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Review article

CNS and inflammation

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CNS immune privilege (or not?)

The central nervous system (CNS) immune privilege is an experimentally defined phenomenon. Tissues that are rapidly rejected by the immune system when grafted in sites, such as the skin, show prolonged survival when grafted into the CNS. Initially, CNS immune privilege was construed as CNS isolation from the immune system by the blood-brain barrier (BBB), the lack of draining lymphatics, and the apparent immunoincompetence of microglia, the resident CNS macrophage[1]. Moreover, except for astrocytes, there is no constitutive expression of MHC molecules in the cells of the CNS. The most convincing evidence of all is that tissue transplanted from one individual into the brain of another individual survives for extended periods of time[2]. The 'immune privilege' of the CNS is indispensable for damage limitation during inflammation in a sensitive organ with poor regenerative capacity. It is a longstanding notion which, over time, has acquired several misconceptions and a lack of precision in its definition[3].

There is no doubt that the brain differs significantly from other tissues in its responses to pathogenic challenges. Infection or inflammation elicits rather different responses in the brain to those in other tissues. This is most evident in leukocyte recruitment, which is rapid in many systemic organs, but modest and delayed in the brain. In spite of these notable differences, the brain does exhibit key features of inflammation (Table 1)[4].

Table 1. Key features of CNS inflammation[4].

Glial activation
Oedema
MHC expression
Systemic acute phase response with general inflammation and acute phase protein synthesis
Complement activation – e.g. anaphylatoxins, membrane attack complex
Synthesis of inflammatory mediators – e.g. cytokines, free radicals, prostaglandins
Expression of adhesion molecules
Invasion of immune cells

Leukocytes have the ability to infiltrate the CNS and cytokines are produced by resident cells, especially during injuries and diseases. Although the cellular source and role of these immune ligands are better known, their exact contribution to brain protection, repair or diseases still remains highly debated today. It is now generally accepted that microglia play a central role in this response, at least for the production of cytokines participating in the innate immune system. Cytokines can also cross the BBB, either by active transport or through leaky regions of endothelia when the BBB is compromised by a pathological condition. Thus the CNS can be affected not only by inflammatory mediators produced within the brain, but also through the actions of mediators originating from the periphery[5-7].

Innate immunity and inflammation are also controlled by the vagus nerve, previously known as a regulator of other vital physiological functions. Activation of vagus nerve cholinergic signalling inhibits TNF (tumour necrosis factor) and other pro-inflammatory cytokine overproduction through 'immune' alpha7 nicotinic receptor-mediated mechanisms. This efferent vagus nerve-based 'cholinergic anti-inflammatory pathway' has been elucidated as a critical regulator of inflammation in several experimental models of disease. Advances in understanding the receptor and molecular mechanisms of cholinergic anti-inflammatory signalling indicate that selective alpha7 nicotinic receptor agonists and centrally acting cholinergic enhancers can be used in the treatment of pathological conditions characterized by cytokine overproduction[8].

The most intense interest in inflammation in the CNS has arisen from its potential role in diseases including acute brain injury, stroke, epilepsy, multiple sclerosis, motor neurone disease, movement disorders, and more recently some psychiatric disorders such as depression, anxiety and schizophrenia.

Stroke and cerebral ischaemia

A growing number of recent investigations have established a critical role for leukocytes in propagating tissue damage after ischemia and

reperfusion in stroke. Inflammatory interactions that occur at the blood-endothelium interface, involving cytokines, adhesion molecules, chemokines and leukocytes, are critical to the pathogenesis of tissue damage in cerebral infarction[9].

Cytokines in ischemic injury

It has been reported that transient forebrain ischemia in animal model was associated with induction of interleukin (IL)-1β mRNA[10], IL-6 mRNA[11], TNFα[12], and transforming growth factor β (TGF-β)[13], and that focal cerebral ischemia caused by middle cerebral artery occlusion (MCAO) induces the mRNA expression for IL-6[14], IL-10[15], granulocyte colony-stimulating factor (G-CSF)[16], TNFα[17], TGFβ[18], and erythropoietin (EPO)[19].

By using recombinant cytokines or their receptor antagonists, neutralizing antibodies or gene manipulation techniques, the role of cytokines in ischemic brain has been examined. Neutralizing antibody against IL-1β[20] and IL-1 receptor antagonist[21] were reported to attenuate brain infarction. This idea was supported by the studies using gene manipulation techniques. IL-1α/IL-1β double knockout mice exhibited reduced ischemic infarct volumes compared with wild type ones after the transient MCAO[22]. Both intracerebroventricular and systemic injection of the anti-inflammatory cytokine IL-10 decreased the infarct volume[23], suggesting that an anti-inflammatory therapy using IL-10 can provide neuroprotection in ischemic stroke. In addition to these cytokines, G-CSF has also been shown to exhibit a significant neuroprotective effect in the rat transient MCAO model[24].

Chemokines in ischemic injury

Enhanced expression of mRNAs for monocyte chemoattractant protein-1 (MCP-1, CCL2), and macrophage inflammatory protein-1α (MIP-1α, CCL3)[25-26] was demonstrated in the ischemic brain using a rat MCAO model. Increase in the peptide contents of MCP-1 /CCL2 has been also shown in the brain after the ischemic insult[27]. Broad-spectrum chemokine antagonists have been reported to decrease the infarct volume in rat[28]. A neuroprotective effect of a small molecule antagonist against CCR2/CCR5 chemokine receptors has also been reported[29].

The mechanism underlying the harmful (or protective) effect of cytokines/chemokines in the ischemic brain remains to be elucidated. One possible site for the action of brain cytokines/chemokines is glial cells such as astrocytes and microglia, which express several types of cytokine/chemokine receptors. Another site of action of brain cytokines/chemokines may be the vascular endothelium[30]. The roles of cytokines and chemokines as mediators for neuro-glio-vascular interaction in the ischemic brain are schematically illustrated in Figure 1.

Brain trauma

Traumatic brain injury (TBI) is a major cause of mortality in young people, and triggers an inflammatory response that is initiated by the release of proinflammatory cytokines. Both mRNA and proteins of cortical IL-1α and IL-1β[31], as well as IL-6 and TNFα mRNA expression[32] were increased after induced traumatic brain injury in adult rats.

IL-1 contributes directly to experimentally-induced traumatic brain injury. The mechanisms of action of IL-1 are largely unknown, but may involve effects on glia, endothelia, and neurones, or on physical parameters within the brain such as temperature or acidity[33]. Agents that inhibit TNF improve both short- and long-term neurological outcome in rats, and IL-6 may be neuroprotective since significant correlation was detected between peak IL-6 levels and Glasgow outcome scores in injured patients. It seems to be an endogenous neuroprotective cytokine produced in response to severe head trauma[34].

PANDAS

In the 1980s, an outbreak of Group A streptococcal tonsillitis in Rhode Island was associated with a 10-fold increase in the incidence of motor tics (without chorea); the concept of post-streptococcal tics was born. Subsequent identification of further patients led to the development of a new acronym: PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections)[35].

PANDAS was defined as post-streptococcal emergence of obsessive compulsive disorders (OCD) and/or tics; however, analysis of 50 patients with PANDAS demonstrated a high incidence of other emotional disorders (major depression 36%, separation anxiety 20%), conduct disorders (oppositional defiant disorder 40%) and attention deficit hyperactivity disorder (ADHD) (40%)[36]. A recent epidemiological community study of 1596 children reported 339 with a history of tics, often associated with co-morbid OCD and ADHD[37]. If the association with streptococcus is correct, collectively these disorders may prove to be the commonest form of autoimmune disease.

The immunopathogenesis of post-streptococcal CNS syndromes is incompletely understood. Most

of the investigations to date have focused on anti-neuronal antibodies as the possible mediators. However, alternative immune mechanisms are possible including cytotoxic T-lymphocyte attack, cytokine-mediated neuronal dysfunction and even superantigen-mediated Immunity[38].

Epilepsy

Seizures are caused by abnormal, high-frequency discharge of groups of neurones. The underlying neurochemical mechanisms are unknown, although increasing evidence implicates proinflammatory cytokines. IL-1 receptor type I knockout animals exhibited enhanced resistance to seizures induced by bicuculline[39]. Furthermore, intrahippocampal injection of recombinant IL-1β in normal animals enhanced the severity of seizures provoked by both bicuculline[39] and kainic acid[40] and selective blocking of caspase-1, which in turn reduces the brain availability of IL-1β, provided an effective anticonvulsive effect in experimental studies[41].

A possible mechanism by which IL-1 receptor type I activation leads to seizure involves increased phosphorylation of the NR2A/B subunit of *N*-methyl-d-aspartate receptor through activation of tyrosine kinases, which results in *N*-methyl-d-aspartate receptor-mediated Ca^{2+} influx[42]. Thus, cytokines would appear to be endogenous proconvulsant factors that contribute to seizures of various origins, including febrile convulsions. On the other hand, a recent study demonstrated experimental evidence of a protective anti-inflammatory role for IL-10 in epileptiform events which are induced by brief episodes of hypoxia in rat hippocampus[43].

Multiple sclerosis

Multiple sclerosis (MS) is a complex genetic disease characterized by inflammation in the CNS white matter mediated by activated autoreactive lymphocytes. Invasion of the CNS by T cells and macrophages leads to damage to the myelin sheaths surrounding axons, loss of neuronal function and neuronal death. Characteristically, the disease progresses in cycles of relapse, often associated with systemic infection and inflammation, and/or remission[44].

Many inflammatory mediators are upregulated in MS and associated with the demyelinating lesions[45]. Increases in T cell IFN-γ and IL-12 secretion[46] and increase in IL-12p40 mRNA with decreases in IL-10 mRNA expression[47] have been observed. Investigators have even demonstrated striking defects in the induction of Tr1 type of regulatory T cells with CD46 costimulation as measured by IL-10 but not IFN-γ secretion in patients with MS as compared to healthy subjects. This loss of Tr1 cell-associated IL-10 secretion was specific to CD46 and not CD28 costimulation and was associated with an altered regulation of the CD46-Cy2 isoform that differentially regulates T cell function in a CD46-transgenic murine model. These data demonstrate a second major regulatory T cell (Treg) defect in human autoimmune disease associated with the CD46 pathway[48].

Other chronic conditions

Inflammation undoubtedly contributes to other chronic CNS disorders. There is mounting evidence that chronic inflammatory processes play a fundamental role in the progression of neuropathological changes of Alzheimer's disease. It has been shown, that a reciprocal relationship exists between the local inflammation and senile plaques and neurofibrillary tangles[49-50].

Amyotrophic lateral sclerosis, a rapidly progressing motor neurone disease, is associated with mutation of superoxide dismutase (SOD1) gene, and mice that overexpress mutant SOD1 show upregulation of TNF-alpha[51], suggesting activation of microglia. Similarly, IL-1 levels are elevated in CSF of Creutzfeldt-Jakob disease (CJD) patients, and activated microglia are detected in mice infected with CJD[52].

In Parkinson's disease, cytokines from activated microglia in the substantia nigra and putamen were seen to be neurotoxic resulting in degeneration of dopamine neurons during the progress of the disease[53].

Recent investigation suggests a strong relationship between immunological effects and the pathophysiology of schizophrenia. Several cytokines, including IL-1β, IL-2, IL-6 and IFN, were found elevated in plasma of working-age adults with depression and dysthymia. Similar associations were reported between cytokines and late-life depression, with IL-1β, IL-6 and TNF-α elevation in both depression and dysthymia. Increased cytokine levels may also serve as an explanation for the increased risk for vascular disease that has been associated with depression[54,55].

Inflammation: Beneficial or Detrimental?

Duality of the innate immune system

The limitation of immune responsiveness in the mammalian CNS has been attributed to the intricate nature of neuronal networks, which would appear to be more susceptible than other tissues to the threat of permanent disorganization when exposed to

massive inflammation. This line of logic led to the conclusion that all forms of CNS inflammation would do more harm than good and, hence, the less immune intervention the better. However, mounting evidence indicates that some forms of immune-system intervention can help to protect or restore CNS integrity[56].

In response to a brain insult, astrocytes become activated, increasing expression of glial fibrillary acidic protein, and producing cytokines; they also contribute to the formation of the glial scar, which isolates the damaged area, but also acts as a barrier to reinnervation. Prevention of this reactive astrogliosis might be predicted to be beneficial for repair and recovery, but in fact this increases neuronal loss from the injury site and inhibits repair of the BBB and axonal remyelination, partly because astrocytes produce neurotrophic factors such as nerve growth factor and brain-derived growth factor that are upregulated by injury[57].

Cytokines themselves may also have dual roles, with detrimental acute effects, but beneficial effects in the longer term. Both TNF-α and IL-1 are strongly implicated in neuronal loss during acute and chronic neurodegenerative disease, but also participate in repair and recovery. Although TNF-α is found associated with active MS lesions, induces death of oligodendrocytes, and increases disease severity in animal models of MS, blocking this cytokine in human clinical trials was not beneficial, and in fact, worsened the disease[58]. Furthermore, cytokine 'priming' or 'preconditioning' prior to disease onset can be beneficial. For example, pretreatment with IL-1 is neuroprotective against ischaemic injury, and reduced neurological deficits in an animal model of MS[59].

In conclusion, exploring these highly complicated pathophysiological mechanisms underlying tissue damage should be a research priority. Inflammatory pathways involving interleukin and cytokine signalling might suggest potential targets for intervention and development of novel therapies to circumvent synaptic and neuronal dysfunction ultimately leading to neuro-degeneration.

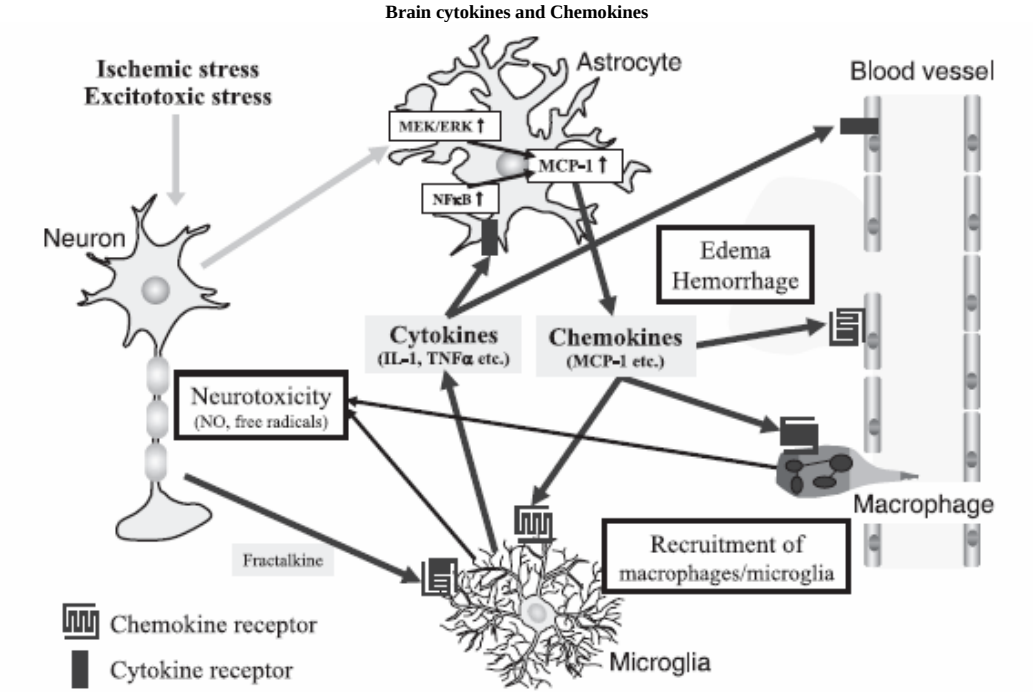

Fig.1. Schematic illustration of neuro-glio-vascular interaction in the ischemic brain. Ischemic or excitotoxic stress induces neuronal injury and thereby chemokine (e.g., MCP-1) production in astrocytes via neuro-glial interaction. Activation of a MEK/ERK cascade is crucial for the induction of MCP-1 in astrocytes. Fractalkine could be released from excited or damaged neurons in the ischemic brain. One possible site for the action of brain chemokines is microglia/macrophages expressing several types of chemokine receptors. Activated microglia and macrophages produce neurotoxic substances including nitric oxide and free radicals, and various types of chemokines such as IL-1 and TNF-α, which in turn act on astrocytes to produce additional chemokines probably via the activation of NFκB. Another possible target for chemokines is the vascular endothelium. Chemokines such as MCP-1, act on the endothelial cells to induce the extravasation of macrophages into the brain parenchyma. Permeability of the blood brain barrier (BBB) is also affected by chemokines. Increased permeability of the BBB leads to brain edema formation and parenchymal hemorrhage.

(Quoted from Minami et al, 2006)[30]

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