

Inflammation and neurodegenerative diseases¹⁻⁴

W Sue T Griffin

ABSTRACT

The decline in mental fitness associated with Alzheimer disease is accompanied by physical changes in the brain, including the development of characteristic plaques and neurofibrillary tangles, but the pathogenesis of those changes is not clear. Recent work suggests that the activation of microglia in response to injury, illness, aging, or other causes begins a cascade of events that can best be characterized as an inflammatory process. This cascade is mediated at first by the proinflammatory cytokine interleukin 1, which is overexpressed by the activated microglia. Through various pathways, interleukin 1 causes neuronal death, which activates more microglia, which in turn release more interleukin 1 in a self-sustaining and self-amplifying fashion. Over a period of years, this slow, smoldering inflammation in the brain destroys sufficient neurons to cause the clinical signs of Alzheimer disease. *Am J Clin Nutr* 2006;83(suppl):470S-4S.

KEY WORDS Microglia, Alzheimer disease, interleukin 1, astrocytes

INTRODUCTION

Originally described by Alois Alzheimer in 1907 (1), Alzheimer disease (AD) is now the most common cause of dementia in the elderly. The 2 major neuropathologic hallmarks of AD are extracellular β -amyloid plaques and intracellular neurofibrillary tangles.

The production of β -amyloid, a seminal event in AD (2), is a result of cleavage of β -amyloid precursor protein (β -APP), which is overexpressed in AD. β -APP has important developmental functions in cell differentiation and possibly in the establishment of synapses (3, 4). Its function in the adult brain is less clear, but it seems to be associated with neuronal growth and survival. What we do know, however, is that it is expressed by neurons in response to cell injury; for example, β -APP is a marker for axonal damage after a head injury (5, 6), and β -APP expression is markedly increased in the affected areas of the brain in temporal lobe epilepsy (7).

Neurofibrillary tangles are composed of the tau (τ) protein. In healthy neurons, τ is an integral component of microtubules, which are the internal support structures that transport nutrients, vesicles, mitochondria, and chromosomes from the cell body to the ends of the axon and back. Microtubules also stabilize the growing axons necessary for the development and growth of neurites. In AD, however, τ becomes hyperphosphorylated, which allows it to bind together and form tangled threads (8).

Gliosis is also seen in AD: activated astrocytes and microglia are characteristically found in abundance near neurons and

plaques, and this can be seen even in a case described by Alzheimer in 1911. This suggests that inflammation may be involved in AD, because glial cells mediate the innate immune response in the central nervous system. When activated, astrocytes and microglia produce several proinflammatory signal molecules, including cytokines, growth factors, complement molecules, and adhesion molecules. Of particular interest in AD are the cytokines S100 β , which is mainly produced by astrocytes, and interleukin 1 (IL-1), which is mainly produced by activated microglia.

ASSOCIATIONS BETWEEN S100 β , INTERLEUKIN 1, AND ALZHEIMER DISEASE

Does anything suggest that these cytokines have a role to play in AD? Over the past years, a body of circumstantial evidence has built up implicating both S100 β and IL-1 in this disease.

S100 β

Under normal circumstances, S100 β promotes the growth of neurites, stimulates astrocyte proliferation, and increases free calcium concentrations in both neurons and astrocytes. However, overexpression of S100 β may have deleterious consequences, including excessive growth of the dystrophic neurites that characterize the neuritic β -amyloid plaques diagnostic of AD.

Marshak et al (9) reported that S100 β is overexpressed in the brains of AD patients, especially in the temporal lobe, where neuritic plaques are concentrated. Furthermore, S100 β , S100 β messenger RNA (mRNA), and specific neurotrophic activity were 10- to 20-fold higher in AD patients than in age-matched controls, and the excess S100 β was localized to activated astrocytes surrounding the neuritic plaques. This led Marshak et al to suggest that elevated levels of S100 β may contribute to AD neuropathology. This idea was substantiated by reports showing that S100 β expression is related to the number of neuritic plaques in the temporal lobe (10) and across brain regions in AD (11).

S100 β and S100 β mRNA expression increases with age in healthy brains (12), as does the risk of AD. Mice that undergo

¹ From the Donald W Reynolds Department of Geriatrics, The University of Arkansas for Medical Sciences, and the Geriatric Research Education Clinical Center, Central Arkansas Veterans Healthcare System, Little Rock, AR.

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⁴ Reprints not available. Address correspondence to S Griffin, 629 Jack Stephens Drive, Room 3103, Little Rock, AR 72205. E-mail: griffinsuet@uams.edu.

premature aging express higher concentrations of S100 β than can be explained by age alone (13).

Interestingly, head injury is also a risk factor for AD (5), and head-injured patients have higher concentrations of S100 β , which have been correlated with negative outcomes (14). Furthermore, in humans, the older the patient is, the more likely it is that β -amyloid deposition will occur after a head injury (5), which provides an interesting correlate between the underlying S100 β activity and one of the characteristic events in AD.

Expression of S100 β also shows remarkable correlations with the number of dystrophic neurites found in plaques in different stages of evolution (15). Plaques start as diffuse nonneuritic deposits, which have the least dense and most widely dispersed β -amyloid but no dystrophic neurites. As the plaque evolves, the β -amyloid becomes more dense and dystrophic neurites proliferate (diffuse neuritic plaques); S100 β expression is highest in these plaques. Dense-core neuritic plaques have both compact and diffuse β -amyloid; these plaques have the next highest expression of S100 β . The most developed plaque, the dense-core nonneuritic plaque, or "burned out" plaque, has only compact β -amyloid, no dystrophic neurites, and virtually no associated S100 β expression (11).

Mrak et al (15) found that the numbers of activated astrocytes overexpressing S100 β are highly correlated with the amount of dystrophic neurites present in plaque-rich brain regions as well as per plaque. S100 β -expressing astrocytes are most abundant in diffuse neuritic plaques, less abundant in diffuse nonneuritic plaques and dense-core neuritic plaques, and rarely present in dense-core nonneuritic plaques. This, they concluded, supports the idea that astrocyte activation and expression of S100 β are involved in the induction and maintenance of dystrophic neurites in amyloid deposits.

Interleukin 1

IL-1 is a well-characterized proinflammatory cytokine that has been implicated in several chronic degenerative disease processes, including the development of atherosclerosis and rheumatoid arthritis (16, 17). In AD, it is associated with both β -amyloid plaque and dystrophic neurite formation.

In terms of β -APP overexpression, after a head injury, the number of activated microglia expressing IL-1 α increases by a factor of 3, and this is associated with a 7-fold increase in the number of neurons with elevated β -APP concentrations (18). What is more, clusters of dystrophic neurites containing β -APP are always associated with activated microglia expressing IL-1 α . Taken together with the role of IL-1 in the regulation of synthesis of β -APP, these data suggest that IL-1 contributes to the rapid overexpression of β -APP after head injury.

A similar pattern was also reported in temporal lobe epilepsy (7): microglia expressing IL-1 were 3 times as common, and neurons containing β -APP were 16 times as common in post-mortem samples from patients with epilepsy than in samples from similar patients whose death was not related to brain injury. Again, the β -APP-containing neurons were often found next to the IL-1-expressing microglia.

The underlying cause of dystrophic neurite formation is the presence of neurofibrillary tangles composed of hyperphosphorylated τ , and in AD, plaques with neurites and neurons that contain τ are found in the same areas of the brain as activated microglia expressing IL-1 α (19). Interestingly, the presence of

activated astrocytes expressing S100 β is also correlated with activated microglia expressing IL-1 α .

As plaques develop, the number of activated IL-1-expressing microglia associated with each plaque also changes and follows a pattern similar to that seen for activated astrocytes expressing S100 β (20): activated microglia are found in diffuse nonneuritic plaques but are most abundant in diffuse neuritic plaques and then become increasingly less common as the plaque evolves, such that none can be found in dense-core nonneuritic plaques. These changes precede those seen for β -APP-positive dystrophic neurites, which suggests that IL-1-expressing activated microglia and S100 β -expressing astrocytes are necessary for the initiation of dystrophic neurite formation in diffuse β -amyloid plaques.

Finally, there are well-characterized polymorphisms of the IL-1 gene cluster, which is located on the long arm of chromosome 2 and which includes the genes coding for IL-1 α (*IL-1A*), IL-1 β (*IL-1B*), and the receptor antagonist IL-1Ra (*IL-1RN*). The C \rightarrow T polymorphism 889 base pairs before the *IL-1A* gene (designated *IL-1A* [-889] allele 2) may cause an overexpression of IL-1 α and is associated with several inflammatory diseases; carriers of this allele also have an increased risk of development of AD (21–23). One study reported that patients homozygous for *IL-1A* [-889] allele 2 show an onset of AD 9 y earlier than in patients with the wild-type genotype (22). A modest increase in risk of late-onset AD was also reported for polymorphisms of the *IL-1B* and *IL-1RN* genes (22), and homozygosity for allele 2 of both *IL-1A* and *IL-1B* confers an even greater risk of AD (23).

These results form a powerful, if circumstantial, body of evidence that inflammation is an intimate component of the development and progression of AD. However, to demonstrate that it is the driving force in AD and not simply a consequence of neuronal distress, we must demonstrate that inflammation precedes the development of plaques.

DOWN SYNDROME AS A MODEL FOR ALZHEIMER DISEASE

Whether inflammatory events precede plaque development raises one of the challenging issues in Alzheimer pathogenesis: AD can only be studied, or in fact definitively diagnosed, post-mortem. However, virtually all persons with Down Syndrome (DS) develop AD in middle age rather than in old age (24). A series of DS cases ranging from fetuses through newborns, children, and adults has provided a way to establish whether inflammation in DS, with its prospect of AD with age, is cause or effect.

In these DS cases, the density of activated microglia overexpressing IL-1 was as much as 30 times higher than in age-matched controls; a similar order of magnitude to that reported in AD (25). This dramatic overexpression of IL-1 was present in both prenatal and postnatal tissue, well before the appearance of β -amyloid deposits, which only sometimes occurs during, and most often after, adolescence (25).

Expression of S100 β in trisomy 21, ie, DS, was expected to be 1.5 times higher than in age-matched controls, because the gene is carried on chromosome 21. However, at all ages in DS, even pre- and postnatally, the number of S100 β -expressing activated astrocytes was at least twice that of age-matched controls and again similar to that reported for AD (25). This increase cannot be accounted for by gene loading and suggests that IL-1 promotes S100 β expression.

Also of interest, β -amyloid plaque deposition is increased in DS (24), and there are significant correlations between this deposition and S100 β expression across and within age groups (26). These findings are consistent with the theory that S100 β overexpression promotes β -amyloid plaque formation.

Finally, to complete this picture, the glial activation and the overexpression of IL-1 and S100- β in DS precedes by decades the appearance of hyperphosphorylated τ , which is required for the formation of neurofibrillary tangles (26). These data demonstrate that in DS the overexpression of IL-1 and S100 β is similar to that seen in AD, except that it precedes the development of β -amyloid plaques and neurofibrillary tangles by a considerable length of time. These data thus show that inflammation is a driving force in the neuropathology of AD in DS.

CONNECTING THE DOTS

How can we connect these facts? For this, we must rely on animal and in vitro data to help elucidate the pathways and control mechanisms involved.

One obvious step would be to see what happens when there is an excess of IL-1. In vitro experiments have shown that IL-1 can up-regulate the expression and processing of β -APP (27–29). This has also been shown in rats: direct injection of IL-1 into the brain results in an increase in β -APP expression compared with that in saline-injected and uninjected controls (30). Injection of IL-1 also increases astrocyte activation, expression of S100 β and S100 β mRNA, and the numbers of astrocytes overexpressing S100 β (30). These findings point to a central role for IL-1 in the development of AD.

As well as its direct effect on β -APP expression, IL-1 exerts an indirect effect via its stimulation of astrocytes to express S100 β . S100 β promotes the formation of dystrophic neurites that express β -APP, and in vitro experiments have shown that S100 β can directly increase the expression of β -APP and β -APP mRNA in a time- and dose-dependent manner (31). Finally, in DS, the number of astrocytes overexpressing S100 β correlates with the number of neurons overexpressing β -APP (32). Thus, not only does IL-1 directly increase β -APP expression, it also activates astrocytes, which then express S100 β , which also stimulates β -APP production.

Transgenic mice that overexpress β -APP have helped to identify another twist in this story. Not surprisingly, these mice develop AD-like neuritic β -amyloid plaques surrounded by astrocytes. What was particularly interesting, however, was that they had increased numbers of activated astrocytes and tissue concentrations of S100 β several months before the age-related appearance of β -amyloid deposits, which suggests that β -APP can activate astrocytes independently of β -amyloid deposits (33). This may provide an explanation of the increased concentrations of S100 β reported in DS decades before the appearance of plaques. Secondly, it suggests that there may be a self-sustaining feedback loop in operation: S100 β can increase the expression of β -APP (31) and β -APP can stimulate the expression of S100 β (33).

In vitro experiments have also shown that S100 β can induce the production of another proinflammatory cytokine: IL-6 (34). IL-6 is produced by astrocytes and microglia (35–37), although neurons can also express IL-6 in response to injury-related stimuli (38). In AD, IL-6 is overexpressed and can be detected in β -amyloid plaques (39). Administration of S100 β induces IL-6 expression in a time- and dose-dependent manner in neurons (and

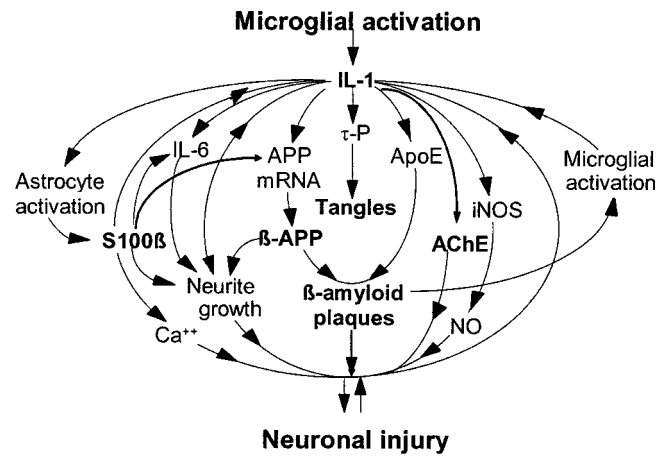


FIGURE 1. The central role of interleukin 1 (IL-1) in the cytokine cycle in Alzheimer disease. The neuropathologic features of Alzheimer disease include neuritic β -amyloid plaques, neurofibrillary tangles, synapse and neuronal dysfunction and loss, reduced neurotransmitter concentrations, and activation of glial cells with expression of proinflammatory cytokines. IL-1 directly regulates molecular aspects of each of these events: expression and processing of β -amyloid precursor protein (β -APP) in neurons, which favors plaque formation and progression; phosphorylation of τ (tau), which favors neurofibrillary tangle formation; increased production and activity of acetylcholinesterase (AChE), the enzyme responsible for breakdown of a neurotransmitter important in learning and memory; decreased production of synaptophysin and increased production of inducible nitric oxide synthase (iNOS), which favors direct cell killing; and activation of astrocytes with overexpression of S100 β , which causes the growth of neurites and increases calcium flux (a deadly event) in neurons. Each of these IL-1-regulated processes results in neuronal stress or injury, which in turn further enhances microglial activation and IL-1 overexpression. The result is a self-propagating cycle—a vicious circle of IL-1 overexpression, neuronal stress, and further neuronal dysfunction and death. ApoE, apolipoprotein E; mRNA, messenger RNA; NO, nitric oxide.

to a lesser extent in nonneuronal cells, probably glia) and is mediated by the transcription factor nuclear factor κ B (34).

Interestingly, S100 β induces the expression of IL-1 β in cultured rat microglia and neurons in a dose- and time-dependent manner (40), a process mediated in microglia by the transcription factors nuclear factor κ B and Sp1. This is another example of a self-sustaining feedback loop in the pathophysiology of AD: IL-1 β activates astrocytes and up-regulates S100 β expression, and S100 β up-regulates the expression of IL-1 β by microglia.

THE CYTOKINE CYCLE

The evidence now points compellingly to a central role for inflammation in AD, mediated by proinflammatory cytokines and creating a chronic and self-sustaining inflammatory interaction between activated microglia and astrocytes, stressed neurons, and β -amyloid plaques. A key initiating factor appears to be overexpression of IL-1, which may be a result of any number of events, including disease, trauma (such as head injury or epilepsy), genetic polymorphisms, or simply age-related wear and tear.

Once IL-1 is present in excess, it starts a cascade of events that includes several feedback loops, setting in motion a self-sustaining cycle resulting in progressive neuronal death (Figure 1; 41). 1) IL-1 activates astrocytes, leading to increased S100 β expression. S100 β overexpression causes dystrophic neurite growth, which in turn stimulates neurons to produce β -APP



(which stimulates S100 β expression); increases intracellular calcium concentrations, which promotes cell death; induces the expression of IL-6; and promotes the expression of IL-1 β . 2) IL-1 directly stimulates neuronal synthesis of β -APP, leading to the production of β -amyloid, which in turn directly activates microglia and increases IL-1 β expression (42). 3) IL-1 directly promotes microglial proliferation (43) and increases microglial expression of IL-1 and IL-6 (37, 44). All these processes act to increase the stress on the neurons (thereby stimulating them to produce yet more β -APP), acting to feed back into the cycle. Thus, we begin to see the outline of a powerful, self-sustaining, and deleterious interaction among the cytokines, neurons, and glia that make up the "cytokine cycle" (41).

ADDITIONAL EFFECTS OF INTERLEUKIN 1 IN ALZHEIMER DISEASE

The multifarious roles of IL-1 in the AD brain do not stop there, however. A central element in AD is cholinergic dysfunction (45, 46), which has been attributed to stress-induced increases in the activity of the enzyme acetylcholinesterase (AChE). (These increases are in fact the target for the only established therapy available for AD, the AChE blockers.) Studies have shown that AChE is overexpressed by neurites in AD plaques (47) and that it regulates the processing of β -APP (48), which suggests a link between AChE and the formation of plaques. An obvious question, in the context of this cytokine cycle, concerns the effect of IL-1 on AChE expression.


If neurons in mixed cell cultures of neurons and glia are traumatized with glutamate, there is an increase in expression and secretion of β -APP (49). This leads to an increased expression of IL-1 from microglia, which in turn promotes neuronal expression and activity of AChE. Similar results were seen in vivo: when slow-release pellets impregnated with IL-1 β were implanted in rat brains, significant increases in AChE mRNA could be detected within 21 days compared with both normal (non-operated) and sham implant controls. In other words, IL-1 is implicated at the root of cholinergic dysfunction in AD.

IL-1 is also implicated in the hyperphosphorylation of τ , a necessary event in the formation of hyperphosphorylated τ , the principal component of the neurofibrillary tangles so characteristic of AD. Implantation of IL-1 slow-release pellets into rat brains with the use of a surgical protocol similar to one described above increases relative levels of τ mRNA and hyperphosphorylated τ (50). This effect is mediated by mitogen-activated protein kinase p38 (MAPK-p38). This enzyme is known to phosphorylate τ at precisely those sites that are hyperphosphorylated in AD (51), and time-release pellets impregnated with IL-1 cause significant increases in the tissue concentrations of MAPK-p38 mRNA in rat brains, as well as increases in the growth of dystrophic neuronal processes (52). In addition, in AD, some 82% of neurons immunoreactive for MAPK-p38 are also immunoreactive for hyperphosphorylated τ . There is also a significant correlation between the numbers of activated microglia overexpressing IL-1 and the numbers of both hyperphosphorylated τ and MAPK-p38-immunoreactive neurons (52). When activated microglia are added to a cell culture of neurons, there is a significant increase in τ phosphorylation (53). A similar effect is seen if IL-1 β is added to the neuron culture instead, and this effect is attenuated by co-treatment with IL-1Ra. Co-treatment with an inhibitor of MAPK-p38 reverses the influence of IL-1 β on τ

phosphorylation (53). So again, IL-1 is playing a seminal role in the pathogenesis of a characteristic element of AD.

Finally, another mechanism may perpetuate the inflammatory processes in AD: dying neurons release significant amounts of fragmented DNA. When microglia are incubated in vitro with these DNA fragments, they become activated and overexpress IL-1 β (54), which will, through the pathways and interactions outlined in this article, promote neuronal dysfunction and death.

CONCLUSION: THE CYCLE CONTINUES

This brings us back to the cytokine cycle: neuronal dysfunction and death result in the cognitive loss and dementia so characteristic of AD and also perpetuate the cycle by stimulating the overexpression of IL-1 β by activated microglia. This once again places IL-1 central to the pathogenesis of AD: it is directly responsible for β -APP production by neurons; it activates astrocytes, which leads to the overexpression of S100 β , which causes the growth of neurites and increases calcium flux (a deadly event) in neurons; it increases the phosphorylation of τ (favoring tangle formation); and it promotes the activation and expression of AChE (thus down-regulating the cholinergic system). But not only does IL-1 cause neuronal injury, it also gives rise, both directly and indirectly, to more inflammation and creates a self-sustaining, vicious circle. It directly stimulates its own production; β -amyloid, produced from β -APP, stimulates its production; S100 β stimulates its production; and, finally, the death of neurons leads to a further increase in microglial activation and still more expression of IL-1. The cytokine cycle continues. 

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