

Review

Fatty acids, lipid metabolism and Alzheimer pathology

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Abstract

Alzheimer's disease is the most common form of dementia in the elderly. The cause of Alzheimer's disease is still unknown and there is no cure for the disease yet despite 100 years of extensive research. Cardiovascular risk factors such as high serum cholesterol, presence of the Apolipoprotein $\epsilon 4$ (APOE $\epsilon 4$) allele and hypertension, play important roles in the development of Alzheimer's disease. We postulate that a combination of diet, lifestyle, vascular, genetic, and amyloid related factors, which enhance each other's contribution in the onset and course of Alzheimer's disease, will be more likely the cause of the disease instead of one sole mechanism. The possibility that the risk for Alzheimer's disease can be reduced by diet or lifestyle is of great importance and suggests a preventative treatment in Alzheimer's disease. Because of the great importance of lipid diets and metabolism in preventative treatment against both Alzheimer's disease and cardiovascular disease, long-chain polyunsaturated fatty acids from fish oil, ApoE genotype and cholesterol metabolism in correlation with Alzheimer's disease will be reviewed. © 2008 Elsevier B.V. All rights reserved.

Keywords: Omega-3 fatty acids; Cholesterol; Apolipoprotein E (ApoE); Alzheimer's disease; Vascular risk factors; Pathology

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1. Introduction

Alzheimer's disease is acknowledged as the most common form of dementia in the elderly, and its cause is still unresolved and no curative treatments are available yet, despite 100 years of extensive investigations.

In 1906 at the 37th Assembly of the Society of Southwest German Psychiatrists in Tübingen, Alois Alzheimer, Director of the Cerebral Anatomical Laboratory of the Ludwig–Maximilians University Munich, presented for the first time his observations about amyloid plaques, neurofibrillary tangles, and arteriosclerotic changes, the neuropathological hallmarks of what later was termed Alzheimer's disease, as found in the post mortem brain of his 55-year old patient Auguste D(eter). Her illness lasted just 5 years in which she developed the neuropathology and progressive cognitive impairment, hallucinations, delusions, and impaired social functioning.

Hundred years later, in 2006, approximately 26.6 million people worldwide suffered from Alzheimer's disease and because of the growing life expectancy we can expect that the global prevalence of Alzheimer's will quadruple by 2050 to more than 100 million, which means that 1 in 85 persons worldwide will be affected by this disease. About 40% of those Alzheimer's disease patients will need nursing home care in the later stage of the disease, which will cause an enormous burden on the healthcare resources (Brookmeyer et al., 2007).

Currently, consensus has been reached about vascular disorders being risk factors for Alzheimer's disease and it has been shown that these vascular-based risk factors can be preventively influenced via lifestyle factors like physical exercise and diet (fish intake, caloric restriction, lowering cholesterol and transfat intake Kivipelto et al., 2002b, 2005). Several studies suggest that physical exercise and diets low in calories and 'bad' fats (cholesterol and saturated fats) (Eckert et al., 2005; Simons et al., 2002; Wolozin, 2004) and high in

"good" fats (polyunsaturated fatty acids from fish oil) may reduce the risk of Alzheimer's disease (Freund-Levi et al., 2006; Green et al., 2007b; Hashimoto et al., 2005b; Mattson, 2003; Petrovitch and White, 2005; Rovio et al., 2005; Schaefer et al., 2006). These findings are also supported by animal studies in which cognition stimulating environments, exercise and caloric restricted diets inhibit neurodegeneration, enhance neurogenesis and improve cognition, (Lee et al., 2002; Young et al., 1999) and furthermore, the intake of DHA or high cholesterol diets influence Alzheimer's disease pathology and cognition in animal models (Hooijmans et al. 2007; de Wilde et al., 2002, 2003; Farkas et al., 2002; Green et al., 2007b; Levin-Allerhand et al., 2002; Mohammad Abdul et al., 2004; Oksman et al., 2006; Lim et al., 2005a). Fish consumption or its main component DHA has been shown to protect against cardiovascular diseases and postpone the process of cognitive decline and Alzheimer's disease in human (Freund-Levi et al., 2006; Schaefer et al., 2006).

However, the cause of Alzheimer's disease is still unrevealed and there is no cure for the disease yet and efforts for the prevention of dementia are needed. The possibility that the risk for Alzheimer's disease can be reduced by preventative strategies like diet or lifestyle is of great importance, and suggests a preventative treatment against both Alzheimer's disease and cardiovascular disease. Therefore we will evaluate vascular-related nutritional factors for Alzheimer's disease in this review in addition to Alzheimer's disease pathology, underlying mechanisms, and risk factors for Alzheimer's disease.

2. Alzheimer's disease pathology

Clinically, Alzheimer's disease is characterized by severe cognitive impairment, memory loss, anomia, apraxia, anosognosia and personality changes (for example mistrust, aggression and delusions). Neuropathologically, Alzheimer's disease is

characterized by intracellular neurofibrillary tangles, extracellular amyloid plaques that accumulate in vulnerable brain regions and neurodegeneration (Sennvik et al., 2000).

2.1. Plaques and tangles

It took over 70 years from the first description of the amyloid plaques in 1906 until it was discovered in the eighties, that the plaques consist of aggregates of extracellular loads of 8 nm filaments of small peptides called β amyloid (amyloid- β) (Kang et al., 1987; Mann, 1989; Masters et al., 1985). Early in the course of the disease specific brain regions like the forebrain and medial temporal lobe structures (hippocampus, amygdala and entorhinal cortex) are affected first (Beach et al., 2000; Braak and Braak, 1995, 1997). Also in the late 1980s, it was discovered that the second lesion described by Alzheimer, the neurofibrillary tangles are composed of aggregates of abnormally hyperphosphorylated tau protein, occurring both in neuronal cell bodies and in axons and dendrites (Arriagada et al., 1992; Hatanpaa et al., 1996).

2.2. Synaptic loss

The amyloid deposits form a good diagnostic marker but do not correlate well with neuronal damage and cognitive decline. Synaptic loss however is an early pathological hallmark of Alzheimer's disease (Masliah et al., 1989) which is age dependent and largely independent of β -amyloid (Masliah et al., 2006).

Studies in early stage Alzheimer's disease patients suggest that the neurodegenerative process initiates in the entorhinal cortex resulting in denervation in the hippocampus followed by loss of synapses in the molecular layer of the dentate gyrus and the nucleus basalis of Meynert (Samuel et al., 1994). Amyloid plaques formation and development of neurofibrillary tangles and gliosis accompany this process. In comparison it has been found in transgenic mice models of Alzheimer's disease that synaptic loss and memory impairment precede amyloid deposits in the limbic system (Mucke et al., 2000). Also in other studies it has been found that Alzheimer's disease is associated with disruption of synaptic contacts in specific cortical and subcortical areas and in early Alzheimer's disease first 20% loss synapses in the outer molecular layer of the hippocampal dentate gyrus has been observed (Samuel et al., 1994). In later stages of Alzheimer's disease, also loss in neocortex and even more damaged synapses has been found in the outer molecular layer of the dentate gyrus. Synaptic loss is correlated with memory impairment being a prodromal stage in the process of Alzheimer's disease (Scheff et al., 2006) and it is accompanied with abnormal processing of APP and soluble β -amyloid consecutively resulting in plaque formation (Lue et al., 1999; Mucke et al., 2000).

No significant change in total neuron number has been found in the entorhinal cortex as function of aging and the age related white matter lesions (WML) must therefore be due to loss of brain connectivity caused by loss of synapses in the early stage of Alzheimer's disease (Hof et al., 2003; Merrill et al., 2001; Price et al., 2001).

3. Generation of β -amyloid

β -amyloid is generated by sequential cleavage of the transmembrane amyloid precursor protein (APP), by groups of enzymes named α -, β - and γ -secretase. The cleavage and processing of APP can be divided into a non-amyloidogenic pathway and an amyloidogenic pathway. In the most common pathway, the non-amyloidogenic pathway, APP is cleaved by the α -secretase, producing a large amino (N)-terminal ectodomain (sAPP α), which is secreted into the extracellular medium. Because this cleavage occurs inside the β -amyloid region, formation of β -amyloid is prohibited. Three enzymes with α -secretase activity have been identified, all belonging to the ADAM family (a disintegrin- and metalloproteinase-family enzyme) (Haass et al., 1993).

In the amyloidogenic pathway, β -amyloid is generated by an initial cleavage of APP at the N-terminus by a β -secretase (BACE; β -site APP cleaving enzyme) (Sinha et al., 1999; Vassar et al., 1999), followed by a cleavage in the transmembrane domain by a γ -secretase. The γ -secretase is a complex of enzymes composed of presenilin 1 or 2 (PS1 and PS2) (Steiner et al., 2002; Wolfe et al., 1999; Yu et al., 2000). γ -secretase cleaves at positions 40 and 42 of the β -amyloid protein, generating β -amyloid 40 and β -amyloid 42, respectively. Approximately 10% of the residues exist of β -amyloid42 whereas the predominant amount produced, exists of β -amyloid40. The β -amyloid42 is the principal isoform in amyloid plaques because of its fibrillary nature.

4. Genetics of Alzheimer's disease

Ageing is the major risk factor for Alzheimer's disease, reflected in increasing prevalence with advanced age. Less than 1% of people of 60–64 years old have Alzheimer's disease whereas 40% of people older than 85 years are affected (Breter et al., 1992). The cut-off to distinguish between early onset and late onset Alzheimer's disease is arbitrarily set at 60–65 years.

The early onset, or presenile Alzheimer's disease, often have a positive family history (Van Duijn et al., 1994) which is the second most important risk factor for Alzheimer's disease (Tanzi and Bertram, 2001). Early onset Alzheimer's disease has so far been linked to mutations in the genes for the amyloid precursor protein (APP) on chromosome 21, presenilin 1 (PSEN1) on chromosome 14, and presenilin 2 (PSEN2) on chromosome 1. The mutations in these genes affect the metabolism or stability of β -amyloid, and they are thought to account for 40% of early onset Alzheimer's disease (Tanzi and Bertram, 2001; Thinakaran, 1999).

The isolation of β -amyloid from the plaques led to the cloning of amyloid precursor protein (APP) (Kang et al., 1987) and the localization of the APP gene to chromosome 21. This finding and the fact that patients with trisomy 21 (Down's syndrome) develop the classical neuropathological features of Alzheimer's disease in their forties (Giaccone et al., 1989; Lemere et al., 1996; Mann, 1989) led to a specific search for families with autosomal dominant Alzheimer's disease with genetic linkage to chromosome 21. This resulted ultimately in

the identification of several missense mutations in APP, associated with familial Alzheimer's disease (Chartier-Harlin et al., 1991; Goate et al., 1991; Hendriks et al., 1992; Mullan et al., 1992; Murrell et al., 1991). However, the mutations in the APP gene counted just for 16% of the early onset Alzheimer's disease (Raux et al., 2005) and therefore the search for other genes responsible for the early onset familial Alzheimer's disease went on and led in 1995 to the discovery of two familial Alzheimer's disease genes, presenilin 1 and presenilin 2 (Levy-Lahad et al., 1995; Rogaev et al., 1995; Sherrington et al., 1995).

Late-onset or senile Alzheimer's disease accounts for 95% of all Alzheimer's disease cases. The late onset Alzheimer's disease genes discovered until now, act as either risk factors and/or genetic modifiers. A number of potential susceptibility genes have been implicated as genetic risk factors for late onset Alzheimer's disease (Saitoh et al., 1995; van Duijn et al., 1999) from which the apolipoprotein E gene is the best known.

The apolipoprotein E gene on chromosome 19 encoding the cholesterol transport protein, apolipoprotein E (ApoE) was identified as risk factor in both familial and sporadic Alzheimer's disease in which the $\epsilon 4$ allele of the APOE gene has been found associated with Alzheimer's disease (Tanzi and Bertram, 2001). Carriers of one or two $\epsilon 4$ alleles of the APOE gene have a considerably higher risk to get Alzheimer's disease on an earlier age of onset (Corder et al., 1993a; Roses and Saunders, 1997), whereas inheritance of the $\epsilon 2$ allele appears to be protective against Alzheimer's disease. The mechanism by which the ApoE4 protein predisposes subjects to Alzheimer's disease is not fully revealed. However evidence is accumulating, that E4 enhances β -amyloid aggregation by stimulating amyloidogenic processing of APP and reduces β -amyloid clearance (Mattson, 2004).

5. Risk factors and cause of Alzheimer's disease

Many theories have been proposed about the cause of Alzheimer's disease and the "amyloid cascade hypothesis", in which amyloid deposition is seen as the primary pathway leading to neurodegeneration and Alzheimer's disease, is one of the most persistent (Masters et al., 1985). However this hypothesis is still under debate because of conflicting results about for example the neurotoxicity of β -amyloid deposition in vivo (Bishop and Robinson, 2002; de la Torre, 2004) and it has been found that also many non-demented persons show large amounts of Alzheimer's disease pathology (Davis et al., 1999; Arriagada et al., 1992). Amyloid deposition is not the earliest neuropathological event observed in the disease (Braak and Braak, 1995, 1997) and is not always correlated to neuronal loss (Hatanpaa et al., 1996). In transgenic mice it has been found that cognitive loss is independent of β -amyloid overexpression and precedes β -amyloid deposition (Koistinaho et al., 2001).

Nowadays, more and more consensus is reached about vascular disorders being major risk factors for Alzheimer's disease (de la Torre and Mussivand, 1993) leading to the vascular hypothesis (de la Torre, 2004). Many large epidemiological studies (Breteler, 2000; Meyer et al., 2000; Skoog and Gustafson, 2002) have revealed that several risk factors for Alzheimer's disease are vascular-related, (Table 1) causing

Table 1
Risk factors for Alzheimer's disease

Ageing ^{1,2}	High intake of saturated fat ^{22,23,24–28}
Presence of APOE $\epsilon 4$ allele ^{3,4,5}	Diabetes mellitus ¹⁸
Hypertension ^{3,5,7,8}	Stroke ^{9,30–33}
Congestive heart failure ⁹	Head injury ³⁴
Atrial fibrillation ¹⁰	Menopause ³⁵
Hyperhomocysteinemia ^{11,12,13}	Lower education ¹²
Atherosclerosis ^{5,14,15}	Depression ^{36,37}
Smoking ^{2,16,17,18}	Sedentary lifestyle ²⁹
Alcoholism ^{7,8,14,21}	Overweight ^{17,18,38–43}
	WML ⁴²

¹(Freemantle et al., 2006) ²(Kivipelto et al., 2005) ³(Sparks, 1997) ⁴(Launer et al., 2000) ⁵(Skoog and Gustafson, 2006) ⁶(Breteler, 2000b) ⁷(Kivipelto et al., 2001) ⁸(Kivipelto et al., 2002b) ⁹(Breteler, 2000a) ¹⁰(Ott et al., 1997) ¹¹(Breteler, 2000b) ¹²(Luchsinger et al., 2007) ¹³(Seshadri et al., 2002) ¹⁴(Cassidy and Topol, 2004) ¹⁵(Hofman et al., 1997) ¹⁶(Meyer et al., 2000) ¹⁷(Whitmer et al., 2007) ¹⁸(Morse, 2006) ²¹(Sjogren et al., 2006) ²²(Kalmijn et al., 1997b) ²³(Luchsinger and Mayeux, 2004) ²⁴(Oksman et al., 2006) ²⁵(Friedland, 2003) ²⁶(Huang et al., 2005) ²⁷(Kalmijn et al., 1997b) ²⁸(Morris et al., 2005) ²⁹(Martins et al., 2006) ³⁰(Skoog, 2000) ³¹(de la Torre, 2002c) ³²(de la Torre, 2002a) ³³(Kalaria, 2000) ³⁴(Ashford and Mortimer, 2002) ³⁵(de la Torre, 2000b) ³⁶(Palmer et al., 2007) ³⁷(Potter and Steffens, 2007) ³⁸(Gunstad et al., 2007) ³⁹(Petrovitch and White, 2005) ⁴⁰(Razay et al., 2006) ⁴¹(Rovio et al., 2005) ⁴²(de Leeuw et al., 2006).

impaired cerebral perfusion, indicating that cerebral hypoperfusion may play an important role in the onset of Alzheimer's disease (Mattson, 2003; Mayeux, 2003).

5.1. Vascular risk factors

Because all these risk factors are vascular-based risk factors for both vascular dementia and Alzheimer's disease (Hofman et al., 1997; Ott et al., 1997; Vermeer et al., 2003), and because clinical symptoms and pathology are also shared (de la Torre, 2002a; Kalaria, 2000), these two disorders should no longer be determined as two separate diseases (de la Torre, 2000c; Kalaria, 1997). Major vascular risk factors for Alzheimer's disease are hypertension and atherosclerosis. Hypertension is a risk factor for stroke, ischemic white matter lesions, silent infarcts, general atherosclerosis, myocardial infarction and cardiovascular diseases, and often clusters with other vascular risk factors, including diabetes mellitus, obesity and hypercholesterolemia. Hypertension is present in approximately 50% of people above 70 years and predicts both Alzheimer's disease and vascular dementia already 20 years before onset of Alzheimer's disease and elevated midlife systolic bloodpressure of 160 mm Hg or above is associated with lower brain weight, white matter lesions and greater numbers of senile plaques in hippocampus and neocortex (de Leeuw et al., 2002; Kivipelto et al., 2001; Launer et al., 2000; Ruitenberg et al., 2001; Skoog and Gustafson, 2006). The development of atherosclerosis also takes decades before it manifests itself and it is logical to assume that diminished blood flow to the brain from stenosed or jammed carotid arteries leading to cognitive dysfunction is a process that likely precedes dementia symptoms by many years. Hypertension and atherosclerosis cause blood vessel wall pathology, leading to dysfunction in the blood brain barrier function, hypoperfusion, ischemia in the brain which may

initiate the pathological process with cognitive impairment (Muller et al., 2007; Grammas et al., 2002; Kalaria, 1999; Skoog et al., 1998). ultimately leading to a significant increase in the incidence of Alzheimer's disease (Casserly and Topol, 2004; Hofman et al., 1997; Qiu et al., 2003; Skoog and Gustafson, 2006). More and more evidence come forward that cerebral ischemia plays an important role in development of Alzheimer's disease and animal studies suggest that cerebral ischemia in the brain may lead to accumulation of APP and β -amyloid (Hall, 1995; Kalaria et al., 1993; de la Torre, 2002c; Kalaria, 2000). de la Torre (2000b) proposed that aging in combination with a vascular risk factor that further decreases cerebral perfusion promotes the Critically Attained Threshold of Cerebral Hypoperfusion (CATCH) which causes oxidative stress, decreased energy metabolism, followed by excessive glutamate production, all these events contribute to progressive cognitive decline synaptic loss, senile plaques, neurofibrillary tangles, tissue atrophy and neurodegeneration (de la Torre, 2000a,b,2002c).

5.2. Lifestyle and diets

Influencing vascular risk factors via diet and lifestyle may influence Alzheimer's disease development. Indeed a correlation exists between Alzheimer's disease and dietary fat as important contributor to familiar atherosclerosis, and a good example is the link between cholesterol metabolism and development of Alzheimer's disease (Canevari and Clark, 2007; Hooijmans et al., 2007; Puglielli et al., 2003; Refolo et al., 2001; Sjogren et al., 2006; Wolozin et al., 2006). On the contrary, omega-3 fatty acids from fish oil might beneficially influence cardiovascular disease (Connor, 2000) by decreasing blood pressure (Geleijnse et al., 2002), and atherosclerosis formation (Okuda et al., 2005; von Schacky and Harris, 2007). The strongest evidence of a relation between omega-3 fatty acid intake and vascular disease is the occurrence of coronary heart disease which have been shown in many experiments and clinical trials (for review (Breslow, 2006; Connor, 2000)). Intervention with cholesterol-lowering agents or fish oil diets to prevent or reduce atherosclerosis could also lessen the prevalence of Alzheimer's disease. Recently performed docosahexaenoic acid (DHA) trials show inhibition of the course of Alzheimer's disease (Freund-Levi et al., 2006) and several trials on cholesterol-lowering statins have shown beneficial effects on inhibition Alzheimer's disease (Eckert et al., 2005; Simons et al., 2002; Vega et al., 2003; Wolozin, 2004).

Western diets consist of high saturated fat and in combination with the sedentary lifestyles they have led to a growing incidence of obesity, hypercholesterolemia, and high blood pressure, causing atherosclerosis, coronary artery disease, and diabetes, major risk factors of Alzheimer's disease, which are even more aggravated in people carrying the APOE ϵ 4 alleles. On the other hand, carrying the APOE ϵ 4 alleles often does not increase the risk for Alzheimer's disease in countries where people have low fat diets and more active lifestyles, and this supports the concept that lifestyle factors may contribute significantly to the risk of Alzheimer's disease.

Summarizing we could postulate that a combination of diet, lifestyle, vascular, genetic, and amyloid related factors, which enhance each other's contribution in the onset and course of Alzheimer's disease will be more likely the cause of the disease instead of one sole mechanism. Because of the great importance of lipid diets and metabolism in preventative treatment against both Alzheimer's disease and cardiovascular disease, omega-3 fatty acids, ApoE and cholesterol metabolism in correlation with Alzheimer's disease will be reviewed more extensively below.

6. Omega-3 fatty acids

The long-chain polyunsaturated fatty acids exist of two key families: omega-3 and omega-6, named after the place of the first double bond in the hydrocarbon chain. Especially docosahexaenoic acid (DHA) is the most abundant (omega-3) fatty acid in the mammalian brain, which levels in brain membrane lipids can be altered by diet, and with life stage, increasing with development and decreasing with aging (de la Torre, 2002b,c; Innis, 2007; Uauy and Dangour, 2006). Very high levels of fatty acids and lipids can be found in the neuronal membrane and the myelin sheath. About 50% of the neuronal membrane is composed of poly unsaturated fatty acids, while in the myelin sheath lipids constitute about 70%. The omega-3 poly unsaturated fatty acids are mainly present in fish, shellfish, and sea mammals and are scarce in land animals and plants, whereas the omega-6 poly unsaturated fatty acids are derived mainly from vegetable oil. The precursors of the omega-3 and omega-6 poly unsaturated fatty acids cannot be synthesized endogenously from carbohydrates and are therefore called essential fatty acids (EFA). The current Western diet is deficient in long-chain omega-3 fatty acids which caused a switch in the ratio of omega-6 to omega-3 intakes from 2 to more than 20 within a century (Tiemeier et al., 2003; Yehuda et al., 2005). This has negative consequences because an excess of omega-6 and a deficient amount of omega-3 is stimulating thrombogenesis, lowering immune response, increasing inflammation and decreasing neuronal membrane fluidity and function (Andriamampandry et al., 1999; Anil, 2007; Calder, 2001; Grundt et al., 1999).

6.1. Omega-3 fatty acids and the brain

Particularly the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are incorporated into neuronal phospholipids (mostly phosphatidylethanolamine and phosphatidylserine) (Yuen et al., 2005) and in retinal pigment epithelium (Heinemann and Bauer, 2006; Marszalek and Lodish, 2005). Incorporation of omega-3 fatty acids in the neuronal membrane increases fluidity of neuronal membranes and herewith improves neurotransmission and signaling via increased receptor binding and enhancement of the number and affinity of receptors and function of ion channels (Farkas et al., 2002; Bourre et al., 1991; Bourre et al., 1989). Omega-3 fatty acids increase membrane fluidity by replacing omega-6 fatty acids and cholesterol from the membrane (Yehuda et al., 1998).

maintaining an optimal membrane fluidity as obligatory for neurotransmitter binding and signaling within the cell (Heron et al., 1980).

Large amounts of DHA are necessary during brain development, for neural membrane production used for synaptogenesis, axonal and dendritic outgrowth, in both brain and retina (Heinemann and Bauer, 2006; Horrocks and YEO, 1999; Marszalek and Lodish, 2005).

It will be clear from the above evaluated involvement of omega-3 fatty acids in neuronal functions, that they may play a role in cognitive development and memory-related learning via increase of neuroplasticity of nerve membranes, synaptogenesis and improvement of synaptic transmission (Fontani et al., 2005).

6.2. Omega-3 fatty acids and cardiovascular disease

In developed countries, consumption of the long-chain omega-3 poly unsaturated fatty acids DHA and EPA protects people against cardiovascular disease (Daviglius et al., 1997; Hu et al., 2002; Thies et al., 2003). These beneficial effects have been explained by the capacity to prevent arrhythmias (Leaf et al., 2003), lowering plasma triacylglycerols (Harris, 1997; Sacks and Katan, 2002) decreasing blood pressure (Geleijnse et al., 2002), decreasing platelet aggregation (Hornstra, 2001), improving vascular reactivity (Goodfellow et al., 2000; Harris, 1997) and decreasing atherosclerosis (Okuda et al., 2005; von Schacky and Harris, 2007) and inflammation (Calder, 2001). Almost 30 years ago studies in Eskimos from Greenland suggested already that ingestion of omega-3 fatty acids protects against cardiovascular diseases (Bang et al., 1976). The Eskimos consumed diets very high in fat from seals, whales, and fish, which contained large quantities of the long-chain polyunsaturated fatty acids EPA and DHA (Dyerberg and Bang, 1979). In other studies it has been found that eating fish once a week significantly decrease coronary heart disease mortality rates (He et al., 2004).

6.3. Omega-3 fatty acids and Alzheimer's disease

A decreased level of plasma Docosahexaenoic acid (DHA) is associated with cognitive impairment with aging (Conquer et al., 2000; Ikemoto et al., 2001; Kyle et al., 1999) and does not seem to be limited to Alzheimer's disease patients (Guan et al., 1994; Tully et al., 2003; Yehuda et al., 2002). There are several possible reasons for this decline: a decrease in the ability of dietary fatty acids to cross the blood brain barrier due to impaired transport function in aging, or lipid peroxidation caused by enhanced free radicals (Bjorkhem et al., 1998), decreased dietary intake or impaired liver docosahexaenoic acid shuttling to the brain (Abad-Rodriguez et al., 2004). The deficiency affected mostly the cortex and hippocampus, areas which mediate learning and memory.

Many animal, epidemiological and clinical studies showed that high DHA consumption is associated with reduced Alzheimer's disease risk (Bourre, 2007; Freemantle et al., 2006; Green et al., 2007a,b; Lim et al., 2005a; Lukiw et al., 2005; Schaefer et al., 2006). In adult rats, learning and cognitive behavior are related to brain DHA status, which, in turn, is

related to the levels of the dietary omega-3 fatty acids (Moriguchi et al., 2000). In fact administration of DHA seems to improve learning ability in β -amyloid-infused rats (Hashimoto et al., 2005a,b) and inhibit decline in avoidance learning ability in the Alzheimer's disease model rats, associated with an increase in the cortico-hippocampal omega-3/omega-6 ratio, and a decrease in neuronal apoptotic products (Hashimoto et al., 2002). Similarly, recent studies showed that dietary DHA in an aged Alzheimer's disease mouse model could be protective against β -amyloid production, deposition in plaques and cerebral amyloid angiopathy (Alessandri et al., 2004; Hooijmans et al., 2007; Lim et al., 2005b), and increases cerebral blood volume (Hooijmans et al., 2007). In other transgenic Alzheimer's disease mouse models DHA also protects against dendritic pathology (Calon et al., 2004) and prevents neuronal apoptosis induced by soluble β -amyloid peptides (Florent et al., 2006), increases synaptic protein and phospholipid densities (Cole et al., 2005; Wurtman et al., 2006) and inhibits degradative endopeptidase activities (Park et al., 2006).

6.4. Omega-3 fatty acids and membrane fluidity

DHA is able to shift cholesterol from the neuronal membrane, increasing membrane fluidity which favours sequencing of APP via the non/amyloidogenic pathway explaining the inhibition of β -amyloid formation due to DHA supplementation according to the Wolozin theory (Wolozin, 2001).

6.5. Omega-3 fatty acids and clinical studies

Recently a large trial have been performed in which the favorable effects of DHA in Alzheimer's disease become visible (Freund-Levi et al., 2006; Schaefer et al., 2006) and in the prospective follow-up study from the Framingham Heart Study it has been found that high DHA levels in plasma correlated with reduction in the risk of developing dementia (Freund-Levi et al., 2006; Schaefer et al., 2006). Moreover, also other epidemiologic studies suggest neuroprotective consequences of diets enriched in omega-3 fatty acids (Barberger-Gateau et al., 2002; Kalmijn et al., 1997a; Morris et al., 2003).

7. Apolipoprotein E

The strongest known risk factor in sporadic or late onset Alzheimer's disease, is the genotype for apolipoprotein E (ApoE), a major carrier of cholesterol in the central nervous system (CNS) and an important component of very low density lipoproteins (VLDL). The ApoE protein has different isoforms, all influencing the risk of developing sporadic Alzheimer's disease in a different manner. The mechanism by which ApoE isoforms influence Alzheimer's disease risk is still unclear, and the proposed mechanisms will be discussed below.

7.1. Metabolism

Apolipoproteins are lipid-binding plasma proteins involved in cholesterol transport. There are five major classes of

apolipoproteins, and several sub-classes, but in this review we will focus only on ApoE. Within the blood, ApoE is an important lipid transporter. ApoE delivers and transports lipids (especially triglycerides and cholesterol) among peripheral tissues, by mediation binding, uptake and catabolism of lipoproteins. ApoE is a component of very low density lipoproteins (VLDL) and chylomicrons and high-density lipoproteins (HDL; transporters of cholesterol and triglycerides) (Mahley and Rall, 2000), and is the main ligand for low density lipoprotein receptors (LDL-receptor) in the periphery, and low density lipoprotein receptor-related protein (LRP) in the central nervous system. To internalise and clear lipoproteins, apoE is needed for binding to for example LDL-receptor.

In the central nervous system lipids are also transported attached to lipoproteins. The major apolipoprotein in the central nervous system is ApoE. In the brain ApoE is mainly synthesized by astrocytes, but there are also studies describing synthesis in microglia, endothelial cells and pericytes (Pitas et al., 1987). Generally it is thought that ApoE is only synthesized under pathological circumstances and during brain injury. However, there are also reports showing that hippocampal and cortical neurons produce ApoE during physiological conditions (Elshourbagy et al., 1985; Xu et al., 1999). Within the brain ApoE is important in cholesterol and phospholipid redistribution during development, regeneration after brain injury, and synaptic plasticity (Laskowitz et al., 1998; Poirier, 1994). In addition to this role, ApoE is also important in deposition and clearance of β -amyloid, inflammatory processes, aggregation of tau, neurotransmission, neuronal survival and sprouting (Gee and Keller, 2005).

7.2. ApoE and epidemiology

In 1993 it was discovered that the APOE gene showed association with the development of Alzheimer's disease (Corder et al., 1993b). The majority of people possess the $\epsilon 3$ allele. The $\epsilon 2$ and $\epsilon 4$ alleles are expressed to a lesser extent and are associated with Alzheimer's disease (Corder et al., 1993b; Eichner et al., 2002). The risk of developing Alzheimer's disease is dependent of which ApoE isoform is expressed. People expressing the $\epsilon 4$ allele have the highest risk (Alzheimer's disease onset: <70 years), followed by APOE $\epsilon 3$ carriers (Alzheimer's disease onset: >80) and subsequently E2 (Alzheimer's disease onset: >90). Except delaying the age of onset, ApoE2 even decreases the risk of developing Alzheimer's disease (Corder et al., 1994).

The APOE $\epsilon 4$ allele also displays a gender effect namely, women APOE $\epsilon 4$ carriers have an increased risk of developing Alzheimer's disease compared to men expressing the APOE $\epsilon 4$ allele (Farrer et al., 1997). There is also a gene dose effect, since individuals homozygous for the APOE $\epsilon 4$ allele have a larger risk of developing Alzheimer's disease compared to individuals carrying only one allele (Corder et al., 1993b). Further, it is suggested that 50% of all Alzheimer's disease cases is associated with $\epsilon 4$ allele (Saunders et al., 1993). All together, it is consistently shown that inheritance of the APOE $\epsilon 4$ allele is a major risk factor for both sporadic and familial Alzheimer's disease (Corder et al., 1993b; Rubinsztein and Easton, 1999).

7.3. ApoE and cholesterol

Since ApoE is involved in Alzheimer's disease development and is the major cholesterol transporter in the central nervous system, playing an important role in the mobilisation and redistribution of cholesterol and other brain lipids in repair, growth and maintenance of nerve cells, a link between cholesterol metabolism and Alzheimer's disease is obvious. Nonetheless there is no consensus about the relation between cholesterol metabolism and ApoE4 in Alzheimer's disease (Kivipelto et al., 2002a; Mulder et al., 1998).

It is known that APOE $\epsilon 4$ carriers display high serum cholesterol levels (Davignon et al., 1988; Eichner et al., 1993) and several experimental animal studies have shown an association between elevated serum cholesterol levels with Alzheimer's disease and β -amyloid levels (Kivipelto et al., 2001; Kuo et al., 1998; Pappolla et al., 2003). In addition, other studies have shown that high brain cholesterol levels increase the amount of β -amyloid depositions and in animal models (Hooijmans et al., 2007; Levin-Allerhand et al., 2002; Shie et al., 2002; Sparks et al., 1994) therefore, it is possible that ApoE4 affects Alzheimer's disease risk by causing high serum cholesterol, leading to increased brain cholesterol levels and ultimately results in increased β -amyloid levels. However, many studies indicate there is no increase in brain cholesterol in APOE $\epsilon 4$ carriers (Ledesma et al., 2003) and brain cholesterol is not influenced by serum cholesterol because cholesterol does almost not cross the blood brain barrier into the central nervous system (Dietschy and Turley, 2001; Hooijmans et al., 2007). Therefore, ApoE4 is involved in brain cholesterol homeostasis but is unlikely to influence total brain cholesterol levels directly. For example a locally increased cholesterol concentration in the neuronal membrane via redistribution of brain cholesterol by ApoE4 provide an enriched environment for β -amyloid production but does not change total brain cholesterol levels.

Since carrying the ApoE4 isoform is a major risk factor for the development of atherosclerosis (Davignon et al., 1988) via hypercholesterolemia, another plausible explanation for the relation between cholesterol levels and ApoE4 in Alzheimer's disease may be cerebrovascular diseases. The APOE $\epsilon 4$ allele increases or aggravates serum cholesterol levels causing atherosclerosis and may subsequently cause hypoperfusion of specific brain regions followed by β -amyloid depositions and neuronal degeneration, emphasizing a role for vascular disease in Alzheimer's disease.

7.4. ApoE and cerebrovascular pathology

ApoE4 is associated with vascular diseases, such as coronary artery disease, hypertension, diabetes, obesity and atherosclerosis (Davignon et al., 1988; Wellington, 2004) probably via its inadequate LDL cholesterol and chylomicron clearance. It has been obviously shown that ApoE4 influences cerebral haemodynamics as well, like leakage of the blood-brain barrier (Zipser et al., 2007) and cerebral amyloid angiopathy (Kinnecom et al., 2007). Kalaria et al. showed that 62% of Alzheimer's disease cases with advanced cerebral amyloid angiopathy and cerebral

hemorrhage carried the APOE $\epsilon 4$ allele (Kalaria and Premkumar, 1995). A strong association between cerebral amyloid angiopathy related cerebral hemorrhage and APOE $\epsilon 4$ has also been shown (Greenberg et al., 1995; Olichney et al., 1996). Amazingly, in this context ApoE2 does not inhibit nor prevent cerebral amyloid angiopathy, but is like ApoE4 a risk factor for cerebral amyloid angiopathy related cerebral hemorrhage as well (McCarron and Nicoll, 1998; Nicoll et al., 1997).

A study from Lehtovirta et al. showed that ApoE polymorphisms are involved in haemodynamic alterations in Alzheimer's disease, and that the most severe cerebral hypoperfusion was found in the APOE $\epsilon 4$ allele subgroup (Lehtovirta et al., 1998). Expansive arterial remodeling has been suggested to be a defense mechanism in atherosclerosis aimed at delaying the development of lumen narrowing. ApoE^{-/-} mice fed a high cholesterol diet showed a failure in arterial expansive remodeling and induced lumen obstructive plaque formation with significant haemodynamic consequences (Johansson et al., 2005).

It is also found that APOE $\epsilon 4$ homozygotes compared to $\epsilon 3$ carriers (Bronge et al., 1999), show more severe white matter lesions (WML) which are associated with Alzheimer's disease (de Leeuw et al., 2006). Further, serum proteins such as ApoE are present in vascular Alzheimer's disease lesions as well directly pointing towards a role for ApoE in the cerebrovascular pathology of Alzheimer's disease.

7.5. ApoE and β -amyloid interactions

It is hypothesized that ApoE is an important player in β -amyloid plaque formation. ApoE is present in β -amyloid plaques and in cerebral amyloid angiopathy (Burns et al., 2003b; Namba et al., 1991) which suggests a role for this protein in β -amyloid deposition. Cholesterol and ApoE are always co-localized in the core of the plaque as an ApoE-cholesterol complex which may indicate a formational role for this complex in the genesis of fibrillar plaques (Burns et al., 2006, 2003b). It has been shown that ApoE4 is more efficient than ApoE3 at enhancing amyloid formation (Castano et al., 1995). These in vitro observations may suggest that ApoE acts as a pathological chaperone, promoting the β -sheet conformation of soluble β -amyloid into amyloid fibers, providing a possible explanation for the association of the ApoE4 genetic isoform with the increased risk of developing Alzheimer's disease (Castano et al., 1995). Lack of ApoE in a transgenic mouse model showed reduced β -amyloid deposition (Bales et al., 1997). This was confirmed in another study showing that the absence of ApoE reduced the amount of both β -amyloid40 and β -amyloid42 immunoreactive deposits as well as astrogliosis and microgliosis in APP transgenic mice (Bales et al., 1999). Moreover, individuals carrying the APOE4 allele show greater amyloid load, plaque size and density (Gearing et al., 1996; Schmechel et al., 1993) and they show increased levels of β -amyloid40 in brain and CSF (Mann et al., 1997).

Subsequently, interactions of ApoE on APP metabolism are also described. Cell culture studies showed a similar decrease in β -amyloid production when ApoE2, E3 or E4 was added and it

was suggested that apoE reduced γ -secretase cleavage of APP. It is suggested that ApoE stimulates the cholesterol efflux causing a change in cholesterol concentration and thereby the properties of cholesterol microdomains affecting access of γ -secretase to APP. Another proposed mechanism is a direct binding of APP to ApoE lowering its accessibility to γ -cleavage and affecting the levels or distribution of APP (Irizarry et al., 2004).

ApoE may also be involved in β -amyloid clearance. It is shown that ApoE regulates low density lipoprotein receptor-related protein (LRP1) mediated transport of β -amyloid across the blood brain barrier into the periphery (Zlokovic, 2004). Further, binding of ApoE to β -amyloid reduces β -amyloid toxicity in cell cultures. Different ApoE isoforms vary in their β -amyloid binding characteristics (Strittmatter et al., 1993b) whereas ApoE4 has the lowest affinity for the β -amyloid peptide (LaDu et al., 1994; Yang et al., 1997; Zhou et al., 1996) and may in this way increase the amyloid pathology in Alzheimer's disease, via a decreased β -amyloid transport across the blood brain barrier. In summary we could state that there is an effect of ApoE4 on β -amyloid metabolism, but it is unclear whether ApoE4 causes decreased clearing of the β -amyloid peptide or increased deposition of β -amyloid.

7.6. ApoE and neuronal plasticity and degeneration

Apart from interfering with β -amyloid metabolism, ApoE is also involved in neuronal plasticity and neurodegeneration. One of the major functions of ApoE in the brain is repair of neurons after injury. ApoE is quickly upregulated after injury (Laskowitz et al., 1998; Poirier, 1994). In addition to upregulation of ApoE after injury, cholesterol synthesis decreases and lipoprotein binding/reuptake to the cell increases (Poirier et al., 1993). These data indicate that ApoE helps to repair neurons by recycling and redistribution of membrane components such as cholesterol (Martins et al., 2006). Therefore, depletion of ApoE could decrease repair of neurons and increases neurodegeneration. Indeed, ApoE knockout mice (ApoE^{-/-}) are very sensitive to age related synaptic loss and neurodegeneration (Buttini et al., 1999). ApoE^{-/-} mice expressing human E3 show less neurodegeneration compared to controls. In contrast ApoE^{-/-} mice expressing ApoE4 show increased degeneration (Buttini et al., 1999). Additionally it has been shown that the same ApoE4 expressing mice showed that especially females, develop progressive impairment in spatial learning and memory (Raber et al., 2000). These results are consistent with the findings in humans, since APOE $\epsilon 4$ carriers have an increased risk of developing cognitive impairments (Yaffe et al., 1997). Mice lacking either ApoE or LDL receptors (a receptor involved in internalization of lipid loaded ApoE) show also impaired learning and memory functions. This might suggest a role for ApoE in synaptic plasticity (Gordon et al., 1996; Mulder et al., 2004).

7.7. ApoE and diet interactions

As mentioned earlier in this review, lifestyle and other environmental factors are associated with Alzheimer's disease

(Greenwood and Winocur, 1996; Kalmijn et al., 1997b, 2004; Solfrizzi et al., 2006). The interesting point is, whether there are also gene-environmental interactions, since different genes are involved in Alzheimer's disease pathogenesis and all may influence the course of disease in a different manner.

It is known that a high caloric diet is a risk factor for the development of Alzheimer's disease. Luchsinger et al. showed that expressing one or two APOE $\epsilon 4$ alleles further increases the risk of developing Alzheimer's disease, and thus acts synergistically (Luchsinger et al., 2002).

Laitinen et al. also showed in a random population based study that intake of saturated fatty acids increase the risk of Alzheimer's disease, especially in APOE $\epsilon 4$ carriers (Laitinen et al., 2006). In addition they showed that a moderate intake of unsaturated fatty acids decreases the risk of developing Alzheimer's disease in ApoE4 expressing individuals (Laitinen et al., 2006). This last finding is in contrast with observations in the Cardiovascular Health Cognition Study (Huang et al., 2005). This study showed that consumption of fatty fish, rich in poly unsaturated fatty acids, reduced the risk of Alzheimer's disease, but not in APOE $\epsilon 4$ carriers (Huang et al., 2005).

All together, many ApoE-diet interactions are observed, and more extensive research is necessary since diet is an easy target for modifying Alzheimer's disease prevalence.

8. Cholesterol

As mentioned above, APOE $\epsilon 4$ carriers have a higher risk of developing Alzheimer's disease (Corder et al., 1993b; Strittmatter et al., 1993a) and since ApoE is the major cholesterol transporter in the central nervous system a link between cholesterol metabolism and Alzheimer's disease is suggested. Subsequently, many genetic studies show association between Alzheimer's disease and other cholesterol related genes such as cholesterol 24-hydroxylase (CYP46A1), ATP-binding cassette transporter A1 (ABCA1), lipoprotein receptor-related protein (LRP) and liver X receptor (all reviewed in (Wellington, 2004)). In addition, hypercholesterolemia is an important risk factor for vascular disorders, and a link between hypercholesterolemia, cardiovascular diseases and Alzheimer's disease has been suggested (Breteler, 2000a; Casserly and Topol, 2004; de la Torre, 2002c; Kivipelto et al., 2001; Luchsinger et al., 2005). Epidemiological studies have indicated that patients treated for cardiovascular disease with cholesterol-lowering therapy (cholesterol synthesis inhibitors; statins) show diminished prevalence of Alzheimer's disease (Jick et al., 2000) and less deterioration of cognitive function (Sparks et al., 2005). These data indicate that cholesterol is involved in Alzheimer's disease pathogenesis, however at present, the mechanism is not completely clear and will be discussed below.

8.1. Cholesterol metabolism

Cholesterol is an essential component of cell membranes and therefore plays an important role in the physical properties of the membrane such as membrane fluidity, membrane permeability and functioning of membrane associated proteins.

Cholesterol is also a precursor of bile acids, and the precursor of all steroid hormones. Cholesterol can be obtained from the diet or synthesized in the body, mainly in the liver and intestine but also in the brain.

The first committed step in cholesterol biosynthesis the conversion of 3 molecules of acetyl-CoA to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) in the cytosol followed by the reduction of HMG-CoA to mevalonate. HMG-CoA reductase catalyzes this reaction, and is the rate-limiting step in the cholesterol synthesis pathway, and is an important target for pharmaceutical interventions, such as with statins. Mevalonate can eventually be converted to cholesterol. Cholesterol homeostasis is maintained by strict regulation of synthesis, uptake and catabolism. Low levels of cholesterol induce the generation of transcription factors leading to increased transcription of target genes, such as HMG-CoA reductase.

When cholesterol levels rise, HMG-CoA reductase production is inhibited and thus cholesterol synthesis is reduced. Excessive cholesterol destined for storage is converted to cholesterol esters in the ER by the Acyl-CoA acyltransferase (ACAT) and stored in fat droplets. This process is important because the toxic accumulation of free cholesterol in various cell membrane fractions is herewith prevented. Excessive cholesterol allocated to elimination may be oxidized by CYP7a to bile acids or binds to the ATP-binding cassette transporter ABCA-1 which is responsible for the transportation of intracellular free-cholesterol and phospholipids from the plasma membrane to lipid free high-density lipoproteins (HDL) acceptor molecules ultimately to the liver (Hayden et al., 2000).

8.2. Cholesterol in the brain

The human brain is the most cholesterol-rich organ of the human body. Almost 25% of the total unesterified cholesterol within the body is present in the brain, especially in the myelin sheath and membranes of neurons and astrocytes. Since cholesterol is necessary for the formation of synapses (Mauch et al., 2001), proper electrical transmission (Dietschy and Turley, 2004) and serves as a important barrier against sodium leakage (Haines, 2001), cholesterol homeostasis is essential and is tightly regulated by controlling uptake, de novo synthesis, esterification, catabolism (oxidation) and release.

Serum cholesterol is almost not able to pass the blood brain barrier (Dietschy and Turley, 2001) and the brain synthesizes its own cholesterol, mainly by astrocytes. Cholesterol binds to ApoE and may be taken up in neurons via LDL receptors, LDL receptor related protein (LRP), VLDL receptors, and ApoE receptor 2 amongst others (Beffert et al., 1998). The neurons internalize cholesterol via endosomes, which fuses with lysosomes causing release of free cholesterol. This intracellular free cholesterol functions as a negative feedback loop to HMG-CoA reductase to reduce synthesis but may also be esterified by ACAT for efficient storage (Poirier, 2003). It also serves as an important source for synaptic plasticity and dendritic formation and remodeling (Pfrieger, 2003). Since there is no degradation mechanism for cholesterol in the brain, cholesterol is released

from the brain after oxidation by for example CYP46 (24-hydroxylase) to 24S-hydroxycholesterol (24SOH) (Bjorkhem et al., 1998; Lutjohann et al., 1996) which easily passes the blood brain barrier (Haines, 2001).

8.3. Cholesterol and amyloid metabolism

Since cholesterol is such an essential component in the brain and many epidemiological studies have suggested a role for cholesterol in Alzheimer's disease development (Breteler, 2000a; Kivipelto et al., 2001; Luchsinger et al., 2005), it is not surprising that cholesterol has an impact on APP processing and subsequently on β -amyloid production (reviewed in (Wolozin, 2001)). Transgenic mice fed cholesterol containing diets showed increased amounts of neuritic plaques (Hooijmans et al., 2007; Levin-Allerhand et al., 2002; Refolo et al., 2001; Shie et al., 2002). It has been suggested that cholesterol increases the activity of β - and γ -secretases (Cordy et al., 2003; Ehehalt et al., 2003), which reside in cholesterol-rich lipid rafts and via this way increases the generation of β -amyloid. α -secretases, which prevent β -amyloid production by cleaving APP within the β -amyloid domain need cholesterol poor membranes, such as phospholipid rich long-chain poly unsaturated fatty acids domains which are more fluid (Kojro et al., 2001). Altogether, this indicates that a high membrane cholesterol content favors β -amyloid production and low membrane cholesterol content prevents β -amyloid production (Wolozin, 2001). Further, cell culture studies showed that reduction of intracellular cholesterol levels in rat hippocampal neurons inhibit the formation of β -amyloid (Simons et al., 1998). Cholesterol-lowering agents (statins) increase processing of APP through the non-amyloidogenic α -secretase pathway in different cell lines because membrane fluidity increases with lower cholesterol concentrations, (Kojro et al., 2001) and as a consequence decrease the amount of β -amyloid via favored β -secretase APP cleavage (Ehehalt et al., 2003; Simons et al., 1998). Moreover, increasing intracellular cholesterol levels in different cell lines upregulate β -amyloid production (Frears et al., 1999). It is suggested that the intracellular cholesterol levels regulate the APP processing, in contrast to total cholesterol levels (Puglielli et al., 2001). Whether cholesterol esters or free cholesterol are responsible for this involvement in APP processing is not completely clear. However, there is a study reporting that an increase in cholesterol esters regulates the generation of β -amyloid (Puglielli et al., 2001) and inhibitors of an enzyme catalyzing the formation of cholesterol esters (ACAT inhibitors) down regulated the generation of β -amyloid (Puglielli et al., 2001). It is however unclear how cholesterol esters modulate APP processing. Since the equilibrium between cellular cholesterol and cholesterol esters is maintained by ACAT, this enzyme may be a potential target in Alzheimer's disease.

Other processes that regulate cholesterol homeostasis also affect APP processing (Wolozin, 2004) such as involvement of LRP (Pietrzik et al., 2002), NPC1 (Burns et al., 2003a), liver X receptor (Koldamova and Lefterov, 2007, 2005b) or ABCA (Koldamova and Lefterov, 2007) receptors. The involvement of these receptors in APP metabolism will be discussed later.

However, there are also studies that did not find relation between cholesterol and amyloid metabolism. It has been shown in APP mice that increased dietary cholesterol led to significant reductions in brain levels of secreted APP derivatives, such as sAPP α , sAPP β , β -amyloid40, and β -amyloid42 (Howland et al., 1998) and a study with 12-month-old female Tg2576 mice fed a high cholesterol diet for 6 weeks showed a decrease in the amount of β -amyloid plaques (George et al., 2004). The results from the first study may be explained by the different transgenes introduced in these mice. Second, in both of these studies the diets were only supplemented for a very short time (6–8 weeks), which may be too short to really display ultimate effects. Further, in the study with the Tg2576 mice, female mice are used which could explain the discrepancy because sex related differences in the response of mice to statins have been shown (Park et al., 2003).

Cholesterol does not only influence β -amyloid metabolism, vice versa β -amyloid metabolism is able to influence cholesterol metabolism. β -amyloid42 causes accumulation of cholesterol in hippocampal neurons, and β -amyloid42 is able to inhibit HMG-CoA reductase, and thus cholesterol synthesis. It is therefore possible, as Canevari and Clark (2007) suggested, that changes in β -amyloid40/ β -amyloid42 ratio in Alzheimer's disease alter membrane lipid composition, alter the activity of membrane associated proteins and subsequently APP processing etc., causing a vicious circle.

8.4. Cholesterol and statins

The effect of cholesterol on β -amyloid deposition and metabolism is also fortified by the beneficial role of statins in the development of Alzheimer's disease. Statins are HMG-CoA reductase inhibitors, inhibiting cholesterol synthesis by slowing down the enzyme (HMG-CoA reductase) catalyzing the rate-limiting step of the cholesterol synthesis pathway. As mentioned earlier, epidemiological studies have shown that treatment of cardiovascular patients with statins diminish the prevalence of Alzheimer's disease (Jick et al., 2000) (also reviewed in (Shobab et al., 2005)). However, there are also studies in which no link between statins and Alzheimer's disease have been found (Shobab et al., 2005). Altogether, these contradicting results led to an enormous amount of research trying to unravel if and how statins may influence Alzheimer's disease pathology.

It is possible that statins decrease cholesterol levels in the brain via an ApoE dependent mechanism, since ApoE deficient mice do not benefit statin treatment (Eckert et al., 2001). A direct effect of statins on brain cholesterol levels is also possible since lipophilic statins are able to cross the blood brain barrier. Surprisingly, hydrophilic statins (such as pravastatin and atorvastatin) also show benefits in decreasing Alzheimer's disease risk (Wolozin et al., 2000). This points more towards an indirect effect of statins on Alzheimer's disease pathology.

It is also possible that statins affect peripheral 27-hydroxy cholesterol levels (27-OHC). 27OHC can cross the blood brain barrier and is taken up by the brain and in this way may influence brain sterol metabolism.

Other studies suggested that statins alter the bilayer distribution of cholesterol. Normally, neurons and glia cell display an asymmetrical distribution of cholesterol among the membrane leaflets, whereas the cytofacial leaflet contains the highest amount. Ageing or ApoE4 genotype decreases the amount of cholesterol in the cytofacial leaflet and it is suggested that statins reverse this effect hereby decreasing the production of β -amyloid (Abad-Rodriguez et al., 2004; Burns et al., 2006) via prevention of APP processing via the amyloidogenic pathway. This data suggests that cholesterol distribution and not total cholesterol levels may be important to β -amyloid production in the central nervous system (Shobab et al., 2005).

Another possibility is that statins do not exert their effects via influencing cholesterol, but via pleiotrophic effects such as influencing brain inflammation, or anti-apoptotic effects although this is beyond the scope of this review. All together, these findings led to prospective clinical trials of cholesterol-lowering statins in Alzheimer's disease patients. However the results of these trials are conflicting (Hajjar et al., 2002; Jick et al., 2000; Rockwood et al., 2002; Woloizin et al., 2000; Yaffe et al., 2002; Kolsch et al., 2003; Lendon et al., 1997; Sanchez-Guerra et al., 2001; Shepherd et al., 2002; Sparks et al., 2005) and there is insufficient evidence to suggest the use of statins for treatment in patients with Alzheimer's disease (Eckert et al., 2005).

8.5. Cholesterol and associated genes

The link between cholesterol and Alzheimer's disease is also amplified by the finding that many other genes than ApoE are involved in cholesterol metabolism and have been shown to be associated with late onset Alzheimer's disease. A few of the most important genes are discussed shortly below.

8.5.1. The ATP-binding cassette transporter A1

The ATP binding cassette transporter ABCA1 is responsible for the transportation of intracellular free-cholesterol (Hayden et al., 2000) and is involved in elimination of excess cholesterol. ABCA1 is expressed in neurons, astrocytes and microglia after for example activation of the liver X receptor (Koldamova et al., 2003), and an increased expression is accompanied by cholesterol efflux from neurons and glia. This affects APP processing, causing a decrease in β -amyloid production.

Individuals with a genetic polymorphism (R219K) in the ABCA1 gene have 30% decreased cholesterol in their cerebrospinal fluid, via modifying brain cholesterol metabolism and a 1.7 year delay in age of onset of Alzheimer's disease. A large genetic association study in 1750 individuals of a European population showed an increased risk in developing both late onset and early onset Alzheimer's disease with different polymorphisms of ABCA1 (Katzov et al., 2004).

Many papers have reported that the lack of ABCA1 causes a significant reduction of ApoE protein level in the brain (Hirsch-Reinshagen et al., 2004; Wahrle et al., 2004). Therefore it could be hypothesized that ABCA1 influences the onset of Alzheimer's disease via effects on ApoE. Indeed different studies show that a lack of ABCA1 decreases brain ApoE level and in

addition increases amyloid deposition in transgenic mice (Koldamova et al., 2005a). Moreover, increased levels of ABCA1 (directly or via stimulating the liver X receptor with a liver X receptor agonist) decreases the generation of β -amyloid (Koldamova et al., 2005a, 2003; Sun et al., 2003).

8.5.2. Liver X receptor

The liver X receptor is a nuclear receptor which is expressed on neurons, endothelial cells and glia cells (Wang et al., 2002; Whitney et al., 2002) and following activation induces a variety of genes involved in pathways of cholesterol metabolism, transport and elimination (i.e. ABCA1, ApoE etc.). An important liver X receptor target gene in the brain is ABCA1. Activation of liver X receptor has been shown to stimulate ABCA1 levels and thereby decreasing β -amyloid concentrations and cholesterol levels (Eckert et al., 2007; Koldamova et al., 2003; Sun et al., 2003). In addition, an in vivo study using an liver X receptor agonist showed lowered hippocampal β -amyloid42 and improved memory in the Tg2576 transgenic mouse (Riddell et al., 2007) and a study from Koldamova et al. showed the liver X receptor ligand T0901317 decreases β -amyloid production in vitro and in a mouse model of Alzheimer's disease (Koldamova et al., 2005b). In summary, liver X receptor may be a potential target for the treatment of Alzheimer's disease possibly by influencing cholesterol and lipid metabolism.

8.5.3. Oxysterols

When excess of cholesterol is oxidized by members of the cytochrome *p450* family oxysterols are formed. Oxysterols are important in lipid gene expression since they can bind liver X receptor and ultimately regulate the transcription of many lipid genes. The most important oxysterols in this perspective are 24-hydroxy cholesterol (24-OHC) and 27-hydroxy cholesterol (27-OHC). These oxysterols can easily pass the blood brain barrier and in this way utilized for further sterol biosynthesis or in the liver being further degraded to bile acids.

Oxysterols may accumulate in vascular tissue, and in this way exert toxic effects, such as development of atherosclerotic plaques (Carpenter et al., 1995). In Alzheimer's disease cholesterol flux is elevated showed by increased levels of 24-OHC (Lutjohann et al., 2000), which may cause vascular problems in Alzheimer's disease. Further, statins decrease the amount of 24-OHC, which may explain part of the beneficial effect of statins on the vasculature (Vega et al., 2003).

Oxysterols may also have effects on β -amyloid formation. Oxidative stress for example promotes the oxidation of 7-OHC and this oxysterol is already neurotoxic in small concentrations and may therefore contribute to β -amyloid related neurodegeneration (Nelson and Alkon, 2005).

8.5.4. Low-density lipoprotein receptor-related protein

Low-density lipoprotein receptor-related protein (LRP) is a low-density lipoprotein predominantly expressed in neurons, but also detected in capillaries and pericytes. LRP is involved in brain lipid and cholesterol distribution, protection against atherosclerosis and neurodegeneration (May et al., 2007).

LRP is able to bind and internalizes β -amyloid–ApoE complexes facilitating degradation of secreted β -amyloid (Puglielli et al., 2003). Moreover, LRP is a substrate, competing with APP for both BACE (von Arnim et al., 2005) and γ -secretase activity (Lleo et al., 2005). LRP has also been shown to be involved in β -amyloid transport over the blood brain barrier to the periphery, and may thus be involved in β -amyloid clearance (Zlokovic, 2004). However it has also been shown that LRP interacts with APP causing APP processing via the amyloidogenic pathway (Pietrzik et al., 2002; Ulery et al., 2000) and recently it has also been found that after internalization, aggregation of β -amyloid takes place, stimulating β -amyloid deposition.

8.5.5. ACAT

Cellular cholesterol may be stored as either free cholesterol or cholesterol esters. Acyl-coenzyme cholesterol acyltransferase (ACAT) catalyzes the formation of cholesterol esters from free cholesterol and controls the equilibrium between cellular cholesterol and free cholesterol. Cholesterol esters are stored in lipid droplets and excessive accumulation of lipid droplets is a hallmark of early atherosclerosis but accumulation of free cholesterol in various cell membrane fractions is also toxic. There are 2 forms of ACAT; ACAT1 and ACAT2. ACAT1 is highly expressed in macrophages in atherosclerotic lesions, however it seems unlikely that it plays an important role in atherosclerosis, and in this way influences Alzheimer's disease, since selective ACAT1 deficiency in two mouse models of atherosclerosis did not prevent the development of this disease, despite causing relatively lower serum cholesterol levels (Accad et al., 2000).

It has been described that an increase in cholesterol esters seems to regulate the generation of β -amyloid (Puglielli et al., 2001). Additionally, mice lacking ACAT1 (i.e. showing decreased levels of cholesterol esters) showed enormous reduced amounts of β -amyloid levels (Hutter-Paier et al., 2004).

8.5.6. LDL-receptor

In the brain the LDL-receptor is predominantly expressed in astrocytes, neurons and endothelial cells. This receptor mediates the endocytosis of cholesterol-rich LDL. LDL is directly involved in the development of atherosclerosis, due to accumulation of LDL-cholesterol in the blood. Dysfunction of the LDL-receptor can lead to hypercholesterolemia, which in turn is an important risk factor in Alzheimer's disease (Breteler, 2000). The most important ligand for LDL-receptor is ApoE and since ApoE is a major risk factor in early onset Alzheimer's disease, this is subsequently also an important link between LDL-receptor and Alzheimer's disease. Mulder et al. showed that LDL-receptor knock out mice have an impaired spatial memory and a decreased synaptic density in the hippocampus (Mulder et al., 2004). This is in agreement with another recent study showing that lack of the LDL-receptor aggravates learning deficits and amyloid deposits in Tg2576 mice (Cao et al., 2006). However conflicting research about the involvement of LDL-receptor in Alzheimer's disease is present (Fryer et al., 2005; Retz et al., 2001; Rodriguez et al., 2006).

8.6. Cholesterol and brain vasculature

Even though many possible mechanisms for the involvement of cholesterol in Alzheimer's disease pathogenesis are described above, the most important one has been neglected so far; i.e. the involvement of cholesterol on brain vasculature. It is well known that cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus and stroke are important risk factors for the development of Alzheimer's disease (de la Torre, 2000a). For example hypercholesterolemic patients have an increased risk of developing Alzheimer's disease and the prevalence of Alzheimer's disease will be reduced by 70% when these patients are treated with statins (Jick et al., 2000; Wolozin et al., 2000). Longstanding elevated hypercholesterolemia leads to accelerated atherosclerosis; this can express itself in a number of cardiovascular diseases such as stroke, myocardial infarction etc., but may also change the brain's haemodynamics. There are studies describing altered haemodynamics in Alzheimer's disease (Harris et al., 1998; Iadecola, 2003; Tohgi et al., 1998), and this in combination with high serum cholesterol being a risk factor may suggest an association between those two. Therefore, we and others suggest that high serum cholesterol may cause Alzheimer's disease via brain hypoperfusion since cholesterol does almost not cross the blood brain barrier (Dietschy and Turley, 2001; Hooijmans et al., 2007) and there is no evidence that Alzheimer's disease patients have a disrupted blood brain barrier causing cholesterol transport into the brain. Therefore, it can be hypothesized that high cholesterol intake impairs the vasculature causing atherosclerosis, hypoperfusion of vulnerable brain areas, ultimately leading to an overproduction of β -amyloid. The increased β -amyloid production may also result in cerebral amyloid angiopathy further exacerbating cerebrovascular degeneration (Bennett et al., 2000; Lin et al., 1999; van Groen et al., 2005). In a study with 15-month-old APP/PS1 mice, supplemented with a typical western diet containing 1% of cholesterol for 12 months we have shown a reduced relative cerebral blood volume, indicating an altered brain perfusion (Hooijmans et al., 2007). No differences in the amount of parenchymal or vascular β -amyloid were found, indicating that a high cholesterol containing diet first alters brain haemodynamics followed by β -amyloid pathology.

De la Torre also proposes that haemodynamic changes occur first in the Alzheimer's disease development (de la Torre, 2000a) which ultimately causes Alzheimer's disease pathology. The hypothesis that brain circulation and vasculature are important in Alzheimer's disease development is also fortified by that fact that statins diminish the prevalence of Alzheimer's disease, since statins diminish serum cholesterol levels and may thereby diminish blood vessel obstruction (Ledesma and Dotti, 2006). Altogether, changes in brain vasculature and haemodynamics are still underexposed in Alzheimer's disease, but may be a key regulator in Alzheimer's disease pathogenesis.

9. Conclusion

Although the cause of sporadic Alzheimer's disease is yet not clear and the amyloid hypothesis is still the most accepted

hypothesis, more and more research accumulates showing the involvement of the vasculature and cerebral hemodynamics in early Alzheimer's disease. We propose that Alzheimer's disease pathology starts with impairment of the peripheral, and consequently cerebral vasculature due to a combination of ageing lifestyle, dietary factors and genetic background, which enhance each other in the onset and course of the disease (Fig. 1). Genetic background also plays an important role in sporadic Alzheimer's disease. People expressing the APOE $\epsilon 4$ allele are predisposed for cardiovascular disorders, but ApoE also plays directly a role in the amyloid metabolism.

Dietary factors such as cholesterol and DHA may influence the course of Alzheimer's disease at many different levels. They are both involved in changing peripheral and cerebral hemodynamics, deposition and clearance of β -amyloid, neuronal dysfunction and neurodegeneration, in which cholesterol aggravates and DHA diminishes the pathology (Fig. 1). Altogether a combination of diet, lifestyle, vascular, genetic, and β -amyloid related factors, which enhance each others' contribution in the onset and course of Alzheimer's disease will be more likely the cause of the disease instead of one sole mechanism.

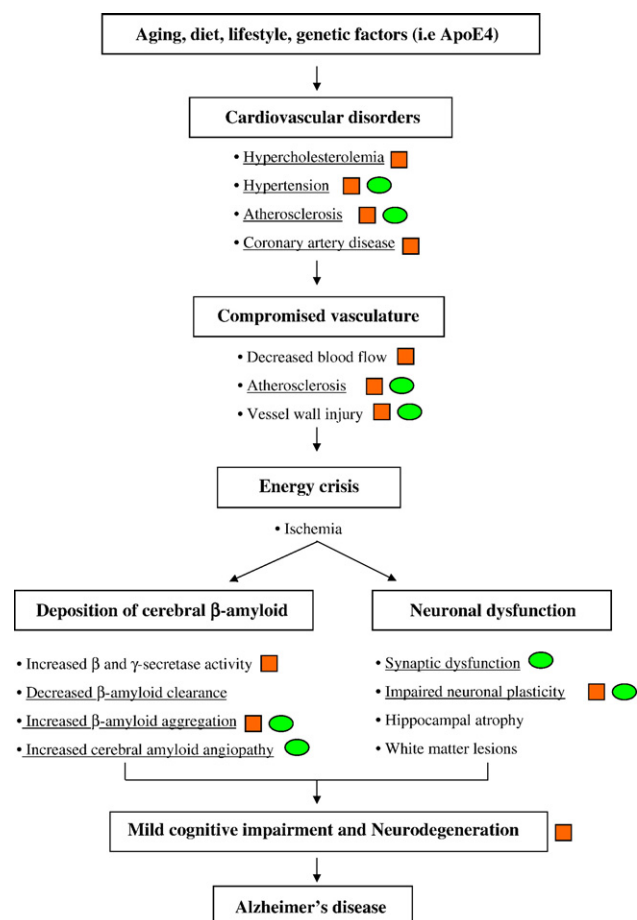


Fig. 1. Proposed sequence of events in the development of Alzheimer's disease and the processes in which ApoE4 and dietary factors may influence the course of the disease. For every process in the sequence of the course of the disease the possible influence of Apolipoprotein E4 (underlined), cholesterol (■) and omega-3 fatty acids (○) are indicated.

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