FEBS Letters 585 (2011) 3798–3805

FEBS Letters

journal homepage: www.FEBSLetters.org

Review

Role of microglia in CNS inflammation

Manuel B. Graeber [a,*], Wei Li [a], Michael L. Rodriguez [b]

[a] Brain Tumor Research Laboratories, The Brain and Mind Research Institute, University of Sydney, 94 Mallett St., Camperdown, Sydney NSW 2050, Australia
[b] Department of Forensic Medicine, Sydney Local Health District, Sydney, Australia

ARTICLE INFO

Article history:
Received 4 August 2011
Revised 20 August 2011
Accepted 22 August 2011
Available online 30 August 2011

Edited by Richard Williams, Alexander Flügel and Wilhelm Just

Dedicated to Professor Bernd W. Scheithauer, Mayo Clinic Rochester, on the occasion of his 65th birthday.

Keywords:
Antigen presentation
Cell death
Granulocytes
Macrophages
Neurodegeneration

ABSTRACT

There is increasing confusion about the meaning of the terms inflammation, neuroinflammation, and microglial inflammation. We aim in this review to achieve greater clarity regarding these terms, which are essential for our understanding of the role of microglia in CNS inflammatory conditions. The important concept of sterile inflammation is explained against the backdrop of classical inflammation, and its key differences from what researchers refer to when they use the terms neuroinflammation and microglial inflammation are illustrated. We propose to replace the term "neuroinflammation" with "microglial activation" or "CNS pseudo-inflammation", if microglial activation does not suffice. In addition, we recommend abandoning the terms "microglial inflammation" and "inflamed microglia" because of the lack of a clear concept behind them.

1. Introduction

Before we can consider the role of microglia (Fig. 1 illustrates their phenotypic plasticity) in central nervous system (CNS) inflammation, we have to define what inflammation in the CNS context means and how the term neuroinflammation is used in comparison. This is necessary because *inflammation* has become an "abused" term [1]. Historically (2000 years ago), the Roman Celsus is credited as first documenting the four cardinal signs of inflammation: *rubor et tumor cum calore et dolore* (redness and swelling with heat and pain); the fifth cardinal sign – *functio laesa*, loss of function – was added by Virchow in 1871 [1]. This descriptive and clinical definition of classical inflammation is still in use and dominates conventional thinking. However, it is only the tissue correlate of the cardinal symptoms, i.e., cellular inflammatory changes, that is readily applicable to CNS pathology. Moreover, in recent years new models of inflammation have been developed that are based on molecular phenomena rather than rooted in a cellular understanding of inflammation. The problem with some of these molecular models is that experimental results are sometimes uncritically translated into clinical medicine and may have significant impact on anti-inflammatory treatments and the use of anti-inflammatory drugs, even though the indications and expected benefits remain far from evidence-based [2]. Every year about 120 billion aspirin tablets are consumed worldwide and contribute to an estimated 100 000 hospital admissions and 16 500 deaths in older people from non-steroidal anti-inflammatory drug (NSAID)-related gastrointestinal complications [2]. As we aim to show in this review, *"neuroinflammation"* represents an even more difficult concept than inflammation and a related term often used in connection with microglia, *"microglial inflammation"* adds confusion. The problem is further aggravated by reviews that propagandize hypothetical roles for the innate and adaptive immune system in common neurodegenerative diseases (Virchow did not provide descriptions of activated microglia as claimed by the same authors) [3].

In his classical textbook on the histopathology of the CNS [4], Spielmeyer points out that the concept of inflammation poses a most difficult problem to both the researcher and the teacher. Specifically, the interpretation and evaluation of its competing individual processes are as difficult as formulating a clear definition of the term. Yet, there appear to be some basic and universally recognized principles of inflammation that can be summarized and applied to most if not all organ systems. Clearly classical inflammation, which involves participation of the body's peripheral innate and adaptive immune systems can affect the brain and spinal cord.

* Corresponding author. Fax: +61 2 93510731.
E-mail address: manuel@graeber.net (M.B. Graeber).

0014-5793
doi:10.1016/j.febslet.2011.08.033

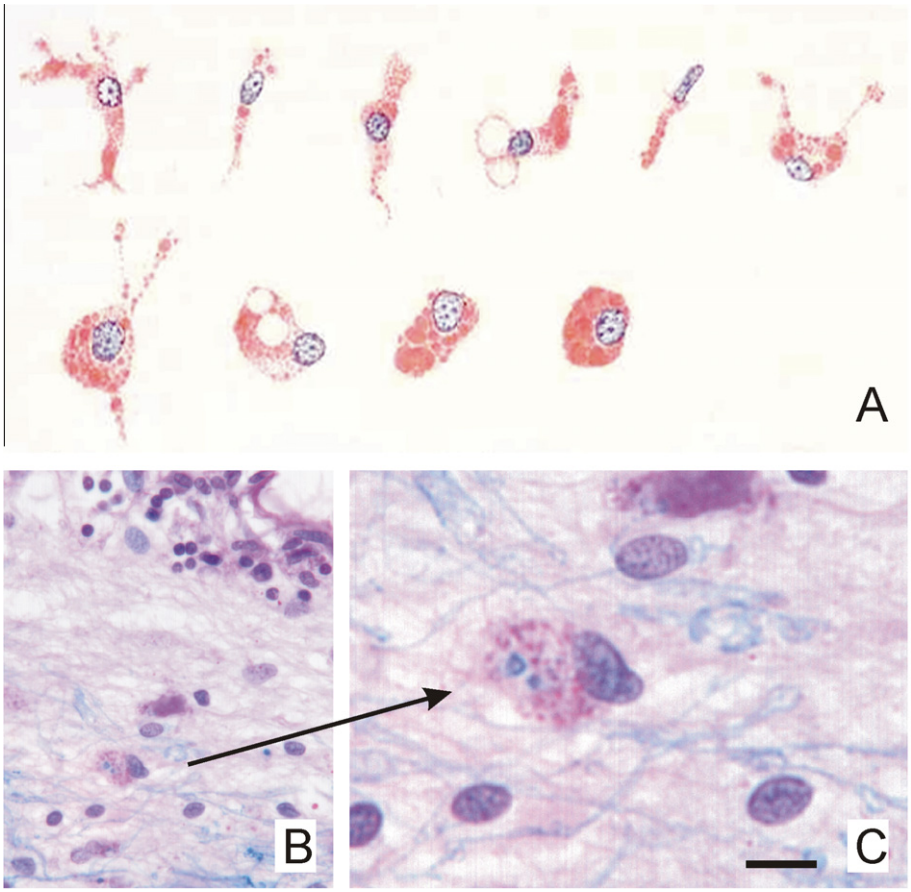

Fig. 1. (A) Microglia and brain macrophages in the cerebral cortex during subacute 'decay of tissue' (Zerfallsprozess). Red colour represents lipid staining (Haematoxylin-scarlet red). Cells become more round with increasing lipid uptake. (B, C) A brain macrophage (arrow) that has taken up a myelin fragment (blue). Chronic multiple sclerosis. Luxol fast blue-PAS. Figure A taken from [4]. Scale bar: 10 μm.

Following Spielmeyer's approach, we begin our review with a discussion of processes that nobody would doubt are clearly inflammatory. Poliomyelitis and other infectious diseases represent good examples. From a histological point of view these diseases are characterized by the presence of infiltrating mobile cells of the innate immune system including granulocytes and macrophages. These mobile cells may so dominate the histological appearance that inflammation is sometimes equated with this reactive infiltration. The latter is incorrect but the presence of mobile cells, most of which have originated outside the affected tissue, is the most widely recognised sign of an inflammatory process. Thus, the cellular elements within inflamed tissue consist of two groups: resident and mobile cells.

2. Classical inflammation

Examples of classical inflammation in the central nervous system include the response to bacterial, parasitic or viral infections. As already indicated, a defining feature of classical inflammation is the accumulation of mobile innate and/or adaptive immune cells in the tissue that are recruited via the bloodstream; although some may also proliferate locally [5]. The latter is certainly true for the microglia of the CNS which, unlike peripheral tissue macrophages, have retained a strong proliferative potential. In addition to the invasion of mobile cells, the classical pathoanatomical definition of inflammation includes a vascular, proliferative and parenchymal tissue-altering component. Traditionally, the term inflammation is applied not only to the reaction associated with, for example, an acute or chronic infection or following toxic damage but also to the reaction accompanying or following tissue repair and regeneration [4]. Recruitment of peripheral mobile cells to the site of inflammation varies. In acute inflammation, if neutrophil recruitment into a tissue is sufficiently pronounced they become visible as pus [6]. The infiltrating mobile cells may also cause tissue destruction. It is worth emphasizing at this point that neutrophils (granulocytes) are far more tissue destructive than macrophages [6] especially when the latter are in a M2-polarised state (CD163 positive) which has been linked to tissue repair. Interestingly, the microglia in the Parkinsonian substantia nigra show this phenotype [7]. Characteristically, granulocytes (Fig. 2 demonstrates their characteristic segmented nuclei) are not seen in conditions that are commonly referred to as "neuroinflammatory" (for a definition of this term see the section on neuroinflammation). The innate immune system in the CNS, in addition to microglia, includes perivascular macrophages (non-committally termed "perivascular cells"). These cells are anatomically and functionally distinct from microglia and serve as the first line of CNS defense. They can be thought of as forming an "immunological blood–brain barrier" [8]. Classical inflammation involves both cell populations.

The fundamental processes that give rise to the cardinal symptoms and signs of classical inflammation (Celsus) are centered on and result from changes in the local vasculature [4,6]. In other words, it is the vasculature where the actual inflammation begins with the consequence that every inflammatory process is predominantly if not exclusively interstitial. In the CNS, an unavoidable consequence of classical inflammation is compromise of the blood-brain barrier.

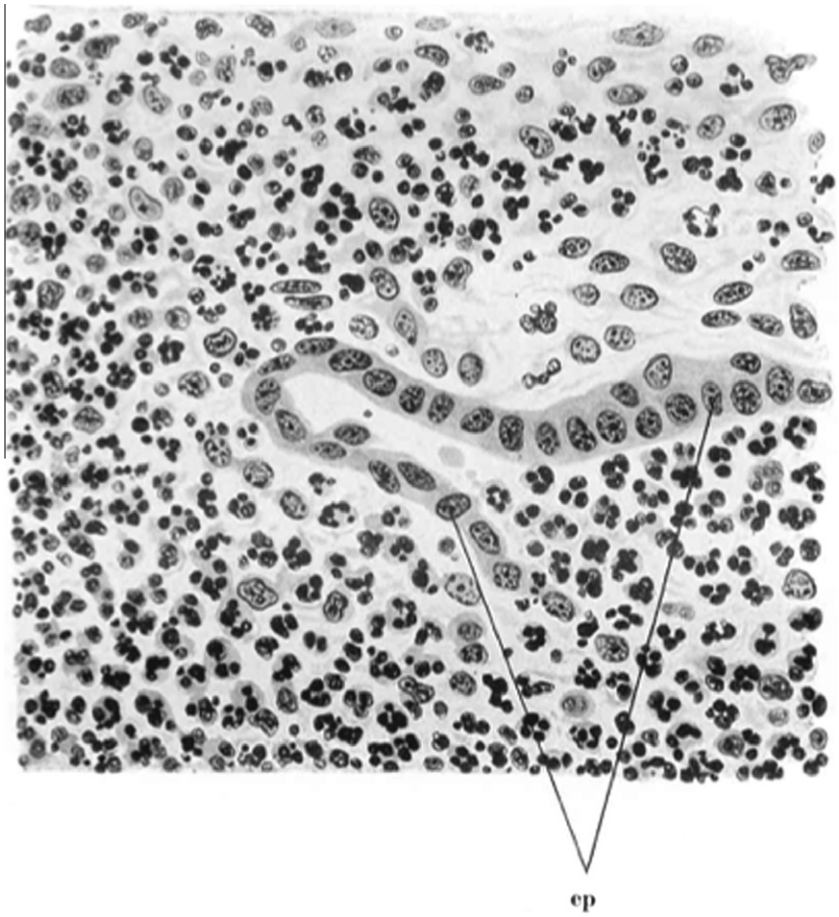

Fig. 2. Purulent myelitis. Destruction of central portions of the cord (ep = remnant of ependyma). Nissl staining. Note the polymorphism of the leukocyte nuclei. Taken from [4].

Although some authors seem to suggest that inflammation can be an exclusively cellular event and have coined the term "inflamed microglia", we believe that the term inflammation should only be used when referring to the classical multicellular process characterized by changes in the vasculature and infiltration of mobile cells. An expanded uncritical use of the term inflammation causes confusion.

One role of histology lies in clarifying whether inflammatory tissue changes represent the primary pathological process or whether they are merely associated secondary phenomena. The latter has been named *symptomatic* or *secondary inflammation* [4]. In our opinion, it is not appropriate to equate all tissue responses with inflammation.

3. Sterile inflammation

Inflammation as a result of trauma, ischaemia–reperfusion injury or chemically induced injury occurs in the absence of microorganisms and has been termed sterile inflammation [9]. Examples of inducers of sterile inflammation include cholesterol crystals [10], hyaluronan [10] and uric acid [6]. The question of how a cell that does not induce inflammation when alive becomes proinflammatory after death is of great interest [6]. One of the presently favored models is that after dying, proinflammatory molecules, normally intracellular and hidden by the plasma membrane, are released from the cell [6].

The inflammasome, a large multimeric intracellular complex that regulates activation of caspase-1 becomes directly and indirectly activated not only during infection or injury but also during sterile inflammation [6,10]. Similar to microbially induced inflammation, sterile inflammation is characterized by a recruitment of neutrophils and macrophages and the production of proinflammatory cytokines and chemokines, notably tumor necrosis factor (TNF) and interleukin-1 (IL-1) [9]. Under conditions of sterile cell death, the inflammatory response, and particularly the infiltration of tissues with neutrophils, can increase the amount of tissue injury [6].

4. Neuroinflammation

A PubMed search for "neuroinflammation" yields more than 2400 hits and indicates that the term was first used in a publication about 15 years ago. A few years into the new millennium, the *Journal of Neuroinflammation* was founded which defines its scope as a journal that focuses on "innate immunological responses of the nervous system, involving microglia, astrocytes, cytokines, chemokines, and related molecular processes". About one third of the PubMed articles containing the term neuroinflammation also contain "microglia"; twice as many as contain "astrocytes" and far more than include "lymphocytes". In contrast, the term neuroimmunology is broader and has a stronger emphasis on cells of the peripheral immune system such as lymphocytes. Accordingly, the *Journal of Neuroimmunology* defines its scope as a "forum for the publication of works applying immunologic methodology to the furtherance of the neurological sciences". Thus, one would assume that the field of neuroinflammation deals less with

the peripheral innate immune system and more with the nervous system's own innate immune cells, the microglia in particular, and their involvement in inflammatory reactions. However, if this is the case then the vast majority of so-called "neuroinflammatory" conditions do not fulfill one of the main criteria of inflammation, namely the presence of mobile cells (granulocytes and/or macrophages and/or lymphocytes). In addition to the mentioned lack of peripheral immune cells, neuroinflammatory conditions are also not usually accompanied by a breach of the blood-brain barrier. A third important argument against "neuroinflammation" being a variant of inflammation comes from the rare human transmissible spongiform encephalopathy, Creutzfeldt-Jakob disease (CJD). The diagnosis of CJD requires absence of classical inflammatory changes. However, microglia, the CNS' innate immune cells, nevertheless up-regulate MHC class II molecules several hundredfold in this condition [11]. Thus, we are left without a sound basis for using the term neuroinflammation and propose to replace it with the term "microglial activation", or, if this does not suffice "CNS pseudo-inflammation" where peripheral immune cells are absent but astrocytes produce "proinflammatory" factors.

Microglial activation represents an increasingly important concept which originated in the late 1980s. The term "activated microglial cells" was formally introduced when it became apparent that intrinsic (resident) microglia are capable of up-regulating certain molecules, including several that are not normally expressed in the CNS [12–14]. Such chameleon-like behaviour illustrates the now well-recognized phenotypic and functional plasticity of microglia [15]. However there remain problems distinguishing microglia, especially after activation, from bone marrow-derived macrophages. Even contemporary microglia markers are cell type-specific only in the sense that they do not label other glia or neurons. They do not readily distinguish resident microglia from macrophages. Consequently, some have suggested that there is no microglia-specific marker. In spite of this, as with macrophages outside the CNS, different functional activation states have been identified in microglia, similar to the well characterized classical (M1) and alternative (M2) activation states in macrophages outside the CNS [16]. Taken together, microglial activation is plastic, finely graded [12] and dynamic. Activated microglia may adopt different phenotypes in response to various stimuli and can become additionally altered following secondary challenges, for example systemic inflammation. There is even evidence that this activation is brain region-specific [17].

5. Multiple sclerosis is not a neurodegenerative disease

Multiple sclerosis (MS) is a characteristic syndrome that, despite protean symptoms reflecting the varying sites of the CNS that can be affected by inflammation and demyelination, is rarely misdiagnosed by an experienced neurologist [18]. This is mirrored by prototypical pathological features where perivascular mononuclear infiltrates and demyelinating lesions of various stages predominate. Perivascular inflammation is so pronounced that residual fibrosis of blood vessels is often found (Fig. 3 illustrates the extent of long-standing perivascular pathology). Many believe that inflammation in MS initiates tissue injury so that degenerative changes which also occur, including axon loss, are considered secondary. It is important to mention in this context that others have suggested that in some patients, albeit with clinically indistinguishable symptoms, the initial change is degenerative rather than inflammatory [18]. In relation to MS, the term neurodegeneration is commonly used to describe neuroaxonal damage [19]. While this may or may not be related to focal demyelinating lesions, most authors currently consider inflammation to be central to its pathogenesis [19]. This can be contrasted with classical neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, where most authors favour a primary CNS-autonomous neurodegenerative process with no accompanying classical or sterile inflammation but frequent pseudo-inflammatory signs, i.e., microglial MHC class II expression in the absence of co-stimulators that would be required for antigen presentation leading to a

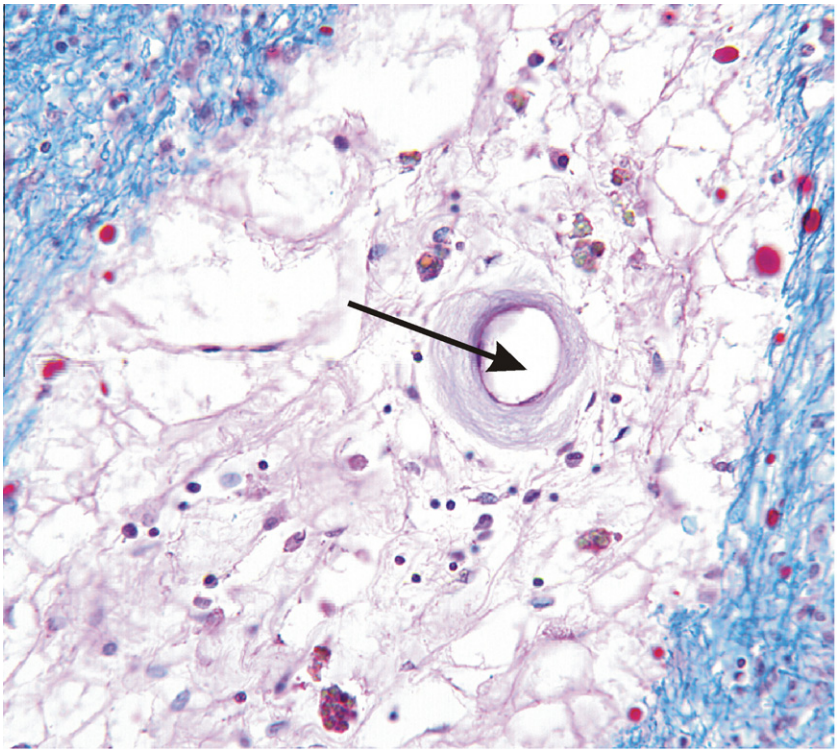

Fig. 3. Perivascular fibrosis of a blood vessel in a case of chronic multiple sclerosis. The arrow points to the blood vessel's lumen. Haemosiderin-containing perivascular macrophages can be seen.

productive T cell response [7]. In other situations, for example the brain pathology in general paralysis of the insane, inflammation, although present does not appear to be the cause of the degenerative changes [4].

It is worth remembering that in classical inflammation different noxae cause different cellular infiltrates and subsequent tissue responses. This is why the histopathology of a multiple sclerosis plaque is characteristic and cannot be mistaken for say an abscess. It is also important to point out that the residual state or end stage of an inflammatory process needs to be distinguished from ongoing inflammation [4] so a burnt-out and highly gliotic (sclerotic) MS plaques can be completely devoid of inflammatory cells. Nevertheless, MS is rightly considered the archetypal inflammatory disease of the CNS, which is characterized by an immune assault on the brain and spinal cord with damage to the myelin sheaths, axons and grey matter [20]. There also is a contribution of systemic inflammation to CNS diseases including MS: it has been shown that systemic infections, typically upper respiratory tract infections, are associated with a significant number of MS relapses [20]. It is further apparent that if systemic infections exacerbate disease processes in the CNS, they may do so by signalling across an intact blood-brain barrier, and microglia could have a role in this peripheral immune system to brain signalling [20].

6. Alzheimer and Parkinson's diseases: Inflammation?

In the 1980s an "imaging revolution" began to take place in histology with the introduction of monoclonal antibodies. Antibodies (and lectins) allowed for the first time the visualization of biological molecules obviating the need to rely on ill-defined tinctorial properties of human tissue and the capriciousness of histochemical stains. The discovery of MHC molecules as markers for activated microglia in common neurodegenerative conditions such as Parkinson's and Alzheimer's diseases (PD and AD) by the McGeer group [21–23] represented a landmark of microglia research which coincided with convergent findings in an experimental, facial nerve axotomy model [24,25]. The description of de novo expression of MHC molecules in the CNS in the conspicuous absence of peripheral immune cells arguably marked the beginning of a paradigm shift. Before this time, researchers mainly looked at immunological phenomena in the CNS "through the eyes of the T-cell". Subsequently, the work of McGeer and colleagues has been used as evidence that inflammation has a key role in AD and PD, and this development has gained additional momentum in recent years. Claims are now being made that microglial activation is one of the causative factors for neuroinflammation, which results in brain damage during neurodegenerative disease [26]. As a consequence, since microglial activation is thought to play an important role in the pathophysiology of neurodegenerative diseases, suppression of microglial activation is hypothesized to prevent the progression of neurodegeneration [27]. While it is still recognised by some authors that inflammation may not typically represent an initiating factor in neurodegenerative diseases, the idea of inflammation being present in essentially all common neurodegenerative conditions is widely publicized: "direct evidence for an innate inflammatory response in AD was described nearly 20 years ago, and subsequent studies have documented inflammatory components in PD, amyotrophic lateral sclerosis (ALS), MS, and a growing number of other nervous system pathologies" [3]. This statement is remarkable because it seems to imply a degree of relatedness between MS, a long-established prototypical inflammatory disease, and diseases such as AD, PD and ALS. Not surprisingly, treatments such as rifampicin for "microglial inflammation" in neurodegenerative diseases have already been proposed [27].

Parkinson's disease

The concept of inflammation acting as a major factor in the pathogenesis of PD can be summarized as follows [28]: "Neuroinflammation, which is characterized by activated microglia and infiltrating T cells at sites of neuronal injury, is a prominent contributor to the pathogenesis of progressive PD. Microglia play a critical role in forming a self-propelling cycle leading to sustained chronic neuroinflammation and driving the progressive neurodegeneration in PD. This activation depends heavily on the respiratory burst within the microglia, which in turn regulates a number of downstream pro-inflammatory activities. On the other hand, the adaptive immune responses, most notably T cells, are now emerging as important components of the inflammatory response that contributes to the pathogenesis of PD." Other authors suggest that activated microglia are widely considered to participate in the progression of PD [29] and advocate a role for the immune system in PD [30]. In PD animal models caused by intoxicating mice with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), the cellular reaction includes MHC class I and II positive microglia, reactive astrocytes and T cells that infiltrate the substantia nigra and striatum and gather in the meninges [31]. However, at least in some model systems, T cell infiltration appears to be species specific. So in a facial nerve injury model, peripheral axotomy results in T cell infiltration into the facial nucleus of the mouse but not the rat (whose neurobiology seems closer to humans) [32]. Some authors even believe that specific T-cell subsets influence PD progression [29]. Yet, this must sound extremely peculiar to anyone who has seen a large number of human PD substantiae nigrae with their striking absence of lymphocytes, or a substantia nigra included in a plaque of multiple sclerosis. The latter is not rare and provides a very informative example of what true inflammatory damage to the human substantia nigra looks like. If one also takes into account that microglia in the PD nigra exhibit an anti-inflammatory phenotype [7], one remains unconvinced of the inflammatory theory of PD. This scepticism seems additionally justified in light of a recent report demonstrating that up-regulation of microglial C1q expression has no effect on nigrostriatal dopaminergic injury in the MPTP mouse model of Parkinson's disease [33]. Instead, complement may well be involved in synaptic changes [34]. While we do not question that genes involved in inflammatory reactions in the periphery are specifically up-regulated in the human PD substantia nigra, as our own work has demonstrated [35], it seems increasingly likely that the products of these genes have a dual and thus different function in the CNS. This view is in keeping with the results of a very large observational study involving 4026 cases of idiopathic PD and 15 969 matched controls [36] where it was found that the long-term use of NSAIDs, aspirin, or acetaminophen was not associated with a substantially altered risk of developing PD [36].

Alzheimer's disease

The enormous interest in inflammation in AD is comparable to that in PD and has a similar historical background [21,22,37]. The driving motivation is also similar, i.e., to develop anti-inflammatory therapies that, while they may not cure AD, will hopefully help slow the progression or delay the onset of this disorder [38]. Yet, NSAIDs were not found to ameliorate Alzheimer neuropathology [37]. Therefore, it is possible, if not likely in our view that activated microglia, identified in the brains of Alzheimer disease patients both histopathologically and in neuroimaging studies [39], and now commonly referred to as "neuroinflammatory", may have a completely different function to activated macrophages in the periphery. For instance, we now know that microglia

themselves are affected by the disease process in AD [40]. Therefore, MHC class II upregulation rather than indicating preparedness of the microglia to engage in a secondary (''recall'') immune reaction in AD, which should be accompanied by components of the classical inflammatory response (which are typically absent from AD brains), these activated microglia could be interpreted as microglia trying to protect already damaged brain tissue [7]. This could explain why anti-inflammatory drugs in AD and PD do not have the desired beneficial effects.

Microglial activation may also be a response to neuronal loss as well as to neuronal dysfunction and their extremely low activation threshold results in their almost universal involvement in even subtle brain pathologies [41]. So in neurodegenerative diseases, widespread microglial activation may reflect widespread neuronal dysfunction in addition to the more apparent alterations of synapses. Direct neuronal attack by microglia (neuronophagia) is tightly controlled, rare and, in all likelihood, a secondary phenomenon [7]. The observation, by human neuropathologists, that microglia do not indiscriminately attack nerve cells in vivo suggests that effective neurotoxicity by activated microglia in the absence of granulocytes or T cells is unlikely or at least uncommon. So while microglial activation may be associated with neuronal loss in neurodegenerative diseases, it is more likely a response to neuronal loss than the cause.

7. Neuroimmunology of psychiatric disorders

Results obtained from imaging activated microglia in vivo [39] have fostered an interest in the role of microglia in psychiatric diseases. Microglial activation, which many authors effectively equate with neuroinflammation, is now considered to be central to the pathogenesis of several psychiatric disorders. Moreover, neuroinflammation has been suggested to involve glial cell-propagated inflammation [42] – in the striking absence of signs of inflammation at the microscopic level. Possibly, researchers in psychiatry (often even more remote from human tissue than basic neuroscientists) do not distinguish between inflammation and neuroinflammation (microglial activation).

Based on the presence of activated microglia, and the recognition that inflammation may represent a common mechanism of disease, some authors have suggested that inflammation is important in the pathophysiology of a number of neuropsychiatric disorders including major depression [43]. One often used argument is that patients with major depression show increased peripheral blood inflammatory biomarkers, including inflammatory cytokines [44]. Indeed, in response to a peripheral infection, pro-inflammatory cytokines are produced by innate immune cells that have an effect on the brain causing sickness behaviour, which may explain the increased prevalence of clinical depression in physically ill people [45]. However, neuropathological criteria of inflammation are again not fulfilled. One author even hypothesizes that ''progress from depression to dementia could result from the activation of macrophages in the blood, and microglia in the brain, that release pro-inflammatory cytokines'' [46] but there is no histological evidence to back this up. Consequently, it appears as though psychiatry is close to adopting a ''neuroinflammation theory of mental diseases''. However, we concur with Bhat and Steinmann [47] that one must look at the boundaries of neurobiology and immunology with a healthy dose of skepticism. It is obvious that there is a great need for more human brain tissue-based studies of psychiatric disorders so that thorough and detailed neuroimaging-tissue correlations can be carried out using brains from donors with a pathologically validated cause of death and information on peripheral co-morbidities. In the absence of convincing evidence and thus a clear rationale, suggestions to target proinflammatory cytokines and inflammation signaling pathways as a strategy to treat psychiatric patients have to be considered premature.

8. Role of microglia in normal brain

Although microglia can express ''immune molecules'', this is not synonymous with inflammation, since these molecules can have CNS-specific roles independent of their roles in the immune or inflammatory response [41]. Similarly, molecules known to neurobiology, including gamma amino butyric acid and the lens protein alpha B crystallin can have intriguing and distinct functions in the immune system [47]. Recently, MHC class I antigens have been implicated in synaptic plasticity and memory function [48]. Tissue damage and classic inflammation could therefore lead to changes in synaptic plasticity and memory function via dysregulation of MHC class I expression [48]. Other important molecules in this context are complement and the CR3 complement receptor [34,41]. Furthermore, the microglial inflammatory signaling molecule DAP-12 has been found to play a role in synaptic plasticity and in modulating glutamatergic neurotransmission [49], and Fourgeaud and Boulang have pointed out a role for immune molecules in the establishment and plasticity of glutamatergic synapses [50]. These mechanisms could underlie the observation that a peripheral inflammatory challenge (lipopolysaccharide injection) results in the parallel activation of microglia and alterations in dendritic spine dynamics [51].

Recently it has been shown that microglial interactions with synapses are physiological and can be modulated by visual experience [52]. During development, microglia actively engulf synaptic material and play a major role in synaptic pruning [53]. It is likely that these normal microglial functions will continue, although perhaps in a somewhat modified way, when various stresses caused by disease impact on the CNS. Importantly, from a quantitative point of view, if confirmed, these normal synapse and spine modulating functions of microglia, are likely to be much more important than their functions as part of an inflammatory response which are utilized only under exceptional circumstances.

It is not usually discussed that microglia differ from all other members of the myeloid lineage in that they live within an electric organ. They also accumulate large amounts of the ''model superparamagnet'' ferritin [54] which can be used as a marker for these cells [55] and although iron metabolism is strictly controlled in the normal CNS where capillaries possess transferrin receptors [56], microglia accumulate iron in a number of degenerative diseases. Although currently speculative, microglia may be in a position to sense pathological alterations of electromagnetic fields, which are generated by axons as well as dendrites [57]. Interestingly, a shared feature of both dendrites and microglia in the cerebral cortex is the presence of angular branching processes; almost as though one was modelled on the other. In contrast, in white matter, microglia are elongated. Unlike astrocytes, microglia are not connected via gap junctions and do not normally respond as a population. Consequently, regional activation of microglia may indicate the presence of a pathological factor that is able to stimulate a large number of individual cells.

Any inflammatory reaction in the brain must be highly regulated to minimize neuronal damage because neurons exhibit a marked sensitivity to inflammatory stimuli such as cytokines [49]. The fact that immune proteins also have normal functions in brain development and plasticity adds novel, non-immune dimensions to their potential role in pathological processes [58]. Understanding how immune proteins in the CNS are regulated by inflammatory signals should provide important clues as to how peripheral immune signaling may affect brain structure and function, and how changes in the expression or function of immune proteins could affect brain

development and plasticity, potentially disrupting the establishment and modification of brain circuitry [58].

9. Microglial inflammation

It is not compatible with neuropathological diagnostic experience and thinking [4] to include isolated MHC class II immunoreactive microglia under the rubric of inflammation in the conspicuous absence of cells of the peripheral immune system. The tissue responses accompanying degeneration in diseases such as AD or PD are not "inflammatory" in the strict sense but are more appropriately termed microglial activation or pseudo-inflammation as detailed earlier. It is the degenerative process, that is at the core of the pathological cascade of events and this has nothing to do with inflammation. Thus, the term inflammation should be reserved for processes where inflammation represents a primary or *independent* process. Based on this definition, one could argue that the mobile cells in the vicinity of a brain area affected by ischemia (stroke), although they may well serve a repair function, do not represent the essence of the ongoing pathology and hence should not be included as "inflammation" since they are secondary changes. Indeed, Spielmeyer suggested the term *symptomatic* inflammation for this.

In this context, "microglial inflammation", is a misnomer since it is neither inflammation of the microglia nor does the phenomenon of microglial activation correlate with inflammation of the brain and spinal cord tissue. The more precise and far more appropriate term for this is *microglia activation* which encompasses both the non-immune and immune functions of the microglia. The last thing one would want to see is clinicians jumping the gun and starting to treat "microglial inflammation" with anti-inflammatory agents in spite of a fundamental lack of evidence that it will do the patient good. Words become obsolete when they lose their usefulness. In our opinion, the terms neuroinflammation and microglial inflammation are being applied so widely and so uncritically that they have effectively lost their meaning. Recent additions to the "inflammation spectrum" of brain disease include epilepsy [59], neurogenesis [60], obesity in mood disorders [61], and alcoholism [62]. While inflammation in the CNS does employ some of the same molecules and processes that occur in both peripheral local and systemic inflammation, the presence of these molecules *per se* should not be considered as inflammation of brain tissue [62]. Thus, although what is termed "neuroinflammation" is often considered to be the equivalent of inflammation in the periphery, these two pathological responses are clearly different [62].

10. Role of microglia in CNS inflammation

In addition to microglia, the normal CNS parenchyma harbors two other glial cell types that have to be considered in the context of brain and spinal cord inflammation. Astrocytes are not commonly associated with immunological reactions and it is well accepted that their role in CNS immunity is largely regulatory while their contribution and capacity to present antigen and activate T cells are still controversial [63]. Oligodendrocytes also do not seem to exert significant immunological or inflammatory functions. Microglia in contrast can serve as activators of naive T cells but probably more importantly, have a role in the reactivation of T cells infiltrating the CNS, i.e., during secondary (recall) reactions and in autoimmune conditions such as MS [63]. Microglia express co-stimulatory and MHC molecules on demand and are capable of presenting antigen to T cells more effectively than astrocytes but less efficiently than dendritic cells [63]. Thus, amongst the CNS resident parenchymal cells, microglia are of greatest interest in the context of neuroimmunology.

Although we introduced the concept of the microglial immune network two decades ago [64] we remain unconvinced that immune and inflammation-related activity is the main function of microglia. It seems more likely to us that their main role is in synaptic plasticity and in the maintenance of synaptic integrity in particular. While there is no doubt that microglia are a CNS tissue alarm system (Kreutzberg's sensor of pathology), the majority of their daily challenges are likely to be subclinical. It is quite conceivable therefore that many of the phenomena in the CNS currently categorized as "inflammatory" represent nothing more than microglia in an increased state of alertness and activity.

An important consequence of considering CNS inflammation and distinguishing it from microglial activation is to reinforce the precautionary clinical principle: primum nil nocere. This means that at the present time a clinical diagnosis of "neuroinflammation" does not provide a sufficient rationale for treatment with anti-inflammatory agents. We do agree however that dissecting the immune component of neurologic disorders represents a grand challenge for the 21st century [65].

References

[1] Scott, A., Khan, K.M., Cook, J.L. and Duronio, V. (2004) What is "inflammation"? Are we ready to move beyond Celsus? Brit. J. Sports Med. 38, 248–249.

[2] Scott, A., Khan, K.M., Roberts, C.R., Cook, J.L. and Duronio, V. (2004) What do we mean by the term "inflammation"? A contemporary basic science update for sports medicine. Brit. J. Sports Med. 38, 372–380, doi:10.1136/bjsm.2004.011312.

[3] Glass, C.K., Saijo, K., Winner, B., Marchetto, M.C. and Gage, F.H. (2010) Mechanisms underlying Inflammation in neurodegeneration. Cell 140, 918–934, doi:10.1016/j.cell.2010.02.016.

[4] Spielmeyer W (1922) Histopathologie des Nervensystems, Springer 493 pp.

[5] Jenkins, S.J., Ruckerl, D., Cook, P.C., Jones, L.H., Finkelman, F.D., van Rooijen, N., Macdonald, A.S. and Allen, J.E. (2011) Local macrophage proliferation, rather than recruitment from the blood, is a signature of TH2 inflammation. Science 332, 1284–1288, doi:10.1126/science.1204351.

[6] Rock, K.L., Latz, E., Ontiveros, F. and Kono, H. (2010) The sterile inflammatory response. Annu. Rev. Immunol. 28, 321–342, doi:10.1146/annurev-immunol-030409-101311.

[7] Graeber, M.B. and Streit, W.J. (2010) Microglia: biology and pathology. Acta Neuropathol. 119, 89–105, doi:10.1007/s00401-009-0622-0.

[8] Graeber, M.B., Streit, W.J. and Kreutzberg, G.W. (1991) Toward an immunological definition of the blood–brain barrier: significance of MHC class II positive perivascular cells. In: Yonezawa T ed. Proceedings of the XIth International Congress of Neuropathology: Satellite symposium on demyelination, mechanisms and background. Neuropathology Supplement 4, 74–79.

[9] Chen, G.Y. and Nuñez, G. (2010) Sterile inflammation: sensing and reacting to damage. Nat. Rev. Immunol. 10, 826–837, doi:10.1038/nri2873.

[10] Davis, B.K., Wen, H. and Ting, J.P.-Y. (2011) The Inflammasome NLRs in immunity, inflammation, and associated diseases. Annu. Rev. Immunol. 29, 707–735, doi:10.1146/annurev-immunol-031210-101405.

[11] v Eitzen, U., Egensperger, R., Kösel, S., Grasbon-Frodl, E.M., Imai, Y., Bise, K., Kohsaka, S., Mehraein, P. and Graeber, M.B. (1998) Microglia and the development of spongiform change in Creutzfeldt-Jakob disease. J. Neuropathol. Exp. Neurol. 57, 246–256.

[12] Graeber, M.B., Streit, W.J. and Kreutzberg, G.W. (1988) Axotomy of the rat facial nerve leads to increased CR3 complement receptor expression by activated microglial cells. J. Neurosci. Res. 21, 18–24.

[13] Graeber, M.B., Streit, W.J. and Kreutzberg, G.W. (1988) The microglial cytoskeleton: vimentin is localized within activated cells in situ. J. Neurocytol. 17, 573–580.

[14] Graeber, M.B., Streit, W.J., Kiefer, R., Schoen, S.W. and Kreutzberg, G.W. (1990) New expression of myelomonocytic antigens by microglia and perivascular cells following lethal motor neuron injury. J. Neuroimmunol. 27, 121–132.

[15] Streit, W.J., Graeber, M.B. and Kreutzberg, G.W. (1988) Functional plasticity of microglia: a review. Glia 1, 301–307.

[16] Michelucci, A., Heurtaux, T., Grandbarbe, L., Morga, E. and Heuschling, P. (2009) Characterization of the microglial phenotype under specific pro-inflammatory and anti-inflammatory conditions: Effects of oligomeric and fibrillar amyloid-beta. J. Neuroimmunol., doi:10.1016/j.jneuroim.2009.02.003.

[17] Choi, H.K., Ryu, H.J., Kim, J.-E., Jo, S.-M., Choi, H.-C., Song, H.-K. and Kang, T.-C. (2011) The roles of P2X7 receptor in regional-specific microglial responses in the rat brain following status epilepticus. Neurol Sci 1, 11–10.1007/s10072–011-0740-z.

[18] Barnett, M.H., Parratt, J.D.E., Pollard, J.D. and Prineas, J.W. (2009) MS: is it one disease? International MS journal / MS Forum 16, 57–65.

[19] Stadelmann, C. (2011) Multiple sclerosis as a neurodegenerative disease: pathology, mechanisms and therapeutic implications. Curr. Opin. Neurol. 24, 224–229, doi:10.1097/WCO.0b013e328346056f.
[20] Perry, V.H. (2010) Contribution of systemic inflammation to chronic neurodegeneration. Acta Neuropathol. 120, 277–286, doi:10.1007/s00401-010-0722-x.
[21] McGeer, P.L., Itagaki, S. and McGeer, E.G. (1988) Expression of the histocompatibility glycoprotein HLA-DR in neurological disease. Acta Neuropathol. 76, 550–557.
[22] McGeer, P.L. and McGeer, E.G. (1999) Inflammation of the brain in Alzheimer's disease: implications for therapy. J. Leukoc. Biol. 65, 409–415.
[23] McGeer, P.L., Yasojima, K. and McGeer, E.G. (2001) Inflammation in Parkinson's disease. Adv. Neurol. 86, 83–89.
[24] Streit, W., Graeber, M.B. and Kreutzberg, G.W. (1989) Peripheral nerve lesion produces increased levels of major histocompatibility complex antigens in the central nervous system. J. Neuroimmunol. 21, 117–123.
[25] Streit, W., Graeber, M.B. and Kreutzberg, G.W. (1989) Expression of Ia antigen on perivascular and microglial cells after sublethal and lethal motor neuron injury. Exp. Neurol. 105, 115–126.
[26] Zhu, L.-H., Bi, W., Qi, R.-B., Wang, H.-D. and Lu, D.-X. (2011) Luteolin inhibits microglial inflammation and improves neuron survival against inflammation. Int. J. Neurosci. 121, 329–336, doi:10.3109/00207454.2011.569040.
[27] Bi, W., Zhu, L., Wang, C., Liang, Y., Liu, J., Shi, Q. and Tao, E. (2011) Rifampicin inhibits microglial inflammation and improves neuron survival against inflammation. Brain Res. 1395, 12–20, doi:10.1016/j.brainres.2011.04.019.
[28] Qian, L., Flood, P.M. and Hong, J.-S. (2010) Neuroinflammation is a key player in Parkinson's disease and a prime target for therapy. J Neural Transm 117, 971–979, doi:10.1007/s00702-010-0428-1.
[29] Cao, J.-J., Li, K.-S. and Shen, Y.-Q. (2011) Activated immune cells in Parkinson's disease. J. Neuroimmune Pharmacol., doi:10.1007/s11481-011-9280-9.
[30] German, D.C., Eagar, T. and Sonsalla, P.K. (2011) Parkinson's disease: a role for the immune system. Curr. Mol. Pharmacol. 4, in press.
[31] Członkowska, A. and Kurkowska-Jastrzębska, I. (2011) Inflammation and gliosis in neurological diseases–clinical implications. J. Neuroimmunol. 231, 78–85, doi:10.1016/j.jneuroim.2010.09.020.
[32] Raivich, Jones.L.L., Kloss, C.U., Werner, A., Neumann, H. and Kreutzberg, G.W. (1998) Immune surveillance in the injured nervous system: T-lymphocytes invade the axotomized mouse facial motor nucleus and aggregate around sites of neuronal degeneration. J. Neurosci. 18, 5804–5816.
[33] Depboylu, C., Schorlemmer, K., Klietz, M., Oertel, W.H., Weihe, E., Höglinger, G.U. and Schäfer, M.K.-H. (2011) Upregulation of microglial C1q expression has no effects on nigrostriatal dopaminergic injury in the MPTP mouse model of Parkinson disease. J. Neuroimmunol., doi:10.1016/j.jneuroim.2011.05.006.
[34] Stevens, B., Allen, N.J., Vazquez, L.E., Howell, G.R., Christopherson, K.S., Nouri, N., Micheva, K.D., Mehalow, A.K., Huberman, A.D., Stafford, B., et al. (2007) The classical complement cascade mediates CNS synapse elimination. Cell 131, 1164–1178, doi:10.1016/j.cell.2007.10.036.
[35] Moran, L.B. and Graeber, M.B. (2008) Towards a pathway definition of Parkinson's disease: a complex disorder with links to cancer, diabetes and inflammation. Neurogenetics 9, 1–13, doi:10.1007/s10048-007-0116-y.
[36] Becker, C., Jick, S.S. and Meier, C.R. (2011) NSAID use and risk of Parkinson disease: a population-based case-control study. Eur. J. Neurol., doi:10.1111/j.1468-1331.2011.03399.x.
[37] Beeri, M.S., Schmeidler, J., Lesser, G.T., Maroukian, M., West, R., Leung, S., Wysocki, M., Perl, D.P., Purohit, D.P. and Haroutunian, V. (2011) Corticosteroids, but not NSAIDs, are associated with less Alzheimer neuropathology. Neurobiol. Aging, doi:10.1016/j.neurobiolaging.2011.02.011.
[38] Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G.M., Cooper, N.R., Eikelenboom, P., Emmerling, M., Fiebich, B.L., et al. (2000) Inflammation and Alzheimer's disease. Neurobiol. Aging 21, 383–421.
[39] Cagnin, A., Brooks, D.J., Kennedy, A.M., Gunn, R.N., Myers, R., Turkheimer, F.E., Jones, T. and Banati, R.B. (2001) In-vivo measurement of activated microglia in dementia. Lancet 358, 461–467, doi:10.1016/S0140-6736(01)05625-2.
[40] Streit, W., Braak, Xue.Q. and Bechmann, I. (2009) Dystrophic (senescent) rather than activated microglial cells are associated with tau pathology and likely precede neurodegeneration in Alzheimer's disease. Acta Neuropathol. 118, 475–485, doi:10.1007/s00401-009-0556-6.
[41] Graeber, M.B. (2010) Changing face of microglia. Science 330, 783–788, doi:10.1126/science.1190929.
[42] Hashioka, S. (2011) Antidepressants and neuroinflammation: can antidepressants calm glial rage down? Mini Reviews in Medicinal Chemistry 11, 555–564.
[43] Raison, C.L., Capuron, L. and Miller, A.H. (2006) Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 27, 24–31, doi:10.1016/j.it.2005.11.006.
[44] Miller, A.H., Maletic, V. and Raison, C.L. (2009) Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. Psychiatry 65, 732–741, doi:10.1016/j.biopsych.2008.11.029.
[45] Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W. and Kelley, K.W. (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56, doi:10.1038/nrn2297.
[46] Leonard, B.E. (2007) Inflammation, depression and dementia: are they connected? Neurochem. Res. 32, 1749–1756, doi:10.1007/s11064-007-9385-y.
[47] Bhat, R. and Steinman, L. (2009) Innate and adaptive autoimmunity directed to the central nervous system. Neuron 64, 123–132, doi:10.1016/j.neuron.2009.09.015.
[48] Shatz, C.J. (2009) MHC Class I: An unexpected role in neuronal plasticity. Neuron 64, 40–45, doi:10.1016/j.neuron.2009.09.044.
[49] Northrup, N.A. and Yamamoto, B.K. (2011) Neuroimmune pharmacology from a neuroscience perspective. J Neuroimmune Pharmacol 6, 10–19, doi:10.1007/s11481-010-9239-2.
[50] Fourgeaud, L. and Boulanger, L.M. (2010) Role of immune molecules in the establishment and plasticity of glutamatergic synapses. Eur. J. NeuroSci. 32, 207–217, doi:10.1111/j.1460-9568.2010.07342.x.
[51] Kondo, S., Kohsaka, S. and Okabe, S. (2011) Long-term changes of spine dynamics and microglia after transient peripheral immune response triggered by LPS in vivo. Mol Brain 4, 27, doi:10.1186/1756-6606-4-27.
[52] Tremblay, M.-È., Lowery, R.L. and Majewska, A.K. (2010) Microglial interactions with synapses are modulated by visual experience. PLoS Biol. 8, e1000527, doi:10.1371/journal.pbio.1000527.
[53] Paolicelli, R.C., Bolasco, G., Pagani, F., Maggi, L., Scianni, M., Panzanelli, P., Giustetto, M., Ferreira, T.A., Guiducci, E., Dumas, L., Ragozzino, D. and Gross, C.T. (2011) Synaptic pruning by microglia is necessary for normal brain development. Science 10.1126/science.1202529.
[54] Kilcoyne, S.H. and Cywinski, R. (1995) Ferritin: a model superparamagnet. J. Magn. Magn. Mater. 140–144, 1466–1467.
[55] Kaneko, Y., Kitamoto, T., Tateishi, J. and Yamaguchi, K. (1989) Ferritin immunohistochemistry as a marker for microglia. Acta Neuropathol. 79, 129–136.
[56] Visser, C.C., Voorwinden, L.H., Crommelin, D.J., Danhof, M. and de Boer, A.G. (2004) Characterization and modulation of the transferrin receptor on brain capillary endothelial cells. Pharm. Res. 21, 761–769.
[57] Richerson, S., Ingram, M., Perry, D. and Stecker, M.M. (2005) Classification of the extracellular fields produced by activated neural structures. Biomed. Eng. 4 (53), 1–23.
[58] Boulanger, L.M. (2009) Immune proteins in brain development and synaptic plasticity. Neuron 64, 93–109, doi:10.1016/j.neuron.2009.09.001.
[59] Aronica, E. and Crino, P.B. (2011) Inflammation in epilepsy: Clinical observations. Epilepsia 52, 26–32, doi:10.1111/j.1528-1167.2011.03033.x.
[60] Molina-Holgado, E., and Molina-Holgado, F. (2010) Mending the broken brain: neuroimmune interactions in neurogenesis. J. Neurochem., doi:10.1111/j.1471-4159.2010.06849.x.
[61] Soczynska, J.K., Kennedy, S.H., Woldeyohannes, H.O., Liauw, S.S., Alsuwaidan, M., Yim, C.Y. and McIntyre, R.S. (2011) Mood disorders and obesity: understanding inflammation as a pathophysiological nexus. Neuromolecular Med. 13, 93–116, doi:10.1007/s12017-010-8140-8.
[62] Kelley, K.W. and Dantzer, R. (2011) Alcoholism and inflammation: Neuroimmunology of behavioral and mood disorders. Brain Behav. Immun. 25, S13–S20, doi:10.1016/j.bbi.2010.12.013.
[63] Chastain, E.M.L., Duncan, D.A.S., Rodgers, J.M. and Miller, S.D. (2011) The role of antigen presenting cells in multiple sclerosis. Biochim. Biophys. Acta 1812, 265–274, doi:10.1016/j.bbadis.2010.07.008.
[64] Graeber, M.B. and Streit, W.J. (1990) Microglia: immune network in the CNS. Brain Pathol. 1, 2–5.
[65] Coyle, P.K. (2011) Dissecting the immune component of neurologic disorders: a grand challenge for the 21st century. Front Neur 2, 1–2, doi:10.3389/fneur.2011.00037.