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Statins and Alzheimer — current stand and further development directions

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ABSTRACT

In an aging society, more emphasis should be placed on prevention rather than treating diseases. Alzheimer's disease is a common sickness affecting older people. It is predicted that the number of cases will have increased up to 131.5 million by 2050. Therefore, the efforts of the scientific community should be focused on finding therapeutics that could stop or delay dementia. Statins are commonly used drugs with interesting pleiotropic effects. Due to its effects such as lowering cholesterol or inhibiting of inflammatory reaction, they give the prospect of being used in dementia therapy. To this day, numerous studies have been done to verify the influence of statins on pathological elements such as beta-amyloid, Tau protein, or inflammatory factors. Unfortunately, a large discrepancy in the results excludes the use of these drugs in therapy today. The aim of our work is to validate these relations and determine the mechanisms of action of statins on the pathophysiology of Alzheimer's disease. Moreover, we want to point out new directions of research, which may not only explain the pathomechanism of dementia but also find means to stop this process.

Key words: Alzheimer's disease, dementia, statins, inflammatory factors, cholesterol, amyloid-beta, Tau protein

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Introduction

Epidemiological studies from the mid-1990s suggested a link between high cholesterol and the increased risk of Alzheimer's disease (AD). It was then suggested that statins, due to their role in reducing cholesterol, may prevent the occurrence of AD or delay its progression [1]. However, two large studies, PROSPER [2] and Heart protection study [3], have quenched the enthusiasm of scientists, suggesting that there is no connection between statin therapy and delay or cognitive degradation. To assess the effect of statins on Alzheimer's disease and its markers we need to get back to basics. Dementia is one of the biggest health problems in the world. The number of patients can double in twenty years and reach up to 131.5 million by 2050 [4–6]. This is a significant problem in both Western and Central Europe, in which older people begin to dominate in demography, which translates into an increase in the number of patients in the coming years [7].

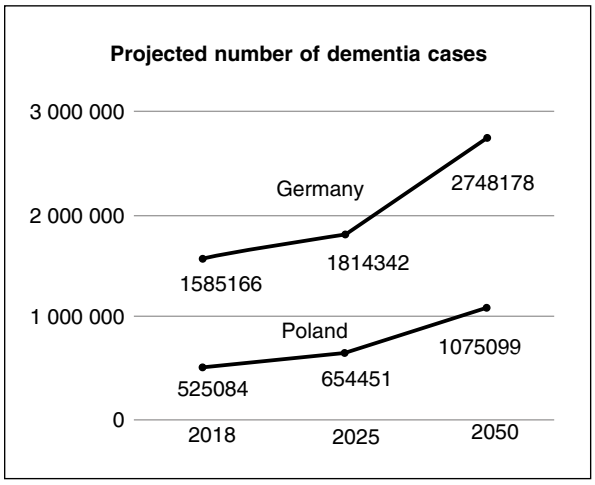

Figure 1. Chart showing the projected increase in the incidence of Alzheimer's disease in 2018, 2025 and 2050 in Poland and Germany [7]

The work is focused on Alzheimer's disease, which accounts for 60–80% of dementia [8]. It is irreversible disease [4], manifested by loss of memory, speech, and cognitive functions, progressing over the years [8]. Most patients have first symptoms before 65 years of age and fully manifest in 30–50% before 85 years of age. However, only 2–10% of patients develop the disease earlier. The main pathological features of brain AD are intracellular neurofibrillary tangles of phosphorylated tau protein, which are believed to have a greater role in pathology [4, 9, 10] and supernormal extracellular accumulation of beta-amyloid protein in amyloid plaques [5] and loss of cholinergic neurons [8]. Changes are correlated with synapses loss and neuronal death [11]. There is a reduction in cerebral blood flow compared to healthy people [12]. Risk factors for AD are inflammation - acute or chronic, high cholesterol, LDL and low HDL, type II diabetes, triglycerides, docosahexaenoic acid 22:6 (DHA), glutamine [11] and genetic mutations, i.e. APOE ε4, PS1 and PS2 [13, 14]. Tissue changes precede the appearance of clinical symptoms for many years and neuropathological changes can be found in people who currently have no symptoms [8]. Numerous works are trying to answer the question of whether statins are suitable for Alzheimer's therapy [15] — we want to answer why they can be suitable.

Statins treatment

Statins, known as HMG-CoA reductase inhibitors, are cholesterol-lowering drugs used to reduce the risk of myocardial infarction. Moreover, they are one of the elements of chronic coronary syndrome therapy [11]. However, due to their pleiotropic effect, we should not limit their use. Experimental studies have shown that statins reduce Aβ production, inhibit inflammatory reactions, protect neurons from neurotoxicity induced by pathological protein, and oxidative stress [8, 16]. We divide statins according to their properties. Hydrophilic statins are more selective to the liver, but are less permeable to BBB, while lipophilic can pass to CSN. GEMS (Ginko Evaluation of Memory Study) showed that lipophilic statins are more effective [17]. There are also statins in the inactive lactone form as a prodrug that passes into the CNS by passive diffusion. Statins in the form of active hydroxy acids are transported to the CNS by OAPT transporting polypeptides [9]. High statin potency is associated with a greater reduction in dementia risk as opposed to lower potency statins [5]. They are quickly eliminated from the CNS due to metabolic changes from CYP3A and active reverse clearance by P-glycoprotein [17]. It should be emphasized that the use of statins in the treatment of AD is not only based on lowering cholesterol [9]. The action of statins is multi-leveled, which is why we have decided to refresh the topic discussed for years and indicate the possible directions of its development for the coming decade. Studies have shown that statins can act preventively in Alzheimer's neuroprotective activity, namely through the ability to improve blood flow, modulation of the immune system, reduction of oxidative damage [18], anti-inflammatory properties and NO production and, of course, lowering LDL levels [19]. The Sacramento Area Latino Study on Aging (SALSA) noted in 5-year studies in the elderly (60-year-olds and older) and the Indianapolis-Ibadan Dementia Project study that it was noted that people who did not use statins had a decrease in cognitive ability faster [20]. On the other hand, other studies show that people not taking statins had a slower decline in cognitive function. The following Table 1 shows examples of studies conducted on popular statins and their properties.

How do statins work on risk factors for Alzheimer's?

Beta-amyloid and tau protein

Cerebrospinal fluid is one of the markers of pathological changes in CNS diseases. Cerebrospinal fluid (CSF) is a plasma-like substance that fills the ventricles and the surroundings of the brain. It performs nutritional functions and is the departure place of brain metabolites, hence the conclusion that biochemical changes in the brain are reflected in CSF. Based on the above sentences, it becomes clear why CNF became one of the examined exponents in the case of dementia suspected. The "amyloid hypothesis" is a theory that originated in 1991 that states that both familial and sporadic Alzheimer's disease is caused by the toxic effects of amyloid overproduction and/or aggregation. Cell and animal studies have linked Aβ production to high cholesterol and statin use. The effect of statins on Aβ plaque has not been disputed since scientists proved, that statins bind directly to Aβ protofibrils — with atorvastatin binding the most [21]. This was also confirmed by studies on animal models [22]. Studies in a mouse model have shown a reduction in Aβ platelet formation in statin therapy, which may suggest a preventative effect of statins in AD therapy [23].

A lot of studies dedicated to biomarkers of the disease focus on the deposition of β-amyloid plaques, and a smaller part of the work is devoted to tau protein, which in its physiological non-phosphorylated form binds to microtubules in neurons and is responsible for their stabilization and binding of microtubules to neurofilaments and cellular organelles [17]. Simvastatin and atorvastatin reduce the amount of phosphorylated

Table 1. Properties of popular statins and sample studies

Statins	Properties and force [4, 5, 17]	Research	Outcome
Simvastatin	lipophilic, strong action	• the CLASP [60] • M. Sjorgen et al. [59] • Liu et al. [57]	• Simvastatin does not inhibit the development of dementia despite significant cholesterol reduction • Decrease of alpha-sAPP and beta-sAPP in CSF and increase of memory capacity • Beneficial effect on the cognitive competence of the hippocampal neural network in rats
Pravastatin	hydrophilic, weak action	• The Prospective Study of Pravastatin in the Eldery at Risk-Prosper [2]	• Decline in cardiovascular illness, but no change in dementia
Lovastatin	lipophilic, weak action	• Z.Zhao et al. [63] • A. Eskandary at al. [10]	• Improves learning and memory, protects neurons from harmful factors • Depending on the dose, reduces the total amount of soluble and fibrillar Aβ peptides and increases the soluble APP protein
Atorvastatin	lipofilic, strong action	• L. Zhao et al. [30] • The LEAD [61] • J. Wang et al. [22]	• Improves cognitive function, protects neurons against inflammation and neurotoxicity Aβ25-35 • No meaningful benefits; does not increase the effect of donepezil • In combination with indomethacin, reduces beta- amyloid plaques, restores immune function and lymphocyte expression in the brains of APP/PS1 transgenic mice
Fluvastatin	lipofilic, weak action	• Tahmina Nasrin Poly et al. [19]	• Positively affects oxidative stress and cognitive dysfun-ction in rats

APP — Amyloid precursor protein; sAPP — soluble amyloid precursor protein; CSF — Cerebrospinal fluid; Aβ — amyloid beta; Aβ25—35 — a fragment of Amyloid β—peptide; APP/PS1 transgenic mice — double transgenic mice expressing a chimeric mouse/human; amyloid precursor protein and a mutant human presenilin 1

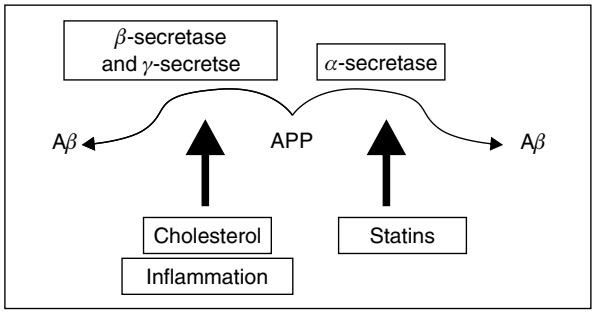

Figure 2. Diagram showing the degradation of the amyloid precursor protein by physiological and pathological pathways. The first takes place in the presence of alpha-secretase, and the second at beta- and gamma--secretase [9, 21]

tau protein [24]. Among the papers on tau protein, the work of Robert G. and co-authors showed that patients, who were treated with simvastatin for 3 months at 20 mg/day for the first 14 days and then with 40 mg/day noted a decrease in the concentration of this protein in CSF [25]. In the O. Gribrib study, simvastatin reduced the CSF level of phospho-tau-181 (p-tau181) in all subjects, compared to atorvastatin, which reduced its level in 54% of subjects. Simvastatin and atorvastatin did not lower CSF or F2-isoprostane levels of βamyloid - markers of oxidative stress [26]. Many studies note changes in the amount of αsAPP and βsApp [27], and Aβ, levels do not change. Looking at the activities of others, annual simvastatin therapy led to a significant increase in CSF levels of αsAPP and p-tau, while other biochemical parameters remained unchanged. Despite this, researchers suggest that lower levels of Aβ in CSF do not mean less production of this amyloid, while its increase is deposited in senile plaques [28]. Statins can prevent pathological tau phosphorylation by inhibiting prenylation-induced activation of one or more MAPK, which is the signaling pathway that statins act on. Simvastatin and atorvastatin allow the degradation of Aβ40 - Aβ42 by expression in the extracellular space of astrocytes by activation of the ERK/Akt pathway [29].

Inflammatory factors

Another mechanism of the potential effectiveness of statin therapy is its immunomodulatory effect. The markers of the inflammatory response have become the focus of attention of researchers looking for therapeutic solutions for people with dementia because as you can see in the studies, inflammation is an important degradation factor. Something that was once a breakthrough today is common knowledge, and the number of works supporting this position is growing all the time. Look at the work of Kyrkanides and colleagues. In 2011, they observed a link between acute and chronic sys-

temic inflammation and brain pathology. He based his conclusions on the results of studies that showed that COX-1 inhibitors with anti-inflammatory effects slow down cognitive decline while reducing Aβ platelets [22]. Sun and colleagues also came to the same conclusions, who showed that the amyloid-beta solution induces an increase in TNF-alpha and IL-6 levels [16]. Moreover, the amyloid β peptide has been shown to increase microglia activation by increasing the production of inflammatory cytokines interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) [30].

As the association of Alzheimer's with inflammatory factors is already clear, we have looked into the therapeutic perspectives of statins. Liandong Zhao et al. in 2016 using atorvastatin on mice for 18 months obtained very promising effects. The exact purpose of their experiment was to measure the level of hs-CRP, TNF-α, MCP-1, IL-1β and IL-6, whose initial levels in the control and research groups were the same. After 18 months from the beginning of statin therapy, inflammation markers were significantly reduced ($p < 0.01$), whereas in the group not treated with a statin such a decrease was not obtained [31]. Another study showed that treatment with simvastatin and atorvastatin showed a reduction of inflammation and memory deficits in vivo among APP/PS1 transgenic mice and in Aβ vaccinated mice [4]. A few more studies known to us achieved a reduction of inflammatory factors by statin therapy [25, 30]. As for the more accurate mechanism of immunosuppression, there are some inconsistencies associated with the fact that the mechanism is not fully understood. It is assumed that statins inhibit NF-kappaB, which initiates inflammatory mechanisms, additionally activating PPARα and PPARγ receptors, which leads to a decrease in the secretion of pro-inflammatory cytokines, CRP protein, chemokines, adhesion molecules, and some extracellular matrix metalloproteinases [17]. By measuring the inflammatory production of IL-1β and TNF-α in the hippocampus by immunohistochemistry — Western blot and RT-PCR, atorvastatin has been shown to protect LTP (long term potentiation) induction and spatial memory by suppressing inflammation induced by Aβ25-35, which has been confirmed by the addition of corticosteroids loaded with Aβ25-35 mice [30]. Numerous Iba-1 positive cells were observed after the administration of Aβ25–35. Iba1 is a calcium binding protein and is specifically expressed in microglia in the brain. The administration of Aβ25–35 not only increased the number of Iba-1 positive cells but also increased the levels of IL-1β mRNA and IL-1β protein. An ATV administration lowered the level of these components [5]. Aβ25-35-induced ATV-inhibited inflammatory response occurs by reducing FPP, and the anti-inflammatory effect can be blocked by supplementing FPP (Isoprenoids, including farnesylopyrophosphate). The anti-inflammatory effect of statins may also result from a decrease in the synthesis of nonsteroidal mevalonate derivatives, which is a precursor of ubiquinone, participates in the transport of electrons in the respiratory chain and performs antioxidant functions [17]. In one study in mice, to determine the effectiveness of inflammation, levels of cytokines such as IL-6, IL-1B, TNF-α and ACT were measured by Real-Time PCR. PCR results reported a decrease in cytokines in the hippocampus of simvastatin-treated mice relative to the control group [23]. On the other hand, simvastatin trials in people at high risk of AD after 9 months did not show a decrease in CRP levels [11]. Our position is supported by researchers observing neuropathology who believe that statins prevent the progression of AD by inhibiting inflammation [32].

The metabolism of brain cholesterol

The brain contains 23% of total cholesterol [5] and is the richest organ in this lipid [33]. The fact that there is so much of it is not without significance. It is synthesized in de novo brain with acetyl-CoA on the mevalonate pathway in the endoplasmic reticulum (ER). It regulates key biological functions such as signal transduction, myelin sheath formation and synaptogenesis [17]. Changing the level of membrane cholesterol may affect the cleavage of APP, favoring the accumulation of Aβ [37]. Mevalonate used together with atorvastatin improves its effect [24]. Removal of cholesterol from membranes has been shown to block long-term synaptic excitation (LTP) in the hippocampus. Rodent study results show that memory impairment in LDLr –/– mice is associated with an increased apoptotic mechanism in the brain region associated with memory formation, but not with the accumulation of cerebral amyloid-beta [24]. In vivo and in vitro studies suggest that an increase in blood cholesterol increases the production of Aβ in AD. CYP46A1 polymorphism (metabolizes cholesterol to 24-OHc) has been shown to correlate with low brain cholesterol and increased risk of AD [17, 34]. Hence, it is worth paying attention to cholesterol metabolites such as 24-hydroxycholesterol (24-OH) and 27-hydroxycholesterol (27-OH). They are brain cholesterol suppressors. 24-OH can cross the blood-brain barrier and on the periphery correlates with the level of cholesterol in the brain [4], reflects the number of active neurons in the brain, and thus the gray matter volume [33, 34]. In contrast, 27-OH accelerates cognitive deficits in AD in the case of hypercholesterolemia, where the increase in cholesterol affects the increase of its inflow to the brain [4]. In the autopsy of brains affected by dementia, 24-OH reduction and 27-OH increase can be seen. Zuliani et al. suggest that 24 (S)-hydroxycho-

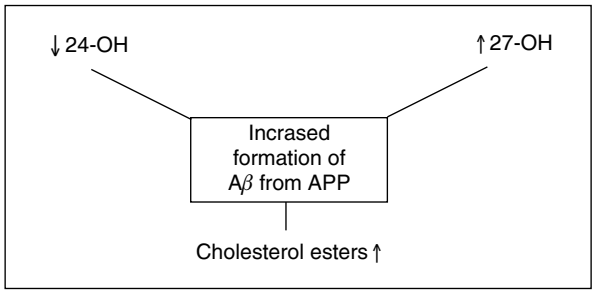

Figure 3. Impact of changes in cholesterol derivatives concentration on amyloid plaque deposition

lesterol levels may be elevated in the early stages of AD due to systemic inflammation [8]. It is suggested that 24S-hydroxycholesterol (SHC) is a biochemical marker of neurodegenerative diseases, as it is responsible for the transport of cholesterol through its enzymatic oxidation [1, 27].

Cholesterol binding to neurofibrillary tangles can be through phytillin, a protein highly expressed in lysosomes of neurons with neurofibrillary degeneration in AD [35]. ApoE is thought to be the major carrier of cholesterol in the CNS. APOEε4 selectively binds β-amyloid peptide, modulating its aggregation and clearance [11]. In addition to lowering Apo A-1 levels, statin therapy lowers ApoE levels [28]. People with the ApoE4/ApoE4 genotype treated with simvastatin showed better ADAS-cog results than those treated with a placebo. Cognitive functions were significantly better during 10 years of observation, which can be seen in the slower decline of the MMSE test [36]. Many studies confirm that the presence of ApoE4 increases the risk of late-onset of AD [32]. On the other hand, cholesterol transport for synaptogenesis and neuronal repair is difficult in patients with this dementia with the ApoE4 allele, so be careful with cholesterol-lowering drugs [37]. LXR (liver X receptor) has been shown to modulate brain cholesterol homeostasis. In AD, in animal models, treatment with LXR receptor agonists reduced inflammation and cerebral amyloid deposits. LXR stimulation increases APOE expression, reduces Tau protein and its hyperphosphorylation, and β-amyloid accumulation, reduces neuronal inflammation in the CNS [14]. Cholesterol esters (CE) induce Alzheimer's disease. By reducing CE, we reduce all varieties of Tau protein. Inhibition of cholesterol esterification by ACAT1 deletions protects against the deposition of pathological Tau protein. In AD, the ubiquitin-proteasome system is reduced, and it regulates the phosphorylation of the tau protein [24]. There is evidence that the low cholesterol characteristic of an aging brain also causes AD. Reducing the amount of cholesterol causes changes in the activity of receptors that inhibit e.g. GABAa and stimulate *e.g.* NMDA in the CNS [17]. Studies on mice with LDL receptor knockout (receptor dysfunction characteristic of hypercholesterolemia) of ApoB100 mice (ldlr 65 –/–) show learning problems in tasks in which the hippocampus is used and these problems become increasingly difficult with age [63]. Research by Hoglund and colleagues confirms that statins reduce cholesterol synthesis in the periphery and the CNS [28]. Atorvastatin reduces the level of desmosterols and lathosterols [24].

Practice and theory — the assessment of the effectiveness of statins in tests

General score

To fully understand the results of human studies, we present two key methods of assessing the effectiveness of therapy: MMSE and ADAS-COG. Mini-Mental State Exam (MMSE), a short screening test assessing cognitive function on a scale of 0 to 30, with higher results indicating better function. The second key way to assess progressive dementia changes is so-called the gold standard — the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) short neuropsychological assessment consisting of 11 questions to determine the cognitive state of the interlocutor. Although the in vitro study in animals is dominated by the tendency that statins reduce the risk of developing Alzheimer's disease, the most common in human studies is the lack of correlation between statin therapy and improved results.

Many people do not support the use of statins [38], and some studies of cholesterol-lowering drugs show that they do not affect AD [12]. In the ADNI cohort database study, researchers came to the conclusion that statins do not slow down the dementia process and although there is some relationship in such therapy in

Table 2. Table showing how the effects of statins on Alzheimer's disease are distributed in studies on dementia patients in the cited articles

Positive influence	Negative influence	Lack of significant influence
9, 16, 17, 25, 26, 27, 30, 32, 36, 41, 42, 44, 45, 59	40	5, 15, 18, 28, 38, 39, 43, 46, 47, 50, 60, 61

people with early cognitive changes, it does not reach value to be seen as a potential therapeutic path [39]. Clinical studies suggest that high doses of statins, although they may reduce Aβ load and delay AD progression but do not prevent the onset of the disease [32]. What's more, imaging studies have shown that statins have no effect seen in neuroimaging methods — and such therapy can potentially be associated with poorer integrity of white matter in the corpus callosum [40]. Considering the relationship between the choice of statin and therapy, one study showed that no significant changes in cognitive functions were observed between the effects of lovastatin, simvastatin and placebo [4]. Of course, there are works supporting statins - a controlled study of 6431 patients with mild to moderate Alzheimer's disease found that statin use was associated with slower AD progression [41]. In one study, the likelihood of AD suffering from statins decreased by 10 percent [42]. Studies on people using statins with heart disease and an APOE gene mutation showed a slower decline in learning ability over 6 years [43]. A recent large population study of several thousand people in Taiwan has shown that statistically, patients with one of the metabolic risk factors have an increased chance of developing AD or other dementias [6]. The study confirming this position showed that among people exposed to hypertension, diabetes, and hyperlipidemia the risk of developing dementia is higher [11]. During the ADAPT (Alzheimer's disease Anti-inflammatory Prevention Trial) study, which examined 2068 patients for three years and 6992 patients during a follow-up of 9.2 years, a 50% decrease in risk of AD was observed [44]. One study showed that continuous use of statins from the outset was associated with a significantly reduced risk of incidental dementia ($p = 0.0336$) and a tendency to reduce the risk of incidental dementia ($p = 0.0609$) compared to those who have never taken statins [45].

Low test results and numerous side effects [46] such as diarrhea or abdominal pain often accompany statin treatment - hence many people are skeptical about such therapy. What is more, some of the medical community believe that it is our duty to avoid excessive unnecessary medication and that statin therapy brings more problems than benefits [47]. In addition, even the most diehard statin defenders cannot deny that the reduction in central nervous system (CNS) cholesterol synthesis and concentration can potentially disrupt the functioning of cholesterol-rich myelin fibers [48]. Simvastatin and atorvastatin cause more death of astrocytes than other cholesterol-lowering drugs (efavirenz) [24]. However, there are also works that do not share the views of their predecessors. According to a meta-analysis from 2015, statins do not reveal side effects in people without dementia [17]. Defenders of the contribution of statins to neuroprotection have tried to use statins along with traditional Alzheimer drugs. In 2007, the effectiveness of galantamine, statin together with galantamine and statin alone was tested, as well as a placebo trial [46]. Although minimal changes were noted in the MMSE and Adas cog tests compared to the statin group and placebo, they were insignificant. The trial showed that these drugs do not exist as an additional element of therapy. However, there is a discrepancy in such research in which one study showed that lovastatin can synergistically enhance the effect of donepezil, which, on the other hand, the authors explain, may result from the fact that the drugs together improve the activity of NMDA receptors and mask acetylcholine by increasing the amount of circulation symptoms of dementia [49]. To our knowledge, another work has shown the addictive potential of donepezil and lovastatin combined therapy in a rat model where it was possible to induce an improvement in cognitive deficits [10].

There is indisputably a large variety of research on this subject. However, the question remains why according to some studies statins offer prospects and other studies dismiss them. Theoretically, blocking the amyloid cascade should translate into slowing down the dementia process. Many authors point out scientific errors in studies that show the relationship between statins and dementia. The testimony to this position is a large study involving 2,629 people showing a significant effect of statin use on reducing the risk of AD. The duration of the study lasted 8 years, which may indicate that the effect of statins is obtained after a long time [45]. General studies on statins show that the strength of a substance is more important than its property, and the duration of action is important. In 2015, atorvastatin and rosuvastatin have been shown to be more effective [17]. Some researchers [40] accuse other studies of excluding people with lipid disorders from the studies, and these had a greater chance of obtaining positive effects of such therapy. It is worth remembering that each study model has its pros and cons. Different study results may be due to the fact that although most studies have included similar variables, some differences can be found that could potentially affect the final result. One of the disadvantages of the study: case-control study, unknown duration of statin use and no data on a specific type of medication, not taking into account comorbidities [17]. As other researchers note [35], the diversity of results may be due to limitations of prospective trials such as short observation time, short statin use time, lack of dementia type classification, lack of control of other vascular risk factors, or monitoring of statin compliance.

The contradictory results observed in the published literature may partly result from differences in the examined patient populations in terms of basic cognitive functions and cholesterol levels, as well as

the target endpoints of individual studies, which limits the proper interpretation of these important data [51]. There is a wide divergence among races regarding the risk of AD, the incidence of AD was higher among Latin and black women (2.29% and 2.11% respectively) than white. White men had the lowest incidence of AD (1.23%), less than "other" women (1.37%) and men (1.29%). The incidence of AD was 1.86% and 1.94%, respectively in Latin and black men [42]. Clinical manipulations of statins to lower cholesterol to prevent and treat neurodegeneration have proved ineffective. It is postulated that the beneficial effect of statins may be due to their anti-inflammatory effect rather than lowering cholesterol [8], which makes sense especially since no correlation was found between the results of ADAS-cog and the concentration of total cholesterol or triglycerides [36]. The problem is that the tests detect only all cholesterol, the free and esterified cholesterol [24].

Further research directions

To make any breakthrough in statin work, you need to focus your ambitions on a specific statin effect. Analyzing the overall work, you can think of two effects — the obvious reduction in cholesterol in the CNS and the fully understood pleiotropic effect on the expression of proapoptotic proteins. Research of the last decade, referring to problems with cholesterol balance and its deficiency leading to potential neurotoxicity, try to understand the pleiotropic effect at the cellular level and the results of such work must be admitted are at least promising. The authors of one of the works [52] devoted to the analysis of Van der Kent and colleagues' results noted in the paper that inhibition of cholesterol synthesis and absence of interruptions of the isoprenoid pathway significantly reduces pTau levels. This in turn indicates that stored cholesterol esters in cells are responsible for the growth of pTau in human neurons, unlike what was thought to be the fault of other cholesterol synthesis intermediates [24]. These studies have shown that although cholesterol esters themselves do not intensify the increase in pTau levels their decreased level intensifies proteasomal activity, which in turn translates into pTau degradation [52]. Van der Kent et al. also confirm the cytotoxicity of statins and although they affect pTau degradation, the consequence of cholesterol-lowering and membrane integrity impairment leads to the destruction of astrocytes, which in the long run translates into further neurological defects. This theory would explain why, despite the observation of pTau protein reduction in other studies, no improvement was observed in the results of Adas-cog or MMSE [42]. Van der Kent finds a solution in the use of Efavirenz, which reduces cholesterol esters without a cytotoxic effect [24]. This suggests that although statins may not be solutions, they can be a hint for an appropriate Alzheimer treatment. Looking further at another aspect of statins, look at research conducted by YUNZI LI, which showed that in cell culture injected with Aβ1-42 plaques, statins reduce caspase-3 levels, inhibit the release of cytochrome C from the mitochondria and increase the amount of Bcl antiapoptotic proteins 2/Bax relative to group Aβ1-42 without statins. In the same study, SV significantly suppressed ROS accumulation at all three concentrations compared to the 10 μM Aβ1-42 treatment group. As the authors of this work emphasize, the mitochondrial pathway is the main pathway signaling apoptosis, and the substance that inhibits the process of apoptosis may prove to be crucial for stopping the progression of AD [53]. More evidence is provided in a 2016 study where, in a rat model, Iranian medical doctors proved that simvastatin induces the expression of the neuroprotective protein Klotho, which prevents oxidative stress by induction of MnSOD in hippocampal neurons. The same researchers showed that statins did not slow down the cognitive deficit, but they prevented the loss of reference memory [64]. Western blotting results have shown that statins reduce the concentration of miR-106b, which leads to apoptosis by increasing the expression of p53, Bax, caspase-3 and -9 [23].

Research in 2019 [54] aimed to show the relationship between the levels of Sestryn, Sirtuin and statins. Researchers chose these proteins because of their potential neuroprotective mechanisms that could prevent amyloid beta-induced neurodegeneration. Sestrins (SESN2), whose expression is higher in cells with DNA damage or in response to Ab proteins. Their growth stimulates autophagy. Sirtuins are a group of deacetylases that regulate transcription and also have other functions, i.e. cell repair, suppression of inflammation. The SIRT1 subgroup lowers Aβ levels, reducing its production from APP. Atorvastatin has been found to enhance the expression of the SIRT1 protein. youth protein, which protects neurons [54]. Hence, this work [54] undertook to measure the level of this protein. Studies [54] noted that inhibition of atorvastatin in the growth of SESN2, which was induced by oxidative stress caused by beta-amyloid, is indicative of the anti-inflammatory effect of statins. In contrast, the increase in SIRT1 induced by this statin indicates its neuroprotective effect. Of course, not all researches support the neuroprotective effect of statins [55], the cholesterol synthesis enzyme DHCR24 (also called Seladin-1; Selective Alzheimer's Disease Indicator-1), which normally acts neuroprotectively, is regulated in affected neurons [56]. By inhibiting caspase 3, Seladin-1 provides protection against apoptosis and oxidative stress and preventing its reduction may be crucial in therapy [55]. Among the works highlighted by us, it is worth pointing out that simvastatin regulates hippocampal cell apoptosis

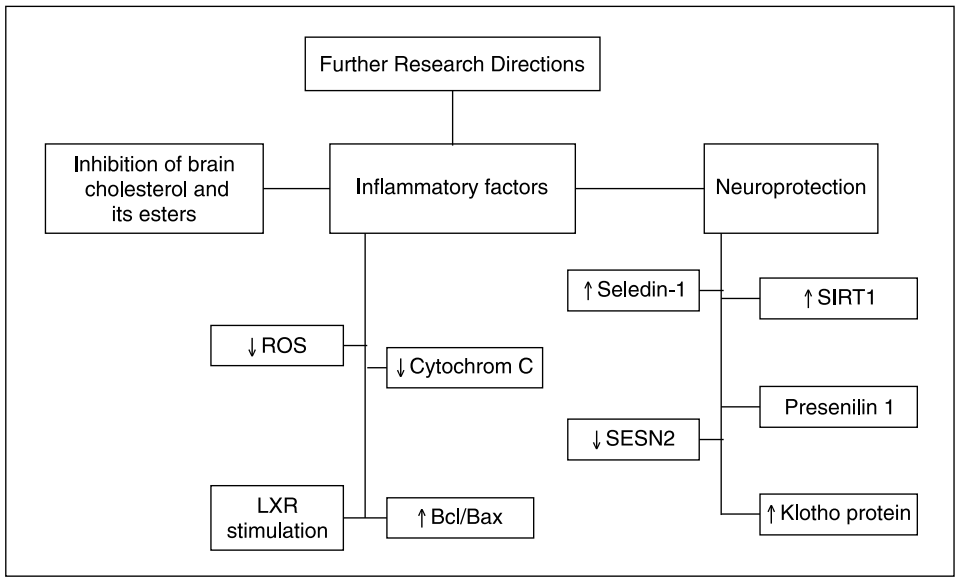

Figure 4. Further research directions [16, 24, 52–56]

by ATF-6 mediated ERK/AKT signaling pathway in the CA1 region [57]. Another potential mechanism may be activation of the phospho-MAPK/ERK pathway by lovastatin, which reduces the neurotoxic effect of β-amyloid, regardless of cholesterol [58]. It is also paying attention to the mutation of presenilin 1 protein (PS1). Research by The Hopkins University in Baltimore shows the relationship between FAD-1 linked PS1 and aggregation of βamyloid. Also observed together with APP [13].

Conclusion

It is known that Aβ and vascular risk factors are involved in the pathogenesis of AD, but many aspects of AD pathogenesis are poorly understood [50]. Therefore, it is too early to say that statins are ineffective in AD. Some researchers [36] hypothesize that if statins have a preventive or therapeutic effect, this would be more pronounced in people bearing the ApoE4 allele and that statins would delay AD symptoms and progression. This indicates another aspect we have discussed - the selection of the right patient for therapy. From the perspective of good therapy, various risk factors for AD need to be considered [12] such as hypertension. According to the researchers, the influence of factors such as atherosclerosis and CNS blood supply disorders can affect different patients to varying degrees. The right type of statin, for the right person, can be an inexpensive way to reduce AD burden at the right time [42].

In 2018, the French Minister of Health decided that the drugs donepezil, galantamine, rivastigmine, and memantine were removed from the list and therefore would no longer be reimbursed by the national health insurance system [6]. That is why it is so important to reduce the occurrence of this disease by eliminating risk factors. Perhaps if statins are not solution, researchers should not give up, because statins can provide more information about the pathophysiology of the disease and cognition will enable targeted therapy. What's more, based on the statins of their metabolites, you can create substances that will be able to give positive influence to statins without their neurotoxic effect. Hence, our work states that there is a potential in statin therapy, but their impact should be fully understood so that they can be used in the prevention and treatment of Alzheimer's.

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References

1. Bernadette McGuinness and Peter Passmore. Can Statins Prevent or Help Treat Alzheimer's Disease? Journal of Alzheimer's Disease 20 (2010) 925–933
2. James Shepherd, Gerard J Blauw, Michael B Murphy, Edward L E M Bollen, Brendan M Buckley, Stuart M Cobbe et al. Pravastatin in

elderly individuals at risk of vascular disease (PROSPER) a ramoized controlled trial; The Lancet 2002 vol.360 1623-1630
3. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in high risk individuals: a randomised placebo-controlled trial. Lancet. 2002 Jul 6;360(9326):7-22.
4. Raúl Loera-Valencia, Julen Goikolea, Cristina Parrado-Fernandez, Paula Merino-Serrais, Silvia Maioli. Alterations in cholesterol metabolism as a risk factor for developing Alzheimer's disease: Potential novel targets for treatment; Journal of Steroid Biochemistry and Molecular Biology 190 (2019); 104 - 114
5. Susanna C. Larsson, Hugh S. Markus. Does treating Vascular Risk Factor Prevent Dementia and Alzheimer's Disease? A systematic Review and Meta Analysis; Journal of Alzheimer's Disease 64 (2018) 657–668
6. R. Sengoku Aging and Alzheimer's disease pathology; Neuropathology 2020 40(1) 22-29
7. Christophe Bintener, Owen Miller, Jean Georges, Alzheimer, Dementia in Europe 2019 Yearbook, Estimating the prevalence of dementia in Europe
8. McFarlane O, Kędziora-Kornatowska K, Cholesterol and Dementia: A Long and Complicated Relationship; Current Aging Science 2020, 13; 42-51
9. M. Rutkowska, W. Słupski Prospects of statins as therapeutic agents in neurodegenerative disorders; Farmakoterapia w Psychiatrii i Neurologii 2015, 31(1) 45-56
10. A. Eskandary, A. A. Moazedi H. Najaph zade varzi, M. R. Akhond. Combined Effects of Donepezil and Lovastatin on Cognition Deficit Induced by Bilateral Lesion of the Nucl. Basalis Magnocellularis in a Rat Model of Alzheimer's Disease; Neurophysiology, Vol. 50, No. 2, April, 2018; 99-107
11. Cuperlovic-Culf M, Badhwar A Recent advances from metabolomics and lipidomics application in Alzheimer's disease inspiring drug discovery; Expert Opin Drug Discov. 2020 Mar;15(3):319-331
12. Simona Luzzi, Lucia Vella, Marco Bartolini, Leandro Provinciali and Mauro Silvestrini. Atherosclerosis in the Evolution of Alzheimer's Disease: Can Treatment Reduce Cognitive Decline? Journal of Alzheimer's Disease 20 (2010) 893–901
13. Jakub Husejko, Monika Prylińska, Natalia Skierkowska et al. What affects the risk of developing Alzheimer's disease? Overview of risk factors; J Educ Health Sport vol. 8 no. 7 (2018)
14. Kevin Mouzat, Aleksandra Chudinova, Anne Polge, Jovana Kantar, William Camu, Cédric Raoul et al. Regulation of Brain Cholesterol: What Role Do Liver X Receptors Play in Neurodegenerative Diseases? Int. J. of Mol. 2019, 20,3858
15. Marta Mejías-Trueba, María Antonia Pérez-Moreno and María Ángeles Fernández-Arche, Systematic review of the effi cacy of statins for the treatment of Alzheimer's disease, Clinical Medicine 2018 Vol 18, No 1:54-61
16. Hande Celik, Hande Karahan and Pelin Kelicen-Ugur Effect of atorvastatin on Ab1–42-induced alteration of SESN2, SIRT1, LC3II and TPP1 protein expressions in neuronal cell cultures; JPP 2019 72(3):424-436
17. Sandra Torres, Carmen M. García-Ruiz, Jose C. Fernandez-Checa. Mitochondrial Cholesterol in Alzheimer's Disease and Niemann-Pick Type C Disease; Frontiers in Neurology 2019, Vol. 10, Article 1168
18. Jana Crum, Jeffrey Wilson, Marwan Sabbagh. Does taking statins affect the pathological burden in autopsy-confirmed Alzheimer's dementia?; Alzheimer's Research&Therapy (2018); 10;104
19. Tahmina Nasrin Poly, Md. Mohaimenul Islam, Bruno Andreas Waltherf, Hsuan-Chia Yang, Chieh-Chen Wu, Ming-Chin Lina et al. Association between Use of Statin and Risk of Dementia: A Meta-Analysis of Observational Studies; Neuroepidemiology 2019
20. C. Cramer, PhD M.N. Haan, DrPH S. Galea, MD, DrPH K.M. Langa, MD, PhD J.D. Kalbfleisch, PhD Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study; Neurology, 2008; 71 (5)
21. Neda Shakour, Vanessa Bianconi, Matteo Pirro, George E. Barreto, Farzin Hadizadeh, Amirhossein Sahebkar, In silico evidence of direct interaction between statins and β amyloid, Wiley Journal of Cellular Biochemistry 2018; 1-6
22. Jianhui Wang, Xiaorui Cheng, Xiaorui ZhangGang Liua, Yongan Wang, Wenxia Zhoua et al. A combination of indomethacin and atorvastatin ameliorates cognitive and pathological deterioration in PrP-h$A\beta$P-Pswe/PS1 E9 transgenic mice; Journal of Neuroimmunology 330 (2019), 108-115
23. Wenzhong Huang, Zhenyu Li, Liandong Zhao, Wei Zhao, Simvastatin ameliorate memory deficits and inflammation in clinical and mouse model of Alzheimer's disease via modulating the expression of miR--106b, Biomedicine & Pharmacotherapy 92 (2017) 46-57 Elsevier
24. Rik van der Kant, Vanessa F. Langness, Cheryl M. Herrera,Steven L. Wagner, Anne G. Bang, Lawrence S.B. Goldstein Cholesterol Metabolism Is a Druggable Axis that Independently Regulates Tau and Amyloid-b in iPSC- Derived Alzheimer's Disease
25. Robert G. Riekse, Eric C. Petrie, James B. Leverenz, Darcy Vavrek, Simona Vuletice. Effect of statins on Alzheimer's disease biomarkers in cerebrospinal fluid; Journal of Alzheimer's Disease 2006 (10) 399-406
26. Othman Ghribi. Preservation of the blood brain barrier integrity may underlie neuroprotective effects of statins in Alzheimer's disease; Journal of Alzheimer's Disease 10 (2006) 407–408
27. Sjogren M, Gustafsson K, Syversen S. Annika Olsson, Åke Edman Pia Davidsson et al. Treatment with simvastatin in patients with Alzheimer's disease lowers both alpha- and beta-cleaved amyloid precursor protein. Dement Geriatr Cogn Disord 2003;16:25–30
28. Hoglund K, Wallin A, Blennow K. E ect of statins on β-amyloid metabolism in humans: potential importance for the development of senile plaques in Alzheimer's disease; Acta Neurol Scand 2006: 114 (Suppl. 185): 87–92. Blackwell Munksgaard 2006
29. Naoki Yamamoto, Yoko Fujii, Rika Kasahara, Mamoru Tanida, Kentaro Ohora,Yoko Ono, Kenji Suzuki et al. Simvastatin and Atorvastatin Facilitates Amyloid β-protein Degradation in Extracellular Spaces by Increasing Neprilysin Secretion from Astrocytes through Activation of MAPK/Erk1/2 Pathways? GLIA Volume 64, No. 6 952-962 2016 Wiley Periodicals
30. Liandong Zhao, Tingting Chen, Chonghui Wang, Guoxi Li, Wenhui Zhi, Jun Yin et al. Atorvastatin in improvement of cognitive impairments caused by amyloid β in mice: involvement of inflammatory reaction; Zhao et al. BMC Neurology (2016) 16:18
31. Liandong Zhao, Qitao Zhao, Yong Zhou, Ying Zhao and Qi Wan. Atorvastatin May Correct Dyslipidemia in Adult Patients at Risk for Alzheimer's Disease Through an Anti-Inflammatory Pathway; CNS&Neurological Disorders - Drug Targets, 2016, 15, 80-85
32. Wolozin B, Manger J, Bryant R, Cordy J, Green RC, McKee A. Re-assessing the relationship between cholesterol, statins and Alzheimer's disease. Acta Neurol Scand 2006: 114 (Suppl. 185): 63–70
33. M. Marciniec, W. Kwak, A. Nowak, A. Filip The metabolism of cholesterol and role of statins in Alzheimer's disease; Neurologia Praktyczna 1/2015; 8-15
34. Lütjohann D, Breuer O, Ahlborg G et al. Cholesterol homeostasis in human brain: evidence for an age-dependent flux of 24S-hydroxycholesterol from the brain into the circulation; Proc Natl Acad Sci U S A. 1996 Sep 3;93(18)
35. Nagaendran Kandiah, Howard H. Feldman, Therapeutic potential of statins in Alzheimer's disease, Journal of the Neurological Sciences 283 (2009) 230-234, Elsevier
36. Nophar Geifman , Roberta Diaz Brinton, Richard E. Kennedy, Lon S. Schneider, and Atul J. Butte, Evidence for benefit of statins to modify cognitive decline and risk in Alzheimer's disease, Geifman et al. Alzheimer's Research & Therapy (2017) 9:10
37. Elisa Biondi, Prescription of lipophilic statins to Alzheimer's disease patients: some controversies to consider, Neurol Sci (2011) 32:195–201, Springer
38. Tess Lang, MD; Joseph Clifton, PharmD, Jon Neher, MD. Do statins alter the risk or progression of dementia? The journal of family practice 2018, vol.67 no.9 578-579
39. Kemp EC, Ebner MK, Ramanan S, Godek TA, Pugh EA, Bartlett HH. Statin Use and Risk of Cognitive Decline in the ADNI Cohort; Am J Geriatr Psychiatry. 2019 Nov 11
40. Vijay K. Ramanan, Scott A. Przybelski, Jonathan Graff-Radford, Anna M. Castillo, Val J. Lowec, Michelle M. Mielke, Rosebud O. Roberts et al. Statins and Brain Health: Alzheimer's Disease and Cerebrovascular Disease Biomarkers in Older Adults, Journal of Alzheimer's Disease
41. Lin FC, Chuang YS, Hsieh HM, Lee TC, Chiu KF, Liu CK et al. Early statin use and the progression of Alzheimer disease: a total population--based case-control study. Medicine. 2015;94:e2143
42. Julie M.Zissimopoulos, PhD; Douglas Barthold, PhD; Roberta Diaz Brinton, PhD; Geoffrey Joyce, PhD,Sex and Race Differences in Association Between Statin Use and the Incidence of Alzheimer Disease, JAMA Neurology American Medical Association
43. Katherine Samaras, Steve R. Makkar, John D. Crawford, Nicole A. Kochan, Melissa J. Slavin, Wei Wen et al. Effects of Statins on Memory, Cognition and Brain Volume in the Elderly; JACC 2019 vol. 74 no. 21 2554-2568
44. D. Larry Sparks, Richard J. Kryscio, Marwan N. Sabbagh, Donald J. Connor, Lisa, M. Sparks and Carolyn Liebsack, Reduced risk of incident AD with elective statin use in a clinical trial cohort, Current Alzheimer Research, 2008, 5, 416-421

45. Hugh C. Hendrie, Ann Hake, Kathleen Lane, Christianna Purnell, Frederick Unverzagt, Valerie Smith-Gamble, Jill Murrell et al. Statin use, incident dementia and alzheimer diSeaSe in elderly african americans, Ethnicity&Disease, Volume 25, Number 3, Summer 2015 (345- 354)
46. Bengt Winblad,Vesna Jelic,nPaul Kershaw and Joan Amatniek. Effects of Statins on Cognitive Function in Patients with Alzheimer's Disease in Galantamine Clinical Trials; Drugs Aging 2007 24(1); 57-61
47. Slade A. Suchecki, DO, Paul V. Aitken, Jr, MD, MPH, Rick Potts, MD. Do statins delay onset or slow progression of Alzheimer's dementia? The Journal of Family Practice 2005 vol.54 no.7 626-627
48. Bob G. Schultz, Denise K. Patten and Daniel J. Berlau, The role of statins in both cognitive impairment and protection against dementia: a tale of two mechanisms, Translational Neurodegeneration (2018) 7:5
49. A. Eskandary, A. A. Moazedi, H. Najaph zade varzi, and M. R. Akhond, Combined Effects of Donepezil and Lovastatin on Cognition Deficit Induced by Bilateral Lesion of the Nucl. Basalis Magnocellularis in a Rat Model of Alzheimer's Disease, Neurophysiology, Vol. 50, No. 2, April, 2018
50. Ting Liang, Rong Li, Oumei Cheng, Statins for Treating Alzheimer's Disease: Truly Ineffective, European Neurology 2015;73:360–366
51. Danielle Yanuck, Christos G. Mihos, and Orlando Santana, Mechanisms and Clinical Evidence of the Pleiotropic Effects of the Hydroxy-Methyl-Glutaryl-CoA Reductase Inhibitors in Central Nervous System Disorders: A Comprehensive Review international Journal of Neuroscience, 122 619-629, 2012
52. Blanchard JW, Tsai LH, Unraveling the Paradox of Statins with Human Neurons: New Leads in Alzheimer's Disease, Cell Stem Cell 24, March 7,2019, 2019 Elsevier Inc. (347-348)
53. Yunzi Li, Qian Liu, Jing Sun, Jin Wang, Xinfeng Liu and Jing Gao, Mitochondrial protective mechanism of simvastatin protects against amyloid β peptide-induced injury in SH-SY5Y cells, INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 41: 2997-3005, 2018
54. Hande Celik, Hande Karahan, and Pelin Kelicen-Ugur. Effect of atorvastatin on Ab1–42-induced alteration of SESN2,SIRT1, LC3II and TPP1 protein expressions in neuronal cell cultures, 2019 Royal Pharmaceutical Society, Journal of Pharmacy and Pharmacology (1-13)
55. Crameri A, Biondi E, Kuehnle K, Lutjohann D, Thelen KM, Perga S, Dotti CG, Nitsch RM, Ledesma MD, Mohajeri MH (2006) The role of seladin-1/DHCR24 in cholesterol biosynthesis and Ab generation in vivo. EMBO 25(2):432–443
56. Brier MR, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J Tau and Aβ imaging, CSF measures and cognition in Alzheimer's disease Tau and A-beta imaging, CSF measures, and cognition in Alzheimer's disease. Sci Transl Med. 2016; 8, 338
57. Naoki Yamamoto, Yoko Fujii, Rika Kasahara, Mamoru Tanida, Kentaro Ohora, Yoko Ono, Kenji Suzuki et al. Simvastatin ameliorates cognitive impairments via inhibition of oxidative stress - induced apoptosis of hippocampal cells through the ERK/AKT signaling pathway in a rat model of senile dementia, 2016 Wiley Periodicals, Inc. Volume 64, No. 6 (952- 962)
58. Liang Zhao, Yan Xiao, Jin Xiu, Long-Chun Tan, Zhi-Zhong Guan, Protection against the Neurotoxic Effects of β-Amyloid Peptide on Cultured Neuronal Cells by Lovastatin Involves Elevated Expression of α7 Nicotinic Acetylcholine Receptors and Activating Phosphorylation of Protein Kinases,.The American Journal of Pathology, 188(4), 1081–1093
59. Magnus Sjögren, Kina Gustafsson, Steinar Syversen, Annika Olsson, Åke Edman, Pia Davidsson, Anders Wallin, Kaj Blennow, Treatment with Simvastatin in Patients with Alzheimer's Disease Lowers both α- and β-Cleaved Amyloid Precursor Protein; Dementia and Geriatric Cognitive Disorders 2003;16:25–30
60. M. Sano, K.L. Bell, D. Galasko, et al., A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease, Neurology 2011;77;556-563 American Academy of Neurology
61. H. H. Feldman, R. S. Doody, M. Kivipelto, et al. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease LEADe, Neurology 2011;77;556-563, American Academy of Neurology
62. Z. ZHAO, S. ZHAO, N. XU, C. YU, S. GUAN, X. LIU, L. HUANG et al. Lovastatin improves neurological outcome after nucleus basalis magnocellularis lesion in rats, Neuroscience 167 (2010) 954 –96
63. Jade de Oliveira, Daiane F. Engel, Gabriela C. de Paula, Helen M. Melo, Samantha C. Lopes,Camila Tiefensee Ribeiro. LDL receptor Deficiency does not Alter Brain Amyloid-Beta Levels but Causes an Exacerbation of Apoptosis; Journal of Alzheimer's Disease 2020, 73, 585-596
64. Soheila Adeli, Maryam Zahmatkesh, Gholamreza Tavoosidana, Morteza Karimian, Gholamreza Hassanzadeh, Simvastatin enhances the hippocampal klotho in rat model of streptozotocin-induced cognitive decline, Progress in Neuro-Psychopharmacology & Biological Psychiatry 72 (2017) 87-94 Elsevier