

Review Article

The Impact of Systemic Inflammation on Brain Inflammation

We have all at one time or another experienced the consequences of a systemic infection – we feel unwell or sick. As formalised by Hart (1988)¹ systemic infections have a profound effect on behaviour giving rise to the spectrum of changes known as “sickness behaviour”. Sickness behaviour is characterised by changes such as fever, reduced appetite, reduced activity and reduced social interaction (see figure). Sickness behaviour is part of our normal homeostasis and evolved not only as a mechanism to fight infections, but also as a possible mechanism to protect individuals, or the group, from spread of infection². This short review summarises what we know about how systemic inflammation is communicated to the brain, and highlights how these pathways may have a significant impact on ongoing brain inflammation associated with neurological disease.

Systemic inflammation communicates with the brain

In response to an infection inflammatory cytokines such as interleukin-1 ϵ (IL-1 ϵ) tumour necrosis factor- α (TNF- α) and interleukin-6 (IL-6) are generated at the site of infection. These cytokines circulate in the blood and communicate with neurons in the brain. There are at least four different pathways by which inflammation in peripheral tissues communicate with the brain³. Firstly, the cytokines may by-pass the blood-brain barrier at the circumventricular organs, and there bind to receptors on macrophages within these organs and activate them. Secondly, the circulating cytokines may activate the cerebral endothelial cells, which in turn activate the perivascular macrophages, that signal to the microglia within the parenchyma. Thirdly, cytokines may activate the sensory afferents of the vagus nerve within the abdominal and thoracic cavity, which communicate with neuronal populations within the brainstem. Finally, there is evidence that cytokines may be actively transported by the endothelium across the blood-brain barrier.

A major component of this signalling by systemic cytokines to the brain is the macrophage populations of the brain the perivascular macrophages and the microglia. These macrophage populations signal the presence of systemic inflammation to neurons by synthesising inflammatory mediators, including some of the same inflammatory cytokines as are induced peripherally. Microinjection of inflammatory cytokines such as IL-1 ϵ into the appropriate regions of the brain will evoke components of sickness behaviour.

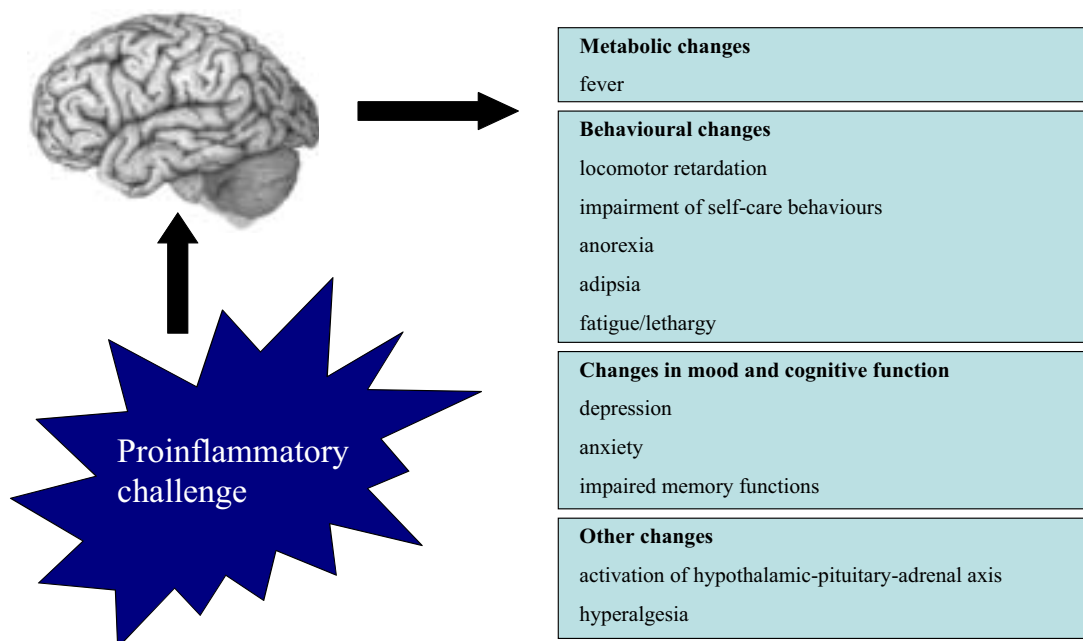
Since the macrophage populations in the brain play an important role in the transduction of signals from the peripheral immune system to neuronal populations in the brain it is clear that they will also play a key role in determining the gain, or amplitude, of the signal that is generated in the brain. It is well established that the resident populations of macrophages in the brain are relatively down regulated or switched off when compared to other tissue macrophages. However, if the perivascular macrophages and microglia in the brain are already activated or “primed” by ongoing pathology in the brain we might expect a systemic inflammatory response to now have a rather different effect from that seen in a normal healthy young brain⁴.

Inflammation in the brain

Multiple sclerosis is an inflammatory disease of the central nervous system with well-defined neuropathology. T-cells and macrophages invade the CNS, they damage the blood-brain barrier, cause demyelination and axon injury⁵. The macrophage populations within the focal plaques, and distal to the plaques, are more activated than those in the normal brain. In chronic neurodegenerative diseases such as Alzheimer’s disease (AD) and Parkinson’s disease (PD) there is also an ongoing inflammatory response, albeit highly atypical⁶. In these chronic neurodegenerative diseases the inflammation is dominated by cells of the mononuclear phagocyte/macrophage lin-



Professor V. Hugh Perry is Professor of Experimental Neuropathology and Director of Southampton Neuroscience Group at the University of Southampton. He has a particular interest in the contribution of inflammatory processes to neurological disease.



age. Macrophages and microglia in the brains of AD and PD patients are morphologically and phenotypically activated and express, or synthesise de novo, a number of cell surface or cytoplasmic antigens not present on resting or quiescent microglia⁷. The contribution of this atypical inflammatory response to disease onset and progression is a matter of interest and debate.

In the ageing brain it is also apparent that the resident macrophage populations are no longer as down regulated as that found in the brains of younger persons⁸. Indeed in a recent community based neuropathology study, it was found that in the brains of at least 30% of elderly persons who were cognitively normal, there was significant neuropathology comparable with that seen in the demented cohort⁹, and this is likely to be associated with microglia activation.

Thus, in diverse disease states, and also as a part of ageing, the resident macrophage populations of the central nervous system "escape" from the mechanisms that normally control their highly down regulated phenotype. However the fact that the macrophages/microglia in these circumstances are morphologically activated does not imply that they synthesise the entire plethora of pro-inflammatory molecules that macrophages are capable of making⁶. Indeed these macrophages appear to be "primed" and thus susceptible to a secondary stimulus. The primed or activated macrophage populations in the diseased or aged brain are likely to amplify signals that pass from the immune system to the brain during the course of a systemic inflammatory insult or infection.

Interactions between systemic and brain inflammation

It has been shown in a number of studies that at least 30% of all relapses that take place in patients with multiple sclerosis are preceded by a systemic infection, commonly an upper respiratory infection¹⁰. In the animal model of multiple sclerosis, experimental allergic encephalomyelitis (EAE), animals challenged systemically with agents that reactivate the immune system, results in relapse or exacerbation of clinical disease¹¹.

The impact of systemic infections on cognition and other aspects of behaviour in the elderly and demented is clinically well known: a systemic infection may lead to delirium, a state characterised by confusion, loss of cognition and hallucinations. Delirium in the demented has a poor prognosis and carries a significant risk factor for rapid decline and an early death¹². The cellular and molecular events underlying delirium have not been extensively investigated and the state of delirium may represent only the most extreme aspect of the impact of a systemic infection.

Experimental evidence that systemic inflammation may impact on ongoing brain inflammation comes from studies of mouse models of prion disease and Alzheimer's disease. In these models the microglia become activated by the presence of the ongoing pathology. Following a peripheral challenge with endotoxin, to mimic aspects of a systemic infection, cytokine synthesis in the brain is exaggerated^{13,14} and so too are the behavioural consequences¹⁴. In a study on a small number of patients with Alzheimer's disease it has been shown that infections in a two month period lead to a more rapid cognitive decline in the subsequent two month period, in the absence of delirium¹⁵. It is not yet known whether these recurrent infections have an impact on the long-term rate of cognition decline. However, it should be noted that activation

of blood monocytes and raised blood cytokine levels occur more readily in aged than in younger subjects¹⁶. Thus infections, surgery, or injuries in the elderly may generate a more pronounced systemic inflammatory cytokine synthesis even before these effects are amplified within the brain.

Conclusion

The evidence available suggests that if the macrophage populations in the brain are activated by ongoing neuropathology, or as a consequence of ageing, the signals from a systemic inflammatory condition may lead to these brain macrophage populations generating excess cytokines which in turn leads to exacerbation of a clinical condition. The extent to which systemic inflammation or disease may accelerate the rates of neuronal degeneration, cognitive decline and other permanent behavioural deficits remains to be studied.

References

- Hart BL. *Biological basis of the behavior of sick animals*. *Neurosci Biobehav Rev*. 1988;12(2):123-37.
- Kiesecker JM, Skelly DK, Beard KH, Preisser E. *Behavioral reduction of infection risk*. *Proc Natl Acad Sci U S A*. 1999;96(16):9165-8.
- Konsman JP, Parnet P, Dantzer R. *Cytokine-induced sickness behaviour: mechanisms and implications*. *Trends Neurosci*. 2002;25(3):154-9.
- Perry VH, Newman TA, Cunningham C. *The impact of systemic infection on the progression of neurodegenerative disease*. *Nat Rev Neurosci*. 2003;4(2):103-12.
- Compston A, Coles A. *Multiple sclerosis*. *Lancet*. 2002;6:359(9313):1221-31.
- Perry VH, Cunningham C, Boche D. *Atypical inflammation in the central nervous system in prion disease*. *Curr Opin Neurol*. 2002;15(3):349-54.
- McGeer PL, McGeer EG. *Inflammation, autotoxicity and Alzheimer disease*. *Neurobiol Aging*. 2001;22(6):799-809.
- Sheng JG, Mrazek RE, Griffin WS. *Enlarged and phagocytic, but not primed, interleukin-1 alpha-immunoreactive microglia increase with age in normal human brain*. *Acta Neuropathol (Berl)*. 1998;95(3):229-34.
- Neuropathology Group MRC CFAS. *Pathological correlate of late-onset dementia in a multicentre, community-based population in England and Wales*. *Lancet* 2001; 357: 169-75.
- Buljevac D, Flach HZ, Hop WC, Hijdra D, Laman JD, Savelkoul HF, van Der Meche FG, van Doorn PA, Hintzen RQ. *Prospective study on the relationship between infections and multiple sclerosis exacerbations*. *Brain*. 2002;125(Pt 5):952-60.
- Crisi GM, Santambrogio L, Hochwald GM, Smith SR, Carlino JA, Thorbecke GJ. *Staphylococcal enterotoxin B and tumor-necrosis factor-alpha-induced relapses of experimental allergic encephalomyelitis: protection by transforming growth factor-beta and interleukin-10*. *Eur J Immunol*. 1995;25(11):3035-40.
- George J, Bleasdale S, Singleton SJ. *Causes and prognosis of delirium in elderly patients admitted to a district general hospital*. *Age Ageing*. 1997;26(6):423-7.
- Sly LM, Krzesicki RF, Brashler JR, Buhl AE, McKinley DD, Carter DB, Chin JE. *Endogenous brain cytokine mRNA and inflammatory responses to lipopolysaccharide are elevated in the Tg2576 transgenic mouse model of Alzheimer's disease*. *Brain Res Bull*. 2001;56(6):581-8.
- Combrinck MI, Perry VH, Cunningham C. *Peripheral infection evokes exaggerated sickness behaviour in pre-clinical murine prion disease*. *Neuroscience*. 2002;112(1):7-11.
- Holmes C, El-Okil M, Williams AL, Cunningham C, Wilcockson D, Perry VH. *Systemic infection, interleukin 1beta, and cognitive decline in Alzheimer's disease*. *J Neurol Neurosurg Psychiatry*. 2003 Jun;74(6):788-9.
- Grimble RF. *Inflammatory response in the elderly*. *Curr Opin Clin Nutr Metab Care*. 2003 Jan;6(1):21-9.

Correspondence to:
Professor V Hugh Perry, School of Biological Sciences, Biomedical Sciences Building, Southampton, SO16 7PX
E-Mail. v.h.perry@soton.ac.uk