Journal of Neuroimmunology 184 (2007) 4 – 16

Journal of Neuroimmunology

www.elsevier.com/locate/jneuroim

Review article

The interplay between inflammation and neurodegeneration in CNS disease

Margaret M. Esiri *

Department of Clinical Neurology, University of Oxford, UK
Department of Neuropathology, Oxford Radcliffe NHS Trust, UK

Received 15 November 2006; accepted 17 November 2006

Abstract

This review considers the manner in which inflammation in the CNS contributes to, and protects against, neurodegeneration. A series of questions are posed, first about primarily inflammatory diseases and the causes of neurodegeneration that occurs in them, and then about neurodegenerative diseases and stroke and the role that inflammation plays there. Common themes as well as disease-specific differences are highlighted in this survey of the recent human disease and animal model literature.

Keywords: Inflammation; CNS diseases; Neurodegeneration; Neuroprotection; Microglia; Neuropathology

Contents

* Neuropathology Department Radcliffe Infirmary Oxford OX2 6HE UK. Tel.: +44 1865 224403; fax: +44 1865 224508.
E-mail address: margaret.esiri@clneuro.ox.ac.uk.

0165-5728/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jneuroim.2006.11.013

1. Introduction

Inflammatory and neurodegenerative diseases of the CNS have long occupied separate chapters in accounts of human neuropathology. In the past the inflammatory process was mainly related to diseases in which microbial invasion of the brain was apparent while neurodegeneration was related to the concept of *abiotrophies* proposed by Gowers at the start of the last century (Gowers, 1902). This term, when applied to the nervous system, means a premature degeneration of nervous system elements independent of external factors, often in a familial setting, implying a process free from any inflammatory influence. Yet from the start it has been recognised that inflammation and neurodegeneration can be found in one and the same disease, as in the cortex in general paralysis of the insane, caused by *Treponema pallidum*, or in the cerebral white matter and spinal cord in multiple sclerosis (MS). More recently there has been recognition of an inflammatory component to the pathology of neurodegeneration, most notably in Alzheimer's disease (AD) but also in Parkinson's disease (PD) and motor neuron disease (MND). The last few decades have afforded opportunities to investigate how inflammation and neurodegeneration in the CNS are related to each other, although we are still some way from achieving a full understanding of the complex interactions that can take place. Much of the progress that has been made has come from animal studies, most recently from transgenic animal models. While the details of these interactions differ from one disease to another there are also some features that diseases share in common. Examples both of differences and similarities are explored in this review. Because the literature on this topic is enormous the review is necessarily selective. In order to provide some focus it takes the form of a series of questions and answers; predominantly inflammatory disease is considered first, followed by neurodegenerative disease.

1.1. In inflammatory diseases what is the extent and site of the neurodegeneration that occurs?

This is extremely variable as the diseases are very diverse. Some microbial diseases, such as herpes simplex encephalitis and toxoplasma encephalitis may be accompanied by extensive regional necrosis in the brain. In other diseases the neurodegeneration is much more subtle but can be extensive as in the chronic measles infection subacute sclerosing panencephalitis (SSPE) in which both neurons and oligodendrocytes are infected and undergo apoptosis. In some diseases the extent of neurodegeneration has been relatively down-played until recently. This is true of MS and the experimental disease experimental allergic encephalitis (EAE). Here the neurodegeneration may not be evident without quantitative studies but overall it is substantial, for example, loss of 40–60% of long tract fibres in the spinal cord in MS (DeLuca et al., 2004). The site of degeneration is usually local to the immune stimulus in microbial infections but it can be more remote. Thus, in bacterial meningitis hippocampal neurons may be damaged while in multiple sclerosis loss of axons is not confined to plaques but occurs also in normal appearing white matter (Bjartmar et al., 2001; Ganter et al., 1999; Lovas et al., 2000). Here it may in part represent Wallerian degeneration (Evangelou et al., 2000) but such degeneration is unable to explain all the spinal cord axon loss in MS (DeLuca et al., 2006). In MS there are also neurodegenerative changes in the cerebral cortex despite very little inflammation being found there (Peterson et al., 2001; Wegner et al., in press) and the same is true of a marmoset model of EAE (Pomeroy et al, submitted for publication). In the spinal cord interneurons and motoneurons are lost in MS predominantly from within grey matter demyelinated plaques (Gilmore et al., 2006).

1.2. In inflammatory diseases how much of the neurodegeneration that occurs in attributable to inflammation per se and how much to other factors?

It is probably true to say that both main arms of the immune response, innate and adaptive, are involved in all forms of CNS inflammatory disease. For example, innate immunity involving the complement system, microglia/macrophages and Toll-like receptors (TLR) expressed on them, is critical in the response to microbial CNS invasion but this is backed up by adaptive immunity particularly in response to viral infections (Hauwel et al., 2005; Medzhitov and Janeway, 2002). Conversely, even in EAE, a prototypical T-cell mediated disease, complement and TLRs play important roles (Prinz et al., 2006; van Beek et al., 2005). But how much of this immune response is directly involved in neurodegeneration?

In viral infections it is frequently difficult to unravel the respective contributions of inflammation and direct viral damage. For example, in experimental herpes simplex type 2 infection in a study comparing the effects of thymidine kinase-competent and deficient viruses there were clear signs of inflammation and damage peaking at day 6 after thymidine kinase-competent viral infection.

The inflammation provoked by this virus was reflected in upregulation of mRNA for NF kβ, TLR-2, tumour necrosis factor alpha (TNFα) and monocyte chemoattractant protein-1 (MCP-1) in pons and medulla. Thymidine kinase-deficient virus showed none of these signs of inflammation and the mice remained clinically well (Boivin et al., 2002). However, these mice infected with thymidine kinase-deficient virus also showed absent viral replication which leaves uncertainty about the roles of viral-inflicted damage or inflammation as the prime cause of neurodegeneration. Other studies in HSV-1 infection have shown that T cell responses, interferon-α (IFN-α) and neutralising antibody control infection and therefore have neuroprotective effects (Bouley et al., 1995; Gresser et al., 1976; Kumano et al., 1987; Schmid and Rouse, 1992; Smith et al., 1994; Wrzos et al., 1986). To take another example: in the viral infection mentioned above,

SSPE, we are unable to say whether the oligodendrocytes and neurons die as a direct consequence of infection with measles virus or as a result of an inflammatory cell attack on the infected or uninfected cells. However, the recent development of a transgenic mouse model of SSPE may now enable this question to be addressed experimentally (Oldstone et al., 2005). In experimental Sindbis virus infection glutamate excitotoxicity appears to be responsible for some of the motor neuron death that occurs among uninfected cells (Darman et al., 2004).

In HIV-associated encephalopathy (HIVE) which affects about 7% of those with AIDS HIV-1 infects predominantly macrophages, multinucleated cells derived from macrophages or microglial cells. Neuron loss and axon damage occur and the pathogenesis of this neurotoxic effect of the infection is not fully understood (Booss and Esiri, 2003; Peruzzi et al., 2005). The two main possibilities are that products of the virus such as gp120 and *tat* proteins, or cytokines and chemokines produced by the infected and uninfected inflammatory cells are responsible (Booss and Esiri, 2003; Peruzzi et al., 2005; Pocernich et al., 2005; Schwartz and Nair, 1997). A further possibility is that changes in the blood–brain barrier contribute to the neurotoxicity (Persidsky et al., 2000). Highly active antiretroviral therapy (HAART) reduces but does not abolish the prevalence of this serious complication of AIDS (Masliah et al., 2000). Neurotoxic effects of HIV infection are thought to be more severe in those that use methamphetamine. It has been shown that in the brains of those that had used methamphetamine and had HIVE there was more up-regulation of IFN-α-inducible genes than in those that had HIVE but did not use methamphetamine. This suggests that the extra burden of neurodegenerative disease associated with methamphetamine use may be a result of dysregulation of IFN-α-inducible genes (Everall et al., 2005). A further study of more general drug abuse in HIV-infected individuals found a greater degree of microglial activation in the drug abusers (Arango et al., 2004).

In bacterial meningitis the brain is susceptible to neuronal injury in cortex and hippocampus (Braun et al., 1999; Nau et al., 1999; Pfister et al., 1994). This is thought to involve both host and microbial factors (reviewed in Kim, 2003). Dexamethasone was shown to exacerbate hippocampus injury in an experimental model of pneumococcal meningitis (Zysk et al., 1996) but reduced mortality in human adults with this condition (de Gans and van de Beek, 2002). Reactive oxygen species and nitric oxide have been suspected to promote neuronal injury in bacterial meningitis, as in many other inflammatory CNS conditions. However, the evidence of neuroprotective effects of antioxidants in models of meningitis have provided conflicting results (Auer et al., 2000; Koedel et al., 1995; Koedel and Pfister, 1997; Leib et al., 1998; Loeffler et al., 2001). TNFα and its active soluble form which is produced by the enzyme TACE are also implicated in neuronal injury in bacterial meningitis. An inhibitor of matrix metalloproteinases (MMPs) and of TACE, BB-1101, reduced cortical necrosis and hippocampal apoptotic injury in a rat model of pneumococcal meningitis (Leib et al., 2001). In contrast, an inhibitor of MMPs with less effect on TACE reduced cortical injury but had no influence on hippocampal apoptosis suggesting that TACE had particular activity in relation to hippocampal damage (Leib et al., 2000), a finding that is supported by showing that an anti-TNFα antibody reduced hippocampal injury but had no effect on cortical injury in streptococcal meningitis in rats (Bogdan et al., 1997).

A further mechanism of neuronal injury in bacterial meningitis, as in some other inflammatory diseases is excess release of excitatory amino acids, especially glutamate. This suggestion is supported by finding raised levels of glutamate in the cerebrospinal fluid (CSF) of patients who fare badly in terms of clinical outcome (Spranger et al., 1996) while elevated CSF levels of glutamate are also found in CSF in pneumococcal and *E. coli* meningitis in rabbits (Perry et al., 1993). Further support comes from studies of streptococcal meningitis in rabbits in which kynurenic acid, an excitatory amino acid receptor antagonist reduced cortical and hippocampal damage (Leib et al., 1996).

Finally, in bacterial meningitis it is thought that damage to the brain may in part be a consequence of hypoperfusion caused by release of endothelins which are potent vasoconstrictors. This view is supported by finding elevated levels of endothelins in CSF at the acute stage of bacterial meningitis and by showing, in a neonatal model of pneumococcal meningitis, that an antagonist of endothelins, Bosentan, reduced cortical damage (Pfister et al., 2000).

Axonal injury also occurs in bacterial meningitis in humans and animals and is thought to be attributable to ischaemic injury (Nau et al., 2004).

Considering the inflammatory diseases in which no microbial elements are currently recognised, MS and EAE, there is evidence that axon damage is closely localised to the regions of inflammation, particularly macrophage infiltration of CNS parenchyma (Bechtold et al., 2004; Bitsch et al., 2000; Diaz-Sanchez et al., 2006; Espejo et al., 2005; Ferguson et al., 1997; Frohman et al., 2006; Kornek et al., 2000; Lassmann, 2003; Trapp et al., 1998; Wujek et al., 2002). This raises the possibility that a direct attack by inflammatory cells or their products may damage axons. Medana et al. (2001) have shown that it is possible for T cells directly to attack axons *in vitro* but it is harder to determine if this occurs *in vivo*. It is theoretically possible that in EAE, an autoimmune disease directed against myelin antigens initially, axonal epitopes may become the focus of later autoimmune attack through the phenomenon of epitope spreading (Ellmerich et al., 2005; Vanderlugt et al., 2000; Yu et al., 1996). In this process it might be envisaged that as myelin is stripped from axons following an immune attack directed against myelin or oligodendrocytes axons are exposed to immune attack as well, with axonal antigens acting as new targets for T cells as well as for macrophage toxicity. However, as yet there is little evidence for such an

effect although antibodies to neurofilaments have been detected in CSF in progressive MS (Silber et al., 2002).

Much interest has focussed in EAE and MS on novel reactions that occur downstream of an immune attack on myelin; notably, re-distribution of ion channels on demyelinated axons (Frohman et al., 2006; Smith, 2005; Waxman et al., 2004). This re-distribution of ion channels from the nodes of Ranvier where they are found normally to the internodal axonal surfaces has been demonstrated in MS (Craner et al., 2004a) and EAE (Craner et al., 2004b). Demyelinated axons have been shown to accumulate toxic amounts of sodium and calcium ions during normal electrical activity which renders them vulnerable to damage from nitric oxide (Smith, 2005; Smith et al., 2001). This may be the basis for axonal loss and cerebral atrophy in MS even when inflammation has been effectively suppressed (Coles et al., 2006). Blockers of sodium and calcium channel entry ameliorate the damage to axons (Bechtold et al., 2004; Brand-Schieber and Werner, 2004; Kapoor et al., 2003; Lo et al., 2003; Stys, 2005). Energy failure in axons due to impaired mitochondrial function is thought likely to compound the problem (Dutta et al., 2006). This wealth of evidence of damaging effects on axons downstream of inflammation offers new opportunities for axonal protection which are already being seized.

1.3. In inflammatory disease what are the mechanisms by which inflammation promotes neurodegeneration?

The effectors of damage due to inflammation are complement, antibody, macrophages, microglial cells, and their secreted products, lymphocytes and NK cells. Blood–brain barrier disruption facilitates access of these cells and molecules to the CNS. Complement, antibody and macrophages are thought to play important roles in myelin destruction in MS and EAE (Gay et al., 1997; Genain et al., 1999; Lucchinetti et al., 2000; Prineas and Graham, 1981) but it is less clear how axons are damaged. Nitric oxide production by macrophages is likely to be an important mechanism in view of the increased vulnerability to this agent of demyelinated axons (Smith et al., 2001). Furthermore, nitric oxide selectively damages small axons which are the ones damaged in MS (Evangelou et al., 2001). Cytokines, free radicals, CD8+ T cells and glutamate are other possible factors along with deprivation of growth factors (Diestel et al., 2003; Lu et al., 2000; Medana et al., 2001; Wegner et al., in press; Wilkins et al., 2001). It is harder to relate the grey matter damage that has been recently documented in MS to cell mediated damage though antibody and complement could certainly have a role to play here, particularly as subpial grey matter — a common site of demyelination in MS (Peterson et al., 2001) and EAE (Pomeroy et al, submitted for publication) can become exposed to serum proteins relatively readily (Broadwell and Sofroniew, 1993).

Innate and adaptive immune systems are involved in clearance of micro-organisms from the nervous system but, as discussed above, it is difficult to distinguish host inflammatory mechanisms that directly damage neurons from those primarily directed against the organisms on the one hand or damage to the nervous system caused directly by the micro-organisms on the other. In viral-induced demyelinating diseases such as that caused by chronic Theiler's murine encephalomyelitis virus in mice the downstream consequences for axonal injury of demyelination can presumably operate as in MS and EAE.

1.4. In inflammatory disease does inflammation also have a protective role against neurodegeneration?

The short answer to this question is 'yes'. Recent studies have shown that inflammatory cells and their products can exert beneficial effects on a number of processes that are required to promote aspects of tissue regeneration some of which might be expected to improve the fate of axons and neurons in inflammatory diseases (reviewed in Schwartz et al., 2006). Activation of microglial cells occupies a critical position here and an important development has been the realisation that microglial cell activation can proceed in two different directions, one of them cytotoxic and the other neuroprotective (or a combination of the two), depending on the manner in which the activation is controlled. Even cytotoxic behaviour of macrophages and microglial cells can be regarded as ultimately assisting regeneration since this cannot proceed until the debris of a damaging reaction has been cleared away. The 2-way alternative routes of microglial reaction depend on whether the activating stimulus is preceded or followed by another stimulus, and on the nature of the two stimuli. An example of a cytotoxic form of microglial cell activation is the response to lipopolysaccharide (LPS) which leads to the expression of MHC Class II antigens and upregulation of production of many of the pro-inflammatory cytokines such as IL-1, IL-6, IL-8, TNF and αMCP-1 (reviewed in Kim and de Vellis, 2005). However, microglia or microglia-conditioned medium have also been demonstrated to produce many trophic factors: nerve growth factor, neurotrophin 3, brain-derived neurotrophic factor, basic fibroblast growth factor, hepatocyte growth factor and plasminogen (refs. in Kim and de Vellis, 2005). Furthermore, survival of neurons in culture can be assisted by microglial cells or microglial cell-conditioned medium (Banati and Graeber, 1994; Zietlow et al., 1999) and microglial cells release substances that induce proliferation in neuronal cultures, possibly through an effect on immature neurons (Morgan et al., 2004), although microglia have also been shown to be capable of blocking neurogenesis (Kempermann and Neumann, 2003; Monje et al., 2003). Exposure of microglia to small amounts of IFN-α or IL-4 enables them to support neuronal survival whereas exposure to LPS renders them cytotoxic to neurons and oligodendrocytes (Butovsky et al., 2005). Differentiation of microglia in a cytotoxic direction, e.g. by LPS, can be altered to a neuroprotective phenotype by exposure to IL-4 suggesting

there can be some reversibility of microglial cell roles. Whether newly recruited macrophages in CNS lesions have a similar flexibility of function is not yet clear.

Some of the influences that determine microglial cell behaviour and its effects on axons and neurons stem from the activity of T cells which are often to be found in the same CNS lesions. Microglia express receptors for many of the cytokines produced by activated T cells and T cells can therefore modulate microglial cell behaviour. Remarkably, autoimmune T cells protect neurons from degeneration after spinal trauma or optic nerve injury, albeit at the expense of a degree of transient EAE (Hauben et al., 2000; Moalem et al., 1999). Even neurons can exert some modulation on local CNS inflammatory reactions through stimulation of proliferation of regulatory T cells and by curbing such proliferation through production of transforming growth factor-β(TGFβ) (Liu et al., 2006).

1.5. In inflammatory disease can neurodegeneration be prevented?

In many experimental disease models it is possible to prevent neurodegeneration using agents that block the inflammatory response or its downstream consequences. With microbial infections the most straightforward way to attempt to deal with the disease is to combat the organism itself but the appropriate anti-microbials are not always available. Even if the organism cannot be eliminated some damage which is due more to bystander and downstream consequences of infection such as glutamate toxicity can be ameliorated (Darman et al., 2004). In idiopathic and autoimmune disease there is an extensive range of interventions that can reduce neurodegeneration some of which is summarised below. The disappointment is that so far interventions that have been shown to be effective in EAE have not translated into effective treatment for the commonest idiopathic inflammatory human disease, MS. It is likely that combined treatments attacking more than one stage of disease pathogenesis will prove more effective than monotherapy (Diem et al., 2005; Giuliani et al., 2005; Kanwar et al., 2004). Interventions in EAE have targeted either the evolution of the inflammatory focus in the CNS or its downstream consequences including:

- Blocking entry of inflammatory cells into the CNS, for example, using antibodies to CD-44 and integrin alpha 4 (Brocke et al., 1999), inhibiting matrix metalloproteinases and microglial activation with microcycline (Brundula et al., 2002; Giuliani et al., 2005) or preventing mononuclear cell migration with lovastatin (Stanislaus et al., 2001).
- Inhibiting pro-inflammatory T helper-1 cytokine production (Platten et al., 2005).
- Blocking ion channels which allow excess calcium to enter axons (Bechtold et al., 2004; Brand-Schieber and Werner, 2004; Kapoor et al., 2003; Lo et al., 2003).
- Blocking glutamate excitotoxicity (Pitt et al., 2000; Smith et al., 2000).
- Using growth factors or hormones to promote neuronal survival. These include erythropoietin (Agnello et al., 2002; Brines et al., 2000; Diem et al., 2005; Hasselblatt et al., 2006) and insulin-like growth factor-1 (Kanwar et al., 2004).
- Using anti-oxidants to neutralise effects of free radical production including metallothioneins (Espejo et al., 2005; Penkowa, 2006; Penkowa and Hidalgo, 2003), flavonoids (Hendriks et al., 2004) and green tea (Aktas et al., 2004).
- Using vitamin D which appears to promote apoptosis of inflammatory cells (Cantorna et al., 1996; Spach et al., 2004).

1.6. In neurodegenerative disease is inflammation simply concerned with clearing away the debris?

No, the situation is much more complicated than that. Debris in the context of the neurodegenerative disease Alzheimer's disease (AD) consists of degenerate neuritic processes and the extracellular deposits of β amyloid and other substances that accumulate in plaques. We will consider each of these in turn:

Degenerate neuritic processes. Degeneration of neurites in AD and probably in other neurodegenerative diseases occurs through an apoptotic-like process and therefore involves innate immune molecules that participate in clearance of debris leading on to tissue repair (insofar as the CNS is capable of 'repair') (Yuan and Yankner, 2000). This depends on microglial cells recognising expression on apoptotic cells of phosphatidylserine residues (PS) for which they carry receptors. PS is normally found on the inner component of the plasma membrane where it is not accessible to the PS receptor but in apoptotic cells it is localised externally thus leading to its recognition (Savill and Fadok, 2000). The role of microglia in recognition of apoptosis in ageing has not been studied in anything like the detail with which microglial responses to β amyloid have been studied (reflecting the current dominance of the amyloid cascade hypothesis of AD (Hardy, 2006) in thinking about AD pathogenesis) but it is well recognised that microglial cell numbers increase with ageing and this may reflect dendritic re-modelling in ageing (Mackenzie and Munoz, 1998; Mattiace et al., 1990).

β amyloid. Microglial cells come to occupy a very precise location in relation to plaques in which there is a core of amyloid and a corona of neuritic processes. Microglia are sandwiched between the core and the corona at a site that implies direct involvement in the disease process. Ultrastructural appearances suggested these cells might be engaged in phagocytosing the amyloid fibrils (Frackowiak et al., 1992; Wisniewski et al., 1991) and the suggestion has been made that the cells have difficulty in degrading the amyloid (Ard et al., 1996; Paresce et al., 1997; Rogers et al., 2002).

Microglial cells in AD are immunoreactive for CD-11a, CD-11b, CD-11c (members of the β_2 integrin family), CD-45, CD-64 (Ig Fcγ receptors), MHC Class II scavenger receptor and complement proteins CI-4 (reviewed in Kim and de Vellis, 2005). They also express the receptor for advanced glycation end-products (RAGE) (Lue et al., 2001). They include cells that have been relatively recently recruited from the blood and it is these newly recruited cells that have a capacity to remove β amyloid (Simard et al., 2006). *In vitro* β amyloid stimulates free radical production, pro-inflammatory cytokine production and neurodegeneration-promoting molecules by microglia (Barger and Harmon, 1997; Giulian, 1999; Meda et al., 1995; Van Muiswinkel et al., 1999). Human microglia can rapidly phagocytose amyloid β fragments *in vitro* (Giulian et al., 1995) but do not seem to do so effectively *in vivo* in AD. The remarkable demonstration that microglia can be induced to phagocytose β amyloid avidly *in vivo* by vaccination with β amyloid has focused great interest on the mechanisms involved in this process (Schenk et al., 1999). It has been proposed that it may be effected by enhanced phagocytosis of Ig-amyloid complexes by microglial Fc receptors. There may also be a role for complement in this clearance process (Hauwel et al., 2005). Complement seems to play a protective role against β amyloid accumulation in a transgenic mouse model of AD since over-expression of a soluble complement inhibitor, Crry, led to an increased burden of β amyloid and inflammation (Wyss-Coray et al., 2002). In summary, whether or not the microglial response to β amyloid consists simply in clearing (or attempting to clear) this debris remains unclear. The question of why there should be a problem for microglial cells with phagocytosing β amyloid cannot be answered unequivocally. They might be overwhelmed by the amount of amyloid, they might be in an activated state that precludes them acting effectively or they might simply be malfunctional because of their age (Streit, 2004, 2005).

1.7. In neurodegenerative disease does inflammation contribute to disease progression?

There is quite a strong body of opinion supporting this possibility. Initial evidence came from clinical studies suggesting that long term use of anti-inflammatory drugs reduced the risk of AD (Breitner, 1996; Broe et al., 2000). This finding is controversial (Heyman et al., 1984), but supported by a meta-analysis of 17 studies (McGeer et al., 1996). Some studies examining the protective effect of non-steroidal anti-inflammatory drugs in preventing or treating AD have shown positive effects (Broe et al., 2000; Prince et al., 1998; Rogers et al., 1993; Stewart et al., 1997), others not (Aisen et al., 2003; Henderson et al., 1997; Reines et al., 2004; Scharf et al., 1999). The other evidence comes from studies of the microglial cells in human and experimental AD in which microglia show evidence of being in an activated state that has been shown *in vitro* to be associated with neurotoxic capability. Some of this evidence is referred to above, and has been reviewed recently (Kim and de Vellis, 2005; Kril and Halliday, 2001; Minghetti et al., 2005; Schwartz et al., 2006).

There is less evidence about a role for inflammation in other neurodegenerative diseases. The simplest model for examining the role of inflammation in neurodegeneration is axotomy, in which a defined axon tract is cut across and the reaction in and around the parent neurons is explored. There is a stereotyped sequence of glial cell reactions that commences with microglial cell activation including increased expression of MHC Class II antigens and complement receptor 3 (Hu et al., 2002; Koliatsos et al., 1994; Kreutzberg et al., 1989; Lundberg et al., 2001; Olsson et al., 1989; Piehl et al., 1999). Recently there has been an interesting genetic approach taken to analysing how the various components of the neuronal and glial cell response to ventral root avulsion (vra) is controlled. With this lesion, placed close to the parent motor neurons of the avulsed root, there is degeneration of 50–75% of neurons affected after 2–3 weeks in adult rats (Koliatsos et al., 1994; Piehl et al., 1999). Inbred stains of rat which differ in the extent of their response to vra were crossed to yield an F2 generation from which further generations of rats were developed. Carrying out phenotype–genotype correlations in the parent, F2 and later generation animals it was possible to identify two quantitative trait loci on different chromosomes affecting the extent of loss of motoneurons, two further non-MHC loci that controlled the extent of T cell infiltration and one further locus that was linked to MHC Class II expression on microglia, though it was not located in the MHC region itself (Lidman et al., 2003; Olsson et al., 2005). It is interesting that these gene effects seemed to be independent of each other. It is likely that the genes concerned will be found to be important in the inflammatory reaction to more complex neurodegenerative processes.

In motor neuron disease there is activation of microglia and adoption by them of a pro-inflammatory phenotype (Henkel et al., 2004; Kawamata et al., 1992). In a mouse model of inherited motor neuron disease in transgenic mice carrying a mutant form of the superoxide dismutase (SOD-1) gene it was found that intraperitoneal administration of the inflammatory agent LPS exacerbated disease progression by 3 weeks and enhanced motor axon degeneration but only if challenges with repeated LPS injections were given in the presymptomatic 6 month-old mice. This exacerbation of disease was associated with enhanced innate immunity with upregulation of TLR2 and pro-inflammatory cytokines in the spinal cord (Nguyen et al., 2004). Inhibition of cyclooxygenase-2, a key enzyme in prostaglandin synthesis, extends survival in SOD-1 mutant mice (Drachman et al., 2002) as does minocycline, an antibiotic that is capable of inhibiting microglial cell activation (Yrjanheikki et al., 1999). In a further exploration of this model it was shown that if expression of the SOD-1 mutation was inhibited in motor neurons the initial onset of weakness and early progression was delayed. In contrast, if the SOD-1 mutant gene

expression was only reduced in microglia the course of the disease progression was slowed particularly in its later stages (Boillee et al., 2006). This suggests that microglial cells can influence some aspects of motor neuron disease progression.

1.8. In neurodegenerative disease can inflammation be neuroprotective?

Yes, probably. The view of microglial influences always being bad is giving way to one where their influence is viewed as mixed, with neuroprotective features being increasingly emphasised. If we return to the axotomy model of neurodegeneration the proliferation and re-positioning of microglia around the neuron cell bodies of the cells with severed axons can be regarded as neuroprotective. In particular, the positioning of microglia between afferent synapses and the cell body protects the neuron from potentially damaging excitatory influences and allows for close exchange of signalling and trophic molecules. Transforming growth factor β(TGFβ) is one such molecule which is neuroprotective and has been localised to activated microglial cells (Lehrmann et al., 1998; Streit et al., 1998). Furthermore, microglial cells *in vitro* release neuron-protective factors (see answer to question 4 above) and when transplanted *in vivo* can aid functional neuronal recovery (Raivich et al., 1994; Rapalino et al., 1998). There is increasing evidence that microglial cells, exposed to apoptotic cell signals differentiate in a neuroprotective, anti-inflammatory direction, producing such molecules as TGF-β, prostaglandin E_2 and IL-10 (De Simone et al., 2003; Minghetti et al., 2005). A similar profile of microglial cell properties is also seen in experimental prion disease (Minghetti, 2004; Perry et al., 2002), and Parkinson's disease (Depino et al., 2003). One important factor that appears to regulate the direction of microglial cell activation is the presence and timing of other stimuli besides the apoptotic one. These stimuli may precede or follow and can modulate the microglial response in inflammatory or protective directions (Butovsky et al., 2005; Schwartz et al., 2006; Shaked et al., 2005). One important determinant of outcome appears to be the amount of IFN-γ to which they become exposed; small amounts of IFN-γ evoke a neuroprotective phenotype and large amounts of cytotoxic one. This cytotoxic effect can, however, be effaced by neutralisation of the TNF-α produced in response to large amounts of IFN-γ (Butovsky et al., 2005). Another agent that stimulates neuroprotective behaviour in microglia is IL-4 (Schwartz et al., 2006).

1.9. In neurodegenerative disease can inflammation be manipulated to reduce damage?

Yes, but we need more understanding in order to do this safely. When the findings in transgenic AD regarding the beneficial effects of β amyloid vaccine were translated into a clinical trial there were unforeseen complications with a few patients developing encephalitis (Barger, 2005; Ferrer et al., 2004).

Some hazard in clinical trials is hard to avoid because there are differences between rodent and human immune-related cells. Microglial cells are clearly potentially exploitable for therapeutic and preventive purposes but we need better information on their repertoires of reaction so that neuroprotection can be upgraded and cytotoxicity reduced. Just one of many promising possibilities, all of which cannot be reviewed here, is use of the fatty acid docosahexanoic acid, a natural dietary constituent, to reduce prostaglandin production by inhibiting cyclooxygenases and reducing their expression (Strokin et al., 2004).

1.10. Is there anything special about the inflammatory CNS response in stroke?

The key factor in stroke that causes CNS inflammatory responses to differ from those in neurodegenerative and most idiopathic or autoimmune disease is necrosis. Stroke shares this feature with some forms of viral infection (e.g. herpes simplex encephalitis) and trauma. The inflammatory response to necrosis includes the influx of neutrophil polymorphs which promote a local strong reactive oxygen burst. There is also rapid build up of oedema which can be fatal. These acute changes occur in advance of an influx of macrophages. Around the zone of necrosis is a penumbra in which apoptotic cell death is common and in which excitotoxicity and free radical damage are contributory causes. Interestingly, if experimental ischaemic necrosis is preceded by a mild ischaemic insult, insufficient in itself to cause necrosis, the necrotic damage is reduced probably through upregulation of heat shock protein production (Kirino et al., 1991; Liu et al., 1992, 1993; Nakata et al., 1993). This phenomenon is referred to as ischaemic pre-conditioning. Pro-inflammatory cytokine production is an important element of the reaction in stroke and its prevention provides an opportunity to limit post-ischaemic damage. A key mechanism that activates production of TNFα, IL-1β, iNOS and K-8 is p38 mitogen activated protein kinase (MAPK), suppression of which has the capacity to reduced the size of an infarct in gerbils and rats (Barone et al., 2001; Legos et al., 2001; Sugino et al., 2000). Infarct size is also reduced by inhibition of iNOS by aminoguanidine (Iadecola et al., 1995) and in mice lacking iNOS (Iadecola et al., 1997). Interestingly, mice over-expressing human amyloid precursor protein show enhanced microglial activation and upregulation of p38 MAPK (Koistinaho et al., 2002; Koistinaho and Koistinaho, 2005). They also show enhanced ischaemic vulnerability which was abolished by p38 MAPK inhibition (Koistinaho et al., 2002; Paris et al., 2000). Other approaches to reducing inflammation-induced injury in stroke might include the use of an antibody to the CD11d integrin which effectively reduced the early neutrophil and macrophage infiltrate in experimental spinal cord injury (Saville et al., 2004).

1.11. Are there any influences outside the CNS that affect the nature and severity of CNS damage in inflammatory or neurodegenerative disease?

Yes, some of the pre-conditioning and post-conditioning stimuli mentioned in answer to questions 4 and 8 are administered from outside the CNS, e.g. intraperitoneal injection of LPS (Davis et al., 2005). In EAE the initiating stimulus to trigger the autoimmune reaction to myelin is administered peripherally. Numerous differences in expression of stimulatory molecules on circulating mononuclear cells in a long-lasting disease such as MS have been described but are beyond the scope of this review. Similarly, in AD monocytes express an activation state not seen in aged control subjects. In experimental prion disease more severe 'sickness behaviour' reflected in temperature and activity measurements was seen in the preclinical stage of the disease when intraperitoneal LPS was administered (Combrink et al., 2002). It was suggested that microglia, already primed by developing prion disease were driven to greater stimulation by the peripherally administered inflammatory stimulus. Another peripheral agent that was shown to affect microglia-driven neurodegeneration in a model of brain trauma, this time in a neuroprotective fashion, is vasoactive intestinal peptide (Delgado and Ganea, 2003). In a more clinical context there is suggestive evidence that AD progresses faster in a transient fashion, in association with systemic infections that raise serum IL-1 levels (Holmes et al., 2003).

2. Conclusions

The complexities of the interactions between inflammation and neurodegeneration are beginning to be exposed in recent clinical and experimental pathological studies. There are important general principles that emerge:

- An immune response — innate, adaptive or both — is stimulated in all these diseases and includes neuroprotective as well as cytotoxic elements.
- Microglial activation, which is a key component of inflammatory CNS responses, is not a unitary process but differs depending on pre-and post-conditioning stimuli and disease state and can include neuroprotective elements.
- Many of the deleterious downstream consequences of inflammation-related CNS damage are probably common to different types of disease; there may be remedies to combat such downstream processes as excess calcium entry into cells, energy depletion through mitochondrial damage or deficiency, and oxidative stress that may have efficacy in different diseases.
- Attempts to limit effectively inflammation-related damage have to tread a tightrope that bears the risk of exposing those treated to serious complications as evidenced by the risk of autoimmune disease when MS is treated with humanised monoclonal antibody to CD-52 (Coles et al., 1999), progressive multifocal leucoencephalopathy when MS is treated with natalizumab (Goodin, 2006) and encephalitis when AD is treated with β amyloid vaccine (Ferrer et al., 2004). However there is considerable optimism that, building on the lessons learnt, future treatments will be developed that have reduced risk while retaining great efficacy.

References

Agnello, D., Bigini, P., Villa, P., Mennini, T., Cerami, A., Brines, M.L., Ghezzi, P., 2002. Erythropoietin exerts an anti-inflammatory effect on the CNS in a model of experimental autoimmune encephalomyelitis. Brain Res. 952, 128–134.

Aisen, P.S., Schafer, K.A., Grundman, M., Pfeiffer, E., Sano, M., Davis, K.L., Farlow, M.R., Jin, S., Thomas, R.G., Thal, L.J., 2003. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA 289, 2819–2826.

Aktas, O., Prozorovski, T., Smorodchenko, A., Savaskan, N.E., Lauster, R., Kloetzel, P.M., Infante-Duarte, C., Brocke, S., Zipp, F., 2004. Green tea epigallocatechin-3-gallate mediates T cellular NF-kappa B inhibition and exerts neuroprotection in autoimmune encephalomyelitis. J. Immunol. 173, 5794–5800.

Arango, J.C., Simmonds, P., Brettle, R.P., Bell, J.E., 2004. Does drug abuse influence the microglial response in AIDS and HIV encephalitis? Aids 18 (Suppl 1), S69–S74.

Ard, M.D., Cole, G.M., Wei, J., Mehrle, A.P., Fratkin, J.D., 1996. Scavenging of Alzheimer's amyloid beta-protein by microglia in culture. J. Neurosci. Res. 43, 190–202.

Auer, M., Pfister, L.A., Leppert, D., Tauber, M.G., Leib, S.L., 2000. Effects of clinically used antioxidants in experimental pneumococcal meningitis. J. Infect. Dis. 182, 347–350.

Banati, R.B., Graeber, M.B., 1994. Surveillance, intervention and cytotoxicity: is there a protective role of microglia? Dev. Neurosci. 16, 114–127.

Barger, S.W., 2005. Vascular consequences of passive Abeta immunization for Alzheimer's disease. Is avoidance of "malactivation" of microglia enough? J. Neuroinflammation 2, 2.

Barger, S.W., Harmon, A.D., 1997. Microglial activation by Alzheimer amyloid precursor protein and modulation by apolipoprotein E. Nature 388, 878–881.

Barone, F.C., Irving, E.A., Ray, A.M., Lee, J.C., Kassis, S., Kumar, S., Badger, A.M., White, R.F., McVey, M.J., Legos, J.J., Erhardt, J.A., Nelson, A.H., Ohlstein, E.H., Hunter, A.J., Ward, K., Smith, B.R., Adams, J.L., Parsons, A.A., 2001. SB 239063, a second-generation p38 mitogen-activated protein kinase inhibitor, reduces brain injury and neurological deficits in cerebral focal ischemia. J. Pharmacol. Exp. Ther. 296, 312–321.

Bechtold, D.A., Kapoor, R., Smith, K.J., 2004. Axonal protection using flecainide in experimental autoimmune encephalomyelitis. Ann. Neurol. 55, 607–616.

Bitsch, A., Schuchardt, J., Bunkowski, S., Kuhlmann, T., Bruck, W., 2000. Acute axonal injury in multiple sclerosis. Correlation with demyelination and inflammation. Brain 123 (Pt 6), 1174–1183.

Bjartmar, C., Kinkel, R.P., Kidd, G., Rudick, R.A., Trapp, B.D., 2001. Axonal loss in normal-appearing white matter in a patient with acute MS. Neurology 57, 1248–1252.

Bogdan, I., Leib, S.L., Bergeron, M., Chow, L., Tauber, M.G., 1997. Tumor necrosis factor-alpha contributes to apoptosis in hippocampal neurons during experimental group B streptococcal meningitis. J. Infect. Dis. 176, 693–697.

Boillee, S., Yamanaka, K., Lobsiger, C.S., Copeland, N.G., Jenkins, N.A., Kassiotis, G., Kollias, G., Cleveland, D.W., 2006. Onset and progression in inherited ALS determined by motor neurons and microglia. Science 312, 1389–1392.

Boivin, G., Coulombe, Z., Rivest, S., 2002. Intranasal herpes simplex virus type 2 inoculation causes a profound thymidine kinase dependent cerebral inflammatory response in the mouse hindbrain. Eur. J. Neurosci. 16, 29–43.

Booss, J., Esiri, M.M., 2003. HIV/AIDS. In: Booss, J., Esiri, M.M. (Eds.), Viral Encephalitis in Humans. ASM Press, Washington, DC, pp. 193–220.

Bouley, D.M., Kanangat, S., Wire, W., Rouse, B.T., 1995. Characterization of herpes simplex virus type-1 infection and herpetic stromal keratitis development in IFN-gamma knockout mice. J. Immunol. 155, 3964–3971.

Brand-Schieber, E., Werner, P., 2004. Calcium channel blockers ameliorate disease in a mouse model of multiple sclerosis. Exp. Neurol. 189, 5–9.

Braun, J.S., Novak, R., Herzog, K.H., Bodner, S.M., Cleveland, J.L., Tuomanen, E.I., 1999. Neuroprotection by a caspase inhibitor in acute bacterial meningitis. Nat. Med. 5, 298–302.

Breitner, J.C., 1996. Inflammatory processes and antiinflammatory drugs in Alzheimer's disease: a current appraisal. Neurobiol. Aging 17, 789–794.

Brines, M.L., Ghezzi, P., Keenan, S., Agnello, D., de Lanerolle, N.C., Cerami, C., Itri, L.M., Cerami, A., 2000. Erythropoietin crosses the blood–brain barrier to protect against experimental brain injury. Proc. Natl. Acad. Sci. U. S. A. 97, 10526–10531.

Broadwell, R.D., Sofroniew, M.V., 1993. Serum proteins bypass the blood–brain fluid barriers for extracellular entry to the central nervous system. Exp. Neurol. 120, 245–263.

Brocke, S., Piercy, C., Steinman, L., Weissman, I.L., Veromaa, T., 1999. Antibodies to CD44 and integrin alpha4, but not L-selectin, prevent central nervous system inflammation and experimental encephalomyelitis by blocking secondary leukocyte recruitment. Proc. Natl. Acad. Sci. U. S. A. 96, 6896–6901.

Broe, G.A., Grayson, D.A., Creasey, H.M., Waite, L.M., Casey, B.J., Bennett, H.P., Brooks, W.S., Halliday, G.M., 2000. Anti-inflammatory drugs protect against Alzheimer disease at low doses. Arch. Neurol. 57, 1586–1591.

Brundula, V., Rewcastle, N.B., Metz, L.M., Bernard, C.C., Yong, V.W., 2002. Targeting leukocyte MMPs and transmigration: minocycline as a potential therapy for multiple sclerosis. Brain 125, 1297–1308.

Butovsky, O., Talpalar, A.E., Ben-Yaakov, K., Schwartz, M., 2005. Activation of microglia by aggregated beta-amyloid or lipopolysaccharide impairs MHC-II expression and renders them cytotoxic whereas IFN-gamma and IL-4 render them protective. Mol. Cell. Neurosci. 29, 381–393.

Cantorna, M.T., Hayes, C.E., DeLuca, H.F., 1996. 1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. Proc. Natl. Acad. Sci. U. S. A. 93, 7861–7864.

Coles, A.J., Wing, M., Smith, S., Coraddu, F., Greer, S., Taylor, C., Weetman, A., Hale, G., Chatterjee, V.K., Waldmann, H., Compston, A., 1999. Pulsed monoclonal antibody treatment and autoimmune thyroid disease in multiple sclerosis. Lancet 354, 1691–1695.

Coles, A.J., Cox, A., Le Page, E., Jones, J., Trip, S.A., Deans, J., Seaman, S., Miller, D.H., Hale, G., Waldmann, H., Compston, D.A., 2006. The window of therapeutic opportunity in multiple sclerosis evidence from monoclonal antibody therapy. J. Neurol. 253, 98–108.

Combrink, M.P., Troskie, P.C., De Waal, D.T., 2002. Residual effect of antibabesial drugs on the live redwater blood vaccines. Ann. N. Y. Acad. Sci. 969, 169–173.

Craner, M.J., Newcombe, J., Black, J.A., Hartle, C., Cuzner, M.L., Waxman, S.G., 2004a. Molecular changes in neurons in multiple sclerosis: altered axonal expression of Nav1.2 and Nav1.6 sodium channels and Na+/Ca2+ exchanger. Proc. Natl. Acad. Sci. U. S. A. 101, 8168–8173.

Craner, M.J., Hains, B.C., Lo, A.C., Black, J.A., Waxman, S.G., 2004b. Co-localization of sodium channel Nav1.6 and the sodium-calcium exchanger at sites of axonal injury in the spinal cord in EAE. Brain 127, 294–303.

Darman, J., Backovic, S., Dike, S., Maragakis, N.J., Krishnan, C., Rothstein, J.D., Irani, D.N., Kerr, D.A., 2004. Viral-induced spinal motor neuron death is non-cell-autonomous and involves glutamate excitotoxicity. J. Neurosci. 24, 7566–7575.

Davis, A.E., Campbell, S.J., Wilainam, P., Anthony, D.C., 2005. Post-conditioning with lipopolysaccharide reduces the inflammatory infiltrate to the injured brain and spinal cord: a potential neuroprotective treatment. Eur. J. Neurosci. 22, 2441–2450.

de Gans, J., van de Beek, D., 2002. Dexamethasone in adults with bacterial meningitis. N. Engl. J. Med. 347, 1549–1556.

De Simone, R., Ajmone-Cat, M.A., Tirassa, P., Minghetti, L., 2003. Apoptotic PC12 cells exposing phosphatidylserine promote the production of anti-inflammatory and neuroprotective molecules by microglial cells. J. Neuropathol. Exp. Neurol. 62, 208–216.

Delgado, M., Ganea, D., 2003. Vasoactive intestinal peptide prevents activated microglia-induced neurodegeneration under inflammatory conditions: potential therapeutic role in brain trauma. Faseb J. 17, 1922–1924.

DeLuca, G.C., Ebers, G.C., Esiri, M.M., 2004. Axonal loss in multiple sclerosis: a pathological survey of the corticospinal and sensory tracts. Brain 127, 1009–1018.

DeLuca, G.C., Williams, K., Evangelou, N., Ebers, G.C., Esiri, M.M., 2006. The contribution of demyelination to axonal loss in multiple sclerosis. Brain 129, 1507–1516.

Depino, A.M., Earl, C., Kaczmarczyk, E., Ferrari, C., Besedovsky, H., del Rey, A., Pitossi, F.J., Oertel, W.H., 2003. Microglial activation with atypical proinflammatory cytokine expression in a rat model of Parkinson's disease. Eur. J. Neurosci. 18, 2731–2742.

Diaz-Sanchez, M., Williams, K., Deluca, G.C., Esiri, M.M., 2006. Protein co-expression with axonal injury in multiple sclerosis plaques. Acta Neuropathol. (Berl) 111, 289–299.

Diem, R., Sattler, M.B., Merkler, D., Demmer, I., Maier, K., Stadelmann, C., Ehrenreich, H., Bahr, M., 2005. Combined therapy with methylprednisolone and erythropoietin in a model of multiple sclerosis. Brain 128, 375–385.

Diestel, A., Aktas, O., Hackel, D., Hake, I., Meier, S., Raine, C.S., Nitsch, R., Zipp, F., Ullrich, O., 2003. Activation of microglial poly(ADP-ribose)-polymerase-1 by cholesterol breakdown products during neuroinflammation: a link between demyelination and neuronal damage. J. Exp. Med. 198, 1729–1740.

Drachman, D.B., Frank, K., Dykes-Hoberg, M., Teismann, P., Almer, G., Przedborski, S., Rothstein, J.D., 2002. Cyclooxygenase 2 inhibition protects motor neurons and prolongs survival in a transgenic mouse model of ALS. Ann. Neurol. 52, 771–778.

Dutta, R., McDonough, J., Yin, X., Peterson, J., Chang, A., Torres, T., Gudz, T., Macklin, W.B., Lewis, D.A., Fox, R.J., Rudick, R., Mirnics, K., Trapp, B.D., 2006. Mitochondrial dysfunction as a cause of axonal degeneration in multiple sclerosis patients. Ann. Neurol. 59, 478–489.

Ellmerich, S., Mycko, M., Takacs, K., Waldner, H., Wahid, F.N., Boyton, R.J., King, R.H., Smith, P.A., Amor, S., Herlihy, A.H., Hewitt, R.E., Jutton, M., Price, D.A., Hafler, D.A., Kuchroo, V.K., Altmann, D.M., 2005. High incidence of spontaneous disease in an HLA-DR15 and TCR transgenic multiple sclerosis model. J. Immunol. 174, 1938–1946.

Espejo, C., Penkowa, M., Demestre, M., Montalban, X., Martinez-Caceres, E.M., 2005. Time-course expression of CNS inflammatory, neurodegenerative tissue repair markers and metallothioneins during experimental autoimmune encephalomyelitis. Neuroscience 132, 1135–1149.

Evangelou, N., Konz, D., Esiri, M.M., Smith, S., Palace, J., Matthews, P.M., 2000. Regional axonal loss in the corpus callosum correlates with cerebral white matter lesion volume and distribution in multiple sclerosis. Brain 123 (Pt 9), 1845–1849.

Evangelou, N., Konz, D., Esiri, M.M., Smith, S., Palace, J., Matthews, P.M., 2001. Size-selective neuronal changes in the anterior optic pathways suggest a differential susceptibility to injury in multiple sclerosis. Brain 124, 1813–1820.

Everall, I., Salaria, S., Roberts, E., Corbeil, J., Sasik, R., Fox, H., Grant, I., Masliah, E., 2005. Methamphetamine stimulates interferon inducible genes in HIV infected brain. J. Neuroimmunol. 170, 158–171.

Ferguson, B., Matyszak, M.K., Esiri, M.M., Perry, V.H., 1997. Axonal damage in acute multiple sclerosis lesions. Brain 120 (Pt 3), 393–399.

Ferrer, I., Boada Rovira, M., Sanchez Guerra, M.L., Rey, M.J., Costa-Jussa, F., 2004. Neuropathology and pathogenesis of encephalitis following

amyloid-beta immunization in Alzheimer's disease. Brain Pathol. 14, 11–20.
Frackowiak, J., Wisniewski, H.M., Wegiel, J., Merz, G.S., Iqbal, K., Wang, K.C., 1992. Ultrastructure of the microglia that phagocytose amyloid and the microglia that produce beta-amyloid fibrils. Acta Neuropathol. (Berl) 84, 225–233.
Frohman, E.M., Racke, M.K., Raine, C.S., 2006. Multiple sclerosis — the plaque and its pathogenesis. N. Engl. J. Med. 354, 942–955.
Ganter, P., Prince, C., Esiri, M.M., 1999. Spinal cord axonal loss in multiple sclerosis: a post-mortem study. Neuropathol. Appl. Neurobiol. 25, 459–467.
Gay, F.W., Drye, T.J., Dick, G.W., Esiri, M.M., 1997. The application of multifactorial cluster analysis in the staging of plaques in early multiple sclerosis. Identification and characterization of the primary demyelinating lesion. Brain 120 (Pt 8), 1461–1483.
Genain, C.P., Cannella, B., Hauser, S.L., Raine, C.S., 1999. Identification of autoantibodies associated with myelin damage in multiple sclerosis. Nat. Med. 5, 170–175.
Gilmore, C., et al., 2006. Evidence of Substantial Spinal Cord Neuronal Pathology in Multiple Sclerosis. (ECTRIMS abstract).
Giulian, D., 1999. Microglia and the immune pathology of Alzheimer disease. Am. J. Hum. Genet. 65, 13–18.
Giulian, D., Haverkamp, L.J., Li, J., Karshin, W.L., Yu, J., Tom, D., Li, X., Kirkpatrick, J.B., 1995. Senile plaques stimulate microglia to release a neurotoxin found in Alzheimer brain. Neurochem. Int. 27, 119–137.
Giuliani, F., Fu, S.A., Metz, L.M., Yong, V.W., 2005. Effective combination of minocycline and interferon-beta in a model of multiple sclerosis. J. Neuroimmunol. 165, 83–91.
Goodin, D., 2006. The return of natalizumab: weighing benefit against risk. Lancet Neurol. 5, 375–377.
Gowers, W., 1902. A lecture on abiotrophy. Lancet 159, 1003–1008.
Gresser, I., Tovey, M.G., Maury, C., Bandu, M.T., 1976. Role of interferon in the pathogenesis of virus diseases in mice as demonstrated by the use of anti-interferon serum. II. Studies with herpes simplex, Moloney sarcoma, vesicular stomatitis, Newcastle disease, and influenza viruses. J. Exp. Med. 144, 1316–1323.
Hardy, J., 2006. Has the amyloid cascade hypothesis for Alzheimer's disease been proved? Curr. Alzheimer Res. 3, 71–73.
Hasselblatt, M., Ehrenreich, H., Siren, A.L., 2006. The brain erythropoietin system and its potential for therapeutic exploitation in brain disease. J. Neurosurg. Anesthesiol. 18, 132–138.
Hauben, E., Butovsky, O., Nevo, U., Yoles, E., Moalem, G., Agranov, E., Mor, F., Leibowitz-Amit, R., Pevsner, E., Akselrod, S., Neeman, M., Cohen, I.R., Schwartz, M., 2000. Passive or active immunization with myelin basic protein promotes recovery from spinal cord contusion. J. Neurosci. 20, 6421–6430.
Hauwel, M., Furon, E., Canova, C., Griffiths, M., Neal, J., Gasque, P., 2005. Innate (inherent) control of brain infection, brain inflammation and brain repair: the role of microglia, astrocytes, "protective" glial stem cells and stromal ependymal cells. Brain Res. Brain Res. Rev. 48, 220–233.
Henderson, A.S., Jorm, A.F., Christensen, H., Jacomb, P.A., Korten, A.E., 1997. Aspirin, anti-inflammatory drugs and risk of dementia. Int. J. Geriatr. Psychiatry 12, 926–930.
Hendriks, J.J., Alblas, J., van der Pol, S.M., van Tol, E.A., Dijkstra, C.D., de Vries, H.E., 2004. Flavonoids influence monocytic GTPase activity and are protective in experimental allergic encephalitis. J. Exp. Med. 200, 1667–1672.
Henkel, J.S., Engelhardt, J.I., Siklos, L., Simpson, E.P., Kim, S.H., Pan, T., Goodman, J.C., Siddique, T., Beers, D.R., Appel, S.H., 2004. Presence of dendritic cells, MCP-1, and activated microglia/macrophages in amyotrophic lateral sclerosis spinal cord tissue. Ann. Neurol. 55, 221–235.
Heyman, A., Wilkinson, W.E., Stafford, J.A., Helms, M.J., Sigmon, A.H., Weinberg, T., 1984. Alzheimer's disease: a study of epidemiological aspects. Ann. Neurol. 15, 335–341.
Holmes, C., El-Okl, M., Williams, A.L., Cunningham, C., Wilcockson, D., Perry, V.H., 2003. Systemic infection, interleukin 1beta, and cognitive decline in Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 74, 788–789.
Hu, J., Fink, D., Mata, M., 2002. Microarray analysis suggests the involvement of proteasomes, lysosomes, and matrix metalloproteinases in the response of motor neurons to root avulsion. Eur. J. Neurosci. 16, 1409–1416.
Iadecola, C., Zhang, F., Xu, X., 1995. Inhibition of inducible nitric oxide synthase ameliorates cerebral ischemic damage. Am. J. Physiol. 268, R286–R292.
Iadecola, C., Zhang, F., Casey, R., Nagayama, M., Ross, M.E., 1997. Delayed reduction of ischemic brain injury and neurological deficits in mice lacking the inducible nitric oxide synthase gene. J. Neurosci. 17, 9157–9164.
Kanwar, J.R., Kanwar, R.K., Krissansen, G.W., 2004. Simultaneous neuroprotection and blockade of inflammation reverses autoimmune encephalomyelitis. Brain 127, 1313–1331.
Kapoor, R., Davies, M., Blaker, P.A., Hall, S.M., Smith, K.J., 2003. Blockers of sodium and calcium entry protect axons from nitric oxide-mediated degeneration. Ann. Neurol. 53, 174–180.
Kawamata, T., Akiyama, H., Yamada, T., McGeer, P.L., 1992. Immunologic reactions in amyotrophic lateral sclerosis brain and spinal cord tissue. Am. J. Pathol. 140, 691–707.
Kempermann, G., Neumann, H., 2003. Neuroscience. Microglia: the enemy within? Science 302, 1689–1690.
Kim, K., 2003. Pathogenesis of bacterial meningitis: from bacteraemia to neuronal injury. Nat. Rev. Neurosci. 4, 376–385.
Kim, S.U., de Vellis, J., 2005. Microglia in health and disease. J. Neurosci. Res. 81, 302–313.
Kirino, T., Tsujita, Y., Tamura, A., 1991. Induced tolerance to ischemia in gerbil hippocampal neurons. J. Cereb. Blood Flow Metab. 11, 299–307.
Koedel, U., Pfister, H.W., 1997. Protective effect of the antioxidant *N*-acetyl-L-cysteine in pneumococcal meningitis in the rat. Neurosci. Lett. 225, 33–36.
Koedel, U., Bernatowicz, A., Paul, R., Frei, K., Fontana, A., Pfister, H.W., 1995. Experimental pneumococcal meningitis: cerebrovascular alterations, brain edema, and meningeal inflammation are linked to the production of nitric oxide. Ann. Neurol. 37, 313–323.
Koistinaho, M., Koistinaho, J., 2005. Interactions between Alzheimer's disease and cerebral ischemia-focus on inflammation. Brain Res. Brain Res. Rev. 48, 240–250.
Koistinaho, M., Kettunen, M.I., Goldsteins, G., Keinanen, R., Salminen, A., Ort, M., Bures, J., Liu, D., Kauppinen, R.A., Higgins, L.S., Koistinaho, J., 2002. Beta-amyloid precursor protein transgenic mice that harbor diffuse A beta deposits but do not form plaques show increased ischemic vulnerability: role of inflammation. Proc. Natl. Acad. Sci. U. S. A. 99, 1610–1615.
Koliatsos, V.E., Price, W.L., Pardo, C.A., Price, D.L., 1994. Ventral root avulsion: an experimental model of death of adult motor neurons. J. Comp. Neurol. 342, 35–44.
Kornek, B., Storch, M.K., Weissert, R., Wallstroem, E., Stefferl, A., Olsson, T., Linington, C., Schmidbauer, M., Lassmann, H., 2000. Multiple sclerosis and chronic autoimmune encephalomyelitis: a comparative quantitative study of axonal injury in active, inactive, and remyelinated lesions. Am. J. Pathol. 157, 267–276.
Kreutzberg, G.W., Graeber, M.B., Streit, W.J., 1989. Neuron-glial relationship during regeneration of motorneurons. Metab. Brain Dis. 4, 81–85.
Kril, J.J., Halliday, G.M., 2001. Alzheimer's disease: its diagnosis and pathogenesis. Int. Rev. Neurobiol. 48, 167–217.
Kumano, Y., Yamamoto, M., Mori, R., 1987. Protection against herpes simplex virus infection in mice by recombinant murine interferon-beta in combination with antibody. Antiviral Res. 7, 289–301.
Lassmann, H., 2003. Axonal injury in multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 74, 695–697.
Legos, J.J., Erhardt, J.A., White, R.F., Lenhard, S.C., Chandra, S., Parsons, A.A., Tuma, R.F., Barone, F.C., 2001. SB 239063, a novel p38 inhibitor, attenuates early neuronal injury following ischemia. Brain Res. 892, 70–77.

Lehrmann, E., Kiefer, R., Christensen, T., Toyka, K.V., Zimmer, J., Diemer, N.H., Hartung, H.P., Finsen, B., 1998. Microglia and macrophages are major sources of locally produced transforming growth factor-beta1 after transient middle cerebral artery occlusion in rats. Glia 24, 437–448.

Leib, S.L., Kim, Y.S., Ferriero, D.M., Tauber, M.G., 1996. Neuroprotective effect of excitatory amino acid antagonist kynurenic acid in experimental bacterial meningitis. J. Infect. Dis. 173, 166–171.

Leib, S.L., Kim, Y.S., Black, S.M., Tureen, J.H., Tauber, M.G., 1998. Inducible nitric oxide synthase and the effect of aminoguanidine in experimental neonatal meningitis. J. Infect. Dis. 177, 692–700.

Leib, S.L., Leppert, D., Clements, J., Tauber, M.G., 2000. Matrix metalloproteinases contribute to brain damage in experimental pneumococcal meningitis. Infect. Immun. 68, 615–620.

Leib, S.L., Clements, J.M., Lindberg, R.L., Heimgartner, C., Loeffler, J.M., Pfister, L.A., Tauber, M.G., Leppert, D., 2001. Inhibition of matrix metalloproteinases and tumour necrosis factor alpha converting enzyme as adjuvant therapy in pneumococcal meningitis. Brain 124, 1734–1742.

Lidman, O., Swanberg, M., Horvath, L., Broman, K.W., Olsson, T., Piehl, F., 2003. Discrete gene loci regulate neurodegeneration, lymphocyte infiltration, and major histocompatibility complex class II expression in the CNS. J. Neurosci. 23, 9817–9823.

Liu, Y., Kato, H., Nakata, N., Kogure, K., 1992. Protection of rat hippocampus against ischemic neuronal damage by pretreatment with sublethal ischemia. Brain Res. 586, 121–124.

Liu, Y., Kato, H., Nakata, N., Kogure, K., 1993. Temporal profile of heat shock protein 70 synthesis in ischemic tolerance induced by preconditioning ischemia in rat hippocampus. Neuroscience 56, 921–927.

Liu, Y., Teige, I., Birnir, B., Issazadeh-Navikas, S., 2006. Neuron-mediated generation of regulatory T cells from encephalitogenic T cells suppresses EAE. Nat. Med. 12, 518–525.

Lo, A.C., Saab, C.Y., Black, J.A., Waxman, S.G., 2003. Phenytoin protects spinal cord axons and preserves axonal conduction and neurological function in a model of neuroinflammation in vivo. J. Neurophysiol. 90, 3566–3571.

Loeffler, J.M., Ringer, R., Hablutzel, M., Tauber, M.G., Leib, S.L., 2001. The free radical scavenger alpha-phenyl-*tert*-butyl nitrone aggravates hippocampal apoptosis and learning deficits in experimental pneumococcal meningitis. J. Infect. Dis. 183, 247–252.

Lovas, G., Szilagyi, N., Majtenyi, K., Palkovits, M., Komoly, S., 2000. Axonal changes in chronic demyelinated cervical spinal cord plaques. Brain 123 (Pt 2), 308–317.

Lu, F., Selak, M., O'Connor, J., Croul, S., Lorenzana, C., Butunoi, C., Kalman, B., 2000. Oxidative damage to mitochondrial DNA and activity of mitochondrial enzymes in chronic active lesions of multiple sclerosis. J. Neurol. Sci. 177, 95–103.

Lucchinetti, C., Bruck, W., Parisi, J., Scheithauer, B., Rodriguez, M., Lassmann, H., 2000. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann. Neurol. 47, 707–717.

Lue, L.F., Walker, D.G., Brachova, L., Beach, T.G., Rogers, J., Schmidt, A.M., Stern, D.M., Yan, S.D., 2001. Involvement of microglial receptor for advanced glycation endproducts (RAGE) in Alzheimer's disease: identification of a cellular activation mechanism. Exp. Neurol. 171, 29–45.

Lundberg, C., Lidman, O., Holmdahl, R., Olsson, T., Piehl, F., 2001. Neurodegeneration and glial activation patterns after mechanical nerve injury are differentially regulated by non-MHC genes in congenic inbred rat strains. J. Comp. Neurol. 431, 75–87.

Mackenzie, I.R., Munoz, D.G., 1998. Nonsteroidal anti-inflammatory drug use and Alzheimer-type pathology in aging. Neurology 50, 986–990.

Masliah, E., DeTeresa, R.M., Mallory, M.E., Hansen, L.A., 2000. Changes in pathological findings at autopsy in AIDS cases for the last 15 years. Aids 14, 69–74.

Mattiace, L.A., Davies, P., Dickson, D.W., 1990. Detection of HLA-DR on microglia in the human brain is a function of both clinical and technical factors. Am. J. Pathol. 136, 1101–1114.

McGeer, P.L., Schulzer, M., McGeer, E.G., 1996. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. Neurology 47, 425–432.

Meda, L., Cassatella, M.A., Szendrei, G.I., Otvos Jr., L., Baron, P., Villalba, M., Ferrari, D., Rossi, F., 1995. Activation of microglial cells by beta-amyloid protein and interferon-gamma. Nature 374, 647–650.

Medana, I., Martinic, M.A., Wekerle, H., Neumann, H., 2001. Transection of major histocompatibility complex class I-induced neurites by cytotoxic T lymphocytes. Am. J. Pathol. 159, 809–815.

Medzhitov, R., Janeway Jr., C.A., 2002. Decoding the patterns of self and nonself by the innate immune system. Science 296, 298–300.

Minghetti, L., 2004. Cyclooxygenase-2 (COX-2) in inflammatory and degenerative brain diseases. J. Neuropathol. Exp. Neurol. 63, 901–910.

Minghetti, L., Ajmone-Cat, M.A., De Berardinis, M.A., De Simone, R., 2005. Microglial activation in chronic neurodegenerative diseases: roles of apoptotic neurons and chronic stimulation. Brain Res. Brain Res. Rev. 48, 251–256.

Moalem, G., Leibowitz-Amit, R., Yoles, E., Mor, F., Cohen, I.R., Schwartz, M., 1999. Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. Nat. Med. 5, 49–55.

Monje, M.L., Toda, H., Palmer, T.D., 2003. Inflammatory blockade restores adult hippocampal neurogenesis. Science 302, 1760–1765.

Morgan, S.C., Taylor, D.L., Pocock, J.M., 2004. Microglia release activators of neuronal proliferation mediated by activation of mitogen-activated protein kinase, phosphatidylinositol-3-kinase/Akt and delta-Notch signalling cascades. J. Neurochem. 90, 89–101.

Nakata, N., Kato, H., Kogure, K., 1993. Inhibition of ischaemic tolerance in the gerbil hippocampus by quercetin and anti-heat shock protein-70 antibody. NeuroReport 4, 695–698.

Nau, R., Soto, A., Bruck, W., 1999. Apoptosis of neurons in the dentate gyrus in humans suffering from bacterial meningitis. J. Neuropathol. Exp. Neurol. 58, 265–274.

Nau, R., Gerber, J., Bunkowski, S., Bruck, W., 2004. Axonal injury, a neglected cause of CNS damage in bacterial meningitis. Neurology 62, 509–511.

Nguyen, M.D., D'Aigle, T., Gowing, G., Julien, J.P., Rivest, S., 2004. Exacerbation of motor neuron disease by chronic stimulation of innate immunity in a mouse model of amyotrophic lateral sclerosis. J. Neurosci. 24, 1340–1349.

Oldstone, M.B., Dales, S., Tishon, A., Lewicki, H., Martin, L., 2005. A role for dual viral hits in causation of subacute sclerosing panencephalitis. J. Exp. Med. 202, 1185–1190.

Olsson, T., Kristensson, K., Ljungdahl, A., Maehlen, J., Holmdahl, R., Klareskog, L., 1989. Gamma-interferon-like immunoreactivity in axotomized rat motor neurons. J. Neurosci. 9, 3870–3875.

Olsson, T., Piehl, F., Swanberg, M., Lidman, O., 2005. Genetic dissection of neurodegeneration and CNS inflammation. J. Neurol. Sci. 233, 99–108.

Paresce, D.M., Chung, H., Maxfield, F.R., 1997. Slow degradation of aggregates of the Alzheimer's disease amyloid beta-protein by microglial cells. J. Biol. Chem. 272, 29390–29397.

Paris, D., Town, T., Mori, T., Parker, T.A., Humphrey, J., Mullan, M., 2000. Soluble beta-amyloid peptides mediate vasoactivity via activation of a pro-inflammatory pathway. Neurobiol. Aging 21, 183–197.

Penkowa, M., 2006. Metallothioneins are multipurpose neuroprotectants during brain pathology. FEBS J. 273, 1857–1870.

Penkowa, M., Hidalgo, J., 2003. Treatment with metallothionein prevents demyelination and axonal damage and increases oligodendrocyte precursors and tissue repair during experimental autoimmune encephalomyelitis. J. Neurosci. Res. 72, 574–586.

Perry, V.L., Young, R.S., Aquila, W.J., During, M.J., 1993. Effect of experimental *Escherichia coli* meningitis on concentrations of excitatory and inhibitory amino acids in the rabbit brain: in vivo microdialysis study. Pediatr. Res. 34, 187–191.

Perry, V.H., Cunningham, C., Boche, D., 2002. Atypical inflammation in the central nervous system in prion disease. Curr. Opin. Neurol. 15, 349–354.

Persidsky, Y., Zheng, J., Miller, D., Gendelman, H.E., 2000. Mononuclear phagocytes mediate blood–brain barrier compromise and neuronal injury during HIV-1-associated dementia. J. Leukoc. Biol. 68, 413–422.

Peruzzi, F., Bergonzini, V., Aprea, S., Reiss, K., Sawaya, B.E., Rappaport, J., Amini, S., Khalili, K., 2005. Cross talk between growth factors and viral

and cellular factors alters neuronal signaling pathways: implication for HIV-associated dementia. Brain Res. Brain Res. Rev. 50, 114–125.
Peterson, J.W., Bo, L., Mork, S., Chang, A., Trapp, B.D., 2001. Transected neurites, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions. Ann. Neurol. 50, 389–400.
Pfister, H.W., Fontana, A., Tauber, M.G., Tomasz, A., Scheld, W.M., 1994. Mechanisms of brain injury in bacterial meningitis: workshop summary. Clin. Infect. Dis. 19, 463–479.
Pfister, L.A., Tureen, J.H., Shaw, S., Christen, S., Ferriero, D.M., Tauber, M.G., Leib, S.L., 2000. Endothelin inhibition improves cerebral blood flow and is neuroprotective in pneumococcal meningitis. Ann. Neurol. 47, 329–335.
Piehl, F., Lundberg, C., Khademi, M., Bucht, A., Dahlman, I., Lorentzen, J.C., Olsson, T., 1999. Non-MHC gene regulation of nerve root injury induced spinal cord inflammation and neuron death. J. Neuroimmunol. 101, 87–97.
Pitt, D., Werner, P., Raine, C.S., 2000. Glutamate excitotoxicity in a model of multiple sclerosis. Nat. Med. 6, 67–70.
Platten, M., Ho, P.P., Youssef, S., Fontoura, P., Garren, H., Hur, E.M., Gupta, R., Lee, L.Y., Kidd, B.A., Robinson, W.H., Sobel, R.A., Selley, M.L., Steinman, L., 2005. Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite. Science 310, 850–855.
Pocernich, C.B., Sultana, R., Mohmmad-Abdul, H., Nath, A., Butterfield, D.A., 2005. HIV-dementia, Tat-induced oxidative stress, and antioxidant therapeutic considerations. Brain Res. Brain Res. Rev. 50, 14–26.
Pomeroy, I., et al, (submitted for publication).
Prince, M., Rabe-Hesketh, S., Brennan, P., 1998. Do antiarthritic drugs decrease the risk for cognitive decline? An analysis based on data from the MRC treatment trial of hypertension in older adults. Neurology 50, 374–379.
Prineas, J.W., Graham, J.S., 1981. Multiple sclerosis: capping of surface immunoglobulin G on macrophages engaged in myelin breakdown. Ann. Neurol. 10, 149–158.
Prinz, M., Garbe, F., Schmidt, H., Mildner, A., Gutcher, I., Wolter, K., Piesche, M., Schroers, R., Weiss, E., Kirschning, C.J., Rochford, C.D., Bruck, W., Becher, B., 2006. Innate immunity mediated by TLR9 modulates pathogenicity in an animal model of multiple sclerosis. J. Clin. Invest. 116, 456–464.
Raivich, G., Moreno-Flores, M.T., Moller, J.C., Kreutzberg, G.W., 1994. Inhibition of posttraumatic microglial proliferation in a genetic model of macrophage colony-stimulating factor deficiency in the mouse. Eur. J. Neurosci. 6, 1615–1618.
Rapalino, O., Lazarov-Spiegler, O., Agranov, E., Velan, G.J., Yoles, E., Fraidakis, M., Solomon, A., Gepstein, R., Katz, A., Belkin, M., Hadani, M., Schwartz, M., 1998. Implantation of stimulated homologous macrophages results in partial recovery of paraplegic rats. Nat. Med. 4, 814–821.
Reines, S.A., Block, G.A., Morris, J.C., Liu, G., Nessly, M.L., Lines, C.R., Norman, B.A., Baranak, C.C., 2004. Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. Neurology 62, 66–71.
Rogers, J., Kirby, L.C., Hempelman, S.R., Berry, D.L., McGeer, P.L., Kaszniak, A.W., Zalinski, J., Cofield, M., Mansukhani, L., Willson, P., et al., 1993. Clinical trial of indomethacin in Alzheimer's disease. Neurology 43, 1609–1611.
Rogers, J., Strohmeyer, R., Kovelowski, C.J., Li, R., 2002. Microglia and inflammatory mechanisms in the clearance of amyloid beta peptide. Glia 40, 260–269.
Savill, J., Fadok, V., 2000. Corpse clearance defines the meaning of cell death. Nature 407, 784–788.
Saville, L.R., Pospisil, C.H., Mawhinney, L.A., Bao, F., Simedrea, F.C., Peters, A.A., O'Connell, P.J., Weaver, L.C., Dekaban, G.A., 2004. A monoclonal antibody to CD11d reduces the inflammatory infiltrate into the injured spinal cord: a potential neuroprotective treatment. J. Neuroimmunol. 156, 42–57.
Scharf, S., Mander, A., Ugoni, A., Vajda, F., Christophidis, N., 1999. A double-blind, placebo-controlled trial of diclofenac/misoprostol in Alzheimer's disease. Neurology 53, 197–201.
Schenk, D., Barbour, R., Dunn, W., Gordon, G., Grajeda, H., Guido, T., Hu, K., Huang, J., Johnson-Wood, K., Khan, K., Kholodenko, D., Lee, M., Liao, Z., Lieberburg, I., Motter, R., Mutter, L., Soriano, F., Shopp, G., Vasquez, N., Vandevert, C., Walker, S., Wogulis, M., Yednock, T., Games, D., Seubert, P., 1999. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature 400, 173–177.
Schmid, D., Rouse, B., 1992. The role of T cell immunity in control of herpes simplex virus. In: Rouse, B. (Ed.), Herpes Simplex Virus: Pathogenesis, Immunobiology and Control, vol. 179. Springer–Verlag, Berlin, pp. 57–74.
Schwartz, S.A., Nair, M.P., 1997. Molecular mechanisms in the pathogenesis of AIDS encephalopathy. Cell Mol. Biol. (Noisy-le-grand) 43, 925–933.
Schwartz, M., Butovsky, O., Bruck, W., Hanisch, U.K., 2006. Microglial phenotype: is the commitment reversible? Trends Neurosci. 29, 68–74.
Shaked, I., Tchoresh, D., Gersner, R., Meiri, G., Mordechai, S., Xiao, X., Hart, R.P., Schwartz, M., 2005. Protective autoimmunity: interferon-gamma enables microglia to remove glutamate without evoking inflammatory mediators. J. Neurochem. 92, 997–1009.
Silber, E., Semra, Y.K., Gregson, N.A., Sharief, M.K., 2002. Patients with progressive multiple sclerosis have elevated antibodies to neurofilament subunit. Neurology 58, 1372–1381.
Simard, A.R., Soulet, D., Gowing, G., Julien, J.P., Rivest, S., 2006. Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. Neuron 49, 489–502.
Smith, K.J., 2005. Nitric oxide and axonal pathophysiology. In: Waxman, S.G. (Ed.), Multiple Clerosis as a Neuronal Disease. Academic Press, New York, pp. 255–273.
Smith, P.M., Wolcott, R.M., Chervenak, R., Jennings, S.R., 1994. Control of acute cutaneous herpes simplex virus infection: T cell-mediated viral clearance is dependent upon interferon-gamma (IFN-gamma). Virology 202, 76–88.
Smith, T., Groom, A., Zhu, B., Turski, L., 2000. Autoimmune encephalomyelitis ameliorated by AMPA antagonists. Nat. Med. 6, 62–66.
Smith, K.J., Kapoor, R., Hall, S.M., Davies, M., 2001. Electrically active axons degenerate when exposed to nitric oxide. Ann. Neurol. 49, 470–476.
Spach, K.M., Pedersen, L.B., Nashold, F.E., Kayo, T., Yandell, B.S., Prolla, T.A., Hayes, C.E., 2004. Gene expression analysis suggests that 1,25-dihydroxyvitamin D3 reverses experimental autoimmune encephalomyelitis by stimulating inflammatory cell apoptosis. Physiol. Genomics 18, 141–151.
Spranger, M., Schwab, S., Krempien, S., Winterholler, M., Steiner, T., Hacke, W., 1996. Excess glutamate levels in the cerebrospinal fluid predict clinical outcome of bacterial meningitis. Arch. Neurol. 53, 992–996.
Stanislaus, R., Singh, A.K., Singh, I., 2001. Lovastatin treatment decreases mononuclear cell infiltration into the CNS of Lewis rats with experimental allergic encephalomyelitis. J. Neurosci. Res. 66, 155–162.
Stewart, W.F., Kawas, C., Corrada, M., Metter, E.J., 1997. Risk of Alzheimer's disease and duration of NSAID use. Neurology 48, 626–632.
Streit, W.J., 2004. Microglia and Alzheimer's disease pathogenesis. J. Neurosci. Res. 77, 1–8.
Streit, W.J., 2005. Microglia and neuroprotection: implications for Alzheimer's disease. Brain Res. Brain Res. Rev. 48, 234–239.
Streit, W.J., Semple-Rowland, S.L., Hurley, S.D., Miller, R.C., Popovich, P.G., Stokes, B.T., 1998. Cytokine mRNA profiles in contused spinal cord and axotomized facial nucleus suggest a beneficial role for inflammation and gliosis. Exp. Neurol. 152, 74–87.
Strokin, M., Sergeeva, M., Reiser, G., 2004. Role of Ca2+-independent phospholipase A2 and n-3 polyunsaturated fatty acid docosahexaenoic acid in prostanoid production in brain: perspectives for protection in neuroinflammation. Int. J. Dev. Neurosci. 22, 551–557.
Stys, P.K., 2005. General mechanisms of axonal damage and its prevention. J. Neurol. Sci. 233, 3–13.
Sugino, T., Nozaki, K., Takagi, Y., Hattori, I., Hashimoto, N., Moriguchi, T., Nishida, E., 2000. Activation of mitogen-activated protein kinases after transient forebrain ischemia in gerbil hippocampus. J. Neurosci. 20, 4506–4514.

Trapp, B.D., Peterson, J., Ransohoff, R.M., Rudick, R., Mork, S., Bo, L., 1998. Axonal transection in the lesions of multiple sclerosis. N. Engl. J. Med. 338, 278–285.

van Beek, J., van Meurs, M., t Hart, B.A., Brok, H.P., Neal, J.W., Chatagner, A., Harris, C.L., Omidvar, N., Morgan, B.P., Laman, J.D., Gasque, P., 2005. Decay-accelerating factor (CD55) is expressed by neurons in response to chronic but not acute autoimmune central nervous system inflammation associated with complement activation. J. Immunol. 174, 2353–2365.

Van Muiswinkel, F.L., Raupp, S.F., de Vos, N.M., Smits, H.A., Verhoef, J., Eikelenboom, P., Nottet, H.S., 1999. The amino-terminus of the amyloid-beta protein is critical for the cellular binding and consequent activation of the respiratory burst of human macrophages. J. Neuroimmunol. 96, 121–130.

Vanderlugt, C.L., Neville, K.L., Nikcevich, K.M., Eagar, T.N., Bluestone, J.A., Miller, S.D., 2000. Pathologic role and temporal appearance of newly emerging autoepitopes in relapsing experimental autoimmune encephalomyelitis. J. Immunol. 164, 670–678.

Waxman, S.G., Craner, M.J., Black, J.A., 2004. Na+ channel expression along axons in multiple sclerosis and its models. Trends Pharmacol. Sci. 25, 584–591.

Wegner, C., Esiri, M.M., Chance, S., Palace, J., Matthews, P.M., (in press). Neocortical neuronal, synaptic and glial loss in multiple sclerosis. Neurology.

Wilkins, A., Chandran, S., Compston, A., 2001. A role for oligodendrocyte-derived IGF-1 in trophic support of cortical neurons. Glia 36, 48–57.

Wisniewski, H.M., Barcikowska, M., Kida, E., 1991. Phagocytosis of beta/A4 amyloid fibrils of the neuritic neocortical plaques. Acta Neuropathol. (Berl) 81, 588–590.

Wrzos, H., Murasko, D.M., Rapp, F., 1986. Effect of antibody to interferon on genital herpesvirus infection in mice. Microb. Pathog. 1, 71–78.

Wujek, J.R., Bjartmar, C., Richer, E., Ransohoff, R.M., Yu, M., Tuohy, V.K., Trapp, B.D., 2002. Axon loss in the spinal cord determines permanent neurological disability in an animal model of multiple sclerosis. J. Neuropathol. Exp. Neurol. 61, 23–32.

Wyss-Coray, T., Yan, F., Lin, A.H., Lambris, J.D., Alexander, J.J., Quigg, R.J., Masliah, E., 2002. Prominent neurodegeneration and increased plaque formation in complement-inhibited Alzheimer's mice. Proc. Natl. Acad. Sci. U. S. A. 99, 10837–10842.

Yrjanheikki, J., Tikka, T., Keinanen, R., Goldsteins, G., Chan, P.H., Koistinaho, J., 1999. A tetracycline derivative, minocycline, reduces inflammation and protects against focal cerebral ischemia with a wide therapeutic window. Proc. Natl. Acad. Sci. U. S. A. 96, 13496–13500.

Yu, M., Johnson, J.M., Tuohy, V.K., 1996. A predictable sequential determinant spreading cascade invariably accompanies progression of experimental autoimmune encephalomyelitis: a basis for peptide-specific therapy after onset of clinical disease. J. Exp. Med. 183, 1777–1788.

Yuan, J., Yankner, B.A., 2000. Apoptosis in the nervous system. Nature 407, 802–809.

Zietlow, R., Dunnett, S.B., Fawcett, J.W., 1999. The effect of microglia on embryonic dopaminergic neuronal survival in vitro: diffusible signals from neurons and glia change microglia from neurotoxic to neuroprotective. Eur. J. Neurosci. 11, 1657–1667.

Zysk, G., Bruck, W., Gerber, J., Bruck, Y., Prange, H.W., Nau, R., 1996. Anti-inflammatory treatment influences neuronal apoptotic cell death in the dentate gyrus in experimental pneumococcal meningitis. J. Neuropathol. Exp. Neurol. 55, 722–728.