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 Aβ (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 IL1β (interleukin-1β) which parallels, and probably contributes to, development of Aβ (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 IL1β in its pathogenesis. Since microglial cells are the primary source of IL1β, it is not surprising that microglial activation is a feature of Alzheimer’s disease where IL1β-positive microglia are found clustered around amyloid plaques [4,5]. Increased expression of MCP1 (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 ICAM1 (intercellular adhesion molecule 1), which is yet another marker of activated microglia, co-localizes with Aβ-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-1β, IL6 and TNFα (tumour necrosis factor α) and chemokines such as MIP1α (macrophage inflammatory peptide-1α), 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 Aβ [11–15] and in transgenic mice.
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 $\beta$ 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$\beta$ 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$\beta$, perhaps by increasing the concentration of IL-1$\beta$ or 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].
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 [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 vitro analysis has also indicated that prior exposure of glia to one inflammatory stimulus triggers an exaggerated response [42,45]. In vitro analysis has also indicated that prior exposure of glia to one inflammatory stimulus triggers an exaggerated response [42,45].

In young rats enhanced the already increased IL-1β 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 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 Aβ is dependent on inflammatory status, thus we have found that concentrations of Aβ which exerted no effect on IL-1β production or LTP in young rats enhanced the already increased IL-1β 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 these experimental models, the exaggerated responses were attributed to increased microglial activation with, in some cases, increased resting concentrations of pro-inflammatory cytokines.

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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-1β concentration in hippocampus prepared from rats treated with Aβ and LPS was significantly greater than that treated with either alone, although both stimuli individually increased IL-1β (Figure 2d). Consistent with a modulatory effect of IL-4 on IL-1β production [14], we show that the Aβ+LPS-induced increase in IL-1β 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 Aβ 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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References


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