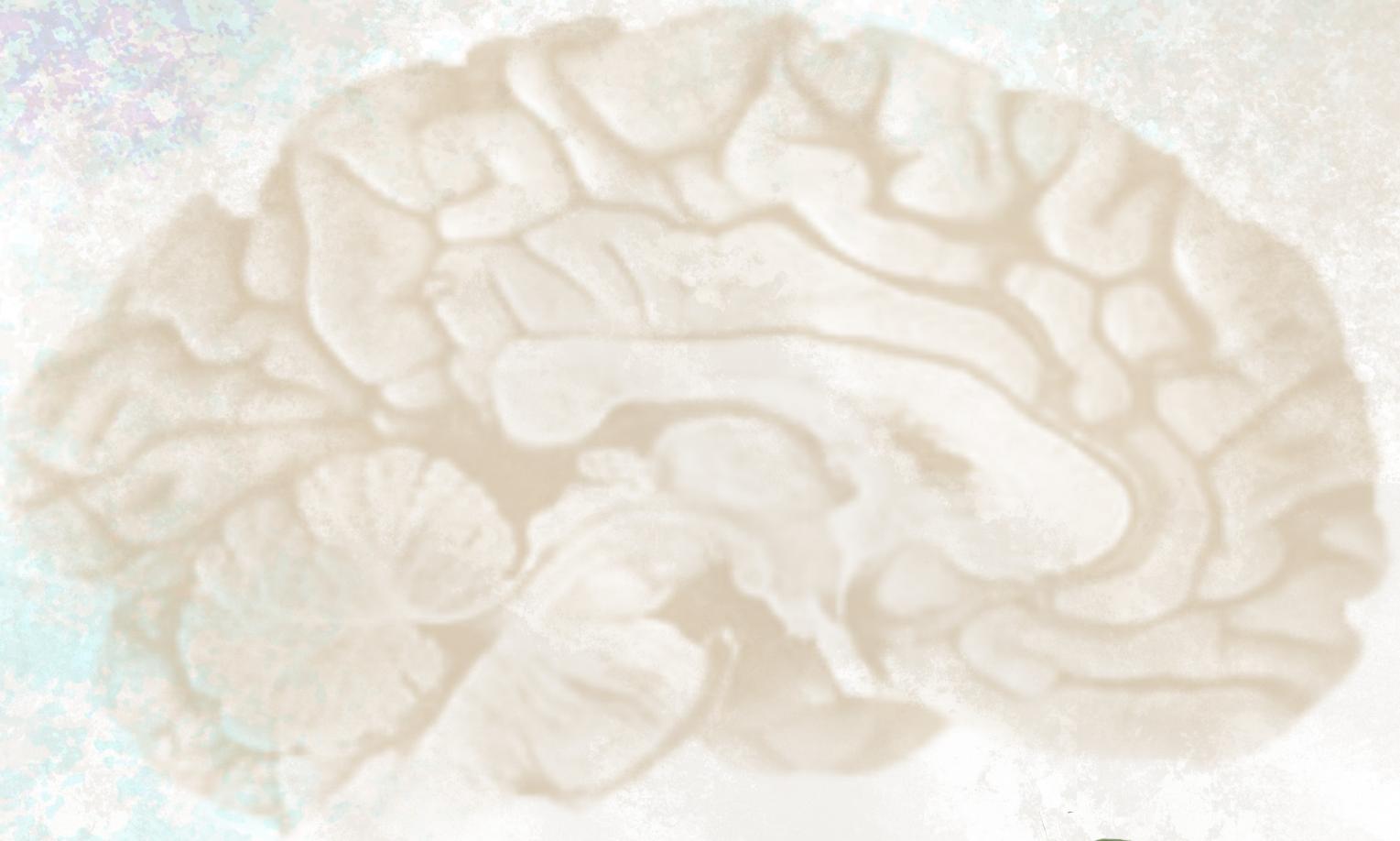


ALZHEIMER'S DISEASE, NEUROINFLAMMATION AND THE INFLUENCE OF DIFFERENT COMBINATIONS OF NUTRIENTS

Can a combination of nutritional components decrease neuroinflammation in Alzheimer's disease, thereby altering its development?



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- ABSTRACT-

Neuroinflammation has shown to play an important role in AD. Nowadays an increasing number of researchers are naming chronic neuroinflammation, manifesting in activated glial cells, as the main component exacerbating AD. Various investigations have shown the effect of nutritional components on certain elements of the pro-inflammatory cascade of AD. For example, nutritional components are able to alter nuclear-factor κ B (NF- κ B) expression and inhibit pro-inflammatory cytokines. Prospective studies investigating the influence of whole food groups and dietary patterns on the onset of AD and/or its cognitive breakdown notably showed more promising results than epidemiological studies focussing on single nutrients. Previous pre-clinical trials have placed too much emphasis on a single nutrient approach, ignoring the importance of a whole diet wherein combined nutrients are able to enhance or catalyze each other. In conclusion, a combination of nutritional components is able to decrease neuroinflammation in AD thereby inhibiting its development. Therefore nutrition can be a 'new' focal point in the treatment of AD. However, it must be taken into account that nutrients may have additive or synergistic effects within and across a range of foods that build up a diet. A full-diet approach is most likely to benefit AD treatment and therefore should be further investigated.

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I. GENERAL INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative illness which affects 10 percent of people older than 65 years and even 50 percent of the population over 85 years of age. AD has an immense influence on the society's health and has high economic costs (Wimo et al., 2006). This results in special attention for the treatment of this disease. AD is characterized by the loss of memory and other mental functions, accumulation of amyloid plaques and neurofibrillary tangles. Also, degeneration of the hippocampus, entorhinal cortex, neocortex, nucleus basalis, locus coeruleus and raphe nuclei can be found. The amyloid plaques consist of β -amyloid proteins. β -amyloid forms due to 'wrong' cleavage of the amyloid precursor protein (APP). APP is cleaved by three secretases: α -, β -, and γ -secretase. The sequential cleaving of APP by β -, and γ -secretase results in the formation of β -amyloid (containing 40 to 42 amino acids), whereas α -secretase prevents β -amyloid formation. The second cut of APP by γ -secretase determines which form (long or short) is produced. Normally only 5 – 10 percent of all β -amyloid proteins have the long form, while in AD this percentage is increased up to 40 percent. This long form often folds incorrectly thereby forming oligomeric aggregations which are toxic to the cell. Normally, the cell is capable of clearing the long β -amyloid proteins, but an AD-system cannot handle such a high amount of this protein. It is unknown if the amyloid plaques cause the disease or are a result of the disease. β -amyloid proteins can combine into oligomers, which can form fibrils. Eventually fibrils can combine to amyloid plaques. Recently it is suggested that instead of the amyloid plaques, the oligomers and fibrils are toxic (Haass and Selkoe, 2007). Neurofibrillary tangles consist of dying neurons, which contain twisted filaments of hyperphosphorylated tau proteins which are accumulated in the cell body of the neuron. Normally, tau protein is a component of microtubules which are the main facilitators in cellular transport. The abnormal tau proteins arise due to excessive amounts of phosphate ions which become attached to strands of the protein, consequently changing its molecular structure. The abnormal filaments induce a disruption in the cellular transport, eventually causing the neurons to die. What remains, is a tangle of protein filaments. Current treatments only intervene by slowing down the progression of the disease, while a greater influence could be achieved by focusing on treatment at the onset of the disease. Nowadays research tries to discover the underlying mechanisms of AD to explain its cause. The greatest part of the investigations is focused around three different hypotheses: the cholinergic hypothesis, the Tau hypothesis and the amyloid hypothesis.

The cholinergic hypothesis is the eldest, formulated in the mid-seventies. The hypothesis states that AD was caused by a reduced production of acetylcholine, due to substantial neocortical deficiency of choline acetyltransferase activity, an enzyme responsible for the synthesis of acetylcholine (Bowen et al., 1976; Davies and Maloney, 1976; Perry

et al., 1977). The first medications focused on enhancing central acetylcholine production through inhibiting its breakdown. However, since this medication only treated the symptoms but did not cure the disease, acetylcholine deficiencies probably do not cause AD.

In the early nineties, the amyloid hypothesis was formulated (Hardy and Allsop, 1991). Initially, it was found that in the Down syndrome almost all patients expressed symptoms similar to AD's symptoms at the age of 40 (Lott and Head, 2005; Nistor et al., 2007). The Down syndrome is caused by a trisomy of chromosome 21. Interestingly, the gene that encodes for amyloid precursor protein (APP) is located on this chromosome. The traditional hypothesis points out mature aggregated amyloid fibrils as toxic, for disturbing the cell's calcium homeostasis which eventually leads to apoptosis (Yankner et al., 1990). Several findings supported this hypothesis. The greatest amount of evidence comes from genetic analysis on familiar AD, in which almost all patients expressed mutations in the APP gene, Presenilin1 (PS1) and Presenilin2 (PS2) gene. These mutations appear to cause the excessive accumulation of β -amyloid (Price et al., 1998). Additionally, more recent studies have proved that PS1 and PS2 altered the APP metabolism in the cell (Duff et al., 1996; Borchelt et al., 1996; Citron et al., 1997) by directly affecting γ -secretase (De Strooper et al., 1998; Wolfe et al., 1999). Moreover, mutations in the gene encoding for the Tau protein caused frontotemporal dementia with parkinsonism (Poorkaj et al., 1998; Hutton et al., 1998; Spillantini et al., 1998). This disorder is characterized by accumulation and deposition of tau neurofibrillary tangles in the brain. However, deposition of amyloid plaques was not found. Therefore Hardy et al. suggested that the neurofibrillary tau deposition had happened after changes in β -amyloid metabolism and initial plaque formation (Hardy et al., 1998). Another investigation showed in APP/tau double transgenic mice that the neurofibrillary tau deposition was enhanced in comparison to the Tau transgenic mice, implicating that APP or β -amyloid influences the neurofibrillary tangle formation (Lewis et al., 2001). Furthermore, investigations indicate that genetic variations in the catabolism and clearance of β -amyloid appear to play a role in the risk of late-onset AD (Wavrant-De Vrièze et al., 1999; Myers et al., 2000; Ertekin-Taner et al., 2000; Bertram et al., 2000; Olson et al., 2002). Finally, an investigation of Iijima et al. found that in *Drosophila* "accumulation of amyloid- β 42 was sufficient to cause memory defects and neurodegeneration resembling AD, suggesting that the molecular basis underlying β -amyloid toxicity is conserved over different organisms" (Iijima et al., 2004). All these findings indicate a primary role of cerebral β -amyloid accumulation in the onset of AD, in which the previous symptoms including neurofibrillary tau formations are all caused by an imbalance between β -amyloid production and clearance (Hardy and Selkoe, 2002). However, some aspects should be considered within this theory. The most important concern is a mismatch between the degree of amyloid plaque formation and the degree of

cognitive impairment (Hardy and Selkoe, 2002). Subsequently, Schmitz et al. found in transgenic mice that the amount of neuronal loss exceeded amyloid plaque deposition. This confirmed that both factors did not correlate well (Schmitz et al., 2004).

These findings contributed to the formation of the tau hypothesis. Investigations of Kim et al. and Lahiri et al. found that the amount of neurofibrillary tangles correlated with neuronal loss (Kim et al., 1999; Lahiri et al., 2003), in contrast to amyloid plaque deposits. The tau hypothesis states that the abnormal or excessive phosphorylation of tau leads to paired helical filaments and neurofibrillary tangles. The hyperphosphorylated tau can form aggregations, thereby depleting itself of its normal function. The depletion causes disassembly of the microtubules and damage of the cell transport mechanism with related axonal transport which eventually leads to cell death (Mudher and Lovestone, 2002).

Nowadays, still not enough evidence exists to state one of these theories as 'the cause of AD'. Moreover, most forms of AD do not even arise from mutation-related causes. Several factors have been associated with increased risk of AD, for example high age, fewer years of education and apolipoprotein E epsilon4 allele. Decreased risk of AD has been associated with nonsteroidal anti-inflammatory drugs, wine consumption, coffee consumption, and regular physical activity (Lindsey et al., 2002). Other epidemiological investigations suggest a link between a balanced diet (Mediterranean diet) and a reduced risk of developing AD (Frisardi et al., 2010). It seems that these variations in lifestyle contribute even more to the risk of developing AD than the mutation-related causes.

Recently, a new theory has attracted more attention: the inflammation hypothesis. β -amyloid and APP have shown to induce cell apoptosis in vitro (Loo et al., 1993; Morishima et al., 2001) and in vivo (LaFerla et al., 1995; Masumura et al., 2000). Furthermore, β -amyloid has shown to activate microglia (Stalder et al., 2001). In vitro studies have shown that β -amyloid and APP, activated microglia in a dose-dependent way (Akama et al., 1998; Barge et al., 1997; Hu et al., 1999). Because nutrients -mainly polyunsaturated fatty acids (PUFAs)- have shown to reduce microglia activation in vitro (Ebert et al., 2009; Lu et al., 2010; Moon et al., 2007; De Smedt-Peyrusse et al., 2008; Lynch et al., 2007; Minogue et al., 2007; Pan et al., 2009; Zhao et al., 2011; Marcheselli et al., 2003; Lukiw et al., 2005) and in vivo (Chen et al., 2011; DeMar Jr et al., 2006; Igarashi et al., 2007; Ramadan et al., 2012; Trepanier et al., 2012; Igarashi et al., 2011) and epidemiological studies indicate a link between certain diets and the risk of developing AD (Frisardi et al., 2010), the following research question was formulated:

“Can a combination of nutritional components decrease neuroinflammation in Alzheimer’s disease, thereby altering its development?”

With the hypothesis:

“If a combination of nutritional components can decrease neuroinflammation in Alzheimer’s disease, nutrition could be a ‘new’ target in the treatment of AD.”

II. SYNERGISTIC EFFECT OF NUTRIENTS

Although certain food components have shown to reduce inflammation in vitro and in vivo, a higher effectiveness was achieved when combinations of nutrients were received. The sum total benefit caused by the interaction of whole foods outweighs the benefit of each food’s individual nutrient. This could be one of the reasons why pre-clinical studies emphasizing on single nutrients have had disappointing results in reference to epidemiological studies. Epidemiological studies found a correlation between certain diets and the risk of developing AD. Subsequently, pre-clinical studies investigated the effect of single nutrients and had a less profound outcome. This may be the cause of the single nutrient approach, which neglects the possible importance of additive or synergistic effects of other nutrients within and across particular foods that form part of a diet (Luchsinger et al., 2007). Another reason for the variation in outcomes could be explained by pre-clinical studies, which almost all aimed at an interference with the disease itself or with its symptoms. However, an interference with the development of the disease is something different than a dietary pattern which has always been there, even before the onset of the disease. Since pre-treatment for a whole society has its practical limitations, this thesis will focus on the treatment of AD-development. Furthermore, following the previous reasoning, this thesis’ emphasis will be on the effect of nutrient combinations instead of single nutrients.

III. NEUROINFLAMMATION & AD

Neuroinflammation has been linked to AD in various investigations. Recently, the inflammation hypothesis of AD has received more attention. The functions and effects of the two most important cellular mediators of inflammation in the brain are thoroughly reviewed: reactive astrocytes and activated microglia (Akiyama et al., 2000a,b; Aschner et al., 1998; Mrak et al., 1995; Streit et al., 1999; Tuppo et al., 2005). Ten percent of the brain’s glial cell population consist of microglia, the resident macrophages of the central nervous system. Normal activation of microglia is necessary for the host defense mechanism, pathogen recognition and initiation of the immune response. However, inappropriate over-activated microglia can become neurotoxic. Astrocytes are the most abundant cells in the CNS (85 percent of the glial cell population) and play a role in the blood brain barrier, homeostasis of the extracellular environment and energy homeostasis. When activated, glial cells produce immune signaling and effector molecules, including pro-inflammatory and anti-inflammatory cy-

tokines (Benveniste et al., 1997), reactive oxygen species (Chao et al., 1997; Juurlink et al., 1997) and growth factors.

IIIa. Microglia

Numerous studies, including a human post-mortem study (Hashioka et al., 2008), have associated microglia with amyloid deposits, (Dickson et al., 1988; Haga et al., 1989; Itagaki et al., 1989; Mattiace et al., 1990; Roher et al., 1988; Wegie et al., 1990; Wisniewski et al., 1989; Wisniewski et al., 1990). But not all studies agree on the effect of microglia on β -amyloid plaque formation. Although some studies suggest a role for the microglia in the phagocytosis of the extracellular amyloid fibrils, other findings concluded that the activation of microglia promotes the forming of amyloid fibrils. The study of Frackowiak was one of the first that showed the engulfment of β -amyloid by microglia (Frackowiak et al., 1992) through electron microscopy. In vitro studies then confirmed this by making use of radio or fluorescent labelling (Paresce et al., 1996; Pluta et al., 1999). However, subsequent findings indicated that, although the microglia ingest the β -amyloid, they are not able to clear either the soluble or fibrillar forms of β -amyloid (Wegiel et al., 2001, 2003, 2004). Furthermore, some studies indicate that the conversion of non-fibrillar β -amyloid into fibrillar β -amyloid eventually leads to the conversion of neuritic plaques into diffuse plaques and is favoured by microglia (Cotman et al., 1996; Griffin et al., 1995; Mackenzie et al., 1997). In the beginning of the 21st century, studies indicated a role of activated microglia in the initiation of a chronic pro-inflammatory environment (Combs et al., 1999, 2001) which may lead to the cognitive deficits seen in AD (Akiyama et al., 2000a). A study of Combs et al. found an increased production of tumor necrosis factor (TNF) after monocyte/microglia stimulation with β -amyloid, eventually leading to inducible nitric oxide synthase (iNOS)-dependent neuronal apoptosis (Fig. 1: Combs et al., 2001). An investigation of Qin et al. tried to discern the mechanisms of inflammation transfer from the periphery to the brain and its neurodegenerative con-

sequences, by administration of lipopolysaccharide (LPS) or TNF- α in the adult wild-type mice and in mice lacking TNF α receptors (TNF R1/R2-/-). They found that systemic LPS administration caused a rapid increase in central TNF- α release, which remained elevated for ten months. Furthermore, systemic injections of TNF- α and LPS activated microglia and increased expression of brain pro-inflammatory factors (i.e., TNF α , MCP-1, IL-1 β , and NF- κ B) in wild-type mice, but not in TNF R1/R2-/- mice (Qin et al., 2007). This indicates that the neurodegenerative consequences of inflammation after LPS or TNF- α administration may have been derived from respectively increased TNF- α release and its action on the TNF- α receptor. A recent study published this year by Krabbe et al. observed in the APP/PS1 mice, a transgenic mouse model for cerebral amyloidosis, that "impairment of microglial function temporally and spatially correlated with β -amyloid plaque deposition" (Krabbe et al., 2013). This implied that the major functions of microglia progressively decline in AD with the appearance of β -amyloid plaques.

IIIb. Astrocytes

Astrocytes in the AD-brain are also associated with β -amyloid plaque formation and with an increased release of immune signaling and effector molecules including interleukin (IL)-1, IL-10, interferon- α (IFN α) and TNF α after activation (Dong and Benveniste, 2001). They particularly produce IL-6, which promotes neuronal survival and astrocyte proliferation (Dong and Benveniste, 2001) and monocyte chemoattractant protein-1 (MCP-1) production, which causes disruption of the blood brain barrier for monocytes recruitment (Dorf et al., 2000). Recent studies suggest a role of astrocytes in the regulation of microglial phagocytosis. Astrocytes create a barrier around the amyloid plaque via deposition of proteoglycans, thereby preventing its phagocytosis by microglia (Shaffer et al., 1995; DeWitt et al., 1998). This implied that astrocytes prevent an effective clearance of the amyloid plaques, eventually promoting its maintenance. Furthermore, astrocytes

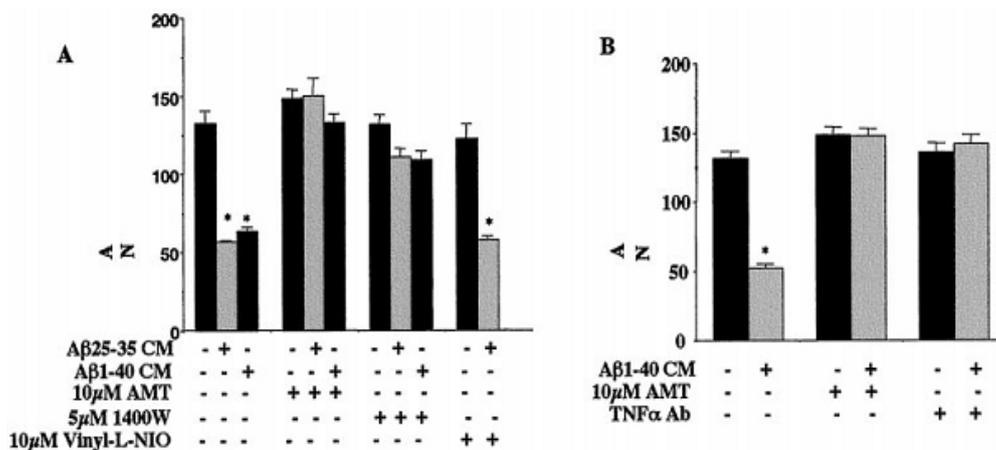


Fig. 1. Conditioned media from Abstimulated monocytes and microglia produces TNF α /iNOS-dependent neuronal apoptosis. Purified cultures of mouse cortical neurons (E16, 5 d in vitro) were treated for 72 hr in Neurobasal media from unstimulated microglia (B) or THP-1 cells (A) or conditioned Neurobasal media (CM) obtained from microglia (B) or THP-1 cells (A) stimulated (48 hr) via surface-immobilized Ab25-35 or Ab1-40 fibrils. The incubations also included, as indicated, 10 mM AMT.HCl, 5 mM 1400W.2HCl, 20 mM Vinyl-L-NIO, and anti-mouse TNF α antibody (5 mg/ml). To terminate experiments, the neurons were fixed and stained for neuron-specific MAP2 protein, and surviving neurons were counted. Neurons from four fields/condition were counted in duplicate wells and averaged 6 SEM. The mean values shown (6SEM) are representative of four independent experiments. Unpaired ANOVA was performed with Tukey-Kramer post-comparison to evaluate statistical significance (*p, 0.001). – Combs et al., 2001.

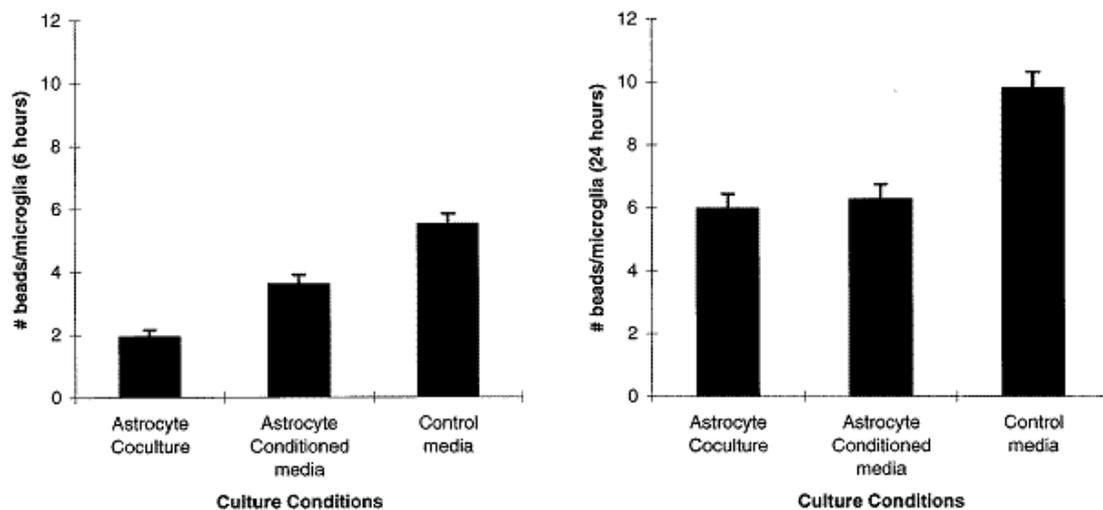


Fig. 2. Phagocytosis of 0.5-µm latex particles conditioned for 24 h with astrocytes, astrocyte-conditioned media, or control media. After 6h, astrocyte-conditioned media suppresses microglial phagocytosis; however, not to the same extent as astrocyte cocultures until 24 h (B) while both are significantly less than control. (Representative data, performed in triplicate.) - DeWitt et al., 1998.

can alter microglia behavior (Abd-El-Basset et al., 1995; Giulian et al., 1995; Liu et al., 1994; McMillian et al., 1994; Sievers et al., 1994; Suzumura et al., 1991; Tanaka et al., 1996). An experiment of DeWitt et al. found that astrocytes strongly suppressed microglial phagocytosis, especially when cells were directly in contact with each other (Fig. 2: DeWitt et al., 1998). Additionally, the microglia cells acquired a ramified morphology when they were in direct contact with astrocytes (DeWitt et al., 1998).

IIIc Neuroinflammation and age

Age –the number one risk factor for AD- seems to affect the inflammatory response. High age has been linked to an enhanced inflammatory brain response. Glial fibrillary acidic protein (GFAP) expression, a protein which is expressed by astrocytes, increased with age in rodents and humans (Nichols et al., 1993). Furthermore, with increasing age, the rat microglia and macrophage cells were increased in number and distribution (Perry et al., 1993). Also, aged astrocytes seemed to be more sensitive to gliotrophic factors, produced more of these factors and slowed down the clearance of the factors (Gordon et al., 1998), indicating a role for glial hypersensitivity in aging. Additionally, after induced brain trauma, older rats showed higher astrocyte reactivity in the cortex than the younger

rats, except in the hippocampus. So aging alters the region of astrocyte reactivity, which may be due to an enhanced sensitivity of the astrocytes (Topp et al., 1989). Finally, fibrillar β -amyloid microinjection in the cerebral cortex of aged rhesus monkeys led to neuronal loss, tau phosphorylation and microglial proliferation. In contrast, fibrillar β -amyloid was not toxic in the young adult rhesus brain (Fig. 3. Geula et al., 1998). Although these results showed great differences between species, the higher order primates seemed to be more sensitive for β -amyloid induced neurotoxicity (Geula et al., 1998). These findings may explain partly why AD is an age-associated disease (Moore et al., 2002).

IIIId. β -amyloid-RAGE mediated NF- κ B activation as primary inflammatory cause

The primary inflammatory stimulus may be β -amyloid itself. As stated previously, in vitro studies showed that β -amyloid and APP activated microglia in a dose-dependent way (Akama et al., 1998; Barge et al., 1997; Hu et al., 1999). Furthermore, β -amyloid and APP induced neuronal apoptosis in vitro (Loo et al., 1993; Morishima et al., 2001) and in vivo (LaFerla et al., 1995; Masumura et al., 2000). Additionally, an experiment of Hu and Van Eldink found that glial proteins which are abundant in amyloid plaques and/or are known

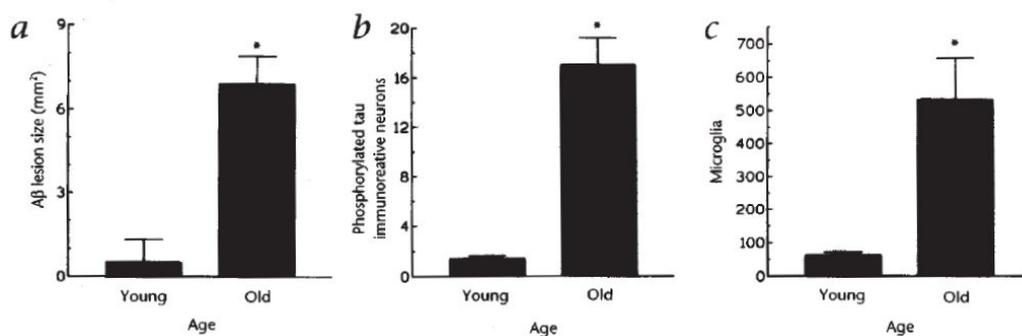


Fig. 3. A β neurotoxicity in the primate cerebral cortex is age-dependent. Quantitative analyses after injection of 200 pg of fibrillar A β in the cerebral cortex of young adult (5 years old) and aged (25-27 years old) rhesus monkeys. a, A β neurotoxicity. b, Neurons with immunoreactivity for phosphorylated tau. c, Microglia. Fibrillar A β induces significant neuronal loss, tau phosphorylation and microglial proliferation in aged rhesus brain, but not in the young adult brain. Values are corrected for vehicle and represent the mean \pm s.e.m., n = 6 animals; *P < 0,01 by ANOVA with post-hoc Neuman-Keuls test. Values in b and c are the mean number of cells per section. - Geula et al., 1998.

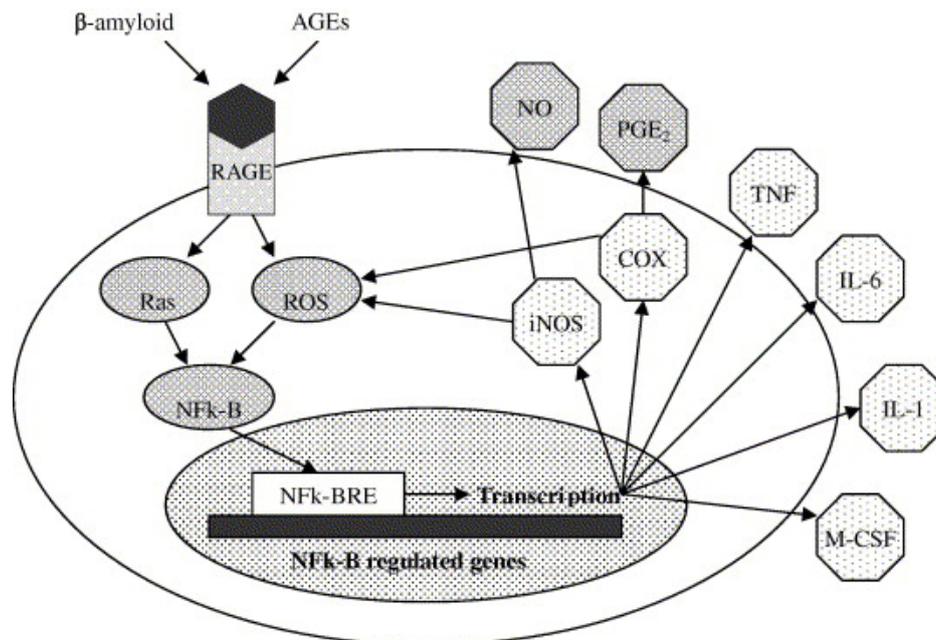


Fig. 5. NF-κB signalling through RAGE. Activation of the receptor for advanced glycation endproducts triggers the transcription factor NF-κB leading to transcription of a variety of cytokines including IL-1, IL-6 and TNF – Steele et al., 2007.

to interact with β -amyloid were able to activate glial cells and to enhance the β -amyloid induced astrocyte activation. This continuous cycle of inflammatory stimuli may contribute to the chronic glial activation which is observed in AD (Hu and Van Eldink 1999: Appendix fig. 4). The underlying molecular mechanism through which β -amyloid stimulates glial cells may be achieved via activation of nuclear-factor κ B (NF- κ B) (Akama et al., 1998; Bales et al., 2000). This activation might be due to β -amyloid activity at formyl chemotactic receptors or through binding on the receptor for advanced glycation endproducts (RAGE) (Akiyama et al., 2000a; Araki et al., 1995; Koenigsnecht and Landreth, 2004; Chaney et al., 2005). NF- κ B can also become activated after stimulation by IL-1, IL-17, TNF and oxidative stress (Barnes and Karin, 1997; Sarkar and Fisher, 2006). Interestingly, activated microglia surrounded by neuritic plaques in the brains of AD patients showed an increased percentage of RAGE expression (Akiyama et al., 2000a; Lue et al., 2001). Activation of RAGE by advanced glycation endproducts and β -amyloid causes the release of free radicals and expression of pro-inflammatory cytokines via NF- κ B. Therefore, RAGE may play a role in initiating the inflammatory cascade which contributes to the development of AD (Fig. 5: Steele et al., 2007).

IIIe. Summary

To summarize the above, neuroinflammation may contribute to the onset of AD and plays an important role in the development of the disease. Increasing age is linked to an enhanced neuroinflammatory response and altered glial functioning. β -amyloid activates microglia, which subsequently releases factors that contribute to a pro-inflammatory milieu, eventually causing neurodegeneration. Furthermore, activated astrocytes seem to decrease the ability of microglia to clear the amyloid plaques. Activat-

ed glial cells seem to enhance each other, releasing pro-inflammatory factors that also activate themselves in response to the activating stimulus of β -amyloid, creating a positive feedback loop. Finally, another indication for the primary role of inflammation in AD are the numerous (epidemiological) studies that have underlined the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on the risk of developing AD (Reviewed by McGeer et al., 1996). In conclusion, neuroinflammation seems to play a prominent role in AD pathology and is a potential target for treatment and prevention of the disease.

IV. UNDERLYING MOLECULAR MECHANISMS: EFFECT OF NUTRIENTS ON (NEURO) INFLAMMATION

Due to interesting outcomes of epidemiological investigations, experiments were performed in search for the underlying molecular mechanism by which food components are able to alter (neuro)inflammation. The single components of the promising diets were tested in vitro and in vivo. Most experiments were done focusing on polyunsaturated fatty acids (PUFAs), because various epidemiological investigations showed that diets enriched with PUFAs decreased the risk of developing AD. Furthermore, vitamins were investigated because of their anti-oxidant capacity. Also, other food components which are known to possess anti-oxidant potential, like polyphenols, were analysed.

IVa. n-3 PUFAs

Several studies implicate that omega-3 (n-3) PUFAs can inhibit neuroinflammatory responses in vitro. The most important factor mediating this is neuroprotectin D1 (NPD1), a substance derived from the selective oxygena-

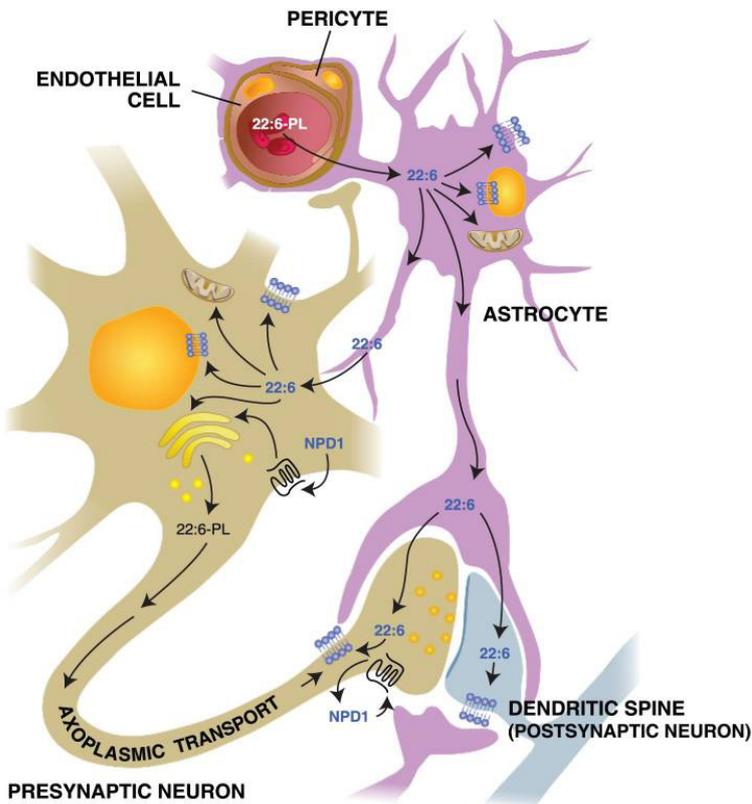
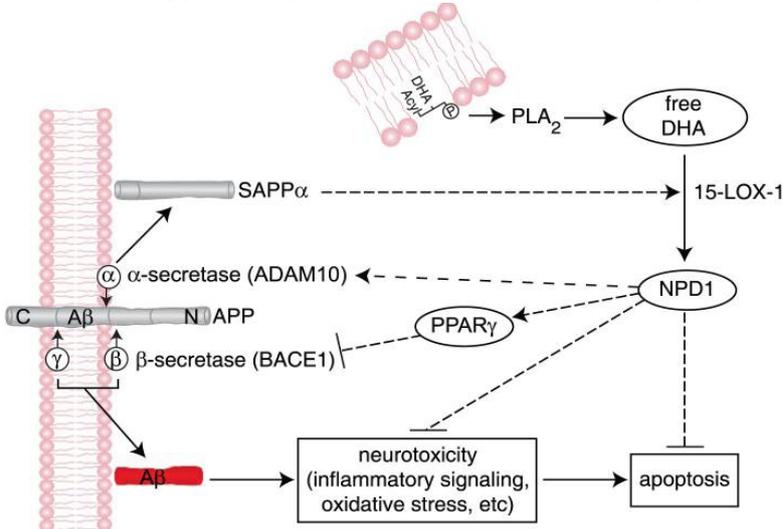


Fig. 6. Movement of docosahexaenoic acid (DHA) (22:6) through the neurovascular unit and its disposition within neurons and astrocytes. 22:6-phospholipids (22:6-PLs) are taken up by endothelial cells from the circulation and transferred to astrocytes within the central nervous system; from there, 22:6 is incorporated into astrocytes or transferred to neurons. 22:6 is also available for conversion to neuroprotectin D1 (NPD1) upon inductive signals. After packaging in the endoplasmic reticulum and the Golgi apparatus, 22:6 is also transported to the synaptic terminal to become incorporated into synaptic elements. Arrows represent possible routes. Molecular characterization of transporter(s) and receptors remains to be done.-Bazan et al., 2011.

tion of docosahexaenoic acid (DHA) by 15-lipoxygenase-1 (15-LOX-1) (Calandria et al., 2009). As stated before, glial cells produces pro-inflammatory cytokines after activation, eventually leading to neurodegeneration. NPD1 opposed this pro-inflammatory response by its anti-inflammatory actions (Marcheselli et al., 2003; Mukherjee et al., 2004; Schwab et al., 2007; Serhan et al., 2006). Interestingly, experiments of Marcheselli also found that NPD1 inhibited activation of NF- κ B and cyclooxygenase-2 (COX-2) expression in brain ischemia-reperfusion (Marcheselli et al., 2003; Appendix fig. 6). NF- κ B, as earlier stated, is proposed



to be the factor causing β -amyloid mediated microglia stimulation and is associated with extracellular signal-regulated kinases and p38 MAPK-NF- κ B-mediated COX-2 up-regulation (Jang et al., 2005). Furthermore, NPD1 activated peroxisome proliferator-activated receptor gamma (PPAR γ) (Zhao et al., 2010), which led to anti-inflammatory, anti-amyloidogenic actions and anti-apoptotic bioactivity (Fig. 8: Bazan et al., 2011). PPAR γ also plays a role in the effect of NPD1 on β -amyloid release. Overexpressing of PPAR γ or incubation with a PPAR γ agonist leads to reductions in β -amyloid, sAPP β , and CTF β , similar to NPD1 treatment. Treatment with PPAR γ antagonists undid these reductions (Bazan et al., 2011). Also, DHA has shown promising results in transgenic models for AD (Akbar et al., 2005; Fotuhi et al., 2009; Green et al., 2007; Lim et al., 2005; Salem et al., 2001). Lukiw et al. did find that brains from people suffering from AD and brains from the transgenic AD mice (3xTg-AD) both had reductions in their NPD1 and DHA expression (Lukiw et al., 2005). NPD1 treatment altered β -amyloid precursor protein (β APP) processing and decreased β -amyloid release (Lukiw et al., 2005). DHA application showed β -amyloid lowering effects both in vivo and in vitro (Lim et al., 2005; Oksman et al., 2006; Sahlin et al., 2007). DHA lowered β -amyloid via stimulation of non-amyloidogenic β APP processing, through reduction of the PS1 expression or by increasing the expression of the sortilin receptor, SorLA/LR11 (Reviewed in Bazan et al., 2011: Lim et al., 2005; Ma et al., 2007; Zhao et al., 2007; Sahlin et al., 2007). Additionally, other investigations showed similar inflammation modularly capacities of DHA. A study of Dah-Yuu Lu and Yin-Yin Tsao found that DHA reduced expression of TNF- α , IL-6, NO synthase and COX-2, induced by interferon- γ , and caused upregulation of heme oxygenase-1 in BV-2 microglia (Lu and Tsao, 2010). Repeated key experiments have shown that eicosapentaenoic acid (EPA), the other important n-3 PUFA, had similar effects. This confirms that DHA and EPA suppressed neuroinflammation in BV-2 microglia. Other studies suggested the same results (De Smedt-Peyrusse et al, 2008; Ebert et al, 2009; Komatsu et al, 2003; Saw et al, 2010). In contrast, some evidence shows that a high dose of n-3 PUFAs can work pro-inflammatory (Brand et al, 2010; Hirafuji et al, 2002). However, other studies indicate that a high dose of DHA/EPA lowered the amount of reactive oxygen species (Varming et al, 1995; Thompson, P. et al. 1992; Luostarinen et al. 1996). Lower doses (0.55–2.3 g/d) seem to have no effect (Thies et al. 2001; Healy et al. 2001; Schmidt et al. 1996;

Fig. 8. Mechanism for neuroprotectin D1 (NPD1) induction of nonamyloidogenic and neurotrophic bioactivity. Docosahexaenoic acid (DHA) (22:6) is 15-lipoxygenated to yield free DHA, in turn, free DHA is 15-lipoxygenated to generate NPD1, which then activates neuroprotective signaling. These events are mediated, in part, by shifting beta-amyloid precursor protein (β APP) processing from an amyloidogenic into a neurotrophic, nonamyloidogenic pathway and by inhibiting apoptosis, blocking inflammatory signaling, and promoting cell survival. Beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1) (β -secretase-1) activity is suppressed, and α -secretase disintegrin and metalloproteinase 10 (ADAM10) activity is stimulated, thus down-regulating amyloid-beta 42 (A β 42) peptide release. NPD1 signaling to BACE1 and ADAM10 may be mediated via other neuromolecular factors. The ADAM10 cleavage product soluble amyloid precursor protein alpha (sAPP α) further induces the conversion of free DHA into NPD1, thus constituting a positive, neurotrophic feedback loop.-Bazan et al., 2011.

Kew et al. 2003; Miles et al. 2004). Additionally, n-3 PUFAs can decrease the capacity of monocytes to synthesize IL-1 and TNF (Weber et al. 1991) and reduce the production of IL-6 (Khalifoun, B. et al. 1997). Nowadays many researchers indicate n-3 PUFAs as an anti-inflammatory agent which can be used as a strategy to treat disorders related with an inappropriately activated immuneresponse (Calder, 2002; Calder and Grimble, 2006).

IVb. Polyphenols

Polyphenols are a structural class of mainly natural, but also synthetic or semisynthetic organic chemicals characterized by the presence of large multiples of phenol structural units. The most important polyphenols that have been linked with anti-oxidative and anti-inflammatory capacities are mega natural grape seed polyphenolic extract (GSPE), epigallocatechin gallate (EGCG), resveratrol and curcumin.

GSPE has shown to significantly inhibit oligomerization of β -amyloid and to restore cognitive deterioration (Wang et al., 2008; Ono et al., 2008). Also GSPE blocks β -amyloid fibril formation, protofibril formation, pre-protofibrillar oligomerization, and initial coil helix/sheet secondary structure transitions. Furthermore, GSPE has shown neuroprotective effects by reducing β -amyloid cytotoxicity (Ono et al., 2008).

Numerous investigations have subscribed the positive health effects of green tea component EGCG. EGCG has shown anti-oxidation and anti-inflammatory effects in

vivo and in vitro (Mandel et al., 2007). Furthermore EGCG is a scavenger of free radicals which provides an increase of the two major anti-oxidant enzymes in the stratum of mice brains: superoxide dismutase and catalase. Moreover, pre-treatment with EGCG suppressed β -amyloid-induced pro-inflammatory response of BV-2 microglia -showed by iNOS, NO and peroxynitrite- and β -amyloid induced cytotoxicity (Chang-Yul et al., 2009). In mutant PS2 AD mice, EGCG reduced the β -amyloid induced memory dysfunction dose-dependently. Furthermore, β -amyloid caused a decrease in α -secretase and an increase in β - and γ -secretase which were respectively enhanced and inhibited by EGCG. EGCG also inhibited LPS-induced increase of β -amyloid levels dose-dependently through attenuation of LPS-induced β - and γ -secretase activities and expression of its metabolic products; C99 and β -amyloid (Lee JW et al., 2009; Lee YK et al., 2009). EGCG decreased β -amyloid activation of extracellular signal-regulated kinase and NF- κ B, and inhibited β -amyloid induced apoptotic neuronal cell death. EGCG also inhibited β -amyloid fibrillization in vitro (Fig. 9: Lee JW et al., 2009). Another investigation found that EGCG decreased the expression of inflammatory factors iNOS and COX-1 and prevented cognitive impairment (Lee YK et al., 2009: Appendix fig. 10).

Resveratrol, a non-flavonoid which is present in red wine, grapes, peanuts, soy beans, and pomegranates (Jang and Surh, 2003; Savaskan et al., 2003; Karuppagounder et al., 2009) has shown anti-inflammatory effects on β -amyloid, by counteracting its induced NF- κ B activation (Jang and Surh, 2003: Appendix fig. 11). Resveratrol has not shown to inhibit β -amyloid production, since it had no effect on the β -amyloid producing enzymes β - and γ -secretases. Instead, resveratrol promotes intracellular degradation of β -amyloid via a mechanism that involves the proteasome (Marambaud et al., 2005), activating the anti-amyloidogenic pathway (Hoult et al., 1994). Additionally, resveratrol-induced decrease of β -amyloid was prevented after addition of several selective proteasome inhibitors. This has further been reviewed by De Vrij et al. (de Vrij et al., 2004). Karuppagounder et al. found resveratrol to diminish plaque formation in a region-specific manner, with the largest reductions in the medial cortex (-48%), striatum (-89%) and hypothalamus (-90%) (Karuppagounder et al., 2009). Additionally, resveratrol seemed to enhance sirtuins, which play a role in cellular longevity (Guarente, 2001). Resveratrol particularly showed to be a potent activator of Sirtuin 1 (SIRT-1) which supports axonal protection (Araki et al., 2004). SIRT-1 inhibited the signaling pathway NF- κ B in microglia and astrocytes resulting in the protection against β -amyloid-induced toxicity (Fig. 12: Chen et al., 2005). Resveratrol also favored protein kinase C phosphorylation (Han et al., 2004) thereby activating the non-amyloidogenic pathway of β APP cleavage, eventually leading to a reduction in β -amyloid release. Finally, a product of the cleavage process $aA\beta PP\alpha$, may activate genes involved in neuroprotection (Ramesh et al., 2010).

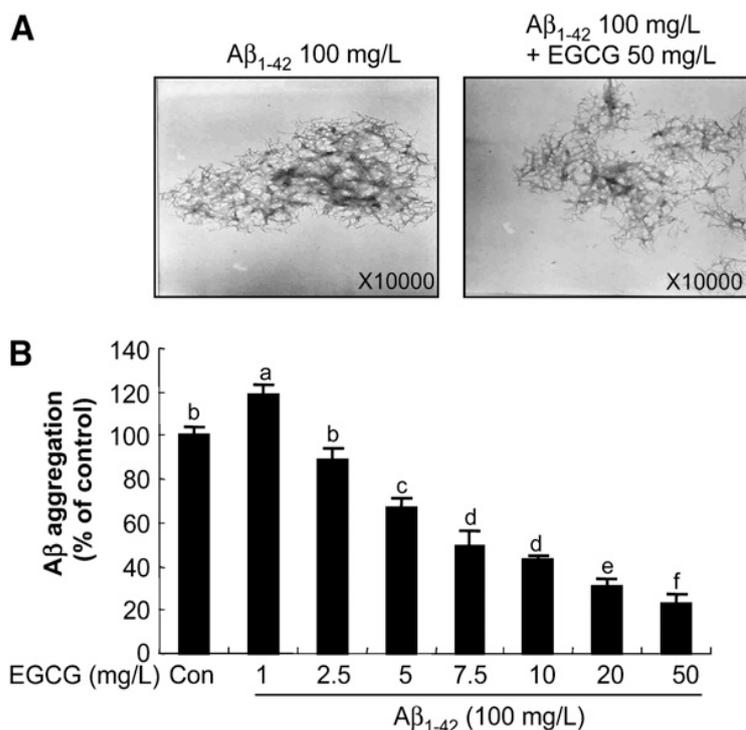


Fig. 9. Ab fibrillogenesis in vitro. (A) Electromicroscopy observation of Ab aggregation (310,000). (B) Value is the mean \pm SEM, n = 3. Means without a common letter differ, P, 0.05. -Lee JW, et al., 2009.

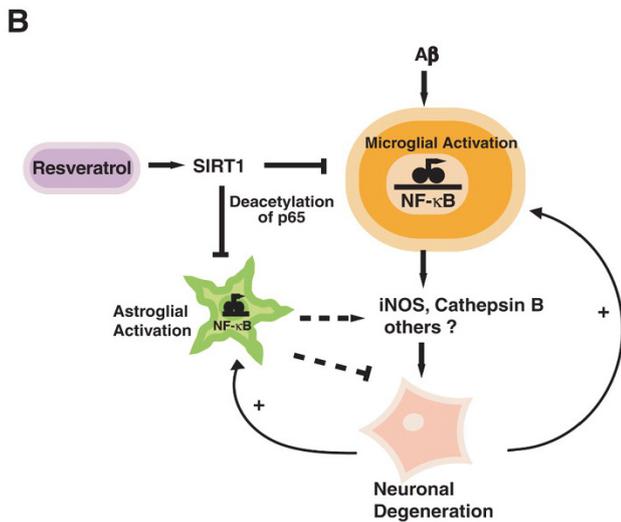


Fig. 12. Potential molecular mechanisms underlying microglia-mediated A β toxicity in mixed cortical cultures. A β activates NF- κ B signaling in microglia, resulting in the up-regulation of various NF- κ B target genes, such as iNOS, cathepsin B, and others, which may be toxic to neurons. Injured neurons secrete factors that further activate NF- κ B signaling in microglia and astrocytes, resulting in a vicious cycle. Specific inhibition of NF- κ B in microglia by overexpression of I κ B α -SR disrupts the toxic pathway and protects against A β toxicity. Modulation of acetylation of RelA/p65 by SIRT1 overexpression or resveratrol also down-regulates NF- κ B signaling, resulting in strong neuroprotective effects. -Chen et al., 2005.

Curcumin, also a non-flavonoid, is a substance derived from the yellow Indian spice Turmeric and has shown to possess anti-inflammatory capacities. Furthermore, it is a better free radical scavenger than vitamin E (Ramesh et al., 2010). Curcumin protects against lipid peroxidation (Martin-Aragon et al., 1997) and is a scavenger for NO radicals (Sreejayan and Rao, 1997). Various investigations observed that curcumin antagonized pro-inflammatory factors as protein-1 transcription, and NF- κ B, iNOS and -c-Jun NH2-terminal kinase (JNK) activation (Pendurthi et al., 1997; Weber et al., 2006). Curcumin also decreased IL-1 levels, astrocytic marker GFAP, amyloid plaque burden, insoluble β -amyloid, soluble β -amyloid, JNK, and carbonyls, and prevented β -amyloid aggregation in an AD transgenic APPSw mouse model (Tg2576) (Aynun et al., 2008; Lim et al., 2001). Also, the β -amyloid induced cognitive memory deficits were reduced after curcumin administration (Frautschy et al., 2001).

IVc. Vitamin A (Retinoid)

The idea of Vitamin A as an immune-regulator and possible anti-inflammatory substance arose in the 1920th, when Edward Mellanby and Harry N. Green stated vitamin A as 'anti-infective vitamin'. More studies were performed and the knowledge about the role of vitamin A in the immune-system was increased. Importantly, clinical evidence showed that brains affected by (late onset) AD had a defective retinoid transport and function (Goodman and Pardee, 2003; Goodman et al., 2006). Also, samples of AD patients showed a deficit of retinoid acid receptor- α (RAR α) together with β -amyloid deposition in surviving neurons (Husson et al., 2006). Vitamin A deficiency led to a disruption of the retinoid signaling pathway in adult rats, eventually leading to deposition of β -amyloid in cerebral

blood vessels, which could be undone by retinoic acid administration (Husson et al., 2006; Corcoran et al., 2004). Experiments indicated that retinoids can cross the blood brain barrier (Jarvis et al., 2010). Also, RAR α showed to possess neuroprotective capacities via suppression of β -amyloid induced neuronal cell death in cortical cultures of AD mice by inhibition of β -amyloid production (Jarvis et al., 2010: Appendix fig. 13 & 14). Retinoids strongly suppressed the IL-6 release by astrocytes and microglia (Zitnik et al., 1994; Kagechika et al., 1997), which is associated with plaque formation. Moreover, retinoids showed inhibition of LPS or β -amyloid induced TNF- α production and iNOS expression in activated microglia (Dheen et al., 2005; Kaur et al., 2006). Another study found that 14 weeks supplementation with retinoid Am80 (tamibarotene) -an selective retinoid acid receptor ligand- in a mutant mouse model for AD (APP23 mice) significantly reduced levels of insoluble β -amyloid in the brain (Kawahara et al., 2009). Furthermore, retinoic acid works as an activator of α -secretase (Prinzen et al., 2005; Fahrenholz et al., 2006; Fahrenholz et al., 2007) and seems to be involved in the regulation of APP processing (Husson et al., 2006). Also, findings of Long, K. Z. et al. suggested that vitamin A has an anti-inflammatory effect in the gastrointestinal tract by reducing the concentration of MCP-1 (Long, et al. 2006). Another study of Kim, B. H. et al. aimed to investigate the underlying anti-inflammatory mechanism of vitamin A (Kim, et al. 2004). The effect of vitamin A on COX-1 and COX-2 associated prostaglandin E2 (PGE2) release from mouse peritoneal macrophages and the release of TNF- α in LPS induced inflammation in rat peripheral blood mononuclear cells was studied. They found that vitamin A worked as an anti-inflammatory agent through inhibiting LPS-induced COX-2 and TNF release.

IVd. Vitamin B

In the literature, B-vitamins and their influence on the conversion of homocysteine, a non-essential protein amino acid, are thoroughly described. Elevated levels of homocysteine are associated with many (neuropsychiatric) diseases (Reynolds et al., 2006), including AD (Clarke et al., 1998; Seshadri et al., 2002). Normally, the homocysteine level is kept low due to the recycling of homocysteine into methionine or conversion into cysteine with the aid of vitamin B6, vitamin B12 and folate (vitamin B9). In the late seventies Manzoor et al. already reported ten patients with severe neurological disease which were all folic deficient, although they were having normal vitamin B12 levels. A treatment with folate led to the a significant reversal of the neuropathology (Manzoor, M. et al. 1976). Homocysteine levels are correlated with the degree of amyloid peptides in plasma of individuals with AD (Irizarry et al., 2005; Luchsinger et al., 2007). Subsequently, the reduction of homocysteine levels may lower the plasma level of amyloid peptides (Flicker et al., 2008). Also, folic acid (the synthetic form of vitamin B9) was found to increase cell viability and mitochondrial membrane potential in

β -amyloid stimulated neurons. Folic acid reduced levels of pro-inflammatory factors p53, bax and caspase-3 and enhanced anti-apoptotic bcl-2 expression, eventually preventing neuronal apoptosis (Yu et al., 2009). Additionally, in vitro experiments showed that hippocampal neurons in folic acid deficient medium or in the presence of methotrexate (an inhibitor of folic acid metabolism) or homocysteine, made the neurons more sensitive to β -amyloid cytotoxicity (Kruman et al., 2002). Also, various other experiments showed the role of B-vitamins in the immuneresponse. An experiment of Olas, B. et al. with blood platelets in vitro, indicated that “a correlation between the increased amount of homocysteine and the oxidative stress” (Olas et al. 2008) exists. Experiments of Dietrich-Muszalska suggested that the elevated homocysteine levels in schizophrenic patients may stimulate the oxidative stress (Dietrich-Muszalska et al. 2012). Additionally, an investigation of Gariballa et al. concluded from their experiments with diabetic patients that supplementation with B-vitamins enhances antioxidant capacity, providing an anti-inflammatory effect in obese diabetic patients (Gariballa, S. et al. 2013). Finally, Solini, A. et al. wanted to investigate the effect of folic acid supplementation on insulin sensitivity and peripheral markers of inflammation in overweight healthy subjects. In healthy overweight subjects “a short-term folic acid supplementation reduced the circulating level of some inflammatory mediators independently of weight change.” Additionally, folic acid decreased the levels of interleukin- and C-reactive proteins. To summarize, folic acid, vitamin B6 and B12 can have an antioxidant effect on ROS, can protect against hyperhomocysteinemia and consequently possess anti-inflammatory capacities (Solini, A. et al. 2006).

IVe. Vitamin C

Vitamin C has shown to reduce ethanol induced immune-activation in human astrocytes, whereas the greatest effect was achieved after pre-treatment (Sánchez-Moreno et al., 2003). Ethanol increased the expression of pro-inflammatory factors COX-2 and PGE2, inflammatory factors that were inhibited by both vitamin C and NSAIDs. Additionally, NSAIDs treatment has already shown improvements in AD patients, suggesting that vitamin C mediated COX-2 and PGE2 decrease may be a possible target in the treatment of AD.

IVf. Vitamin D

Many publications state that vitamin D has a protective role in some inflammatory based diseases. β -amyloid triggers neurodegeneration partly by dramatically suppressing the expression of the vitamin D receptor (Dursun et al., 2011). Vitamin D administration protected neurons against β -amyloid induced cytotoxicity and apoptosis. Also, vitamin D downregulated A1C L-type voltage sensitive calcium channels, upregulated the vitamin D receptor and brought the nerve growth factor expression to a state of equilibrium (Dursun et al., 2011). A study of Nonn found

that 1,25-di-hydroxyvitamin-D3 (1,25D) inhibited p38 signaling via MKP5 up-regulation (Nonn, L. et al. 2006). IL-6, a downstream of p38 activation was similarly inhibited by 1,25D. Previous mentioned findings were done in human primary prostatic epithelial and stromal cells that were derived from radical prostatectomy specimens. Other studies indicate a more immunoregulatory role of 1,25D. Like the study of Rigby et al. who found that 1,25D suppressed the IL-2 production of PHA-stimulated peripheral blood mononuclear cells in a concentration-dependent manner (Rigby et al. 1989). On the other hand, studies did indicate that the response of monocytes and macrophages to a bacterial infection was stimulated by 1,25D, like the differentiation of macrophages (Xu, H. et al. 1993; Abu-Amer, Y. et al. 1993). However, at the same time 1,25D prevented the macrophages from releasing more inflammatory cytokines and chemokines than required (Alappat, L. et al. 2010). Further on, 1,25D decreased TNF- α , IL-1, IL-6 and IL-23 production in macrophages, decreased IL-6, IL-12, and IL-23 synthesis in dendritic cells, inhibited production of IL-2, IFN- γ , TNF- α and IL-5 in T-lymphocytes, increased IL-27-mediated IL-10 release and decreased IL-2 levels of T-regulatory lymphocytes. Finally 1,25D supported death of proliferating B cells, reduced Immunoglobulin(Ig)-secreting cells and Ig production of plasma cells and inhibited NF- κ B release of B cells (M. Di Rosa et al. 2011).

IVg. Vitamin E

Treatment with vitamin E has shown to slow down the progression of AD (Sano et al., 1997). This may be due to vitamin E-mediated lowered neuroinflammation, since vi-

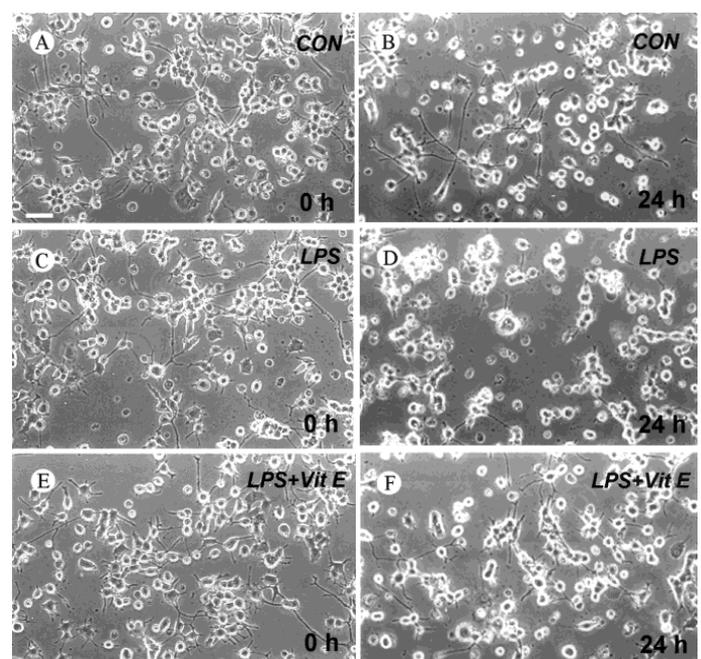


Fig. 15. Vitamin E reduces toxic effects of activated microglia on neuronal cells. Phase-contrast photomicrographs of differentiated PC12 cells before (A,C,E) or after 24 hr of (B,D,F) coculture with N9 microglia. Before coculture, N9 cells were pretreated for 2 hr with LPS (30 ng/ml) alone (LPS) or LPS plus vitamin E (50 mM) pretreatment (LPS + Vit E) or without treatment (CON), and then the N9 culture inserts were completely washed with fresh medium and cocultured with differentiated PC12 cells. Scale bar 50 μ m. Li et al., 2001.

tamin E significantly suppressed LPS-induced microglial activation, associated NO production, and IL-1 α , TNF- α , and iNOS expression in vitro (Fig. 15: Li et al., 2001). Additionally, vitamin E inhibited p38 MAPK phosphorylation and NF- κ B activity. However, other studies did not find significant results in treatment of AD with vitamin E (Petersen et al., 2005; Lloret et al., 2009; Farina et al., 2012). These differences could be due to wrong dosage, wrong timing, unbalanced monotherapy or wrong target (Brewer, 2010).

IVh. Combined therapies

Besides the above single nutrient approaches, several combined-nutrient experiments have been performed. An investigation of Harkany et al. found that vitamin E and C both significantly decreased β -amyloid induced behavioral and biochemical changes in Wistar Rats. Moreover, the combined treatment significantly increased the explorative activity and prevented loss of cortical acetylcholinesterase, choline acetyltransferase and manganese superoxide dismutase. Consequently, combined treatment with vitamin E and C led to neuroprotection (Harkany et al., 1999). The proposed molecular cascade wherein vitamin E serves as a potential anti-oxidant can be seen in figure 16 (Harkany et al., 1999). Treatment with PUFAs and vitamins alone resulted in respectively neurite outgrowth in neuroblastoma cells and enhanced neuronal cell numbers. However, treatment with PUFAs and vitamins together increased the number of neuronal cells, the number of neuritis and their length (Shrivastava et al., 2005). Indicating a synergy based mechanism. Also, uridine monophosphate (UMP) and DHA together increased levels of synaptic proteins and supported brain phosphatides synthesis (Wurtman et al., 2006). Combined administration of GLA and EPA

after LPS-injection increased hippocampal levels of anti-inflammatory IL-4, whereas both nutrient components alone prevented only the decline of IL-4 hippocampal levels (Kavanagh et al., 2004). Further on, Holguin et al. found that rats that were kept in an impoverished environment improved their performance on the Morris water maze after administration of UMP or DHA. Administration of both UMP and DHA further enhanced this performance, improving the impaired memory (Holguin et al., 2008).

V. EPIDEMIOLOGICAL & INTERVENTION STUDIES: CERTAIN DIETS AND THE RISK OF DEVELOPING AD

Different epidemiological and intervention studies suggest a possible effect of nutrition on AD. However, many studies did not find (significant) results. There seems to be a difference between studies that focused on single nutrients and studies that investigated whole diets.

Va. Single nutrient approach

Current antioxidant users showed a lower risk of cognitive decline (Gray et al., 2003). Supplementation with vitamin E was associated with reduced risk of developing AD (Morris et al., 2005; Morris et al., 2002) and slower rate of cognitive decline (Morris et al., 2005). In contrast, other studies did not find any changes after vitamin E supplementation (Kang et al., 2009; Petersen et al., 2005; Wolters et al., 2005; Kang et al., 2006). The combination of vitamin E supplementation with vitamin C was associated with reduction of AD incident, but only in the combination (Zandi et al., 2004). The combination was also associated with a lower risk of AD (Engelhart et al., 2002) and with decreased cog-

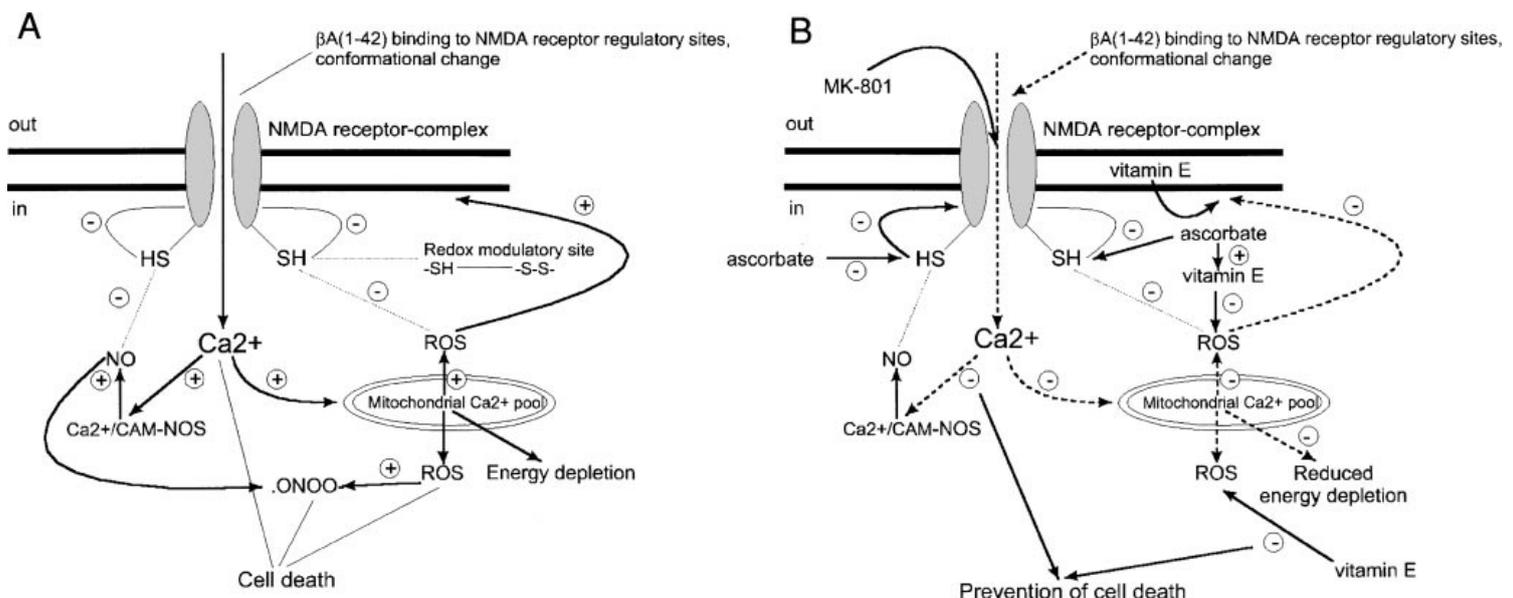


Fig. 16. Schematic outline of a proposed molecular cascade involving activation of N-methyl-D-aspartate (NMDA) receptors, enhancement of Ca²⁺ influx, and generation of free radicals mediating neurotoxicity (A) and the actions of MK-801, vitamin E, and ascorbate (B). In (A) thick arrows indicate the β A-induced molecular events leading to cell death, whereas in (B) point to the distinct sites of drug actions. Moreover, dashed lines indicate the pathways potentially blocked following administration of the neuroprotectants. +, Indicates positive feedback mechanisms. -, Indicates negative feedback mechanisms. Abbreviations: out/in, extra/intacellular space; NMDA-SH, redox modulatory site of the NMDA receptor; NO, nitric oxide; Ca²⁺/CAM-NOS, Ca²⁺/calmodulin-dependent nitric oxide synthase; ROS, reactive oxygen species; .ONOO, peroxynitrite. - Harkany et al., 1999.

nitive decline (Maxwell et al., 2005). Furthermore, the combination had better global scores at cognitive tests (Grodstein et al., 2003). Also, vitamin E complemented with vitamin C resulted in reduced lipoprotein oxidation. Even though vitamin E alone had no effect (Kontush et al., 2001). Moreover, studies indicate an association between hyperhomocysteinemia and the risk of developing AD (Ravaglia et al., 2005; Seshadri et al., 2002). Low folate levels were associated independently with an increased risk of developing AD (Wang et al., 2001; Ravaglia et al., 2005). Additionally, folate administration was associated with a lower risk of developing AD (Luchsinger et al., 2007), better performance on cognitive tasks regardless of homocysteine levels (Durga et al., 2007), increased cognitive function (de Lau et al., 2007) and better memory performance (Bryan et al., 2002). Folate supplementation also showed a decline in the constructional praxis and protected against a decline in verbal fluency (Tucker et al., 2005). In contrast, other studies did not find any association between folate supplementation and AD (Morris et al., 2006; McMahan et al., 2006; Sun et al., 2007; Aisen et al., 2008). Low levels of vitamin B12 were also associated with a doubled increased risk of developing AD (Ravaglia et al., 2005). Besides the mentioned studies no studies found any influence of vitamin B6 or vitamin B12 or their combination with folate on cognitive performance (Eastley et al., 2000; Fioravanti et al., 1997; Sommer et al., 2003; Luchsinger et al., 2007; Morris et al., 2006; Morris et al., 2005; McMahan et al., 2006; Sun et al., 2007; Aisen et al., 2008). Although one study invested a daily supplementation with 750 µg folate, 15 µg vitamin B12 and 75 µg of vitamin B6 and found a significant positive effect on memory performance (Bryan et al., 2002). Another study of Stott et al. found that an intervention with vitamin B12 and folic acid together decreased homocysteine levels (Stott et al., 2005) and enhanced memory function, attention and processing speed (Nilsson et al., 2001).

In 2006, the first epidemiological evidence associating curcumin with cognition was found. It showed that an intake of curcumin, even low intake, was associated with improved cognitive function including memory, attention, language, praxis, and visuospatial ability (Ng et al., 2006). A population based study found a significant negative correlation between intake of flavonoids and disability-adjusted life years due to AD and related dementias (Beking and Vieira, 2010). Further on, dietary intake of n-3 PUFAs and weekly consumption of fish were associated with a reduced risk of AD (Morris et al., 2003). Fish consumption was found to be inversely associated with the risk of getting AD (Barberger-Gateau et al., 2002; Kalmijn et al., 1997). Also, the blood of AD patients showed significantly reduced levels of plasma n-3 PUFAs. (Conquer et al., 2000)

Vb. Whole diet approach

As stated before, food components are likely to work in a synergistic way. For this reason recently the diet-approach in nutritional epidemiology has emerged (Jacobs et al., 2009; Hu, 2002). Prospective studies that investigated whole food groups and dietary patterns, showed more promising results. Dietary consumption of fruit, vegetables and fish was associated with a reduced risk of AD (Barberger-Gateau et al., 2007). The consumption of vegetables alone was associated with slower cognitive decline, but fruit intake alone showed no changes (Morris et al., 2006). The most promising results came from studies that focused on the influence of a Mediterranean diet. Various studies have already underlined the effect of the Mediterranean diet on the risk of developing AD (Scarmeas et al., 2006; Scarmeas et al., 2006). The Mediterranean diet showed to even slow down the progression of the disease (Scarmeas et al., 2007) and was associated with a reduced risk of developing mild cognitive impairment and conversion of mild cognitive impairment to AD (Scarmeas et al., 2009). A meta-analysis of Sofi et al. systematically reviewed all the prospective cohort studies that analyzed the relation between adherence to a Mediterranean diet and the risk of developing AD (Fig. 17: Sofi et al., 2008). Furthermore, a diet enriched with antioxidants vitamin E, C and carotenoids and vitamin B6, B12 and folate was associated with a decreased risk of developing AD. Further analysing showed that this decrease was due to folate, vitamin E and vitamin B6. When this three vitamins were taken together, only folate was associated with a reduced risk of developing AD (Corrada et al., 2005). Supplementation with multivitamins resulted in better results at cognitive tasks (McNeill et al., 2007; Remington et al., 2009). Finally, a recent study of Gu and Scarmeas tried to compose, by screening already done epidemiological investigations, the best diet associated with lower odds of cognitive deficits or reduced risk of AD. The resulting diet was enriched with n-3 PUFAs, n-6 PUFAs, vitamin E and folate, but with lower saturated fatty acids and vitamin B12. Moreover, the dietary habits were characterized with a high intake of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables and low intake of high-fat dairy, red meat, organ meat, and butter (Gu and Scarmeas, 2011).

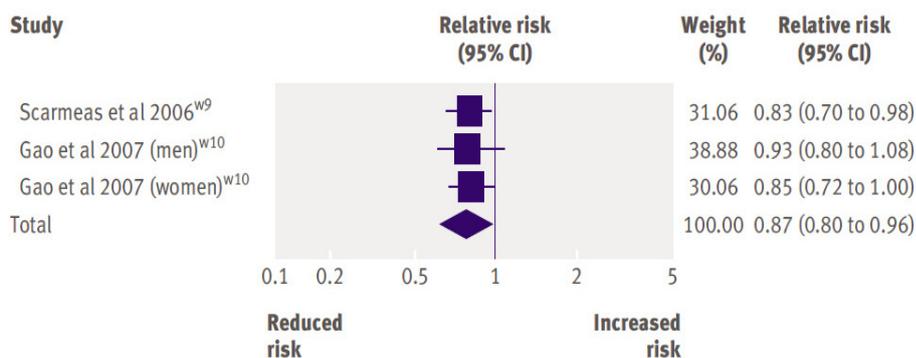


Fig. 17. Risk of Parkinson's disease and AD associated with two point increase in adherence score for Mediterranean diet. Squares represent effect size; extended lines show 95% confidence intervals; diamond represents total effect size – Sofi et al., 2008.

VI. CONCLUSION

Neuroinflammation has shown to play an important role in AD. Nowadays an increasing number of researchers are naming chronic neuroinflammation, manifesting in activated glial cells, as the main component exacerbating AD. This assumption is supported by investigations that confirm the presence activated astrocytes and microglia in the AD brain. Although microglia can ingest amyloid plaques, they appeared unable to clear either the soluble or fibrillar forms of β -amyloid. Activated microglia increased TNF production leading to iNOS dependent neuronal apoptosis. Activated astrocytes altered microglia behaviour and hindered microglia-phagocytosis of amyloid plaques. Also one of the most important risk-factors for AD, high age, is linked to an enhanced inflammatory brain response. High age was associated with elevated number and distribution of microglia as well as with glial hypersensitivity. Glial hypersensitivity may contribute to the chronic glial activation which is observed in AD, by inducing a continuous cycle of inflammatory stimuli. Activated glial cells release pro-inflammatory factors which further activate themselves and their surroundings, forming a positive feedback loop of pro-inflammatory stimuli. Glial activation itself may be initiated by β -amyloid-induced release of NF- κ B via RAGE. Subsequent research revealed that this RAGE expression was increased in the characteristicly activated microglia in AD. Further supported by convincing epidemiological results of NSAIDs on AD onset, the discussed neuroinflammation appears to be a likely primary cause of AD.

In addition, various investigations have shown the effect of nutritional components on certain elements of the pro-inflammatory cascade of AD. For example, through altering the NF- κ B expression or inhibiting pro-inflammatory cytokines. Combined nutritional therapies have sometimes shown positive effects whereas application of their separate components did not. Prospective studies investigating the influence of whole food groups and dietary patterns on the onset of AD and/or its cognitive breakdown, notably showed more promising results than epidemiological studies focussing on single nutrients. This further supports the notion that a whole diet treatment is more beneficial than supplementation with single food components. Previous pre-clinical trials have placed too much emphasis on a single nutrient approach, ignoring the importance of a whole diet wherein combined nutrients are able to enhance or catalyze each other. This synergistic mechanism of food has of late become more recognized and promoting its employment is therefore the main message of this thesis.

It seems remarkable that although in, in vitro and in vivo investigated nutrients have shown to possess anti-inflammatory capacities, these nutrients failed to show the same positive results in pre-clinical studies. This may be due to an unbalanced monotherapy or suggests that very early intervention is needed in contrast to an interference in the development of the disease. A proper diet can be auxiliary

in the treatment of AD and the patient's surroundings should take care in providing such a diet. The previous aspect is crucial: not only are AD patients strongly dependent of their caretakers, also the disease often is accompanied by a scala of nutritional deficiencies due to a dramatic decrease in food intake.

In conclusion, a combination of nutritional components is able to decrease neuroinflammation in AD thereby inhibiting its development. Therefore nutrition can be a 'new' focal point in the treatment of AD. However, it must be taken into account that nutrients may have additive or synergistic effects within and across a range of foods that build up a diet. A full-diet approach is most likely to benefit AD treatment and therefore should be further investigated.

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- VIII. APPENDIX -

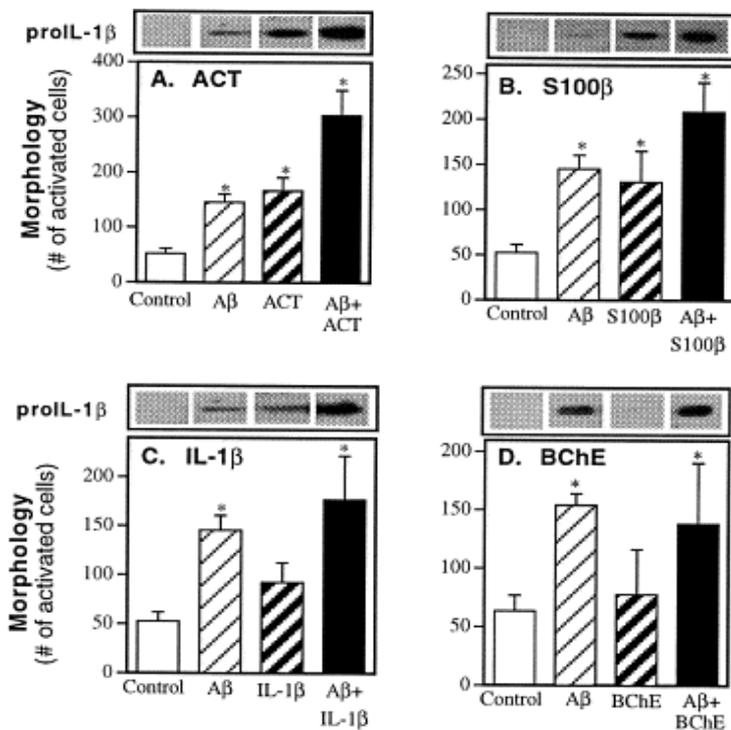
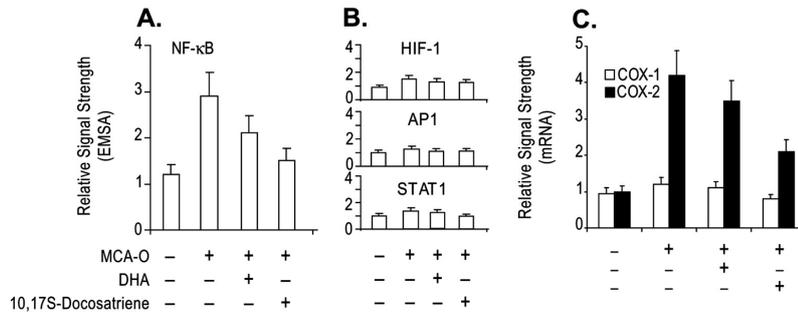


Fig. 4. Effects of ACT, IL-1 β , S100 β , and BChE on the ability of A β 1-42 to activate astrocytes. Cells were treated with control buffer, A β alone (10 μ M), glial protein alone (ACT: 0.3 μ M (panel A), S100 β : 20 μ g/ml (panel B), IL-1 β : 30 ng/ml (panel C), BChE: 3 U/ml (panel D)), or a mixture of co-incubated A β and glial protein. Activation was assessed after 12 h by measurement of morphological activation and proIL-1 β levels. Morphological data shown are the means \pm S.E.M. from 2 to 11 independent experiments; IL-1 β Western blot data are from one representative experiment of three to four independent experiments. *, p<0.05 vs. control. -Hu and van Eldink, 1999

Hippocampus After MCA-O



Neural Cells in Culture

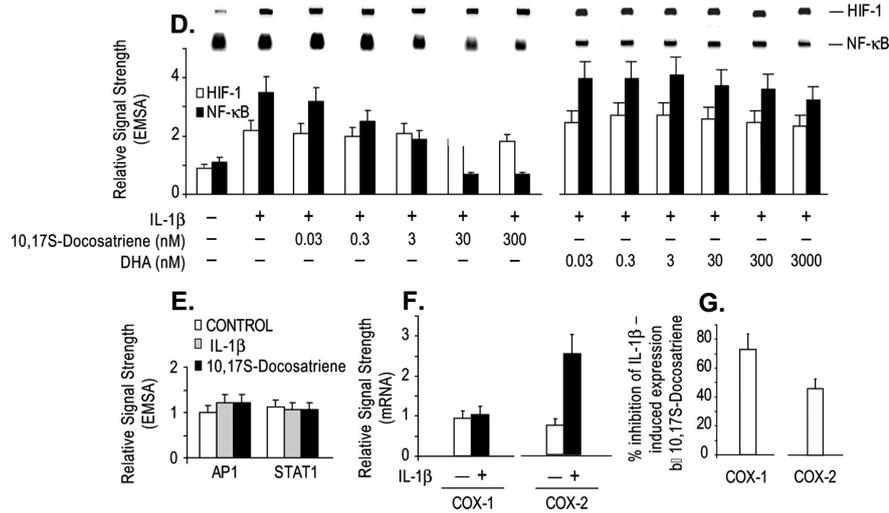


Fig. 7. 10,17S-docosatriene inhibited MCA-O- and IL-1 β -induced NF κ B activation and COX-2 expression. A–C, mouse hippocampus after 1 h of MCA-O followed by 2 h of reperfusion. Vehicle or 10,17S-docosatriene (0.16 μ g/ml) was infused into the third ventricle for 3 h at 0.25 μ l/h. A, enhanced NF κ B-DNA binding activity, determined by electrophoretic mobility shift assay after MCA-O, was inhibited by 10,17S-docosatriene or DHA. B, AP1 and STAT-1, unlike HIF-1 α , were not affected by MCA-O. Only STAT-1-DNA binding was reduced by 10,17S-docosatriene. C, COX-2 expression was greatly increased by MCA-O-reperfusion in hippocampus, and 10,17S-docosatriene or DHA inhibited this enhanced expression. D, IL-1 β -induced NF κ B activation, but not IL-1 β -induced HIF-1 α activation, was inhibited by 10–17S-docosatriene. Free docosahexaenoic acid added in concentrations up to 30 μ M was ineffective in modulating either NF κ B or HIF-1 α induction by IL-1 β . E, as monitored by electrophoretic mobility-shift assay, 10,17S-docosatriene did not affect the small increase in IL-1 β -induced AP1-DNA binding activity; STAT-1 was unaffected by IL-1 β or the lipid under these conditions. F, IL-1 β prominently activates COX-2 expression but not that of COX-1. G, IL-1 β -induced expression of COX-2 mRNA was inhibited by 10,17S-docosatriene ($p < 0.05$). There was also a small effect of the lipid on IL-1 β induction of COX-1 ($p > 0.05$, analysis of variance). -Marcheselli et al., 2003.

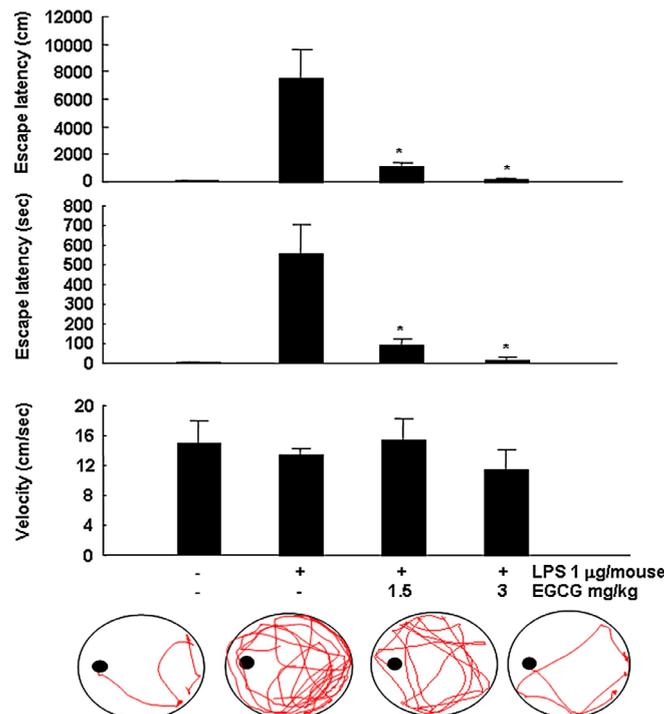


Fig. 10. Inhibitory effect of EGCG on memory impairment induced by LPS using the water maze test. EGCG at 1.5 and 3 mg/kg was orally administered in drinking water for 3 weeks. The pretreated mice were used to assess memory functions as described in Experimental procedures. Each value is mean \pm S.E. from 10 mice/group. #Significant difference from control group ($p < 0.05$). *Significant difference from LPS treated group ($p < 0.05$). -Lee YK et al., 2009.

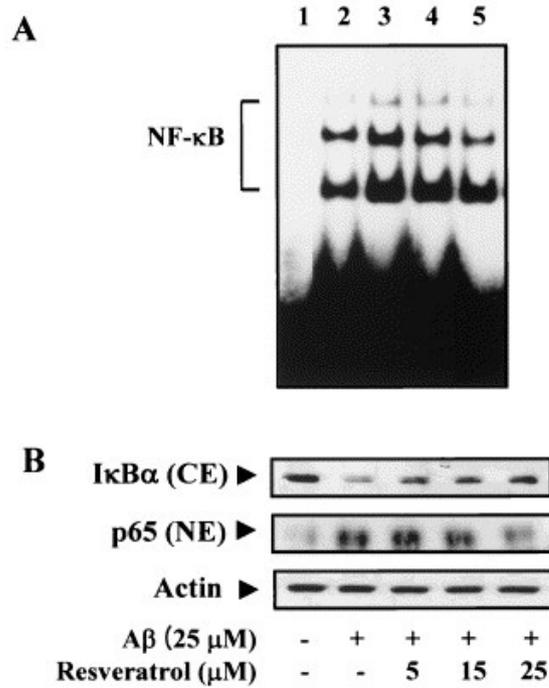


Fig. 11. The inhibitory effect of resveratrol on Aβ₂₅₋₃₅-induced NF-κB activation. (A) Effect of resveratrol on Aβ₂₅₋₃₅-induced DNA binding activity of NF-κB. Nuclear extracts prepared from PC12 cells that were treated with Aβ₂₅₋₃₅ for 1 h in the absence or presence of varying concentrations of resveratrol were subjected to EMSA. Lane 1: probe only; lane 2: DMSO control; lane 3: Aβ₂₅₋₃₅ (25 μM) alone; lane 4: Aβ₂₅₋₃₅ (25 μM) + resveratrol (5 μM); and, lane 5: Aβ₂₅₋₃₅ (25 μM) + resveratrol (25 μM). (B) Effect of resveratrol on the levels of cytoplasmic IκBα and nuclear p65. Immunoblots of cytoplasmic and nuclear lysates from treated PC12 cells were probed with antibodies specific for IκBα (upper panel) and p65 (lower panel), respectively. CE = cytoplasmic extract; and, NE = nuclear extract. -Jang and Surh, 2003.

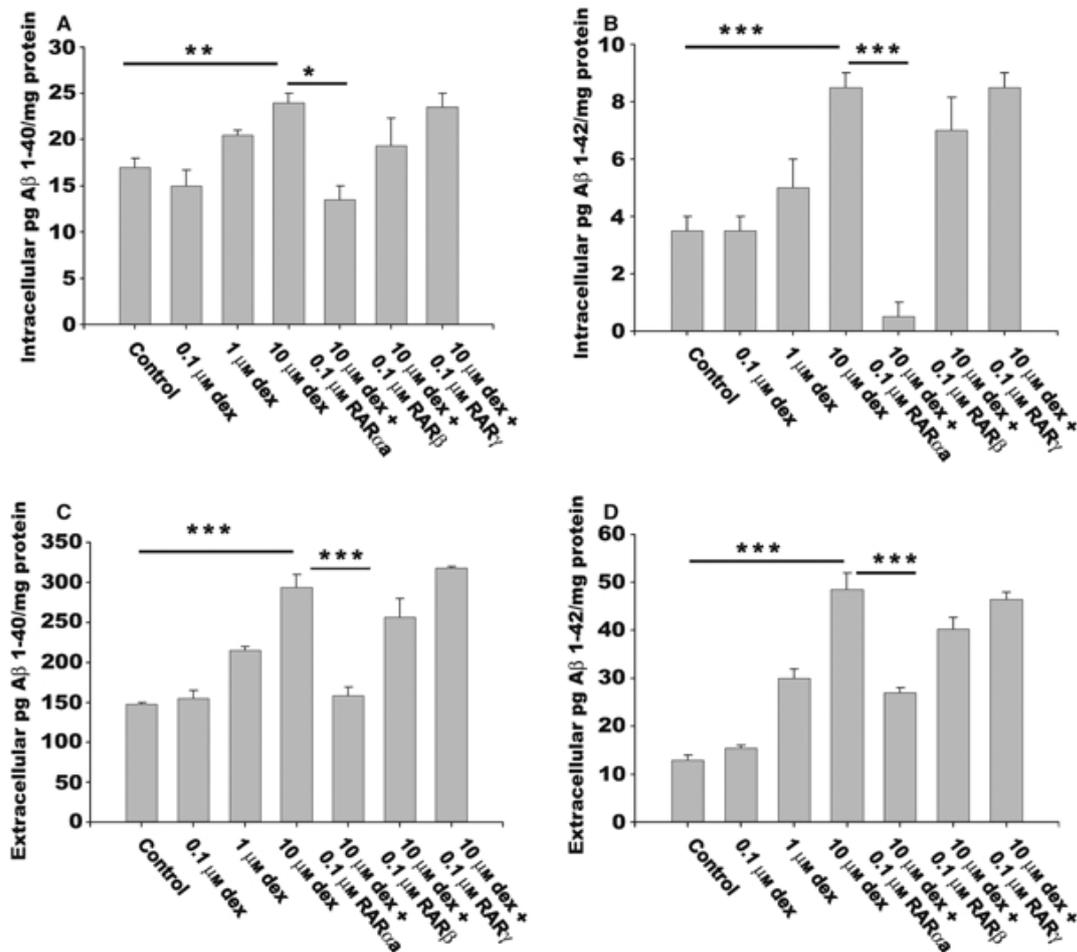


Fig. 13. RARα signalling prevents both intracellular and extracellular Aβ accumulation. Cortical neurons were cultured in the presence of either 0.1, 1 or 10 μm dexamethasone (Dex) with or without 0.1 μm retinoids for 3 days; they were then assayed for intracellular and extracellular Aβ₁₋₄₀ and Aβ₁₋₄₂ by ELISA. (A) Intracellular Aβ₁₋₄₀. (B) Intracellular Aβ₁₋₄₂. (C) Extracellular Aβ₁₋₄₀. (D) Extracellular Aβ₁₋₄₂. With increasing amounts of dexamethasone, there were increases in both extracellular and intracellular Aβ₁₋₄₀ and Aβ₁₋₄₂ accumulation as compared with control cultures. In the presence of RARα agonist and 10 μm dexamethasone, there were decreases in the amounts of both extracellular and intracellular Aβ₁₋₄₀ and Aβ₁₋₄₂ as compared with the 10 μm dexamethasone-treated cultures. Student's t-test for dose-response study and one-way anova followed by Tukey's test for comparison between retinoid treatments. Results are mean ± SE (n = 3; *P < 0.05, **P < 0.005, ***P < 0.001). -Jarvis et al., 2010.

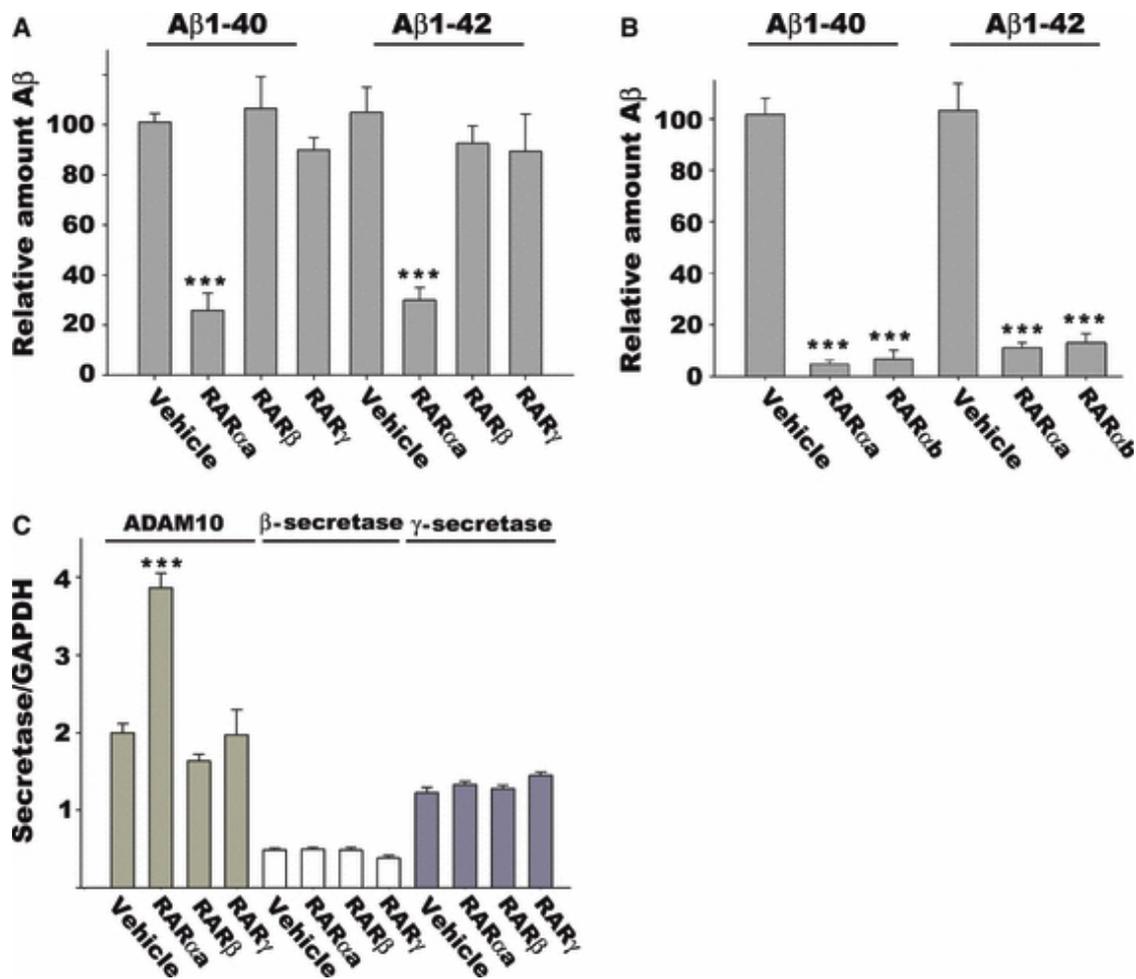


Fig. 14. RAR α signalling prevents A β accumulation in Tg2576 mice by upregulating ADAM10 expression. Mice were injected intraperitoneally with 1 mg/kg retinoids from 3 to 7 months of age every 3 days, or they were fed RAR α agonists, 3.6 mg/kg, from 3 to 7 months of age. A β 1-40 and A β 1-42 levels were measured by ELISA. (A) A β 1-40 and A β 1-42 levels in intraperitoneal RAR agonist-treated mice. (B) A β 1-40 and A β 1-42 levels in RAR α agonist-fed mice. (C) Expression of secretases in intraperitoneal RAR agonist-treated mice. There were significant decreases in A β 1-40 and A β 1-42 levels in the RAR α agonist-treated mice as compared with the vehicle-treated ones, whereas the other RAR agonists did not alter A β load. In only the RAR α agonist-treated mice was there a significant increase in ADAM10 expression as compared with the vehicle-treated ones; none of the retinoid agonists affected β -secretase or γ -secretase. One-way anova, followed by Tukey's test. Results are mean \pm SE (n = 3-5; ***P < 0.001).- Jarvis et al., 2010

