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Review article

Neuroinflammation: The role and consequences

Monty Lyman[a,1], Dafydd G. Lloyd[a,1], Xunming Ji[b], Marcela P. Vizcaychipi[a], Daqing Ma[a,*]

[a] Section of Anaesthetics, Pain Medicine & Intensive Care, Department of Surgery and Cancer, Imperial College London, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, UK
[b] Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China

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ABSTRACT

Neuroinflammation is central to the common pathology of several acute and chronic brain diseases. This review examines the consequences of excessive and prolonged neuroinflammation, particularly its damaging effects on cellular and/or brain function, as well as its relevance to disease progression and possible interventions. The evidence gathered here indicates that neuroinflammation causes and accelerates long-term neurodegenerative disease, playing a central role in the very early development of chronic conditions including dementia. The wide scope and numerous complexities of neuroinflammation suggest that combinations of different preventative and therapeutic approaches may be efficacious.

Contents

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta; CDK5, cyclin-dependent kinase 5; CNS, central nervous system; COX, cyclooxygenase; CRP, C-reactive protein; FADD, Fas-Associated protein with Death Domain; GSK3, glycogen synthase kinase-3; IFN-γ, interferon-γ; IL, interleukin; IL-1β, interleukin-1beta; iNOS, nitric oxide synthase; LPS, lipopolysaccharide; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase pathways; NO, nitric oxide; NPCs, neural progenitor cells; NSAIDs, non-steroidal anti-inflammatory drugs; PAMPs, pathogen-associated molecular patterns; POCD, postoperative cognitive dysfunction; SGZ, subgranular layer; TLRs, toll-like receptors; TNF, tumour necrosis factor; TRADD, tumour necrosis factor receptor type 1-associated Death domain protein; TRAIL, tumour-necrosis-factor-related-apoptotic-ligand.

* Corresponding author. Tel.: +44 0203315 8495; fax: +44 0203315 5109.
E-mail address: d.ma@imperial.ac.uk (D. Ma).
[1] These authors contributed equally.

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1. Introduction

Inflammation is a response of the innate immune system that aims to protect and defend the body. Triggers can be an aseptic insult such as sterile surgery (where tissue damage caused by mechanical injury induces an inflammatory response), or non-aseptic (such as bacterial or viral invasion). The inflammatory response is orchestrated by the mobilisation and interaction of several cell types and signalling molecules, producing a response that is both local and systemic. The cell types central to the inflammatory response are white blood cells (leucocytes) and endothelial cells. Leucocytes, including monocytes, are derived from the mononuclear phagocyte system (bone marrow, lymph nodes and spleen) and can penetrate tissue where their functions include phagocytosis and antigen presentation. Signalling molecules include locally acting small molecules such as nitric oxide (NO), lipid compounds, e.g. prostaglandins and complex circulating proteins, cytokines. Innate immunity comprises of generic, non-specific responses of the immune system, usually triggered by distinctive pathogen-derived molecules known as pathogen-associated molecular patterns (PAMPs). This is an immediate, and often short-lived, response. This differs from the adaptive immune response, which involves T and B lymphocytes, begins to take effect two to three weeks following infection and produces a highly specialised response to pathogens. Processes such as somatic hypermutation enable a relatively small number of genes to encode a huge array of receptors.

Initially, tissue resident leucocytes stimulate endothelial cells to present cellular adhesion molecules that recruit more leucocytes to the site of tissue damage. Adhesion molecules weakly bind circulating leucocytes, slowing them down and enabling their adherence to signalling endothelium. Such endothelium undergoes a phenotypic change becoming permeable to the leucocytes that are drawn towards a high concentration of cytokine near the stimulus. Within the tissue, monocytes differentiate to macrophages capable of phagocytosis and secretion of further signalling molecules, which mobilise and recruit more effector cells from the periphery. Thereby the inflammatory response is maintained and amplified, spreading from a local focus to a systemic response.

Inflammation aims to clear and control the initial stimulus, for example, through phagocytosis and activation of the inflammasome (which triggers apoptosis (Fernandes-Alnemri et al., 2009)), to ultimately enable tissue regeneration and scarring. However, although intended to be protective and beneficial, an excessive inflammatory response can cause or contribute to tissue damage and disease pathology. Once deployed, activated cells target not only the initial site of inflammation, but also remote sites that are responding to the inflammatory stimulus.

Peripheral inflammation triggers a neuroinflammatory response involving blood–brain barrier, glia and neurons. Neuroinflammation is a term used to describe the broad range of immune responses of the central nervous system, differing from peripheral inflammation in a number of ways, primarily concerning the principle cells involved (such as microglia and astrocytes). The blood brain barrier, a highly specialised form of endothelium, was previously thought to completely separate the central nervous system from the peripheral immune system. However, it is not only permeable to pro-inflammatory mediators derived from peripheral inflammation, but can also be stimulated to both release and transmit these mediators and allow leucocyte migration into the brain (de Vries et al., 1996; Laflamme et al., 1999). This neuroinflammatory response results in synaptic impairment, neuronal death and an exacerbation of several disease pathologies within the brain (Cunningham et al., 1996; Kitazawa et al., 2005; Micheau and Tschopp, 2003).

This review will focus on the consequences of excessive and prolonged neuroinflammation, particularly its damaging effects on brain function. Its relevance to disease progression, ranging from acute conditions including delirium and postoperative cognitive dysfunction to chronic diseases such as Alzheimer's disease and multiple sclerosis, will be explored briefly, along with possible interventions. The evidence gathered here suggests that neuroinflammation causes and accelerates long-term neurodegenerative disease, playing a central role in the very early development of chronic conditions including dementia. The wide scope and numerous complexities of neuroinflammation suggest that combinations of different preventative and therapeutic approaches may be efficacious.

2. Neuroinflammation

2.1. Cellular components of neuroinflammation

The endothelial layer known as the blood–brain barrier (BBB) and transport of molecules across it is key to understanding how peripheral inflammation can cause prolonged and damaging neuroinflammation. Inflammatory cytokines and other proteins were originally thought to be too large to enter the brain from the blood, but a number of transport mechanisms have come to light over the last two decades. BBB active transport systems have been observed facilitating the delivery of TNF and IL cytokines into the brain (Gutierrez et al., 1993). Circumventricular organs, which have an incomplete barrier at the blood–brain interface, are particular areas of concentrated cytokine transport (Quan et al., 1999). TNF-α, IL-6, IL-1β and other cytokines also have adverse affects on the integrity of the BBB, allowing it to become more permeable and enabling the entry of leucocytes into the brain (Laflamme et al., 1999; Terrando et al., 2011). Cytokine levels are known to modulate the permeability of the BBB by altering the resistance of tight junctions in endothelial cells in brain vasculature (Wong et al., 2004), high levels up-regulating inflammatory cytokines and COX-2 transcription in the endothelium (de Vries et al., 1996). Damage to integral tight junction proteins such as occludin results in an increased tight junction permeability, possibly through affecting its interaction with the cell cytoskeleton. Vagal stimulation by peripheral cytokines has direct influence on the central nervous system (CNS) and induces sickness behaviour (Goehler et al., 1999) and this presents another interesting area in the translation of peripheral inflammation to neuroinflammation, as recently reviewed (Fung et al., 2012). The movement of leucocytes across the BBB is also regulated to some extent by other humoral factors such as chemokines. For example, chemokines CCL19 and CCL21 enable T cell adhesion to the BBB, whereas CXCL12 may play a pivotal role in reducing T cell infiltration (Engelhardt., 2010). Many of these humoral factors are produced by astrocytes, and upregulation of molecules produced by these glial cells have important effects on the integrity of the BBB. An example is shown in bradykinin triggering the release of IL-6 from astrocytes during inflammation (Schwaninger et al., 1999).

Microglial cells, which are the resident macrophages of the CNS, play a crucial role in the process of neuroinflammation. In response to cytokines and other signalling molecules from acute inflammation, microglia transform from a ramified, inactivated state to an activated phagocytic one, releasing pro-inflammatory mediators in the process. In terms of chronic neuroinflammation, these cells can remain activated for extended periods, releasing quantities of cytokines and neurotoxic molecules that contribute to long-term neurodegeneration (Liu and Hong, 2003). Macrophages are activated in a number of different ways along a spectrum that has been divided into M1 or M2 activation. M1 (or classically activated) macrophages are effector macrophages stimulated by interferon (IFN)-γ and tumour necrosis factor and produce an aggressive first-line immune response. M2 (or alternatively activated) macrophage is the term used to describe all other types of macrophages. These are usually stimulated by IL-4 and have roles in wound healing and regulation of the macrophage response. Switching from M2 states to the pro-inflammatory M1 state may have a significant effect on the intensity and development of peripheral inflammation. This effect may also be of importance with microglia in the CNS, although there is little known about the relationship between microglia activation states and neuroinflammation. Astrocytes comprise the other family of glial cells that release pro-inflammatory signalling molecules such as TNF-α when stimulated in the cortex and midbrain (Kipp et al., 2008). These cells also play important roles in synaptic function and regulation (see Section 3.1). Although microglia show much greater inflammatory cytokine release (Liu et al., 2012), the combined glial response could be very influential in the development of neurodegeneration seen in dementia (Cagnin et al., 2001; Xing et al., 2011). It is established that a dynamic crosstalk exists between BBB endothelial cells, glia and neurons (Abbott et al., 2006) and it is likely that a neuroinflammatory response from one type of cell will directly impact another.

Toll-like receptors (TLRs) are important signal transduction proteins in the innate immune system and the inflammatory response. These are pattern recognition receptors that are activated on detection of a foreign microbe and initiate downstream signalling cascades. A common example is the MyD88 pathway, which involves the stimulation of protein kinase IRAK-4 to initiate a signalling pathway that regulates gene transcription. TLR-4 is of particular importance as it is induced by lipopolysaccharide (LPS). LPS is an endotoxin found in the outer membrane of gram-negative bacteria and through TLR signalling it induces systemic inflammatory response syndrome (SIRS) and sepsis in animals, with humans being particularly sensitive (Warren et al., 2010). This pathway is commonly used to induce an inflammatory response in animal models (Hoshino et al., 1999). TLR-4 activation induces TNF-α and IL-1β release and is a key receptor in pro-inflammatory signalling. Astrocytes and microglia express a range of TLRs that activate these cells and initiate a neuroinflammatory reaction. Microglia express the two classes of major histocompatibility complex, MHC class 1 and MHC class 2, and although these antigen presenters are mainly involved in the reaction to infectious disease, they are thought to play a role in the development of neuroinflammation (Al Nimer et al., 2011). These complexes are examples of a multitude of receptors on cells involved in inflammation in the CNS.

2.2. Molecular components of neuroinflammation

Cytokines are cell-signalling proteins that mediate neuroinflammation, causing its exacerbation or reduction. Pro-inflammatory cytokines such as the biologically similar interleukin-1 (IL-1) and tumour necrosis factor (TNF) play an integral role in pathological inflammation and the acceleration of disease. Conversely, several cytokines, including IL-4, are largely anti-inflammatory (Opal and DePalo, 2000). Pro- and anti-inflammatory distinctions, however, should not be rigidly attributed to specific cytokines in all cases of normal physiology and disease pathology as the effects of a signalling molecule may differ, depending on its location within the CNS and in the context of disease.

Initial cytokine release can initiate the further production of signalling molecules and this is shown in IL-6 activating T cells and stimulating production of other inflammatory markers including C-reactive protein (CRP) and fibrinogen (Jung et al., 2002). On binding to the extracellular TNF receptor-1, TNF-α sets off a number of signalling cascades that affect gene transcription. An example of one common cascade that leads to inflammation and degeneration is that of tumour necrosis factor receptor type 1-associated Death domain protein (TRADD) and TNF receptor-associated factor 2 protein (TRAF2) recruiting enzymes to activate transcription factor NF-κB. These proteins also induce c-jun N-terminal kinase (JNK) pathways, which activate various other transcription factors that modulate apoptosis and inflammation (Hohmann et al., 1990). TNF signalling is also directly pro-apoptotic through the Fas-Associated protein with Death Domain (FADD) mediated production of enzyme Caspase-8, an enzyme strongly linked with apoptosis and neurodegeneration (Kischkel et al., 2000). IL-1β, when bound to the IL-1 Receptor complex is also a critical initiator of a number of signal transduction cascades, namely mitogen-activated protein kinase pathways (MAPK) (Ridley et al., 1997). p38 MAPK is, like JNK, a stress-activated protein kinase and its activation results in many pro-inflammatory responses and the production of IL-8 and IL-6 (Jung et al., 2002). Chemokines are small chemotactic cytokines that also play a role in neuroinflammation. Although they have very low physiological concentrations within the CNS, levels of certain chemokines such as monocyte chemoattractant protein-1 are strongly upregulated in chronic neuroinflammation (Sokolova et al., 2009). These molecules are involved in the upregulation and chemotaxis of astrocytes and microglia in response to an inflammatory stimulus and they may also disrupt neuronal function and adversely affect neurogenesis.

The complement cascade, activated by the alternative, classical and lectin-binding pathways, is an important feature of immunity and inflammation. It contributes to processes such as mast cell degranulation, chemotaxis and cell lysis. Complement was not perceived to play a role within the CNS until relationships between complement proteins and glial cells were observed, for example the roles of C3a, C3b, C5a in the chemotaxis and phagocytic functions of microglia in neuroinflammation (Eikelenboom and Veerhuis, 1996). The autoimmune disease neuromyelitis optica is an example of complement-induced damage of the CNS. IgG autoantibodies combined with complement proteins downregulate aquaporin-4 water channel expression in astrocytes and cause the break down of myelin in the CNS (Saadoun et al., 2010). A recent trial using eculizumab, a C5 inhibiting monoclonal antibody, suggests that targeting the complement system may be efficacious in reducing neuroinflammation (Pittock et al., 2013). As with many aspects of innate immunity the complement cascade is generally considered a double-edged sword within the CNS, exhibiting a protective effect at physiological and acute levels but causing damage if stimulated chronically.

The enzyme cyclooxygenase (COX) converts arachidonic acid to eicosanoid groups (Hamberg and Samuelsson, 1973) such as prostaglandins and thromboxanes and has various inflammatory functions. The pathways of its two common isoforms COX-1 and COX-2 are becoming increasingly associated with neuroinflammation and neurodegeneration, with COX inhibitors such as non-steroidal anti-inflammatory drugs (NSAIDs) presenting several therapeutic potentials (see Section 5). Both these isoforms have different roles both in normal physiology and pathology. COX-1 expression leading to prostaglandin synthesis is seen in microglia

(Hoozemans et al., 2001), and it is thought that an activation of these cells could lead to an excessive release of prostaglandins. Many aspects of the COX-1 pathway are pro-inflammatory, resulting in damaging neuroinflammation and cognitive impairment (Matousek et al., 2010) and pathological associations have been observed in traumatic brain injury (Schwab et al., 2002) and neurodegenerative diseases such as Alzheimer's disease (Sung et al., 2004). COX-2 expression is mainly observed in neurons and it is associated with synaptic functioning and memory formation (Cowley et al., 2008; Wang et al., 2005). COX-2 has notably been shown to have anti-inflammatory properties (Aid et al., 2008; Gilroy et al., 1999), which highlights the complexities of eicosanoid signalling in neuroprotection and neurodegeneration and the difficulties in forming therapeutic strategies. The strong involvement of COX-1 in neuroinflammation compared to COX-2 could be related to its expression in microglia, whereas COX-2 overexpression may only be exhibited in direct neuronal damage. Cytokine signalling also interacts with these pathways. IL-1β induced MAPK activation promotes COX-2 gene expression (Lacroix and Rivest, 1998) and the cyclooxygenase pathway itself stimulates the production of IL-6, which shows one of many positive feedback loops in the systemic inflammatory response (Anderson et al., 1996).

The role of existing pathology in the translation of peripheral inflammation to neuroinflammation is also of importance. For example, Alzheimer's disease (AD) is an example of a neurodegenerative disease that has many interactions between its pathology and inflammation, whether systemic or brain-derived. The presence of existing amyloid beta (Aβ) plaques, one of the pathological hallmarks of AD, appears to facilitate the movement of components of the peripheral immune system such as T cells and macrophages into the brain (Stalder et al., 2005). Leucocyte migration across a damaged BBB is also influenced by COX-2 production (Fiala et al., 2002), so it seems likely that the net effect of increased peripheral inflammation is capable of propagating sustained and damaging neuroinflammation in a positive feedback loop.

3. Outcomes of neuroinflammation

3.1. Neuroinflammation and synaptic dysfunction

Synaptic impairment in its various forms is not only a hallmark of late stage neurodegenerative disease but also a feature of the early progression of dementia (Masliah et al., 2001). Emerging evidence suggests that neuronal apoptosis is an insufficient measure of neurodegeneration as a number of processes, including synaptic impairment, render neurons damaged and inadequate for neurotransmission a long time before cell death. Synaptic dysfunction is manifested in a number of ways including complete loss of synaptic function and impairment of synaptic plasticity. Plasticity concerns the variable nature of synapse impulse strength and it is associated with the formation and consolidation of memories. One feature of synaptic plasticity, long-term potentiation, affects cognitive function and long-term memory and is discussed in Section 3.2. Although some physiological levels of TNF-α and IL-1β appear beneficial for synaptic plasticity, synaptic scaling (the regulation of pre- and postsynaptic strengths relative to each other) and other functions (Avital et al., 2003; Stellwagen and Malenka, 2006), pro-inflammatory mediators also have deleterious effects (Cumiskey et al., 2007; Cunningham et al., 1996). IL-1β production results in the loss of synaptic connections through sensitising of NDMA receptors to glutamate in pre- and post-synaptic terminals (Mishra et al., 2012). This process requires the involvement of COX-2, which itself presents paradoxical protective and damaging actions at the synapse, perhaps explained by a difference in prostaglandin production between synaptic and extrasynaptic NDMA receptors (Stark and Bazan, 2011). Synaptic impairment is not only the end result of CNS insults and prolonged inflammation, but synaptic loss and reduced synaptic function also precedes neuronal pathology such as tauopathies (Yoshiyama et al., 2007). Although the causes behind these striking findings are unclear, glia-mediated damage is implicated, suggesting a possible role of neuroinflammation in the very early stages of disease development.

The role of glial cells in neurotransmission is not fully understood, but it is likely that these cells modulate activity at the synapse and contribute to synaptic damage in inflammation. A growing body of evidence describes a tripartite synapse model consisting of not only pre- and post-synaptic terminals but also an astrocytic interaction (Faissner et al., 2010). Astrocytes may have an integral function in regulating maintenance and development at the synapse through its interactions with the extracellular matrix so astrocyte mediated inflammatory responses, including cytokine release and astrogliosis, could have detrimental long-term effects on synaptic function. The damaging excessive secretion of pro-inflammatory cytokines from astrocytes can result from both pathological activation (Hu et al., 1998) and various reactions to stress, which could be induced by a number of factors such as surgery. Cytokines also exhibit effects on astrocytic reactivity (for example TNF-α has been shown to reduce glutamate induced intracellular Ca^{+} increase in astrocytes (Koller et al., 2001)), which may impair synaptic function. Existing pathology in the CNS, such as Aβ plaques, induce astrocytic reactivity (Smits et al., 2002) and a strong involvement of cytokines IL-1β and TNF-α is evident in astrocyte activation by Aβ oligomers (Carrero et al., 2012; Medeiros et al., 2010). The balance of neuroprotective and neurotoxic functions of hippocampal microglia concerning synaptic function is complex and is greatly altered when the transition is made from a resting to an activated cell. Ramified microglia exert a protective influence over synaptic excitotoxicity (Vinet et al., 2012) and increase neuronal adenosine A1 receptors through CXC3CL1 expression (Lauro et al., 2010). In activated microglia, however, reduction of MK2 and p38 MAPK expression in microglia has been shown to be neuroprotective (Culbert et al., 2006), suggesting that these pathways are important in the progression of neuroinflammation and microglial activation may contribute to synaptic damage through these pathways.

Synaptic dysfunction is not only a consequence of prolonged neuroinflammation and pathology but also features in the very early stages of pathology, suggesting that inflammatory processes modulate the change from healthy, physiological synaptic transmission to impaired functioning. This implies that therapeutic interventions should target inflammation, these interventions potentially playing a role in preventing the onset and early development of neurodegenerative disease. A tripartite synapse that includes glia as well as the synaptic terminals should also feature in pharmacological targets.

3.2. Neuroinflammation and the inhibition of neurogenesis

Neurogenesis (the differentiation of neural progenitor cells (NPCs) to neurons) in adults occurs in the subgranular layer (SGZ) of the dentate gyrus of the hippocampus as well as other areas such as the subventricular zone of the lateral ventricles and the amygdala (Bernier et al., 2002). Studies showing an age-related decline in hippocampal neurogenesis suggest that it may contribute to the cognitive deficits observed in the early stages and indeed later stages of neurodegenerative diseases, particularly dementia (Kuhn et al., 1996). The fact that impairment of neurogenesis begins to occur in the early stages of diseases such as AD gives credence to the theory that the inhibition of this process forms a part of early pre-symptomatic pathology. The extent to which neurogenesis affects the development of dementia is currently unknown but it is clear that the process is modulated, usually negatively,

by neuroinflammation. Neurogenesis is inhibited by a number of pro-inflammatory cytokines such as IL-6, TNF-α and IL-18 through neuronal death of NPCs and an inhibition of cell differentiation (Liu et al., 2005). LPS-stimulated microglia release these cytokines, which reduce the total number of differentiated neurons, suggesting that microglia-mediated neuroinflammation has a detrimental effect on neurogenesis. Microglia are located in areas of neuronal differentiation and a correlation has been observed between the number of hippocampal microglia and impairment of neurogenesis (Ekdahl et al., 2003). A different change of microglial phenotype, however, can aid the differentiation of NPCs (Butovsky et al., 2006) so the specific type of molecules inducing microglia may actively increase or decrease neurogenesis. TLR2 and TLR4 mechanisms appear to play a part in the modulation of neurogenesis in the SGZ of the hippocampus (Rolls et al., 2007), suggesting a route by which NPCs can be affected by neuroinflammation. Acute inflammation caused by surgery or infection clearly has influences on the extent of hippocampal neurogenesis, but it is not yet known if this is an integral stage in neurodegeneration.

3.3. Neuroinflammation and neuronal death

Neuronal death may either be necrotic, where cells are destroyed by acute ischaemia or trauma, or apoptotic, which is programmed cell death that is a part of healthy physiology but can also occur in acute and chronic neurodegeneration. Many pro-apoptotic pathways are mediated by signalling molecules that are produced in excess during neuroinflammation, which suggests that neuroinflammation could directly influence neuronal apoptosis and thus cause acute neurological damage and accelerate long-term neurodegeneration. The tumour necrosis factor family of cytokines, to which TNF-α belongs, display direct biological effects on neuronal survival and apoptosis (Harry et al., 2008). Two membrane TNF receptors involved in these processes are TNF receptor-1 (TNFR1) and TNF receptor-2 (TNFR2). The TNFR1 signalling pathway induces apoptosis through the formation of a protein complex by recruiting adaptor protein FADD and caspase-8 and inhibition of this via the transcription factor NF-κB promotes cell survival (Micheau and Tschopp, 2003). The exact potency of TNF-α in inducing apoptosis is unclear, but it is known that the degree of hippocampal neuron apoptosis is related to TNF-α mRNA levels and there is a possibility that a threshold for TNF-α concentration is required for the initiation of apoptotic pathways (Liu et al., 2005). The TNF superfamily also contains other pro-apoptotic molecules that have been shown to cause neuronal death such as tumour-necrosis-factor-related-apoptotic-ligand (TRAIL) (Nitsch et al., 2000).

The synthesis and release of nitric oxide (NO) via the enzyme inducible nitric oxide synthase (iNOS) from astrocytes and microglia is another way in which neuroinflammation can directly influence neuronal apoptosis. NO causes neuronal apoptosis by inhibiting neuronal respiration, which increases glutamate release resulting in NMDA receptor-mediated excitotoxic cell death (Bal-Price and Brown, 2001). As the concentrations of iNOS required to cause significant damage are very high, it has been suggested that NO from iNOS couples with superoxide (produced from NADPH oxidase in microglia) to cause neuronal death via peryoxynitirite (Mander and Brown, 2005).

While the study and therapeutic prospects of apoptosis related mechanisms are interesting, the current evidence is not definitive. Molecules released in inflammation are capable of initiating and sustaining individual neuronal death pathways. However, the true extent of apoptotic neurodegeneration depends on the balance of pro- and anti-apoptotic signalling molecules released from glia, the existing pathology, and numerous other factors that make up the complex interplay of inflammation within the human brain.

3.4. Neuroinflammation and microglial priming

The emerging evidence for the phenomenon of microglial priming suggests that microglia play a key role in accelerating neurodegeneration in response to peripheral inflammation. Priming occurs when acute or chronic inflammatory insults sensitise immune cells, producing an exaggerated pro-inflammatory response when triggered by a secondary stimulus. This has long been observed in the peripheral immune system, shown primarily by macrophages (Nestel et al., 1992), but it is also clear that microglia share some of these characteristic responses (Frank et al., 2007). Studies using ME7 prion models have shown that acute systemic challenges in the form of lipopolysaccharide (LPS) induce exacerbated cytokine responses from microglia with priming associated with neurodegeneration (Cunningham et al., 2005, 2009; Murray et al., 2012). Microglial priming may also play a part in the development of neurodegenerative diseases. For example, both soluble and fibrillar Aβ have been shown to induce NADPH oxidase mediated priming in microglia that results in a heightened release of reactive oxygen species (ROS), which in turn contributes to oxidative stress and neurotoxicity (Schilling and Eder, 2011).

3.5. Neuroinflammation and GSK regulation

Glycogen synthase kinase-3 (GSK3) is a constitutively active serine/threonine protein kinase with a number of biological functions that has recently been identified as a mediator of inflammation. Following the observation that inhibition of the enzyme led to an increase in the anti-inflammatory cytokine IL-10 and a significant decrease in a number of pro-inflammatory cytokines following TLR stimulation (Martin et al., 2005), various roles of GSK in neuroinflammation have been described. GSK3 appears to be highly involved in the promotion of microglial migration and inflammatory activation (Yuskaitis and Jope, 2009). It positively regulates the production of TNF-α via NF-κB (Wang et al., 2010), IL-6 (Beurel and Jope, 2009) and NO (Huang et al., 2009) in microglia. GSK3 levels are also associated with increased monocyte migration across the BBB and reduced BBB integrity (Ramirez et al., 2010).

Although presently only partly understood, GSK plays an intrinsic aspect in many areas of inflammation and its modulation could prove to have therapeutic benefits. Although molecules shown to inhibit GSK (such as lithium chloride) have been used at concentrations higher than the clinical dose in some studies (Huang et al., 2009; Martin et al., 2005), recent evidence suggests that low, non-toxic concentrations also have anti-inflammatory effects (Green and Nolan, 2012).

The emergence of GSK as a pro-inflammatory mediator has also prompted the examination of its roles in neurodegenerative disease, notably AD pathology (Phiel et al., 2003). This enzyme shows potential as an anti-neuroinflammation drug target, but further work is required to establish any clinical role.

3.6. Neuroinflammation and Aβ

Aβ monomers, oligomers and plaques, are potent promoters of neuroinflammation and neurodegeneration. A product of the proteolytic cleavage of amyloid precursor protein, Aβ exists in 2 main forms of 40 and 42 amino acid residue length (Aβ 1–40 and 1–42), the longer being considered a more potent amyloidogenic and neurotoxic form. Found in normal brain, the biological function of Aβ remains unclear, although several physiological roles are described (Pearson and Peers, 2006). Aβ peptides are potent neurotoxins, causing membrane permeabilisation, increase in intracellular calcium and neuronal death by both necrosis and apoptosis. Aβ is pro-inflammatory, activating astrocytes and microglia, which

transform to a phagocytic phenotype and release pro-inflammatory mediators, initiating a vicious cycle of inflammation and cell death.

Aβ is a hallmark of AD, and a strong association exists between the onset of neuroinflammation and the development of Alzheimer's pathology. A chronic increase in pro-inflammatory cytokines leads to both a rise in APP synthesis (its C-terminal fragments also having pro-inflammatory properties (Ghosal et al., 2009)) and tau phosphorylation (Krstic et al., 2012). Using γ-secretase cell-based assays, TNF-α, IL-1 β and IFN-γ have been shown to initiate APP cleavage through an MAPK pathway (Liao et al., 2004). A recent study also showed that TNF-α activated NF-κB signalling resulted in an increase of Aβ synthesis through BACE-1 transcription (Chen et al., 2011). The relationship between microglia-mediated neuroinflammation and Aβ plaque deposition, however, is not straightforward. The complexity of this relationship is evident through divided opinion and conflicting results, with evidence pointing towards neuroinflammation reducing Aβ load instead of contributing to it (DiCarlo et al., 2001; Herber et al., 2004). These mixed results suggest that the type, duration and intensity of neuroinflammation, and the way in which it is mediated, have significant bearing on its relationship to the pathology of dementia.

3.7. Neuroinflammation and tau hyperphosphorylation

Another pathological hallmark of AD (as in several neurodegenerative diseases, collectively known as tauopathies) is the formation of neurofibrillary tangles of hyperphosphorylated tau protein. Tau protein is associated with microtubule stability and it is thought that hyperphosphorylation of tau results in axonal microtubule disintegration and the aggregation of the protein in neurofibrillary tangles (NFTs) (Alonso et al., 1996; Bancher et al., 1989). Although the role of tau in disease pathogenesis is not yet fully understood, it is clear that neuroinflammation facilitates tau hyperphosphorylation. Increased tau pathology is observed both with an age related increase in microglial activation and LPS-stimulated glial activation (D.C. Lee et al., 2010), and this hyperphosphorylation is mediated by a number of kinase pathways, for example cyclin-dependent kinase 5 (CDK5) (Kitazawa et al., 2005). This pathway can be overexpressed through an increase in neuronal p35, a protein responsible for activating CDK5, stimulated by the pro-inflammatory cytokine IL-6 (Quintanilla et al., 2004). IL-1β released from microglia also increases tau phosphorylation, in this case through a p38 MAPK pathway (Li et al., 2003). Inflammatory molecules such as NO, when secreted in high concentrations from activated astrocytes, increase tau phosphorylation levels through these kinase pathways (Saez et al., 2004), the glial activation itself caused by Aβ induced inflammation.

This Aβ-tau relationship is one example of the inflammatory crosstalk between the pathologies of neurodegenerative diseases and could be of critical importance in the understanding of neuroinflammation in their pathology.

3.8. Neuroinflammation and cognitive impairment

Even today, many of the underlying mechanisms of the formation and storage of memory remain a mystery, making it difficult to understand the exact involvement and contribution of inflammation to short and long term memory impairment. Since its description in 1973 (Bliss and Lomo, 1973), the phenomenon of long-term potentiation (LTP), where the simultaneous repetitive stimulation of two hippocampal neurons increases synaptic strength, has been one of the most commonly used models of measuring hippocampal-associated memory. Affects on LTP, alongside behavioural methods of assessing spatial memory such as the Morris water maze (Morris et al., 1982), are used to view the effects of neuroinflammation on cognitive function. It is important to note however that they assess only a few aspects of learning and memory and do not cover the complexity of the relationship between inflammation and cognitive function.

Spatial memory, assessed by means of a Morris water maze, is impaired by IL-1β injection alone (Gibertini et al., 1995), and other products and mediators of neuroinflammation also have direct effects on cognition and memory. IL-1β, IL-18 and other inflammatory mediators such as reactive oxygen species impair cognitive function (manifested in inhibited LTP) by triggering JNK and p38 MAPK pathways (Cumiskey et al., 2007; O'Donnell et al., 2000; Vereker et al., 2000). Interestingly, basal levels of IL-1β appear to have a positive effect on LTP, with LTP-induced gene expression of IL-1β decreasing with age (Balschun et al., 2003). This suggests that certain cytokine levels are beneficial, but an increase or decrease in concentrations may have detrimental effects. Elevated TNF-α also directly contributes to cognitive impairment (Belarbi et al., 2012). As with IL-1β, physiological levels of TNF-α can be beneficial but an exaggerated production of this cytokine is detrimental to the induction of LTP and both its early and late phases (Butler et al., 2004). Age appears to be a considerable, if not the most important, risk factor concerning cognitive impairment following inflammation and infection (Barrientos et al., 2006; Buchanan et al., 2008; Chen et al., 2008). This supports the hypothesis that neuroinflammation and its various detrimental effects build up over time (particularly in the case of disease pathology), with episodes of acute inflammation causing irreversible damage in the CNS many years before it causes permanent functional changes (such as impaired working memory). The source and effects of pro-inflammatory cytokines and other pro-inflammatory molecules are summarised in Table 1.

The detrimental outcomes to a variety of brain functions caused by prolonged neuroinflammation are clear. The nature of inflammation, however, is complicated by its 'double-edged sword' characteristics, providing some aspects of neuroprotection alongside neurodegeneration even in chronic inflammation. As described earlier, this is most apparent in the complex complement system and eicosanoid pathways. The complexity is caused by a multitude of interactions between differing cell types, activation states and fluctuating balances of pro and anti-inflammatory molecules, which can present a problem when planning a therapeutic strategy.

4. Neuroinflammation after remote injury in neurologic disease and disorder

Neuroinflammatory state is the common feature of acute and chronic neurological diseases. It can be a cause or effect during the course of disease development depending on the stage of disease per se. Herein the role of neuroinflammation in two disease conditions are reviewed below.

4.1. Acute neuroinflammation: delirium and POCD

Delirium is defined as an acute onset fluctuating change in mental status characterised by a reduced awareness of the environment and disturbance of attention (Breitbart et al., 1997). Delirium can manifest as hyper, hypo or mixed psychomotor behaviours, is transient, but known to be associated with increased morbidity and mortality. There is also an increasing body of evidence suggesting that neuroinflammation can play a causative role in the onset of delirium (Cerejeira et al., 2012; Munster et al., 2011; Rudolph et al., 2008a, 2008b).

Postoperative cognitive dysfunction (POCD) is a condition characterised by a decline in memory and other cognitive functions following surgery and anaesthesia. First described in patients

Table 1
The source and effects of common inflammatory cytokines and other pro-inflammatory molecules.

	TNF-α	IL-1β	IL-6	NO	IFN-γ	References
CNS origin	Glia, mast cells and other leucocytes	Microglia	Microglia	Astrocytes	T-cells	Al Nimer et al. (2011) DiCarlo et al. (2001) D.C. Lee et al. (2010) and M. Lee et al. (2010) Liu et al. (2012) Townsend et al. (2004) Xing et al. (2011)
Effects on neurons	↓Neurogenesis ↑Apoptosis	↑Apoptosis	↓Neurogenesis	↑Apoptosis excitotoxicity ↓Cellular respiration	↑Apoptosis	Cunningham et al. (2009) Frank et al. (2007) Murray et al. (2012) Nitsch et al. (2000)
Effects on glia	Microglial priming Astrocyte activation	Microglial priming Astrocyte activation	Glial activation		Microglial activation	Alonso et al. (1996) Stark and Bazan (2011) Yoshiyama et al. (2007)
Synaptic effects	Synaptic excitotoxicity LTP reduction	LTP inhibition Synaptic dysfunction	LTP reduction Synaptic dysfunction	LTP reduction	LTP reduction	Butler et al. (2004) Cumiskey et al. (2007) Lacroix and Rivest (1998)
Other effects	↓BBB integrity ↑Aβ synthesis	BBB inflammation COX stimulation	Tau phosphorylation	↓BBB integrity Tau phosphorylation	↑Aβ synthesis NO induction	Goehler et al. (1999) Hamberg and Samuelsson (1973) Liao et al. (2004) Wang et al. (2010) Yuskaitis and Jope (2009)

CNS: central nervous system; TNF-α: tumour necrosis factor alpha; IL: interleukin; NO: nitric oxide; IFN-γ: interferon gamma; LTP: long term potentiation; BBB: blood brain barrier; Aβ: amyloid beta.

undergoing cardiac surgery (Folks et al., 1988; Shaw et al., 1986) and later major non-cardiac surgery (Moller et al., 1998), POCD is a subtle condition reliably diagnosed only by neuropsychological testing and describes cognitive deficits that can be permanent. POCD is known to occur in all age groups and after any invasive surgery, with minor procedures being adequate to initiate neuroinflammation in older subjects (Rosczyk et al., 2008).

Major surgery has been shown to induce strong inflammatory responses that are key in the signalling process leading to cognitive change and decline. For example, both on- and off-pump coronary bypass surgery increases plasma levels of cytokines TNF-α and IL-6 (Parolari et al., 2007) as well as the inflammatory marker C-reactive protein (CRP), an increase of which is associated with cognitive decline (Ramlawi et al., 2006). Surgery-induced IL-1β appears to play key role in the pathogenesis of POCD as specific inhibition of the cytokine reduces cognitive dysfunction, although the role of other cytokines is also implicated in this process (Cibelli et al., 2010; Thomson and Sutherland, 2005). Cytokine dependent glial activation and glial release of IL-1β are strongly implicated in hippocampal associated memory impairment (Wan et al., 2007), suggesting a cycle of inflammation that not only results in short term POCD but also contributes to the various pathologies that characterise irreversible neurodegeneration. Levels of anti-inflammatory cytokines such as IL-4 have been observed to rise in the months following a neuroinflammatory response (Kalman et al., 2006) and this could implicate a role of anti-inflammatory molecules in the resolution of POCD seen several months after surgery.

Although distinct conditions, delirium and POCD are linked (Rudolph et al., 2008a) and share common neuroinflammatory pathology. Indeed the neuroinflammatory insult causing delirium and POCD is mediated by the same cells, proteins and other molecules that have a causal role in the permanent neuronal damage of neurodegenerative disease including AD. A common link or mechanism is yet to be defined, but the key will likely involve neuroinflammation.

4.2. Chronic neuroinflammation: Alzheimer's disease

The presence of Aβ aggregates and hyperphosphorylated tau can be accelerated by the excessive production of pro-inflammatory mediators. What is also of significant importance, however, is the ability of AD pathology to initiate and contribute to neuroinflammation. Aβ and tau have been shown to produce pro-inflammatory cytokines and mediator molecules (Vukic et al., 2009), giving rise to the idea that the formation of AD pathology leads to the initiation of several self-propagating cycles. An example of this is IL-6 induced APP synthesis contrasted with Aβ peptides producing IL-6 through a TLR2 pathway (Jana et al., 2008; Ringheim et al., 1998). Glial-mediated inflammatory responses are also induced by Aβ and this activation of astrocytes and microglia results in the further production of cytokines and inflammatory molecules such as NO (Saez et al., 2004). In animal models, high levels of TNF-α are seen in the AD brain as compared to controls, and behavioural deficits in these models is reduced by blocking TNF-α (Gabbita et al., 2012). This suggests that inflammatory cytokine release and its effects are closely related to AD pathology. Clinical studies looking for prognostic biomarkers for AD suggest a link between inflammation and the development of the disease. Increased levels of TNF-α and IL-1 are associated with the progression of the disease (Tan et al., 2007), CSF $A\beta_{1-42}$ has proved to be a reliable biomarker for AD (Shaw et al., 2009) and levels of the novel neuroinflammatory biomarker YKL-40 are elevated in this disease (Craig-Schapiro et al., 2010).

AD pathology is strongly linked to synaptic impairment, with Aβ protein depressing synaptic transmission through the over-expression of APP and inducing plaque-independent damage to presynaptic terminals (Kamenetz et al., 2003; Mucke et al., 2000). There is a two-way relationship between Aβ concentration and synaptic function, with synaptic activity modulating the deposition of plaques (Cirrito et al., 2005) as well as Aβ contributing to synaptic impairment. This impairment is manifest as a loss of synaptic gain (Ricoy et al., 2011), a function of the number of active synapses

and the number of post-synaptic receptors. The COX-2 pathway is also of particular relevance to AD, as it appears to play a role in Aβ mediated loss of synaptic function and presents a direct inflammatory route to long-term memory loss (Kotilinek et al., 2008). Chronic neuroinflammation in AD contributes to synaptic impairment and the build up of irreversible CNS damage that, over time, manifests as symptoms. It would be interesting to see if, and how, acute inflammation resulting from aseptic surgical stress or infection contributes to synaptic dysfunction.

BBB permeability is of great importance to the development and effects of AD pathology, suggesting a link between the progression of the disease and peripheral immunity and inflammation. LPS stimulation of cytokines IL-6, IL-10 and IL-13 may increase the influx of Aβ across the BBB alongside up-regulating APP cleavage in the brain (Jaeger et al., 2009). There is evidence that prostaglandins formed by LPS insult are heavily involved in regulation of influx and efflux of Aβ across the BBB. Various mechanisms of Aβ migration to the brain have been shown, including modulation by the receptor for advanced glycation end products (RAGE) (Deane et al., 2003), but the contribution to long-term neurodegeneration and AD is inferred and not proven. Many proteins in the plasma bind to Aβ and it seems that low-density lipoprotein receptor-related protein 1 (LRP1), which binds to the C-terminals of Aβ, plays a significant part in the transport of these proteins across the BBB (Pflanzner et al., 2011). The relationship between AD and acute POCD is in many cases 'acute on chronic', meaning that a temporary flare-up of symptoms stems from an existing chronic disease that continues after the acute condition has died down. It is likely that a strong neuroinflammatory insult can cause a greater acute condition to patients with an existing chronic disease than those without, and it is important for research to try to discern the stage of chronic disease affecting the acute condition and see whether successive acute disorders affect the progression of chronic disease.

The microglial priming model (see Section 3.7) suggests a novel role of surgery in the development of AD. Pre-symptomatic Alzheimer's pathology, which releases low levels of pro-inflammatory mediators (Vukic et al., 2009), could prime microglial cells over a number of years. Stress, inflammation and infection resulting from surgical trauma would act as a secondary trigger, phenotypically changing these primed cells to an activated state with the ensuing inflammatory response (Cunningham et al., 2009) contributing to neuronal damage, synaptic impairment and increased AD pathology. Surgery-induced stress itself could also help potentiate microglia to a primed state, as stress-induced glucocorticoid release has a sensitising effect on these cells (Frank et al., 2007, 2012). Repeated surgical procedures could therefore both trigger exaggerated cytokine release and help prime microglia, accelerating neurodegeneration and the development of AD (Fig. 1).

4.3. Chronic neuroinflammation: multiple sclerosis

Another chronic disease strongly associated with neuroinflammation is multiple sclerosis (MS). This is an immune-mediated inflammatory disease with a pathophysiology characterised by CNS demyelination and inflammation. There is a relationship between systemic inflammation and the development of the disease, but little is known concerning the interplay between pro-inflammatory stimuli and the damage to axons and myelin-producing cells. Activation of innate immune responses, in the form of macrophages and microglia, contribute to axonal damage similar to that seen in MS (Moreno et al., 2011). Systemic inflammation may contribute to the damage of myelinated cells in MS and this relationship could help explain the increased likelihood of relapse following infection. Inflammation in MS is caused and compounded by the adaptive immune response, specifically T helper cells Th1 and Th17 (Fransson et al., 2009) and also B cells (Hauser et al., 2008).

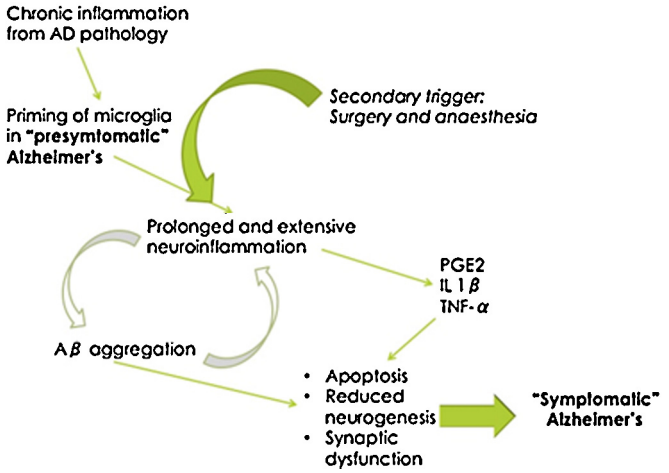

Fig. 1. The possible role of neuroinflammation in acceleration of Alzheimer's disease. Inflammation 'primes' microglia within the CNS. Consequently these respond in an exaggerated manner to any secondary inflammatory trigger, including peripheral surgery, infection or injury. This inappropriate neuroinflammatory response activates several self-propagating cycles, causing perpetual apoptosis, synaptic dysfunction, impaired regeneration and the production and deposition of Aβ, which further drive the inflammatory process. Aβ: amyloid beta; AD: Alzheimer's disease; IL1β: interleukin 1β; PGE2: prostaglandin E2; TNF-α: tumour necrosis factor alpha.

Pro-inflammatory molecules produced by these lymphocytes and also glial cells contribute to the development of MS (Tzartos et al., 2008), suggesting common pathologies associated with neuroinflammation may be shared between a number of chronic diseases.

5. Clinical strategies: anti-inflammatory treatment

With the role of COX pathways in neuroinflammation becoming better established, NSAIDs have been identified as a class of drug with potential therapeutic effects. As COX-1 is expressed in microglia it is thought to play a more significant role in neuroinflammation than COX-2, which is confined to neurons, implying that COX-1 inhibitors may be effective at reducing inflammation. Indeed, aspirin (an irreversible COX-1 inhibitor) reduces neuroinflammatory and oxidative insults by reducing prostaglandins and increasing anti-inflammatory lipoxin (Arfi et al., 2011; Basselin et al., 2011; Wu et al., 2012). However evidence is lacking for clinical benefit of NSAIDs and selective COX-2 inhibitors in patients with neurodegenerative diseases. Cochrane studies have found no significant improvement resulting from NSAIDs in established AD (Jaturapatporn et al., 2012) and Parkinson's disease (Rees et al., 2011). The most recent results of a large clinical trial, the Alzheimer disease anti-inflammatory prevention trial (ADAPT), suggest that certain NSAIDs may reduce the chances of an asymptomatic individual developing this disease but these same drugs exacerbate later stage Alzheimer's (Breitner et al., 2011). The anti-inflammatory properties of some compounds released as by-products of NSAID and other drug activity, however, may present interesting therapeutic possibilities, for example hydrogen sulphide releasing compounds which have recently shown promise in reducing neuroinflammation (M. Lee et al., 2010; Xuan et al., 2012).

Alongside their well-established role in reducing cholesterol, HMG-CoA reductase inhibiting drugs, statins, have various anti-inflammatory and immunomodulating effects in several effector cells (reviewed by Terblanche et al., 2007). Peripherally, statin pre-treatment dampens TLR4 and TLR2 expression resulting in a decrease in TNF-α and a suppression of innate immunity (Niessner et al., 2006). The endothelial stabilising properties of statins are also beneficial to maintaining the integrity of the BBB in inflammatory

conditions. This is observed in the restriction of the leucocyte migration across the blood brain barrier and impaired migration within the CNS (Ifergan et al., 2006; Waiczies et al., 2007). A further role for statins may lie in glial mediated neuroinflammation as they decrease glial activation and reduce microglial production of TNF-α, IL-1β and IL-6 (Li et al., 2009; Townsend et al., 2004) as well as astrocytic cytokines and iNOS (Pahan et al., 1997). This production is reduced in microglia stimulated by both IFN-γ and Aβ and this could prove to be an important benefit of HMG-CoA reductase as inhibiting microglial activity is an key factor in stemming the tide of chronic neuroinflammation. Protective properties of stains such as atorvastatin have been shown to include neuroprotection through reduction in hippocampal IL-1β and COX-2 production and inactivation of GSK3 (Vizcaychipi et al., 2013).

There is clinical evidence supporting the use of statins in reducing cognitive impairment, for example a prospective cohort study showed statin administration significantly reducing postoperative delirium (Katznelson et al., 2009), but there is a need for more studies as there is currently a lack of literature concerning the role of statins in neuroinflammation.

6. Summary

Whether derived from the CNS or peripherally, neuroinflammation causes and exacerbates neurological damage and contributes to existing pathology in several ways. Dampening this response with anti-inflammatory drugs is yielding promising results and their use as a preventative treatment is suggested. Other pharmacological solutions could be found in the modulation of specific signalling molecules and enzymes, including GSK3.

The consequences of neuroinflammation in surgical patients is emerging as we better understand how surgical insults enhance the neuroinflammatory response through activation of primed glial cells, to accelerate irreversible neurodegeneration. Understanding these neuro-immune interactions is a research priority as, by clarifying the links between neuroinflammation, reversible cognitive dysfunction and neurodegenerative diseases, strategies to limit the structural and functional damage of extensive and prolonged neuroinflammation may be found.

Competing interests

The authors declare that they have no competing interests.

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