Editorial

Behavioural aspects of neuroinflammation

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Homeostatic control of the neuronal milieu is of fundamental importance for neuronal activity within and outside the central nervous system (CNS). Endogenous or exogenous factors can threaten this homeostasis, leading to the activation of resident immune cells in the brain such as microglia, astrocytes, and perivascular macrophages. Microglia are the resident macrophages of the brain and their activation and proliferation represent a hallmark of neuroinflammation. Over the past decades, neuroinflammatory responses have been reported for all neurodegenerative and psychiatric disorders, and intense research has been undertaken to determine the critical elements of such responses and putative therapies for their suppression. In this Special Issue, we have compiled five authoritative review articles addressing the role of neuroinflammation in a variety of neurological and neuropsychiatric conditions and five empirical studies pointing to potential novel treatment strategies.

The first review article, by Altinoz and Ozpinar, considers the place of the classic nonsteroidal anti-inflammatory drug, acetyl salicylic acid (ASA: aspirin) as an adjunct in the treatment of psychiatric disorders. They focus in particular on the role of inflammation in schizophrenia and bipolar disorder, and review clinical evidence that ASA augments the therapeutic efficacy of drugs used in the treatment of these disorders. In the second half of their review, they present evidence that the ASA metabolite gentisic acid (GA) has more potent antioxidant and anti-inflammatory effects than ASA, along with fewer side effects. Accordingly, they call for research on the effects of GA, or ASA-GA combinations, in animal models of psychiatric disorders.

A second review, by Garabadu and colleagues, considers the potential contribution of mitochondrial metabolic pathways in the pathogenesis of neuroinflammation and neurodegeneration. They review evidence that both the mitochondrial pyruvate carrier and pyruvate dehydrogenase and the mitochondrial citric acid cycle can regulate the pathogenesis of neuroinflammation and neurodegeneration, as well as a potential role for the mitochondrial urea cycle and malate-aspartate shuttle. The authors call for research on drugs that interact with these mitochondrial pathways as potential therapeutic agents for neurodegenerative disorders.

In the third article, Wong and Holahan have compiled a systematic review of the effects of exercise on inflammatory markers in people with multiple sclerosis (MS). They note that inflammation is a driver in the demyelination and can influence disability levels, and that both single and repeated bouts of exercise can decrease inflammatory markers in people with MS. However, the conclusion of their review is that while exercise interventions can have an impact on the quality of life of people with MS by improving functional outcome measures and perceived disability status, they do not significantly attenuate the inflammatory process or decrease inflammation itself.

More encouraging data are reported by Mahfoz and Shahzad for another under-researched disability, epilepsy. From a review of the contribution of neuroinflammatory markers to the development of epilepsy, the authors propose that targeting inflammatory pathways may be an effective therapeutic strategy for its prevention or treatment. Evidence is presented from preclinical and pilot clinical studies that vitamin D, which has been shown to have prophylactic and therapeutic potential in a variety of neurological disorders, also has neuroprotective effects in epilepsy, by a variety of mechanisms including its antioxidative and anti-inflammatory effects.

The final review article, by Rodrigues and colleagues, considers the role of neuroinflammation in the development and treatment of Parkinson's disease (PD). They note, first, that there is strong evidence to suggest that PD begins with an inflammatory process. Yet, notwithstanding the failure of prodromal disturbances, which include olfactory loss, cognitive impairments, depression and anxiety, sleep disturbances, and autonomic disorders, to respond to the classical dopaminergic therapies for PD, no anti-inflammatory drugs are used in the treatment of PD. They discuss the potential role, as adjuncts to regular PD therapy, of a range of drugs that have been extensively investigated as anti-inflammatory agents, including cannabinoids, caffeine, melatonin, and dietary compounds.

The importance of inflammation in PD is further highlighted in the first of the empirical studies featured in this Special Issue. Singh and colleagues examined neuroinflammation in the mouse 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced model of PD. They report that the degeneration of dopamine (DA) neurons

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following MPTP caused an increase in oxidative and inflammatory markers in the hippocampus, resulting in a decrease in hippocampal neurogenesis. This raises the possibility of anti-inflammatory therapeutics with which to improve the endogenous regenerative capacity of the aging or neurodegenerative brain.

A related study, by Xue and colleagues, addresses the role of the brain renin-angiotensin system in the modulation of the neuroinflammatory responses and the progression of dopaminergic degeneration. Intracerebral administration of angiotensin II (Ang II) to the substantia nigra induces microglial activation via the angiotensin II type 1 receptor (AT1R), which in turn affects the function of DA neurons. The study found that subchronic (7 days) treatment with the phytoestrogen biochanin A attenuated the behavioural dysfunction, inhibited the microglial activation, and prevented dopaminergic neuron damage, in rats treated with Ang II. Further evidence suggests that biochanin A achieves these effects through inhibition of a variety of inflammatory responses, increased expression of endophilin A2, and a decrease in ATR1 expression.

On similar lines, D'Souza and colleagues studied the role in Ang II-induced brain oxidative stress and inflammation of a regulator of G-protein signalling 5 (RGS5) protein, which regulates AT1R activity. They hypothesized that deletion of the RGS5 protein in mice would increase the oxidative stress and neuroinflammatory effects of Ang II, as well as amplifying Ang II-induced anxiety- and depression-like behaviours. However, rats administered with Ang II systemically did not show increases in cerebral oxidative or inflammatory markers – which contrasts with results following intracranial administration, as reported in the previous study. RGS5 deletion also was without oxidative or inflammatory effects, but did increase anxiety-like behaviour in the elevated plus-maze and Ang-II-induced depression-like behaviour in the tail suspension test, suggesting that RGS5 may play a protective role in emotional behaviours.

Chronic unpredictable stress (CUS), a widely used animal model of depression, has also been extensively shown to cause neuroinflammation. Zhang and colleagues used a rat CUS model to study the effects of piperlongumine, an alkaloid extracted from the long pepper plant that may produce anti-inflammatory effects. After 4 weeks of treatment, piperlongumine reversed both the behavioural abnormalities and the increase in proinflammatory cytokines in the hippocampus, with the inference that the anti-inflammatory effects may have been responsible for the behavioural recovery.

Finally, chronic inflammation is known to play an important role in the development of anaesthesia-induced cognitive dysfunction, but less is known about the mechanisms that may link inflammation and cognitive decline. Yin and colleagues hypothesized that inflammation alters the activity of the alpha 7 nicotinic acetylcholine receptor (α7nAChR) cholinergic anti-inflammatory pathway. They found that the anaesthetic sevoflurane both impaired cognitive function in aged rats and increased levels of the proinflammatory cytokine TNF α and acetylcholinesterase activity in the hippocampus. All of these effects were rescued by an α7nAChR agonist, but aggravated by an α7nAChR antagonist, confirming that the development of inflammation in sevoflurane-induced cognitive decline is associated with downregulation of the α7nAChR cholinergic anti-inflammatory pathway in aged rats.

The above reviews and empirical reports provide some sense of the excitement that has attended the development of our admittedly incomplete understanding of the role of neuroinflammatory processes in CNS disorders. Although it is clear that there are multiple mechanisms that can instigate neuroinflammation, sorting out which mechanisms may be most salient for particular disorders remains a daunting task. It will be similarly challenging to develop a rigorous understanding of which types of medicinal approaches may be most suitable under which conditions and at what times in their ontogeny. Notwithstanding such caveats, developments in this area of research undoubtedly will lead to dramatic advances in our understanding of the delicate interplay of inflammatory and anti-inflammatory processes in conditions of health as well as the derangement of such homeostatic processes in various types of CNS disorders. We are therefore delighted to share this Special Issue with you, and we look forward to further developments in this fascinating research field.

Paul Willner
Louk Vanderschuren
Jack Bergman
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