Neuroinflammatory changes increase the impact of stressors on neuronal function

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Abstract

In the last few years, several research groups have reported that neuroinflammation is one feature common to several neurodegenerative diseases and that similar, although perhaps less profound, neuroinflammatory changes also occur with age. Age is the greatest risk factor in many neurodegenerative diseases, and the possibility exists that the underlying age-related neuroinflammation may contribute to this increased risk. Several animal models have been used to examine this possibility, and it is now accepted that, under experimental conditions in which microglial activation is up-regulated, responses to stressors are exacerbated. In the present article, these findings are discussed and data are presented from *in vitro* and *in vivo* experiments which reveal that responses to A β (amyloid β -peptide) are markedly up-regulated in the presence of LPS (lipopolysaccharide). These, and previous findings, point to a vulnerability associated with inflammation and suggest that, even though inflammation may not be the primary cause of neurodegenerative disease, its treatment may decelerate disease progression.

Neuroinflammation is a feature of Alzheimer's disease

In the last decade or so, there has been a consolidation of the evidence demonstrating a causal relationship between neuroinflammatory changes and age-related deterioration in neuronal function. This correlation has been observed in several neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [1]. Since the original observation that the risk of developing Alzheimer's disease was demonstrated to be reduced in patients on long-term non-steroidal anti-inflammatory treatment [1], a great deal of interest has focused on examining the role of inflammation in the pathogenesis of the disease, in the anticipation that appropriate anti-inflammatory therapy may alleviate or limit the symptoms of the disease. Interestingly, some of the neuroinflammatory changes characteristic of Alzheimer's disease also occur in normal aging [2]; this is significant since age is the greatest risk factor for Alzheimer's disease and therefore it might be speculated that this risk is related to the underlying age-related inflammation.

One indicator of neuroinflammatory change which has been demonstrated in Alzheimer's disease is an increase in expression of pro-inflammatory cytokines, particularly IL (interleukin)-1 β which parallels, and probably contributes to, development of A β (amyloid β -peptide)-containing plaques [3]. This observation, and the finding that polymorphisms in genes encoding pro-inflammatory cytokines is associated with increased risk of developing Alzheimer's disease [3],

suggest a role for IL-1 β in its pathogenesis. Since microglial cells are the primary source of IL-1 β , it is not surprising that microglial activation is a feature of Alzheimer's disease where IL-1 β -positive microglia are found clustered around amyloid plaques [4,5]. Increased expression of MCP-1 (monocyte chemoattractant protein-1), which is another indicator of activated microglia, has been reported in serum and peripheral blood mononuclear cells of Alzheimer's disease patients and the evidence revealed that it correlated significantly with MMSE (Mini-Mental State Examination) score [6], whereas expression of ICAM-1 (intercellular adhesion molecule 1), which is yet another marker of activated microglia, co-localizes with A β -containing lesions [7]. It is interesting that up-regulation of inflammatory markers co-localizes with those areas of the brain which are mainly affected by the disease and are low or minimal in brain regions with very low Alzheimer's disease susceptibility [8].

Animal models of Alzheimer's disease exhibit neuroinflammatory changes

Much of the data suggesting that inflammatory changes occur in Alzheimer's disease have been supported by findings from animal models. First, in animal models, the increase in microglial activation in brain tissue is accompanied by up-regulation of pro-inflammatory cytokines such as interleukin-1 β , IL-6 and TNF α (tumour necrosis factor α) and chemokines such as MIP-1 α (macrophage inflammatory peptide-1 α), whereas nNOS (neuronal nitric oxide synthase) has been shown to co-localize with activated glia [9,10]. Secondly, there is evidence of increased microglial activation and increased pro-inflammatory cytokine production following injection of A β [11–15] and in transgenic mice

Key words: aging, amyloid β -peptide (A β), interleukin-1 β (IL-1 β), long-term potentiation (LTP), microglial activation, neurodegeneration.

Abbreviations used: A β , amyloid β -peptide; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; IFN γ , interferon γ ; LPS, lipopolysaccharide, LTP, long-term potentiation.

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which overexpress APP (amyloid precursor protein) [16]. Thirdly, the clustering of activated microglia around A β deposits which has been demonstrated in post-mortem tissue is also observed in animal models [17,18]. Finally, the evidence indicates that treatment of animals with cyclo-oxygenase inhibitors or agents which have been shown to possess anti-inflammatory properties such as the PPAR γ (peroxisome-proliferator-activated receptor γ) agonist pioglitazone or polyunsaturated fatty acids, such as docosapentaenoic acid or eicosapentaenoic acid, reduces markers of inflammation, reduces plaque burden and/or ameliorates A β -induced impairment in hippocampal functioning [11,13,14,16,19].

Neuroinflammatory changes are evident in other neurodegenerative conditions

In addition to Alzheimer's disease, neuroinflammatory changes have also been described in Parkinson's disease [20]. It is known that the underlying cause of Parkinson's disease is degeneration of dopaminergic neurons in the substantia nigra, and, although genetic and environmental factors are known to be major risk factors, it has been acknowledged that inflammatory changes are a feature of the disease. It remains to be established whether these inflammatory changes contribute to the pathogenesis of the disease or are a consequence of the cell loss. Among the indicators of neuroinflammation in Parkinson's disease is increased microglial activation in the substantia nigra [20], and polymorphisms in genes encoding pro-inflammatory cytokines have also been reported [21]. Consistent with evidence for inflammatory changes is the finding that non-steroidal anti-inflammatory treatment has beneficial, although limited, effects in modulating the symptoms of the disease [22].

An association between inflammatory changes and prion diseases, multiple sclerosis, amyotrophic lateral sclerosis and HIV has also been established [23–26]. Consistent with a role for inflammatory changes in the pathogenesis of these diseases is the finding that anti-inflammatory treatment, at least in some cases, can be beneficial. It should be acknowledged that, whereas neuroinflammation is a factor common to several neurodegenerative diseases, it may not be the initiator of the disease, but rather a secondary effect. However, there is undisputed evidence that neuroinflammatory changes trigger detrimental effects and, consequently, it is vital to consider the causes, consequences and strategies for limiting these detrimental effects.

Inflammatory changes and the aged brain

There is an increasing acceptance that normal aging is also associated with evidence of inflammatory change, and it is significant that some of the neuroinflammatory changes which have been observed in these neurodegenerative conditions also occur in normal aging, e.g. microglial activation, increased IL-1 expression and increased S100 β expression [2]. The age-related increase in microglial activation [27] has been associated with evidence of morphological changes including

loss of processes, dystrophic processes and pyknotic nuclei [4], and studies in aged animals have confirmed these observations [28], where an increase in expression of pro-inflammatory cytokines such as IL-1 β or IL-6 have been consistently reported [29,30]. These age-related changes are associated with a decrease in synaptic plasticity, specifically a reduction in LTP (long-term potentiation) [14,31], and a decrease in cognitive function, specifically poorer performance in hippocampal-dependent tasks [30].

It has been consistently shown that decreasing the inflammatory phenotype in the brain of aged animals decreases these impairments, therefore reducing the hippocampal concentration of IL-1 β , perhaps by increasing the concentration of the anti-inflammatory cytokine, IL-4, ameliorates the age-related impairment in LTP [14,31] and the deficit in spatial learning [32,33]. Similarly, an impairment in the hippocampal-dependent object-recognition task was observed with age, and this impairment was attenuated by dietary supplementation with blueberries which possess anti-oxidant and anti-inflammatory properties [32,34].

Microglial activation affects synaptic function

The probable source of the inflammatory cytokines is activated microglia, and there are several reports indicating that microglial activation accompanies increased expression of pro-inflammatory cytokines [28,33,35,36]; paired increases have been reported in aged and A β -treated rats, and, importantly, it has been shown that when microglial activation is decreased, IL-1 β concentration is also decreased. It has also been shown that the inhibitor of microglial activation, minocycline, restores LTP in aged rats [28] and A β -treated rats [12]. These findings illustrate the importance of maintaining microglia in a resting state for the preservation of synaptic function, and they highlight the need to understand the mechanisms involved in modulation of microglial function.

Among the most potent activators of microglia is IFN γ (interferon γ) [37], and the evidence shows that intracerebroventricular injection of IFN γ increases microglial activation [38], and that the age-associated [31] and A β -induced [12] increases in microglial activation are accompanied by increased hippocampal concentration of IFN γ . However recent data have highlighted the fact that microglial activation is also modulated by interaction of these cells with others. Data from this laboratory show that engagement of the cell-surface glycoprotein receptor CD200R, which is expressed on microglia, with its ligand CD200, which is expressed on neurons, maintains microglia in a quiescent state [39]. It is likely that a similar interaction with endothelial cells, which also express CD200, occurs and that other interactions between microglia and neurons, e.g. engagement of the fractalkine receptor (which is expressed on microglia) by fractalkine (which is mainly expressed on neurons) also affect microglial activation (A. Lyons, A.M. Lynch, E. Downes, R. Hanley, J.B. O'Sullivan, A. Smith and M.A. Lynch, unpublished work).

Figure 1 | LPS and A β exert an additive effect on mixed glia

(a) Incubation of mixed glia in the presence of LPS (10 ng/ml), but not A β ^{1–42} (2 μ M), significantly increased MHCII mRNA (** P < 0.01; ANOVA); co-incubation in the presence of both further increased MHCII mRNA (*** P < 0.001; ANOVA). (b) Co-incubation in the presence of LPS and A β significantly increased IL-1 β concentration (* P < 0.05; ANOVA), but neither agent alone exerted any significant effect. Results are means $\pm$ S.E.M. for six observations.

Evidence that increased microglial activation imposes vulnerability to stress

There is a growing awareness that underlying inflammation can exert a negative impact on the progression in some neurodegenerative diseases. Specifically, it has been shown that systemic infections can exacerbate symptoms and trigger rapid progression in Parkinson's disease [40], multiple sclerosis [41] and Alzheimer's disease [42], and that infection influences recovery in stroke [43].

It has been proposed that this increased susceptibility to a stressor is a consequence of an underlying increase in the activation state of microglia, which leads to release of inflammatory mediators, and this is borne out by findings from several laboratories using several model systems. Thus exposure of an animal to inescapable shock increases the response to LPS (lipopolysaccharide) [44], whereas, in a model of prion disease, induced by injecting mice with scrapie-infected brain homogenate, Perry and colleagues reported a more profound LPS-induced effect on temperature and locomotor activity compared with non-infected mice; these changes were paralleled by more marked changes in IL-1 β in the brain [45]. Consistently, treatment of aged mice with LPS or *Escherichia coli* or HIV-1 gp120 (glycoprotein 120), which stimulates the innate immune system, exacerbates depressive-like symptoms and sickness behaviour and exerts a greater effect on working memory [46–49]. In these experimental models, the exaggerated responses were attributed to increased microglial activation with, in some cases, increased resting concentrations of pro-inflammatory cytokines.

The evidence suggests that the effect of A β is dependent on inflammatory status, thus we have found that concentrations of A β which exerted no effect on IL-1 β production or LTP

Figure 2 | LPS and A β *in vivo* exert an additive effect on neuroinflammatory changes in hippocampus

MHCII mRNA (a), ICAM (b), IL-1 β (d) and IL-1 β mRNA (e) were significantly increased in hippocampal tissue prepared from rats which received chronic intracerebroventricular administration of LPS (0.5 mg/ml), A β (18.9 μ M A β ^{1–40} and 26.6 μ M A β ^{1–42}) alone or in combination for 28 days (* P < 0.05; ** P < 0.01; ANOVA), whereas CD200 (c) and IL-4 mRNA (f) were significantly decreased (* P < 0.05; ANOVA). A β alone exerted no significant effects on any measure except on IL-1 β , whereas LPS alone increased both IL-1 β and IL-1 β mRNA (* P < 0.05; ANOVA). Results are means $\pm$ S.E.M. for six to twelve observations.

in young rats enhanced the already increased IL-1 β concentration in hippocampus of aged rats and inhibited further the ability of these rats to sustain LTP [13]; we proposed that this was due to the underlying inflammation which is a feature of the aged brain. This additive effect of endogenous and exogenous stimuli, or even a synergism between them, has been described by several authors and has led to the proposal that, under circumstances in which microglia are in a primed state, inflammatory stimuli triggers an exaggerated response [42,45]. *In vitro* analysis has also indicated that prior exposure of glia to one inflammatory stimulus leads to a greater response to a second stimulus. For example, the data presented in Figure 1 indicate that incubation of rat glial cells in the presence of LPS and A β increased MHCII mRNA and IL-1 β production in an additive or even synergistic manner which is similar to results reported previously [50]. We have recently assessed the interaction of A β and LPS *in vivo* and show that, whereas chronic infusion with A β or LPS alone did not significantly affect hippocampal expression of MHCII mRNA, ICAM-1 or CD200, infusion of both significantly increased MHCII mRNA and ICAM-1

and significantly decreased CD200 (Figures 2a–2c); this inverse relationship supports the proposal that CD200 plays a role in modulating microglial activation [39]. The data also show that IL-1 β concentration in hippocampus prepared from rats treated with A β and LPS was significantly greater than that treated with either alone, although both stimuli individually increased IL-1 β (Figure 2d). Consistent with a modulatory effect of IL-4 on IL-1 β production [14], we show that the A β +LPS-induced increase in IL-1 β mRNA was accompanied by a decrease in IL-4 mRNA (Figures 2e and 2f). These findings are consistent with others which have also shown that coincident exposure to two stressors can result in amplification of the effect of either alone [46–49].

Conclusion

The data described here, and elsewhere [19], which demonstrate an interaction between A β and LPS and the finding that systemic infections can exacerbate symptoms and/or trigger the progression of some neurodegenerative diseases [40–42], suggest that reducing underlying inflammatory changes in the brain may be beneficial in limiting responsiveness to additional stressors. However the challenges are (i) to identify the time at which this intervention may be most effective, and (ii) to recognize that the limited success in clinical trials to date, in which anti-inflammatory agents are assessed in late chronic neurodegenerative disease, may be due to inappropriate timing of the intervention.

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