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REVIEW ARTICLE

Alzheimer Disease—No Target for Statin Treatment. A Mini Review

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Abstract Nosologically, Alzheimer disease (AD) is not a single disorder. A minority of around 400 families worldwide can be grouped as hereditary in origin, whereas the majority of all Alzheimer cases (approx. 25 million worldwide) are sporadic in origin. In the pathophysiology of the latter type, a number of susceptibility genes contribute to the disease among which are allelic abnormalities of the apolipoprotein E4 gene pointing to a link between disturbed cholesterol metabolism and sporadic AD. Cholesterol is a main component of membrane composition enriched in microdomains and is functionally linked to the proteolytic processing of amyloid precursor protein (APP). In sporadic AD, a marked diminution of both membrane phospholipids and cholesterol has been found. Evidence has been provided that high plasma cholesterol may protect from AD. In contrast to these well documented abnormalities observed in AD patients, it was assumed that an elevated cholesterol concentration might favour the generation of β-amyloid and, thus, AD. However, a series of in vitro-and in vivo-studies did not provide evidence for the assumption that an enhanced cholesterol concentration increased βA4-production. A harsh reduction of membrane cholesterol only caused a ''beneficial'' effect of APP metabolism. However, this experimentally induced condition may not be compatible to sporadic AD. The application of statins in sporadic AD did not yield results to assume that this therapeutic strategy may prevent or treat successfully sporadic AD.

Keywords Alzheimer disease · Membrane · Cholesterol · Statins · Amyloid

Introduction

Alzheimer disease (AD) is the most prominent neurodegenerative disorder. With respect to its nosology, AD is not a single disorder although both its clinical phenotype and morphologic brain abnormalities are fairly uniform. Evidence has been provided that a very small proportion of 404 families worldwide (by August 2006) of all Alzheimer cases is caused by missense mutations in the presenilin gene 1 on chromosome 14 (315 families ~78%), in the presenilin gene 2 on chromosome 1 (18 families ~4%), and in the amyloid precursor protein (APP) gene on chromosome 21 (71 families ~18%) (http://molgen-www.uia.ac.be//ADMutations//) leading to autosomal dominant familial AD with an early onset. These mutations explain well the genetically induced excess formation of the APP derivative βA4 which aggregates to form amyloid deposited as neuritic plaques [1]. In contrast, the great majority of patients suffering from AD (approx. 25 million patients worldwide) is sporadic in origin.

Beside age as the main risk factor, a number of susceptibility genes were found contributing to the

Dedicated to Professor John P. Blass.

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generation of sporadic AD. Of greatest significance in this respect are a single nucleotide polymorphism in the gene coding for 11β-hydroxysteroid dehydrogenase I [2], and allelic abnormalities of the apolipoprotein E4 (APOE) gene on chromosome 19 (for review see 3) affecting cholesterol metabolism in that plasma total and low-density lipoprotein cholesterol were found to be elevated [4–6].

The association of APO E4 allele and an increased risk of AD may point on a link between elevated cholesterol and AD. However, several clinico-epidemiological studies did not yield uniform results. Increased cholesterol levels at ages 70 were not found to be associated with an elevated risk of dementia between ages 79 and 88 [7, 8]. In contrast, exposure to vascular risk factors inclusive enhanced cholesterol during midlife increased the risk of dementia in late life which was reduced by lipid-lowering agents [9, 10]. In a predictive study, most AD patients carrying the APOE 4 gene were found to have lower total cholesterol levels than controls in a case–control study [11]. Otherwise, APOE-4 allele carriers with high serum levels of total cholesterol and high systolic blood pressure at midlife were at an elevated risk to develop AD in older ages. This risk was highest in subjects carrying the APOE-4 allele and having high serum cholesterol and increased systolic blood pressure [12–14]. In all studies cited above, the diagnosis of AD was made on the basis of clinico-psychometric tests only demonstrating the existence of dementia symptoms without detailed differentiation of its origin. However, the ascertainment of the causatively different AD needs neuroimaging, EEG and cerebrospinal fluid (CSF) markers additionally.

Based on the above epidemiological studies, on the strong connection found between elevated plasma cholesterol and βA4 generation in transgenic mice [15], and on the association of both APP and βA4 with cholesterol-rich membrane domains [16, 17], it was assumed that both the generation and clearance of βA4 are regulated by cholesterol [18]. Finally, this concept that high concentration of brain cholesterol leads inevitably to abnormal βA4 accumulation as the main cause of AD [1] prompted investigatiors to use statins for prevention and treatment of AD in experimental and clinical studies. However, a number of issues do not support this concept. (1) It has not been proven that excess formation of βA4 is necessary for the generation and the development of sporadic AD [19]. (2) Transgenic mice models of AD may represent its hereditary type and have not been shown to be valid for sporadic AD. (3) Serum cholesterol has not been demonstrated to penetrate the blood–brain barrier, i.e. provided cholesterol were increased in the serum compartment in sporadic AD, it might have no impact on its concentration in the brain compartment ([20, 21]; see also below). (4) The state of the neuronal membranes of AD patients, in particular its composition of phospholipids and cholesterol, may not have been considered in the therapeutic strategy using statins.

It becomes, thus, obvious that the role of brain cholesterol is conflicting for the development of sporadic AD. Therefore, in this short review, its role is discussed in terms of the physiological significance and in terms of the pathophysiological impact to sporadic AD, also contributing to the question whether or not the use of statins to reduce brain cholesterol is of benefit for patients suffering from sporadic AD.

Formation and function of cholesterol in the healthy adult brain

In the mammalian central nervous system (CNS), cholesterol is synthesized exclusively by de novo synthesis reaction from acetyl-CoA in the 3-hydroxy-3-methylglutaryl-CA (HMG-CoA) reductase reaction by oligodendrocytes, astrocytes and neurons [22]. In vitro studies showed a cholesterol shuttle from astrocytes to neurons that is mediated by apoE [23]. Plasma lipoproteins are unable to cross the blood–brain barrier [20, 21]. Serum cholesterol levels have been demonstrated to have no effect on HMG-CoA reductase and its activity in the brain [24], and on total brain cholesterol levels [25].

Cholesterol synthesis via the HMG-CoA reductase reaction needs additional proteins such as seladin-1 which is highly expressed in almost all neurons, and energy [20, 26, 27]. The formation/availability of both acetyl-CoA and energy as ATP in the brain has been demonstrated to be controlled by the neuronal insulin/insulin receptor signal transduction cascade [28]. Cholesterol is removed from the brain by the neural rate-limiting enzyme cholesterol 24-hydroxylase which mediates the hydroxylation of cholesterol to 24-hydroxycholesterol the concentration of which was found in the brain compared to other organs and that can pass the blood–brain barrier. Cholesterol 24-hydroxylase is encoded by the CYP46 gene [29–31].

Cholesterol serves as the basic compound from which neurosteroids derive [32]. Glia-derived cholesterol has been demonstrated to promote synaptogenesis in nervous tissue [23]. Cholesterol has been found to stimulate neurite outgrowth in rabbit dorsal root ganglion neurons what was accentuated by apoE [23a]. Synaptic plasticity depends on a well-balanced cholesterol

homeostasis mediated by apoE [33]. The latter also has been shown to play an important role in the translocation of cholesterol from astrocytes to neurons in mouse brain under long-term (24 weeks) environmental stimulation [23b]. Its greatest significance, however, has cholesterol as an important component of plasma membranes of every brain cell. Its concentration in the CNS has been found to be higher than in any other tissue and accounts for 23% of the sterol of the whole body pool [22]. In cell membranes, cholesterol is asymmetrically distributed in the cytofacial and exofacial layer with higher concentration in the former ensuring fluidity and function [34].

Concentration and distribution of membrane cholesterol are tightly regulated by the cell [35] whereby around 75% of free cholesterol resides in the cytofacial layer and around 25% in the exofacial layer. Cholesterol plays an essential role in the regulation of synaptic function and plasticity [36]. In the exofacial leaflet of the lipid bilayer, microdomains (lipid rafts) are located that are enriched in cholesterol, glycosphingolipids and acylated proteins. Beside its essential role in signal transduction, they are assumed to be involved in processing of the APP [37–39].

The asymmetric distribution of cholesterol in the exofacial and cytofacial layers along with predominance of fatty acids in the exofacial layer maintains the distance between the two layers and, thus, the biophysical properties of membranes, also supported by the asymmetric distribution of the phospholipids, ethanolamine phosphoglyceride (PE) mainly facing the inside, and choline phoshoglyceride the outside of the membrane [40]. Intercalated in this fluid structure are proteins such as ion channels, receptors, membrane-bound enzymes etc [41]. Both structure and function of membranes have been found to be also ensured by a normal cellular energy state [42].

Cerebral membranes, cholesterol and aging

There is ample evidence to show that aging is the main risk factor for neurodegenerative processes such as sporadic AD. With aging, a multitude of inherent variations in fundamental metabolic processes mainly in glucose/energy metabolism, and in related metabolism, and its control are set into motion at the cellular, molecular and genetic levels which frequently result in functional imbalancies of regulative systems [43]. Age-related changes in membrane composition inclusive cholesterol will have to be discussed in more detail. Two different aspects may be of significance for membrane function: Loss of lipids, and displacement of constituents within the bilayer. In human brain, the concentrations of the major membrane lipids decreased by 18% and 21% (phospholipids), by 18% and 19% (cholesterol), and by 11% and 18% (gangliosides) in frontal and temporal cortices between 20 and 100 years of age [44, 45]. In another study, cholesterol started to fall beyond the age of 69 years in cerebral gray and white matter, and in very old age in the hippocampus, too [46]. In contrast, the cholesterol concentration did not change in cerebral cortex and hippocampus of 24-month-old (aged) rats [47]. With respect to the relation of unsaturated and saturated fatty acids in membranes, a shift was found in favour of the latter [48]. The decreased insertion of arachidonic acid in membrane lipids associated with an increase in arachidonoyl-CoA [49], and the increase of cholesterol in the exofacial layer associated with a reduction in the cytofacial layer altering cholesterol asymmetry [34] were found to be age-related changes. All together, these changes are in agreement to that normal aging changes both structure and function in brain membranes leading to varied function of e.g. ion channels, membrane fluidity, receptors, etc. The latter are markedly modified in structure [49a] and number comprising the insulinergic [43], acetylcholinergic [49b] glutamatergic [49c] and dopaminergic transduction systems [49d]. These changes may have marked impacts in the development of multifold disturbances accompanying neurodegenerative diseases in general and sporadic AD in particular.

Cholesterol metabolism in sporadic AD brain

One major metabolic abnormality in sporadic AD is perturbed cerebral glucose metabolism [50–52]. At the cellular level, the diminished cerebral glucose utilization may be mediated by reduced capacities of key enzymes working in glycolytic glucose breakdown leading to both reduced formation and oxidation of acetyl-CoA [53–55]. The reduced availability of acetyl-CoA has been found to reduce both the synthesis of acetylcholine in the presynaptic neuron [56] and the formation of ATP [57, 58]. In context with this article, both less acetyl-CoA and the depletion of ATP may have marked effects on the activity of HMG-CoA reductase which is inactivated by the ATP-dependent activation of the AMP-mediated kinase [59] although mRNA HMG-CoA reductase was not found to be modified [60]. This concerted action may cause a reduced level of cholesterol in brain tissue what is mirrored in the cerebral spinal fluid [61]. Since seladin-1 which participates in the formation of cholesterol has

been demonstrated to be downregulated in AD brain [26], an increased synthesis of cholesterol in sporadic AD brain may not be assumed to occur. Otherwise, the cholesterol-catabolising enzyme CYP 46 has been found to be abnormaly induced in glial cells [62] the gene of which shows polymorphism associated with AD [63]. As a result of the increased cholesterol catabolism, its metabolite 24S-hydroxycholesterol was found to be enhanced in both plasma [64, 65] and CSF [66].

The depletion of ATP, as was found in SAD brain [57, 58], may have marked impacts on the maintenance of the non-equilibrium distribution of Na^+, K^+ and Ca^{2+} in that the intracellular concentrations of both Na^+ and Ca^{2+} may rise whereas K^+ is released from the cell. The increase of intracellular cytosolic Ca^{2+} concentration causes the activation of phospholipases which degrade phospholipids ([67], for review [68, 69]). Energy depletion has been assumed to enhance also the catabolism of membrane cholesterol [42].

Membrane composition in sporadic AD brain

It has been well documented in several studies that membranes undergo marked changes in sporadic SAD. First data were reported on the catabolic metabolites glycerophosphocholine and glycerophosphoethanolamine which both were found to be enhanced [70]. The degradation of structural membrane compounds such as phosphatidylcholine and phosphatidylethanolamine associated with an increase in both glycerophosphocholine and glycerophosphoethanolamine in a nearly stoichiometric relationship pointed to an increased activity of phospholipases [71]. Regional differences became obvious in the phospholipid contents as a whole in that decreases were found in frontal white matter and the caudate nucleus whereas the Alzheimer-specific areas frontal and temporal cortex and hippocampus showed insignificant decreases only [72]. Interestingly, the same authors reported on an Alzheimer-specific change of the fatty acid composition involving an increase of saturated and a decrease of unsaturated fatty acids [48]. Gangliosides were found to be reduced in temporal cortex, hippocampus and frontal white matter, but phospholipids did not show significant changes. Likewise, cholesterol decreased insignificantly by around 10% in temporal lobe and caudate nucleus [73]. A stronger reduction of brain membrane cholesterol by 30% [39] was found to be associated with an 50% increase in BACE1 in the soluble fractions [74]. Reduced cholesterol has been demonstrated to accentuate the membrane disturbing effects of βA4 on individual hippocampal membranes from AD patients [75, 76]. In AD brains exhibiting morphological changes of an early disease stage, GM1 ganglioside-bound βA4 was found [77] which, in in vitro-studies, showed a confirmation different from that of soluble βA4 and which accelerated the rate of amyloid fibril formation of soluble βA4 [78–80]. The increase in membrane-bound βA4 concentration triggered its conformational transition from helix-rich to β-sheet-rich structures [81]. Marked structural membrane changes in temporal gyrus membranes of AD patients became obvious by lipid and protein analyses showing an unchanged phospholipids: protein mass ratio but a decrease by 30% of the unesterified cholesterol: phospholipids ratio [82].

More detailed studies on cholesterol metabolism/concentration in sporadic AD brain revealed no uniform data. No differences were found in the 3-hydroxy-3-methylglutaryl-CoA reductase mRNA in Alzheimer and control brain pointing to a robust capacity to synthisize cholesterol in AD brain [60]. However, the activity of HMG-CoA reductase is reduced due to an energy-deficit [59]. The undisturbed or even elevated synthesis of cholesterol associated with its increased catabolism (see above) might explain the higher concentration/turnover of free cholesterol in (damaged) tangle-bearing neurons compared to adjacent tangle-free neurons [83]. These findings may indicate a dysregulation of cholesterol homeostasis what may include cholesterol metabolism in the membrane. The cholesterol-binding protein caveolin involved in cellular cholesterol transport has been found to be increased in both mRNA and protein [84]. As a result of this dysregulated metabolism, the depletion of cholesterol in the—normally cholesterol-enriched-lipid rafts—may be assumed [85, 86]. Both, dysregulation of metabolism and disorganization of membrane structure may have considerable impact on the function of proteins, and the formation of its metabolites such as βA 1–40 and βA 1–42 [87]. Otherwise, both, ceramides and cholesterol increased in association with disease severity in membranes of brain areas affected by AD (middle frontal gyrus) but not in a non-vulnerable brain region (cerebellum) [88]. Ceramides derive from sphingolipids which are enriched in membrane microdomains as cholesterol is (see above).

As a result in between, it may be deduced that both phospholipids and cholesterol in membranes diminish in sporadic AD brain. However, whereas the biochemical processes in the breakdown of membrane constituents by phospholipases due to acute pathological conditions such as ischemia and hypoglycaemia have

been clearly demonstrated (for review [89]), there is no direct evidence of the maintenance of an elevated activity of phospholipases in chronic diseases such as sporadic AD, and in its post mortem state. The activity of the major catabolic enzyme phospholipase A2 was found to be decreased and the extend of the reduction correlated with the disease process [90]. Otherwise, the activities of lysophospholipid acyltransferase which recycles lysophospholipids into phospholipids, and glycerophosphocholine phosphodiesterase contributing to phospholipid resynthesis were found to be enhanced [90a] suggesting compensatory mechanism to reduce the primarily occurring phospholipid loss in the incipient disease state.

Plasma cholesterol and AD

Although the cholesterol metabolism in the brain has been found to be regulated independently from non-nervous tissues (see above), some findings point to an interrelationship between these two compartments. In a late-life/post mortem autopsy study, a strong linear association was found between increasing late-life HDL-cholesterol and increasing number of neuritic plaques in neocortex and hippocampus and neurofibrillary tangles in neocortex [91]. In contrast, AD patients revealed significantly higher LDL cholesterol and significantly lower HDL cholesterol related to the amount of βA 1–42, but not βA 1–40 in AD brains [92]. The latter findings may be in agreement with data showing that high cholesterol in late life was associated with a decreased dementia risk [8]. In a subject sample representing a cognitive continuum from normal cognitive function to mild dementia, low HDL-cholesterol was found to be associated with a higher risk of dementia whereas high HDL-cholesterol was associated with a larger hippocampal volume (less hippocampal atrophy as an index of AD pathology) and was assumed to be protective against dementia/AD [93].

The use of statins—a rational therapy for Alzheimer disease?

Pharmacology

Statins are inhibitors of the 3-hydroxy-3-methylglutaryl-CoA reductase, representing the rate-limiting enzyme in cholesterol biosynthesis. Statins exist in two different forms: (1) the lactone form is lipophilic comprising e.g. lovastatin, simvastatin and cerivastatin which are able to pass the blood–brain barrier; (2) the acid from is hydrophilic comprising e.g. atorvastatin, fluvastatin and pravastatin which do not pass the blood–brain barrier to any significant extent [94, 95]. Both lovastatin and simvastatin were found to reduce the cholesterol content in the cytofacial membrane leaflet, and lovastatin in the exofacial membrane leaflet, too. Interestingly, pravastatin—although not passing the blood–brain barrier—reduced cholesterol in the exofacial membrane leaflet, and was also shown to affect gene regulation in the brain [96, 97].

Effects on membranes, tau-protein and APP/β-amyloid in experimental in vitro- and in vivo-studies

Lovastatin treatment (100 mg/kg/day) over a period of 23 days caused a marked reduction in brain cholesterol content associated with decreased pyrene-excimer fluorescence indicating altered membrane function in young and middle-aged mice [98]. This cholesterol-induced reduced membrane lipid fluidity was assumed to dysregulate membrane-bound allosteric enzymes, membrane permeability and to modulate the phospholipid–protein interaction [99, 100]. Treatment of hippocampal neurons with lovastatin (≥10 μM) induced cell death within 72 h [101]. The latter is a generally observed phenomenon after reduction of cholesterol [20]. Before complete destroyment of the neuritic network a decrease in dendritic outgrowth, attenuated axonal branching and depolymerization of microtubules associated with hyperphosphorylation of tau protein were observed [101–103].

In numerous studies, a combination of statins and methyl-β-cyclodextrin of both different concentrations and duration was used to markedly reduce the cholesterol level in membranes and to induce effects on APP/β-amyloid metabolism. Methyl-β-cyclodextrins have been demonstrated to selectively extract cholesterol from plasma membranes [104, 105], i.e. the application of both compounds may cause a harsh membrane damage. In vivo- and in vitro-studies showed that a reduction of membrane cholesterol content deteriorated membrane properties such as fluidity, and that the cholesterol content of membranes was negatively correlated with the membrane perturbing effect of β-amyloid [76]. Synaptic plasticity was impaired in that the formation of neurodegenerative fragmentation and teardrop varicose widening of neurites were found to be associated with a damage of long-term potentation [33]. However, most studies focus on the relationship between membrane cholesterol content and β-amyloid formation to demonstrate the beneficial effect of statins as a therapeutic strategy in the treatment of

AD. In different cell lines (HEK cells, neuroblastoma SH-SY5Y cells, human astroglioma cells, primary neurons), around 60% of cholesterol was removed from the cell by methyl-β-cyclodextrin or was reduced by around 50% by lovastatin. This harsh membrane damage resulted in a drastic increase of secreted-α-secretase cleaved soluble APP, in a decreased secretion of βA4-peptides by around 20% and in increase membrane fluidity. It is deduced from the data that cholesterol reduction promotes the non-amyloidogenic α-secretase pathway and that this strategy may be useful for the prevention of or therapy for AD [106]. In other studies, α-secretase cleaved APP (secreted APP) was found to be unchanged or reduced [107, 108] and βA4-formation was reduced between 50% and 70% when cellular cholesterol was diminished by 50–70% by lovastatin, or methyl-β-cyclodextrin, or by both. It was concluded that cholesterol is required for the formation of βA4 and that this process may be inhibited by the depletion of cholesterol [108, 109]. However, in studies more relevant to the reduction of cholesterol in sporadic AD brain membranes (see above), the latter was diminished by 30% only what was accompanied by an increase in β-secretase, a higher β-secretase/APP colocalization and an increased Aβ-production. In contrast, a harsh reduction of cholesterol by more than 35% of control induced less Aβ-production most likely due to an overall marked disruption of membrane integrity [74, 109a], not described in postmortem AD brain (see above).

In most of the in vivo-studies investigating the cholesterol-lowering effects of statins transgenic animals were used. The results are incomplete (e.g. no determination of cholesterol content) and with respect to βA4-formation not uniform: reduction of the latter up to 60% were found as well as no changes, and increases up to 50% (for review [110]). In one study only, wild-type adult male guinea pigs were used which received simvastatin over three weeks in a 227–407 times higher dose than applied in human beings [111]. Whereas the plasma cholesterol level was found to be markedly reduced (16% of control), no significant change in total brain cholesterol level was found. However, the cholesterol precursor lathosterol was diminished indicating a reduction of de novo brain cholesterol synthesis. Simvastatin treatment reduced βA4 concentration in both CSF and brain tissue between around 50–60%.

Taken together, the results from the in vitro- and in vivo-studies discussed above do not provide evidence for the assumption that an enhanced cholesterol content in membranes increased βA4-production. All experiments started in normal conditions i.e. normal cholesterol concentration. The application of statins in combination with, or without methyl-β-cyclodextrin, caused ''beneficial'' effects of APP metabolism associated with reduced βA4-production first when the cholesterol content of membranes was reduced by 50–60% of normal. Applied to AD brain, the abnormal but moderate decrease of cholesterol (around –15% to –30%) might have to be diminished about 2-to 3-fold stronger to achieve a ''beneficial'' effect on APP/βA4-metabolism. It is not clear as yet whether or not a neuron would survive such a harsh procedure.

Another aspect might also be taken in account. APP (and presenilin) mutations are found to be rare in AD brain, and the hereditary form of the disease represents a very small proportion of AD patients only (see Introduction). Mutated APP used in cell culture studies or in transgenic animals is produced in excess causing an increased amount of cleaved APP, and, thus, an increased formation of Aβ. This process may be diminished by the harsh membrane damage due to cholesterol reduction by more than 35% of normal. This experimental condition may not be assumed to mirror the pathology of sporadic AD brain membranes.

Effects of statins in the treatment of dementia in human beings

Sporadic AD is the most frequent form of all dementias in the elderly, but other causations than that for sporadic AD (the causation(s) of which is (are) as yet unknown) will have to be considered for treatment strategies. To give one example only: vascular dementia is different from sporadic AD in origin, and, thus, different therapeutic strategies may have to be applied.

Studies on unclassified dementias

The most frequently cited articles in this context are from Wolozin et al. [112] and Jick et al. [113]. The latter retrospective study included 284 subjects who had a first-time diagnosis, 84% of whom were classified as having possible or probable AD. Different statins were applied over a period of more than four years. This treatment was associated with a substantial lowered risk of developing dementia whereby it was emphasized that no distinction between AD and other forms of dementia was possible. Wolozin et al. [112] evaluated the records of nearly 57,000 patients in a cross-sectional analysis retrospectively. The diagnoses were made by documentation of cognitive impairment,

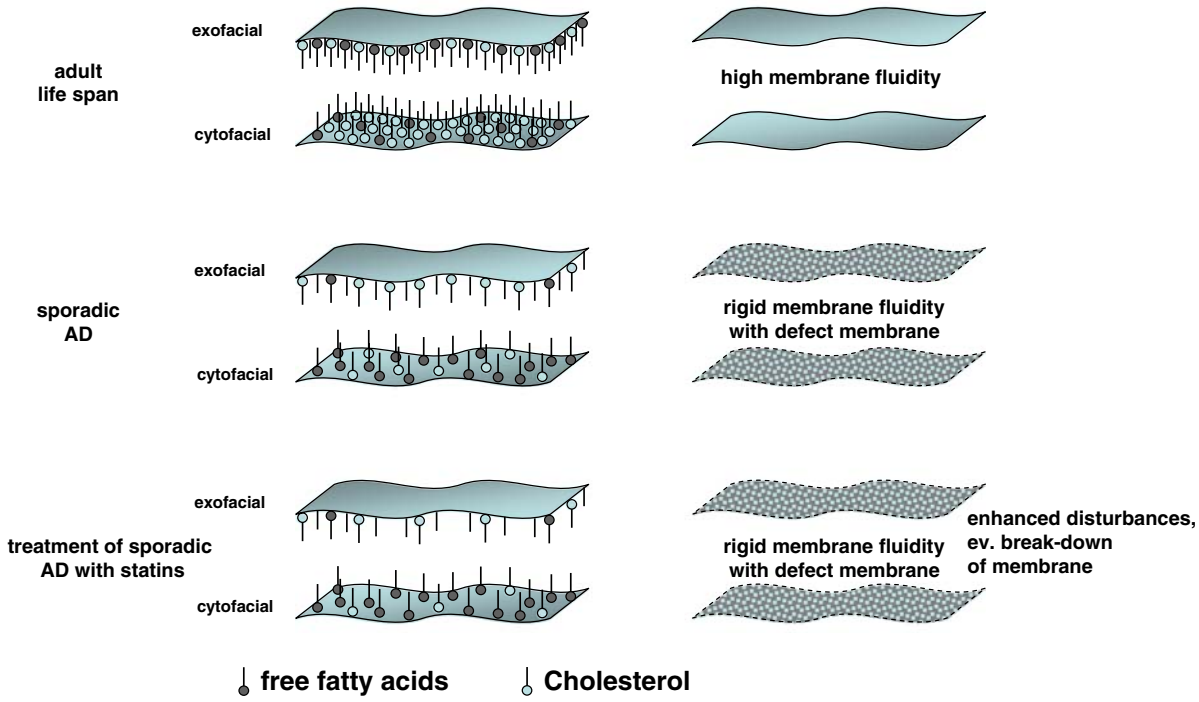

Fig. 1 Simplified membrane structure demonstrated as fatty acids and cholesterol in healthy adult life time, sporadic AD and in sporadic AD + statin treatment. Membrane cholesterol is reduced in sporadic AD. Statins inhibit cholesterol synthesis and further damage membrane structure

neuropsychological examination, computed tomography and magnetic resonance imaging of the brain. The diagnosis of AD referred to probable AD and did not exclude confounding vascular disease factors, i.e. a population of mixed causes of dementias was included in the evaluation comprising 753 patients both taking and not taking medications. As a result, a lower prevalence (60–73%) of dementia of the cohort taking statins during the study interval (October 1996 through August 1998) was found. In a subsequent case–control and retrospective cohort study on patients diagnosed as suffering from hypercholesterolemia or dementia (AD, vascular dementia, mixed-type dementia, Lewy body dementia), patients on statins showed an improvement on their MMSE score by 0.7 as compared to a decline by 0.5 in controls. The data also suggested that the use of statins was associated with a lower prevalence of vascular dementia and AD [114].

None of the above studies gave information on drugs used additionally to treat the different types of dementias.

Studies on classified dementias

In smaller samples of well diagnosed AD patients ($n = 44$), CSF markers such as βA40, βA42, tau-protein, lathosterol and cholesterol were included in the studies. A 26-week treatment with 80 mg/day simvastatin reduced serum cholesterol by around 50%, CFS lathosterol by around 10% and CSF 24S-hydroxycholesterol by around 10%. The patients were allowed to take acetylcholinesterase blockers during the 26-week study period. In a subgroup of mildly diseased AD patients (MMSE21-26: $n = 8$), CSF βA40 fell significantly accompanied by no changes in CSF βA42. Simvastatin treatment maintained the MMSE score at baseline level [115]. Nineteen AD-patients received simvastatin (20 mg/day) for 12 weeks in an open trial, leading to a slight increase of the ADAS-cog score, a decrease in serum total cholesterol and LDL cholesterol, and a reduction of both the α-secretase-cleaved and the β-secretase-cleaved APP, but without any variations in CSF βA42, tau-protein, and phospho-tau-protein [116], largely confirmed in a small, 1 year open-label study [117]. Sixty seven patients with mild to moderate AD were included in a 1-year pilot proof-of-concept, double blind, placebo-controlled, randomized study and treated with atorvastatin known not to pass the blood–brain barrier. The drug treatment was 80 mg/day atorvastatin while continuing to take cholinesterase inhibitors. Atorvastatin caused decreases in serum total cholesterol, LDL-cholesterol and VLDL-cholesterol. Improvement on the ADAS-cog score

were observed after a 6-months treatment first what was maintained until 12 months. No significant changes were found during the period of 1-year treatment in several other psychometric test procedure applied [118].

The data of the above studies do not support the assumption that the application of statins may be of benefit for AD patients. Remarkably, the clinical outcome of AD patients after a long-term treatment [115, 118] was very limited in improvement (8 out of 40 patients in [115]) and significance at the level of a trend [118]. These results are somewhat surprising in so far that a stronger improvement of clinical symptoms has been found in many studies using acetylcholinesterase inhibitors only. Therefore, drug interactions may not be excluded causing a reduced efficacy of acetylcholinesterase inhibitors by statins.

To summarize, the data discussed above do not support the assumption that the application of statins may prevent or treat AD and may inhibit β-amyloid production [119–122]. In contrast, statin treatment intensifies the disease-induced cholesterol deficits in membranes rendering the latter prone to collaps (Fig. 1). Otherwise, statins may be helpful in the treatment of vascular dementia and vascular-related cognitive impairment associated with cardiovascular disease and hypercholesterolemia, i.e. in secondary dementia [122].

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