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Review

The role of chronic self-propagating glial responses in neurodegeneration: Implications for long-lived survivors of human immunodeficiency virus

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Within the last decade there has arisen increasing appreciation of the role of glia-derived immune and neurotrophic cytokines, especially microglia-derived interleukin-1 and astrocyte-derived S100β, in the pathophysiology of Alzheimer's disease and of neurodegeneration in general. Available evidence now suggests that these neurotrophic and immune cytokines, produced in response to neuronal cell dysfunction or death, may elicit cellular and molecular responses resulting in further activation of glia and glial cytokine secretion, producing a *cytokine cycle*. In conditions characterized by chronic glial activation this cycle becomes self propagating, promoting further neurodegeneration and subsequent further induction of glial cell activation with production of cytokines. In Alzheimer's disease, for instance, such self-propagation is essential to the progressive accumulation of neuropathological changes that underlie progressive dementia. Conditions that predispose one to Alzheimer-type 'senile' neuropathological changes, and to later development of Alzheimer's disease, also exhibit glial activation and overexpression of glial cytokines, providing further evidence of a pathogenic role for glial activation and cytokine cycle elements in the initiation and propagation of Alzheimer lesions. HIV produces a chronic viral infection of the central nervous system that has been associated with chronic glial activation and overexpression of some of the same cytokines that have been implicated in Alzheimer pathogenesis. These observations, together with established functions of cytokine cycle elements, suggest that chronic HIV infection in sufficiently long-lived HIV-infected individuals might confer additional risk for later development of Alzheimer's disease.

Keywords: AIDS; Alzheimer's disease; astrocytes; interleukin-1; microglia; S100β; inflammation

Introduction

Glial activation has long been recognized as a 'normal' or reparative response to tissue injury and death in the brain. The molecular mechanisms underlying the postulated 'reparative' functions, however, are only now beginning to be understood. Glial activation (or 'reaction', as it was called) was once thought to either resolve or to result in a static state characterized by prominent process-bearing astrocytes ('gliosis'). Activated glia – both astrocytes and microglia – are now known to elaborate and secrete a number of neuroactive molecules – glial cytokines – that have potentially beneficial neurotrophic and immune effects in coordinating responses to tissue injury and perhaps in ameliorating damage to and loss of neurons subjected to sublethal insults. However, it is now recognized that chronic activation of glia, with chronic overexpression of these same glial cytokines, promotes and sustains potentially damaging effects that result in further neurodegeneration. Two cytokines in particular, microglia-derived interleukin-1 (IL-1) and astrocyte-derived S100β, appear to be driving factors in chronic neurodegeneration.

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Chronic glial activation in Alzheimer's disease

Chronic glial activation with overexpression of cytokine cycle elements is a prominent feature of Alzheimer's disease (Griffin *et al*, 1989). Activated glia overexpressing IL-1 and S100β are found in association with every stage of neuronal degeneration (Sheng *et al*, 1997) and with the formation of neuritic plaques – the key diagnostic histopathologic feature of the disease. This, together with the known functions of these cytokines suggest that the progression of both neuronal degeneration and plaque formation is driven by these glia-derived molecules (Sheng *et al*, 1994b; Griffin *et al*, 1995a; Mrak *et al*, 1996a). Further evidence for this suggestion is provided by two findings. One is the distributions across brain regions of activated glia, overexpressing IL-1 and S100β, which correlates with the pattern of spread of neuronal degeneration and of neuritic plaques in Alzheimer's disease (Sheng *et al*, 1995; Van Eldik and Griffin, 1994). The other is that the so-called benign amyloid deposits that are found sometimes in neurologically normal patients (Crystal *et al*, 1988; Katzman *et al*, 1988) do not have associated activated microglia (Mackenzie *et al*, 1995). This suggests that the conversion of benign non-neuritic amyloid deposits into diagnostic neuritic plaques requires the actions of glia-derived neurotrophic and immune cytokines. These two lines of evidence suggest that glial activation and glial cytokine elaboration are key pathogenic factors in the two neurodegenerative events most characteristic of Alzheimer's disease.

The known trophic and toxic effects of the cytokines elaborated by neuron- and plaque-associated glia suggest a mechanism for driving disease progression (Mrak *et al*, 1995). Interleukin-1 promotes synthesis (Goldgaber *et al*, 1989; Forloni *et al*, 1992) and processing (Buxbaum *et al*, 1992) of β-amyloid precursor protein (β-APP), a normal membrane protein that can be cleaved to form either the amyloidogenic peptide, deposited in neuritic plaques, or neurotrophic fragments (Barger *et al*, 1993). This provides mechanisms both for further neuronal β-APP expression, with amyloid production and deposition, and, because amyloid is neurotoxic (Yankner *et al*, 1990), for injury to the neurons and neurites present within neuritic plaques.

The findings that IL-1 activates astrocytes (Giulian *et al*, 1988) and stimulates astrocytic overexpression of S100β (Sheng *et al*, 1996b) are of prime importance as these actions thus may be responsible for attracting the shell of activated astrocytes that encircle neuritic plaques (Sheng *et al*, 1994b; Mrak *et al*, 1996a). IL-1 has also been shown to induce astrocytic expression of many other molecules known to be deposited in neuritic plaques, including α_1-antichymotrypsin (Das and Potter, 1995), apolipoprotein E (Das and Potter, 1995), and the complement protein C3 (Barnum and Jones, 1995). Interleukin-1-induced, astrocyte-derived S100β is a neurite growth-promoting cytokine (Kligman and Marshak, 1985) that has been implicated in promoting the growth of the abnormal, swollen ('dystrophic') neurites that characterize neuritic plaques (Sheng *et al*, 1994b). Tissue levels of biologically active S100β are elevated in brains of Alzheimer patients (Marshak *et al*, 1992). Moreover, the cross sectional area of dystrophic neurites correlates with the number of plaque-associated, S100β-immunoreactive astrocytes in individual neuritic plaques in Alzheimer's disease (Mrak *et al*, 1996a).

The observations discussed above suggest that IL-1 and S100β are key components of a cascade of events that is initiated by microglial responses to neuronal dysfunction or loss (Figure 1). In this *cytokine cycle*, containing components of 'normal' reparative responses to tissue injury, activated microglia are responsible for clearing cellular debris and expressing IL-1 which, in turn, activates astrocytes and stimulates expression of S100β for maintenance and repair of damaged neurons, growth of neurites and synthesis of membrane proteins such as β-APP. Chronic high levels of glial activation and cytokine overexpression may, however, result in neuronal injury arising indirectly from excessive protein expression and growth of processes as well as directly from the neurotoxic effects of these cytokines at elevated levels. A similar pattern of degenerative effects resulting from excessive expression of inflammatory cytokines such as IL-1 is also observed in various peripheral degenerative diseases (Dinarello and Wolff, 1993).

Chronic glial activation in conditions predisposing to Alzheimer's disease

The idea that chronic glial activation is a key pathogenic component underlying the initiation and progression of degenerative changes in Alzheimer's disease yields two testable predictions: (i) that conditions known to predispose to Alzheimer's disease or to Alzheimer-type neuropathological changes should show chronic activation of glia with chronic overexpression of glial cytokines, and (ii) conversely, that diseases or conditions characterized by chronic glial activation and overexpression of glial cytokines should place patients at increased risk for the latter development of Alzheimer's disease. There is now evidence supporting the validity of both these predictions.

The prime risk factor for the development of Alzheimer's disease is aging itself. We have shown progressive overexpression of microglial IL-1 and astrocytic S100β with normal aging – an observation that may explain in part the age-associated incidence of this disease (Sheng *et al*, 1996a; Mrak *et al*, 1996b). Another important risk factor for the

later development of Alzheimer's disease is head injury (Gautrin and Gauthier, 1989; Graves *et al*, 1990; Edwards *et al*, 1991; Gentleman and Roberts, 1992; Mortimer *et al*, 1991; Williams *et al*, 1991; van Duijn *et al*, 1992; Mayeux *et al*, 1993). Acute head injury is associated with amyloid deposition (Roberts *et al*, 1991, 1994; Graham *et al*, 1995), especially in genetically susceptible individuals (Nicoll *et al*, 1995; Graham *et al*, 1997), and we have shown glial activation with IL-1 and S100β overexpression associated with neuronal overexpression of β-APP occurring within hours of fatal head injury (Griffin *et al*, 1994; Gentleman *et al*, 1997).

Down's syndrome patients carry a near-100% risk for the development of early (fourth or fifth decade) dementia associated with severe Alzheimer-type neuropathological changes (Wisniewski *et al*, 1985). We have shown a sustained overexpression of microglial IL-1 and astrocytic S100β in Down's syndrome that is evident even before birth (Griffin *et al*, 1989; McKenzie *et al*, 1997).

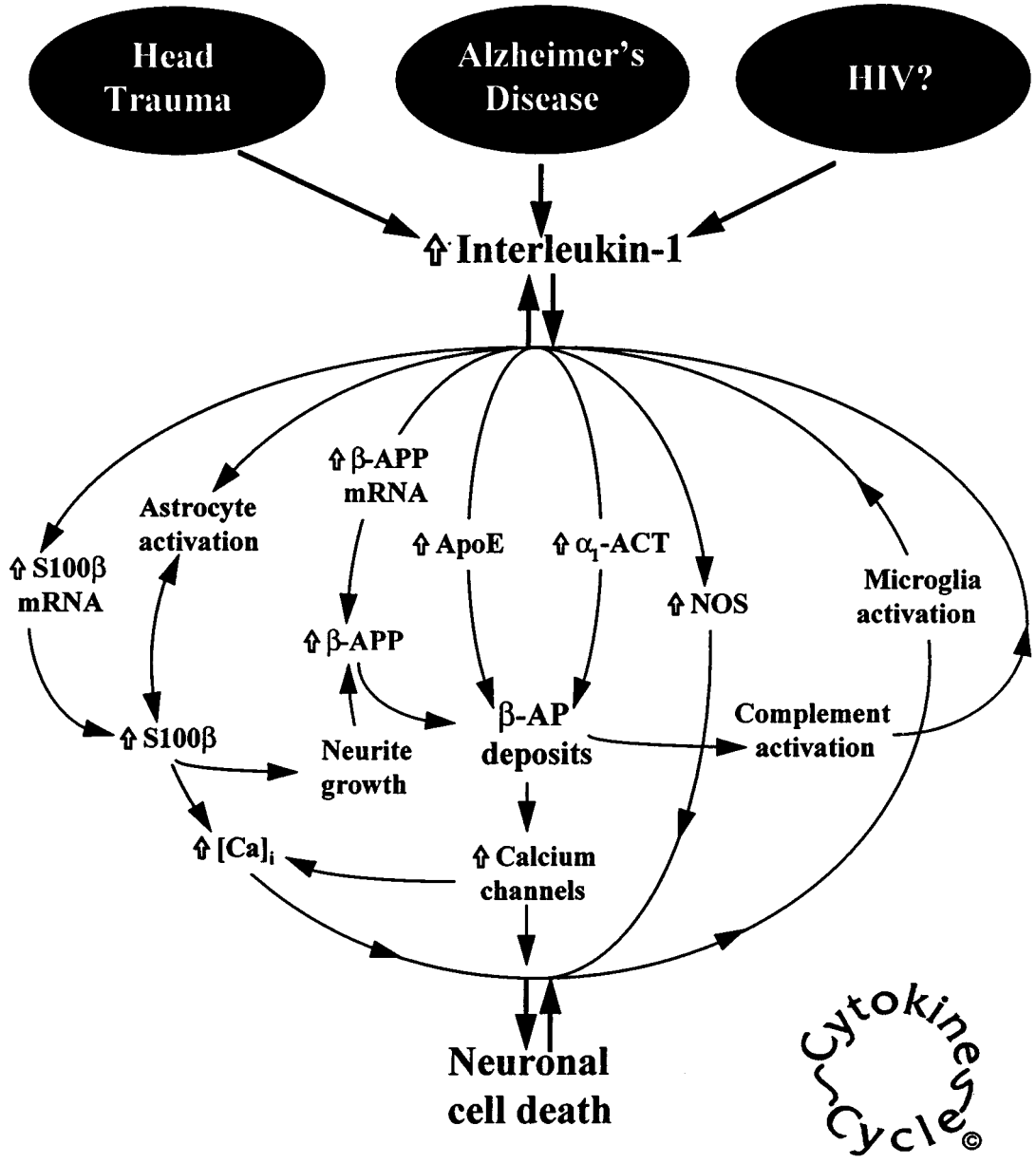

Figure 1 Diagrammatic representation of mechanisms by which insults such as head injury, Alzheimer's disease, and HIV infection may propagate neuronal dysfunction and death through glial activation with overexpression of interleukin-1 (IL-1). β-APP is β amyloid precursor protein; ApoE is apolipoprotein E; α_1-ACT is α_1-antichymotrypsin; NOS is nitric oxide synthase; and β-AP is β-amyloid protein.

In contrast to head injury and Down's syndrome, chronic epilepsy is a condition that has not been previously associated with increased risk for development of Alzheimer's disease. We have shown chronic glial activation and glial cytokine overexpression in temporal lobe specimens resected for intractable partial complex epilepsy (Sheng *et al*, 1994a; Griffin *et al*, 1995b). These latter findings are significant in light of reports of accelerated development of Alzheimer-type 'senile' changes in such patients (Mackenzie and Miller, 1994), and recent epidemiological data suggesting that these patients may carry an increased risk of Alzheimer's disease itself (Breteler *et al*, 1995).

Glial activation in HIV infection

The work reviewed here supports our early suggestion (Griffin *et al*, 1989) that glial activation and glial cytokine overexpression are common pathogenic mechanisms underlying the increased risk of Alzheimer's disease, and suggests that any condition resulting in sustained glial activation and chronic glial cytokine overexpression may confer increased risk of Alzheimer-type neurodegenerative changes. Transient activation of glia accompanies many viral encephalitides, but the chronicity of viral infection seen in HIV-infected patients is unusual if not unique. Chronic microglial activation, resulting directly from HIV infection of microglia, is well recognized in HIV-infected individuals (Kure *et al*, 1990), and we have shown microglial overexpression of IL-1 and astrocytic overexpression of S100β in the brains of HIV-positive individuals, even those dying before the onset of AIDS or of HIV-associated dementia (Stanley *et al*, 1994). These changes are accompanied by increased expression of β-APP in neurons and in overgrown (dystrophic) neurites, and by the occasional appearance of *tau* immunoreactive intraneuronal inclusions similar to the neurofibrillary tangles of Alzheimer's disease (Stanley *et al*, 1994).

Progression of neurodegenerative changes after eradication of viral infection has been described for other virus-related encephalopathies (Lohler, 1988), and pathogenic similarities between Alzheimer's disease and HIV-associated dementia have been proposed (Manuelides and Manuelides, 1989). This, together with the neurodegenerative effects of chronic activation of cytokine cycle elements, suggest that neurodegeneration arising from chronic glial activation in HIV infection might persist or progress even following successful eradication of the virus. If so, long-lived or even cured HIV patients may carry increased risk of later neurodegeneration and development of Alzheimer's disease. Intervention in the neurodegenerative cascade, perhaps at the level of IL-1, has been suggested for Alzheimer's disease (Royston *et al*, 1992; Roberts *et al*, 1993) and might be helpful in preventing such neurodegenerative progression following HIV infection as well.

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