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REVIEW ARTICLE

Targeting Neuroinflammation to Treat Alzheimer's Disease

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Abstract Over the past few decades, research on Alzheimer's disease (AD) has focused on pathomechanisms linked to two of the major pathological hallmarks of extracellular deposition of beta-amyloid peptides and intra-neuronal formation of neurofibrils. Recently, a third disease component, the neuroinflammatory reaction mediated by cerebral innate immune cells, has entered the spotlight, prompted by findings from genetic, pre-clinical, and clinical studies. Various proteins that arise during neurodegeneration, including beta-amyloid, tau, heat shock proteins, and chromogranin, among others, act as danger-associated molecular patterns, that—upon engagement of pattern recognition receptors—induce inflammatory signaling pathways and ultimately lead to the production and release of immune mediators. These may have beneficial effects but ultimately compromise neuronal function and cause cell death. The current review, assembled by participants of the Chiclana Summer School on

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Neuroinflammation 2016, provides an overview of our current understanding of AD-related immune processes. We describe the principal cellular and molecular players in inflammation as they pertain to AD, examine modifying factors, and discuss potential future therapeutic targets.

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Key Points

Neuroinflammation plays an important part in the pathogenesis of Alzheimer's disease (AD), with both positive and negative consequences.

Induction of inflammatory signaling pathways leads to the production and release of immune mediators, which ultimately compromises neuronal function and causes cell death.

Anti-inflammatory therapeutic approaches to modify AD progression are the basis for ongoing and future therapeutic trials in this area.

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1 Introduction

Dementias and related diseases of cognitive decline pose an enormous and growing disease burden on our societies and health economies. According to the most recent World Health Organization (WHO) global disease burden report [1], deaths from neurological diseases have risen by 114% over the past 20 years to 1.2 million in 2010. The increase is largely driven by neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease and by an aging population in general. Not surprisingly, the development of strategies to curb this frightening surge is a high priority for life science research. The responsible allocation of these resources requires the identification of valid therapeutic targets. The immune system is particularly alluring in this regard.

How the immune system and peripheral infections contribute to cognitive decline remains incompletely understood, but the past 15 years have established a key role for inflammation in the progression of age-related neurodegeneration. The immune privilege of the brain is

clearly not absolute, and cells of the central nervous system (CNS) are sensitive to inflammatory events occurring both within and outside of the brain.

We summarize the current state of neuroinflammation research from cellular to molecular mechanisms, as they pertain to the pathogenesis of AD. Further, we outline leverage points for preventive strategies and therapeutic approaches to stem the daunting surge in dementia diseases facing our society.

2 Cellular Players

2.1 Microglia

Microglia are the principal innate immune cells in the brain, and they are often considered the macrophages of the CNS. Recent studies have shed light on their origin from erythromyeloid progenitors from the yolk sac [2, 3], which migrate into the brain at embryonic day 7.5 where they further differentiate into microglial cells [2]. Microglia exhibit the capacity of self-renewal within the brain [4, 5], likely arising from a newly identified progenitor [6]. Microglia continuously survey their microenvironment and monitor ongoing synaptic activity, including synapse remodeling, debris clearance, and trophic support for neurons. In addition, they drive a major part of the innate immune response. Microglia react to pathological triggers via pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) [7–9].

Microglia are also phagocytic cells and can ingest amyloid β (Aβ) through a range of cell surface receptors, including cluster of differentiation (CD)-14, toll-like receptor (TLR)-2, TLR4, α6β1 integrin, CD47, and scavenger receptors, such as CD36 [10–13]. It has been suggested that, in AD, a key factor in the accumulation of Aβ throughout the brain is the failure of microglia to remove extracellular amyloid [14–16]. Indeed, in cortical tissue specimens from patients with AD, the microglia surrounding plaques are impaired at Aβ uptake [15, 17, 18]. Newly developed positron emission tomography (PET) techniques employ radio ligands to detect activated microglia in vivo [19–21]. Many tracers target the 18 kDa translocator protein (TSPO) [19], an outer mitochondrial membrane protein present in microglia, which is upregulated during activation [22–24]. The ^{11}C-PK11195 ligand was the first prototypical TSPO ligand, although second-generation tracers have been developed more recently with improved signal-to-noise ratios [25]. However, a common polymorphism significantly influences the binding affinity of these new compounds [26], thus making genetic screening a necessary step for accurate quantification [27]. TSPO upregulation has been described in prodromal AD

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and in manifest AD dementia, using both ^{11}C-PK11195 [28–31] and second-generation tracers [32–36] in regions known to be affected by AD pathology and beyond. Mixed evidence has emerged regarding the relationship between in vivo microglial activation and Aβ plaque burden [29, 31, 32, 37, 38].

2.2 Astrocytes

Under pathological conditions, astrocytes exhibit morphological changes, including hypertrophy and upregulation of glial fibrillary acidic protein (GFAP). Astrocytes can detect aggregated proteins such as Aβ or respond to inflammatory molecules (e.g., cytokines, chemokines, see below). Indeed, significant astrocyte reactivity has been reported in sporadic [39–41] and familial AD [42]. Similar to microglia, reactive astrocytes can polarize their processes around amyloid plaques and are capable of amyloid plaque degradation [43, 44]. Altered calcium signaling [45], impaired glutamate homeostasis [46, 47], and increased production of inflammatory mediators by astrocytes are also observed in AD.

2.3 Oligodendrocytes

The involvement of oligodendrocytes in AD remains poorly understood, although there is emerging evidence that these cells contribute to the pathogenesis and progression of neurodegenerative disorders, including AD [48]. Bartzokis et al. [49–52] demonstrated that the loss of myelin integrity that normally occurs during aging is strongly aggravated in human presenilin-1 familial, pre-clinical, and sporadic AD cases, particularly near Aβ plaques. In addition, focal loss of oligodendrocytes has been observed in sporadic cases of AD. This demyelination was also found in transgenic mouse models of AD, specifically at the core of Aβ plaques [52]. Focal oligodendrocyte loss has also been detected in Tg2576 and APP/PS1 transgenic mice [52], a phenomenon that may negatively influence cortical processing and neurite formation. Several cellular processes such as neuroinflammation, oxidative stress, and/ or apoptosis may contribute to oligodendrocyte dysfunction and death [52]. In addition, Aβ can impair the survival and maturation of oligodendrocyte progenitor cells and the formation of the myelin sheath [53].

2.4 Myeloid Cells Other than Microglia

In addition to microglia, a variety of other monocytic cells have been found in the brain, including perivascular cells, meningeal macrophages, choroid plexus macrophages, and peripheral blood-derived monocytes [54]. These cells may, under certain circumstances, also phagocytize and degrade amyloid plaques in a transgenic model of AD [55]. Migration of peripheral monocytes is dependent on C-C chemokine receptor type 2 (CCR2), as its ablation in Tg2576 mice results in decreased recruitment of these cells and a corresponding increase in amyloid pathology [56]. In contrast, blocking transforming growth factor (TGF)-β signaling increased peripheral myeloid cell infiltration into the CNS and significantly reduced the amyloid burden [57]. Glatiramer acetate has also been shown to increase recruitment of peripheral monocytes to the CNS, and this reduces amyloid deposition. Ablation of bone marrow-derived myeloid cells in this model exacerbated amyloid pathology [58]. In contrast, when resident microglia were ablated from the APP/PS1 and APP23 mouse models, recruitment of peripheral myeloid cells was not sufficient to clear amyloid load [59, 60]. Furthermore, a recent parabiosis experiment found no evidence of monocyte infiltration around amyloid plaques [61]. Thus, the extent of myeloid infiltration into the brain and its contribution to damage or clearance of pathological proteins is still not fully understood. A particularly critical aspect of this body of work is the complexity and toxicity of experimental approaches used.

3 PAMPs and DAMPs: Inducers and Modulators of Neuroinflammation in Alzheimer's Disease

During periods of pathogen invasion or tissue damage, DAMPs and PAMPs alert the immune system of the host and trigger an appropriate response to the insult.

DAMPs encompass a diverse class of molecules. A well-characterized group of DAMPs consists of intracellular proteins that are expressed at a basal level within a cell and are released after injury. These include high-mobility group protein B1 (HMGB1), S100 proteins, heat shock proteins (HSPs), chromogranin A, and Aβ. A second class of DAMPs comprises nucleic acids and nucleotide derivatives, such as mitochondrial DNA (mt-DNA), DNA, and adenosine triphosphate (ATP) [62]. In contrast, PAMPs mainly include microbial molecules that are normally not present in human cells, such as lipid A, flagellin, lipoproteins from Gram-positive and Gram-negative bacteria, bacterial DNA containing particular CpG motifs, and fragments of bacterial peptidoglycan [63].

Both PAMPs and DAMPs contribute to neuroinflammation in AD. Aβ can induce inflammatory responses [64] via activation of pattern recognition receptors (PRRs) of the innate immune system, including TLR2 [65], TLR4, and TLR6, as well as their co-receptors, CD36, CD14, and CD47. Neutralization by CD14 antibodies can reduce the Aβ-induced microglial activation [66]. Furthermore, the NLRP1 and NLRP3 inflammasome can sense a range of

aggregated proteins, including Aβ [67]. Indeed, lack of NLRP3 and caspase-1 has been shown to protect mice from AD pathology [67, 68].

HMGB1 levels are increased in AD brains and are associated with senile plaques, promoting their stabilization [69]. It has been shown that microglia stimulation by HMGB1 can reduce Aβ phagocytosis [69]. HMGB1 promotes the migration and proliferation of immune cells through binding to advanced glycation end-product receptors (RAGE) and TLRs [70]. HMGB1 can also act in concert with other factors such as chemokines, growth factors, and PAMPs, together promoting immune system activation [71, 72].

Chromogranin A is associated with microglial activation in neurodegeneration [73, 74] and induces the release of interleukin (IL)-1β, indicating that TLRs and the NLRP3 inflammasome are involved in this pathway [75]. In AD, increased levels of chromogranin A have been observed in senile plaque dystrophic neurites [76]. Interestingly, the immune stimulatory potential appears almost identical to bacterial lipopolysaccharide (LPS), at least in vitro [77].

Many S100 proteins are involved in AD, including S100A9, S100A8, and S100B. S100A8 and S100A9 form a complex that is increased in the brain and cerebrospinal fluid (CSF) of patients with AD [78, 79] and can activate microglia through TLR4. Furthermore, S100A8-mediated inflammatory stimuli are connected with the upregulation of the β-site β-amyloid precursor protein (APP)-cleaving enzyme BACE1, which is involved in APP processing [80, 81]. S100B has been observed in both Aβ plaques and in the CSF [82, 83], and overexpression of human S100B exacerbates amyloidosis and gliosis in the Tg2576 AD mouse model [84].

Likewise, mt-DNA and DNA can be released from the cells and act as DAMPs upon entering the blood circulation, causing inflammation [85]. mt-DNA can bind to TLR-9 and mediate the release of tumor necrosis factor (TNF)-α and type I interferons (IFNs) [86]. Moreover, cell free DNA can bind to TLR and non-TLR receptors. Upon TLR binding, DNA activates the nuclear factor (NF)-κB pathway, thereby promoting pro-inflammatory cytokine production [87]. DNA can also bind to the absent in melanoma 2 (AIM2) inflammasome, releasing IL-1β, through the caspase-1 activation pathway.

HSPs bind to several receptors, such as TLR2 and TLR4, resulting in the production of inflammatory cytokines, such as TNFα and IL-1β [88–90]. Furthermore, HSPs may also exert beneficial effects in AD, thus, HSP70 can bind to APP and reduce the secretion of Aβ1-40 and Aβ1-42 through interference with the APP processing pathway [91]. HSP70, together with HSP90, can also interact with tau and Aβ oligomers and degrade them by employing proteasomal degradation [92].

4 Endogenous Modulators

Neurotransmitters such as ATP, glutamate, dopamine, and various neurotrophic factors, e.g., brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), can act as endogenous modulators. Microglial cells are equipped with a plethora of neurotransmitter receptors, which makes them a primary target, particularly as sites of non-synaptic release [93]. In AD, ATP production from neurons declines. Mitochondrial dysfunction, as evidenced by reduced ATP, is related to oxidative stress in AD pathology [94]. Oxidative stress can also initiate inflammatory responses and contributes to the etiopathology of AD [95].

In AD, glutamatergic neurotransmission is disturbed because of an increased amount of soluble Aβ oligomers [96]. The possible inflammatory process occurs subsequently through activation of microglia with TNFα release, synergizing with N-methyl-D-aspartate (NMDA)-mediated neurodegeneration [97]. However, the modulation of glutamate can be either pro- or anti-inflammatory depending on the expression of different groups of glutamate receptors (GluRs) on microglia and, most likely, on astroglial uptake capabilities [98, 99].

Dopamine possibly mediates the activation of microglia by triggering the mitogen-activated protein kinase (MAPK)–NFκB cascade and inducing toxicity versus dopaminergic neurons [100, 101]. In general, acetylcholine prevents the inflammatory response in microglia via α7-nicotinic acetylcholine receptors, mediated by the PLC/IP3/Ca2+ signaling pathway [102]. In patients with AD, significant loss of cholinergic neurons is tightly related to the progression of the disease. Failure in cholinergic neurotransmission decreases the cholinergic input to microglia, which in turn results in microglial activation [103]. In addition, stimulation of microglia with norepinephrine suppressed inflammation through cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling cascades [104, 105]. Of note, the locus ceruleus, the chief source of noradrenaline (NA) in the human brain, degenerates very early in the disease course. Thus, its projection regions, most prominently the limbic system and neocortex, experience decreased levels of NA. Modeling this in rodents increased Aβ-induced inflammation [106, 107] and substantially increased neuronal death and memory deficits [108]. Using 2-photon laser microscopy, it was demonstrated that depletion of NA in APP/PS1 transgenic mice caused complete inhibition of microglial Aβ clearance, and, subsequently, an increase in the number and volume of Aβ deposits [104]. The replenishment of NA levels in the cortex and hippocampal after treatment with L-threo-DOPS, an NA precursor, partly rescued this phenotype.

The levels of BDNF and NGF are severely altered in the brains of patients with AD. BDNF is released by activated microglia and inhibits the release of TNF-α and IFN-γ, whereas it promotes the expression of anti-inflammatory cytokines IL-4, IL-10, and IL-11 [109]. However, an in vitro study has also shown prolonged microglial activation through a positive feedback loop by autocrine BDNF [110], demonstrating that BDNF may modulate inflammation at various levels. In addition, evidence from a human microglial cell line suggested that NGF synthesis is potentially stimulated by inflammatory signals (cytokines and complement factors), as well as by exposure to Aβ25-35, through NFκB-dependent and -independent mechanisms.

5 Inflammatory Mediators

5.1 Cytokines

Cytokines are released by glial cells, such as astrocytes and microglia, upon every inflammatory challenge [111–113]. Many cytokines, such as IL-1β and IL-12, have been related to the progression of AD pathology [114, 115]. Increased IL-1β serum levels have been linked to AD and patients with mild cognitive impairment, a putative prodromal phase of dementia [114, 116]. Several studies have reported associations between IL-1β polymorphisms and the onset of AD pathology [115, 117, 118], linking both IL-1β polymorphisms and apolipoprotein E (APOE)-ϵ4 to higher levels of IL-1β in the blood and sleep disturbance in patients [119]. IL-12 is related to the regulation of the adaptive and the innate immune system [120], and an IL-12 polymorphism has been linked to AD in a Han Chinese population [121]. Vom Berg et al. [122] suggested that inhibition of the IL-12/IL-23 pathway may attenuate AD pathology and cognitive deficits due to a decrease in the IL-12p40 subunit and its receptor activity [122]. In this study, the concentration of IL-12p40 was increased in the CSF of patients with AD. Regarding anti-inflammatory cytokines, IL-10 deletion attenuated AD-related deficits, such as altered synaptic integrity and behavioral deficits in APP/PS1 mice [123]. Chakrabarty et al. [124] showed that the overexpression of IL-10 using adeno-associated viruses (AAVs) increased amyloid deposition, behavioral deficits, and synaptic alterations and impaired microglial phagocytosis of Aβ in the APP transgenic mouse model [124].

Another major regulator of inflammation is TGF-β. Increased TGF-β has been observed in amyloid plaques [125] and in the CSF of patients with AD [126, 127]. However, this cytokine plays a dual role in AD. Overexpression of TGF-β in vivo induces Aβ deposition in cerebral blood vessels, but it may also decrease microgliosis while increasing Aβ phagocytosis [128]. A link between TGF-β and neuro-fibrillary tangles (NFTs) has also been reported [129].

5.2 Chemokines

Chemokines participate in the chemoattraction of immune cells from the periphery to the brain and in the recruitment and activation of resident glial cells. In AD, chemokines are implicated in both the resolution and the propagation of pathology [130]. The most intensively studied chemokines in AD are CX3C chemokine ligand 1 (CX3CL1) and chemokine ligand 2 (CCL2).

CX3CL1, also termed fractalkine, is expressed by neurons, whereas its receptor, CX3CR1, is predominantly expressed by microglia [131, 132]. The participation of this chemokine in the pathophysiology of AD is complex since CX3CL1/CX3CR1 signaling can have a beneficial role in the context of tau pathology [132–135] or a detrimental role in an amyloid context [136]. In fact, in an amyloid model, deficiency of CX3CR1 decreased Aβ deposition [136] but worsened tau pathology and lowered cognitive performance [133, 134]. Moreover, the expression of CX3CL1 has been shown to be increased in tau-injured neurons but decreased in the brains of APP transgenic mice [137]. However, in human patients, the level of CX3CL1 is inversely correlated with AD severity [138]. Together, this may point to the possibility that the same inflammatory mediator may adopt various, if not opposing, effects and properties during disease progression.

CCL2 has also been associated with a dominant role in chronic inflammation [139]. A recent study has demonstrated that the CCL2/CCR2 pathway of astrocyte-induced microglial activation is associated with "M1-polarised" and enhanced microglial activity [140]. In AD, CCL2 levels were increased in mild but not in severe AD, suggesting that elevated CCL2 may play a pathogenic role during early AD stages [141]. In agreement with this, Westin et al. [142] showed that CCL2 is associated with a faster cognitive decline in early disease stages. Kiyota et al. [143] found accelerated neurodegeneration in APP/CCL2 transgenic mice, indirectly suggesting that direct inhibition of CCL2 signaling may modify microglial activation, resulting in lower Aβ deposition and improving behavioral outcomes. CCL2 overexpression accelerated oligomeric and diffuse Aβ deposition and led to spatial and working memory deficits by affecting Aβ seeding in Tg2576 mice [143].

5.3 Other Mediators

Nitric oxide (NO) is synthesized by three different isoforms of NO synthase (NOS). Each isoform plays a role in either

AD progression or prevention, suggesting that NO can be neuroprotective or neurotoxic. High doses of LPS induced robust CNS inflammation and microglia-induced release of NO. NO in the CNS can influence many signaling pathways, including protein nitrosylation, impairment of long-term potentiation, or inhibition of mitochondrial respiration. The impact of NO signaling depends on the local cellular environment. In the AD brain, NO mainly derives from the inducible isoform of NOS, NOS2, which is expressed by neurons [144], microglia, and astrocytes [145]. Nitrosative stress has been shown to affect all types of cellular proteins, including, but not restricted to, synaptic proteins. Post-translational protein modification can take place either by s-nitrosylation of cysteine residues or by nitration of tyrosine residues. Importantly, Aβ itself represents a nitration target at tyrosine 10 of its amino acid sequence. Nitration at this position strongly increases the peptide's propensity to aggregate, and nitrated Aβ predominantly resides in the core of the deposits, suggesting that this mechanism contributes to the initiation of deposition [146].

6 Effect of Neuroinflammation on Neuronal Function

6.1 Cytokines and Synaptic Scaling

Synaptic plasticity is strongly influenced by basal levels of cytokines [147]. Emblematic is the case of "synaptic scaling," a well-defined form of homeostatic plasticity that regulates the density of GluRs at presynaptic and postsynaptic sites [148]. A homeostatic reduction of neuronal excitability by withdrawal of GluRs is termed down-scaling, whereas the increase of neuronal excitability (by accumulation of GluRs) is known as up-scaling. TNFα has been shown to support synaptic up-scaling by increasing AMPA receptor-dependent miniature excitatory postsynaptic currents (mEPSC). Importantly, TNFα required for up-scaling synapses is derived from glial cells [149] and not from neurons themselves. Such evidence implies that glial cells are able to release cytokines in response to changes in neuronal activity. By contrast, enhanced release of inflammatory cytokines, for instance during chronic peripheral inflammation, can disrupt the physiological mechanisms of synaptic plasticity, promoting neuronal hyper-excitability and increased susceptibility to seizure generation [150].

A growing body of evidence demonstrates that microglia can actively respond to increased neuronal excitability, and microglial processes make physical contact with excitatory synapses [151–154]. This type of microglia–synapse interaction has been shown to reduce neuronal excitability [110, 155], potentially as a form of a regulatory mechanism for preventing glutamatergic excitotoxicity [152].

6.2 Microglia and Synaptic Pruning

Microglia can actively participate in remodeling synaptic connections ("synaptic pruning"). A pathological form of synaptic pruning may represent a commonly shared mechanism among several neurological conditions of different nature: a recent study in a murine model of chronic stress, showed electron-dense (dark) microglia co-localized with synaptic terminals. This microglial phenotype associated with synaptic pruning appeared clearly reactive, possibly accounting for an increased loss of synapses during chronic inflammation [156]. Microglia may also remove synapses in a complement-dependent manner in a mouse model of West Nile virus-induced neuroinflammation [157]. Mice with either a deficit in the number of microglia (IL-34$^{-/-}$) or a deficiency of complement components (such as C3 protein or complement receptor 3 knock-out) were protected from inflammation-induced synaptic loss [157].

An alternative hypothesis suggests that pathological pruning of synapses during inflammation may also represent a form of "tissue remodeling" for auto-protective purposes [158]. A study suggested that upon LPS injection, microglia pruned preferentially GABAergic terminals, thereby increasing excitatory synaptic activity and induction of neurotrophic pathways in downstream neurons. This mechanism has been interpreted as an attempt to promote neuronal viability in a pathological context, although the price was a temporary imbalance of synaptic connectivity [159].

In mouse models of Aβ deposition, complement protein C1q was elevated as early as 1 month of age in both DG and frontal cortex. At this timepoint, neither plaques nor synaptic loss are detectable. At a later age (mice aged 3–4 months), the number of synapses decreased significantly; however, synaptic loss was rescued almost completely in the absence of either C1q, C3, or CR3. Additionally, intracerebroventricular (ICV) injection of oligomeric Aβ in wild-type mice induced synapse loss and activated a phagocytic phenotype in microglia. Moreover, synapse loss in response to oligomeric Aβ was not observed in C1q or CR3 knock-out mice [160] (Table 1).

Similar findings have been obtained in a mouse model deficient for the *progranulin* gene, typically associated with frontotemporal dementia (FTD) in humans [161, 162]. Lack of progranulin has been shown to trigger an exaggerated inflammatory reaction in microglia and macrophages [161, 163]. Interestingly, the brains of *progranulin*-deficient mice showed increased levels of complement

Table 1 Randomized clinical trials of non-steroidal anti-inflammatory drugs in patients with Alzheimer's disease

Drug	Trial details (phase, design, duration of treatment)	Participants	Primary endpoint (s)	Main effect	References
Aspirin 75 mg od	Phase III, randomized open-label, 3 years	310 AD pts	MMSE and BADLs	No effect on cognition, increased risk of bleeds	[388]
Indomethacin 100–150 mg od vs. PL	Pilot study, randomized 1:1, 6 months	28 AD dementia pts	Psychometric tests	Positive effects on a battery of psychometric tests	[357]
Indomethacin 100 mg od with omeprazole vs. PL	Pilot study, randomized 1:1, 1 year	51 pts with mild-to-moderate AD	ADAS-cog score	Not significant effect on ADAS-cog score	[389]
Naproxen sodium or rofecoxib 220 mg naproxen bid or rofecoxib 25 mg od vs. PL	Phase III, randomized 1:1, 1 year	351 pts with mild-to-moderate AD	ADAS-cog score	Not significant effect on ADAS-cog score	[390]
Nimesulide 100 mg bid vs. PL	Pilot study, randomized 1:1 and open-label, 3 months	40 AD dementia pts	Tolerability and short-term cognitive/behavioral effects	Not apparent effect on a composite of cognitive, behavioral and functional outcomes	[391]
Rofecoxib 25 mg od vs. PL	Phase III, randomized 1:1, 4 years	1457 MCI pts	Annual AD diagnosis	Lower annual AD diagnosis but no significant effect on ADAS-cog score	[392, 393]
Celecoxib or naproxen sodium 100 mg bid or naproxen sodium 220 mg bid vs. PL	Phase III, randomized 1:1:1.5, 1–3 years	2528 healthy individuals with family history of AD	Seven tests of cognitive function and a global summary score measured annually	Not significant effect on a battery of neuropsychological tests	[394] ADAPT study
Celecoxib or naproxen sodium, follow-up ADAPT study	2–4 years follow-up after termination of treatment	2071 participants randomized in ADAPT	Incidence of AD	Not significant effect for celecoxib. Reduced AD onset and CSF tau to Aβ1-42 ratio for naproxen	[358]
Celecoxib or naproxen sodium follow-up	5–7 years follow-up after termination of treatment	1537 participants randomized in ADAPT	Cognitive evaluation test scores	Not significant delay on onset of AD	[395]

AD Alzheimer's disease, *ADAPT* Alzheimer's Disease Anti-inflammatory, *ADAS-cog* Alzheimer Disease Assessment Scale-cognitive portion, *BADLs* basic activities of daily living, *bid* twice daily, *CSF* cerebrospinal fluid, *MCI* mild cognitive impairment, *MMSE* Mini-Mental State Examination, *od* once daily, *PL* placebo, *pt(s)* patient(s)

Adapted from Heneka et al. [396]

proteins, a prominent pro-phagocytic activation of microglia, and enhanced pruning of synapses [164].

6.3 Inflammation and Neurogenesis

Under homeostasis, immunological signals can actively shape adult neurogenesis. Microglia were shown to rapidly engulf and remove apoptotic neuronal progenitors, remarkably, without any trace of inflammatory reaction [165, 166]. Other evidence has pinpointed a close interplay between different immune proteins and the neurogenic process [167, 168]. IL-1β has often received particular

attention because of its anti-neurogenic activity [169–175]. One may assume that microglia are primarily responsible for this reduction of neurogenesis during inflammatory challenges. An interesting molecular player is the CX3C axis between neurons and microglia, which is known to preserve the microglial "resting" phenotype under physiological conditions [176, 177]. Several consistent findings showed reduced neurogenesis in CX3CR1-deficient mice, along with increased NF-κB activation and IL-1β expression in microglia [178–181]. Consistently, when an inflammatory challenge is applied under CX3CR1-deficient conditions, microglia release an increased and uncontrolled

amount of inflammatory mediators and free radicals, causing neurotoxicity and cognitive/behavioral deficits [132, 182]. Interestingly, during ageing, neurons decrease expression of CX3CL1 [183], which likely would result in a general downregulation of the CX3C axis and pro-inflammatory skewing of microglia [184, 185]. Pro-inflammatory microglial priming has been suggested as a possible mechanism leading to the dysregulated microglial function and the ensuing stepwise decline of neurogenesis (and potentially neurodegeneration) during senility [186–192]. In contrast, several lines of evidence point towards the pro-neurogenic function of microglia, especially during the period of early brain development. These indications suggest that microglia play an important role during brain development, axonal guidance, and formation of neuronal networks.

6.4 Astrocytes and Glutamate Reuptake

In the CNS, extracellular levels of glutamate are tightly regulated by astrocytes in order to modulate GluR activity and prevent potential excitotoxicity [193]. Once in the synaptic cleft, excess glutamate is promptly scavenged by the excitatory amino acid transporters (EAATs) expressed on both neurons and astrocytes [194]. The astrocytic EAAT2 is thought to be responsible for about 90% of all glutamate uptake in the brain [195, 196]. There are no synaptic enzymes that otherwise would degrade glutamate. Therefore, astrocyte-mediated glutamate uptake represents the primary mechanism for the homeostatic regulation of glutamate bioavailability [197]. Impairment of glutamate uptake causes excitotoxicity characterized by overload of cellular calcium, generation of free radicals, and protein/lipid oxidation. Notably, astrocyte glutamate transporters (EAAT1 and EAAT2) were shown to be reduced in the cortex and hippocampus of patients with AD [46, 198]. Moreover, Aβ-induced neurotoxicity in vivo has been associated with NMDA receptor-dependent excitotoxicity [199]. In conclusion, pharmaceutical compounds aiming to modulate glutamate excitotoxicity have revealed a certain therapeutic potential for neurodegenerative diseases (Table 2).

6.5 Function and Dysfunction of the Blood–Brain Barrier

Dysfunction of the blood–brain barrier (BBB) is a relatively new frontier in AD research [200–202]. The fully functional BBB is a highly specialized monolayer of endothelial cells lining the cerebrovasculature and separating the circulating blood from the brain parenchyma. The integrity of the BBB depends critically on the functional state of the associated pericytes, astrocytes, and

microglia and is compromised during neuroinflammation [203]. Aβ binds to low-density lipoprotein receptor-related protein-1 (LPR1) on the endothelial cells of the brain capillaries and is then released into the bloodstream [204, 205]. Vice versa, in the BBB, RAGE are upregulated with aging and facilitate the influx of Aβ from the blood into the brain [206]. Deficient Aβ clearance from the brain parenchyma is thus proposed to be, at least in part, the result of its faulty transport across the BBB [207–209].

7 Modifiable Risk Factors for AD

A plethora of exogenous factors exert both beneficial and detrimental modulating effects on the inflammatory state of an organism. This, in turn, has direct and important consequences for the risk of developing AD. As these factors are amenable to non-pharmacological interventions and can be mitigated (or promoted) by preventive measures or lifestyle choices, they deserve special attention.

7.1 Infections

The evidence pointing to infections as risk factors for AD stems from epidemiological and neuropathological studies. Prospective cohort studies show that infection represents an important risk factor in the progression of dementia and AD [210, 211]. A case–control study suggested that multiple infections double the risk of developing dementia [212]. In studies of a large AD patient cohort, peripheral infection was associated with accelerated cognitive decline [213, 214]. Conversely, the frequency of various infections, including urinary and respiratory tract infections is higher among individuals with AD than among healthy, age-matched controls [215]. Indeed, pneumonia is one of the most common causes of death in AD [204, 205, 216–218]. In contrast, vaccination against influenza and other infectious conditions is associated with a significantly lower risk of developing AD [219, 220].

A number of specific viral, bacterial, and fungal infections has been detected by polymerase chain reaction (PCR) in human AD brain tissue and have been implicated in AD development. One example is herpes simplex virus type 1 (HSV-1) [221–223], which is an AD risk factor in people carrying the *APOE4* allele [224, 225]. Chlamydia pneumonia, a Gram-negative bacteria, has been detected via PCR in the brain tissue of patients with AD [226, 227], where it was found to have infected microglia, astrocytes, and neurons [227]. Interestingly, fungal proteins and DNA have been identified in the brain tissue and CSF of patients with AD [228, 229]. In postmortem AD brains, co-infection with many fungi has also been reported, with fungal material identified inside neuronal cells and in many

Table 2 Clinical trials of non-non-steroidal anti-inflammatory drugs in patients with Alzheimer's disease

Drug and dosage regimen	Trial details (phase, design, duration of treatment)	Participants	Primary endpoint (s)	Main effect	Reference
PPARγ antagonists					
RSG 2, 4, or 8 mg od vs. PL	Phase III, ran 1:1, 24 wk	511 pts mild-to-moderate AD	ADAS-Cog and CIBIC + in ITT population	Significant interaction between *APOEε4* allele status and ADAS-cog. Significant improvement in ADAS-cog in APOEε4-negative pts on RSG 8 mg	[371]
PIO 15–30 mg od	Pilot study, ran, ol, 6 mo	42 pts mild AD	rCBF and plasma levels of Aβ40 and Aβ42	Improved cognition and rCBF in parietal lobe	[367]
PIO 45 mg od vs. PL, and Vit. E 200 IU od	Pilot study, ran 1:1, 18 mo	25 pts probable AD	Frequency of reported AEs	Principal AE was peripheral edema (28.6% PIO vs. 0% PL)	[369]
PIO	Pro cohort study, 6 y	145,928 subjects aged ≥ 60 y		Long-term use of PIO reduced dementia risk by 47%	[368]
RSG od PL, 2 or 8 mg RSG XR or DON 10 mg (control)	Phase III, ran 1:1, 24 wk	639 pts probable AD	Change in ADAS-Cog score and CIBIC+	Significant difference CIBIC+. Peripheral edema was the most common AE for RSG XR 8 mg (15%)	[397]
RSG 4 mg od vs. PL	Pilot study, ran 1:1, 6 mo	30 subjects mild AD or amnestic MCI	Cognitive performance and plasma Aβ levels	Better delayed recall (at 4 and 6 mo) and selective attention (6 mo)	[370]
RSG 2 or 8 mg od	Phase III, ran 1:1 48 wk	2981 pts mild-to-moderate AD	Change from baseline in ADAS-cog and CDR-SB scores	Relevant differences between treatment groups	[398]
TNFα inhibitors					
Perispinal ETA 25–50 mg ow	pro, single-center, ol, pilot (proof-of-concept) study, 6 mo	15 pts mild-to-severe AD	MMSE, ADAS-cog, SIB	Significant improvement by all primary efficacy variables	[373]
Perispinal ETA 25–50 mg ow	pro, single-center, ol, pilot study, 6 mo	12 pts mild-to-severe AD	California Verbal Learning Test-Second Edition, Adult Version; WMS-LM-II, TMT; Boston Naming Test FAS, and category verbal fluency	Significant improvement by all primary efficacy variables except Boston Naming Test	[372]
SC ETA 50 mg ow	Pilot study, ran 1:1, 24 wk	41 pts mild to moderate AD	Cognition, global function, behavior, systemic cytokine levels	Trends but no statistically significant changes in cognition, behavior, or global function	[399]
Microglia inhibitor					
ITA (CHF5074; CSP1103) 200, 400 or 600 mg od or PL	Pilot study, ran 1:1, pg, ascending dose, 12 wk	96 pts MCI	Vital signs, cardiac safety, neuropsychological performance, safety clinical laboratory parameters	sCD40L and TNFα in CSF inversely related to CHF5074 dose. Plasma levels of sCD40L with 600 mg/day significantly lower. Positive dose–response trend was found on executive function in APOE4	[400]

Table 2 continued

Drug and dosage regimen	Trial details (phase, design, duration of treatment)	Participants	Primary endpoint (s)	Main effect	Reference
MAPKα					
Neflamapimod (VX745)	NA https://clinicaltrials.gov/ (NCT02423122; NCT02423200)	Cytokines, Aβ, phospho-tau, neurofilament light chain and butyrylcholinesterase in CFS, and fludeoxyglucose PET	Treatment effects on immediate and delayed recall aspects of episodic memory		
Other agents					
PRE 20 mg od for 4 wk, maintenance dose 10 mg od vs. PL	Phase II, ran 1:1, 1 year	138 pts AD	ADAS-cog	No change in ADAS-cog score	[374]
HYD 200–400 mg od by body weight vs. PL	Phase II, ran 1:1, 18 mo	168 pts mild AD	ADL, cognitive function, behavioral abnormalities	Any specific subgroup benefited from hydroxychloroquine	[378]
SIM up to 80 mg as tolerated vs. PL	Pilot study, ran 1:1, 26 wk	44 pts AD	CSF biomarkers Aβ1–40 and Aβ1–42	Significantly decreased Aβ1–40 in mild AD	[376]
ATO 80 mg od vs. PL	Pilot study, ran 1:1, 1 y	67 pts mild AD	ADAS-cog, CGI LOCF analysis	Significant change in the scales	[377]
ATO 80 mg od vs. PL	Phase III, ran 1:1, 72 wk	640 pts mild-to moderate AD (MMSE 13–25)	ADAS-cog, CGI (co-primaries)	Not associated with significant clinical benefit	[375]
IV Ig 0.2 or 0.4 g/kg q2w vs. PL	Phase III, ran 1:1, 18 mo	390 subjects mild to moderate AD	ADCS-AD	No beneficial effects	[401]
TRI 900 mg od vs. PL	Phase II, ran 1:1, 18 mo	257 amnestic MCI	ADAS-cog, conversion to dementia	Significantly lower rate of conversion to dementia	[402]
OFA 2.3 g	Pilot study, ran 1:1, 6 mo	35 pts mild AD	sIL-1RII and Aβ1–42 in CSF	Influence on inflammatory or biomarkers in CSF or plasma	[403]
CIL 100 mg od vs. control (ASA 100 mg or CLO 50–75 mg od)	Pilot study, ran 1:1, 6 mo	20 pts AD and CVD	ADAS-cog, Wechsler Memory Scale, TMT-A	Preventive effect on cognitive decline	[404]
HG-CSF 5-day schedule vs. PL	Pilot (proof-of-concept) study, ran 1:1, cross-over design	8 pts mild to moderate AD	CANTAB computerized system	Positive change in hippocampal-dependent task of cognitive performance	[405]

Table 2 continued

Drug and dosage regimen	Trial details (phase, design, duration of treatment)	Participants	Primary endpoint (s)	Main effect	Reference
RES 500 mg od (escalation by 500 mg increments q13w, ending with 1000 mg bid)	Phase II, ran 1:1 52-wk	119 pts mild-to moderate AD	Aβ1–40 biomarkers in CSF and serum, brain volume	CSF Aβ40 and plasma Aβ40 levels declined more with PL; brain volume loss increased	[406]

Aβ amyloid beta, *AD* Alzheimer's disease, *ADAPT* Alzheimer's Disease Anti-inflammatory, *ADAS-cog* Alzheimer Disease Assessment Scale-cognitive portion, *ADCS-AD* Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory, *ADL* activities of daily living, *AE* adverse effect, *ASA* acetylsalicylic acid (aspirin), *ATO* atorvastatin, *bid* twice daily, *CDR* Clinical Dementia Rating, *CGI* Clinical Global Impression, *CIBIC-+* Clinician's Interview-Based Impression of Change Plus Caregiver Input, *CIL* cilostazol, *CLO* clopidogrel, *CVD* cardiovascular, *DON* donepezil, *ETA* etanercept, *HG-CSF* human granulocyte colony-stimulating-factor, *HYD* hydroxychloroquine, *Ig* immunoglobulin, *ITA* itanapraced, *ITT* intention-to-treat, *IV* intravenous, *LOCF* last observation carried forward, *MAPK* mitogen-activated protein kinase, *MCI* mild cognitive impairment, *MMSE* Mini-Mental State Examination, *mo* months, *od* once daily, *OFA* omega-3 fatty acids, *ol* open-label, *ow* once weekly, *pg* parallel-group, *PIO* pioglitazone, *PL* placebo, *PPAR* peroxisome proliferator-activated receptor, *PRE* prednisone, *pro* prospective, *pt(s)* patient(s), *qxw* every x weeks, *ran* randomized, *rCBF* regional cerebral blood flow, *RES* resveratrol, *RSG XR* rosiglitazone extended release, *SC* subcutaneous, *SIB* Severe Impairment Battery, *SIM* simvastatin, *TMT* Trail Making Test, *TNF* tumor necrosis factor, TRI triflusal, *Vit.* vitamin, *wk* weeks, *WMS-LM-II* Logical Memory I and II from the Wechsler Memory Scale-Abbreviated, *y* year

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regions [230, 231]. The significance of these findings remains uncertain because several factors, including post-mortem time and handling, must be considered before conclusions are drawn. In addition, causality is notoriously difficult to ascertain in these scenarios. Systemic inflammation certainly has an impact on the brain, which is not at all "immune privileged," as textbooks still suggest. Thus, higher rates of cognitive decline have been observed in patients with AD with acute systemic inflammation [214]. Leaky gut may be one of the drivers of systemic inflammation and is directly related to an imbalance of gut microbiota [232].

7.2 Traumatic Brain Injury

Traumatic brain injury (TBI) leads to damaged blood vessels, axons, nerve cells, and glia of the brain in a focal, multifocal, or diffuse pattern, resulting in impaired brain function [233, 234]. A single moderate or severe TBI may increase the risk of developing late-onset AD, whereas repetitive mild TBI (e.g., through contact sport) is associated with an elevated risk of chronic traumatic encephalopathy [235, 236]. Two key meta-analyses of case–control studies found a significant association between moderate-severe TBI and AD [237, 238]. Furthermore, human pathological studies evince abnormal accumulation of AD-related pathological proteins, including soluble and insoluble Aβ and hyperphosphorylated tau aggregates, following TBI. This, in turn, is supported by studies in large animals [239, 240]. Aggregation and

deposition of Aβ is accelerated after an acute TBI event, with changes within a mere 24 h up to 2 months after injury in animal studies [240–244]. Further, aggregation and deposition of Aβ have been associated with memory impairments in 3xTg-AD mice [244]. Aberrant tau phosphorylation has also been described in several models after TBI [245–248]. The formation of misfolded Aβ and tau oligomeric seeds triggered by TBI may lead to spreading of the pathology in a prion-like manner, causing a faster and more severe onset of the disease [249].

7.3 Smoking

The role of smoking as a modifiable risk factor in AD is controversial. Some early case–control studies reported smoking had a beneficial effect on AD [250, 251]. In contrast, more recent cohort studies without affiliation to the tobacco industry clearly point towards a deleterious impact [252, 253]. Meta-analyses of these studies showed that smoking during a lifetime is associated with at least a 1.7 times higher risk of AD [254]. Although this increase obviously correlates with smoking intensity and duration [255], the findings regarding former smoking status are more heterogeneous. Reitz et al. [252] observed no association between past smoking and AD, whereas Aggarwal et al. [253] reported a lower risk for former smokers carrying the *ApoEε4* allele than for those who never smoked.

It is estimated that, today, smoking accounts for 4.7 million AD cases worldwide [256]. Evidence from various in vitro and in vivo studies suggests that sustained cigarette

smoke exposure facilitates the emergence of regional Aβ and tau pathology [257, 258]. Several possible pathways are likely to contribute to the development of pathological AD features in smokers. These include cerebrovascular dysfunction [259], neuroinflammation [258], and protein misfolding and aggregation [260, 261], which all may be triggered by an increase in oxidative stress [262–264]. However, human postmortem studies yielded contradictory results concerning the link between smoking and AD neuropathology, as Aβ levels were reduced in the brains of active smoker AD cases compared with never-smoking patients [265]. Remarkably, nicotine and some related compounds exert neuroprotective effects in a variety of model systems [266–268], for example via activation of nicotinic acetylcholine receptors [269] or direct binding to Aβ fibrils [270].

7.4 Physical Activity

A case–control study showed patients with AD were less active in midlife [271]. Physical inactivity is accompanied by several secondary effects, including obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM), and cardiovascular disease [272]. In contrast, regular physical exercise positively influences neurogenesis, brain plasticity, and metabolic function, reduces levels of pro-inflammatory cytokines and oxidative stress [273–275], and can alter disease-related biomarkers in patients with dementia [276]. Thus, it is not surprising that cognitive function and mental processing speed in elderly people could be significantly improved with leisure time activities and exercise programs [256, 277–279]. However, Küster et al. [280] showed that a (self-reported) active lifestyle rather than the exercise itself is associated with a decreased risk of AD. Whether physical exercise benefits all patient populations equally remains controversial [276, 281]. Some studies report a stronger effect of physical activity among *APOE4* carriers compared with non-carriers [282–284], whereas others could not replicate these results [285–287]. Analysis of different animal models suggests positive effects of physical exercise on BDNF levels, oxidative stress and even Aβ and tau pathology, resulting in delayed disease onset and progression [288–291].

7.5 Diet and Obesity

Many specific dietary components have been studied in relation to AD. In clinical studies, a higher intake of unsaturated fatty acids, antioxidants, and vitamins B_{12} and folate have been associated with a lower risk for AD and cognitive decline [292–294]. However, the opposite or even no effect has also been found for these factors [295–297]. Instead of focusing on individual dietary components, the effect of overall dietary patterns (which incorporates nutrient interaction) has been examined, including the Mediterranean Diet (MeDi) [298], Dietary Approaches to Stop Hypertension (DASH) [299], and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) [300]. These studies point towards diet as having a protective effect against cognitive decline and development of AD [299, 301–307].

In contrast, overnutrition can lead to obesity, which in turn has been associated with AD development. Obesity is characterized by leptin and insulin resistance, leading to impaired energy metabolism and chronic inflammation [308]. This chronic inflammatory status can cause cellular stress and neurodegeneration and is thought to be the link between obesity and its adverse effects on cognitive performance and AD development [309–313]. Most importantly, some of these effects may occur as early as midlife. Thus, increased body mass index and sagittal abdominal diameter in men aged 40–45 years has been associated with an increased risk of AD in later life [314].

7.6 Lifetime Distress

Lifetime frequency of stress exposure is consistently associated with the incidence of mild cognitive impairment (MCI) and may increase the risk of late-onset AD [315–317]. In particular, higher levels of the stress hormone cortisol are associated with an accelerated age-related decline in cognition [318, 319]. The hypothalamic–pituitary–adrenal (HPA) axis regulates the release of cortisol in humans or the corresponding corticosterone in rodents. This system is dysregulated in patients with AD, with higher cortisol levels found in the blood plasma and CSF of subjects with AD than in age-matched controls [318, 320].

Interestingly, exposing rodents to stressful experiences increases corticosterone levels and glucocorticoid receptor activation, resulting in aggravation of AD-related neuropathology in various transgenic models [321–326]. Microglia are highly responsive to glucocorticoids, with abundant glucocorticoid receptor expression levels [327]. Furthermore, glucocorticoids can induce a pro-inflammatory microglial phenotype upon stress, especially following a secondary inflammatory challenge [328–330].

7.7 Diabetes Mellitus

T2DM affects approximately 370 million people worldwide, accounting for 90–95% of all patients with diabetes [331]. The disease is characterized by hyperglycemia, insulin resistance, and relative lack of insulin [332]. People with T2DM have a 73% greater risk of developing dementia [333] and decreased white and grey matter

volume of the temporal and frontal lobes [334, 335]. Cortical and hippocampal atrophies have also been observed in diabetic mice (db/db) [336].

Importantly, insulin resistance leads to the generation of NFTs: decreased activation of protein kinase B in T2DM results in ineffective inhibition of glycogen synthase kinase 3, thus mediating tau phosphorylation and formation of NFTs [337, 338]. In addition, insulin levels in patients with diabetes mean the insulin-degrading enzyme is sequestered away from Aβ, which fosters the accumulation of Aβ in the brain [339, 340]. Patients with T2DM have impaired immunological defense mechanisms, resulting in frequent infections, which may contribute to the development of AD [341]. The concentration of pro-inflammatory cytokines in the CSF is increased in patients with T2DM [342]; indeed, chronic sub-acute inflammation can also induce insulin resistance and cause T2DM [343].

8 Protection by Anti-inflammatory Strategies

8.1 Past and Present Strategies

Various anti-inflammatory therapeutic approaches have been taken to modify AD progression over the past 2 decades, ranging from non-steroidal anti-inflammatory drugs (NSAIDs) to TNFα inhibition.

8.1.1 Non-steroidal Anti-inflammatory Drugs (NSAIDs)

One of those approaches was ADAPT (Alzheimer's Disease Anti-inflammatory Prevention Trial). This trial was constructed to examine whether NSAIDs could prevent or delay the onset of AD and whether such treatment could impact cognitive decline associated with aging [344].

Early epidemiological studies had suggested that long-term treatment with NSAIDs decreased the risk of AD development [345–348]. Additionally, strong experimental evidence has emerged supporting the positive effect of NSAIDs in AD animal models [80, 349]. NSAIDs have been shown to reduce Aβ secretion and accumulation, both in vitro and in vivo, to modulate γ-secretase activity, to exert an anti-inflammatory effect, and to improve cognitive function in AD mouse models [350–355].

However, most NSAIDs have not convincingly shown any beneficial effects during clinical trials in patients with AD [356]. Only a small, early study using indomethacin in patients with AD [357], which has not been replicated, and a follow-up analysis from the ADAPT research group using naproxen [358] have shown positive effects. Aspirin also did not prove effective against AD but increased the risk of serious bleeds (AD2000 trial).

8.1.2 Non-NSAIDs

Peroxisome proliferator-activated receptor (PPAR)-γ agonism has consistently been shown to reduce the production of inflammatory cytokines and amyloid accumulation in AD mouse models [351, 359–362]. Rosiglitazone induces activation of the ERK pathway, leading to cognitive enhancement in AD models [363–366]. Pioglitazone has been found to improve cognition and cerebral blood flow in mild AD [367]. Additionally, pioglitazone treatment reduced dementia risk in patients with initially non-insulin-dependent diabetes mellitus in a case–control study [368]. However, a pilot randomized clinical trial for the safety of this drug in patients with AD found no significant effect [369]. Rosiglitazone has been found to delay cognitive decline in patients with early AD and MCI [370]. Another study showed improvement in cognitive function using pioglitazone, which was restricted to *APOEε4* non-carriers [371]. The TOMORRW study is ongoing and will evaluate the efficacy of pioglitazone versus placebo in delaying the onset of MCI-AD in cognitively normal participants who are at high risk for developing MCI within the next 5 years (NCT01931566).

8.1.3 Tumor Necrosis Factor-α Inhibitors

Inhibiting TNFα signaling has also become an interesting and promising approach to the treatment of AD. A clinical case report found that intrathecal administration of infliximab (an antibody against TNFα already approved for other indications) reduced Aβ plaques and tau pathology in APP/PS1 mice and enhanced cognitive function. Additionally, two small pilot clinical studies using a different TNFα inhibitor, etanercept, showed cognitive improvement in patients with AD [372, 373]. However, these studies used small sample sizes and an open-label design and lacked a placebo group. Thus, a larger well-designed placebo-controlled study would be necessary to assess the possible utility of TNFα in AD [349].

8.1.4 Other Anti-inflammatory Drugs

Trials have examined other anti-inflammatory drugs, such as prednisone, hydroxychloroquine, simvastatin, and atorvastatin, but have shown no significant positive cognitive effects in patients with AD [368, 374–378].

8.2 Future Strategies

Recently, fenamate NSAIDs including mefenamic acid were found to selectively inhibit NLRP3 through the inhibition of volume-regulated ion channels (VRACs), thereby preventing cognitive impairments in rodent models

of AD. Mefenamic acid is already on the market and is used for abdominal pain in premenstrual syndrome. MCC950, a new potent NLRP3-selective inhibitor has been developed but is not yet available for clinical use [379]. Anakinra, an IL-1 receptor antagonist, and a neutralizing antibody, canakinumab, have been proposed to work by inhibiting this NLRP3 axis, but the cost benefit and bioavailability in the brain remains a concern [380].

CSP-1103 (also known as CHF 5074 or Itanapraced) is now in phase III clinical trials as a microglia modulator. It may inhibit Aβ plaque deposition, reduce tau pathology, restore normal microglial function by increasing phagocytosis, and decrease production of pro-inflammatory cytokines [381].

Some other new therapeutic targets have been proposed. MAPKα inhibitors (e.g., Neflamapimod [VX-745]) could reduce IL-1β levels [382] (NCT02423200). Administration of low-dose IL-2 could increase plaque-associated microglia and improve cognitive performance [383]. C3aR antagonist SB290157 could decrease amyloid load and microgliosis [384]. PD-1 inhibitors could reduce plaque load and improve cognition [385]. Blocking the p40 common subunit of IL-12 and IL-23 could decrease amyloid burden [122, 359, 386]. A CD33 inhibitor might promote microglial phagocytosis of Aβ [387].

9 Summary and Conclusions

Neuroinflammation in AD is likely to arise from the recognition of Aβ by PRRs on the surface of innate immune cells in the brain. Once initiated, sustained inflammation and neurodegeneration may unleash further factors, which, in turn, act as DAMPs and thereby contribute to the persisting and chronic sterile immune reaction in the brain. Several mechanisms of interaction by which inflammatory processes contribute to disease progression have been identified. Given that deposition of Aβ occurs decades prior to the first amnestic and cognitive deficits, such mechanisms may represent promising therapeutic targets. Identification of suitable mode and site of intervention models, which better target the human cerebral innate immune system, and associated biomarkers, is urgently required.

Compliance with Ethical Standards

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