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Inflammation and Alzheimer's disease

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Abstract

Inflammation clearly occurs in pathologically vulnerable regions of the Alzheimer's disease (AD) brain, and it does so with the full complexity of local peripheral inflammatory responses. In the periphery, degenerating tissue and the deposition of highly insoluble abnormal materials are classical stimulants of inflammation. Likewise, in the AD brain damaged neurons and neurites and highly insoluble amyloid β peptide deposits and neurofibrillary tangles provide obvious stimuli for inflammation. Because these stimuli are discrete, microlocalized, and present from early preclinical to terminal stages of AD, local upregulation of complement, cytokines, acute phase reactants, and other inflammatory mediators is also discrete, microlocalized, and chronic. Cumulated over many years, direct and bystander damage from AD inflammatory mechanisms is likely to significantly exacerbate the very pathogenic processes that gave rise to it. Thus, animal models and clinical studies, although still in their infancy, strongly suggest that AD inflammation significantly contributes to AD pathogenesis. By better understanding AD inflammatory and immunoregulatory processes, it should be possible to develop anti-inflammatory approaches that may not cure AD but will likely help slow the progression or delay the onset of this devastating disorder.

Keywords

Alzheimer's disease; Inflammation; Nervous system; Neuroinflammation; Complement; Cytokine; Chemokine; Acute phase protein; Microglia; Astrocyte; Neuron

1. Introduction

A virtual textbook of inflammatory mediators has been observed in the Alzheimer's disease (AD) brain over the last 15 years. These mediators are typically at undetectable or background levels in samples from nondemented elderly (ND) patients, and have been investigated at immunohistochemical, biochemical, and molecular levels. As with all new developments in science, perception of these findings has evolved over time. Initially, resistance was high. Many of the early results were dismissed as artifact, an impossibility given the "immunologic privilege" of the brain. This narrow view, however, gradually

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eroded thanks to seminal work in classical neuroimmunology [cf. 209,210,591,592] as well as a burgeoning literature confirming and extending the presence of inflammatory molecules in AD brain [for previous reviews, see 6,350,384,453,457]. It is now clear that the brain may have many unique immunologic properties, but it is by no means an immunologically isolated organ.

With this understanding, new challenges have arisen. Are inflammatory mechanisms actually causing damage in AD or are they present merely to remove the detritus from other, more primary pathologic processes? Are anti-inflammatory drugs a viable therapeutic option for AD? Such questions, too, are beginning to find answers. Direct and tangential evidence of a neurodegenerative role for AD inflammatory processes has been provided from basic research studies, and clinical research, although still inconclusive with respect to the best choice of an anti-inflammatory therapeutic, has widely suggested that conventional nonsteroidal anti-inflammatory drugs (NSAIDs) may delay the onset and slow the progression of AD [reviewed in 351].

Many misunderstandings and gaps in our knowledge about AD inflammation nonetheless persist. The fact that AD inflammation appears to arise from within the CNS, with little or no involvement of lymphocytes or monocytes beyond their normal surveillance of brain [591], has put it out of the realm of conventional neuroimmunologic studies that focus largely on humoral aspects of such CNS inflammatory disorders as multiple sclerosis. How and when inflammation arises in the course of AD has not yet been fully resolved, and for some the pathophysiologic significance of AD inflammation itself still remains an issue. Perhaps most of all, AD inflammation research has most often been compartmentalized, with some groups specializing in cytokines, others in complement, chemokines, growth factors, oxidative stress, microglial activation, astrocyte reactivity, or other areas. In fact, however, inflammatory mechanisms are highly interactive and almost never occur in isolation from each other.

For these reasons, a review that goes beyond the simple tabulation of AD inflammatory mediators may be timely. Here, we have attempted to martial the evidence for a pathophysiologically relevant role of AD inflammation and to take into account the myriad interactions of inflammatory mediators. By doing so, it may be possible to gain new insights into how inflammation fits into the overall framework of AD pathology as well as how best to design new therapeutics to combat AD inflammation.

2. Inflammatory pathways in the AD brain

From immunohistochemical, biochemical, and molecular studies of AD and ND postmortem tissue, and, in particular, by reference to known inflammatory pathways in the periphery, it has become tenable to attempt to organize the many inflammatory mediators uncovered in the AD brain into a working model (see enclosed poster). At its center are amyloid β peptide (Aβ), neurofibrillary tangles, and neuronal degeneration, the hallmarks of AD for nearly a century. Just as damaged tissue and the chronic presence of highly inert abnormal materials are classical stimulants of inflammation in the periphery, so also Aβ, tangles, and neurodegeneration are the most likely sources for inflammation in the AD brain. From there, as in the periphery, a nearly bewildering number of inflammatory subsystems comes into play, each characterized by an abundance of amplifying and dampening loops, as well as multiple interactions with the other subsystems. Like a web, these interactions of different inflammatory pathways make it possible, even likely, for one set of mediators ultimately to induce most of the others. For this reason, the selection of any particular starting point for explicating the role of inflammatory mechanisms in AD must be taken as a matter of convenience. Among complement, cytokine, chemokine, acute phase, and other pathways,

there is presently no reason to believe that any one set of mechanisms is more primary than the others in AD pathophysiology.

2.1 Complement

2.1.1. Activation of the classical pathway—The classical complement pathway is made up of some 20 or more components, many of them serine proteases that can be sequentially activated as an amplifying cascade. Binding of C1q, the first component, activates C1r, which then cleaves and activates C1s. C1s, in turn, has two substrates, C4 and C2. Hydrolysis of C4 forms two proteolytic fragments (activation fragments), C4a and C4b. C4b binds back to the complement activator (or to antibody molecules) via a covalent amide or ester bond, and is joined by C2. Cleavage of C2 by C1s yields an activated C4/C2 complex (C4b2a) called C3 convertase, named for its potent ability to cleave multiple C3 molecules to two proteolytic fragments, C3a and C3b. C3b can bind back to C3 convertase to form a trimolecular complex, C5 convertase, which possesses the ability to cleave C5 into two fragments, C5a and C5b. C5b, together with C6, C7, C8, and multiple C9 components, may then come together to form C5b-9, the membrane attack complex (MAC). When assembled on a cell membrane, this macromolecular terminal reaction complex of the classical (and alternative) pathway forms a ring-like structure, the size of which is determined by how many C9 molecules have been incorporated. The transmembrane channel caused by MAC assembly at the cell surface permits the free diffusion of ions and small molecules into and out of the cell, disrupting cellular homeostasis, particularly Ca^{++} homeostasis, and ultimately resulting in cell lysis if a sufficient number of MAC complexes have assembled on the cell. Notably, the MAC can also cause bystander lysis of healthy adjacent tissue [273].

β-pleated, fibrillar Aβ [4,78,243,452,582,584] and, more recently, tau-containing neurofibrillary tangles [456] have been shown to directly activate the classical complement pathway fully in vitro, and to do so in the absence of antibody. For Aβ the details of binding and activation are now relatively clear. A 13–15 amino acid sequence on the human C1q A chain collagen-like tail contains five cationic side chains that bind in a charge-based fashion to anionic side chains along the N-terminus of human Aβ [243]. This binding is not without precedent as many antibody-independent activators of the classical pathway, including C-reactive protein, DNA, and serum amyloid P (SAP), activate the classical pathway by binding to the collagen-like region of the C1q A chain [156]. Notably, rodent Aβ differs from human Aβ by three amino acids in the N-terminal region [565] and mouse C1q lacks two of the positively charged residues in the A-chain site critical to Aβ/C1q binding [78,243]. The latter finding may have implications for transgenic mouse models of AD that express human Aβ but do not express human C1q: human Aβ activates human C1 more efficiently than mouse C1 [588].

C1q is a hexamer made up of six identical subunits such that the C1q A chain binding site is replicated at intervals six times on each molecule. Structural studies of the spacing between C1q A chains in the collagen-like region and Aβ molecules when the latter is in its aggregated β-pleat configuration suggest a close fit [583]. By binding multiple Aβ molecules in positions that approximate those of the Aβ β-sheet, or by stabilizing already-formed oligomers of Aβ, C1q appears to nucleate the formation of Aβ fibrils [583, 585,587]. These structural considerations also have clear implications for C1 activation. At the globular head region, where antibodies bind C1q, interactions with a single binding site only activate C1 weakly, whereas antibody binding of multiple globular head sites causes potent activation. The same may be true for the six antibody-independent sites on the C1q A chain collagen-like tail since C1 activation increases substantially as both Aβ and tau samples become more aggregated [456,582].

In addition to Aβ aggregates and neurofibrillary tangles, other potential sources for classical pathway activation exist in the AD brain. Neurodegeneration, for example, may ultimately expose DNA and neurofilaments to the extracellular environment. DNA [156] has been shown to activate C1 by binding the same C1q A chain site used by Aβ, tau, and other antibody-independent activators [156,244]. Neurofilaments also activate complement [300], and probably do so by binding the C1q A chain site, although this has not been conclusively demonstrated. In addition, oligodendrocyte myelin glycoprotein activates the classical pathway in vitro [244], as do other myelin-derived proteins [reviewed in 513]. It is therefore possible that the increased availability of complement in the AD brain might ultimately impact myelinated axons, perhaps helping to account for AD white matter changes that have recently been noted [540].

In summary, viewed from the prospect of well established complement interactions in the periphery, there are at least five unsurprising sources of classical pathway activation in the AD brain: highly insoluble deposits of abnormal proteins, Aβ and tangles, and the exposed cellular byproducts of degeneration, naked DNA, neurofilaments, and myelin fragments.

2.1.2. Activation of the alternative pathway—In addition to the classical complement pathway, direct antibody-independent activation of the alternative pathway by β-pleated fibrillar Aβ has been demonstrated [51,525, 579]. Activation of the classical and alternative complement pathways by β-pleated fibrillar Aβ appears to be a highly specific process because other peptides of similar size and charge to Aβ (e.g., the β-pleated fibrillar peptide amylin) lack the ability to activate the classical or alternative pathways in either monomeric or aggregated form [51]. Furthermore, previous research has demonstrated that activation of both complement pathways leads to the formation of covalent, ester-linked complexes of Aβ with activation fragments of the third complement component, C3 [51], as is characteristic of complement activation reactions. The resistance to dissociation of covalent complexes likely provides an explanation for the presence of C3 in association with fibrillar Aβ in senile plaques [51]. In addition, complement activation by fibrillar, β-pleated Aβ leads to generation of C5a, a potent cytokine-like cleavage product of C5, and to assembly of the pro-inflammatory C5b-9 MAC in vitro [51,584]. These mechanisms seem to operate in vivo because many complement proteins—including C1q, C4, C3, C5, C6, C7, C8, C9, activation fragments of C3 and C4, and the C5b-9 MAC—are highly colocalized with Aβ deposits and neurofibrillary tangles in the AD brain [115,346, 452,456,491,584].

2.1.3. Complement activation products—The activation of complement produces multiple molecules that have cytopathic relevance. The anaphylatoxins C3a and C5a and the opsonins C4b, C3b, and C5b, for example, provide chemotactic and activating signals to inflammatory cells bearing appropriate receptors, and microglia and astrocytes reportedly express complement receptors, including C1qR$_P$, CR1, CR3, CR4, C3aR, and C5aR [151,152,277,546,586]. For this reason, if the complement signal for chemotaxis is generated at sites of aggregated Aβ deposits, then one would expect a high degree of microglia and astrocyte clustering at those sites. This is precisely the case in the AD brain where complement activation fragments, reactive astrocytes, and activated microglia are all highly co-localized with plaques containing aggregated Aβ [233,310,346,347,452,455,491,527,584]. Neurons also reportedly express receptors for the C3a and C5a anaphylatoxins [99,399], but the functional significance of this finding has not been conclusively determined. Mice genetically deficient in C5, for example, are reportedly more susceptible to hippocampal excitotoxic lesions [424,543], and the C5-derived activation fragment C5a is apparently neuroprotective against excitotoxicity in vitro and in vivo [413]. Potential mechanisms for the latter have been suggested to be activation of mitogen-activated protein (MAP)-kinase [412] and inhibition of caspase 3 [413]. Whether these novel actions in brain dominate, balance, or are overwhelmed by the potent cytopathic

actions of C5a—effects that have been widely documented over decades of study in the periphery—remains to be determined.

With respect to the opsonins, fibrillar Aβ is opsonized by C3b [51]. The opsonization of neurites in the vicinity of Aβ deposits may also target the fibers for subsequent damage [347], although this remains to be conclusively demonstrated.

2.1.4. Membrane attack complex—The C5b-9 MAC complex results from activation of the classical and alternative complement pathways. As a result of complement activation by Aβ or tangles, it is natural that high levels of the MAC are found in the vicinity of these pathologic hallmarks. However, as implied by its name, the MAC requires a membrane or other lipid bilayer structure for binding. In the vicinity of Aβ aggregates, dystrophic neurites that are decorated with MAC fixed to their membranes are observed ultrastructurally [235,584]. These neurites exhibit characteristic responses of living cells under active complement attack: blebbing and endocytosis of that portion of their membranes where complement is fixed [584].

2.1.5. Complement defense proteins—Upregulation of complement defense proteins, including C4 binding protein (C4bp), vitronectin, and clusterin (apolipoprotein J) (ApoJ), also occurs in the AD brain. Although it was once held that AD inflammation occurred merely to remove the detritus, the dead tissue, left behind by other more primary AD pathogenic processes (e.g. Aβ and tangle toxicity), blebbing, endocytosis, and upregulation of defense proteins signify a pathophysiologically relevant attack on living neural tissue in the AD brain. Thus, whereas AD inflammation most likely arises as a reaction to other more primary pathogenic processes, there is abundant evidence that it comes to be a further source of neurodegeneration that could ultimately be as important as the conditions that gave rise to it.

Of the complement regulatory elements, C1 inhibitor (C1-inh), ApoJ, and CD59 (membrane inhibitor of reactive lysis, MIRL, protectin), have been especially well studied in AD. In situ hybridization experiments have demonstrated that, in addition to brain endothelial cells, AD and ND neurons, but not microglia and astrocytes, express C1-inh mRNA [564]. In primary cell cultures from postmortem AD and ND microglia and astrocytes, as well as neuroblastoma cell lines, the plaque-associated cytokines interleukin-1 (IL-1), IL-6, and TNF-α (TNF-α) can stimulate the production of C1s and C1r, but not C1-inh [563]. AD microglia constitutively secrete C1q [315,563]. These in vitro findings are in line with very modest upregulation of C1-inh mRNA compared to the high upregulation of mRNAs for the C1 subcomponents in AD brains [625]. Such an imbalance could lead to ongoing activation at the C1 level.

ApoJ is associated with senile plaques and may be expressed by several brain cell types [reviewed in 130]. In astrocytes ApoJ is secreted as a unique lipoprotein particle that also contains apolipoprotein E (ApoE) [278]. Some neurons also contain ApoJ mRNA, which is induced in response to excitotoxins [371]. In addition to its role in complement regulation, ApoJ has been shown to bind Aβ, potentially facilitating Aβ transport across the cerebrovasculature [634,635]. Although the receptors for ApoJ transport are not well understood at this time, they may include gp330 as well as an endocytosing member of the low density lipoprotein (LDL) receptor family [81]. Another result of ApoJ/Aβ binding is to increase the formation of oligomeric (although not necessarily fibrillar) Aβ, which is neurotoxic in cell and slice models [280].

CD59 is a complement regulatory molecule that is widely expressed in many organ systems, including brain. A GPI-anchored protein at the cell surface, CD59 interferes with assembly

of autologous but not heterologous MAC [490], thereby protecting the cell from bystander actions of host MAC while permitting lysis of foreign cells (e.g., bacteria). Whereas many of the complement regulatory proteins that have been so far examined (i.e. C4bp, ApoJ, vitronectin) show increases in the AD brain, presumably reflecting the need to protect against ongoing complement activation, recent studies of CD59 suggest that its expression may be decreased in AD [493]. This phenomenon, which also occurs in myocardial infarct reperfusion injury [221,551], could be of paramount importance because MAC attack on homologous tissues, as noted above, is normally held in check by CD59. By contrast, a CD59 deficit in AD would be permissive for MAC fixation.

2.1.6. Endogenous CNS sources for complement proteins in the AD brain—

Not only the proteins but also the respective mRNAs for virtually all the classical pathway, most of the alternative pathway, and most of the complement regulatory proteins have been detected in the brain [132,245,491,525,574,626]. Furthermore, mRNA levels for these proteins seem to be markedly upregulated in affected areas of AD brain. For example, C1q mRNA levels are reportedly increased 11- to 80-fold, and C9 mRNA levels 10- to 27-fold over those found in the same areas of brain from nondemented individuals [626]. Similarly, Western blot and ELISA analyses show significant levels of the C4d and C3d complement cleavage fragments, as well as the assembled C5b-9 complex in hippocampal extracts from AD but not normal brains [626].

At the cellular level, three endogenous sources for complement proteins have been suggested. Microglia, like their close cousins, peripheral macrophages, produce complement proteins [180,563,571,572] and cultures of AD microglia seem to constitutively secrete approximately twice as much C1q as cultured ND microglia [315]. Astrocytes also reportedly possess the ability to synthesize several complement proteins [148–150,294,573]. Perhaps surprisingly, however, in situ hybridization studies suggest that neurons exhibit more abundant signal for complement mRNAs than any other cell type in AD brain [132,491]. Several of these mRNAs are also increased after brain injury [281,422,465]. Finch and colleagues first identified mRNAs for the key complement proteins C1qB and C4 in neurons in AD brain, as well as in lesioned rat brain [245,246,465]. These observations were confirmed and extended by others [4,132,542], such that it now appears that neurons can express virtually all the proteins of the classical complement pathway [491, 542]. Increased neuronal expression of complement genes has, in particular, been detected in AD compared to control brains [245,491]. Thus, multiple endogenous sources of complement exist in brain, and at least two of these, neurons and microglia, show complement upregulation in AD. Based on hybridization results, one study has, in fact, suggested that complement production in the AD brain may be as great as that in the liver, the primary source of complement in the periphery [626]. Given the ability of Aβ and neurofibrillary tangles to activate complement, their profuse and chronic presence in the AD cortex, and a highly competent endogenous source for complement, it is difficult to imagine that a chronic state of complement activation would not occur in the AD brain.

2.2. Cytokine and chemokine pathways

Cytokines and chemokines presumably subserve similar intercellular and intracellular signaling processes in microglia and astrocytes as they do in the periphery, although cytokine and chemokine mechanisms unique to the CNS have also been proposed. Virtually all the cytokines and chemokines that have been studied in AD, including IL-1β, IL-6, TNF-α, IL-8, transforming growth factor-β (TGF-β), and macrophage inflammatory protein-1α (MIP-1α), seem to be upregulated in AD compared to ND samples (see below).

2.2.1. IL-1—IL-1 is an immunoregulatory cytokine that is overexpressed within affected cerebral cortical regions of the AD brain, as shown by quantitative assays of tissue IL-1 concentrations and by increased numbers of IL-1 immunoreactive microglia associated with AD plaques [174,175,437, 497]. IL-1 overexpression seems to occur early in plaque evolution. It is, for example, already evident in diffuse, non-neuritic Aβ deposits, and can be observed in autopsied brain samples from fetuses and young children with Down's syndrome [174,176]. Both Aβ precursor protein (APP) and IL-1 are dramatically increased in cognitively intact individuals with epilepsy [494], a condition that may predispose to precocious development of AD pathological changes. Similarly, APP and IL-1 are elevated within 12 h of head injury, a risk factor for later development of AD [173,174].

The early overexpression of IL-1 in AD, coupled with the observation that the number and staining intensity of IL-1-immunoreactive microglia waxes and wanes with the proliferation and subsequent disappearance of dystrophic neuritic elements in Aβ plaques [174], has led to the suggestion that IL-1 plays a key orchestrating role in plaque evolution, an idea supported by the multiple trophic actions of this cytokine. In particular, IL-1 promotes the synthesis [164,319] and processing [63] of APP and may therefore promote further amyloid production and deposition in plaques. A reciprocal relationship also seems to exist wherein the secreted form of APP (sAPP) activates microglia and induces excessive expression of IL-1 [28]. IL-1 activates astrocytes [161] and induces their expression of seceral acute phase and/or Aβ-binding proteins, including α_1-antichymotrypsin (α1-ACT) [96], ApoE [96], and the complement component C3 [31]. All these proteins are found in increased concentrations in the Aβ plaques of AD [2,346,495].

One of the most important trophic actions of IL-1 is induction of S100β overexpression by reactive astrocytes [497]. S100β, an astrocyte-derived, neurite growth-promoting cytokine [267], is markedly elevated at protein and mRNA levels in brains of AD patients [327], and the S100β extracted from such tissue is biologically active [327]. Like IL-1 overexpression by activated microglia associated with Aβ deposits, S100β overexpression by reactive astrocytes in these deposits [496,555] waxes and wanes through plaque evolution [375], emphasizing the high potential for signaling among the various glial cell types through cytokines. Moreover, in AD there is a significant correlation between the cross-sectional area of dystrophic neurites in Aβ plaques and the number of plaque-associated S100β immunoreactive astrocytes [375], suggesting that the neurite growth-promoting actions of S100β might be directly responsible for dystrophic neurite growth near Aβ deposits. IL-1 and S100β could therefore be key components of a self-propagating cascade, the cytokine cycle, wherein microglial overexpression of IL-1 in diffuse, non-neuritic plaques promotes astrocytic overexpression of S100β that, in turn, drives dystrophic neurite outgrowth and culminates in the formation of neuritic plaques [175].

IL-1 may also influence AD pathopharmacology through its ability to influence neuronal expression and activity of acetylcholinesterase (AChE). That is, IL-1 secreted by activated microglia is reported to induce expression of AChE protein and mRNA and to increase AChE enzyme activity [296]. Presumably such an effect would exacerbate cholinergic decline and dysfunction in AD.

2.2.2. IL-6—IL-6 is a pleiotropic cytokine that mediates immune responses and inflammatory reactions affecting CNS cell growth and differentiation [202,211]. These actions occur through interactions with specific soluble or membrane bound receptors that form the biologically active IL-6 receptor complex (IL-6RC) [407,466,474]. In addition to the 19.5–26 kDa (depending on glycosylation) cytokine IL-6, two membrane glycoproteins help form the IL-6RC, an 80 kDa protein referred to as the ligand-binding α-subunit (gp80, IL-6R, or CD126) and a 130 kDa protein referred to as the nonligand binding, affinity

converting, and signal transducing β-receptor (gp130 or CD130) [207,628]. All members of the IL-6 cytokine family—IL-6, IL-11, oncostatin M (OSM), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), and cardiotrophin-1 (CT-1)—share gp130 as a component critical for signal transduction [207,208,232,260,426,534]. Soluble forms of the two receptors (sIL-6R, sgp130) arise by limited proteolysis (shedding) or differential splicing (sIL-6R with 55 kDa and sgp130 with 100 kDa) [206,378,380,382,448]. It has been reported that sIL-6RC forms a hexameric structure in solution consisting of its three different subcomponent proteins with a stoichiometry of 2:2:2 [415,510,577,632]. There is a complex regulatory interaction between all these sIL-6R components. sIL-6R enhances IL-6 effects by making the ligand accessible to the membrane-bound, signal-transducing β-subunit [207]. However, sIL-6R has also been shown to augment the action of sgp130 [382], which neutralizes IL-6 signals [369,382,396].

IL-6 is expressed in the nervous system during development. Normally at barely detectable levels in the adult CNS, it is strongly induced under pathological conditions [552]. Microglia, astroglia, neurons, and endothelial cells all seem capable of synthesizing IL-6 [142,328,477,560] and gp130 [207,329,477,578]. IL-6R has also been detected on neurons [228,329,448], and neuropil immunoreactivity for gp130 has been observed in telencephalic structures including the hippocampus, cerebral cortex, and caudate-putamen [578]. At the molecular level, many peptides upregulate brain IL-6. In astrocytes, particularly strong induction of IL-6 is obtained with TNF-α, OSM, OSM plus IL-6/sIL-6R, and IL-1β plus IL-6/sIL-6R [560].

Although IL-6 overexpression is generally detrimental and can add to the pathology associated with several CNS disorders, there is evidence that IL-6 may also have anti-inflammatory, immunosuppressive, and other beneficial properties under restricted conditions and levels of exposure. For example, IL-6 has been suggested to play a key role in regulating neuronal survival and function [66,145, 178,184,228,275,276,328,386,451]. It may cooperate with high-affinity neurotrophin receptor Trk signaling mechanisms [518] and, as shown in mice deficient in gp130 (the signal transducing component of IL-6), it may be essential for neuron and astrocyte differentiation [394]. Activation of membrane bound gp130 by IL-6 and the soluble IL-6R has been reported to generate a neuronal differentiation signal [474].

In the CNS, IL-6 can also act as an indirect immunosuppressant because it dramatically stimulates the pituitary-adrenal axis [334] to elicit release of adrenocorticotropic hormone (ACTH). ACTH, in turn, increases the synthesis of glucocorticoids by the adrenal gland [9]. Although IL-6 alone does not alter intracellular adhesion molecule-1 (ICAM-1) gene expression by cultured astrocytes or microglia, it does inhibit the ability of other factors to induce ICAM-1 expression at mRNA and protein levels [500]. IL-6 also inhibits interferon-γ (IFN-γ), IL-1β, and lipopolysaccharide (LPS) induced synthesis of TNF-α protein in glial cells at the post-transcriptional and/or post-translational level [91].

More commonly, IL-6 is viewed as a destructive, pro-inflammatory cytokine that induces acute phase proteins, acts as a major pyrogen, and increases vascular permeability, lymphocyte activation, and antibody synthesis. When viewed in whole animal rather than in vitro preparations, elevated levels of IL-6 cause significant CNS damage and behavioral deficits. Transgenic mice that chronically overexpress IL-6 under the control of an astrocyte-specific promoter, GFAP, for example, exhibit dose- and age-related deficits in avoidance learning that closely correlate with specific neuropathological changes [206]. Moreover, IL-6 has been shown to induce cellular neuropathological changes indicative of a chronic inflammatory response in another transgenic mouse model that develops motor impairment

and seizures [66,67]. IL-6-deficient mice exhibit sensory impairments and delayed regeneration of axons [633].

From its first identification in the AD brain [34,520], numerous findings have continued to indicate a prominent role for IL-6 in the disorder. For example, the IL-6 gene is located on chromosome 7p21, and the C allele of a variable number tandem repeat polymorphism of IL-6 is correlated with reduced IL-6 activity in humans [388]. Recently, it has been reported that the C allele of the IL-6 polymorphism is also associated with delayed development of AD [416]. Other reports have suggested that IL-6 may modulate APP synthesis [561], and enhancement of APP transcription and expression by the IL-6/sIL-6R-complex has been demonstrated [448]. Conversely, elevated IL-6 mRNA levels in cultured rat cortical glial cells occurs after stimulation with the carboxy-terminal 105 amino acids of APP [80]. IL-6 may also act on neurons, inducing ERK1/ERK2 and STAT3 activation [483] as well as the expression of such acute phase proteins as α2-macroglobulin (α2-MAC) and metallothionine [32,146].

Astrocyte expression of IL-6, IL-6R, and gp130 has been detected in frontal, temporal, parietal, and occipital cortex samples from rapid autopsies of AD and ND subjects [477]. In addition, neuronal expression of gp130 and IL-6 has been reported in AD and ND cortex [477]. In supernatants of tissue homogenates from hippocampus and area 22 of AD patients, expression of sIL-6RC (IL-6, sIL-6R, sgp130) could be measured, and in the corresponding pellets the membrane-bound IL-6RC (IL-6R, gp130) was detectable. Although elevated IL-6 mRNA was found in hippocampus and area 22, membrane-bound IL-6R and gp130 were not significantly altered [631]. Elevated temporal cortex IL-6 levels in AD compared to ND samples have been observed, along with increased concentrations of α2-MAC and C-reactive protein [520,602]. IL-6 immunoreactive plaques also show co-localized increases in acute phase proteins such as α2-MAC [520]. Finally, histologic studies have demonstrated clear IL-6 immunoreactivity co-localized with diffuse plaques lacking neuritic pathology in AD frontal, temporal, and parietal cortex and hippocampus. Such immunoreactivity was rare in classical plaques and absent in compact or burned-out plaques [34,222]. Based on these findings, it has been suggested that IL-6 may appear before neuritic changes rather than after neuritic degeneration.

In the CSF, AD patients exhibit significantly decreased concentrations of soluble IL-6 receptors (sIL-6R, sgp130) compared to healthy, age-matched controls, whereas IL-6 protein levels are unaltered [186–188]. Interestingly, patients with multiple sclerosis, like AD patients, show decreased CSF sgp130 concentrations [414]. Geriatric patients with major depression present with decreased CSF concentrations of IL-6 and sIL-6R compared to healthy controls, whereas sgp130 is not altered [526].

2.2.3. TNF-α—Elevated in AD serum [128], CSF, cortex [538], and glial cell cultures after exposure to Aβ [315], the pathophysiologic actions of TNF-α in AD are surprisingly controversial given its role as a potent pro-inflammatory, cytotoxic polypeptide in the periphery and in such other CNS disorders as brain trauma [379], multiple sclerosis [19,102], ischemic injury [144], and Parkinson's disease [219]. Excess TNF-α is reported to kill human cortical neurons [94, 167,352,366] for example, but TNF-α has also been reported to be trophic to rat hippocampal neurons [28] and to protect against glutamate, free radical, and Aβ toxicity in enriched cultures of primary neurons [29]. Consistent with a neuroprotective role, studies using TNF receptor (TNFR) deficient mice have shown that these animals develop greater neuronal loss after lesioning compared to mice possessing TNFR [60]. These studies have further suggested that activation of neurons by TNF-α induces the expression of protective molecules, including manganese superoxide dismutase [59,529]. By contrast, pharmacological inhibition of TNF-α release or activity ameliorates

tissue damage in ischemia models [124]. TNF-α is a potent stimulator of NF-κB, a transcription factor that elevates expression of pro-inflammatory factors such as complement and cyclooxygenase (COX) [68,617], as well as survival factors such as calbindin, manganese-superoxide dismutase, and Bcl-2 [255,337,536].

The dichotomy of results with TNF-α in the CNS could be explained by several factors. Some of the findings suggest that the species or type of cell evaluated can be crucial. The toxic actions of TNF-α on human cortical neurons and neuron-like cells [94,167,352,366] and the trophic actions of TNF-α on rat cortical neurons [28], for example, are consistent with such an idea. It has also been suggested that transformed cell lines are more susceptible to TNF-α toxicity than untransformed lines [69]. A second possibility follows from the fact that TNF-α elicits its biological effects through the activation of two distinct receptors, the p55 TNF receptor (type I TNFR) and the p75 TNF receptor (type II TNFR) [103,163,309]. These two receptors share low homology in the extracellular region (22%) and less than 10% homology in the intracellular domain. The p55 TNF receptor contains an intracellular "death domain" and contributes to cell death when activated [19,368]. By contrast, recent knockout studies indicate that the p75 TNF receptor plays a trophic or protective role in neuronal survival [352]. Thus, the study cited earlier [60] reporting a neuroprotective effect of TNFR deficiency was, in fact, based on animals deficient in both the p55 and p75 forms of TNFR. More direct in vivo studies with specific knockout of the p55 receptor have nonetheless supported the idea that both TNFRs are involved in neuroprotective phenomena [147], although there are significant caveats for knockout approaches to immunologic research [reviewed in 517]. Further clouding the issue, transgenic mice that overexpress TNF-α under the control of GFAP or neuronal promoters consistently exhibit severe inflammation, encephalopathy, and neurodegeneration that is fatal in many cases [8,439, 514].

2.2.4. TGF-β—TGF-βs are multifunctional peptide growth factors that play prominent roles in tissue development, homeostasis, and repair [47,449]. All three known mammalian isoforms, TGF-β1, 2, and 3, are expressed in the CNS and have been implicated in the pathogenesis of AD.

In their active forms, TGF-βs are 25-kDa disulfide-linked homodimers of two peptide subunits that are synthesized as the carboxyl-terminal portion of larger precursors of approximately 390 amino acids [reviewed in 333,449]. After dimerization of two TGF-β propeptides, the amino terminal TGF-β precursor protein, called latency-associated peptide (LAP), is proteolytically cleaved from the mature TGF-β domain. The mature TGF-β dimer remains noncovalently associated with LAP, and this latent form of TGF-β is released from most cell types. Conversion to the bioactive form is an important mechanism by which TGF-β1 activity is regulated in vivo in the extracellular space [reviewed in 385]. Despite high levels of sequence homology among TGF-β1, TGF-β2, and TGF-β3, the promoter regions vary considerably. Whereas the TGF-β1 promoter is activated by wounding or ischemia, the TGF-β2 and TGF-β3 promoters respond primarily to hormonal and developmental signals [449]. In addition, TGF-β1 induces its own synthesis in an autocrine fashion [449].

The biological actions of TGF-βs are mediated by a high-affinity transmembrane receptor complex consisting of the type I and type II serine/threonine kinase receptor subunits [reviewed in 333,449]. Most cell types also express a medium-affinity type III receptor, called betaglycan, that is thought to regulate ligand availability to type I and II receptors. An additional type III receptor, endoglin, has a high sequence similarity to betaglycan and is expressed preferentially on endothelial cells [reviewed in 333,449].

TGF-βs have been shown to modulate a wide range of processes that are implicated in AD, including brain injury response and astrocytosis, brain inflammatory response and microglial activation, extracellular matrix production, accumulation and regional distribution of amyloid, regulation of known or potential AD risk factors (e.g., APP, ApoE, α2-MAC, and COX-2), and inhibition of cell death. In the normal CNS, TGF-β isoforms and their receptors are expressed within neurons, astrocytes, and microglia [23,50,86, 95,201,272,303,502,549,576]. TGF-β1, the most abundant and best studied isoform, is expressed in the adult CNS predominantly as a response to CNS injury [131]. It is, for example, upregulated in glial cells in response to focal brain lesioning [301,307], deafferentation [370,423], lesioning with excitatory amino acids [370], transient forebrain ischemia in rodent brains [268], and after stroke in human brains [384]. In addition, blood-derived TGF-β1 stored in platelets is released in large amounts at sites of traumatic brain injury [449]. Immunoreactivity to TGF-β2 and TGF-β3 is detected in astrocytes and neurons in the normal CNS [134] and, like TGF-β1, is increased in neurodegenerative conditions [134] or after stroke in humans [427].

In vivo and in cell culture, TGF-βs have actions that suggest a role in the formation of glial scars [131,306]. TGF-β1 induces the production of extracellular matrix proteins, proteases, and protease inhibitors [47,227,450,607], many of which are deposited together with Aβ in plaques [129,131,262,293,350]. TGF-β1 also seems to be an important modulator of glial cell activation and function, causing hypertrophy of these cells [76] while inhibiting their proliferation [566].

In AD, TGF-β1 has been detected in plaques [554], and higher TGF-β1 levels were found in cerebrospinal fluid [73] and serum [72] of AD cases than in nondemented controls. Furthermore, cortical TGF-β1 mRNA levels correlated positively with the degree of cerebrovascular amyloid deposition in AD cases, and analysis of mildly fixed cortical tissues showed TGF-β1 immunoreactivity in these cerebral amyloid angiopathy (CAA) cases was elevated along cerebral blood vessels [611] and in perivascular astrocytes [608]. Prominent immunostaining for TGF-β2 was observed in reactive astrocytes, ramified microglia, and a portion of tangle-bearing neurons in AD cases [608], and TGF-β2 levels were three-fold higher in AD brains than in controls as measured by ELISA [133]. Finally, immunoreactivities for TGF-β type I and II receptors were higher in reactive glia in AD cases than in nondemented controls [303].

Although well known as an anti-inflammatory cytokine, TGF-β1 also exerts proinflammatory effects in certain pathological conditions, such as fibrotic kidney disease [47] and, possibly, CNS inflammation in acquired immunodeficiency syndrome [570]. TGF-β1 is a potent chemoattractant for microglia [623], which may explain some of the proinflammatory actions of this cytokine. In addition, TGF-β1 stimulates prostaglandin-E_2 (PGE_2) synthesis [364] and increases COX-1 expression in astrocytes and COX-2 expression in both astrocytes and neurons [316]. Altered levels of TGF-β in AD could therefore affect COX levels. Interestingly, COX-2 is elevated in neurofibrillary tangles and damaged axons in brains from patients with Down's syndrome or AD [408] and in CA1-CA4 of the hippocampal formation in sporadic AD in general [214] (see section on COX).

Experiments in transgenic mice identified TGF-β1 as an inducer of vascular amyloid deposition and modulator of Aβ accumulation in the neuropil. Transgenic mice expressing a constitutively bioactive form of TGF-β1 in astrocytes developed cerebrovascular amyloid deposits and showed endothelial cell degeneration [607,610,611]. In addition, overexpression of TGF-β1 in mice expressing human APP/Aβ in neurons accelerated vascular deposition of human Aβ. In TGF-β1 transgenic mice a prominent perivascular astrocytosis and the accumulation of the basement membrane proteins fibronectin and

perlecan preceded the accumulation of vascular amyloid deposits and the degenerative changes. Cerebrovascular amyloid deposition or CAA and microvascular degeneration are frequently associated with AD, but the etiology or pathogenetic role of these abnormalities is unknown. CAA is considered a prime cause of intracerebral hemorrhages, often with a lethal outcome in the elderly [172]. The observation that TGF-β1 immunoreactivity is detected in perivascular astrocytes and vascular cells in human cases with CAA but not in nondemented controls [607,608,611] together with the findings of transgenic studies suggest that chronic overproduction of TGF-β1 might indeed play an important role in AD-associated vascular amyloidosis and degeneration. Increased astroglial TGF-β1 production in aged doubly-transgenic mice expressing human APP and TGF-β1 caused extensive microglial activation in the hippocampus and cortex. Unexpectedly, these mice had a 75% reduction in parenchymal amyloid plaques and significantly lower Aβ levels than hAPP singly-transgenic littermate controls [609]. Virtually all remaining plaques in these aged bi-transgenic mice were located around cerebral blood vessels and not in the parenchyma, consistent with the above-mentioned effects of TGF-β1 on the cerebral vasculature [610,611]. Furthermore, a modulatory role of TGF-β1 in Aβ accumulation and amyloid formation has previously been suggested based on studies in a rat model, where intracerebroventricular infusion of Aβ produced cerebral deposits only if the animals also received a single ventricular injection of recombinant TGF-β1 [140]. In addition, administration of recombinant TGF-β1, TGF-β2, and TGF-β3 promoted the accumulation or deposition of Aβ in hippocampal slice cultures [189]. In these two model systems, Aβ-immunoreactive microglia were associated with diffuse Aβ deposits in the extracellular matrix [140,189]. These data suggest that local expression of TGF-β1 may affect the accumulation, redistribution, and clearance of Aβ in the brain.

TGF-βs may also modulate the expression of several known or potential risk factors for AD. Thus, TGF-β1 increases APP expression in cultured astrocytes and microglia [170,367] and ApoE production in brain slice cultures [190]. TGF-β1 and, more strongly, TGF-β2 bind to α2-MAC [581] and this interaction is suppressed by heparin [341]. Because both heparin and α2-MAC bind to Aβ, they may regulate its cellular uptake.

In contrast to these proinflammatory and amyloidogenic properties, TGF-β1 and TGF-β2 may serve to protect against neuronal cell damage in the brain parenchyma [reviewed in 131,134]. TGF-β protected against Aβ and glutamate neurotoxicity in cell culture and against ischemic injury in rodents [134], possibly by upregulating antiapoptotic or calcium-stabilizing factors such as Bcl-2, Bcl-$_{XL}$, and calbindin [reviewed in 134]. Alternatively, TGF-β protection against Aβ toxicity may be limited to paradigms involving only short term Aβ exposure, as long term exposure has the opposite effect [437].

2.2.5. Chemokines—In addition to the emerging role of cytokines in the pathogenesis of AD, recent studies have begun to focus attention on the role of chemokines and chemokine receptors in neuroinflammatory diseases of the CNS. The chemokines constitute a large family of over 50 cytokines that induce chemotaxis, tissue extravasation, and functional modulation of a variety of leukocytes during inflammation [317]. Although the term “chemokine” reflects the findings that most family members have leukocyte chemoattractant and cytokine-like activity, the chemokines are structurally divided into four distinct subfamilies, α (CXC), β (CC), γ (C), and δ (CX$_3$C), based on the number and spacing of their conserved amino-terminal cysteines [438].

The CXC or α subfamily, in which positionally-conserved cysteine residues at the amino-terminus are separated by one amino acid, is considered one of the two major chemokine subfamilies. The CXC chemokines such as IL-8 are primarily chemotactic for neutrophils and endothelial cells, and possess a conserved glutamate-leucine-arginine (ELR) motif in the

receptor-binding domain located at the amino-terminus [523]. Non-ELR CXC chemokines such as IP-10, on the other hand, are chemotactic for activated T cells and block the angiogenic effects of the ELR-containing family members [523].

The other major chemokine subfamily is the CC or β subfamily, where the two corresponding cysteines are adjacent. In general, the CC chemokines, including MIP-1α, MCP-1, and RANTES, have no effects on neutrophils but are primarily chemotactic for monocytes/macrophages, T lymphocytes, basophils, or eosinophils [476]. In humans, CXC chemokines are found on chromosome 4, whereas CC chemokines are encoded on chromosome 17.

The C or γ subfamily is currently represented by a single member named lymphotactin, and is structurally distinct in containing only two of the four conserved cysteines found in the CXC and CC subfamilies [257]. Lymphotactin is chemotactic for T cells and NK cells [200].

The sole member of the fourth chemokine subfamily, CX_3C, is neurotactin/fractalkine, a type I transmembrane protein that contains a chemokine-like domain (CX_3C) within the amino-terminus; however, a soluble chemokine can be generated by proteolysis or alternative processing of the mRNA precursor [36].

Chemokines mediate their biological activities through seven transmembrane, G-protein-coupled cell-surface receptors. These receptors are named according to their chemokine subfamily classification. At present there are five CXC receptors termed CXCR1 to CXCR5 and nine CC receptors termed CCR1 to CCR9. In addition, single receptors named XCR1 [630] and CX_3CR1 [229] bind lymphotactin and neurotactin/fractalkine, respectively. The relationship between chemokines and their receptors is complex, in that individual chemokines can often bind to several different receptors and a single chemokine receptor can be activated by multiple chemokines. The promiscuous nature of chemokine binding can even extend to binding interactions between different chemokine subfamilies. It has recently been demonstrated, for example, that several CC chemokines are capable of binding to CXCR3. However, the binding of CC chemokines does not activate the CXCR3 receptor but, instead, effectively blocks receptor activation mediated by the CXC chemokines [593]. Although there appears to be a tremendous amount of functional overlap and redundancy among the chemokines, it should be noted that chemokines and their receptors are stringently regulated by inflammatory stimuli and are minimally expressed in healthy individuals.

Increasing evidence indicates potential roles for chemokines in normal brain physiology [reviewed in 22,204], but the majority of studies have focused on the expression pattern of chemokines and chemokine receptors in diseases of the CNS—including multiple sclerosis, brain trauma, infections, human immunodeficiency virus (HIV) encephalopathy, and stroke—in which the blood-brain barrier is compromised and leukocyte infiltration is found at the lesion site [reviewed in 162]. Although the role of leukocytic inflammation in promoting or hindering nervous tissue repair is poorly understood, early evidence supporting a role for chemokines in CNS disorders came from the finding that passive immunization with antibodies to MIP-1α prevented the development of experimental autoimmune encephalomyelitis [252]. More recently, the finding that chemokine receptors, such as CXCR4, CCR3, CCR5, CCR8, CCR9, CXCR4, and CX_3CR1, can function as co-receptors with CD4 for HIV-1 infection [reviewed in 304] has generated speculation that chemokine receptors may directly play a role in HIV-1-associated neuropathology and AIDS dementia syndrome [reviewed in 22,360].

In AD, unlike the aforementioned neurological disorders characterized by leukocyte infiltration, abnormal or excessive migration of inflammatory cells into the CNS has not been definitively shown to occur. Nonetheless, there is growing evidence that chemokines and chemokine receptors are upregulated in resident CNS cells in AD brain [reviewed in 612], and chemokines may contribute to plaque-associated inflammation and neurodegeneration. Upregulation of CXCR2 expression has been observed on some dystrophic neurites in senile plaques [218,613]. In addition, the expression of CCR3 and CCR5 is increased on some reactive microglia in AD, and MIP-1β is found in a subpopulation of reactive astrocytes [614]. MCP-1 has also been localized to mature senile plaques and reactive microglia, but is not found in immature senile plaques [234]. Furthermore, in vitro studies have demonstrated the ability of Aβ to stimulate the production of IL-8, MCP-1, MIP-1α, and MIP-1β from human monocytes. For example, microglia cultured from rapid autopsies of AD and ND patients exhibit significant, dose-dependent increases in IL-8, MCP-1 and MIP-1α after exposure to Aβ [315]. Although more studies are certainly needed, it is likely that plaque-associated chemokine production plays a role in the recruitment and accumulation of astrocytes and microglia in senile plaques. Future studies using targeted disruption of chemokines and chemokine receptors in mouse models of AD should help clarify the role of chemokines in plaque-associated inflammation and neurodegeneration.

2.2.6. Endogenous cytokine and chemokine sources in the AD brain—Multiple endogenous sources for cytokines and chemokines have been reported in the AD, ND, or rodent brain. Viewed overall, microglia appear capable of producing IL-1 [28,64,174,176,315,354,495], IL-6 [148,285,315], TNF-α [315], TGF-β1 [272,549], TGF-β2 [133,427], MIP-1α [315,354], and MCP-1 [315]. Astrocytes are reported to express IL-1 [104], S100-β [267,375,496,497,555], IL-6 [148,285,560,604], TGF-β1 [23,50,86,95,201,272,303,502, 549,576,608], TGF-β2 [133,134,427], and TGF-β3 [134, 427]. Brain endothelial cells can be immunoreactive for IL-1 [531], IFN-γ [531], and IL-6 [148,285]. Neurons have been observed that are positive for IL-6 [142,240,328,619, 621], TGF-β1 [23,50,86,95,201,272,303,502,549,576], TGF-β2 [116,134,427], and TGF-β3 [134]. Although this synopsis is made over a wide range of conditions and experimental preparations, virtually all the cytokines and chemokines listed are easily identified in the AD brain and most, if not all, are clearly upregulated there. Moreover, as with complement and acute phase proteins in general, the present list of elevated cytokines and chemokines is unlikely to be exhaustive.

2.2.7. Interactions of cytokines and chemokines with AD pathology—In addition to their traditional actions as pro-inflammatory molecules, AD-specific interactions of certain cytokines and chemokines with Aβ may be pathophysiologically relevant. Cultured rat cortical glia exhibit elevated IL-6 mRNA after exposure to the carboxy-terminal 105 amino acids of APP [80]. IL-1, IL-6, TNF-α, MIP-1α, and MCP-1 increase in a dose-dependent manner after cultured AD and ND microglia are incubated with Aβ [315]. Rat primary astroglial cultures show concentration- and time-dependent NF-kB increases, with subsequent upregulation of IL-1β and IL-6 [25]. Human monocytes and mouse microglia show increased IL-1β, IL-1Ra, and MIP-1α (but not IL-6, IL-10, or TGF-β1) mRNA and protein expression when stimulated in vitro with Aβ25–35 [354]. Aβ25–35 also induces astroglial IL-1 but not IL-6 mRNA in astrocytes [104]. In human endothelial cells, Aβ elevates IFN-γ, IFN-γ receptor, CD40, and IL-1β [531]. Production of IL-6 and macrophage colony stimulating factor (M-CSF) by human neurons is reportedly stimulated by advanced glycation endproducts-modified tau and Aβ [619,621]. Both these inducers are believed to activate the neuron through the receptor for advanced glycation endproducts (RAGE) [619,621]. Induction of M-CSF by stressed neurons may have particular significance as this

agent can cause the attraction, activation, and proliferation of surrounding microglia. The net effect may then be to amplify a localized inflammatory response.

A reciprocal relationship, wherein certain inflammatory mediators both induce and are induced by Aβ, may also be possible. For example, IL-1 and IL-6 have been suggested to modulate Aβ precursor protein (APP) synthesis [104,108, 164,279,561], and the IL-6/sIL-6R complex is reported to enhance APP transcription and expression [448]. IL-1 interactions with APP have recently been worked out in fine detail at the molecular level [458]. IL-1α and IL-1β increase APP synthesis by up to 6-fold in primary human astrocytes and by 15-fold in human astrocytoma cells without changing the steady-state levels of APP mRNA. A 90-nucleotide sequence in the APP gene 5′-untranslated region (5′-UTR) conferred translational regulation by IL-1α and IL-1β to a chloramphenicol acetyltransferase (CAT) reporter gene. Steady-state levels of transfected APP(5′-UTR)/CAT mRNAs were unchanged, whereas both baseline and IL-1-dependent CAT protein synthesis were increased. The APP mRNA translational enhancer mapped from +55 to +144 nucleotides from the 5′-cap site and was found to be homologous with related translational control elements in the 5′-UTR of the light and heavy ferritin genes [458]. An NF-kB-related nuclear complex that is constitutively expressed by rat primary cerebellar neurons and upregulated by IL-1 specifically binds to two identical APP promoter sites, positively modulating APP transcription [177]. APP constructs transfected into cultured hippocampal neurons are stimulated more than two-fold by exposure to IL-1 [622]. IL-1 injection into rat brain or innoculation into cultured C6 glioma cells results in significant increases in S100-β and APP [497].

The TNF-α converting enzyme (TACE) may also act on APP metabolism by helping regulate α-secretase processing [62]. TGF-β exposure increases total APP mRNA by about 6-fold in cultured astrocytes [170]. In addition, the positive correlation of TGF-β levels with cerebrovascular amyloidosis [72], and the development of cerebrovascular amyloidosis in TGF-β transgenics [607,611] suggest an enhancing effect of this cytokine on cerebrovascular Aβ mechanisms.

Cytokine interactions, not only with classical AD pathology but also with other cytokines, must be considered in order to grasp the full relevance of this class of inflammatory mediator to AD pathophysiology. Within the brain, autocrine-paracrine cytokine interactions among cells that produce cytokines (e.g. cerebrovascular endothelial cells, brain macrophages, T-cells, microglia, astrocytes) are likely to occur, with net effects on cellular responses that can be additive, synergistic, inhibitory, or antagonistic [433]. Interactions among pro-inflammatory cytokines and chemokines, for example, can result in synergistic activities in cytokine production and actions, including effects on Aβ secretion (see above). Although the cytokine network involves various cytokine families (e.g. interleukins, chemokines) and members of each cytokine family use distinct receptors and signaling systems, their pathways can converge on downstream intracellular targets to amplify cellular processes. An example is the convergence of IL-1 and TNF-α signaling pathways to activate NF-kB-inducing kinase (NIK), a MAP3K related kinase [114,153,323]. This convergence results in the synergistic activation of transcriptional mechanisms.

A second general category of cytokine action is manifested by inhibitory, anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1Ra), IL-4, IL-10, and TGF-β. These inhibitory cytokines can suppress pro-inflammatory cytokine production and action, an effect that is critical to the concept of balance among pro- and anti-inflammatory cytokines. Cytokine balance considers two components, the first within a cytokine system (e.g. IL-1 and IL-1Ra), and the second among different cytokine systems (e.g. anti-inflammatory cytokines that inhibit pro-inflammatory IL-1 and TNF-α activities). The clinical

consequence of a CNS dysregulation in this balance (high levels of pro-inflammatory cytokines, low levels or activity of anti-inflammatory cytokines) can lead to cytokine production and synergistic cytokine actions, and can induce a deleterious amplification cycle of cellular activation and cytotoxicity [434]. Thus, both cytokine-cytokine interactions and cytokine interactions with existing AD pathology may play critical roles in AD neuroinflammation.

2.3. Cyclooxygenase

Cyclooxygenase (COX) is an enzyme that plays a pivotal role in the arachidonate cascade leading to prostaglandin synthesis. Because the latter is so deeply entwined with other inflammatory mechanisms, the inhibition of COX, with its attendant inhibition of prostaglandins, has become a central target for NSAID therapy. Although NSAIDs may have other effects as well, it is generally assumed that their primary mechanism of action is by competitive inhibition of COX activity, thereby reducing the production of inflammatory prostaglandins from membrane-derived arachidonate. COX not only helps mediate production of prostaglandins and other inflammatory factors, it is itself upregulated by pro-inflammatory mediators. For example, IL-1 and TNF-α regulate COX expression [404,617], and reactive oxygen and nitrogen intermediates enhance COX activity [123,467]. Thus, this enzyme sits in a pivotal amplifying position for inflammatory reactions.

Recently, two isoforms of COX that are coded for by distinct genes on different chromosomes [135,274,405,406] have been identified in the periphery and in the brain [reviewed in 403]. The two isoforms share approximately 80% homology and have similar catalytic activity, but are nonetheless physiologically distinct. COX-1 is constitutively expressed by many cell types, and the prostaglandins it helps produce are not all pro-inflammatory. In the gut, for example, one of the prostaglandins is critical for maintenance of the gastric mucosa, accounting for the propensity of NSAIDs to cause gastric irritation and ulceration. Thus, COX-1 inhibition by conventional NSAIDs can result in gastrointestinal, as well as renal and platelet toxicity. COX-2, on the other hand, is induced at sites of inflammation rather than being constitutively expressed. As such, specific inhibition of COX-2 should, in theory, direct anti-inflammatory actions to sites where inflammation is ongoing, sparing uninflamed sites where COX-produced prostaglandins are beneficial. This is clearly the case in peripheral inflammatory processes, as evidenced by recent approval of COX-2 selective drugs for the treatment of arthritis. These drugs show efficacy in alleviating symptoms without the gastrointestinal side effects common to standard NSAIDs that inhibit both COX-1 and COX-2 [reviewed in 199,562].

Accumulating evidence indicates that COX-2 protein levels are increased in AD brain and may correlate with levels of Aβ peptide [263,420]. Thus, elevated COX-2 is observed in subsets of hippocampal neurons in AD [214] and is correlated with neuronal atrophy and amyloid plaque density in this structure [214]. COX-2 (but not COX-1) is elevated in AD frontal cortex as well [420]. There is also one report of COX-2 protein co-localizing with tangle-bearing neurons in AD and Down's syndrome cortex [408]. In human [214,419] and rodent [213,543] brain, COX-2 immunoreactivity is primarily localized in neurons and shows profound upregulation with synaptic stimulation following seizures and ischemia [77,82,324,543,616]. Following focal ischemia, global ischemia, and kainate-induced seizures, COX-2 selective inhibitors attenuate the loss of specific neuronal populations expressing COX-2, [395,402].

COX elevations influence multiple downstream mechanisms of inflammation that are well known in the periphery (e.g. cytokine stimulation). Similar downstream mechanisms are likely to occur in brain. In vitro culture experiments, for example, indicate that both astrocytes and microglia have the capacity to produce excess prostaglandins in response to

treatment with proinflammatory molecules through new expression of COX-2 [35,363,404]. Glial culture studies also indicate that prostaglandins, particularly PGE_2, alter the production of several inflammation-related molecules, including IL-6, chemokines, and APP [44,126, 239,287]. Although in vivo the majority of COX-2 appears to be made in neurons, COX-2 is also seen in rat astrocytes and microglia [212]. COX-inhibiting NSAIDs reduce microglial activation following infusion of Aβ in rats [198, 401]. Moreover, numbers of activated microglia are reduced in nondemented elderly arthritic individuals who used NSAIDs compared to individuals with no history of routine anti-inflammatory medication usage [321]. These effects may be secondary to inhibition of COX-2 because a COX-2 selective NSAID (NS-398) attenuated expression of a variety of inflammation-related genes following brain irradiation (Kyrkanides and O'Banion, unpublished observations).

In addition to the more traditional inflammatory mechanisms associated with COX, unique mechanisms for COX-mediated damage may also occur in the AD brain. For example, several of the prostanoid products of arachidonate metabolism potentiate glutamate excitotoxicity, and COX-2 overexpressing transgenic mice exhibit increased neuronal susceptibility to excitotoxic insult [256]. The studies of COX in ischemia noted above also suggest that intraneuronal COX-2 levels may contribute to neuronal death by production of free radicals [419]. The appearance of apoptotic features in affected neurons after kainic acid treatment is paralleled by a marked upregulation of COX-2 mRNA [543]. Thus, NSAID actions to inhibit COX-mediated production of apoptotic factors by neurons could be one of the mechanisms by which these drugs seem to exert beneficial effects in AD. Alternatively, increased COX-2 levels in AD neurons may directly damage neurons or increase their vulnerability to other detrimental processes occurring in AD brain [419].

Although multiple clinical reports have suggested a beneficial action of NSAID COX inhibitors as a treatment for AD (see below), it may be worth noting that a definitive mechanism (or mechanisms) of action underlying the therapeutic effect remains completely uncertain. An effect on COX-2 versus COX-1 cannot be unequivocally stated because virtually all previous NSAID clinical studies have perforce used inhibitors with activities directed against both COX-1 and COX-2 isoforms: COX-2 selective NSAIDs have only recently become available, and virtually all conventional NSAIDs marketed at the time of earlier studies exhibit mixed COX-1/COX-2 activity. Despite the preponderance of basic research studies on COX-2, it still remains true that COX-1 is expressed by neurons and microglia and may be elevated in AD [263], [629].

Finally, some COX-inhibiting NSAIDs have been shown to attenuate inflammatory processes in a non-COX-dependent manner by directly activating the peroxisome proliferator-activated receptor gamma (PPARγ), a receptor and nuclear transcription factor [242,289,291,447]. PPARγ is a member of the orphan nuclear receptor family and in cells of monocytic lineage, including microglia, acts to suppress the expression of a broad range of proinflammatory genes [242,447]. Some NSAIDs act as PPARγ agonists, directly binding to it and initiating its transcriptional activity. Activation of PPARγ inhibits the Aβ-stimulated activation of microglia and monocytes and their secretion of proinflammatory and neurotoxic products. For example, PPARγ agonists act to inhibit the Aβ-stimulated expression of IL-6, TNF-α [84], and complement receptor CR3 (Mac1) [85] by microglia and monocytes, and to prevent Aβ-mediated conversion of microglia into an activated phenotype [85]. These findings raise the possibility that the therapeutic effects of NSAIDs that have been reported in AD might actually follow from PPARγ actions rather than effects on COX. Consistent with such an idea is the fact that indomethacin, an NSAID previously reported to significantly slow AD progression in a small prospective clinical trial [454], potently activates PPARγ whereas prednisone, a steroid anti-inflammatory that failed to alter

AD progression in a recent prospective trial (L. Thal, personal communication), has little or no effect on PPARγ [290].

2.4. Blood coagulation and fibrinolysis systems

Originally discovered as mechanisms that regulate the flow and coagulation of blood in the vasculature and at sites of vascular injury, the blood coagulation and fibrinolysis systems have more recently been recognized as playing important roles in inflammatory and tissue repair processes in extravascular tissues. Thus, inflammation in peripheral organs leads to the activation of blood coagulation and fibrinolysis systems. The utility of this mechanism is nicely illustrated even in primitive host defense responses such as activation of the blood clotting cascade by bacterial endotoxin in the horseshoe crab. Such clotting results in immobilization of the bacteria, preventing further dissemination to the rest of the body [425].

Many molecules in the major host defense systems have striking genomic similarities and are likely to have evolved from common ancestral genes. Perhaps for this reason, there is often substantial crossover and synergism between molecules within the various major host defense systems. Some coagulation and fibrinolysis proteases, for example, can mediate cleavage of complement proteins [530].

Among the molecules of the coagulation system, tissue factor [342], a membrane protein that initiates the coagulation cascade, and thrombin [10], a central protease of the cascade, have been found in association with senile plaques. A number of protease inhibitors that can inhibit thrombin have also been detected. These include protease nexin-1 (PN-1) [459], antithrombin III [247], plasminogen activator inhibitor type I (PAI-1) [442], and α2-MAC [34,520]. In homogenates from AD cortex, decreases in free PN-1 and increases in protease-bound PN-1 have been reported [569]. Binding of PN-1 and anti-thrombin III to thrombin is dramatically enhanced by heparin. Therefore, the presence of heparin sulfate proteoglycans in senile plaques [509] may be significant in view of the effective regulation of thrombin activity by such heparin-dependent inhibitors.

Like tissue factor and thrombin, tissue plasminogen activator (tPA), urokinase plasminogen activator (uPA), and PAI-1 are present in senile plaques [442]. In extravascular tissue, plasmin cleaves extracellular matrix proteins such as collagen and vitronectin. Cultured microglia secrete both uPA [393] and its substrate, plasminogen [392], leading to the possibility that microglia may use regulation of the plasminogen activator and plasmin system for migration in brain.

Some molecules that interact with the multiple plasma host defense systems are also found in AD lesions. These include Hageman factor (factor XII) [627], C1-inh [575], C4bp [248], and vitronectin [11]. Interestingly, a secreted form of APP with a Kunitz-type inhibitor domain is identical to protease nexin-2, a potent inhibitor of factor IX and XI [479,507,559].

A subpopulation of reactive microglia in AD brain express coagulation factor XIIIa [13], although the pathophysiologic significance of this process to AD has not been investigated. In the periphery, factor XIIIa is known to cross-link fibrin monomer, collagen, fibronectin, vitronectin, and thrombospondin [183], and may also function as a transglutaminase to cross-link cytoplasmic proteins upon apoptotic cell death [171].

2.5. β2-Integrins

Proteins of the integrin family promote adherence of cells possessing the integrin to surfaces that express appropriate ligands. This molecular mechanism has been particularly well studied in the context of the extravasation (penetration and entry) of lymphocytes,

monocytes, and neutrophils into inflamed tissue. The circulating cells express the β2-integrin LFA-1 and tend to adhere to the vascular endothelium at sites of inflammation due to the endothelial upregulation of the LFA-1 ligand ICAM-1. The β2-integrins LFA-1, CR3, and CR4 may also play a role in AD inflammation, as they appear to be increased at sites of AD pathology [462]. LFA-1 expression by microglia, for example, is highly upregulated in senile plaques [14]. Such increases could readily account for astrocytic margination of plaques, since peri-plaque astrocytes profusely express the LFA-1 ligand ICAM-1 [12].

2.6. Other inflammatory and acute phase proteins

The acute phase proteins are a diverse set of molecules that arise early in inflammation as the acute phase response. Many of these proteins have been covered in earlier sections because of their interactions with other inflammatory pathways. For example, many of the acute phase mechanisms are orchestrated by pleiotropic, overlapping actions of IL-1, IL-6, and TNF-α, which induce each other, chemokines such as IL-8, cell adhesion molecules such as ICAM-1, colony stimulating factors such as M-CSF, and acute phase proteins such as C-reactive protein, serum amyloid A, and transthyretin (TTR). Not all acute phase responses are pro-inflammatory, however, as simultaneous signals to control and ultimately quench inflammation are also generated through proteins such as TGF-β1.

Like many other inflammatory mediators, a wide range of acute phase reactants have been found in association with senile plaques and extracellular neurofibrillary tangles. These include the pentraxins SAP [87,112] and C-reactive protein [237], as well as the protease inhibitors α1-ACT [2], α1-antitrypsin [165], and α2-MAC [34].

2.6.1. α1-ACT—α1-ACT is consistently co-localized with Aβ deposits in the AD brain, and has been suggested to play a role in their formation by enhancing conversion of nonfibrillar forms of the molecule to Aβ fibrils [119,138,318]. Polymorphisms in α1-ACT, the most common of which is located in the signal peptide [250], have been investigated as risk factors for AD in over 20 studies, around half of which found a weak association [cf. 250].

2.6.2. α2-MAC and the α2-MAC receptor—α2-MAC is a potent, broad-spectrum protease inhibitor belonging to a group of proteins characterized by a unique internal cyclic thiol ester bond. This protein group, which includes complement components C3 and C4, probably evolved as elements of primitive host defense systems. α2-MAC has a bait region that acts as a substrate for a wide variety of proteases [48,511]. Formation of a protease/α2-MAC complex exposes a receptor-binding domain. The complex is removed by endocytosis following binding of this domain to the α2-MAC receptor/low density lipoprotein receptor-related protein (α2-MACR/LRP).

In addition to protease inhibition and protease removal, α2-MAC and α2-MACR/LRP function as a clearance system for inflammatory proteins [48], including α2-MAC itself, ApoE, APP, lactoferrin, tPA, uPA, PAI-1, lipoprotein lipase, receptor associated protein (RAP) [271,597], IL-1β, TGF-β, platelet-derived growth factor (PDGF), and fibro-blast growth factor (FGF) [48,111,220].

In keeping with their multi-functional roles, α2-MAC and α2-MACR/LRP have been implicated in several AD pathophysiologic processes. Both are immunohistochemically detected in association with neuritic plaque amyloid and neurofibrillary tangles [34,443,520,544,600], as are virtually all the α2-MACR/LRP ligands noted above [122,254, 397]. Like the latter set of inflammatory peptides, Aβ also reportedly forms a complex with α2-MAC that is subsequently removed through α2-MACR/LRP endocytic clearance

mechanisms [397]. Further promoting Aβ removal, α2-MAC may inhibit Aβ aggregation and fibril formation [110].

Recently, a new locus for familial Alzheimer's disease (FAD) has been proposed on chromosome 12 [428]. Both α2-MAC and α2-MACR/LRP genes are located on the short arm of chromosome 12 and have been suggested to be candidate genes for late onset FAD. The most common polymorphism in the α2-MAC gene is a five nucleotide deletion in the 5′-splice site of exon 18 [42,436]. Several reports have found an association between α2-MAC polymorphisms and the risk of AD [42,251,297], although some controversy remains [90,580].

2.6.3. ApoE—ApoE has been widely documented to play a role in sporadic AD. Long-known to be upregulated at sites of inflammation, and to play a role in peripheral amyloidosis [261], ApoE first came to light in AD as a susceptibility gene [524]. Whereas the ApoE2 and ApoE3 alleles have no effect or even a beneficial effect, possession of the ApoE4 allele, especially homozygosity for ApoE4, appears to shorten the date of AD onset by some 5–10 years [524]. The precise mechanism for this effect is still under intense experimental scrutiny. APP overexpressing transgenic mice that also have an ApoE knockout do not form expected Aβ deposits [217], clearly linking ApoE to Aβ deposition. Whether this result owes to an ApoE interaction with Aβ aggregation is less clear, however, as in vitro studies of this phenomenon have been inconsistent [71,318,468,524,599]. AD patients who are heterozygous, and especially those who are homozygous for ApoE4 tend to have more congophilic angiopathy [314], perhaps suggesting a connection with current vascular/cholesterol hypotheses of AD [512]. Still other alternatives may follow from the finding that ApoE can influence microglial expression of several inflammatory indicators [283,284], and this effect appears to be isoform-dependent [28,308].

2.6.4. sAPP as an acute phase protein—sAPP bears a number of properties in common with acute phase proteins. It is elevated at sites of tissue damage [26], and its synthesis and release are at least partly mediated by such pro-inflammatory stimuli as IL-1β and TACE [62,164]. Depending on concentration, sAPP may have either toxic or trophic actions, leading to the suggestion that it may be involved in the clearance and subsequent rebuilding of tissue after injury [20], another property of the acute phase reactants. When applied to microglia at subnanomolar concentrations, sAPP stimulates NF-κB activity, IL-1 and inducible nitric oxide synthase (iNOS) expression, and neurotoxicity [28]. This pro-inflammatory activity of sAPP is inhibited by binding to ApoE, with ApoE3 being more effective than ApoE4.

Alternatively, numerous studies have also reported neurotrophic actions of sAPP. These include protection from transient ischemia [505], HIV-1/gp120-induced brain damage [376], and acute and chronic excitotoxic injury [332, 338]. Cultured neurons also show general trophic responses when incubated with sAPP [20,618] and synaptotrophic effects of sAPP have been reported in transgenic mice [377].

2.6.5. Interactions of acute phase proteins with APP and Aβ—Like C1q nucleation of Aβ aggregation and cytokine interactions with APP synthesis and secretion (see above), several acute phase reactants may play roles in AD inflammation that go beyond their traditional actions in the periphery. Interactions with APP and Aβ at multiple levels are particularly well documented for a class of inflammatory mediators called the Aβ binding proteins. Some of these seem to modulate the ability of Aβ to be taken up and/or transported by cells. Phagocytosis of Aβ is enhanced by α2-MAC, for example, by augmentation of LRP [397]. Indeed, it is interesting to note that LRP-binding is common to several of the acute phase reactants, including ApoE, sAPP, and some α1-ACT/protease

complexes, a connection that becomes increasingly intriguing given recent genetic findings on LRP in AD [38,216]. Other acute phase proteins that may influence Aβ clearance include ApoJ, which has been shown to augment transport of Aβ across vascular endothelial cells [634]. By contrast, proteoglycans inhibit phagocytosis of Aβ by cultured rat microglia [488], and TTR inhibits the uptake of Aβ by dog smooth muscle cells [340].

A second form of Aβ binding protein interaction is hindrance of access to Aβ by proteolytic enzymes, as has been demonstrated for proteoglycans and SAP [179,541]. This may be significant to AD pathogenesis because cultured microglia have been shown to release proteolytic factors that are capable of degrading Aβ [358,441]. By inhibiting access of microglia to Aβ deposits, Aβ clearance could therefore be impacted. In addition, ApoJ can induce formation of small diffusible forms of Aβ, termed ADDLs, that possess enhanced toxic properties [280].

Perhaps the most studied form of interaction between acute phase proteins and Aβ has been the ability of the Aβ binding proteins to influence Aβ aggregation. Proteins that have been reported to have this property include C1q [583, 585,587], ApoE [71,318,468,524,599], α1-ACT [119,138, 318], α2-MAC [110,220], TTR [340,484], and SAP [185, 240]. These molecules are found associated with Aβ in plaques, but their roles in plaque formation are still incompletely understood. Indeed, with the exception of C1q, which has consistently been found to facilitate amyloid fibrillogenesis [583,585,587], and α2-MAC, which has consistently been found to inhibit amyloid fibrillogenesis [110, 220], most studies of the amyloid binding proteins have given very mixed results depending on the experimental conditions and laboratory. TTR, ApoE, ACT, and SAP, for example, enhanced Aβ aggregation in some studies [71, 185,318,468,587,599] and inhibited it in others [119,121, 138,240,484].

2.7. Free radicals

There has been intense interest in the role of oxygen free radicals as a contributing factor in AD pathology [39,305, 325,326]. Immunohistochemical data, for example, have demonstrated many of the hallmark modifications of oxidative damage in AD brain, including the presence of proteins modified with advanced glycation end products [535], malondialdehyde, 8-hydroxy-deoxyguanosine, 4-hydroxynonenal [18,326] and nitrotyrosine [167,506,528], along with increased amounts of lipid peroxidation [326]. Oxygen free radical-mediated stress not only leads to direct cellular injury, it may also influence neuronal integrity by triggering redox-sensitive, NF-kB-mediated transcription of various proinflammatory and/or apoptosis-related genes in surrounding cells [249].

Although the majority of the research on AD oxidative stress has focused on the possibility of free radical generation by affected neurons [39,335,339] as a result of impaired electron transport chain functioning during mitochondrial oxidative metabolism [39,335], the concept of free radical toxicity actually has its roots in inflammation biology, where the secretion of reactive oxygen and nitrogen species by inflammatory cells is a major mechanism for attacking opsonized targets. Alternative sources of free radicals in the AD brain are therefore likely to include activated microglia, which have the potential to produce large amounts of reactive oxygen species as a result of activation of the nicotin-amide adenine dinucleotide phosphate (NADPH) oxidase complex.

Free radical generation by activated microglia has been demonstrated by a wide range of in vitro experiments using monocytes/macrophages and microglia from humans and rodents [105,264,265,344,557,558]. It has been shown that Aβ peptides can directly activate the NADPH oxidase complex of these cells. The components of this complex are present in an inactive form in neutrophils and monocytes/macrophages/microglia. Upon activation they

combine, with the result that the cell produces a burst of superoxide radicals. This has been detected using several different assays, all demonstrating that there is increased production of superoxide radicals and increased formation of hydrogen peroxide in Aβ-treated inflammatory cells [105,264,265, 344,557,558]. Moreover, it has been shown that Aβ can potentiate or prime the production of free radicals by phagocytic cells when they are treated with other stimulating agents [264,355,558]. Controversy exists, however, with respect to the region of Aβ responsible for the activation of NADPH oxidase. Several authors have shown that the Aβ25–35 fragment can have the same effect as the complete Aβ peptide, whereas Van Muiswinkel and colleagues [557, 558], in agreement with the Aβ activation studies of Giulian and colleagues [159], have shown that amino acids present in Aβ1–16 are required for NADPH oxidase activation.

In vitro, NADPH oxidase activation is rapid and transient and may habituate with persistent stimulation. Moreover, new gene expression is not required for NADPH oxidase activation to occur. Rather, agents that prime NADPH oxidase activation are believed to function by increasing the assembly of already existing components of the complex [105,355]. Recently, microglial expression of NADPH-oxidase subunit p22-phox was reported to be enhanced in the AD brain, suggesting enhanced microglial respiratory burst activity [556]. Although the cellular content of p22-phox has previously been shown to correlate well with respiratory burst activity of human phagocytes [615], it should be noted that p22-phox but not other NADPH-oxidase components such as gp91-phox, p47-phox, and RAC was measured, so that it remains unknown whether these other components exist in sufficient quantity in the AD brain to support full NADPH-oxidase activity. Thus, reliable detection of increased NADPH complex activation in the AD brain would likely require an antibody directed at a neoepitope expressed by the assembled complex rather than an epitope expressed by one or another of the complex components and, unfortunately, no such antibody presently exists.

In addition to oxygen free radicals, there is also evidence for the involvement of nitric oxide (NO) in the pathological processes of AD. The footprints of excess NO production are observed in AD tissue as increased amounts of nitrotyrosine-modified proteins [167,203,506,528]. It has been assumed that these occur because increased amounts of peroxynitrite are being formed. Peroxynitrite arises from the interaction of superoxide with NO, and is potentially very damaging to cells. Although NO can be produced by neurons, endothelial cells, and reactive glia, its precise source in the AD brain remains undetermined. Large amounts of NO can be produced by activated astrocytes and microglia following induction of the iNOS gene, but there is controversy as to whether human microglia express the iNOS gene under conditions of inflammatory activation [75,288,572]. It is clear that human microglia do not produce NO in response to the same stimuli that cause large amounts of NO production by rodent microglia [508,568]. Expression of iNOS was detected in astrocytes surrounding plaques in AD brains, but not in microglia [288]. A similar finding was observed in progressive supranuclear palsy brains [269]. Microglia that are immunoreactive for iNOS have been observed in multiple sclerosis tissue [24], and in Parkinson's disease tissue [224], so the situation in AD brains still remains to be definitively resolved.

Recent data have indicated that microglia may be a source of the enzyme myeloperoxidase (MPO) in AD brains [445]. That is, increased expression of MPO mRNA is detected in microglia-like cells upon treatment with aggregated Aβ peptide and MPO immunoreactivity has been observed in microglia that are co-localized with Aβ plaques, but not in all of the highly activated microglia that are present in such AD-affected tissue [445]. In the periphery, MPO is found in neutrophils and blood monocytes in large amounts, but not generally in more highly differentiated tissue macrophages. MPO catalyzes a reaction between hydrogen peroxide, produced by superoxide dismutase, and chloride to generate

hypochlorous acid, a potent oxidizing agent. Hypochlorous acid can further react with other molecules to generate other reactive oxygen species, including hydroxyl ions. Recent results have indicated that MPO can also catalyze the formation of nitrotyrosine-modified proteins [435], as well as cause advanced glycation end product modifications [17]. AD is known to be more prevalent in females than males, and possession of the SpSp alleles for MPO, which affects the promoter activity of the MPO gene, is prevalent in a higher percentage of female than male AD patients [445].

3. Cell mediators of inflammation in the AD brain

3.1. Microglia

Activated microglia cluster at sites of aggregated Aβ deposition and deeply interdigitate neuritic plaques. Because they are related to peripheral macrophages [97,302], they are one of the most obvious targets for research in AD inflammation and, indeed, much of the early impetus for research into inflammatory processes in AD came from the discovery that, like activated peripheral macrophages, many of the microglia in pathologically vulnerable areas of the AD brain express major histocompatibility complex type II (MHCII) cell surface glycoprotein, whereas MHCII expression is substantially decreased in the ND brain [181,310, 347,455,527].

By numerous criteria, including their altered morphology and increased expression of MHCII, cytokines, chemokines, and complement, microglia in the AD cortex, like microglia in a variety of neuropathologic conditions [154,372,373, 521,522] are appropriately referred to as being activated. There are several caveats, however. Precise definitions of glial activation differ dramatically depending on whether in vivo or in vitro preparations are being considered [225,522]. Astrocytes in culture, for example, may express MHCII [109], but they do not do so in the AD brain [192]. By the criterion of MHCII expression, an astrocyte in the AD cortex is therefore not necessarily an activated astrocyte in the conventional immunologic sense. “Reactive astrocyte” might be a better term. In addition, activation is not synonymous with proliferation. For example, expression of immunologically important surface antigens, particularly MHCII molecules, increases gradually with normal aging in both rodent and human microglial cells [430,521]. However, in contrast to acute neuropathological conditions where microglial activation is rapid and may involve proliferation [373], there is little direct evidence that the total number of microglial cells increases with normal aging. The number of MHCII-immunoreactive microglia does increase, perhaps giving the impression of an increase in total cell number, but there are no DNA-labeling or other studies that demonstrate proliferation of all microglia with age.

Although in the normal brain microglia also play neurotrophic roles [reviewed in 522], their potential neurotoxic actions have been emphasized in AD research. Once activated in vitro, microglia are capable of producing a variety of pro-inflammatory mediators [142,157,174,182,347,475, 624] and potentially neurotoxic substances [27,83] that could contribute to localized or more widespread CNS injury. These include complement, cytokines, reactive oxygen intermediates, secreted proteases, excitatory amino acids, and NO [27,83,157,182,391,475,624]. Isolated AD microglia in culture constitutively secrete two-fold more complement component C1q than cultured ND microglia [315]. Moreover, conditions in the AD brain may enhance constitutive production of inflammation-related molecules. Aβ, for example, stimulates microglial production of IL-1, IL-6, TNF-α, MIP-1α, MCP-1, and superoxide free radicals [89, 160,168,266,315,344]. Consistent with these observations in vitro, immunohistochemical and in situ hybridization studies of AD and ND cortical samples have revealed plaque-associated microglia expressing IL-1 [174], IL-6 [107], TNF-α [107], chemokine receptors (CCR3, CCR5) [47], and MCP-1 [234].

Consistent with MHCII findings in AD brain sections, cultured AD and ND microglia also exhibit increased MHCII immunoreactivity when exposed to aggregated Aβ deposits in vitro [315]. In rats with chronic intraventricular infusion of Aβ, treatment with the Aβ sequence HHQK reduces microglial activation, presumably by blocking Aβ interactions with receptors on the microglial cell surface [159]. Collectively, these findings suggest that activation of microglia by exposure to Aβ may be a crucial step in the initiation of the inflammation seen in AD. Alternatively, immune system proteins (e.g. complement) from other sources (e.g. neurons) co-localize with Aβ deposits and these molecules may subsequently attract and stimulate microglia, thus amplifying the inflammatory process.

Activated microglia release the excitotoxins glutamate [431] and quinolinic acid [120], and microglia activated by AD plaques produce an apparently novel amine that evokes fulminant excitotoxicity [158]. One interesting implication of an excitotoxic contribution to inflammatory mechanisms is the potential for limited damage to functional cellular compartments. Because excitatory amino acid receptors are restricted to synapses and dendrites, these subcellular compartments are preferentially vulnerable. Exposures that do not kill the entire cell could therefore result in a disastrous degree of dendritic pruning [336]. Thus, microglia-produced excitotoxins may lead to cognitive impairment that is not necessarily correlated with neuronal cell loss.

Plaque-associated microglia exhibit elevated levels of phosphotyrosine [603], suggesting that these cells have persistently activated tyrosine kinase-based intracellular signaling cascades. In vitro studies have shown that exposure of microglia to fibrillar forms of Aβ results in the activation of complex signal transduction pathways [84,322,344]. The interaction of the Aβ fibrils with the cell surface induces the activation of the membrane associated tyrosine kinase Lyn and the subsequent activation of tyrosine kinase Syk [344]. These two enzymes then act in concert to stimulate downstream signaling elements, including the activation of the tyrosine kinases FAK and Pyk2, which help mediate morphological changes in the cells and activation of the MAP kinase cascades, respectively [84]. A critical signaling intermediate in these events is calcium ion, which is liberated from intracellular membranes and is essential for the activation of Pyk2 and a classical isoform of PKC [84]. Aβ stimulation of microglia results in the activation of two parallel MAP kinase cascades, the ERKs and p38 MAP kinases. These protein kinase cascades are directly responsible for the phosphorylation of transcription factors and the subsequent activation of proinflammatory gene expression [343]. It is of importance that these Aβ-stimulated signaling pathways are similar to those used by classical immune stimuli, providing evidence that Aβ can initiate a broad-based proinflammatory response by these cells. As a consequence of the Aβ-stimulated activation of intracellular signaling pathways in microglia, reactive oxygen species are produced through activation of NADPH oxidase and the synthesis and secretion of neurotoxins [85,344]. Drugs that target individual protein kinases within these signal transduction pathways block the production of the toxins [84].

3.1.1. Relationship of microglia to the deposition of Aβ—In situ, microglia cluster at sites of Aβ deposition. This is clearly evident not only in AD brain [346,455,527] but also in the Aβ plaques that APP transgenic mice develop [141,515]. As noted earlier, such clustering is readily explained by chemotactic signaling by Aβ itself [98] and by several inflammatory mediators that are associated with Aβ in senile plaques: complement activation fragments, cytokines, and chemokines. In addition, AD microglia reportedly upregulate their expression of the macrophage scavenger receptor (MSR) [117] and RAGE [620], both of which may have Aβ as ligands [117,620]. Stimulation of the RAGE receptor, in turn, induces M-CSF [619]. This growth factor seems to stimulate cultured AD microglia (L.-F. Lue, personal communication), just as it does macrophages, providing yet another mechanism for clustering of the former at sites of Aβ deposition. It has also been shown that

adhesion of microglia to Aβ fibrils via class A scavenger receptors leads to immobilization of the cells and induces them to produce reactive oxygen species [117,118].

Beyond their chemotaxis and physical proximity to Aβ deposits, the relationship of microglia to plaque evolution is still open to conjecture. One possibility is that microglia play a direct role through synthesis, processing, or catabolism of APP or Aβ. Of these alternatives, primary synthesis of APP leading to Aβ deposition is the least clear. On the one hand, cultured microglia can secrete Aβ and metabolize APP in a manner that might favor Aβ deposition [33,41]. However, microglia in AD brain do not appear to express APP mRNA [485]. Neurons, by virtue of their high expression of APP, have been postulated as the primary source of brain Aβ, and neurons and neuron-like cells produce Aβ in culture [286].

A second potential role for microglia in plaque formation, microglial processing of APP and Aβ (derived from other cellular sources), has broad research support, beginning with the simple fact that microglia aggregate much more around amyloid-containing neuritic plaques than diffuse plaques in AD, normal aging [88,236,321,463], and APP transgenic mice [141,515]. This association has been taken to suggest that microglia may be involved in the conversion of nonfibrillar Aβ into amyloid fibrils, a role similar to that ascribed to peripheral macrophages in systemic amyloidosis [499]. Other studies of the association of microglia with various stages of plaque formation in both ND and AD patients also support a role for microglia in transforming diffuse plaques into neuritic plaques [89,174, 320,473]. Moreover, Wisniewski, Terry, and colleagues have provided ultrastructural evidence that microglia may participate in the laying down of amyloid fibrils within plaques [598].

Microglia may also play a role in plaque evolution by phagocytosing and/or degrading deposited Aβ, in keeping with the emerging view that the amyloid burden in AD brain is determined by a dynamic balance between amyloid deposition and removal [226]. The fibrillar amyloid in Aβ deposits is opsonized by complement component C3b [51], which should direct C3 receptor-expressing AD microglia to remove it. In fact, many different laboratories have shown that microglia, both in vivo and in culture, phagocytose exogenous fibrillar Aβ [21,139,410,418,488,489]. Cultured AD microglia, for example, actively phagocytose aggregated Aβ deposits dried down to the well floor [313]. Following the injection of kainic acid into rat brain, reactive microglia also phagocytose the APP produced by damaged neurons [498]. Aβ inoculated into rat microglial cultures is taken up and degraded [488], and rat microglia are capable of breaking apart phagocytosed plaque cores [106]. Paresce et al. [418] found that cultured mouse microglia have a limited capacity to degrade internalized Aβ, and Ard et al. [21] reported similar findings for rat microglia. Although, as noted above, cultured AD microglia phagocytose Aβ, it is presently unknown whether or not they can degrade it or resecrete it in some other form. That they remove amyloid deposits, however, is strongly suggested by the recent demonstration of Aβ co-localized with a microglial activation marker, MHCII, in Aβ-immunized PDAPP transgenic mice, where amyloid deposits were apparently cleared [478]. Interestingly, C1q, which binds to Aβ [5,78,243,582,584] and may therefore block critical Aβ epitopes, inhibits Aβ uptake by cultured microglia [589].

Although phagocytosis of Aβ has generally been considered beneficial, there is also the possibility that this process may encourage microglial activation to a neurocytopathic state. Phagocytosis by peripheral macrophages is widely recognized to be accompanied by a respiratory burst and the release of cytotoxic compounds [reviewed in 3]. Moreover, phagocytosis by brain-derived macrophages in culture results in the release of potentially neurodestructive reactive oxygen species [83], reactive nitrogen species [74,553], and TNF-α [553], all of which have been argued to be associated with AD [reviewed in 100,107,383].

Aβ also stimulates nonspecific phagocytosis of latex beads by cultured microglia [270], further underscoring the prospect that particulate deposits of this protein in brain may function as irritants that instigate the neuroinflammatory process.

3.2. Astrocytes

Like microglia, astrocytes cluster at sites of Aβ deposition. A few reactive astrocytes are present in virtually all diffuse (noncongophilic) plaques, but the highest densities of these cells are in neuritic plaques. Astrocytes are rarely associated with dense core, non-neuritic ("burned out") plaques [375].

The positioning of astrocytes in plaques differs from that of microglia. Astrocyte somas form a corona at the perimeter of the neuritic halo that, in turn, may surround a dense core Aβ deposit. Processes from the astrocytes cover and interdigitate the neurite layer [375] in a manner reminiscent of glial scarring, and there is, in fact, recent evidence that plaque-associated astrocytes may be creating barriers. When cultured microglia are presented with naked Aβ deposited onto the culture substratum, for example, they can readily clear the deposit. However, if the Aβ is first exposed to astrocytes, they deposit proteoglycans that greatly inhibit the microglial attack [106,488]. Astrocytes may therefore impair the natural ability of microglia to clear plaques. This is consistent with the preferential localization of proteoglycans to mature, neuritic plaques [509].

Under various conditions in vitro or in situ, astrocytes seem capable of expressing a wide range of inflammatory mediators, including complement receptors [151,152,277, 546,586], complement components [30,148–150,294,563, 573], an ApoJ/ApoE complex [278], IL-1 [104], IL-6 [477, 560], gp130 [477], S100-β [267,375,496,497,555], TGF-β1 [23,50,86,95,201,272,303,502,549,576,608], TGF-β2 [133, 134,427], TGF-β3 [133,134,427], α1-ACT [96], ICAM-1 [12,500], prostaglandins and COX-2 [35,212,363,404], and iNOS [288].

3.3. Neurons

Perhaps surprisingly, neurons themselves have been consistently identified as a cell type capable of producing inflammatory mediators. These include complement [132, 422,491,542], COX [214,395,402,408,543,616], the cytokines IL-1, IL-6, and TNF-α [49,53,166,387,411,532, 539,621], the IL-6 receptor signal transducing component gp130 [232], and M-CSF [619]. α2-MAC is also expressed by neuroblastoma cells in culture [146]. As reviewed in earlier sections, virtually all these molecules are significantly increased in the AD brain. It is therefore possible that neurons themselves may exacerbate inflammatory reactions in their vicinity and so contribute to their own destruction in AD. Alternatively, some investigators contend that classical pro-inflammatory mediators such as TNF-α may confer neuroprotection in brain and therefore constitute a defense mechanism against local inflammatory reactions.

4. Animal models of AD neuroinflammation

A novel animal model has been reported that uses chronic, low-dose infusion of the inflammogen LPS into the ventricular system. Several parallels with AD inflammation are observed in this model, including increased activation of microglia, astrogliosis, increased tissue levels of IL-1β and TNF-α, elevated APP induction, temporal lobe pathology associated with cell loss and microglial reactivity [195,594], and a working memory deficit [195,197,198]. Magnetic resonance imaging studies have further quantified volumetric changes in these animals. Paralleling early stages of AD [46,92,137,238,258,259,486], hippocampus and entorhinal atrophy are especially prominent [196]. Similar chronic LPS

infusion into the ventral forebrain [596], as well as chronic IL-1β or TNF-α infusion [595], selectively destroys cholinergic cells in a time- but not dose-dependent manner.

The behavioral, biochemical, and pathological deficits induced by chronic LPS infusion are reversible with chronic administration of either an NSAID [197,198] or an IL-1RA [45]. Surprisingly, the beneficial NSAID effect is observed only in young rats, with no significant attenuation of the deficits in old rats [198], suggesting to the authors that NSAID therapies that are currently being designed to influence the onset and progression of AD should be initiated in genetically predisposed young adults before age-associated inflammatory processes within the brain have a chance to develop [198].

Overexpression of cytokines in transgenic mice using astrocyte-specific promoters reveals profound biological influences of these molecules in the CNS. For example, mice overexpressing IL-3, a cytokine that activates microglia, show a progressive motor disorder with multifocal areas of white matter damage reminiscent of multiple sclerosis [79]. Such animals also exhibit increased neuronal expression of the C5a receptor [417]. IFN-α transgenics (GFAP promoter) develop progressive inflammatory encephalopathy accompanied by gliosis and neurodegeneration [15]. Overexpression of TNF-α with a GFAP promoter also leads to chronic inflammatory encephalopathy, here with monocyte infiltration, induction of adhesion molecules and chemokines, demyelination, and, ultimately, fatal neurodegenerative disease [514]. Another set of TNF-α transgenics, either with a GFAP promoter [8] or a promoter leading to neuronal expression [439], are reported to exhibit very high TNF-α levels in the CNS that are associated with widespread, severe, and rapidly fatal CNS inflammation and degeneration. TGF-β overexpression under the control of a GFAP promoter leads to perivascular astrocytosis and Aβ deposition in transgenic mice [607,611]. Finally, transgenic mice that chronically overexpress IL-6 in astrocytes under the control of a GFAP promoter show behavioral effects that may parallel those observed in AD. Specifically, these mice exhibit dose- and age-related deficits in learning tasks that closely correspond to such neuropathological changes as microglial activation and loss of synapses and calbindin-containing neurons [206]. Again underscoring the interactive nature of inflammatory processes, the IL-6 transgenic mice also evidence increased levels of complement component C3 in those areas where IL-6 is expressed and inflammatory changes are most prominent [31].

As can be seen in this brief review, transgene studies of the effects of cytokine overexpression in the CNS have focused almost exclusively on astrocyte overexpression. This should not be taken to mean that the increases in cytokines observed in AD are exclusively due to astrocytic mechanisms or that cytokine mechanisms are exclusively the province of astrocytes. Rather, it should be recognized that transgenic methods find a unique and readily available promoter for astrocytes, GFAP, that is lacking for microglia. Microglia clearly express cytokines and chemokines, but are so closely related to peripheral macrophages that it is difficult to imagine a microglia-specific promoter that would not lead to expression of a cytokine or chemokine transgene by macrophages throughout the body.

5. Inflammation as a cause of damage to theAD brain

Inflammation, whether in the brain or the periphery, is almost always a secondary response to some more primary pathogen. This does not mean, however, that it is unimportant. In head trauma, for example, the blow to the head is the primary event. What will typically concern the neurologist and neurosurgeon more, however, is the secondary inflammatory response that will ensue and likely cause more neuron loss than the initial injury. Thus, a secondary inflammatory response often comes to be as pathophysiologically relevant as the more primary mechanism that gave rise to it.

The pathophysiologic relevance of inflammation to AD neurodegeneration has been established by multiple lines of converging tangential and direct evidence. First, many of the inflammatory mechanisms that have been uncovered in the AD brain are overtly cytotoxic in the periphery; it would therefore be surprising if they were not also cytotoxic in the brain, an organ that is exquisitely sensitive to inflammation (e.g. bacterial meningitis, edema). Although paradoxical protective effects of C5a [413,424,543] and TNF-α [28,29, 124] have been suggested, they have generally been found in restricted experimental settings where potent cytotoxic interactions with other systems and mechanisms may not obtain. Moreover, transgenic animals that express these inflammatory proteins under brain-specific promoters invariably exhibit profound pathologic changes [8,15,79,439, 514,607,611].

A second basis for ascribing pathophysiologic significance to AD inflammation follows from the fact that upregulated inflammatory mechanisms co-localize in the AD brain with those regions that exhibit high levels of AD pathology (e.g. frontal neocortex, limbic cortex) and are absent or minimal in brain regions with low AD pathologic susceptibility (e.g. cerebellum). Third, at the microscopic level, inflammatory mediators are most highly expressed in the vicinity of Aβ deposits and neurofibrillary tangles, classical AD hallmarks where neurodegeneration is known to occur. Fourth, patients without history of dementia but who nonetheless exhibit sufficient limbic Aβ and neurofibrillary tangles at autopsy to otherwise qualify for the diagnosis of AD show only modest elevations of inflammatory markers significantly greater than typical ND patients but dramatically less than AD patients [312]. Fifth, direct evidence of inflammatory toxicity can be observed in the AD brain. For example, complement fixation and lysis of neurites can be demonstrated ultrastructurally [584]. Sixth, nearly two dozen clinical studies, briefly reviewed below, have strongly suggested that conventional anti-inflammatory drugs may delay the onset or slow the progression of AD. Although many of these studies have been retrospective, with all the caveats that obtain in such work, a few, particularly recent studies at Johns Hopkins University, Duke University, and Sun Health Research Institute, have been more directly prospective, including a double-blind, placebo-controlled trial of a conventional NSAID in 28 AD patients [454].

6. Anti-inflammatory drug studies

As the previous sections establish, chronic, local inflammatory responses occur in pathologically vulnerable areas of the AD brain. These responses orchestrate numerous well-known phenomena in AD pathology such as microglial clustering at sites of Aβ deposition and exacerbate the damage done by other AD pathogenic factors. It follows, then, that anti-inflammatory therapy should be beneficial in delaying the onset or slowing the progression of AD. This hypothesis has been directly and indirectly tested with generally favorable but still far from conclusive results [reviewed in 223,351]. Indeed, it is still not entirely clear what conditions would constitute an adequate trial, as several key issues have never been fully addressed. How long, for example, should an anti-inflammatory intervention study last? Conventionally, intervention trials have been able to trade off the decreased power of a 1-year or even 6-month study with the increased power of more subjects. This may not be tenable, however, for anti-inflammatory drug studies if, as has been suggested [cf. 453], AD inflammation is chronic but weak, cumulating significant damage only over many years duration. The type of anti-inflammatory drug to be used is also an open question, as will be seen below. And, finally, can we assume that a minimal effective dose of a particular anti-inflammatory for AD can be estimated reasonably from its therapeutic window in peripheral inflammatory disorders?

6.1. Inferred anti-inflammatory treatment

Some 18 epidemiologic studies have now been published in which anti-inflammatory drugs or arthritis, a condition generally requiring chronic anti-inflammatory treatment, have been considered in risk determinations for AD [reviewed in 351]. These include seven case control studies wherein arthritis was included as a factor. A nested cohort of 40 AD patients who had previously participated in genetic and epidemiologic evaluations at Duke University was found to have an odds ratio of 1.19 for arthritis compared to a matched community group selected by random digit telephone dialing [205]. In six subsequent case control studies, however, odds ratios less than 1 were consistently found. A comparison of 78 AD patients from the Veterans Administration Medical Center in Minneapolis against a control group chosen from records at the same hospital gave an odds ratio of 0.62 [143]. An Australian study of 178 AD and 178 control patients found an odds ratio of 0.56 for arthritis [56]. A series of 70 AD patients and 140 controls from the same general neighborhoods in China reported a 0.16 odds ratio [295]. In the Canadian Health Study, 201 AD patients were matched against 468 controls, and a 0.54 odds ratio was obtained [1]. Breitner and colleagues evaluated 26 pairs of elderly twins in whom one twin developed AD 3 or more years before the other. A 0.64 odds ratio for arthritis was found [54]. A subsequent study by this group examined sibships with differential onsets of AD. Here, a 0.45 odds ratio was reported [55].

The two major forms of arthritis, osteoarthritis and rheumatoid arthritis, were not distinguished in the above studies, but two subsequent efforts have focused specifically on rheumatoid arthritis as a determinant of AD risk. Graves and co-workers [169] selected 130 AD patients from Seattle area clinics and contrasted them with 130 controls matched from friends, surrogates, or nonblood relatives of the patients. Among several factors examined, rheumatoid arthritis gave an age-adjusted odds ratio of 1.18. Jenkinson et al. [241] specifically evaluated AD and rheumatoid arthritis in 96 AD and 92 non-AD patients in a London geriatric unit and found a 0.17 odds ratio.

In addition to case control studies, three population-based reports have been published. Analysis of the medical records of 973 established rheumatoid arthritis patients age 65 or over in Saskatchewan and Arizona clinics turned up only four cases of dementia [349]. Of hospitals in three Canadian provinces and one geriatric hospital in Arizona, 7490 patients age 65 or over were found whose medical records carried a diagnosis of rheumatoid arthritis. Only 0.39% of these cases had a concomitant diagnosis of AD [349]. A Rochester, Minnesota study [37] found a much higher, 4.4% prevalence of AD among rheumatoid arthritis patients, although age of the patients was not specified. It has also been argued [351] that the Minnesota patient data derived from an earlier era when salicylates, rather than the more potent NSAIDs now available, were widely used to treat rheumatoid arthritis. From government statistics on the causes of death in Finland for the year 1989, only two rheumatoid arthritis patients (0.12% of the rheumatoid arthritis population) died with AD, whereas in the general population some 0.54% died with AD [389].

6.2. NSAIDs

Five case control epidemiologic surveys, three population-based epidemiologic studies, and one prospective clinical trial have specifically investigated currently available NSAIDs and their potential use for AD. Using data from four of the case control studies [1,54,55,519], McGeer and colleagues [351] computed an overall odds ratio of 0.475 for NSAID use and AD. Interestingly, in one of these studies [519] as well as a report by Veld et al. [231] prolonged use of NSAIDs appeared to further reduce the risk of AD. An Italian population-based study reviewed the data from two AD clinical trials that were not per se related to anti-inflammatory therapy. Only 0.8% and 0.0% of the total cohorts (195 AD patients) were

NSAID users. This contrasted with 22.8%, 20.3%, and 18.5% in a general survey of elderly patients conducted by the investigators [311]. Similarly, only 1.4% of NSAID users age 55 or more in the Ommoord district of Rotterdam suffered from AD, whereas 2.5% of the total 5893 member cohort carried an AD diagnosis [16]. In Baltimore, 32 AD patients who used NSAIDs were compared to 177 non-NSAID users with AD. Over a 1-year longitudinal study period, the NSAID users exhibited significantly slower disease progression [446]. Finally, one double-blind, placebo-controlled trial of the NSAID indomethacin was conducted in 28 AD patients [454]. Over 6 months of evaluation, the indomethacin patients exhibited significantly less cognitive decline than the placebo group.

Both Merck & Co. and Monsanto/Searle have selective inhibitors of COX-2 that have been approved for arthritis indications. Both drugs have the advantage of convenience of use, because Merck's rofecoxib (Vioxx) and Searle's celecoxib (Celebrex) are dosed, respectively, once and twice a day. By virtue of their selectivity for COX-2, both drugs are expected to avoid serious gastrointestinal side effects, unlike the NSAIDs that also inhibit COX-1. It has yet to be reported how these selective COX-2 inhibitors function in animal models of brain inflammation, although inhibitors in this class are reported to inhibit brain damage caused by a variety of noxious insults [198]. Both COX-2 drugs are reported to be in clinical trials for the treatment and/or prevention of AD.

Postmortem evaluation of the effects of antemortem NSAID use and AD pathology has also been conducted. Brain tissue from ND elderly individuals with a history of chronic NSAID use was compared with tissue from age-matched controls [321]. The two groups showed a similar degree of senile plaque and neurofibrillary tangle pathology. However, NSAID use was associated with a significant reduction in the number of senile plaque-associated, activated microglia. These findings are consistent with animal and in vitro culture research on the effects of NSAIDs. In one such study, Aβ was infused into the lateral ventricles of rats [401]. Activated microglia surrounded the intraparenchymal Aβ deposits, but this response was significantly attenuated in animals receiving indomethacin. Three differentially acting anti-inflammatory drugs, indomethacin, dexamethasone, and colchicine, blocked Aβ-induced neurocytopathic activity of human monocyte/macrophages [113]. Thus, one of many possible therapeutic actions of NSAIDs in the AD brain may be suppression of microglial activation associated with Aβ deposits.

Ibuprofen, a commonly used over-the-counter NSAID that is a COX-1 and COX-2 inhibitor as well as a PPARγ agonist, has also been investigated in the aging HuAPPSw (Tg2576) transgenic mouse model [298], where amyloid deposition, glial activation, and CNS inflammation resembling that found in AD develops [141]. At 10 months of age outbred Tg (+) and (−) 2576 mice (n = 8) were fed diets with and without 375 ppm ibuprofen for 6 months [298]. This dose was chosen because it is in the range of relatively nontoxic analgesic doses and yet reduced microgliosis and oxidative damage in a rat Aβ infusion model. When sacrificed at 16 months, the ibuprofen-fed APP transgenic mice had significant reductions in CNS IL-1β, activated microglia, GFAP, ubiquitin, Aβ immunoreactive plaques, and total Aβ burden. Ibuprofen treatment also corrected the hyperactivity observed in open field activity in comparisons of APP transgenics and control, transgene-negative littermates [298].

6.3. Steroid anti-inflammatory agents

Synthetic glucocorticoids are potent anti-inflammatory agents that act by antagonizing AP-1 and NF-kB promoter elements regulating transcription of inflammatory molecules [52,547,548]. They inhibit production of two key enzymes mediating inflammation-induced prostaglandin synthesis: COX-2 [330,406] and phospholipase A2 [331]. Glucocorticoid treatment also reduces numerous proinflammatory cytokines, including IL-1β and TNF-α

[61,481]. Consistent with an anti-inflammatory action in the brain, microglial ramification, proliferation, and increased lysosomal vacuolation are all inhibited by glucocorticoids in vitro [537]. Synthetic glucocorticoids also inhibit MHC-II expression in microglia after facial nerve axotomy [50]. Depending on dose, glucocorticoids can induce macrophage apoptosis [481] or microglial cell death [253]. They induce expression of microglial lipocortin, which inhibits microglial activation and is neuroprotective [362].

Glucocorticoids alter expression of complement proteins, generally down-regulating factors involved in complement activation as well as those involved in complement suppression [282,292,545]. Glucocorticoids activate the PPARγ pathway in adipocytes [22]. They may also do so in microglia where PPARγ activation and glucocorticoid receptor occupancy both seem to lead to inhibition of cytokine responses via an inhibition of transcription events that are coordinately regulated by AP-1 and NF-kB. Notably, however, Lehman et al. [290] found little or no PPARγ activation by prednisone compared to NSAIDs.

In summary, glucocorticoids inhibit inflammatory pathways (e.g. COX-2, complement) that have been implicated in AD [7], and for these reasons a multicenter, parallel-design, placebo-controlled trial by the Alzheimer's Disease Cooperative Study was initiated several years ago [7]. In a pilot 7-week study used for dose selection, AD patients treated with 20 mg/day prednisone followed by a maintenance dose of 10 mg/day showed reduced levels of the serum inflammation markers α1-ACT and the complement anaphylatoxin C3a. The multicenter trial that followed used a placebo-controlled parallel groups design of 138 patients randomized to drug or placebo. AD patients receiving drug were given an initial dose of 20 mg/day prednisone for the first 4 weeks, followed by a maintenance dose of 10 mg/day for the remainder of the 1-year trial. The major outcome measures were the ADAS and the Clinical Dementia Rating. Although the results of the Alzheimer's Disease Cooperative Study of prednisone have not yet been published, anecdotal reports have been discouraging. Moreover, three [1,55,169] out of four [54] previous epidemiological studies failed to obtain a significant odds ratio indicative of a therapeutic action of steroid anti-inflammatories in AD, and a pilot trial in four AD patients even suggested adverse reactions [454].

Although steroid anti-inflammatory agents do have properties that should be useful for treating AD inflammation, they also have actions that may make them less than ideal for administration to AD patients. Globally, chronic exposure to glucocorticoids during prolonged stress has been repeatedly demonstrated to result in such adverse effects as immunosuppression, infertility, and neurodegeneration [345,487]. However, the situation may be worse in AD patients because of specific interactions of steroids with existing biochemical, systemic, and behavioral problems they often suffer. AD patients, for example, have been reported to exhibit hypercortisolism and other symptoms of adrenal hyperactivity (e.g. elevated dihydroepiandosterone) as a result of a higher mass of cortisol secreted per burst [191,533]. In other studies, elevated corticosteroids in AD have been associated with an impaired hypothalamic-pituitary-adrenal axis, including blunted pituitary ACTH responsiveness to hypothalamic corticotropin releasing factor [398] and impaired negative feedback reflected in a reduced response to the dexamethasone suppression test [194]. Hypersecretion of the adrenal steroids, including cortisol, has been found to correlate positively with AD disease severity in cross-sectional studies [361,533,590]. Collectively, these findings suggest that steroid administration might actually exacerbate an underlying tendency to hypercortisolism in AD patients.

Steroid use and hypercortisolism, in turn, have further deleterious effects on brain function, particularly the impairment of glucose utilization. Corticosteroid challenge in normal subjects, for example, has been shown to impair hippocampal glucose utilization by PET

imaging [101]. High levels of cortisol in rodents and primates are correlated with neurodegeneration that can be reversed by glucose or mannose administration [471,472,516]. Because AD patients already exhibit reduced region-dependent glucose hypometabolism in the posterior cingulate cortex [444], pre-frontal cortex [43], parietal-temporal frontal cortex, and parietal association cortex [230,356,357,359,365], further deficits induced by steroids or hypercortisolism would obviously be problematic. Indeed, cortical glucose hypometabolism in AD subjects with the ApoE4 allele [460,504] as well as those without ApoE4 [444] has been suggested to precede onset of symptoms by several years, and baseline parietal FDG PET asymmetry in subjects with age-associated memory impairment seems to predict future visual-spatial decline [503].

Steroid effects on mood and cognition may provide yet another contraindication for the use of such anti-inflammatory agents in AD. In one study, 8-day treatments with corticosteroids induced organic mood disorder, hypomanic syndrome, depressive syndrome, and impaired performance on the Auditory-Verbal Learning and the Digit Symbol neuropsychological tests [390]. Treatments for 4 days resulted in increased negative emotions and fewer objects recalled in a memory task [480]. With long term, high dose administration, steroid psychosis and other cognitive difficulties can ensue [601]. Moreover, patients treated with steroids for lupus often experience a reversible dementia-like syndrome [193].

A wide range of in vitro studies also suggest that steroid anti-inflammatory drugs may sometimes have paradoxical actions in the nervous system. For example, in an optic nerve injury model, microglial proliferation or expression of C3b or MHC-II antigen was unaffected by steroid treatment [70]. Glucocorticoids reportedly reduced sprouting and neurogenesis in the hippocampus [65], and further impaired the reinnervation process after deafferentation by preventing the removal of degenerating terminals [215]. Despite the fact that exogenous doses of glucocorticoids in vivo can inhibit GFAP mRNA in the rat hippocampus and cortex, glucocorticoid treatment exacerbated the astrocytic response to perforant path lesion [567]. Although glucocorticoids generally inhibit cytokine responses, they can augment TNF-α, TNF-β, or IL-1β responses to hippocampal toxins, astrogliosis, and neuronal necrosis [58]. Chronic glucocorticoids can activate the lipoxygenase pathway, stimulating 5-lipoxygenase mRNA in human monocytes and in the brain [550]. Despite the known effect of glucocorticoids to inhibit complement activation, they have been shown to increase C1q mRNA in activated or resident macrophages [545] and to increase C1q protein secretion by human macrophage-like cells [571], an effect that would intensify Aβ-dependent activation of complement [452]. PPARγ, which generally downregulates inflammation, was reportedly stimulated by glucocorticoids in adipocytes, but in another study prednisone was found to have little or no effect on PPARγ compared to NSAIDs [290]. In a mouse model of AIDs dementia, glucocorticoid treatment increased viability of HIV-infected macrophages and had minimal effect on suppressing neurotoxic inflammatory factors, raising questions about the in vivo efficacy of glucocorticoid CNS anti-inflammatory activity in HIV-related models [299]. Finally, whereas chronic NSAID use has been shown to be related to decreased numbers of activated, plaque-associated microglia in ND elderly patients [321], chronic steroid use has no effect [319].

Duration of steroid exposure may be an important factor in unraveling anti-inflammatory versus pathophysiologic effects of steroids in the CNS. In neurons, for example, short-term glucocorticoid treatment attenuates post-traumatic and post-ischemic central neuronal damage [64], but long-term exposure to high levels of glucocorticoids can prevent recovery from brain injury by reducing the hippocampal sprouting response to entorhinal cortex deafferentation in general [374] and deafferentation-induced microglial insulin growth factor 1 in particular [605]. In the frontal cortex, acute treatment of rats with glucocorticoids increases, but chronic treatment reduces levels of neuronal cell adhesion molecule (NCAM),

a glycoprotein affecting synapse function [469]. Depending on duration of treatment and the presence of neurons, glucocorticoids can stimulate or inhibit transcription of the astrocyte intermediate filament protein GFAP [464].

6.4. Other anti-inflammatory approaches

Alternatives to steroids and to the conventional COX-inhibiting actions of NSAIDs exist and may ultimately prove relevant to AD treatment. The NSAIDs tepoxalin and tenidap, for example, have been shown to inhibit astrocytic and microglial IL-6 synthesis, in addition to their ability to inhibit COX and lipoxygenase activity [125,127]. Moreover, tepoxalin inhibits the synthesis of IL-1β in microglial cells and α1-ACT in astrocytes by preventing NF-kB activation, all factors that are involved in the inflammatory events of AD. Antioxidant approaches might also be legitimately considered as a form of anti-inflammatory therapy. Results from a 2-year-long clinical trial studying the effects of the antioxidants α-tocopherol (vitamin E) and selegeline, a monoamine oxidase inhibitor and antioxidant, were reported in 1997 [470]. The study consisted of 341 AD patients in a placebo-controlled, randomized, multicenter trial consisting of treatments with placebo, 2000 IU of vitamin E/day, 10 mg selegeline/day, or vitamin E and selegeline together. The primary outcomes of this study were delayed times to death, institutionalization, inability to perform activities of daily living, or severe dementia. Both selegeline and vitamin E, but not the combination, resulted in improved performance in the primary outcome scores. However, it remains somewhat controversial if the treatment had beneficial effects on AD or rather contributed to better health in the study participants.

An extract from the leaves of the Chinese tree Ginkgo biloba has been for years advised by herbalists as a remedy for “cerebral insufficiency” [429]. A more contemporary perspective is that extracts from these leaves, designated Egb761, are rich in flavinoids, well known antioxidants, as well as other potentially pharmacoactive/antioxidant substances (terpenoids, ginkgolides, and bilobalide). The anti-oxidant properties are suspected of restoring blood supply to the brain, reducing oxidative stress and improving brain cholinergic function, although these claims remain largely untested. Regardless, several clinical studies of Ginkgo biloba have been conducted in AD patients. A meta-analysis of these studies, restricted to those meeting conventional criteria for AD trials, revealed a positive, albeit modest, clinical effect of the Ginkgo extracts [93,409]. The benefits seen in these studies were reported to approach those seen with the cholinesterase inhibitor, donepezil. Because there is widespread use of the Ginkgo extract among some aging individuals who fear dementia, concerns have been raised that such self-medication is occurring without compelling evidence of efficacy. In response to this situation, the National Institutes of Health has solicited proposals (RFA-99–01, Healthy People 2000 Initiative) for a double-blind, randomized, placebo-controlled, multi-center prevention trial of Ginkgo extract in individuals at least 75 years of age.

Propentofylline is a neuroprotective glial cell modulator that acts as a cAMP/cGMP phosphodiesterase inhibitor and increases the effective extracellular concentration of adenosine by blocking its cellular reuptake [482]. This combination of effects seems to mitigate damage in animal models of neurodegeneration [353] and in cell culture studies [501], as well as to inhibit microglial activation. Treatment of cultured microglia with propentofylline reduces LPS-induction of IL-6 and TNF-α [501]. Although the pharmacology of propentofylline is complicated, it clearly has anti-inflammatory actions. In a 52-week placebo-controlled clinical trial of 901 patients with mild-to-moderate AD, those receiving propentofylline (300 mg, three times daily) showed a modest improvement in their cognition as measured by the mini-mental state score (MMSE) and in global inventories of daily living relative to the placebo group [461]. After 56 weeks, patients who were treated

with propentofylline continued to show the same level of improvement, whereas the placebo group declined substantially. The drug-treated group continued to show improvement for up to 8 weeks after the patients were withdrawn from propentofylline. Approval for the use of propentofylline in AD is currently being sought.

7. Future directions

One of the issues that has not achieved complete consensus among the multiple authors of this review concerns cytoprotective versus cytopathic actions of several inflammatory mediators, particularly TNF-α and the complement anaphylatoxins. On the one hand, the very name for TNF-α, tumor necrosis factor-α, much less its potent effects on angiogenesis and its potent ability to activate other destructive inflammatory mechanisms, makes it implausible that this cytokine would not, overall, exert deleterious effects on the AD brain: the brain does require a competent vasculature, and it does possess resident inflammatory cells, microglia, that are responsive to TNF-α. TNF-α-overexpressing transgenic mice exhibit rampant, fatal inflammation and encephalopathy [8,439,514]. On the other hand, there is multiple converging evidence to support cytoprotective roles for both C5a and TNF-α in brain, and there are numerous precedents for brain idiosyncratic actions of signaling molecules that are different from and can even be the reverse of their actions in the periphery.

When one looks at the nature of the inflammatory response in the periphery (always a good exercise for neuroscientists, who typically lack formal training in immunology), it may be that these difficulties in brain become less perplexing. First, in vitro studies, on which most of the present data are based, make abundantly clear that diverse effects can be obtained depending on concentration of the mediator being studied, duration of exposure, timing of exposure, and the particular experimental model. Second, in vitro studies with individual inflammatory mediators are unlikely to replicate faithfully the full gamut of effects each may manifest when other mediators are present or when the experimental paradigm is not slanted toward the detection of a single action. Third, because the inflammatory response has so much potential for amplification, its onset is invariably accompanied by signals to regulate and quench it. Dual actions of individual inflammatory mediators may, therefore, not be so unusual and, indeed, one finds a similar cytotoxic/cytoprotective dichotomy of actions for TNF-α in the periphery [400]. The real issue, then, is not whether only a cytotoxic or a cytoprotective mechanism is exerted by an inflammatory mediator in AD, but rather which of the two dominates under in vivo conditions that permit the full complexity of inflammatory interactions to be expressed [432].

A second difficult issue is neuronal expression of inflammatory mediators. Whereas it is relatively simple to deduce functional roles for these molecules in macrophage-like cells such as microglia, there is little or no precedent to go on for neurons. When a neuron secretes complement, for example, has it sown the seeds of its own destruction [492], or has complement come to take on some new role in brain? If the latter, what role? The answer could be more important to our understanding of normal brain function than our understanding of inflammatory mechanisms in AD.

The role of brain-endogenous, nonlymphocyte-mediated inflammatory responses also needs to be more thoroughly investigated in other CNS disorders. Prion disorders such as Creuzfeldt-Jakob disease were initially thought not to have an inflammatory component [57,440], for example, but more recent studies have challenged this view [40,136]. Inflammatory markers have been reported in substantia nigra of Parkinson’s disease patients [348]. Complement reactions to myelin constituents in multiple sclerosis [244] may have received inadequate research attention. Given that tissue degeneration is a ubiquitous

stimulus for inflammation and that the CNS is capable of mounting endogenous inflammatory responses, it would be surprising if at least some inflammation did not occur in virtually all neurodegenerative disorders.

Finally, for a disorder such as AD, where the clearest risk factor is age, surprisingly little is known about why the risk of AD accelerates as humans grow older. Information about age-related changes in the neuroinflammatory capacity of the human CNS could be highly informative. In primate brain there is increased glial activation in response to Aβ infusion [155] and, indeed, region-specific glial activation, as well as increases in C1q and TGF-β1 mRNA, seem to occur with normal aging in rodent brain [371,421].

8. Conclusion

It is indisputable that neuroinflammation occurs in the AD cortex. Mechanisms that parallel those encountered in localized peripheral inflammatory responses are readily identified, along with detailed pathways for how the mechanisms interact. There are also obvious parallels in the AD brain to the conditions that stimulate localized peripheral inflammation: the chronic presence of highly insoluble deposits of abnormal proteins, as well as chronic damage to tissue. What is, in fact, surprising is that it took so long to notice AD inflammation. The issue, now, is what all these myriad findings mean to the condition of patients who already have or may develop AD. On balance, it is likely that AD neuroinflammation exacerbates AD pathogenesis. As such, therapies that ameliorate AD neuroinflammation are indicated as an adjunct to treatments that more directly address the etiologic roots of AD, whatever those etiologic roots ultimately prove to be. No more than NSAIDs cure arthritis will anti-inflammatory drugs cure AD. However, if AD neuroinflammation is approached with realistic expectations and rational drug design, AD patients should significantly benefit from anti-inflammatory treatment.

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