of statins on mitochondria. Statins may adversely affect the functioning of mitochondria by (i) blocking the synthesis of coenzyme Q10, which is an integral component of the respiratory chain [29]; (ii) reducing the mitochondrial membrane potential (mΔΨ) [25,50]; (iii) inhibition of respiratory chain complexes and ATP synthase, and uncoupling of the respiratory chain [29,46,47,48]; (iv) excessive mitochondrial production of ROS [53]; (v) inhibition of β-oxidation [25]; (vi) reduction of mitochondrial DNA content in cells [66,67]; (vii) induction of apoptosis via the mitochondrial pathway, accompanied by an increase in the level of the pro-apoptotic BAX protein and suppression of anti-apoptotic Bcl-2 [50,53], the release of cytochrome *c* [25,54] and Smac/DIABLO protein [54] into the cytoplasm, and activation of mitochondrial megachannel PTP (permeability transition pore), which allows for the escape of ions and small molecules from the mitochondria, resulting in the final collapse of the membrane potential and discontinuity of the outer mitochondrial membrane [68]. Abbreviations: BAX - BAX protein; c - cytochrome *c*; F_oF_1 - ATP synthase; PTP - mitochondrial permeability transition pore; mtDNA - mitochondrial DNA; Q - coenzyme Q10; ROS - reactive oxygen species; SD – Smac/DIABLO; mΔΨ - mitochondrial membrane potential; I-IV - complexes of the respiratory chain.

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Statyny a mitochondria

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Słowa kluczowe: mitochondria, statyny, łańcuch oddechowy, koenzym Q10

STRESZCZENIE

Statyny należą do leków obniżających poziom cholesterolu we krwi. Ich działanie polega na odwracalnym hamowaniu jednego z enzymów szlaku mewalonowego, reduktazy 3-hydroksy-3-metyloglutarylo-koenzymu A (HMGCoA), przez co zostaje zatrzymana endogenna synteza cholesterolu. Wiele badań wskazuje na uszkodzenie funkcji mitochondriów przez statyny, co objawia się m.in.: nieprawidłową morfologią mitochondriów, spadkiem wydajności fosforylacji oksydacyjnej, spadkiem potencjału błonowego oraz aktywacją apoptozy na drodze indukowanej czynnikami wewnętrznymi. Mechanizm, w wyniku którego statyny wpływają na nieprawidłowe funkcjonowanie mitochondriów nie jest jeszcze w pełni poznany. Proponowane przyczyny dysfunkcji to niedobór koenzymu Q10, mitochondrialnego nośnika elektronów w łańcuchu oddechowym, zahamowanie działania kompleksów łańcucha oddechowego oraz obniżony poziom prenylacji białek wywołany zablokowaniem szlaku mewalonowego, będącego źródłem substratów do prenylacji. Opisywane zjawiska pełnią istotną rolę w etiologii miopatii postatynowych, ale mogą też stanowić punkt wyjścia do opracowania nowej metody leczenia nowotworów. W niniejszej pracy został przedstawiony aktualny stan wiedzy na temat wpływu statyn na funkcjonowanie mitochondriów.