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CHOLESTEROL-INDEPENDENT NEUROPROTECTIVE AND NEUROTOXIC ACTIVITIES OF STATINS: PRESPECTIVES FOR STATIN USE IN ALZHEIMER DISEASE AND OTHER AGE-RELATED NEURODEGENERATIVE DISORDERS

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Abstract

Statins, long known to be beneficial in conditions where dyslipidemia occurs by lowering serum cholesterol levels, also have been proposed for use in neurodegenerative conditions, including Alzheimer disease. However, it is not clear that the purported effectiveness of statins in neurodegenerative disorders is directly related to cholesterol-lowering effects of these agents; rather, the pleiotropic functions of statins likely play critical roles.

Moreover, it is becoming more apparent with additional studies that statins can have deleterious effects in preclinical studies and lack effectiveness in various recent clinical trials. This perspective paper outlines pros and cons of the use of statins in neurodegenerative disorders, with particular emphasis on Alzheimer disease.

1. Basic pharmacology of statins

Statins are a family of drugs with pleiotropic functions. To this class belong 8 drugs: mevastatin and lovastatin, which were the first developed and studied in humans; pravastatin and simvastatin, which can be considered as derivatives of the parental lovastatin; and atorvastatin, fluvastatin, rosuvastatin and pitavastatin, which are distinct synthetic compounds [1]. Due to their main mechanism of action, namely the inhibition of the hydroxyl-methyl-glutaryl-CoA (HMG-CoA) reductase, statins are widely used for the treatment of dyslipidemias [1]. By inhibiting HMG-CoA reductase, statins block the conversion of HMG-CoA into mevalonate, the first step in cholesterol biosynthesis [1,2]. As a result of statin administration, low-density lipoprotein (LDL)-cholesterol synthesis decreases in hepatocytes and this reflects a reduced cholesterol blood level. In addition to this effect, statins have been shown to reduce triglyceride and increase HDL-cholesterol plasma levels. Taken together, the composite effect of statins in reducing triglycerides and

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LDL-cholesterol, coupled with the increase in HDL-cholesterol, put these drugs in the arena of cardiovascular agents, due to their ability to counteract hyperlipidemias, the major cause of atherosclerosis which, in turn, is a common pathogenetic mechanism for coronary artery disease, ischemic cerebrovascular disease and peripheral vascular disease [1,2].

Although statins share the same main mechanism of action, their pharmacokinetic profile is quite different (Table 1). All statins are well absorbed by the intestine when given by orally, even though they undergo marked first-pass effects by the liver, which reduces the systemic bioavailability (5–30%) [1]. With the exception of simvastatin and lovastatin, which are pro-drugs and require hepatic activation, other statins are administered as β -hydroxy-acids. Upon administration, statins reach peak plasma concentration, ranging from 10–448 ng/ml, within 0.5–4 h. In the plasma, statins are bound to albumin (43–99%) and this binding accounts for their variable half-life [1]. Atorvastatin and rosuvastatin are the statins with the longest half-life (15–30 and 20.8 h, respectively), whereas fluvastatin, lovastatin, pravastatin and simvastatin have half-lives around 0.5–3 h [1]. All statins are metabolized by the liver through the isoforms 3A4 (atorvastatin, lovastatin and simvastatin) and 2C9 (fluvastatin and rosuvastatin) of the cytochrome-P-450 (CYP) system, whereas pravastatin undergoes sulfation. The primary route of elimination is fecal, and only a minor fraction of statins is eliminated via urine [1,2].

The main adverse effects of statins are hepatotoxicity and myopathy. A transient elevation of serum transaminases (up to 3-times the baseline value) is a common outcome of statin therapy [2]. However, the incidence of this side effect is low and dose-dependent and does not imply the contraindication of statins in individuals with concomitant liver diseases such as hepatitis C [2]. Myalgia is often associated with statin use and is paralleled by an increase in plasma creatine kinase up to 10 times [2]. Rhabdomyolysis is quite rare, and the risk to develop this side effect of statins is correlated to the dose and plasma concentration [2]. About 30 cases of serious hepatic failure and 42 cases of death due to rhabdomyolysis associated with statin administration were reported to the FDA over the last 15 years [2,3]. In order to reduce the incidence of hepatotoxicity and myopathy, statins should not be associated with inhibitors of CYP3A4 such as azole antifungals, erythromycin, ritonavir and grapefruit juice. Also the association statins and fibrates should be avoided, in particular gemfibrozil [2].

2. Pleiotropic effects of statins

The debate about statin treatment regards the mechanism of action by which statins mediate their potentially beneficial effects. In particular, are these benefits due to the well known ability of statins to lower cholesterol or to their so called pleiotropic effects [4–6]? Statins can modulate several cellular pathways, independent of their ability to inhibit HMG-CoA reductase. These processes include isoprenylation and myelination, modulation of immune response, and effects on oxidative and nitrosative stress levels.

Isoprenylation

The isoprenylation process is significantly and directly affected by HMG-CoA reductase activity. Through the inhibition of HMG-CoA reductase activity, statins reduce the formation of L-mevalonic acid and subsequent prevention of isoprenoid synthesis [4,7,8]. The seventh step of the cholesterol synthesis yields farnesyl pyrophosphate (FPP), which can be converted into squalene and hence to cholesterol, but is also used for the production of geranylgeranyl pyrophosphate (GGPP). Both FPP and GGPP are required to enable proper subcellular localization and trafficking of intracellular proteins [4,9]. FPP is also the substrate for production of coenzyme Q10 (CoQ10) and dolichol [10]. Coenzyme Q10 is an antioxidant, and dolichol may function as a radical scavenger. Of these two, only CoQ10 has

been seriously studied in relation to statin treatment: statins decrease CoQ10 levels in plasma and tissue, which may be responsible for several of statins' side effects [11,12]. Farnesyl pyrophosphate and GGPP on the other hand have received much attention as possible mediators of the non-cholesterol-dependent effects of statins [5,13]. In particular, small GTP-binding proteins, including members of the Ras and Rho GTPase family, require prenylation post-translational modifications to function as modulators of the actin cytoskeleton and to participate in intracellular signaling [9]. However, depending on statin type, length of treatment, and cellular type the final outcome could be different. First of all, statins exhibit inhibitory effects on small G proteins, by altering the isoprenylation process [4,14]. Neuroprotective effects of simvastatin for example, include the improvement of behavioral function associated with an inhibition of Rho-associated kinase (ROCK) in a rabbit model of ischemic stroke [15], and the prevention of dopaminergic neuronal loss through the inhibition of p21(ras)-induced NF-kappaB increase in a mouse model of Parkinson's disease [16] (Figure 1). Conversely, prolonged treatment of human mature oligodendrocyte with simvastatin was associated with cell death [17] (Figure 1). Moreover, evidence for decreased learning and memory following long-term simvastatin treatment exists [18]. Lovastatin, was effective to ameliorate experimental autoimmune encephalomyelitis by reducing the activities of Rho/Ras family GTPase in glial cells [19]. In contrast, the same drugs efficiently inhibited Ras-induced ERK1/2 phosphorylation in rat brain neuroblasts [20], as well as geranylgeranylation of Rho family GTPase in neurons [21], leading to an increase in apoptosis and tau phosphorylation, respectively [20,21] (Figure 1). Noting that inflammatory processes occur in several neurodegenerative disorders, such as Alzheimer disease, statin-mediated inhibition of Rho GTPases seems to attenuate beta-amyloid (A β) peptide-stimulated inflammation in microglia [8]. Moreover, mevastatin and lovastatin were reported to, respectively, decrease and increase neurite outgrowth in different strains of PC12 cells through different mechanisms [22,23].

Downstream consequences of reduced isoprenoid synthesis may include changes in vascular function, modulation of the insulin/phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) pathway [24] and possibly a reduction in reactive oxygen species production [25]. Thus, statin-mediated reduction of protein isoprenylation could have widespread effects on protein transport, trafficking, mRNA stability and gene transcription [4]. However, the clinical significance of the results discussed above is debatable. The question whether inhibition of isoprenylation process occurs in the brain therefore remains open.

Myelination

Although initially statins were thought to be beneficial for myelination and proposed as a treatment for multiple sclerosis (MS), a demyelinating condition [26,27], these benefits are being re-evaluated, since contradictory results have been described. As for isoprenylation processes, both *in vitro* and *in vivo* results suggest that statin- and cell type play pivotal roles in the final outcome. Simvastatin treatment had a detrimental effect on oligodendrocyte outgrowth, a key step in the re(myelination) process [28], particularly in the early myelination stage [29] (Figure 1). Interestingly, simvastatin and lovastatin had an opposite effect on the myelin basic protein (MBP), since simvastatin treatment greatly increased the densities of MBP in oligodendrocytes of neonatal rats after hypoxia-ischemia damage [30], whereas lovastatin reduced MBP expression in primary oligodendrocytes, probably by impairment of the isoprenylation process [31] (Figure 1).

Immunomodulatory effects

The immune response plays a role in neurodegeneration, not only in MS, but also in Alzheimer and Parkinson diseases [32]. Statins may have immunomodulatory effects, which also could be mediated through reduced protein prenylation, although, so far, no singular

mechanism has been proposed [13]. *In vitro*, lovastatin prevents expression of TNF and IL-1 β [33], and prubocol reduces glial activation [34]. In addition, microglial cultures exposed to atorvastatin and simvastatin showed reduced levels of the pro-inflammatory cytokine, IL-6 [35] (Figure 1). However, the effects of statins on the immune cells of the CNS, the microglia, have received little attention and need to be further explored.

Oxidative and nitrosative stress

Another intriguing aspect related to the pleiotropic effects induced by statin treatment regards the modulation of oxidative stress-related modifications that occur in neurodegenerative disorders [36]. Statins can inhibit endothelial O₂^{•-} formation by preventing the isoprenylation of p21 Rac, which is critical for the assembly of NADPH oxidase after activation of PKC [37] (Figure 1). In addition, SOD3 activity was more than doubled by simvastatin, and simvastatin treatment also increased the number of functionally active endothelial progenitor cells [38] (Figure 1). Moreover, statins increase the expression of endothelial nitric oxide synthase (eNOS) by inhibition of Rho isoprenylation [39], and statins can also directly activate eNOS via post-translational mechanisms involving activation of the PI3K/Akt pathway [40] (Figure 1). Statins showed positive effects against Alzheimer-relevant A β -induced oxidative stress in mice models of AD [41,42] as well as a reduction in CSF tau protein phosphorylation in humans [43]. However, although statin treatment appears to provide greater benefits, it is difficult to tease out whether the benefits are really due to lower cholesterol levels or to statin pleiotropy [6]. Atorvastatin treatment was neuroprotective against cell degeneration induced by A β (1–40), reducing inflammatory and oxidative responses and increasing the expression of glutamatergic transporters [44]. Murphy et al. (2010) showed that long-term atorvastatin did not affect A β levels, despite a significant reduction in β -secretase 1 (BACE1) protein levels and activity in the brain of aged beagles [45]. Later, we found that although no change in A β levels occur, long-term atorvastatin significantly reduced lipoperoxidation, protein oxidation and nitration, and increased GSH levels in parietal cortex of the same animals [46] (Figure 1). This effect was cholesterol- and A β -independent and specific for brain [46]. Conversely, side effects of long-term statin treatment include a decrease in CoQ10 levels resulting in energy metabolism impairment in heart, skeletal muscle, and liver [47] (Figure 1). Supplementation of the diet with CoQ10 was reported to reverse many of these alterations [48]. At the same time, the effect of lipophilic statins can result in elevated tissue oxidative stress through NO reacting with metabolically derived O₂^{•-} to form peroxynitrite and other reactive oxidants, which can have negative effects on endothelial cells [49] (Figure 1).

Cholesterol oxidation products

Statin effects on oxidative stress should take into account cholesterol reduction, considering that cholesterol itself, can be oxidized with likely loss of its functions. Cholesterol can undergo oxidative modifications at least by two mechanisms: a direct radical attack involving ROS or RNS (non-enzymatic mechanism), or by the activity of a specific enzymes (enzymatic mechanism). This leads to the formation of cholesterol oxidation products, i.e., oxysterols. These latter moieties are major regulators of cholesterol homeostasis in the central nervous system [50]. Among oxysterols, 7-ketocholesterol (7-K) and 25-hydroxycholesterol (25-OH) have been shown to cause apoptotic neuronal death by inducing mitochondrial dysfunction [51], Ca²⁺ influx and perturbation of intracellular ionic homeostasis [52,53].

Although some evidence suggests the importance of cholesterol oxidation products both as *in vivo* markers of oxidative stress [54–56], as well as for their pro-oxidant features [51–53,57], few studies exist regarding the effect of statins on cholesterol oxidation products *in vivo* [54,58,59]. Our group showed that atorvastatin can have two independent effects on

cholesterol and cholesterol oxidation products, since a reduction of cholesterol was not associated with a reduction of 7-K or 25-OH and *vice versa*. In fact, the levels of both 7-K and 25-OH were reduced in brain, while 7-K levels were significantly increased in serum in dogs receiving atorvastatin [46] (Figure 1).

These results, together with those showing a marked peripheral reduction of CoQ10 after long-term treatment with statins, suggest that statins can exert antioxidant/pro-oxidant effects depending on the site of action and on the mechanisms modulated. Due to duration of statin treatment, it would be interesting to carry out *in vivo* studies to analyze in the brain changes that occur to cholesterol oxidation products and CoQ10. Can these changes be correlated? Do statins decrease CoQ10 in the brain? Is reduction/increase of CoQ10 associated with different levels of oxysterols?

We believe that more detailed research into the pharmacology of statins, particularly the concentrations achieved in the CNS and the level at which they block the production of cholesterol and they modulate all the above pathways, may prove beneficial to better understating of the potential use of statins in neurodegenerative disorders.

3. Statins and dementia: suggestion to use evidence-based medicine as a basis of future studies

Although the several lines of preclinical evidence showed neuroprotective effects of statins in ameliorating cognitive dysfunction, clinical data largely have not supported such a conclusion. In addition, clinical studies show opposite results depending whether or not they were observational studies or randomized clinical trials (RCT).

Early clinical data based on cohort and case-control studies, demonstrated that statins reduced the risk to develop dementia, including Alzheimer disease (AD), and this protective effect was maintained over a 6 year follow-up period [60–67]. These findings were recently contradicted by Benito-Leon et al., who demonstrated that statins did not improve cognition in elderly subjects with a median age of 72 years [68]. Similar results, were obtained in a large cohort study, which involved more than 2 million subjects aged 30–84 years of whom 10.7% received statins [69]. Only a weak improvement in cognitive performance (evaluated by the Hopkins word list and Rivermead paragraph) was found in individuals with mild cognitive impairment, arguably the earliest form of AD, treated with statins [70].

In order to confirm these epidemiological studies, some RCT were performed with comparable outcomes. The PROSPER study, which involved about 6,000 people aged 70–82 years, demonstrated that pravastatin (40 mg/day) did not improve cognitive function over a follow-up of 3 years [71,72]. The LEADe study tested the hypothesis that atorvastatin (80 mg/day) over 72 weeks delayed cognitive decline in subjects with mild-moderate AD. The results of this study, did not support any significant positive effect of atorvastatin on cognitive or global functions in patients receiving the statin compared to those with placebo [73]. In 2008 the CLASP study was designed to evaluate the neuroprotective role of simvastatin (20–40 mg/day) for 18 months in mild-moderate AD patients [74]. The results of this trial, not yet published, failed to demonstrate a therapeutic role for simvastatin [74]. On the other hand, the ADCLT trial demonstrated that atorvastatin (80 mg/day) for 1 year exhibited a significant positive effect on cognitive performance after 6 months of therapy compared with placebo. However, this beneficial effect was narrowed to individuals who matched restricted criteria, such as a higher MMSE score at the baseline, total cholesterol levels higher than 200 mg/dl and the presence of an apolipoprotein-E-4 allele [75,76]. With the purpose to put together and analyze the results from all the RCT trials about statins and dementia, McGuinness et al. performed a meta-analysis and concluded that there is not

evidence strong enough to recommend statins for the treatment of dementia and AD [77]. This statement agrees with the guidelines of the British Association for Psychopharmacology who do not recommend statins for the prevention or treatment of AD [78].

Pitfalls

The conflicting results described above prompt the question, “what are the reasons why statins had such inconsistent beneficial effects in aged or demented individuals?” Even if it is not possible to single out the main drawback, some criticisms need to be addressed and carefully evaluated.

Ability to cross membranes—Due to different chemical structures, different statins exhibit a variable degree of lipophilicity. The prodrugs simvastatin and lovastatin have the the highest logD (index of lipophilicity), atorvastatin, fluvastatin and pitavastatin an intermediate logD while pravastatin has the lowest [1]. Such considerations might suggest use of lipophilic statins in demented patients to increase the fraction that reaches the brain. However, both the LEADe and CLASP trial failed to demonstrate a beneficial effects of atorvastatin and lipophilic simvastatin on cognitive function in AD subjects, consistent with those obtained in the PROSPER study performed with lipophobic pravastatin. Therefore, the different degree of liposolubility likely is not the key determinant that limited effectiveness of statins in these clinical trials.

Age—Epidemiological data demonstrate the incidence of AD increases with age and doubles every 5 years after 65 years of age with 1275 new cases/100000 persons/year [79]. In the Western hemisphere, the prevalence of AD was calculated as about 1% in subjects aged 60–64 but increased to between 33% and 50% in people aged 85 or older [80]. Keeping this in mind, both cohort studies and RCT that examined the role of statins in AD were based on populations aged 65–84 years. Although the clinical studies and the meta-analysis discussed above do not support an overall beneficial effect for statins in dementia and AD, it is noteworthy that those studies in which statins had a major effect on cognitive functions recruited individuals aged 68–74 years [61,63,81]. Consequently, it is possible that 68–74 years of age should not be considered as a “threshold” or upper limit for statin efficacy in preventing dementia, since both the LEADe and PROSPER studies enrolled individuals within the same range of age, and these studies failed to demonstrate any beneficial effect of statins in people with AD. Subjects aged 80 or older also did not have any beneficial effects from statins [61].

Cholesterol blood levels at baseline—An important issue to consider when giving a statin is the degree of reduction of cholesterol levels in serum. Recalling that cholesterol is a main component of cell membranes, in particular myelin [82], if cholesterol blood levels fall due to uncontrolled therapy with lipid lowering agents, nervous function would also decrease. An increase in total blood cholesterol levels at midlife age was associated with an increased risk to develop AD [83,84]. As summarized by McGuinness et al. in two recent meta-analyses, AD subjects recruited for large clinical trials had serum LDL cholesterol around 131–147 mg/dL [85]. The same authors reported that after the administration of atorvastatin (80 mg) for 52 weeks or simvastatin (40 mg) for 26 weeks a reduction of LDL-cholesterol of 50–54% in AD patients was observed [77,85]. These values of LDL-cholesterol, before and after statin treatment, are still acceptable and do not imply any possible adverse effects. However, although there was beneficial effect of statins on LDL-cholesterol plasma levels, no beneficial effect on cognitive function was observed [77,85]. Even in hypercholesterolemic patients, statins did not reduce A β in both plasma and cerebrospinal fluid (CSF), suggesting the lack of any statin-mediated on A β deposition or

clearance [43,86]. Considering that an excessive reduction in cholesterol plasma levels is not advisable, statins could not be administered to AD patients with low cholesterol plasma levels such as those affected by liver failure. Evans et al. showed that in AD patients heterozygous for APOE4 allele or carriers of PS1 mutations, the administration of simvastatin or atorvastatin slightly reduced the concentration of CSF-cholesterol at 6–7 months followed by a peak at 2 years and a return to baseline levels after three years [87]. This finding lends support to the idea that, despite the changes in plasma cholesterol levels, only minimal changes in brain cholesterol occur after statin therapy and, therefore, the effect on cognitive functions are independent of the “local” cholesterol metabolism.

Interaction with xenobiotics—Patients with AD, as well as other types of dementia, usually take other drugs for other age-related disorders or co-morbidities associated with AD. As mentioned above, all statins, with the exception of pravastatin, are metabolized by CYP3A4 or CYP2C9, and their plasma levels could be reduced or increased in the case of concomitant administration of drugs that induce or inhibit these CYP isoforms. Drugs used in AD, such as donepezil and galantamine, also are metabolized by CYP3A4 [88], and, therefore, could compete with statins. As a consequence of this interaction, statin plasma levels could increase as well as the risk of side effects. Also, AD patients can often be supplemented with dietary products including curcumin, grapefruit juice and green tea as these natural substances are widely considered as free radical scavenger and therefore neuroprotective. Unfortunately, these natural substances are inhibitors of CYP3A4 and, therefore, increase plasma concentrations of statins [89–91]. Interestingly, it was reported that the concomitant assumption of simvastatin and grapefruit or green tea originated rhabdomyolysis [92,93].

Taken together, the results from evidence-based medicine suggest that the ideal AD subject with some possibility to have an increased cognitive performance upon treatment with statins is aged 65–74 years, harbors an ApoE-4 allele [76], is normocholesterolemic and sparingly uses drugs that inhibit CYP3A4.

Conclusions

Although the evidence provided with preclinical data substantiated the potential beneficial effects of statins in dementia and AD, the results provided by epidemiological studies and RCT are quite contradictory. Several criticisms related to the rate of inhibition of cholesterol synthesis in normocholesterolemic patients, age and concomitant administration of drug or dietary supplements also should be considered. Increased selectively in RCT involving AD subjects aged 65–75 years, the age which seems to receive more benefit from statin therapy, in which the primary end-point is the careful analysis of cognitive function through a battery of neurological tests, should be carried out. Another recommendation to consider is to study in-depth the effect of statins in individuals with mild cognitive impairment in order to understand whether or not the antioxidant effect of these drugs could block or slow the transition phase to AD. This recommendation could be especially important since preclinical studies with atorvastatin decreased brain-resident oxidative stress in beagle dogs, and this benefit was correlated with decreased levels of A β (1–42), which has the same sequence as that of humans [46]. Of course, oxidative stress is strongly associated with amnesic MCI and AD [94–96], and A β is hypothesized to contribute to this oxidative stress [97].

In conclusion, our opinion is that current clinical evidence is not strong enough to support the widespread use of statins to treat dementia and AD. However, strong consideration for researchers and clinicians in the near future to investigate whether or not statin therapy should be restricted to selected populations of demented individuals with the best chance of efficacy derived from evidence-based medicine is recommended.

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Figure 1.

Cholesterol-independent neuroprotective versus neurotoxic effects of statins. Black arrows: stimulation; dotted lines: inhibition.

Table 1

Pharmacokinetic parameters of statins.

	T_{max} (h)	C_{max} (ng/mL)	B (%)	L	Pb (%)	M	$T_{1/2}$ (h)	E (%)
Atorvastatin		2-3	27-66	12	Yes	80-90	CYP3A4	15-30	Urinary 2 Fecal 70
Fluvastatin		0.5-1	448	19-29	Yes	>99	CYP2C9	0.5-2.3	Urinary 6 Fecal 90
Fluvastatin XL		4	55	6	Yes	>99	CYP2C9	4.7	Urinary 6 Fecal 90
Lovastatin		2-4	10-20	5	Yes	>95	CYP3A4	2.9	Urinary 10 Fecal 83
Pitavastatin		1.2	41	~ 80	Yes	96	CYP2C9	11	Urinary < 2 Fecal 90

	T _{max} (h)	C _{max} (ng/mL)	B (%)	L	Pb (%)	M	T _{1/2} (h)	E (%)
Pravastatin	0.9–1.6	45–55	18	No	43–55	Sulfation	1.3–2.8	Urinary 20 Fecal 71
Rosuvastatin	3	37	20	No	88	CYP2C9	20.8	Urinary 10 Fecal 90
Simvastatin	1.3–2.4	10–34	5	Yes	94–98	CYP3A4	2–3	Urinary 13 Fecal 58

B, bioavailability; C_{max}, peak plasma level; E, excretion; L, lipophilicity; M, metabolism; Pb, protein binding; T_{1/2}, half life; T_{max}, time to reach peak plasma concentration. (Adapted from references [1,98,99])