Systemic inflammation and Alzheimer’s disease

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Abstract

A number of studies demonstrate disturbances of the central innate immune system in AD (Alzheimer’s disease). In animal and human studies, there is evidence of close communication between systemic and central innate immune systems. Animal models of neurodegeneration show evidence of an exaggerated central innate immune response following systemic inflammation. Clinical studies of AD show evidence of increased cognitive decline and exaggerated sickness behaviour in response to systemic inflammation. Recognition of this communication pathway offers alternative explanations for a number of recognized risk factors in the development and progression of AD and highlights the potential of the manipulation of systemic innate immunity as a novel therapeutic approach.

Introduction

In humans, evidence of communication between systemic inflammation and the CNS (central nervous system) is visible in a range of largely self-limiting and clinically benign behaviours, including lethargy, apathy, decreased social interaction and poor concentration, that become apparent following common systemic inflammatory events such as respiratory or urinary tract infections. These centrally derived behaviours are known collectively as ‘sickness behaviour’ and are not merely unpleasant side effects of infection; together they form an important, evolutionarily conserved, homoeostatic mechanism that allows the body to adapt to infection or injury [1]. Four major routes of communication from the periphery have been proposed, all of which lead to the secondary synthesis of cytokines and inflammatory mediators in the brain. First, inflammatory events in the thoracic abdominal cavity are signalled to the brain through vagal nerve sensory afferents, and in turn the vagal efferent outflow modifies these inflammatory events through acetylcholine secretion. Secondly, circulating cytokines and other inflammatory mediators (e.g. pathogen-associated molecular patterns) enter the blood and communicate directly with perivascular macrophages and other cells in circumventricular organs that lack a BBB (blood–brain barrier), initiating the transcription of pro-inflammatory cytokines across the brain parenchyma. Thirdly, cytokines and other inflammatory mediators interact by means of the induction of lipid mediators (e.g. prostaglandin E2) that communicate directly across the BBB [2]. Finally, there is evidence of the longer-term direct entry of immune cells (monocytes and possibly bone marrow derived microglial cells) from the periphery into the brain [3].

Thus communication between systemic and central immune systems can occur in the presence of an intact BBB. In AD (Alzheimer’s disease), where there is evidence of a breakdown in BBB permeability [4], there is an even greater likelihood of communication by means of inflammatory mediators between the CNS and periphery.

The innate immune response in AD

In the CNS, microglial cells are largely down-regulated with low or undetectable expression of cell surface antigens such as MHC class I and II molecules [5]. However, following an acute insult, such as a head injury or a CNS infection, resident microglia, like tissue macrophages, transform from their normal quiescent state to a morphologically different activation state that is characterized by the production of pro-inflammatory cytokines such as IL (interleukin)-1, IL-6 and TNFα (tumour necrosis factor α) and by an up-regulation or de novo synthesis of cell surface receptors or cytoplasmic antigens [6]. This up-regulation is tightly controlled at the translational level by anti-inflammatory molecules such as TGFβ1 (transforming growth factor β1) and IL-10 and also by interactions with neuronal cells. Thus neurons are known to express ligands, e.g. CD200, that interact with receptors, e.g. CD200R, on the surface of microglia to generate a down-regulated phenotype [7].

Expression of MHC class II is found at increased levels on the surface of microglia cells in AD in comparison with that of control brain tissue [8]. Microglia aggregate to a greater extent around amyloid-containing neuritic plaques than they do around diffuse plaques in AD, and many different laboratories have shown that microglia, in vivo as well as in culture, phagocytose exogenous fibrillar Aβ (amyloid β-peptide) [9]. These interactions are modulated in part by Toll-like receptors, suggesting that the expression of these innate immune receptors might be a mechanism to prevent the accumulation of Aβ in a CNS that may be impaired in AD [10]. Indeed, it has been suggested that Aβ may be considered to be an invading pathogen, since

Key words: Alzheimer’s disease (AD), amyloid β-peptide (Aβ), central nervous system (CNS), microglial cell, systemic inflammation.

Abbreviations used: Aβ, amyloid β-peptide; AD, Alzheimer’s disease; Apol, apolipoprotein E; APP, amyloid precursor protein; BBB, blood-brain barrier; CNS, central nervous system; CRP, C-reactive protein; IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; TGFβ1, transforming growth factor β1; TNFα, tumour necrosis factor α.

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bacteria produce similar amyloidogenic aggregates on their cell surfaces [11]. However, although phagocytosis of Aβ has generally been considered beneficial, there is also the possibility that this process may be harmful. Phagocytosis by peripheral macrophages is accompanied by the release of cytotoxic compounds. Moreover, phagocytosis by brain-derived macrophages in culture results in the release of potentially destructive reactive oxygen and nitrogen species [12] and TNFα [13]. Evidence of increased pro-inflammatory cytokines in AD brain has largely been obtained from studies of IL-1, with relatively few studies examining or showing elevation of IL-6 or TNFα levels in an AD brain [14–16]. In addition, it is important to note that the elevations of pro-inflammatory cytokines, when found in AD, are small in comparison with that which might occur following a direct microbial challenge. Thus, in a fashion analogous to inflammatory events following an acute central insult, in AD there is likely to be tight control of chronic inflammation within the CNS by means of anti-inflammatory molecules such as TGFβ1 [17].

We have hypothesized that the exposure of partially activated or ‘primed’ microglial cells (arising from their chronic exposure to amyloid or degenerating neurones) to recurrent acute and chronic pro-inflammatory systemic signals may lead to a switch in their phenotype from a largely down-regulated and controlled inflammatory state to one with an up-regulated and pro-inflammatory cytokine profile that may act as a potent driver of neuronal degeneration [18].

This hypothesis has been supported by a number of animal studies (see the accompanying review by Colm Cunningham in this issue of Biochemical Society Transactions [18a]) and in clinical studies of AD. A number of clinical studies have suggested an association between peripheral blood indicators of systemic inflammation and the subsequent development of AD. Thus inflammatory proteins in plasma, notably CRP (C-reactive protein) and IL-6, have been found to be elevated 5 years before the clinical onset of dementia in a number of studies [19–21]. More recently, a prospective study [22] suggested that cognitively intact individuals in the top tertile of studies [19–21] and TNFα [18] have been found to be elevated in serum 5 years before the clinical onset of dementia in a number of studies [19–21]. More recently, a prospective study [22] suggested that cognitively intact individuals in the top tertile of peripheral blood mononuclear cell TNFα (or IL-1β) production are at risk of developing AD, to a level that is thrice as high in comparison with those in the lowest tertile. We have shown that, in AD subjects, high serum levels of TNFα at baseline (top three quartiles as opposed to the bottom quartile) and increases in serum TNFα associated with intermittent systemic infections are associated with a marked increase in the rate of cognitive decline in AD subjects over a 6-month period that is independent of the acute effects of delirium [23].

Genetic risk factors
In a small number of individuals, less than 0.1% of the total AD population, mutations in one of three genes, PSEN1 (encoding presenilin 1), PSEN2 (encoding presenilin 2) and APP (amyloid precursor protein), or a duplication of the APP gene is directly responsible for the prevalence of the early onset of AD, which alters APP processing such that Aβ deposition is greatly enhanced. However, the majority (95%) of the cases of AD is of late onset. Until recently, the only established genetic risk factor in the development of late onset of AD was ApoE (apolipoprotein E) ε4. The role of ApoE ε4 in AD is still debated, but it is noteworthy that it has been shown to influence the degree of activation and neurotoxin production of microglia cells to Aβ [24] and is also a risk factor in other chronic neurodegenerative conditions including Parkinson’s disease that do not have Aβ plaques as a feature [25]. ApoE ε4 has also been suggested to influence outcomes in a number of CNS and systemic infections [26,27] and, more recently has been shown to be associated with attenuation of CRP peripheral blood levels in non-demented subjects [28]. In addition to ApoE ε4, a large number of other genetic polymorphisms in pro-inflammatory genes, either alone or in association with ApoE ε4, have also been implicated as risk factors in the development of AD. These include IL-1, IL-6, TNFα and α1-antichymotrypsin. These findings have not, however, always been replicated, possibly due to the small individual effect size of these polymorphisms. However, more recently, two large-scale genome-wide association studies have been performed that have placed the direct role of genetic variation in innate immunity into a clearer perspective. These studies [29,30] suggest that genes with important roles in immunity are genetic risk factors in the development of late onset AD.

Environmental risk factors
In late-onset AD, twin studies have suggested a heritability of approximately 60%, with non-shared environmental risk factors playing an increasingly important role in the aetiology of the disease with increasing age [31]. Research into the role of environmental infectious agents in the aetiology of AD has largely followed the hypothesis that there are specific CNS pathogens (in a fashion analogous to established pathogens in other chronic neurodegenerative diseases, e.g. HIV dementia or CJD (Creutzfeldt–Jakob disease) that have a direct influence on the pathogenesis of AD. Thus HSV (herpes simplex virus) type 1, Chlamyphila pneumoniae and Borrelia burgdorferi have all been proposed to be potential pathogens contributing to AD development. Each of these different pathogens has its own protagonists but there is a general paucity of consistent experimental evidence [32]. However, systemic infections in general are the major cause of delirium in the elderly, and delirium has been shown in a number of studies to be associated with an increased risk of development of dementia. Thus, in one study, this increased risk was found to be substantial, with a cumulative incidence of 55% with regard to the subsequent development
of dementia in cognitively intact individuals after a 1-year follow-up [33]. In addition, the risk of developing AD also increases following the development of an infection in the absence of an obvious delirium. Thus, in a retrospective general practitioner database, the presence of one or more infections over a 5-year follow-up period increased the odds of developing AD approximately 2-fold. This risk increased with increasing age; a finding that is consistent with the known decline of genetic stability with increasing age [34]. Other chronic inflammatory diseases, e.g. depression, atherosclerosis and obesity, have a clearer epidemiological basis for one to propose that they are risk factors in the development of AD. In the case of all of these risk factors, their individual attributable risk is likely to be small [35–37]. However, their combined cumulative effects over time might be considerable. Thus it is known that the sum of acute and chronic inflammatory events that the immune system experiences throughout life is accompanied by an age-dependent up-regulation of the inflammatory response [38]. This suggests that increasing age, the biggest risk factor in the development of AD, could be considered to be a proxy for increased time of exposure to systemic inflammation.

**Therapeutic implications**

It follows from the discussion regarding the close relationship between systemic and central innate immunity that systemic interventions might have beneficial effects with regard to preventing the activation of ‘primed’ central innate immunity. It also raises the question as to why some of the interventions aimed at central inflammation, also having peripheral anti-inflammatory effects [e.g. NSAIDs (non-steroidal anti-inflammatory drugs) and statins], have not been successful in AD treatment studies.

NSAID dosage in normal clinical practice reduces inflammation at locally inflamed sites, such as affected joints in rheumatoid arthritis, but has little effect on systemic inflammation and circulating cytokines [39]. Indeed, animal studies suggest that NSAIDs may paradoxically cause increased production of IL-1 and TNF-α in response to an intravenous endotoxin [42]. This paradoxical increase in systemic TNF-α in response to NSAID treatment might thus mitigate any central effects. Furthermore, the lack of appreciation of deleterious effects of systemic inflammation on cognitive outcomes in AD might explain why observational studies in populations with chronic inflammatory conditions might reap more benefits from NSAIDs than do randomized placebo control trials, where co-morbid disease is often an exclusion criterion. Similar considerations apply to statin therapy, and there are reports showing that statins have no effect on peripheral markers of inflammation in patients with AD [43]. To date, there has only been the exploratory use of systemic anti-TNF-α in human subjects [44]; the drug was well tolerated, but the study was too small to reveal any clinical benefit. A closer examination of the effects of systemic anti-TNF-α agents is warranted in view of the effective use of peripheral anti-TNF treatment in mouse models of AD [45].

Novel approaches require a greater understanding of the communication pathways lying between systemic and central innate immune systems. Manipulation of the inflammatory reflex has a number of potential applications in AD [46]. The finding that peripheral immune cells can be mobilized to the CNS [3] has also raised the controversial [47] possibility that stimulation of bone-derived microglia by the systemic M-CSF (macrophage colony-stimulating factor) might be beneficial in AD [48] as might other approaches, including genetic engineering of bone-derived microglial cells to favour their polarization towards neuroprotection [49]. What is clear is that our knowledge of the molecular communication between systemic and central immunity is in its infancy [18].

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**References**


