The complement system (C) system is a key-component of the innate immune system, playing a central role in host defense against pathogens and in the initiation of inflammation. Complement activation is triggered through three different pathways, the classical, the lectin-dependent and the alternative pathway. The central nervous system (CNS) by itself can design an immune and inflammatory response. Pioneering experiments carried out by Levi-Strauss and Mallat have led to the first report on the ability of brain cells to produce C proteins, which were demonstrated to recognize and kill pathogens while preserving normal cells in the CNS. Numerous additional data have clearly confirmed that expression of C by resident cells is activated and is greatly increased following brain infection or injury [1]. In the CNS, C has been involved in the worsening of many neurodegenerative disorders such as Alzheimer disease (AD), Pick’s disease and demyelinating diseases such as MS [2, 3]. However, neuroprotective effects of complement activation have been recently shown, suggesting that the C might play also an important role in neuroprotection [3, 4]. In this review, we will discuss the data that point to the dual role of complement proteins in the CNS.

### THE “BAD SIDE” OF COMPLEMENT IN THE CNS

The primary site of complement protein synthesis is the liver, but CNS complement production in microglia, astrocytes, and neurons has been confirmed [1, 4]. Furthermore, an endogenous synthesis and expression of complement pathway in healthy human peripheral nerves has been recently shown. Epithelial cells, fibroblasts, Schwann cells and macrophages can synthesize complement in vitro. Several reports clearly showed that

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>BBB</td>
<td>blood-brain barrier</td>
</tr>
<tr>
<td>C</td>
<td>complement</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>MS</td>
<td>multiple sclerosis</td>
</tr>
</tbody>
</table>

This review has been prepared by Muriel Tahtouh based upon her PhD Thesis report. It has been rewarded by an ECN/ECS Junior review prize. It has been slightly modified as recommended by independent expert referees. Joel Pestel contributed, acting as Scientific Tutor.
increased local C biosynthesis and uncontrolled C activation in the CNS are factors contributing to the pathology of inflammatory and degenerative disorders [4].

The complement system represents an essential, innate immune defense mechanism [5], however, complement activation may contribute to neuronal loss in chronic inflammation reactions. Indeed, bidirectional, molecular communication between the CNS and the periphery contributes to the development of inflammation, which is required to initiate many neuronal disorders. Thus, complement activation leads to the release of various fragments, such as C3a and C5a (obtained by specific cleavage as summarized in figure 1) that might exert many immunological activities after binding to specific membrane receptors coupled to G proteins, as demonstrated for C3aR and C5aR, respectively. By inducing the recruitment of immune cells to the inflammation site, and by allowing the production of various chemokines or cytokines, these complement-derived peptides can modulate the immune response. For example, human, immature, plasmacytoid dendritic cells (pDC) (obtained from peripheral blood precursors after culture with IL-3) that express specific receptors for C3a and C5a, might migrate towards a gradient of both these anaphylatoxins. Interestingly, a similar chemotactic effect was described to represent a new pathway to recruit pDC to sites of inflammation [6].

Furthermore, through this anaphylatoxin release, the C system may initiate a cytokine production cascade. The interaction between proinflammatory cytokines and anaphylatoxins C3a and C5a was specifically investigated. For example, C3a and C5a enhance monocyte gene expression and protein synthesis of IL-1β, tumor necrosis factor α (TNF-α), IL-6 and IL-8 by myeloid cells. In addition, C3a and C5a can play a crucial role in the activation of T cells, to favor the production of proinflammatory cytokines such as IL-17 and INF-γ [8], to which brain cells can respond. Thus, in most CNS-associated diseases that are accompanied by chemokine expression, complement anaphylatoxins play a key role in the initial triggering of neuroinflammation mechanisms [2, 9, 10].

In Alzheimer’s disease (AD), the level of C1q mRNA was increased compared to normal brain [1, 11]. Complement activation mediates neuronal injury via MAC-induced neurite disintegration and increased levels of reactive oxygen species [4]. In the AD brain, microglial cells are activated and show a dose-dependent increase in pro-inflammatory cytokine production [12, 13]. Activation of microglia by amyloid beta (Aβ) is associated with a specific recruitment of microglia cells responding to chemotactic factors and consequently induces Aβ fibril phagocytosis. Evidence for complement involvement in microglial response to Aβ has been reported [14, 15]. Indeed, the presence of C1q, locally produced by activated microglia in close proximity to the amyloid plaques, suggests that C1q may interact with the Aβ or

**Figure 1**

C activation pathways. Activation of the classical, alternative and lectin pathways leads to the generation of C3 and C5 component fragments following regulated activation of specific C3 and C5 convertases. The cleavage of C5 leads to the initiation of membrane attack complex (MAC) formation. These pathways are regulated by several inhibitors, either cell-surface complement inhibitors: MCP (membrane cofactor protein), CD46, CD55 (or DAF, decay accelerating factor), CR1 (also known as CD35, C3b/C4b receptor) CD59 and/or serum complement inhibitors: C1 inhibitor, Factor I (C1 INH), Factor H, C4bp, clusterin and S-protein (vitronectin).
other components of the amyloid plaques, such as serum amyloid P. Interaction of C1q with Aβ can result in activation of complement when C1q is complexed with the serine proteases C1r and C1s, or in the induction of Aβ aggregation in the absence of C1r, C1s, and other complement proteins (as summarized in figure 2). In this second case, C1q can block access of microglia to Aβ and may contribute to the accumulation of the peptides in plaques, which is considered to be lethal [16, 17]. To avoid this self-destructive tendency, host cells are protected by a battery of regulatory molecules (C inhibitors), as recently underlined in some reviews (figure 1) [1, 4, 5], which mainly act at the level of the C3- or C5-cleaving enzymes and under the control of the final, membrane attack complex (MAC) formation. C1 inhibitor (C1-INH), C4b binding protein (C4 BP), Factor H, Factor I, S-protein (also called vitronectin) and clusterin are all soluble C inhibitors, which may be secreted and present in the fluid phase. The other C inhibitors, including membrane cofactor protein (MCP, CD46), decay accelerating factor (DAF, CD55) and CD59 are expressed on the cell membrane surface. Indeed, in brains with chronic, but not acute experimental autoimmune encephalomyelitis (EAE) model of MS, a pathological role of complement factors has been suggested in the selective cell lysis of neurons and oligodendrocytes [4, 19]. This deleterious effect was also suggested for C1q in adult glaucomatous retinas, where it tags synapses for elimination even at early stages of disease. This early complement-dependant synapse loss could drive axon degeneration [20].

C has been also implicated in neurological diseases associated with pain although its role in neuropathic pain has
not yet been clearly defined. Disorders of the immune system, involving the activation of complement, play an important role in several neurological diseases in which chronic pain is significant. Complement activation in the peripheral nerve contributes to recruitment of immune cells and to neuropathic pain due to nerve injury. As complement activation following nerve injury has multiple consequences, further studies are needed to investigate the importance of these factors in neuropathic pain [21]. Gene expression microarray analysis performed on the rat spinal nerve ligation (SNL) model of neuropathic pain revealed that several complement components were upregulated in microglia of the dorsal horn (CNS), while inhibitors such as DAF (decay accelerating factor) were downregulated. The complement pathway might be a novel target for the development of neuropathic pain treatments [22].

THE “GOOD SIDE” OF COMPLEMENT IN THE CNS

However, the same system responsible for deleterious effects can be, in some circumstances, beneficial to the host [23-25]. Complement is of special importance in the brain, where the entrance of elements of the adaptive immune system is restricted by the blood-brain barrier (BBB). Local production of complement factors in the peripheral nerve could protect the healthy nerve from infections, and could facilitate regeneration of injured axons by the clearance of myelin debris, thought to be inhibitory to axon growth. Indeed, complement activation accelerates the vacuolated myelin elimination by macrophages [3]. In addition, C1q has an important role in the clearance of apoptotic cells. It can bind directly to the surface blebs of ultraviolet light-induced apoptotic cells [26]. In AD pathology, some authors have suggested a potential neuroprotective role for complement by reducing the accumulation of degenerating neurons and brain Aβ deposits and by promoting their clearance [27]. Indeed complement is known to be actively involved in the removal of targeted molecules by phagocytes, which supports the notion that complement components are upregulated in Aβ-rich areas of the AD brain [16]. Incidentally, microglial cells that express C1q receptors behave in this immune-privileged site as efficient macrophages, and the increase in C1q receptor expression is linked to the enhancement of the phagocytosis capacity observed. Thus, C1q may have opposing effects on the development of the disease, either by accelerating its aggregation as previously indicated, or by enhancing Aβ immune complex uptake [17]. Indeed, in Alzheimer’s disease, the specific role of C1q in the ingestion of the amyloid β peptide, might be used as a potential therapeutic target (figure 2).

C1q was also shown to be expressed transiently by postnatal neurons and to mediate synapse elimination during development. Several reports have underlined the crucial activity of C1q and/or C3 in synapse elimination mechanisms [20, 28]. Mice deficient in C1q or C3 complement components exhibit large defects in CNS synapse elimina-
tion or clearance of harmful pathogen deposits. C plays a critical role in host defense, in this removal of bacteria. Brain cells can generate C to kill pathogens while they are relatively well protected from direct complement factors lysis by expressing soluble and membrane inhibitors [30]. Thus, this new data reported for the neuroinflammatory disorders, seem to indicate that complement factors might have similar, dual effects at the level of the CNS. Finally, it might be hypothesized that their involvement in neuronal systems is part of an ancestral mechanism. Indeed, in the Hirudo medicinalis invertebrate CNS, we have identified, for the first time, a molecule homologous to mammalian C1q. Its chemoattractant activity on microglia highlights a new field of investigation, which might lead to a better understand of leech nerve cord repair, during which complement seems to be well regulated [31].

CONCLUSION

C is one of the most critical defence mechanisms of innate immunity against cerebral infection by viruses, bacteria and fungi, with different molecular pathways contributing to the clearance of the invading pathogens. C is now described as having special importance in the CNS. Complement activation can be neurotoxic as well as neuroprotective, and can lead to nerve recovery and repair [23, 25]. Therefore, a tight balance between complement activation and regulation is essential to protect and maintain healthy tissues [5]. With the aim of proposing alternative therapeutic agents, it is necessary to take into account the fact that, in neurodegenerative disorders, a more severe and chronic inflammation can ultimately result in a worsening of these diseases. An ideal treatment for reducing many CNS disorders would boost the clean-up function of complement, but suppress any excessive inflammatory effect. It should harness the “good side of complement activation” and suppress their “bad side”. Up to now, the results obtained in the leech nerve CNS seem to indicate that complement-like factors are involved in the efficient nerve cord repair seen following a nervous system injury. In this ancient invertebrate, complement factors seem to preserve its bright side of protection, preventing harmful inflammation caused by long lasting complement activation.

REFERENCES


