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Statins and ALS: The possible role of impaired LXR signaling

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Summary

Statins, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, are commonly used in the therapy of cardiovascular diseases. Recent studies suggest that statins may induce amyotrophic lateral sclerosis (ALS) in some patients, but no pathogenic mechanism has been proposed for this association. Herein the hypothesis is proposed that statins may induce or aggravate ALS by impairing liver X receptor (LXR) signaling. The hypothesis is supported by the following observations: 1) statins inhibit the synthesis of endogenous LXR agonists, oxysterols, and decrease the expression of LXR target genes in many cells, 2) mice lacking LXRβ exhibit sn ALS-like phenotype, 3) statins increase the concentration of plant sterols in plasma and tissues, partially by impairing LXR-dependent signaling, which results in augmented intestinal absorption and impaired biliary excretion of plant sterols, and 4) some plant sterols are toxic to motor neurons of the spinal cord, which are primarily affected in ALS patients. If this hypothesis is confirmed, LXR agonists could be used together with statins in patients predisposed to develop ALS or in those known to have the disorder to prevent motor neuron degeneration.

key words: **statins • 3-hydroxy-3-methylglutaryl-coenzyme A reductase • amyotrophic lateral sclerosis • liver X receptor • oxysterols • phytosterols**

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BACKGROUND

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme in cholesterol biosynthesis which converts HMG-CoA to mevalonate (Figure 1). Several statins are currently available in clinical practice, including the fungal metabolite lovastatin, its derivatives pravastatin and simvastatin, and fully synthetic compounds such as fluvastatin, atorvastatin, and rosuvastatin. Statins decrease plasma low-density lipoprotein (LDL) cholesterol by inducing intracellular cholesterol depletion and upregulating hepatic LDL receptors. Many clinical trials have demonstrated that statins effectively prevent acute cardiovascular events and reduce mortality in the primary and secondary prevention of ischemic heart disease [1,2]. Initially introduced as cholesterol-lowering drugs, statins possess several other lipid-independent or "pleiotropic" atheroprotective activities such as improvement of endothelial function, inhibition of vascular inflammation, platelet aggregation and thrombosis, and amelioration of oxidative stress. Therefore, the beneficial effects of statins are observed not only in patients with hyperlipidemia, but also in those with normal cholesterol level. In addition to ischemic heart disease, statins may reduce the risk of ischemic stroke, left ventricular hypertrophy, arrhythmias, Alzheimer disease, and type 2 diabetes, slow the progression of chronic nephropathies, rheumatoid arthritis, and multiple sclerosis, and increase bone mineral density [3–6].

Statins are safe and usually well tolerated. In clinical trials, adverse effects of statins are very rare. However, patients enrolled in trials are usually strictly selected and carefully monitored, and in routine clinical practice adverse effects of these drugs seem to be much more frequent. The most common adverse consequences of statin therapy include myopathy and hepatotoxicity [7]. However, as statins are used in an increasing number of patients, new side effects of these medications are continuously being described [8]. Although most of them are very rare, some, such as autoimmune disorders, may be potentially fatal. Since statin use is expected to increase, it is essential to unravel the mechanisms of these complications, the methods of identifying patients susceptible to develop them, and methods of their potential therapy. Herein I propose a hypothesis which could explain the recently described link between statins and amyotrophic lateral sclerosis (ALS).

STATINS AND ALS

ALS is an adult-onset neurodegenerative disease characterized by progressive degeneration and loss of spinal cord, bulbar, and cortical motor neurons. This leads to generalized muscle weakness and atrophy, speech and swallowing disabilities, and progressive paralysis until death is caused by respiratory failure [9]. ALS is one of the most common neurodegenerative disorders, with an incidence of 1–2/100,000 and a prevalence of 4–6/100,000; typical survival time is 2–5 years after diagnosis. Approximately 10% of ALS cases are familial (inherited), with the remaining 90% of cases being sporadic in origin [10]. Of the familial cases, approximately 20% (i.e. 2% of all ALS) are due to mutations in the gene for the cytosolic copper-zinc superoxide dismutase (SOD1), which detoxifies superoxide anion radicals to hydrogen peroxide. The pathogenesis of ALS is multifactorial and incompletely understood; factors such as oxidative stress, mitochondrial dysfunction, abnormal protein aggregation, glutamate-mediated excitotoxicity, and neuroinflammation are involved [9,10]. Effective treatment of this disorder is not currently available.

Recently, two studies have been published in which a disproportionately high reporting of ALS-like syndromes in statin users was noted in Vigibase (the database of the WHO Program for International Drug Monitoring) [11] and in the Food and Drug Administration's (FDA) spontaneous Adverse Event Reporting system (AERS) [12]. By using the data mining method, Edwards et al. found that ALS was reported among statin users more frequently than among non-users [11]. They extracted 40 cases of ALS among statin users. For 34 reports, statin was the single suspected drug, whereas in the remaining 6 cases there were also some co-suspected drugs. Some patients also suffered from neurological disturbances atypical for ALS, such as ataxia, dyskinesia, abnormal coordination, hypoesthesia, paresthesia, and peripheral neuropathy. In 8 patients, the results of electromyograms were consistent with a diagnosis of ALS. Interestingly, statins were the most frequently reported suspected cause of ALS among all drugs. The time from start of statin therapy and onset of ALS varied from 1 month to more than 2 years. Although a retrospective analyses of 41 statin clinical trials did not reveal an increased incidence of ALS in subjects treated with a statin compared with placebo, disproportionately frequent reporting of ALS among statin users was also noted in the AERS [12]. Drory et al. found no difference in survival time between patients with ALS treated with statins due to hyperlipidemia and those not receiving statins [13]. However, in another study [14], a highly significant 63% increase in the rate of decline of motor function in 32 patients with ALS receiving statins compared with 132 ALS patients not treated with these medications was described. In addition, Golomb et al. analyzed 10 cases of patients' self-reported ALS or ALS-like syndromes associated with statin use. All ten patients reported amelioration of symptoms with drug discontinuation and/or onset or exacerbation of symptoms with drug re-challenge or dose increase [15]. Although all these studies were retrospective, taken together their results suggest that statins may increase the incidence and severity of ALS. Until now, no pathogenic mechanism has been proposed to explain the link between statins and ALS.

ALS: THE CONSEQUENCE OF DEFICIENT LXR SIGNALING

Liver X receptor (LXR) is a ligand-activated transcription factor which forms a heterodimer with the retinoid X receptor (RXR) and, upon ligand binding, regulates the expression of target genes. LXR exist in two isoforms; LXRα is expressed in the liver, intestine, adipose tissue, and macrophages and LXRβ is expressed ubiquitously. Initially described as orphan receptors, the LXRs are now identified as "sterol sensors" which are activated by oxygenated cholesterol derivatives (oxysterols) and stimulate the expression of genes involved in reverse cholesterol transport and excretion, such as: 1) ABCA1 and ABCG1 transporters, which extrude cholesterol from the plasma membrane to apolipoprotein A-I or to high-density lipoproteins (HDL), 2), cholesterol 7α-hydroxylase (CYP7A1), a rate-limiting enzyme in bile-acid synthesis in the liver, 3) apolipoproteins E, C-I, C-II, and C-IV, extracellular cholesterol acceptors, and 4)

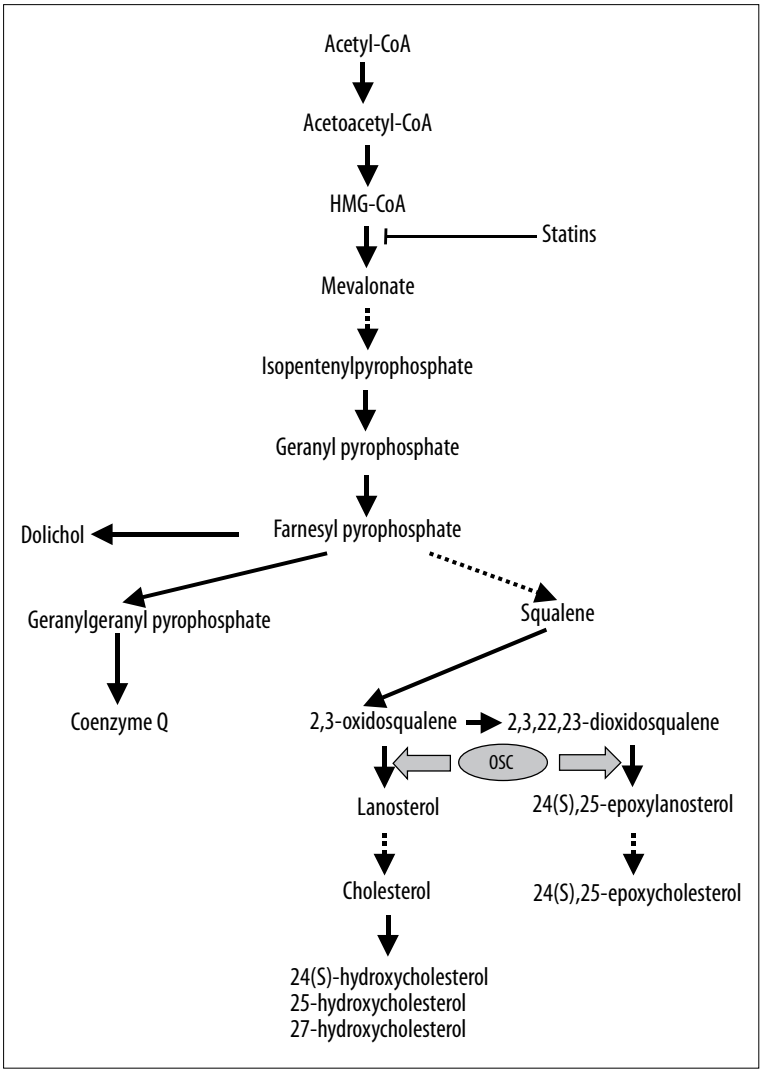

Figure 1. Mevalonate cascade, mechanism of action of statins, and formation of LXR-activating oxysterols. Broken arrows abbreviate multiple-step reactions. HMG-CoA – 3-hydroxy 3-methylglutaryl-coenzyme A, OSC – oxidosqualene: lanosterol cyclase.

ABCG5 and ANCG8, which extrude cholesterol from enterocytes to the gut lumen, thus limiting its net intestinal absorption [16]. In addition, LXR agonists inhibit inflammatory reaction both *in vitro* and *in vivo* and reduce atherosclerosis in animal models such as LDL receptor or apolipoprotein E knockout mice [17,18]. Apart from regulating systemic cholesterol balance, the LXRs are essential for maintaining the cholesterol homeostasis of many specific cells, as evidenced by pleiotropic abnormalities of the endocrine, immunologic, reproductive, gastrointestinal, and nervous systems in mice lacking these receptors [19].

Interestingly, male LXR$\beta^{-/-}$ mice develop severe motor impairment closely resembling ALS at 7 months of age which later progresses to hind-limb paralysis [20]. This is accompanied by lipid accumulation and loss of large α motor neurons in the lateroventral horns of the spinal cord, axonal atrophy, and increased number of astrocytes. It is likely that these changes are associated with the accumulation of excessive amounts of cholesterol in motor neurons due to deficiency of ABCA1. Indeed, increased cholesterol content in the motor neurons of patients with ALS was reported [21]. Surprisingly, the motor function of female LXR$\beta^{-/-}$ mice is intact and no degeneration of motor neurons is observed. Interestingly, most patients affected by sporadic ALS are males, although the mechanism of this gender difference is unknown.

Effect of Statins on LXR Signaling

I suggest that the association between statins and ALS may result from the impairment of LXR signaling. Statins inhibit the synthesis of mevalonate, the common precursor of not only cholesterol, but also many other biologically relevant compounds, including electron carrier and antioxidant coenzyme Q, farnesyl- and geranylgeranyl pyrophosphate necessary for the posttranslational isoprenylation of proteins, dolichol involved in protein glycosylation, and isopentenyl adenosine, which is necessary for selenoprotein synthesis (Figure 1). Deficiency of these nonsteroid isoprenoids may mediate adverse effects of statins. Oxysterols, endogenous LXR agonists, are either synthesized from cholesterol by cholesterol hydroxylases, including 24(S)-, 25-, and 27-hydroxylases, or are produced in the mevalonate cascade (24(S),25-epoxycholesterol) [22]. In particular, 24(S)-hydroxycholesterol is produced in large amounts in the central nervous system and is the principal endogenous LXR agonist therein. Deficiency of endogenous oxysterols induced by combined knockout of

cholesterol 24(S)-, 25-, and 27-hydroxylases markedly reduces the expression of LXR target genes [23].

Several studies have demonstrated that the concentrations of 24(S)- and 27-hydroxycholesterol decrease slightly in the blood, cerebrospinal fluid, and/or brain of statin-treated animals and humans [24-29]. Wong et al. [30] showed that mevastatin (compactin) reduces 24(S),25-epoxycholesterol level in cultured human macrophages. This observation was subsequently confirmed in other macrophage cell lines, in primary macrophages, and for various statins currently used in clinical practice [31]. Several *in vitro* studies have demonstrated a considerable impairment of LXR signaling by statins. Forman et al. [32] first demonstrated that mevastatin or lovastatin reduced the transcriptional activity of LXR/RXR heterodimer in cultured cells and that this effect was reversed by mevalonate and by LXR-activating oxysterols, but not by farnesol or geranylgeraniol. In rat hepatoma cells, mevastatin reduced the expression of the LXR target gene sterol regulatory element binding protein-1c and this effect was reversed by mevalonate, synthetic LXR agonist, T0901317, or a natural LXR agonist, 22(R)-hydroxycholesterol [33]. In murine RAW264.7 macrophages, pravastatin reduced the expression of ABCA1 and ABCG1 and their levels were restored by mevalonate and 22(R)-hydroxycholesterol [34]. Consistent with this, Sone et al. [35] observed that atorvastatin, fluvastatin, simvastatin, and lovastatin reduced ABCA1 mRNA level by almost 90% in various human and murine macrophage cell lines. Recently it was demonstrated that atorvastatin suppresses not only the LXR target genes ABCA1 and apo-E, but also cholesterol 27-hydroxylase in THP-1 macrophages [36]. Atorvastatin inhibited ABCA1 expression in human monocyte-derived macrophages and in phorbol ester- stimulated THP-1 monocytes. Apolipoprotein A-I-mediated cholesterol efflux was reduced in THP-1 cells treated with atorvastatin and this effect was abolished by acetylated LDL (a source of oxysterols) [37]. T01901317 and 22(R)-hydroxycholesterol also prevented any reductions in cholesterol efflux or ABCA1 expression associated with atorvastatin treatment. Zanotti et al. [38] observed that mevastatin and pitavastatin impaired cholesterol and phospholipid efflux from murine peritoneal macrophages, which was accompanied by reduced ABCA1 expression, and mevalonate, as well as a mixture of 22(R)-hydroxycholesterol and 9*cis*-retinoic acid (an RXR agonist), reversed this effect. Reduction of ABCA1 by statins was also observed in cultured human keratinocytes [39] and in lymphocytes [40]. Gouedard et al. [41] demonstrated that statins reduce the expression of paraoxonase-1 (PON1), an antioxidant and atheroprotective enzyme, in cultured human hepatocytes and that 22(R)-hydroxycholesterol normalized PON1 synthesis, secretion, and activity. It was recently demonstrated that statins inhibit differentiation and induce apoptosis of 3T3-L1 adipocytes and that this effect is prevented by LXR agonists [42]. Finally, in THP-1 macrophages either T0901317 or 22(R)-hydroxycholesterol rescued lipoprotein lipase expression impaired by atorvastatin [43]. Taken together, these data indicate that statins may impair LXR signaling in different cell types.

STATINS, PHYTOSTEROLS, LXR, AND ALS

Plant cells do not synthesize cholesterol, but several other sterols with similar chemical structure, such as sitosterol, stigmasterol, campesterol, brasicasterol, and ergosterol. Similarly to cholesterol, plant sterols are absorbed by the Niemann-Pick C1-like 1 (NPC1L1) protein contained in the apical membrane of enterocytes but, in contrast to cholesterol, are not incorporated into chylomicrons but back-extruded to the gut lumen by ABCG5/ABCG8 heterodimer. In addition, plant sterols are effectively excreted to the bile by ABCG5/ABCG8 complex in the canalicular membrane of hepatocytes [44]. It has been demonstrated that plasma and tissue concentrations of plant sterols increase by 50–100% during statin treatment [45-48]. Because ABCG5 and ABCG8 are stimulated by LXR and NPC1L1 is inhibited by LXR, it is likely that elevation of plant sterols in statin-treated patients may result from the impairment of LXR signaling.

Interestingly, excessive dietary intake of β-sitosterol glucuronides contained in cycad seeds (*Cycas circinalis*) was implicated as the cause of ALS and parkinsonism dementia (PD) frequently observed in the population of Guam. Indeed, feeding mice with cycad flour induces the ALS/PD-like syndrome and plant sterols contained in it are toxic for large motor neurons of the spinal cord [49,50]. Administration of β-sitosterol accelerated and augmented the ALS-like phenotype of LXRβ$^{-/-}$ mice [51]. Thus, statins may increase the risk of ALS by inducing LXR-dependent perturbations of cholesterol/phytosterol metabolism in the CNS.

TESTING THE HYPOTHESIS

Several attempts could be made to test the proposed hypothesis. Until now it has not been observed that statins induce motor neuron disorders in wild-type animals. However, the effect of statins on the severity and progression of ALS could be tested in animal models of this disease such as mutant SOD1 transgenic mice. In addition, the effect of statins on LXR signaling measured as oxysterol level and the expression of LXR target genes in motor neurons or the entire spinal cord should be evaluated. The effect of statins on the ALS-like phenotype in LXRβ$^{-/-}$ mice is also of interest. Although statins could not directly affect LXR signaling in motor neurons in this model, they could affect systemic cholesterol and plant sterol metabolism by impairing the function of LXRα outside the CNS. In addition, baseline oxysterol level and the expression of LXR target genes without statin treatment should be evaluated in animal models of ALS other than LXRβ$^{-/-}$ mice as well as in humans with this disease.

There are several important arguments against the hypothesis presented above. First, the level of β-sitosterol was similar in wild-type and LXRβ$^{-/-}$ mice not receiving this compound [51]. Second, β-sitosterol did not induce neurological injury in young LXRβ$^{-/-}$ mice before the age at which they spontaneously exhibit first signs of motor impairment. Third, the expression of ABCG5, ABCG8, and NPC1L1 in the small intestine was intact in these mice. However, the expression of these proteins in the intestine could be maintained by operative LXRα, which is not expressed in the spinal cord, and their expression in the spinal cord was not examined. Finally, no signs of ALS are observed in sitosterolemia, although the level of plant sterols is markedly elevated in these patients. However, it is clear that ALS is not a common complication of statin therapy and it may develop only in some predisposed patients. This predisposition may be

associated with genetic polymorphisms of LXR or oxysterol-synthesizing enzymes, making them highly susceptible to statin-induced impairment of LXR signaling. Otherwise, statins could impair LXR signaling in all patients, but could induce or aggravate ALS only in some of them in whom motor neurons are particularly vulnerable due to other genetic or environmental injuries. It should be noted that in addition to systemic or local cholesterol/plant sterol homeostasis, other mechanisms could also provide the link between statin-induced depression of LXR activity and ALS. For example, T cell-mediated immunity may be involved in ALS [52]. Recent studies suggest that T-cell activation and proliferation are enhanced in LXRβ$^{-/-}$ mice [40]. Statins deplete oxysterols also in lymphocytes [39] and may induce autoimmune diseases [53].

If LXR is a link between statins and ALS, some new therapeutic options will emerge for predisposed patients. First, synthetic LXR agonists could be supplemented to prevent statin-induced impairment of LXR signaling. Second, oxidosqualene: lanosterol cyclase (OSC) has greater affinity for 2,3,22,23-dioxidosqualene than for 2,3 oxidosqualene (Figure 1), and partial inhibition of this enzyme reduces cholesterol formation while augmenting 24(S),25-epoxycholesterol synthesis and LXR signaling [54]. Thus, OSC inhibitors could be an alternative for statins in patients with hyperlipidemia suspected to develop motor neuron disorders and for those with existing ALS.

Conclusions

Recent studies suggest that statins may induce or aggravate amyotrophic lateral sclerosis in some patients. This effect may result from the depletion of oxysterols – oxygenated cholesterol derivatives which are endogenous LXR agonists. Statins have been demonstrated to inhibit oxysterol formation and to impair LXR signaling in various experimental models. Moreover, the ALS-like phenotype develops in mice lacking LXRβ. Impaired LXR signaling may contribute to ALS by interfering with local cholesterol balance of motor neurons, and/or by leading to the accumulation of plant sterols which are also elevated by statin therapy. LXR agonists and more selective inhibitors of the mevalonate cascade which do not interfere with LXR signaling could be useful in the prevention and treatment of ALS in statin users.

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