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) 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 infection. 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 (IL-1), tumour necrosis factor- (TNF-) 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 brain. 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 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 brain.

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 injury. 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 atypical. In these chronic neurodegenerative diseases the inflammation is dominated by cells of the mononuclear phagocyte/macrophage lin-
eage. Macrophages and microglia in the brains of AD and PD patients are morphologically and phenotypically acti-
vated and express, or synthesise de novo, a number of cell surface or cytoplasmic antigens not present on resting or
quiescent microglia8. 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 macrophage populations are no longer as down regulated inflammatory response to disease onset and progression rapid decline and an early death12. The cellular and mole-

cular events underlying delirium, a state characterised by confusion, loss of cog-

nitive impairment, are clearly understood. However, it is well known: a systemic infection may lead to delirium15. It is not yet known whether these recurrent infections 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