

Anti-inflammatory and Immune Therapy for Alzheimer's Disease: Current Status and Future Directions

Douglas Walker* and Lih-Fen Lue

Laboratory of Neuroinflammation, Sun Health Research Institute, Sun City, Arizona, USA

Abstract: From the initial characterizations of inflammatory responses in Alzheimer's disease (AD) affected brains, namely the demonstration of activated microglia and reactive astrocytes, complement system activation, increased production of proinflammatory cytokines, and evidence for microglial-produced neurotoxins, there was hope that reducing inflammation might be a feasible treatment for this memory-robbing disease. This hope was supported by a number of epidemiology studies demonstrating that patients who took non-steroidal anti-inflammatory drugs had significantly lower risk of developing AD. However, clinical trials of anti-inflammatories have not shown effectiveness, and in recent years, the concept of immune therapy has become a treatment option as animal studies and clinical trials with A β vaccines have demonstrated enhanced amyloid removal through stimulation of microglial phagocytosis.

This review will examine the current status of whether inhibiting inflammation is a valid therapeutic target for treating AD; what lessons have come from the clinical trials; what new pathways and classes of agents are being considered; and how this field of research can progress towards new therapeutics. We will examine a number of agents that have shown effectiveness in reducing inflammation amongst other demonstrated mechanisms of action. The major focus of much AD drug discovery has been in identifying agents that have anti-amyloid properties; however, a number of these agents were first identified for their anti-inflammatory properties. As drug development and clinical testing is a costly and lengthy endeavor, sound justification of new therapeutic targets is required. Possible future directions for AD anti-inflammatory or immune clearance therapy will be discussed based on recent experimental data.

Key Words: Neurodegeneration, NSAIDs, cytokines, microglia, vaccination, neuroprotection, dementia, amyloid beta.

INTRODUCTION

Alzheimer's disease (AD) represents one of the most serious health issues for the elderly. With the aging of the population, particularly in western societies, the increase in AD is going to be a major health-care crisis. For example, in the United States AD currently affects approximately 4.5 million, but this is predicted to rise to 16 million by 2050. Although heart disease and cancer cause higher rates of mortality, effective treatments are available for these conditions, while this is not the situation for AD. Patients diagnosed with AD are currently treated with acetylcholinesterase inhibitors (donepezil, rivastigmine or galantamine), with memantine, an NMDA receptor antagonist, being an additional treatment option for more severely-affected AD patients. These agents have been demonstrated to have a significant effect on slowing the progression of the disease, as measured by different psychometric parameters; however, it is widely accepted that their effectiveness is limited and the need for new therapeutic agents is urgent [35,58,144,184].

Pathology of AD

AD can only be definitively diagnosed by a pathological examination of the brain postmortem. Histological examination of vulnerable brain areas of an AD case (for example, hippocampus, entorhinal, temporal, frontal and parietal cortex) with appropriate histochemical stains or immunological reagents will identify profuse numbers of extracellular amyloid beta peptide (A β) plaques, and also large numbers of neurofibrillary tangles (NFTs). A β is derived from the pathological processing of the amyloid precursor protein (APP) at the β -secretase and γ -secretase sites to produce the 4 kD A β fragments of 40 or 42 amino acids [64,168]. NFTs are insoluble structures and represent the remains of the cytoskeleton of dead or dying neurons. The insolubility of these structures arise on account of the hyperphosphorylation of the microtubule-associated protein tau [47]. With the availability about 20 years ago of appropriate antibodies that could localize proteins in formaldehyde-fixed brain tissues, studies identified the presence of a type of chronic microglial inflammatory response in AD brain tissues, especially associated with the hallmark plaque and tangle pathological structures [83,104,116]. Activated microglia were particularly evident using antibodies that recognize the class II major histocompatibility complex protein HLA-DR. The insolubility and persistence of these

pathological structures appears to incite this microglial inflammatory response, though cellular contents of damaged cells also contribute to microglial activation; microglia being a population of brain-resident cells with most of the characteristics of macrophages/monocytes [178]. The normal function of microglia within the brain is immune surveillance; they are the first cell type to respond to any perturbation or injury within the CNS. Although T lymphocytes, B lymphocytes and peripheral macrophages have been identified in AD brains [49,82,147], it appears that the inflammatory response in the brain neuropil is not primarily being mediated by these invading peripheral immune cells, but by brain-resident cells. A major discriminating feature of AD inflammation compared to multiple sclerosis is the lack of significant numbers of infiltrating leukocytes. As the inflammation in AD is not being driven by IFN- γ [149], it appears to develop and persist in a chronic manner. Increased expression by microglia in AD brains of the cytokine IL-1 was also initially reported as a feature of microglial activation [66]. Other features of an immune response in AD brains include activation of the complement system, which has the potential to further damage neurons and amplify any ongoing inflammatory response. Plaques and tangles in AD brains are immunoreactive for activation fragments of the complement pathway [41, 114,145]. From these pathological observations, a wide range of experimental studies using cultured microglia isolated from rodent or human brains demonstrated that A β peptide, when in an aggregated, fibril or oligomeric form, could activate microglia to a proinflammatory state (reviewed in [178]), which included increased production of proinflammatory cytokines, reactive oxygen species, degradative proteases and neurotoxic factors [16,54,62,177]. The characterization of inflammatory responses in postmortem brain led to an "inflammatory hypothesis" for AD, which suggested that the inflammatory factors produced in the brain, particularly as a result of microglial activation by A β , could be causing a loss of healthy neurons or damaging axonal processes or synapses. Positron emission tomography studies of living AD patients with the ligand PK11195, which binds to the peripheral benzodiazepine receptor and specifically identifies activated microglia, has shown greater binding in neocortical areas of brains of AD subjects, even patients with early stage AD [21,175]. This is indicative of inflammation being an event occurring early in the pathogenesis of the disease [21,175].

Risk Factors for AD

AD is the most common form of dementia, accounting for up to 60% of all cases. Aging is the most important risk for developing

*Address correspondence to this author at Laboratory of Neuroinflammation, 10515 W. Santa Fe Drive, Sun Health Research Institute, Sun City, AZ 85351, USA; Tel: (623) 876 5623; E-mail: douglas.walker@sunhealth.org

AD, as its incidence is around 1% in the 60-64 year age-group, but rising to about 30% in those aged 85 years or older. Associated risk factors are head trauma, small brain size, female gender, low educational status and reduced physical and mental ability in later life [20,57,98]. The major genetic risk factor is possession of the apolipoprotein E (apoE) $\epsilon 4$ allele [110]. Other risk factors of AD, all of which are associated with vascular disease, and some that can be affected by possession of the apoE $\epsilon 4$, include diabetes, hypercholesterolemia, hypertension, coronary heart disease, obesity, smoking and atherosclerosis [36]. A strong association between cerebral atherosclerosis and the development of AD pathology has recently been demonstrated [13,23,148]. To date, the only consistent data from case-control, cross-sectional epidemiological, and prospective incidence studies of subjects concerning what reduces the risk of AD were a history of taking NSAIDs (examples [17,18,22,80,97,117]). Although some of these earlier studies have limitations due to possible selection biases [97], the Baltimore Longitudinal Study of Aging, a prospective incidence study, did confirm a reduced risk of AD in subjects taking NSAIDs [163]. Similarly, the Rotterdam Study of Aging prospective study has demonstrated a relative risk of 0.2 (with range 0.05-0.83 at 95% confidence interval) for developing AD in those taking NSAIDs for more than 24 months [81].

There is no doubt that the pathogenesis of AD is multifactorial involving a combination of genetic factors and non-genetic components, which together can lead to the generation of toxic processes involving dysregulation of amyloid precursor protein metabolism, inflammation, oxidative stress, apoptosis, proteasome inhibition, mitochondrial dysfunction, imbalances in antioxidant production, and glutamate excitotoxicity, amongst others [133]. As such, it appears important that new therapeutic agents have multiple targets of action that affect a number of these processes.

Inflammation and AD

A comprehensive summary of inflammation and AD was compiled about 7 years ago, with the conclusion that inflammation must be contributing to AD pathology on account of the many toxic inflammatory proteins that are upregulated in AD brains [123]. With the apparent lack of effect in clinical trials of tested agents (primarily COX inhibitors) on slowing the progression of mental deterioration, we should consider whether inflammation is still a relevant target for AD. A scheme for how inflammation and A β could inter-

act to cause AD pathology is presented in Fig (1). This model makes the assumption that the initiating events for neuropathology in the brain start in the periphery (i.e. vascular inflammation, atherosclerosis, coronary heart disease) and lead to the initial A β deposition; this progression of events is not universally accepted [201]. A β deposition due to reduced clearance can initiate a cascade of events leading to accelerated A β oligomerization and aggregation that can directly cause synaptic loss and neurodegeneration, and ultimately dementia. A β is considered by most as the primary driving force of AD, due to its neurotoxic, oxidative stress and pro-inflammatory effects on multiple cell types. There is evidence that cerebral inflammation can lead to increased A β production [77]; the question that remains to be answered is to what extent inflammatory factors produced in brain directly lead to synaptic damage and neurodegeneration; answering this question is central to deciding which anti-inflammatory agents should be tested.

To be effective, the appropriate anti-inflammatory agent must be administered to the appropriate clinical population, who are not too far advanced in the disease. If one considers at what stage of the disease to administer anti-inflammatory therapeutics, Fig. (2) is derived from data from two publications on the relative staging of microglia, plaques and NFT in hippocampus and entorhinal cortical sections of subjects with progressively increasing clinical dementia rating (CDR) scores [170,187]. There is a progressive increase in each of these parameters as dementia increases, though both studies show a decline in microglia scores as the neuritic plaque progresses from stage 3 to 5, or NFT progresses from 5 to terminal stage 6. This would indicate that microglia activation could "burn out" at the last stages of pathology once mental decline can not be further measured. It would appear that at early and moderate stages of AD, there is the potential to reduce inflammation, and plaque and tangle formation, using drugs that target all features of this pathology.

Clinical Trials of Anti-Inflammatory Agents with AD Subjects

Prospective double-blind placebo-controlled trials are considered the standard for determining whether an agent is effective for a particular disease. A number of trials of anti-inflammatory agents have been carried out with AD subjects. The design, dosage, degree of severity and inclusion criteria of the patient population was not consistent between the trials. The first such trial for AD of a NSAID involved a small group of patients treated for 6 months with indomethacin or placebo [146]. The indomethacin-treated patients

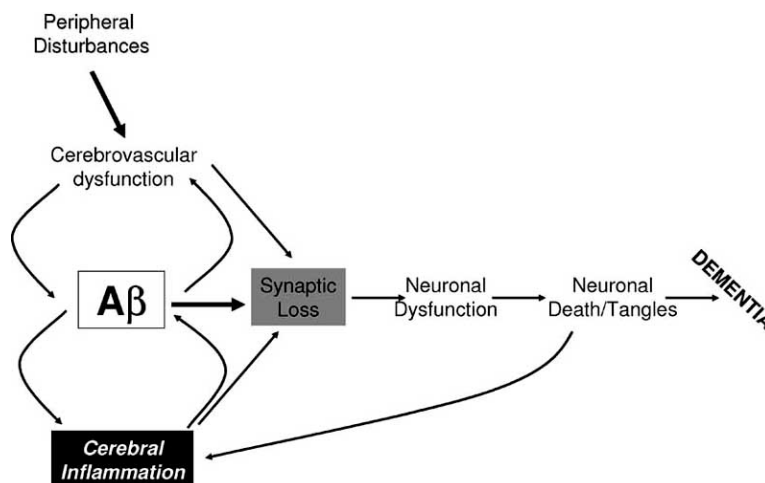


Fig. (1). Potential interactions of A β peptide, vascular inflammation and cerebral inflammation in precipitating AD pathogenesis. In this scheme, peripheral disturbances (e.g. high levels of cholesterol, vascular inflammation, atherosclerosis) lead to compromise/inflammation of the cerebrovasculature. This will reduce transport of oxygen and glucose, creating conditions of oxidative stress that can increase A β production and aggregation, and neuronal stress directly. Deposition of A β can lead to cerebral inflammation, which can feedback to increase production of A β . The contribution of cerebral inflammation separate from A β to the progression of pathological changes is unclear, but inflammatory factors can mediate many of the neurotoxic events occurring in AD (tau hyperphosphorylation, synaptic loss, neuronal cell death).

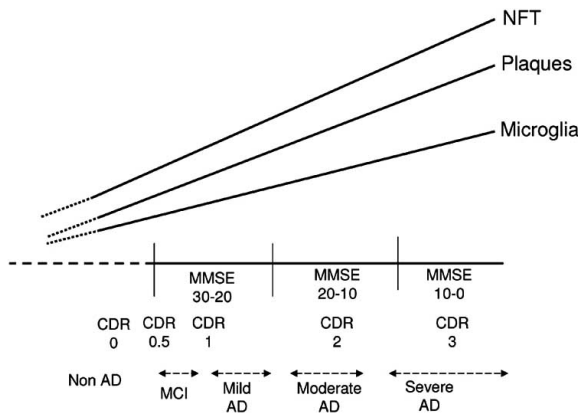


Fig. (2). When is the optimal stage of the disease to most effectively treat AD with anti-inflammatory agents. Figure shows progression of AD pathology, namely that the density of plaques, NFTs and activated microglia increase in the hippocampus/entorhinal cortex with decline in cognitive performance. MMSE – mini-mental status exam; the primary physician screening test of patient for cognitive decline. CDR – clinical dementia rating; a more detailed patient and informant assessment of cognitive decline.

showed no decline in mental function, while the control group declined by 8.4 %. A pilot trial of the NSAID diclofenac in combination with misoprostol, to provide gastrointestinal protection, in a group of mild to moderate AD patients showed no significant difference in indices of cognitive decline between treated and placebo subjects after 25 weeks [155]. A small scale study of the NSAID nimesulide, a preferential COX-2 inhibitor, for 24 weeks showed no significant differences in rates of cognitive changes [6]. A larger scale trial for 1 year of refecoxib, another selective COX2 inhibitor, or of naproxen, a non-selective COX inhibitor, versus placebo was ineffective at slowing cognitive decline [5]. The lack of effect of refecoxib was confirmed in a 1-year trial of mild to moderate AD subjects [139]; similarly the anti-inflammatory agent hydroxychloroquine showed no protective effect in preventing decline in memory function in a large 18-month trial [171]. A trial of low-dose prednisone, a potent steroid anti-inflammatory, for 1 year showed no difference in cognitive decline between the treated and placebo groups [4].

The pronounced dichotomy that has still to be resolved is that epidemiological data showing that subjects taking NSAIDs for more than 2 years are protected from AD [81,97,117,195], while the clinical treatment trials of anti-inflammatories with diagnosed AD subjects have generally been negative in preventing cognitive decline. It had been hoped that the Alzheimer Disease Anti-Inflammatory Prevention Trial on normal elderly with a family history of AD would determine whether NSAIDs could prevent or delay the onset of AD [118]. However, these will remain unanswered as this trial with celecoxib, naproxen, or placebo was terminated before completion due to cardiovascular and cerebrovascular side-effects from the active drugs, particularly naproxen [1].

THERAPEUTIC AGENTS AND TARGETS FOR ALZHEIMER'S DISEASE

At the experimental level, new classes of therapeutic agents are being examined that have one or several targets in the pathways believed to be involved in AD pathogenesis. Agents being tested at different levels include those that inhibit the β - and γ -secretase enzymes, thus preventing A β peptide being formed [76,96]; statin agents that lower circulating levels of cholesterol, but which also have anti-inflammatory properties [38]; agents that inhibit the aggregation of A β into toxic oligomers and fibrils [61]; agents that inhibit kinases (e.g. glycogen synthase kinase (GSK) 3 and cell

division cycle kinase (CDC) 25) that are involved in the phosphorylation of tau [15]; cytoskeletal modifying agents; thiazolidinedione agents used to treat type 2 diabetes; and anti-oxidants and anti-inflammatory agents [200]. A number of agents being tested for effectiveness in AD, for example statins and curcumin have activities against multiple relevant targets in pathways involved in AD pathogenesis. Fig. (3) outlines the properties and pathways that an "ideal" AD treatment agent might need to modulate in order to modify AD pathogenesis. Data from studies with these different types of agents will be discussed to consider why future clinical trials of agents with anti-inflammatory properties should focus only on those with multiple additional relevant mechanisms of action.

Inhibition of Cyclooxygenase

The majority of the anti-inflammatory agents tested on AD patients are prostaglandin H synthase (COX) inhibitors. Although some of these agents have other less-well defined modes of actions, as trials with these agents have not shown positive results, it might indicate that inhibition of the prostaglandin pathways might not be a suitable target for retarding the pathogenesis of established AD [72]. The role of COX metabolites in AD pathogenesis is still unclear. In human brain, COX-2 is primarily localized to neurons, and not in activated microglia as would be expected [71,73]. Induction of COX-2 immunoreactivity in neurons of AD brains is an early event in the disease pathogenesis being maximal at Braak tangle stage 0-II before microglial activation is a prominent feature [74], but declining as the disease progresses [192]. Measurements of COX-2 mRNA in AD brains generally showed increased levels associated with pathology [108,130,191]. As some COX metabolites (prostaglandins PGD₁, PGD₂, PGJ₂, and 15d-PGJ₂) are agonists for PPAR- γ , activation of which can induce anti-inflammatory pathways in macrophages, microglia and astrocytes, inhibition of synthesis of proinflammatory PG (e.g. PGE₂) will also reduce the amounts of anti-inflammatory PG. Similarly, PGE₂ has a role in neuroprotection; treatment of primary neurons with PGE₂ or agonists for the EP-2 and EP-4 PG receptors resulted in significant neuroprotection from A β toxicity [40], an effect mediated by increased intracellular levels of cyclic AMP. Activation of microglia EP2 receptor with PGE₂ increased A β phagocytosis and reduced the microglial-mediated neurotoxicity [159]. Crossing transgenic mice overexpressing COX-2 in neurons with a line of A β plaque-developing mice (APPswe/PS1-A246E) resulted in enhanced production and deposition of A β (40) and A β (42) at 24 months [189], but not at 12 months [188], although a greater percentage of hippocampal neurons from COX2APPswe/PS1-A246E mice showed apoptosis in response to A β (1-42) than neurons from APPswe/PS1-A246E mice. Thus, it can be seen that the role of COX and inhibition of PG synthesis in AD pathology is complex; inhibiting the production of PGs with protective/anti-inflammatory properties might be more detrimental for chronic AD pathogenic events than preventing the effects of proinflammatory PGs. Even though the trials with agents that had preferential COX-1 inhibiting activity were generally unsuccessful, a role for COX-1 in AD inflammation is still possible as COX-1 immunoreactivity is found in microglia in AD brains, particularly in microglia associated with amyloid plaques [73,193].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Most NSAIDs - aspirin, ibuprofen, indomethacin, sulindac, and flurbiprofen - have inhibition of COX as their major mechanism of anti-inflammatory activity. These agents, most of which are available without prescription, have preferential activity in inhibiting COX-1, but also have some activity against COX-2, a form of the enzyme primarily induced during inflammatory responses. The new generations of COX-2 specific inhibitors, which appear effective for controlling arthritis, have also been considered as AD therapeutic agents. In recent years, A β lowering or aggregation inhibition mechanisms of action of NSAIDs have been identified that are not

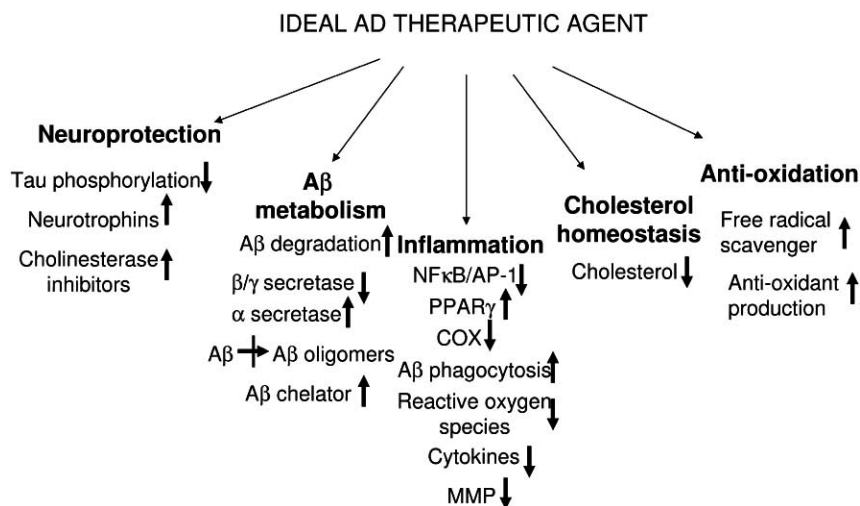


Fig. (3). Potential targets that an "ideal AD therapeutic agent" might modulate to reduce the progression of AD pathology.

related to COX inhibition or anti-inflammatory properties. In a series of studies, treatment of cultured cells (neural and non-neural) with diclofenac, flurbiprofen (R and S and mixed enantiomers), ibuprofen, indomethacin, sulindac sulfide and meclofenamic acid resulted in lower levels of A β (42), but not A β (40), production [43,181] by modulating γ -secretase activity [14,34]. In order of effectiveness at lowering A β 1-42 production by H4 cells were flurbiprofen, meclofenamic acid, sulindac, fenoprofen, indomethacin, diclofenac and ibuprofen [43]. Agents that showed no activity in this assay included acetaminophen, aspirin, dapsone, fenbufen, ketoprofen, meloxicam and sulindac or sulindac sulfone [43]. The effectiveness of flurbiprofen, ibuprofen and sulindac sulfide for lowering A β production has been confirmed using primary neurons as the target cell [56], but this study did not report the specific effect to A β (42) as these agents were effective at lowering A β (40) production as well. These authors concluded that the mechanism of action of these NSAIDs is not related to their COX, lipoxygenase, NF κ B or I κ B inhibiting-, or PPAR γ -activating-, properties, as specific agents for these targets did not affect A β levels in the assays used [151]. The effect appeared to be due to inhibition of Rho and a Rho-kinase [199]. A β -lowering activity was also being observed using specific Rho-kinase inhibitors, although cells deficient in Rho-kinase activity did not demonstrate reduced amounts of A β production. The NSAIDs that demonstrated significant A β -lowering properties in cultured cells were also effective in lowering A β (1-42) in brains of transgenic Tg2576 mice [43]. By contrast, another study that administered indomethacin or the COX-2 inhibitor nimesulide to Tg2576 mice for 8 months, from 7-15 months of age, showed significant A β -lowering effect with indomethacin alone [165]. These authors suggested that the effect was due to inhibition of NF κ B as cells deficient in NF κ B activity did not show the same response. Certain NSAIDs also exert anti-inflammatory activity through activation of the nuclear hormone receptor class of transcription factors PPAR [99]. PPAR- γ belongs to this group of nuclear receptors that include PPAR- α and PPAR- δ , which control lipid and glucose metabolism, energy levels, monocyte differentiation and inflammatory responses. As mentioned in a previous section, natural ligands for PPAR- γ include certain COX and lipoxygenase metabolites, but of the NSAIDs, indomethacin has highest affinity and selectivity for PPAR- γ , with diclofenac, ibuprofen, flufenamic acid having lower affinities. PPAR can function through several mechanisms, including formation of heterodimers with retinoid-x-receptors [166]; these complexes bind to PPRE and activate transcription of certain genes. Inhibition of inflammatory processes is believed to occur by a mechanism of receptor-dependent

transrepression, whereby activated PPAR- γ interacts with other transcription factors or transcriptional co-activators, to prevent the activation of inflammatory-associated transcription factors such as NF κ B, STAT-1, C/EBP and AP-1 from activating inflammatory gene expression [60].

Thiazolidinediones

Thiazolidinediones, which are prescribed for the treatment of type 2 diabetes to increase insulin sensitivity, are PPAR agonists. Agents under investigation as potential AD therapeutics include pioglitazone, rosiglitazone, troglitazone and ciglitazone, which also act as agonists for PPAR- α , but with lower degrees of affinity. However, they can also induce significant anti-inflammatory activity on microglia and macrophages through this pathway. PPAR- γ agonists ibuprofen, indomethacin, pioglitazone, ciglitazone, and 15d-PGJ₂ were effective in preventing toxicity to cultured neurons from media of A β -stimulated monocytes or microglia [31]. Treatment of murine microglia and astrocytes with 15d-PGJ₂, rosiglitazone, pioglitazone, or ciglitazone reduced secretion of nitric oxide, TNF- α , IL-1 β , IL-6 and MCP-1, with the natural ligand 15d-PGJ₂ being more effective than the thiazolidinediones [164]. Two studies using a rodent model of focal cerebral ischemia demonstrated that pioglitazone [109] and rosiglitazone [198] have significant acute neuroprotective activities. Treatment of lesioned animals down-regulated microglial activation, reduced levels of inflammatory cytokine synthesis, and reduced infarct volumes in both studies. Treatment of 10 month-old APPV717I transgenic mice with ibuprofen or pioglitazone for only 7 days reduced numbers of activated microglia and astrocytes in cortex and hippocampus. These mice also showed significant reduction in COX-2 and iNOS mRNA, BACE-1 mRNA and protein levels, and reduction in area occupied and staining intensity of A β (42) plaques. Pioglitazone-treated animals showed a 27% reduction in levels of soluble A β (42) [70]. Anti-inflammatory properties for PPAR- γ ligands on expression of myeloperoxidase (MPO) mRNA were shown in granulocyte-macrophage colony stimulating factor (GM-CSF) treated human macrophages and macrophages from MPO expressing mice, though these same agents had a stimulatory effect on MPO expression when applied to macrophage colony stimulating factor (M-CSF) treated macrophages [95]. A role in AD for MPO, an enzyme secreted by phagocytic cells that catalyzes the production of the potent pro-oxidant hypochlorous acid from hydrogen peroxide, has been suggested as it colocalizes with plaques and plaque-associated microglia in AD brains, and can be expressed by A β -stimulated microglia *in vitro* [140]. Aberrant induction of MPO in AD brains

has the potential to contribute to oxidative stress. Two studies have shown that polymorphisms in the promoter gene of MPO that alter its levels of expression were more abundant in female AD patients [140], or those showing cognitive decline [135].

A clinical trial with rosiglitazone was carried out for 24 weeks on mild to moderate AD patients. Overall there was no significant improvement in treated patients using the ADAS-Cog test, though it was shown that there was a significantly different response to the drug depending on whether the subject possessed an apoE ϵ 4 allele [142]. ApoE ϵ 4 positive patients continued to show cognitive decline, while apoE ϵ 4 negative patients showed slight improvement.

Polyphenolic Anti-Oxidants

Curcumin

There has been much attention on the yellow curry spice curcumin as a therapeutic agent for AD [9,11,30,101]. When one considers the properties of a hypothetical ideal agent for treating AD (Fig. 3), curcumin has many features that meet these requirements. Curcumin, an extract of turmeric, is a non-flavonoid polyphenol and has been widely used as a safe food additive for many centuries, particularly in India. It has been reported that AD incidence is significantly lower in Asian-Indian populations [25], who use this spice extensively in food. The biochemical pathways affected by this agent are extensive, and many of these could be of significance in inhibiting AD pathological changes. Curcumin has identified anti-inflammatory properties due to inhibiting activation of the NF κ B, AP-1 and STAT inflammatory pathways [30,88,90, 91,161]. It also has defined anti-oxidant properties [51,111,137,154,185, 190], which can be partially due to the induction of anti-oxidant defensive genes heme oxygenase-1, glutathione S transferase and quinone reductase in oxidatively-stressed neurons [154], and heat shock proteins [111]. Other properties relevant to AD include cholesterol-lowering activity [134], iron chelation [86], A β aggregation inhibiting properties [127,190] and inhibition of expression of MMP-1, -3, -9, -14 [91]. *In vitro*, curcumin inhibited the formation of A β fibrils and oligomers from A β (40) and A β (42), and also induced dissociation of preformed fibrils [127,190]. Curcumin reversed markers of oxidative stress in brains of mice caused by treatment with the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [137]; reversal of oxidative stress due to traumatic brain injury in rats has been reported [185]. A study involving feeding curcumin to transgenic APP (Tg2576) mice in their diet for 6 months demonstrated significant reduction in A β load, and in levels of the proinflammatory cytokine IL-1 β and numbers of activated microglia and reactive astrocytes [101]. A more recent study demonstrated that curcumin fed orally to aged Tg2576 mice for 5 months reduced A β levels and plaque load [190]. It was also shown in this study that curcumin could be localized to cerebral plaques. Administration of curcumin to aged rats injected intracerebrally with A β reduced oxidative damage, memory deficits and synaptophysin loss [30,52]. Clinical trials sponsored by the National Institutes of Health on the effectiveness of curcumin as a treatment for AD are underway [2,141]. It is not clear whether the anti-amyloid properties of curcumin are more significant than the anti-inflammatory or anti-oxidant properties, but having a combination of all should be beneficial in inhibiting different pathological processes.

Resveratrol

Resveratrol is the principal non-flavonoid polyphenol found in grapes and red wine and, similar to curcumin, possesses a range of pharmacological properties including anti-oxidation, anti-inflammation, neuroprotection and inhibition of A β aggregation [7,112, 143,153,158]. Both compounds have similar chemical structures. Resveratrol has anti-inflammatory properties due to its activation of SIRT-1, a class III histone deacetylase; activation of SIRT-1 by resveratrol inhibited NF- κ B signaling by promoting deacetylation

of a lysine residue on RelA/p65 [194]. Its effectiveness in inhibiting A β -stimulated microglia-mediated neurotoxicity through this mechanism has been demonstrated [27]. Neuronal protection from A β toxicity, along with promotion of clearance of A β peptides, are additional properties associated with resveratrol [84,112]. Interestingly, although moderate wine consumption has been associated with some protection from AD [138], due to the low amounts of resveratrol in red wine, other components have also been implicated. Administration of red wine to transgenic Tg2576 mice was effective in lowering plaque load, even though the amount of resveratrol present in the wine was considered to be too low to be therapeutically effective [180].

Statins

Statins are widely used to lower circulating levels of cholesterol through their activity as HMG-CoA reductase inhibitors and are the primary treatment for reducing the risk of coronary heart disease. High levels of circulating cholesterol are considered a risk factor for developing AD due to its effect on accelerating atherosclerosis and vascular inflammation, both of which can promote production of A β . There has been much interest in the use of statins as preventive therapy for AD, although the epidemiological data are conflicting to their effectiveness at lowering the risk of dementia [87,100, 196,197]; however, as a recent clinical trial of mild AD patients with atorvastatin demonstrated promising improvement in certain cognitive parameters, further trials of statins are underway [162]. A number of studies have also shown that high cellular cholesterol levels promote the β secretase pathway of A β formation and reduce the α -secretase formation of soluble APP (examples [93,129]). Treatment of hippocampal and cortical neurons with simvastatin and lovastatin reduced amounts of secreted A β (40) and A β (42), while treatment of guinea pigs with simvastatin reduced cerebral and CSF levels of A β (40) and A β (42) [45].

There are now well characterized anti-inflammatory properties for statins that are distinct from their cholesterol-lowering properties. These effects include lowering circulating levels of C-reactive protein [24], reducing A β -stimulated expression of IL-1 β and iNOS in cultured macrophages or microglia [32], and reducing expression of IL-6 by rodent microglia [102].

Lovastatin, simvastatin, pravastatin and atorvastatin were all shown to have significant activity of lowering expression of myeloperoxidase (MPO) mRNA expression by human and murine macrophages, adding evidence for the anti-inflammatory properties of these agents [95]. In addition, simvastatin lowered MPO mRNA and enzyme activity even after 1 day in human MPO overexpressing transgenic mice fed drug for 1- 21 days [95].

Lovastatin was effective in reducing the severity of EAE through reduction in the number of infiltrating T cells and monocytes and reduced secretion of inflammatory cytokines [122]; one mechanism appeared to be the reduction of endothelial cell adhesion molecules through inhibition by lovastatin of the phosphoinositide 3 kinase-Akt (protein kinase B)-NF κ B pathways.

Differences were also seen in statin effectiveness in AD mice models. One study showed that lovastatin and pravastatin lowered A β levels in TgCRND8 mice [26], while lovastatin increased A β levels in the brains of female Tg2576 mice, but not male animals [128]. Treatment of non-transgenic mice with atorvastatin, simvastatin, or lovastatin lowered endogenous levels of A β 40 and 42 [19].

Antibiotics

Minocycline

Minocycline is a tetracycline family antibiotic widely prescribed for treating acne skin condition, but also for respiratory and neurological infections. However, its other identified anti-inflammatory and neuroprotective properties have indicated its possible use for treating neurodegenerative diseases including AD. Mino-

cycline was effective in reducing inflammatory cytokines IL-1 β , IL-6, and TNF- α levels in an AD transgenic mouse model, and improving cognitive performance though not reducing A β levels [157]. Also, minocycline reduced IL-6 and TNF- α production by A β -stimulated human microglia [44]; this study also demonstrated that minocycline *in vitro* could inhibit A β aggregation. Minocycline has shown activity as a neuroprotective agent through inhibition of microglial activation in a number of animal disease models of neurodegeneration or neuronal damage. Minocycline slowed disease progression in a transgenic model of amyotrophic lateral sclerosis [94]. In a model of spinal cord injury, animals administered minocycline showed reduced neuronal apoptosis, reduced amounts of caspase-3, reduced microgliosis and increased functional recovery [48]; one suggested mechanism of action was reduced TNF- α production by microglia. In three different PD animal models of dopaminergic cell loss, induced by thrombin [28], paraquat [136], or MPTP [186], administration of minocycline inhibited microglia activation, and reduced free radical production by inhibiting the microglial NADPH oxidase respiratory, iNOS and cytokine production, which resulted in significant reduction in the loss of dopaminergic neurons.

Dapsone

Interest in the anti-leprosy antibiotic dapsone (4,4'-diaminodiphenylsulfone) as an AD therapy came from initial observations of lower incidence of AD in a population of Japanese leprosy patients, who had been treated for many years with this or similar anti-leprosy antibiotics [115]. Pathological examination of brains of leprosy patients indicated significantly fewer amyloid plaques than in age-matched controls [79,121], though the numbers of NFTs were either unchanged or increased; however, other studies did not confirm these findings [65,92]. Dapsone was not effective in lowering production of A β (42) in an *in vitro* assay [43]. An additional mechanism of action for dapsone has been proposed, besides its antibiotic properties, namely as an anti-inflammatory. Dapsone has significant anti-inflammatory properties as an inhibitor of the enzyme myeloperoxidase (MPO) [89,173], but a small clinical trial of dapsone in AD patients was unsuccessful [79].

Neuro-Receptor Modulators

Nicotine

Smoking is a significant risk factor for the development of AD [3,105], likely due to the effects of the many toxic components of cigarette smoke (e.g. carbon monoxide, phenols, formaldehyde, benzene etc) on the vasculature, and can promote atherosclerosis, oxidative stress and hypertension, all risk factors for AD. However, nicotine alone has many potential therapeutic properties. Nicotine is a potent ligand for a large family of NACHR that are expressed in brain and the peripheral nervous system. Tg 2576 transgenic mice administered acute and chronic doses of nicotine showed significantly less accumulation or load of A β in their brains [67,125]; this effect was not replicated in a different triple transgenic (APP/tau) mouse model [126], where non-significant changes in A β levels were detected in treated animals, and where nicotine increased the proportion of phosphorylated tau. However, recently a significant reduction of A β (40) and A β (42), both soluble and insoluble forms, was demonstrated in APP(V717)L transgenic mice administered nicotine for 5 months from 9 to 14 months of age. Accompanying these findings was the demonstration of significant reduction of levels of activated NF κ B and MAPK pathway components. Inhibition of these pathways resulted in downregulation of expression of apoptosis and cell cycle genes, and reduced amounts of the inflammatory-associated iNOS [103].

It has been shown that smokers with AD had significantly less soluble and insoluble A β (40) and A β (42) in hippocampus and temporal cortex brain samples than non-smokers with AD [68], while smoking non-demented controls had significantly less soluble

A β (40) and A β (42) than non-smoking controls. Although these data do not indicate a protective role for smoking in AD, they do suggest nicotine as a therapeutic agent for AD warrants further investigation. This agent can not only inhibit A β aggregation and prevent its resulting cytotoxicity *in vitro* [119], but it has significant demonstrated anti-inflammatory properties. Nicotine in combination with galantamine (an acetylcholinesterase inhibitor that has nicotinic receptor binding activity) inhibited microglia activation induced by HIV gp120 and IFN- γ [63]; in another study, nicotine or acetylcholine significantly inhibited microglia secretion of tumor necrosis factor- α (TNF- α) induced by LPS [160], an effect mediated by inhibiting the phosphorylation of p42/44 ERK1/2 and p38 MAPK, and attenuated by the NACHR α -7 antagonist alpha bungarotoxin. Rodent microglia were demonstrated to express NACHR α -7 mRNA by RT-PCR [160]. Treatment of rodent microglia with nicotine was effective at reducing LPS-induced TNF- α secretion, but also induced expression of COX-2 and production of PGE₂. NACHR α -7 is the receptor mediating the anti-inflammatory effects of acetylcholine or nicotine on macrophages, as NACHR α -7 deficient mice did not show reduced TNF- α secretion in response to acetylcholine stimulation [179]. Human monocytes responded to nicotine by downregulation of proinflammatory cytokines mediated by inhibition of I κ B phosphorylation and reduced transcription of NF κ B. A role for acetylcholine in mediating the "cholinergic anti-inflammatory pathway" has been established in the periphery, for example bacterial peritonitis in mice was exacerbated if cholinergic vagus input was prevented [172], and reduced following nicotine administration. An early deficit in acetylcholine has been repeatedly demonstrated in AD [50], and is the target for currently prescribed acetylcholinesterase drugs to enhance acetylcholine neurotransmission. These recent data indicate that an acetylcholine deficit may contribute to perpetuating the chronic inflammation in AD brains. These anti-inflammatory mechanisms could function in human brains as we show in Fig. (4) that NACHR α -7 mRNA is expressed by human microglia derived from postmortem elderly brain, while NACHR α -4 and NACHR β 2 are not.

IMMUNE THERAPY AND AMYLOID SEQUESTRATION

The other side of the issue of anti-inflammatory therapy for treating AD is the use of immune therapy to induce circulating antibodies to the A β peptide so that they can either bind and sequester the circulating A β from the blood [37], inhibit A β fibrillogenesis or toxic oligomer formation [53], or bind to plaques in the brain and stimulate Fc- receptor mediated phagocytosis by microglia [12]. It appears that all three mechanisms could be involved in immune clearance of A β in mice [120]. The initial findings were that immunizing PDAPP plaque developing mice with aggregated A β (42) to raise an antibody response to the peptide prevented A β deposition if mice were immunized at a young age, or aided in the clearance of A β deposits if mice were immunized at an older age [156]. These findings opened up the concepts of immune stimulation as a therapeutic approach to AD in a manner that would previously have been considered as pathogenic. These findings were widely replicated in different transgenic mouse models of AD (reviewed in [59]) with either active peptide immunization or passive transfer of antibodies, many of which demonstrated improvement in memory tasks in immunized mice. Utilizing microglia to phagocytose antibody-opsonized A β through binding to their Fc- immunoglobulin receptors does involve cellular activation with transient increased production of free radicals and proinflammatory cytokines [10,106]. As microglial activation appears necessary for efficient clearance of plaques, this strategy has the potential to exacerbate ongoing neuroinflammatory processes before the benefits of A β removal are realized.

Due to the dramatic reduction of A β observed in vaccinated mice, human clinical trials of the A β vaccine (AN1792) on human subjects were carried out up to the phase IIa stage, when they were

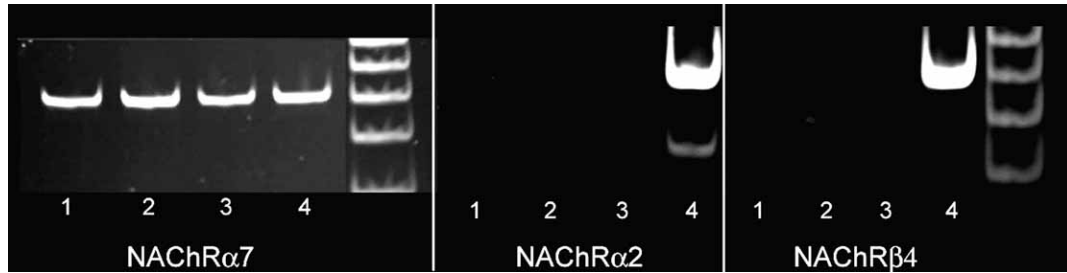


Fig. (4). Human microglia express mRNA for nicotinic acetylcholine receptor $\alpha 7$. Panel A –Reverse transcription-polymerase chain reaction showing expression by different isolates of human microglia of $\alpha 7$ nicotinic acetylcholine receptor mRNA (NACHR $\alpha 7$) (lanes 1-3). Panels B and C: show that human microglia do not express $\alpha 2$ (NACHR $\alpha 2$) or $\beta 4$ (NACHR $\beta 4$) nicotinic acetylcholine receptor mRNA (lanes 1-3). As positive controls (panels A, B, C: lane 4), cDNA from a sample of differentiated SH-SY5Y neuronal-like cells showing positive expression of nicotinic acetylcholine receptor $\alpha 7$, $\alpha 2$ and $\beta 4$.

halted due to meningoencephalitis developing in 18 of 298 vaccinated subjects. It appeared that a T-cell mediated autoimmune response was responsible for the inflammatory response. Although the vaccine trial was terminated, the brains of certain vaccinated participants became available for pathological studies. These demonstrated extensive regional plaque clearance [113,124], with evidence for microglial phagocytosis of A β ; however, tangles were not cleared from the cortex and there was persistence of cerebral amyloid angiopathy. A recent study of A β species in the brains of two additional AN1792 vaccinated subjects demonstrated that although plaques had been dissolved, the total load of A β was not reduced, but moved into a soluble oligomeric form. These cases also had high levels of A β in the white matter, and pronounced deposition of A β on vessels. These data indicate that antibody-mediated mobilization of A β from plaques has the potential to transform A β into more toxic and inflammatory soluble oligomeric forms [131].

AD ANTI-INFLAMMATORY DRUG DISCOVERY

Identifying new relevant targets using cell culture models for a particular disease provides the basis for drug discovery of potentially specific anti-inflammatory targets for AD inflammation. Our laboratory took the approach of global gene expression profiling employing human postmortem brain-derived microglia stimulated with aggregated/oligomeric A β (1-42) to identify all possible genes induced by this interaction [177]. The use of human postmortem microglia is a well-established model of microglial interactions with A β plaques for studying the activation of microglia by aggregated A β [106,107,140,176]. Our laboratory has shown that blocking the A β -binding receptor for advanced glycation endproducts (RAGE) on A β -treated human microglia has significant anti-inflammatory properties [107]. RAGE, which is upregulated on a number of cell types in AD brains including microglia, astrocytes, vascular cells and neurons, is currently a drug target for AD, and a number of other vascular and inflammatory diseases [75]. We have also used an expression profiling approach, the simultaneous induction by microglia of multiple inflammatory pathways was demonstrated; these included a range of inflammatory cytokines (e.g. IL-1 β , IL-6) chemokines (e.g. IL-8, MCP-1, -2, -3, MIP-1 α , -1 β , -2 α , -2 β , -3 α); proteases (e.g. MMP-1, -3, -9, -12), enzymes (e.g. COX-2, indoleamine-pyrole 2,3, dioxygenase) and inflammatory receptors (e.g. urokinase plasminogen activator receptor and immunoglobulin Fc- receptor-IIa) [177]. In this model for inflammation in the AD brain, we identified a range of genes whose expressions were induced more than 3-fold in all of the 5 separate isolates of microglia used in the study. Although the changes in gene expression by human microglia following activation by A β were predominantly proinflammatory, we also identified a limited number of potentially anti-inflammation molecules that were induced in parallel. These included IL-1 receptor antagonist, somatostatin receptor-2, vitamin D receptor, endothelial cell protein C receptor, and adenosine 2A receptor. Upregulation of these proteins on microglia, particularly the anti-inflammatory receptors, as a result of

A β stimulation suggests a potential target for downregulation of the inflammation by administering the receptor ligand or agonist. All of these targets have been characterized in different inflammatory paradigms, but not as potential therapeutic targets for AD. For example, somatostatin receptor-2 is the most abundant of the somatostatin receptors expressed by inflammatory cells [42]; activation of somatostatin receptors with somatostatin or agonists can downregulate proinflammatory cytokine secretion by human macrophages, epithelial cells or rodent microglia [8,29,46,169]. In keeping with our hypothesis that an AD drug should have multiple therapeutic mechanisms, it was demonstrated that somatostatin treated cortical neurons upregulate the expression of the A β peptide degrading protease neprilysin. A mouse model with a genetic deficiency of somatostatin had reduced neprilysin and increased A β (42) [152]. As somatostatin levels decline in aging and AD brains, supplemental therapy for somatostatin is considered a feasible therapeutic option [33,39]. We also propose the vitamin D receptor as a novel AD inflammatory target. It is a member of the large family of nuclear receptor transcription factors and specifically binds the micronutrient-derived hormone 1 α , 25-dihydroxyvitamin D3. Vitamin D is an essential factor in stimulating or maintaining bone formation; however, this agent has also been shown effective in inhibiting inflammation [69,150,174]. For example, 1 α , 25-dihydroxyvitamin D3 treatment of IFN- γ stimulated macrophage inhibited the macrophage respiratory burst and reduced expression of a number of IFN- γ induced inflammatory genes [69]. Also, vitamin D3 was effective in protecting culture neurons from the toxic effects of glutamate or reactive oxygen species [78,167]. *In vitro*, vitamin D3 treatment of rats with chronic relapsing EAE was effective in reducing disease severity by inhibiting microglia and T cells activation and iNOS expression [55]. Although use of the active agent may not be possible due to the side-effect of hypercalcemia, vitamin D agonists lacking these properties, such as elocalitol, have anti-inflammatory properties *in vivo* [132].

CONCLUSIONS

It is still not possible to conclude if anti-inflammatory treatment alone is no longer a valid approach for treating AD. It seems that the central focus of pharmaceutical drug development will remain on inhibiting A β production and aggregation, with anti-inflammatory properties of any such agents being a bonus. As discussed, there is a large body of experimental data from animal or cell culture models demonstrating that A β - or cytokine-activated microglia can produce factors that are neurotoxic, epidemiological data showing the protective effect from developing AD of taking NSAIDs, pathological studies of postmortem AD brains showing many features of inflammation; and that anti-inflammatory drugs are effective for treating other neurodegenerative diseases or disease models, e.g., multiple sclerosis, HIV-associated dementia, PD, ALS, or stroke. All of the above suggest (*but do not prove*) that an inflammatory component must be involved in the pathogenesis of AD. It is clear that cerebral or peripheral inflammation can be an early

event in the AD degenerative process, occurring before memory loss; however, separating the inflammatory pathology from the effects of A β on neurotoxicity and neuroinflammation may not be possible, or necessary. Many of the NSAIDs that have been shown to be effective in protecting against AD in epidemiological studies, though not in clinical studies, also have defined A β -lowering properties [14,43,85,182,183]. Although, it has been suggested that the effective doses of NSAIDs so as to have A β -lowering properties were above the physiological doses that can be used to treat patients, the effect of long-term use of these drugs at lower doses on A β production in presymptomatic subjects remains to be determined. Much research is still being carried out on producing and testing a modified A β vaccine, or testing whether passive immunization with anti-A β antibodies have similar A β clearing effects. This approach might always have limitations as it is focused on the single target of A β removal and actually has a proinflammatory effect due to the stimulation of microglia to phagocytose antibody-opsinized plaques.

At present, the agent curcumin, which ironically has been available for centuries as a food additive, appears to have the great potential, based on convincing experimental data of its efficacy as an anti-oxidant, anti-inflammatory and anti-amyloid agent, to be an effective AD therapeutic agent. The phase II clinical trial of curcumin is scheduled to be completed by December 2007 [2].

ACKNOWLEDGEMENTS

The authors work is supported by grants from the National Institutes of Health, Alzheimer's Association, Michael J. Fox Foundation for Parkinson's Research, Arizona Alzheimer's Consortium, and the Science Foundation of Arizona.

ABBREVIATIONS

A β	= Amyloid beta
AP-1	= Activator Protein-1
APP	= Amyloid precursor protein
APOE	= Apolipoprotein E
AD	= Alzheimer's disease
BACE-1	= Beta-Site APP-Cleaving Enzyme 1
COX	= Cyclooxygenase
EAE	= Experimental Autoimmune Encephalomyelitis
HIV	= Human Immunodeficiency Virus
IFN- γ	= Interferon gamma
IL	= Interleukin
iNOS	= Inducible Nitric Oxide Synthase
LPS	= Lipopolysaccharide
MAPK	= Mitogen-Activated Protein Kinase
MCP	= Monocyte Chemoattractant Protein
MMP	= Matrix Metalloproteinase
MIP	= Macrophage Inflammatory Protein
NACHR	= Neuronal Acetylcholine Receptor
NFTs	= Neurofibrillary tangles
NF κ B	= Nuclear Factor κ B
NSAIDS	= Non-steroidal Anti-inflammatory Drugs
PD	= Parkinson's disease
PG	= Prostaglandin
PPAR	= Peroxisome proliferator-activated receptor
STAT	= Signal Transducer and Activators of Transcription
TNF	= Tumor Necrosis Factor

REFERENCES

- (2006) Cardiovascular and Cerebrovascular Events in the Randomized, Controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). *PLoS. Clin. Trials*, **1**, e33.
- Clinical Trials-Curcumin <http://www.clinicaltrials.gov/ct/show/NCT00099710> 2006 <http://www.clinicaltrials.gov/ct/show/NCT00099710>.
- Aggarwal, N. T., Bienias, J. L., Bennett, D. A., Wilson, R. S., Morris, M. C., Schneider, J. A., Shah, R. C., Evans, D. A. (2006) The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population. *Neuroepidemiology*, **26**, 140-146.
- Aisen, P. S., Davis, K. L., Berg, J. D., Schafer, K., Campbell, K., Thomas, R. G., Weiner, M. F., Farlow, M. R., Sano, M., Grundman, M., Thal, L. J. (2000) A randomized controlled trial of prednisone in Alzheimer's disease. Alzheimer's Disease Cooperative Study. *Neurology*, **54**, 588-593.
- Aisen, P. S., Schafer, K. A., Grundman, M., Pfeiffer, E., Sano, M., Davis, K. L., Farlow, M. R., Jin, S., Thomas, R. G., Thal, L. J. (2003) Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. *JAMA*, **289**, 2819-2826.
- Aisen, P. S., Schmeidler, J., Pasinetti, G. M. (2002) Randomized pilot study of nimesulide treatment in Alzheimer's disease. *Neurology*, **58**, 1050-1054.
- Anekonda, T. S. (2006) Resveratrol—a boon for treating Alzheimer's disease? *Brain Res. Brain Res. Rev.*, **52**, 316-326.
- Armani, C., Catalani, E., Balbarini, A., Bagnoli, P., Cervia, D. (2007) Expression, pharmacology, and functional role of somatostatin receptor subtypes 1 and 2 in human macrophages. *J. Leukoc. Biol.*, **81**, 845-855.
- Atamna, H., Boyle, K. (2006) Amyloid-beta peptide binds with heme to form a peroxidase: relationship to the cytopathologies of Alzheimer's disease. *Proc. Natl. Acad. Sci. USA*, **103**, 3381-3386.
- Bacskai, B. J., Kajdasz, S. T., Christie, R. H., Carter, C., Games, D., Seubert, P., Schenk, D., Hyman, B. T. (2001) Imaging of amyloid-beta deposits in brains of living mice permits direct observation of clearance of plaques with immunotherapy. *Nat. Med.*, **7**, 369-372.
- Bala, K., Tripathy, B. C., Sharma, D. (2006) Neuroprotective and anti-ageing effects of curcumin in aged rat brain regions. *Biogerontology*, **7**, 81-89.
- Bard, F., Cannon, C., Barbour, R., Burke, R. L., Games, D., Grajeda, H., Guido, T., Hu, K., Huang, J., Johnson-Wood, K., Khan, K., Kholodenko, D., Lee, M., Lieberburg, I., Motter, R., Nguyen, N., Soriano, F., Vasquez, N., Weiss, K., Welch, B., Seubert, P., Schenk, D., Yednock, T. (2000) Peripherally administered antibodies against amyloid beta-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nat. Med.*, **6**, 916-919.
- Beach, T. G., Wilson, J. R., Sue, L. I., Newell, A., Poston, M., Cisneros, R., Pandya, Y., Esh, C., Connor, D. J., Sabbagh, M., Walker, D. G., Roher, A. E. (2007) Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. *Acta Neuropathol. (Berl)*, **113**, 13-21.
- Behr, D., Clarke, E. E., Wrigley, J. D., Martin, A. C., Nadin, A., Churcher, I., Shearman, M. S. (2004) Selected non-steroidal anti-inflammatory drugs and their derivatives target gamma-secretase at a novel site-evidence for an allosteric mechanism. *J. Biol. Chem.*, **279**, 43419-43426.
- Bhat, R. V., Budd Haeberlein, S. L., Avila, J. (2004) Glycogen synthase kinase 3: a drug target for CNS therapies. *J. Neurochem.*, **89**, 1313-1317.
- Bianca, V. D., Dusi, S., Bianchini, E., Dal, P., I. Rossi, F. (1999) Beta-amyloid activates the O-2 forming NADPH oxidase in microglia, monocytes, and neutrophils. A possible inflammatory mechanism of neuronal damage in Alzheimer's disease. *J. Biol. Chem.*, **274**, 15493-15499.
- Breitner, J. C., Gau, B. A., Welsh, K. A., Plassman, B. L., McDonald, W. M., Helms, M. J., Anthony, J. C. (1994) Inverse association of anti-inflammatory treatments and Alzheimer's disease: initial results of a co-twin control study. *Neurology*, **44**, 227-232.
- Breitner, J. C., Welsh, K. A., Helms, M. J., Gaskell, P. C., Gau, B. A., Roses, A. D., Pericak-Vance, M. A., Saunders, A. M. (1995) Delayed onset of Alzheimer's disease with nonsteroidal anti-inflammatory and histamine H2 blocking drugs. *Neurobiol. Aging*, **16**, 523-30.
- Burns, M. P., Igbavboa, U., Wang, L., Wood, W. G., Duff, K. (2006) Cholesterol distribution, not total levels, correlate with altered amyloid precursor protein processing in statin-treated mice. *Neuromolecular Med.*, **8**, 319-328.
- Caamano-Isorna, F., Corral, M., Montes-Martinez, A., Takkouche, B. (2006) Education and dementia: a meta-analytic study. *Neuroepidemiology*, **26**, 226-232.
- Cagnin, A., Brooks, D. J., Kennedy, A. M., Gunn, R. N., Myers, R., Turkheimer, F. E., Jones, T., Banati, R. B. (2001) *In-vivo* measurement of activated microglia in dementia. *Lancet*, **358**, 461-467.
- Canadian Study of Health and Aging. (1994) The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada. *Neurology*, **44**, 2073-2080.
- Cassidy, I., Topol, E. (2004) Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. *Lancet*, **363**, 1139-1146.
- Chan, K. Y., Boucher, E. S., Gandhi, P. J., Silva, M. A. (2004) HMG-CoA reductase inhibitors for lowering elevated levels of C-reactive protein. *Am. J. Health Syst. Pharm.*, **61**, 1676-1681.

- [25] Chandra, V., Ganguli, M., Pandav, R., Johnston, J., Belle, S., DeKosky, S. T. (1998) Prevalence of Alzheimer's disease and other dementias in rural India: the Indo-US study. *Neurology*, **51**, 1000-1008.
- [26] Chauhan, N. B., Siegel, G. J., Feinstein, D. L. (2004) Effects of lovastatin and pravastatin on amyloid processing and inflammatory response in TgCRND8 brain. *Neurochem. Res.*, **29**, 1897-1911.
- [27] Chen, J., Zhou, Y., Mueller-Stieber, S., Chen, L. F., Kwon, H., Yi, S., Mucke, L., Gan, L. (2005) SIRT1 protects against microglia-dependent amyloid-beta toxicity through inhibiting NF-kappaB signaling. *J. Biol. Chem.*, **280**, 40364-40374.
- [28] Choi, S. H., Lee, D. Y., Chung, E. S., Hong, Y. B., Kim, S. U., Jin, B. K. (2005) Inhibition of thrombin-induced microglial activation and NADPH oxidase by minocycline protects dopaminergic neurons in the substantia nigra *in vivo*. *J. Neurochem.*, **95**, 1755-1765.
- [29] Chowers, Y., Cahalon, L., Lahav, M., Schor, H., Tal, R., Bar-Meir, S., Levite, M. (2000) Somatostatin through its specific receptor inhibits spontaneous and TNF-alpha- and bacteria-induced IL-8 and IL-1 beta secretion from intestinal epithelial cells. *J. Immunol.*, **165**, 2955-2961.
- [30] Cole, G. M., Morihara, T., Lim, G. P., Yang, F., Begum, A., Frautschy, S. A. (2004) NSAID and antioxidant prevention of Alzheimer's disease: lessons from *in vitro* and animal models. *Ann. N. Y. Acad. Sci.*, **1035**, 68-84.
- [31] Combs, C. K., Johnson, D. E., Karlo, C., Cannady, S. B., Landreth, G. E. (2000) Inflammatory Mechanisms in Alzheimer's Disease: Inhibition of beta-amyloid stimulated proinflammatory responses and neurotoxicity by PPAR-gamma agonists. *J. Neurosci.*, **20**, 558-567.
- [32] Cordle, A., Landreth, G. (2005) 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors attenuate beta-amyloid-induced microglial inflammatory responses. *J. Neurosci.*, **25**, 299-307.
- [33] Craft, S., Asthana, S., Newcomer, J. W., Wilkinson, C. W., Matos, I. T., Baker, L. D., Cherrier, M., Lofgreen, C., Latendresse, S., Petrova, A., Plymate, S., Raskind, M., Grimwood, K., Veith, R. C. (1999) Enhancement of memory in Alzheimer disease with insulin and somatostatin, but not glucose. *Arch. Gen. Psychiatry*, **56**, 1135-1140.
- [34] Czirr, E., Weggen, S. (2006) Gamma-secretase modulation with Abeta42-lowering nonsteroidal anti-inflammatory drugs and derived compounds. *Neurodegener. Dis.*, **3**, 298-304.
- [35] Dantoin, T., Auriacombe, S., Sarazin, M., Becker, H., Pere, J. J., Bourdeix, I. (2006) Rivastigmine monotherapy and combination therapy with memantine in patients with moderately severe Alzheimer's disease who failed to benefit from previous cholinesterase inhibitor treatment. *Int. J. Clin. Pract.*, **60**, 110-118.
- [36] de la Torre, J. C. (2002) Alzheimer's disease: how does it start? *J. Alzheimers Dis.*, **4**, 497-512.
- [37] DeMattos, R. B., Bales, K. R., Cummins, D. J., Dodart, J. C., Paul, S. M., Holtzman, D. M. (2001) Peripheral anti-A beta antibody alters CNS and plasma A beta clearance and decreases brain A beta burden in a mouse model of Alzheimer's disease. *Proc. Natl. Acad. Sci. USA*, **98**, 8850-8855.
- [38] Devaraj, S., Rogers, J., Jialal, I. (2007) Statins and biomarkers of inflammation. *Curr. Atheroscler. Rep.*, **9**, 33-41.
- [39] Doggrell, S. A. (2004) The potential of activation of somatostatinergic neurotransmission with FK960 in Alzheimer's disease. *Expert. Opin. Investig. Drugs*, **13**, 69-72.
- [40] Echeverria, V., Clerman, A., Dore, S. (2005) Stimulation of PGE receptors EP2 and EP4 protects cultured neurons against oxidative stress and cell death following beta-amyloid exposure. *Eur. J. Neurosci.*, **22**, 2199-2206.
- [41] Eikelenboom, P., Hack, C. E., Rozemuller, J. M., Stam, F. C. (1989) Complement activation in amyloid plaques in Alzheimer's dementia. *Virchows Arch. B. Cell Pathol.*, **56**, 259-262.
- [42] Elliott, D. E., Li, J., Blum, A. M., Metwali, A., Patel, Y. C., Weinstock, J. V. (1999) SSTR2A is the dominant somatostatin receptor subtype expressed by inflammatory cells, is widely expressed and directly regulates T cell IFN-gamma release. *Eur. J. Immunol.*, **29**, 2454-2463.
- [43] Eriksen, J. L., Sagi, S. A., Smith, T. E., Weggen, S., Das, P., McLendon, D. C., Ozols, V. V., Jessing, K. W., Zavitz, K. H., Koo, E. H., Golde, T. E. (2003) NSAIDs and enantiomers of flurbiprofen target gamma-secretase and lower Abeta 42 *in vivo*. *J. Clin. Invest.*, **112**, 440-449.
- [44] Familian, A., Boshuizen, R. S., Eikelenboom, P., Veerhuis, R. (2006) Inhibitory effect of minocycline on amyloid beta fibril formation and human microglial activation. *Glia*, **53**, 233-240.
- [45] Fassbender, K., Simons, M., Bergmann, C., Stroick, M., Lutjohann, D., Keller, P., Runz, H., Kuhl, S., Bertsch, T., von, B. K., Hennerici, M., Beyreuther, K., Hartmann, T. (2001) Simvastatin strongly reduces levels of Alzheimer's disease beta-amyloid peptides Abeta 42 and Abeta 40 *in vitro* and *in vivo*. *Proc. Natl. Acad. Sci. USA*, **98**, 5856-5861.
- [46] Feindt, J., Schmidt, A., Mentlein, R. (1998) Receptors and effects of the inhibitory neuropeptide somatostatin in microglial cells. *Brain Res. Mol. Brain Res.*, **60**, 228-233.
- [47] Ferrer, I., Gomez-Isla, T., Puig, B., Freixes, M., Ribe, E., Dalfó, E., Avila, J. (2005) Current advances on different kinases involved in tau phosphorylation, and implications in Alzheimer's disease and tauopathies. *Curr. Alzheimer Res.*, **2**, 3-18.
- [48] Festoff, B. W., Ameenuddin, S., Arnold, P. M., Wong, A., Santacruz, K. S., Citron, B. A. (2006) Minocycline neuroprotects, reduces microgliosis, and inhibits caspase protease expression early after spinal cord injury. *J. Neurochem.*, **97**, 1314-1326.
- [49] Fiala, M., Liu, Q. N., Sayre, J., Pop, V., Brahmandam, V., Graves, M. C., Vinters, H. V. (2002) Cyclooxygenase-2-positive macrophages infiltrate the Alzheimer's disease brain and damage the blood-brain barrier. *Eur. J. Clin. Invest.*, **32**, 360-371.
- [50] Francis, P. T., Palmer, A. M., Snape, M., Wilcock, G. K. (1999) The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J. Neurol. Neurosurg. Psychiatry*, **66**, 137-147.
- [51] Frank, B., Gupta, S. (2005) A review of antioxidants and Alzheimer's disease. *Ann. Clin. Psychiatry*, **17**, 269-286.
- [52] Frautschy, S. A., Hu, W., Kim, P., Miller, S. A., Chu, T., Harris-White, M. E., Cole, G. M. (2001) Phenolic anti-inflammatory antioxidant reversal of Abeta-induced cognitive deficits and neuropathology. *Neurobiol. Aging*, **22**, 993-1005.
- [53] Frenkel, D., Katz, O., Solomon, B. (2000) Immunization against Alzheimer's beta-amyloid plaques via EFRH phage administration. *Proc. Natl. Acad. Sci. USA*, **97**, 11455-11459.
- [54] Gan, L., Ye, S., Chu, A., Anton, K., Yi, S., Vincent, V. A., Von Schack, D., Chin, D., Murray, J., Lohr, S., Pathy, L., Gonzalez-Zuluetta, M., Nikolich, K., Urfer, R. (2004) Identification of Cathepsin B as a Mediator of Neuronal Death Induced by A[beta]-activated Microglial Cells Using a Functional Genomics Approach. *J. Biol. Chem.*, **279**, 5565-5572.
- [55] Garcion, E., Sindji, L., Nataf, S., Brachet, P., Darcy, F., Montero-Menei, C. N. (2003) Treatment of experimental autoimmune encephalomyelitis in rat by 1,25-dihydroxyvitamin D3 leads to early effects within the central nervous system. *Acta Neuropathol. (Berl)*, **105**, 438-448.
- [56] Gasparini, L., Rusconi, L., Xu, H., del, S. P., Ongini, E. (2004) Modulation of beta-amyloid metabolism by non-steroidal anti-inflammatory drugs in neuronal cell cultures. *J. Neurochem.*, **88**, 337-348.
- [57] Gatz, M., Prescott, C. A., Pedersen, N. L. (2006) Lifestyle risk and delaying factors. *Alzheimer Dis. Assoc. Disord.*, **20**, S84-S88.
- [58] Gauthier, S. G. (2005) Alzheimer's disease: the benefits of early treatment. *Eur. J. Neurol.*, **12**(Suppl. 3), 11-16.
- [59] Gelinas, D. S., DaSilva, K., Fenili, D., St George-Hyslop, P., McLaurin, J. (2004) Immunotherapy for Alzheimer's disease. *Proc. Natl. Acad. Sci. USA*, **101**(Suppl. 2), 14657-62.
- [60] Genolet, R., Wahli, W., Michalik, L. (2004) PPARs as drug targets to modulate inflammatory responses? *Curr. Drug Targets Inflamm. Allergy*, **3**, 361-375.
- [61] Gervais, F., Paquette, J., Morissette, C., Krzykowski, P., Yu, M., Azzi, M., Lacombe, D., Kong, X., Aman, A., Laurin, J., Szarek, W. A., Tremblay, P. (2007) Targeting soluble Abeta peptide with Tramiprosate for the treatment of brain amyloidosis. *Neurobiol. Aging*, **28**, 537-547.
- [62] Giulian, D., Haverkamp, L. J., Yu, J., Karshin, W., Tom, D., Li, J., Kazanaka, A., Kirkpatrick, J., Roher, A. E. (1998) The HHQK domain of beta-amyloid provides a structural basis for the immunopathology of Alzheimer's disease. *J. Biol. Chem.*, **273**, 29719-29726.
- [63] Giunta, B., Ehrhart, J., Townsend, K., Sun, N., Vendrame, M., Shytle, D., Tan, J., Fernandez, F. (2004) Galantamine and nicotine have a synergistic effect on inhibition of microglial activation induced by HIV-1 gp120. *Brain Res. Bull.*, **64**, 165-170.
- [64] Golde, T. E. (2005) The Abeta hypothesis: leading us to rationally-designed therapeutic strategies for the treatment or prevention of Alzheimer disease. *Brain Pathol.*, **15**, 84-87.
- [65] Goto, M., Kimura, T., Hagio, S., Ueda, K., Kitajima, S., Tokunaga, H., Sato, E. (1995) Neuropathological analysis of dementia in a Japanese leprosarium. *Dementia*, **6**, 157-161.
- [66] Griffin, W. S., Stanley, L. C., Ling, C., White, L., MacLeod, V., Perrot, L. J., White, C. L., Araoz, C. (1989) Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. *Proc. Natl. Acad. Sci. USA*, **86**, 7611-7615.
- [67] Hellstrom-Lindahl, E., Court, J., Keverne, J., Svedberg, M., Lee, M., Marutle, A., Thomas, A., Perry, E., Bednar, I., Nordberg, A. (2004) Nicotine reduces A beta in the brain and cerebral vessels of APPsw mice. *Eur. J. Neurosci.*, **19**, 2703-2710.
- [68] Hellstrom-Lindahl, E., Mousavi, M., Ravid, R., Nordberg, A. (2004) Reduced levels of Abeta 40 and Abeta 42 in brains of smoking controls and Alzheimer's patients. *Neurobiol. Dis.*, **15**, 351-360.
- [69] Helming, L., Bose, J., Ehrchen, J., Schiebe, S., Frahm, T., Geffers, R., Probst-Keppler, M., Balling, R., Lengeling, A. (2005) 1alpha,25-Dihydroxyvitamin D3 is a potent suppressor of interferon gamma-mediated macrophage activation. *Blood*, **106**, 4351-4358.
- [70] Heneka, M. T., Sastre, M., Dumitrescu-Ozimek, L., Hanke, A., Dewachter, I., Kuiperi, C., O'Banion, K., Klockgether, T., Van, L. F., Landreth, G. E. (2005) Acute treatment with the PPARgamma agonist pioglitazone and ibuprofen reduces glial inflammation and Abeta1-42 levels in APPV717I transgenic mice. *Brain*, **128**, 1442-1453.
- [71] Ho, L., Pieroni, C., Winger, D., Purohit, D. P., Aisen, P. S., Pasinetti, G. M. (1999) Regional distribution of cyclooxygenase-2 in the hippocampal formation in Alzheimer's disease. *J. Neurosci. Res.*, **57**, 295-303.
- [72] Ho, L., Qin, W., Stetka, B. S., Pasinetti, G. M. (2006) Is there a future for cyclo-oxygenase inhibitors in Alzheimer's disease? *CNS Drugs*, **20**, 85-98.

- [73] Hoozemans, J. J., Rozemuller, A. J., Janssen, I., De Groot, C. J., Veerhuis, R., Eikelenboom, P. (2001) Cyclooxygenase expression in microglia and neurons in Alzheimer's disease and control brain. *Acta Neuropathol. (Berl.)*, **101**, 2-8.
- [74] Hoozemans, J. J., van Haastert, E. S., Veerhuis, R., Arendt, T., Scheper, W., Eikelenboom, P., Rozemuller, A. J. (2005) Maximal COX-2 and ppRb expression in neurons occurs during early Braak stages prior to the maximal activation of astrocytes and microglia in Alzheimer's disease. *J. Neuroinflamm.*, **2**, 27.
- [75] Hudson, B. I., Schmidt, A. M. (2004) RAGE: a novel target for drug intervention in diabetic vascular disease. *Pharm. Res.*, **21**, 1079-1086.
- [76] Hyde, L. A., McHugh, N. A., Chen, J., Zhang, Q., Manfra, D., Nomeir, A. A., Josien, H., Bara, T., Clader, J. W., Zhang, L., Parker, E. M., Higgins, G. A. (2006) Studies to investigate the in vivo therapeutic window of the gamma-secretase inhibitor N2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyethanoyl]-N1-[(7S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-L-alaninamide (LY411,575) in the CRND8 mouse. *J. Pharmacol. Exp. Ther.*, **319**, 1133-1143.
- [77] Iadecola, C. (2003) Cerebrovascular effects of amyloid-beta peptides: mechanisms and implications for Alzheimer's dementia. *Cell Mol. Neurobiol.*, **23**, 681-689.
- [78] Ibi, M., Sawada, H., Nakanishi, M., Kume, T., Katsuki, H., Kaneko, S., Shimohama, S., Akaike, A. (2001) Protective effects of 1 alpha,25-(OH)₂D₃ against the neurotoxicity of glutamate and reactive oxygen species in mesencephalic culture. *Neuropharmacology*, **40**, 761-771.
- [79] Imbimbo, B. P. (2004) The potential role of non-steroidal anti-inflammatory drugs in treating Alzheimer's disease. *Expert Opin. Investig. Drugs*, **13**, 1469-1481.
- [80] Launer, V. B. A., Hoes, L. J., Ott, A. W. A., Hofman, A., Breteler, M. M., Stricker, B. H. (1998) NSAIDs and incident Alzheimer's disease. The Rotterdam Study. *Neurobiol. Aging*, **19**, 607-611.
- [81] Ruitenber, V. B. A., Hofman, A., Launer, A., van Duijn, L. J., Stijnen, C. M., T., Breteler, M. M., Stricker, B. H. (2001) Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. *N. Engl. J. Med.*, **345**, 1515-1521.
- [82] Itagaki, S., McGeer, P. L., Akiyama, H. (1988) Presence of T-cytotoxic suppressor and leucocyte common antigen positive cells in Alzheimer's disease brain tissue. *Neurosci. Lett.*, **91**, 259-264.
- [83] Itagaki, S., McGeer, P. L., Akiyama, H., Zhu, S., Selkoe, D. (1989) Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. *J. Neuroimmunol.*, **24**, 173-182.
- [84] Jang, J. H., Surh, Y. J. (2003) Protective effect of resveratrol on beta-amyloid-induced oxidative PC12 cell death. *Free Radic. Biol. Med.*, **34**, 1100-1110.
- [85] Jantzen, P. T., Connor, K. E., DiCarlo, G., Wenk, G. L., Wallace, J. L., Rojiani, A. M., Coppola, D., Morgan, D., Gordon, M. N. (2002) Microglial activation and beta-amyloid deposit reduction caused by a nitric oxide-releasing nonsteroidal anti-inflammatory drug in amyloid precursor protein plus presenilin-1 transgenic mice. *J. Neurosci.*, **22**, 2246-2254.
- [86] Jiao, Y., Wilkinson, J., Christine, P. E., Buss, J. L., Wang, W., Planalp, R., Torti, F. M., Torti, S. V. (2006) Iron chelation in the biological activity of curcumin. *Free Radic. Biol. Med.*, **40**, 1152-1160.
- [87] Jick, H., Zornberg, G. L., Jick, S. S., Seshadri, S., Drachman, D. A. (2000) Statins and the risk of dementia. *Lancet*, **356**, 1627-1631.
- [88] Jung, K. K., Lee, H. S., Cho, J. Y., Shin, W. C., Rhee, M. H., Kim, T. G., Kang, J. H., Kim, S. H., Hong, S., Kang, S. Y. (2006) Inhibitory effect of curcumin on nitric oxide production from lipopolysaccharide-activated primary microglia. *Life Sci.*, **79**, 2022-2031.
- [89] Kettle, A. J., Winterbourn, C. C. (1991) Mechanism of inhibition of myeloperoxidase by anti-inflammatory drugs. *Biochem. Pharmacol.*, **41**, 1485-1492.
- [90] Kim, H. Y., Park, E. J., Joe, E. H., Jou, I. (2003) Curcumin suppresses Janus kinase-STAT inflammatory signaling through activation of Src homology 2 domain-containing tyrosine phosphatase 2 in brain microglia. *J. Immunol.*, **171**, 6072-6079.
- [91] Kim, S. Y., Jung, S. H., Kim, H. S. (2005) Curcumin is a potent broad spectrum inhibitor of matrix metalloproteinase gene expression in human astrogloma cells. *Biochem. Biophys. Res. Commun.*, **337**, 510-516.
- [92] Kimura, T., Goto, M. (1993) Existence of senile plaques in the brains of elderly leprosy patients. *Biotech. Histochem.*, **342**, 1364.
- [93] Kojro, E., Gimpl, G., Lammich, S., Marz, W., Fahrenholz, F. (2001) Low cholesterol stimulates the nonamyloidogenic pathway by its effect on the alpha-secretase ADAM 10. *Proc. Natl. Acad. Sci. USA*, **98**, 5815-5820.
- [94] Kriz, J., Nguyen, M. D., Julien, J. P. (2002) Minocycline slows disease progression in a mouse model of amyotrophic lateral sclerosis. *Neurobiol. Dis.*, **10**, 268-278.
- [95] Kumar, A. P., Piedrafita, F. F., Reynolds, W. F. (2004) Peroxisome proliferator-activated receptor gamma ligands regulate myeloperoxidase expression in macrophages by an estrogen-dependent mechanism involving the -463GA promoter polymorphism. *J. Biol. Chem.*, **279**, 8300-8315.
- [95] Kumar, A. P., Reynolds, W. F. (2005) Statins downregulate myeloperoxidase gene expression in macrophages. *Biochem. Biophys. Res. Commun.*, **331**, 442-451.
- [96] Lahiri, D. K., Chen, D., Maloney, B., Holloway, H. W., Yu, Q. S., Utsuki, T., Giordano, T., Sambamurti, K., Greig, N. H. (2007) The experimental Alzheimer's disease drug posiphen [(+)-phenserine] lowers amyloid-beta peptide levels in cell culture and mice. *J. Pharmacol. Exp. Ther.*, **320**, 386-396.
- [97] Launer, L. (2003) Nonsteroidal anti-inflammatory drug use and the risk for Alzheimer's disease: dissecting the epidemiological evidence. *Drugs*, **63**, 731-739.
- [98] Lautenschlager, N. T., Almeida, O. P. (2006) Physical activity and cognition in old age. *Curr. Opin. Psychiatry*, **19**, 190-193.
- [99] Lehmann, J. M., Lenhard, J. M., Oliver, B. B., Ringold, G. M., Kliewer, S. A. (1997) Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs. *J. Biol. Chem.*, **272**, 3406-3410.
- [100] Li, G., Higdon, R., Kukull, W. A., Peskind, E., Van Valen, M. K., Tsuang, D., van, B. G., McCormick, W., Bowen, J. D., Teri, L., Schellenberg, G. D., Larson, E. B. (2004) Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. *Neurology*, **63**, 1624-1628.
- [101] Lim, G. P., Chu, T., Yang, F., Beech, W., Frautschy, S. A., Cole, G. M. (2001) The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. *J. Neurosci.*, **21**, 8370-8377.
- [102] Lindberg, C., Crisby, M., Winblad, B., Schultzberg, M. (2005) Effects of statins on microglia. *J. Neurosci. Res.*, **82**, 10-19.
- [103] Liu, Q., Zhang, J., Zhu, H., Qin, C., Chen, Q., Zhao, B. (2007) Dissecting the signaling pathway of nicotine-mediated neuroprotection in a mouse Alzheimer disease model. *FASEB J.*, **21**, 61-73.
- [104] Luber-Narod, J., Rogers, J. (1988) Immune system associated antigens expressed by cells of the human central nervous system. *Neurosci. Lett.*, **94**, 17-22.
- [105] Luchsinger, J. A., Reitz, C., Honig, L. S., Tang, M. X., Shea, S., Mayeux, R. (2005) Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology*, **65**, 545-551.
- [106] Lue, L. F., Walker, D. G. (2002) Modeling Alzheimer's disease immune therapy mechanisms: interactions of human postmortem microglia with antibody-opsinized amyloid beta peptide. *J. Neurosci. Res.*, **70**, 599-610.
- [107] Lue, L. F., Walker, D. G., Brachova, L., Beach, T. G., Rogers, J., Schmidt, A. M., Stern, D., Yan, S. D. (2001) Involvement of microglial Receptor for Advanced Glycation Endproducts (RAGE) in Alzheimer's disease: Identification of a cellular activation mechanism. *Exp. Neurol.*, **171**, 29-45.
- [108] Lukiw, W. J., Bazan, N. G. (1997) Cyclooxygenase 2 RNA message abundance, stability, and hypervariability in sporadic Alzheimer neocortex. *J. Neurosci. Res.*, **50**, 937-945.
- [109] Luo, Y., Yin, W., Signore, A. P., Zhang, F., Hong, Z., Wang, S., Graham, S. H., Chen, J. (2006) Neuroprotection against focal ischemic brain injury by the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone. *J. Neurochem.*, **97**, 435-448.
- [110] Mahley, R. W., Weisgraber, K. H., Huang, Y. (2006) Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc. Natl. Acad. Sci. USA*, **103**, 5644-5651.
- [111] Mancuso, C., Scapagini, G., Curro, D., Giuffrida Stella, A. M., De, M. C., Butterfield, D. A., Calabrese, V. (2007) Mitochondrial dysfunction, free radical generation and cellular stress response in neurodegenerative disorders. *Front Biosci.*, **12**, 1107-1123.
- [112] Marambaud, P., Zhao, H., Davies, P. (2005) Resveratrol promotes clearance of Alzheimer's disease amyloid-beta peptides. *J. Biol. Chem.*, **280**, 37377-37382.
- [113] Masliah, E., Hansen, L., Adame, A., Crews, L., Bard, F., Lee, C., Seubert, P., Games, D., Kirby, L., Schenk, D. (2005) Abeta vaccination effects on plaque pathology in the absence of encephalitis in Alzheimer disease. *Neurology*, **64**, 129-131.
- [114] McGeer, P. L., Akiyama, H., Itagaki, S., McGeer, E. G. (1989) Activation of the classical complement pathway in brain tissue of Alzheimer patients. *Neurosci. Lett.*, **107**, 341-346.
- [115] McGeer, P. L., Harada, N., Kimura, H., McGeer, E. G., Schulzer, M. (1992) Prevalence of dementia amongst elderly Japanese with leprosy: apparent effect of chronic drug therapy. *Dementia*, **3**, 146-149.
- [116] McGeer, P. L., Itagaki, S., Tago, H., McGeer, E. G. (1987) Reactive microglia in patients with senile dementia of the Alzheimer type are positive for the histocompatibility glycoprotein HLA-DR. *Neurosci. Lett.*, **79**, 195-200.
- [117] McGeer, P. L., Schulzer, M., McGeer, E. G. (1996) Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. *Neurology*, **47**, 425-432.
- [118] McGeer, P. L., Schulzer, M., McGeer, E. G. (1996) Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. *Neurology*, **47**, 425-432.
- [119] Moore, S. A., Huckerby, T. N., Gibson, G. L., Fullwood, N. J., Turnbull, S., Tabner, B. J., El-Agnaf, O. M., Allsop, D. (2004) Both the D-(+) and L-(-) enantiomers of nicotine inhibit Abeta aggregation and cytotoxicity. *Biochemistry*, **43**, 819-826.
- [120] Morgan, D. (2005) Mechanisms of A beta plaque clearance following passive A beta immunization. *Neurodegener. Dis.*, **2**, 261-266.
- [121] Namba, Y., Kawatsu, K., Izumi, S., Ueki, A., Ikeda, K. (1992) Neurofibrillary tangles and senile plaques in brain of elderly leprosy patients. *Biotech. Histochem.*, **340**, 978.

- [122] Nath, N., Giri, S., Prasad, R., Singh, A. K., Singh, I. (2004) Potential targets of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor for multiple sclerosis therapy. *J. Immunol.*, **172**, 1273-1286.
- [123] Neuroinflammation Working Group. (2000) Inflammation and Alzheimer's disease. *Neurobiol. Aging*, **21**, 383-421.
- [124] Nicoll, J. A., Barton, E., Boche, D., Neal, J. W., Ferrer, I., Thompson, P., Vlachouli, C., Wilkinson, D., Bayer, A., Games, D., Seubert, P., Schenk, D., Holmes, C. (2006) Abeta species removal after abeta42 immunization. *J. Neuropathol. Exp. Neurol.*, **65**, 1040-1048.
- [125] Nordberg, A., Hellstrom-Lindahl, E., Lee, M., Johnson, M., Mousavi, M., Hall, R., Perry, E., Bednar, I., Court, J. (2002) Chronic nicotine treatment reduces beta-amyloidosis in the brain of a mouse model of Alzheimer's disease (APPsw). *J. Neurochem.*, **81**, 655-658.
- [126] Oddo, S., Caccamo, A., Green, K. N., Liang, K., Tran, L., Chen, Y., Leslie, F. M., LaFerla, F. M. (2005) Chronic nicotine administration exacerbates tau pathology in a transgenic model of Alzheimer's disease. *Proc. Natl. Acad. Sci. USA*, **102**, 3046-3051.
- [127] Ono, K., Hasegawa, K., Naiki, H., Yamada, M. (2004) Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils *in vitro*. *J. Neurosci. Res.*, **75**, 742-750.
- [128] Park, I. H., Hwang, E. M., Hong, H. S., Boo, J. H., Oh, S. S., Lee, J., Jung, M. W., Bang, O. Y., Kim, S. U., Mook-Jung, I. (2003) Lovastatin enhances Abeta production and senile plaque deposition in female Tg2576 mice. *Neurobiol. Aging*, **637**-643.
- [129] Parvathy, S., Ehrlich, M., Pedrini, S., Diaz, N., Refolo, L., Buxbaum, J. D., Bogush, A., Petanceska, S., Gandy, S. (2004) Atorvastatin-induced activation of Alzheimer's alpha secretase is resistant to standard inhibitors of protein phosphorylation-regulated ectodomain shedding. *J. Neurochem.*, **90**, 1005-1010.
- [130] Pasinetti, G. M., Aisen, P. S. (1998) Cyclooxygenase-2 expression is increased in frontal cortex of Alzheimer's disease brain. *Neuroscience*, **87**, 319-324.
- [131] Patton, R. L., Kalback, W. M., Esh, C. L., Kokjohn, T. A., Van Vickle, G. D., Luehrs, D. C., Kuo, Y. M., Lopez, J., Brune, D., Ferrer, I., Masliah, E., Newel, A. J., Beach, T. G., Castano, E. M., Roher, A. E. (2006) Amyloid-beta peptide remnants in AN-1792-immunized Alzheimer's disease patients: a biochemical analysis. *Am. J. Pathol.*, **169**, 1048-1063.
- [132] Penna, G., Amuchastegui, S., Cossetti, C., Aquilano, F., Mariani, R., Sanvito, F., Doglioni, C., Adorini, L. (2006) Treatment of experimental autoimmune prostatitis in nonobese diabetic mice by the vitamin D receptor agonist elocalcit. *J. Immunol.*, **177**, 8504-8511.
- [133] Pereira, C., Agostinho, P., Moreira, P. I., Cardoso, S. M., Oliveira, C. R. (2005) Alzheimer's disease-associated neurotoxic mechanisms and neuroprotective strategies. *Curr. Drug Targets CNS Neurol. Disord.*, **4**, 383-403.
- [134] Peschel, D., Koerting, R., Nass, N. (2007) Curcumin induces changes in expression of genes involved in cholesterol homeostasis. *J. Nutr. Biochem.*, **18**, 113-119.
- [135] Pope, S. K., Kritchevsky, S. B., Ambrosone, C., Yaffe, K., Tyllavsky, F., Simonsick, E. M., Rosano, C., Stewart, S., Harris, T. (2006) Myeloperoxidase polymorphism and cognitive decline in older adults in the Health, Aging, and Body Composition Study. *Am. J. Epidemiol.*, **163**, 1084-1090.
- [136] Purisai, M. G., McCormack, A. L., Cumine, S., Li, J., Isla, M. Z., Di Monte, D. A. (2007) Microglial activation as a priming event leading to paraquat-induced dopaminergic cell degeneration. *Neurobiol. Dis.*, **25**, 392-400.
- [137] Rajeswari, A. (2006) Curcumin protects mouse brain from oxidative stress caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Eur. Rev. Med. Pharmacol. Sci.*, **10**, 157-161.
- [138] Ramassamy, C. (2006) Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets. *Eur. J. Pharmacol.*, **545**, 51-64.
- [139] Reines, S. A., Block, G. A., Morris, J. C., Liu, G., Nessly, M. L., Lines, C. R., Norman, B. A., Baranak, C. C. (2004) Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. *Neurology*, **62**, 66-71.
- [140] Reynolds, W. F., Rhees, J., Maciejewski, D., Paladino, T., Sieburg, H., Maki, R. A., Masliah, E. (1999) Myeloperoxidase polymorphism is associated with gender specific risk for Alzheimer's disease. *Exp. Neurol.*, **155**, 31-41.
- [141] Ringman, J. M., Frautschy, S. A., Cole, G. M., Masterman, D. L., Cummings, J. L. (2005) A potential role of the curry spice curcumin in Alzheimer's disease. *Curr. Alzheimer Res.*, **2**, 131-136.
- [142] Risner, M. E., Saunders, A. M., Altman, J. F., Ormandy, G. C., Craft, S., Foley, I. M., Zvartau-Hind, M. E., Hoford, D. A., Roses, A. D. (2006) Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics J.*, **6**, 246-254.
- [143] Riviere, C., Richard, T., Quentin, L., Krisa, S., Merillon, J. M., Monti, J. P. (2007) Inhibitory activity of stilbenes on Alzheimer's beta-amyloid fibrils *in vitro*. *Bioorg. Med. Chem.*, **15**, 1160-1167.
- [144] Robinson, D. M., Keating, G. M. (2006) Memantine: a review of its use in Alzheimer's disease. *Drugs*, **66**, 1515-1534.
- [145] Rogers, J., Cooper, N. R., Webster, S., Schultz, J., McGeer, P. L., Styren, S. D., Civin, W. H., Brachova, L., Bradt, B., Ward, P., Lieberburg, I. (1992) Complement activation by beta-amyloid in Alzheimer disease. *Proc. Natl. Acad. Sci. USA*, **89**, 10016-20.
- [146] Rogers, J., Kirby, L. C., Hempelman, S. R., Berry, D. L., McGeer, P. L., Kaszniak, A. W., Zaluski, J., Cofield, M., Mansukhani, L., Willson, P. (1993) Clinical trial of indomethacin in Alzheimer's disease. *Neurology*, **43**, 1609-1611.
- [147] Rogers, J., Luber-Narod, J., Styren, S. D., Civin, W. H. (1988) Expression of immune system-associated antigens by cells of the human central nervous system: relationship to the pathology of Alzheimer's disease. *Neurobiol. Aging*, **9**, 339-349.
- [148] Roher, A. E., Esh, C., Kokjohn, T. A., Kalback, W., Luehrs, D. C., Seward, J. D., Sue, L. I., Beach, T. G. (2003) Circle of willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. *Arterioscler. Thromb. Vasc. Biol.*, **23**, 2055-2062.
- [149] Rota, E., Bellone, G., Rocca, P., Bergamasco, B., Emanuelli, G., Ferrero, P. (2006) Increased intrathecal TGF-beta1, but not IL-12, IFN-gamma and IL-10 levels in Alzheimer's disease patients. *Neuro. Sci.*, **27**, 33-39.
- [150] Sadeghi, K., Wessner, B., Lagner, U., Ploder, M., Tamandl, D., Friedl, J., Zugel, U., Steinmeyer, A., Pollak, A., Roth, E., Boltz-Nitulescu, G., Spittler, A. (2006) Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. *Eur. J. Immunol.*, **36**, 361-370.
- [151] Sagi, S. A., Weggen, S., Eriksen, J., Golde, T. E., Koo, E. H. (2003) The non-cyclooxygenase targets of non-steroidal anti-inflammatory drugs, lipoxigenases, peroxisome proliferator-activated receptor, inhibitor of kappa B kinase, and NF kappa B, do not reduce amyloid beta 42 production. *J. Biol. Chem.*, **278**, 31825-31830.
- [152] Saito, T., Iwata, N., Tsubuki, S., Takaki, Y., Takano, J., Huang, S. M., Suemoto, T., Higuchi, M., Saido, T. C. (2005) Somatostatin regulates brain amyloid beta peptide Abeta42 through modulation of proteolytic degradation. *Nat. Med.*, **11**, 434-439.
- [153] Savaskan, E., Olivieri, G., Meier, F., Seifritz, E., Wirz-Justice, A., Muller-Spahn, F. (2003) Red wine ingredient resveratrol protects from beta-amyloid neurotoxicity. *Gerontology*, **49**, 380-383.
- [154] Scapagnini, G., Colombrina, C., Amadio, M., D'Agata, V., Arcelli, E., Sapienza, M., Quattrone, A., Calabrese, V. (2006) Curcumin activates defensive genes and protects neurons against oxidative stress. *Antioxid. Redox. Signal.*, **8**, 395-403.
- [155] Scharf, S., Mander, A., Ugoni, A., Vajda, F., Christophidis, N. (1999) A double-blind, placebo-controlled trial of diclofenac/misoprostol in Alzheimer's disease. *Neurology*, **53**, 197-201.
- [156] Schenk, D., Barbour, R., Dunn, W., Gordon, G., Grajeda, H., Guido, T., Hu, K., Huang, J., Johnson-Wood, K., Khan, K., Kholodenko, D., Lee, M., Liao, Z., Lieberburg, I., Motter, R., Mutter, L., Soriano, F., Shopp, G., Vasquez, N., Vandever, C., Walker, S., Wogulis, M., Yednock, T., Games, D., Seubert, P. (1999) Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature*, **400**, 173-177.
- [157] Seabrook, T. J., Jiang, L., Maier, M., Lemere, C. A. (2006) Minocycline affects microglia activation, Abeta deposition, and behavior in APP-tg mice. *Glia*, **53**, 776-782.
- [158] Sharma, S., Chopra, K., Kulkarni, S. K., Agrewala, J. N. (2007) Resveratrol and curcumin suppress immune response through CD28/CTLA-4 and CD80 co-stimulatory pathway. *Clin. Exp. Immunol.*, **147**, 155-163.
- [159] Shie, F. S., Montine, K. S., Breyer, R. M., Montine, T. J. (2005) Microglial EP2 as a new target to increase amyloid beta phagocytosis and decrease amyloid beta-induced damage to neurons. *Brain Pathol.*, **15**, 134-138.
- [160] Shytle, R. D., Mori, T., Townsend, K., Vendrame, M., Sun, N., Zeng, J., Ehrhart, J., Silver, A. A., Sanberg, P. R., Tan, J. (2004) Cholinergic modulation of microglial activation by alpha 7 nicotinic receptors. *J. Neurochem.*, **89**, 337-343.
- [161] Siddiqui, A. M., Cui, X., Wu, R., Dong, W., Zhou, M., Hu, M., Simms, H. H., Wang, P. (2006) The anti-inflammatory effect of curcumin in an experimental model of sepsis is mediated by up-regulation of peroxisome proliferator-activated receptor-gamma. *Crit. Care Med.*, **34**, 1874-1882.
- [162] Sparks, D. L., Sabbagh, M. N., Connor, D. J., Lopez, J., Launer, L. J., Browne, P., Wasser, D., Johnson-Traver, S., Lochhead, J., Ziolkowski, C. (2005) Atorvastatin for the treatment of mild to moderate Alzheimer disease: preliminary results. *Arch. Neurol.*, **62**, 753-757.
- [163] Stewart, W. F., Kawas, C., Corrada, M., Metter, E. J. (1997) Risk of Alzheimer's disease and duration of NSAID use. *Neurology*, **48**, 626-632.
- [164] Storer, P. D., Xu, J., Chavis, J., Drew, P. D. (2005) Peroxisome proliferator-activated receptor-gamma agonists inhibit the activation of microglia and astrocytes: implications for multiple sclerosis. *J. Neuroimmunol.*, **161**, 113-122.
- [165] Sung, S., Yang, H., Uryu, K., Lee, E. B., Zhao, L., Shineman, D., Trojanowski, J. Q., Lee, V. M., Pratico, D. (2004) Modulation of nuclear factor-kappa B activity by indomethacin influences A beta levels but not A beta precursor protein metabolism in a model of Alzheimer's disease. *Am. J. Pathol.*, **165**, 2197-2206.
- [166] Tan, N. S., Michalik, L., Desvergne, B., Wahli, W. (2005) Multiple expression control mechanisms of peroxisome proliferator-activated receptors and their target genes. *J. Steroid Biochem. Mol. Biol.*, **93**, 99-105.
- [167] Taniura, H., Ito, M., Sanada, N., Kuramoto, N., Ohno, Y., Nakamichi, N., Yoneda, Y. (2006) Chronic vitamin D3 treatment protects against neurotoxicity by glutamate in association with upregulation of vitamin D receptor

- mRNA expression in cultured rat cortical neurons. *J. Neurosci. Res.*, **83**, 1179-1189.
- [168] Tanzi, R. E., Bertram, L. (2005) Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. *Cell*, **120**, 545-555.
- [169] ten Bokum, A. M., Hofland, L. J., van Hagen, P. M. (2000) Somatostatin and somatostatin receptors in the immune system: a review. *Eur. Cytokine Netw.*, **11**, 161-176.
- [170] Thal, D. R., Arendt, T., Waldmann, G., Holzer, M., Zedlick, D., Rub, U., Schober, R. (1998) Progression of neurofibrillary changes and PHF-tau in end-stage Alzheimer's disease is different from plaque and cortical microglial pathology. *Neurobiol. Aging*, **19**, 517-525.
- [171] van Gool, W. A., Weinstein, H. C., Scheltens, P., Walstra, G. J. (2001) Effect of hydroxychloroquine on progression of dementia in early Alzheimer's disease: an 18-month randomised, double-blind, placebo-controlled study. *Lancet*, **358**, 455-460.
- [172] van Westerloo, D. J., Giebelen, I. A., Florquin, S., Daalhuisen, J., Bruno, M. J., de Vos, A. F., Tracey, K. J., van Der, P. T. (2005) The cholinergic anti-inflammatory pathway regulates the host response during septic peritonitis. *J. Infect. Dis.*, **191**, 2138-2148.
- [173] van Zyl, J. M., Basson, K., Krieger, A., van der Walt, B. J. (1991) Mechanisms by which clofazimine and dapsone inhibit the myeloperoxidase system. A possible correlation with their anti-inflammatory properties. *Biochem. Pharmacol.*, **42**, 599-608.
- [174] Veldman, C. M., Cantorna, M. T., DeLuca, H. F. (2000) Expression of 1,25-dihydroxyvitamin D(3) receptor in the immune system. *Arch. Biochem. Biophys.*, **374**, 334-338.
- [175] Versijpt, J. J., Dumont, F., Van Laere, K. J., Decoo, D., Santens, P., Aude-naert, K., Achten, E., Slegers, G., Dierckx, R. A., Korf, J. (2003) Assessment of neuroinflammation and microglial activation in Alzheimer's disease with radiolabelled PK11195 and single photon emission computed tomography. A pilot study. *Eur. Neurol.*, **50**, 39-47.
- [176] Walker, D. G., Kim, S. U., McGeer, P. L. (1995) Complement and cytokine gene expression in cultured microglia derived from postmortem human brains. *J. Neurosci. Res.*, **40**, 478-493.
- [177] Walker, D. G., Link, J., Lue, L. F., Dalsing-Hernandez, J. E., Boyes, B. E. (2006) Gene expression changes by amyloid β peptide-stimulated human postmortem brain microglia identify activation of multiple inflammatory processes. *J. Leukoc. Biol.*, **79**, 596-610.
- [178] Walker, D. G., Lue, L. F. (2005) Investigations with cultured human microglia on pathogenic mechanisms of Alzheimer's disease and other neurodegenerative diseases. *J. Neurosci. Res.*, **81**, 412-425.
- [179] Wang, H., Yu, M., Ochani, M., Amella, C. A., Tanovic, M., Susarla, S., Li, J. H., Wang, H., Yang, H., Ulloa, L., Al-Abed, Y., Czura, C. J., Tracey, K. J. (2003) Nicotinic acetylcholine receptor $\alpha 7$ subunit is an essential regulator of inflammation. *Nature*, **421**, 384-388.
- [180] Wang, J., Ho, L., Zhao, Z., Serer, I., Humala, N., Dickstein, D. L., Thiyagarajan, M., Percival, S. S., Talcott, S. T., Pasinetti, G. M. (2006) Moderate consumption of Cabernet Sauvignon attenuates Abeta neuropathology in a mouse model of Alzheimer's disease. *FASEB J.*, **20**, 2313-2320.
- [181] Weggen, S., Eriksen, J. L., Das, P., Sagi, S. A., Wang, R., Pietrzik, C. U., Findlay, K. A., Smith, T. E., Murphy, M. P., Bulter, T., Kang, D. E., Marquez-Sterling, N., Golde, T. E., Koo, E. H. (2001) A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. *Nature*, **414**, 212-216.
- [182] Weggen, S., Eriksen, J. L., Sagi, S. A., Pietrzik, C. U., Golde, T. E., Koo, E. H. (2003) Abeta42-lowering nonsteroidal anti-inflammatory drugs preserve intramembrane cleavage of the amyloid precursor protein (APP) and ErbB-4 receptor and signaling through the APP intracellular domain. *J. Biol. Chem.*, **278**, 30748-30754.
- [183] Weggen, S., Eriksen, J. L., Sagi, S. A., Pietrzik, C. U., Ozols, V., Fauq, A., Golde, T. E., Koo, E. H. (2003) Evidence that nonsteroidal anti-inflammatory drugs decrease amyloid β 42 production by direct modulation of gamma-secretase activity. *J. Biol. Chem.*, **278**, 31831-31837.
- [184] Winblad, B., Wimo, A., Engedal, K., Soininen, H., Verhey, F., Waldemar, G., Wetterholm, A. L., Haglund, A., Zhang, R., Schindler, R. (2006) 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. *Dement. Geriatr. Cogn. Disord.*, **21**, 353-363.
- [185] Wu, A., Ying, Z., Gomez-Pinilla, F. (2006) Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. *Exp. Neurol.*, **197**, 309-317.
- [186] Wu, D. C., Jackson-Lewis, V., Vila, M., Tieu, K., Teismann, P., Vadseth, C., Choi, D. K., Ischiropoulos, H., Przedborski, S. (2002) Blockade of microglial activation is neuroprotective in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson disease. *J. Neurosci.*, **22**, 1763-1771.
- [187] Xiang, Z., Haroutunian, V., Ho, L., Purohit, D., Pasinetti, G. M. (2006) Microglia activation in the brain as inflammatory biomarker of Alzheimer's disease neuropathology and clinical dementia. *Dis. Markers*, **22**, 95-102.
- [188] Xiang, Z., Ho, L., Valdeleon, J., Borchelt, D., Kelley, K., Spielman, L., Aisen, P. S., Pasinetti, G. M. (2002) Cyclooxygenase (COX)-2 and cell cycle activity in a transgenic mouse model of Alzheimer's disease neuropathology. *Neurobiol. Aging*, **23**, 327-334.
- [189] Xiang, Z., Ho, L., Yemul, S., Zhao, Z., Qing, W., Pompl, P., Kelley, K., Dang, A., Qing, W., Teplow, D., Pasinetti, G. M. (2002) Cyclooxygenase-2 promotes amyloid plaque deposition in a mouse model of Alzheimer's disease neuropathology. *Gene Expr.*, **10**, 271-278.
- [190] Yang, F., Lim, G. P., Begum, A. N., Ubeda, O. J., Simmons, M. R., Ambegaokar, S. S., Chen, P. P., Kaye, R., Glabe, C. G., Frautschi, S. A., Cole, G. M. (2005) Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid *in vivo*. *J. Biol. Chem.*, **280**, 5892-5901.
- [191] Yasojima, K., Schwab, C., McGeer, E. G., McGeer, P. L. (1999) Distribution of cyclooxygenase-1 and cyclooxygenase-2 mRNAs and proteins in human brain and peripheral organs. *Brain Res.*, **830**, 226-236.
- [192] Yermakova, A. V., O'Banion, M. K. (2001) Downregulation of neuronal cyclooxygenase-2 expression in end stage Alzheimer's disease. *Neurobiol. Aging*, **22**, 823-836.
- [193] Yermakova, A. V., Rollins, J., Callahan, L. M., Rogers, J., O'Banion, M. K. (1999) Cyclooxygenase-1 in human Alzheimer and control brain: quantitative analysis of expression by microglia and CA3 hippocampal neurons. *J. Neuropathol. Exp. Neurol.*, **58**, 1135-1146.
- [194] Yeung, F., Hoberg, J. E., Ramsey, C. S., Keller, M. D., Jones, D. R., Frye, R. A., Mayo, M. W. (2004) Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. *EMBO J.*, **23**, 2369-2380.
- [195] Yip, A. G., Green, R. C., Huyck, M., Cupples, L. A., Farrer, L. A. (2005) Nonsteroidal anti-inflammatory drug use and Alzheimer's disease risk: the MIRAGE Study. *BMC Geriatr.*, **5**, 2.
- [196] Zamrini, E., McGwin, G., Roseman, J. M. (2004) Association between statin use and Alzheimer's disease. *Neuroepidemiology*, **23**, 94-98.
- [197] Zandi, P. P., Sparks, D. L., Khachaturian, A. S., Tschanz, J., Norton, M., Steinberg, M., Welsh-Bohmer, K. A., Breitner, J. C. (2005) Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. *Arch. Gen. Psychiatry*, **62**, 217-224.
- [198] Zhao, Y., Patzer, A., Herdegen, T., Gohlke, P., Culman, J. (2006) Activation of cerebral peroxisome proliferator-activated receptors gamma promotes neuroprotection by attenuation of neuronal cyclooxygenase-2 overexpression after focal cerebral ischemia in rats. *FASEB J.*, **20**, 1162-1175.
- [199] Zhou, Y., Su, Y., Li, B., Liu, F., Ryder, J. W., Wu, X., Gonzalez-DeWhitt, P. A., Gelfanova, V., Hale, J. E., May, P. C., Paul, S. M., Ni, B. (2003) Nonsteroidal anti-inflammatory drugs can lower amyloidogenic Abeta42 by inhibiting Rho. *Science*, **302**, 1215-1217.
- [200] Zimmermann, M., Gardoni, F., Di, L. M. (2005) Molecular rationale for the pharmacological treatment of Alzheimer's disease. *Drugs Aging*, **22**(Suppl. 1), 27-37.
- [201] Zlokovic, B. V. (2005) Neurovascular mechanisms of Alzheimer's neurodegeneration. *Trends Neurosci.*, **28**, 202-208.