

Involvement of Pro- and Anti-Inflammatory Cytokines and Chemokines in the Pathophysiology of Traumatic Brain Injury

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Summary: Despite dramatic improvements in the management of traumatic brain injury (TBI), to date there is no effective treatment available to patients, and morbidity and mortality remain high. The damage to the brain occurs in two phases, the initial primary phase being the injury itself, which is irreversible and amenable only to preventive measures to minimize the extent of damage, followed by an ongoing secondary phase, which begins at the time of injury and continues in the ensuing days to weeks. This delayed phase leads to a variety of physiological, cellular, and molecular responses aimed at restoring the homeostasis of the damaged tissue, which, if not controlled, will lead to secondary insults. The development of secondary brain injury represents a window of opportunity in which pharmaceutical compounds with neuroprotective properties could be administered. To establish effective treatments for TBI vic-

tims, it is imperative that the complex molecular cascades contributing to secondary injury be fully elucidated. One pathway known to be activated in response to TBI is cellular and humoral inflammation. Neuroinflammation within the injured brain has long been considered to intensify the damage sustained following TBI. However, the accumulated findings from years of clinical and experimental research support the notion that the action of inflammation may differ in the acute and delayed phase after TBI, and that maintaining limited inflammation is essential for repair. This review addresses the role of several cytokines and chemokines following focal and diffuse TBI, as well as the controversies around the use of therapeutic anti-inflammatory treatments *versus* genetic deletion of cytokine expression. **Key Words:** Inflammation, traumatic brain injury, cytokines, chemokines, human TBI.

INTRODUCTION

With increasing information on the pathological changes induced after traumatic brain injury (TBI), it is becoming clear that brain trauma is a complex neurodegenerative disease, involving many cellular and molecular pathways, including inflammation.¹ Previously, the brain was considered to be an immune privileged organ, neither susceptible to nor capable of eliciting an inflammatory response. Nonetheless, it is well established that inflammation represents a common pathological reaction to almost every neurological disease including brain trauma. To review the entire body of research on the inflammatory response after TBI would be an enormous task. Instead, here we will briefly discuss the general processes of cerebral inflammation before focusing on

specific cytokines and chemokines that have been abundantly characterized over the past 20 years in patients and in animal models of TBI.

Post-traumatic cerebral inflammation is characterized by glial activation, leukocyte recruitment, and upregulation and secretion of mediators such as cytokines and chemotactic cytokines (chemokines).² Although it was previously thought to be deleterious for the injured brain, cerebral inflammation is now considered to have both beneficial and detrimental roles. Clear benefits can be achieved if the inflammation is controlled in a regulated manner and for a defined period of time. When sustained or excessive, however, inflammation is the main cause of numerous neuropathologies.³

Among the pathological changes of the brain tissue, impairment of the blood-brain barrier (BBB) has been demonstrated in the acute post-traumatic period, allowing the entry of circulating neutrophils, monocytes, and lymphocytes to the injured site, directly affecting neuronal survival and death⁴⁻⁸ (FIG. 1). The accumulation of blood-borne immune cells within the parenchyma has

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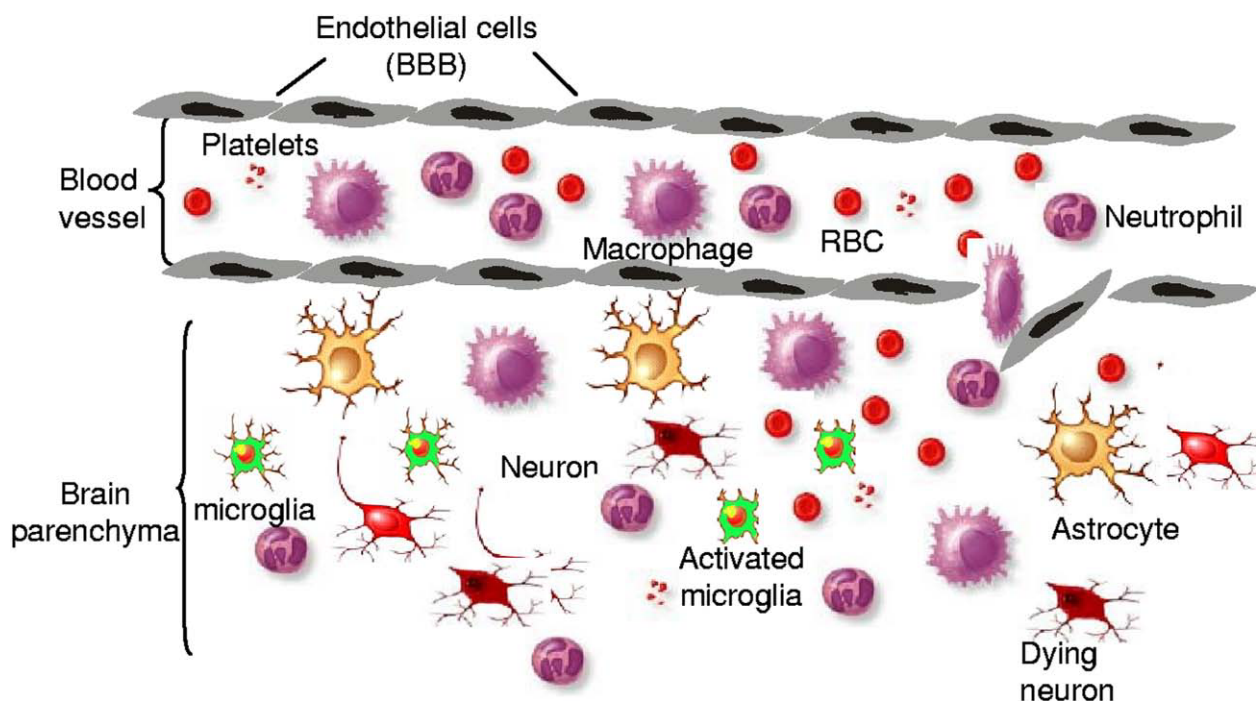


FIG. 1. Blood–brain barrier (BBB) dysfunction following traumatic brain injury. The BBB is the physical interface between the brain parenchyma and the vascular system. It consists of tightly placed endothelial cells, which regulate the passage of cells, molecules, and ions into the brain tissue. Following brain injury, the integrity of the BBB is disrupted, resulting in the infiltration of red blood cells (RBCs) and white blood cells into the parenchyma, thus allowing communication between the peripheral and resident immune cells; this communication is mediated by the release and exchange of cytokines and other toxic or neurotrophic factors. Some of these mediators can lead to the activation of glial cells, as well as neuronal cell death, whereas others promote regenerative mechanisms of the damaged brain.

been reported in both head-injured patients and in animal models of brain trauma.² These activated cells release mediators including prostaglandins, free radicals, complement factors, and pro-inflammatory cytokines,¹⁰ which in turn induce the expression of chemokines and cell adhesion molecules and mobilize immune and glial cells to the injured site.¹¹ Over time, subsequent production of anti-inflammatory mediators suppresses both humoral and cellular immune activation.

In addition to the infiltration of blood cells, the activation of resident microglia plays multiple roles within the injured brain. The major task of microglia is the removal of cell debris, which is required to attenuate inflammatory processes and promote tissue remodeling. In addition, however, activated microglia also release various neurotoxic substances, such as reactive oxygen and nitrogen species and glutamate, that may exacerbate neuronal death.¹² Although astrocyte reactivity, proliferation, and migration induced after brain trauma seems to impair axonal regrowth, the presence of these cells around the lesion provides a supporting milieu via the release of neurotrophic factors promoting tissue repair and neurogenesis.¹³

Over time, the sites of BBB leakage become sealed by repair mechanisms; however, there is a period during which the endothelium located in the region of damage

remains permeable to small molecules,¹⁴ thus sustaining an altered homeostasis of the brain parenchyma and affecting neuronal function. Studies from our laboratory on a mouse model of focal TBI have recently demonstrated that at 1 to 2 h after injury there is extensive diffusion of intravenously injected horseradish peroxidase (a 40-kDa glycoprotein) in the pericontusional tissue, which by 4 h was no longer observed.¹⁵ At 4 days post-injury, however, markers of smaller molecular weight (<10 kDa) continued to diffuse into the pericontusional cortex. Thus, the complete restoration of the barrier seems to require a time course that is much longer than that observed for large molecules. This prolonged permeability has the advantage of providing a window of opportunity through which drugs normally excluded from the CNS can reach the injured brain tissue.

CYTOKINES AND CHEMOKINES PRODUCED IN THE INJURED BRAIN

The inflammatory cascade activated after TBI is mediated by the release of pro- and anti-inflammatory cytokines, which are polypeptides, normally barely detectable in healthy tissue but rapidly upregulated in response to pathological or stressful challenges.^{11,16} Besides their involvement in immune processes, cytokines also func-

Table 1. Pivotal Studies on the Multiple and Opposing Roles of Cytokines Following Traumatic Brain Injury

Role after TBI (References)
Interleukin-1 Exacerbates neuronal injury (Rothwell, ¹⁶ 1999) Interleukin-1ra reverses its neurotoxicity (Relton et al., ²⁷ 1992; Loddick and Rothwell, ²⁶ 1996; Lawrence et al., ⁹⁷ 1998)
Interleukin-6 Astrocyte overproduction is beneficial (Penkowa et al., ³⁷ 2003) Deficiency is detrimental (Penkowa et al., ³⁸ 2000) Neuronal overexpression does not alter neurological outcome (Fattori et al., ⁹⁸ 1995)
Interleukin-10 General neuroprotective effects (Knobloch and Faden, ⁴³ 1998; Csuka et al., ⁴⁵ 1999; Kremlev and Palmer, ⁴⁴ 2005) Associated with adverse outcome in TBI in children (Bell et al., ⁴⁷ 1997)
Granulocyte Colony-Stimulating Factor Antiapoptotic (Schneider et al., ⁹⁹ 2005) Promotes neurogenesis (Sehara et al., ¹⁰⁰ 2007)
Tumor Necrosis Factor-α Induces cerebral inflammation, BBB breakdown, and leukocyte recruitment (Ramilo et al., ⁵⁶ 1990; Kim et al., ⁵⁵ 1992) Inhibition with HU-211, PTX, and TNF-binding protein reduce BBB dysfunction and edema (Shohami et al., ⁵¹ 1997) No differences reported in clinical trial with HU-211 (Maas et al., ⁵⁷ 2006) TNF or TNF receptor knockout mice display exacerbated tissue and BBB damage, as well as impaired neurological recovery (Scherbel et al., ⁵⁸ 1999; Sullivan et al., ⁶⁰ 1999)
Fas Ligand Implicated in neuronal apoptosis (Grosjean et al., ⁶⁶ 2007)
Interleukin-8* Promotes neutrophil infiltration (Whalen et al., ⁷⁸ 2000) Increases BBB dysfunction (Morganti-Kossmann et al., ⁷⁹ 1997) Stimulates neurotrophic factors in cultured astrocytes (Morganti-Kossmann et al., ⁷⁹ 1997)
Monocyte Chemoattractant Protein 1[†] Promotes macrophage infiltration (Stirling et al., ⁹⁵ 2004; Xu et al., ⁹⁶ 2004; Maier et al., ⁹⁴ 2005)

BBB = blood-brain barrier; HU-211 = dexanabinol; PTX = pentoxifylline; TBI = traumatic brain injury.

*Corresponding to the rodent homolog macrophage inflammatory protein-2 (MIP-2).

[†]Also known as C-C motif chemokine 2 or CCL2.

tion as mediators of intracellular communication¹⁷ and play a pivotal role in tissue homeostasis of the mature organism.

The chemotactic cytokines, or chemokines, comprise a small group of inflammatory mediators that regulate leukocyte activation and migration¹⁸ and play a fundamental role in embryogenesis of the nervous system, homeostasis, and host defense (Table 1). In the nervous

system, chemokines are secreted by glia and neurons; these cells also express a variety of chemokine receptors. Generally, chemokine receptors are classified into two groups, based on the presence and position of conserved cysteine residues: CXC, or α -chemokines (e.g., MIP-2/IL-8 and KC), which act as neutrophil and lymphocyte chemoattractants, and CC, or β -chemokines (e.g., MIP-1 α and MCP-1), which are chemotactic for monocytes and T cells.^{19,20}

Considering the functional properties of cytokines, it is thought that neuronally derived cytokines are predominantly involved in cellular communication, whereas cytokines from glial cells mediate neuronal growth, survival, and repair, but may also direct chronic pathological changes associated with some neurodegenerative diseases.²¹

Interleukin-1

The interleukin-1 (IL-1) family of cytokines includes two agonist proteins, IL-1 α and IL-1 β , which trigger cell activation upon binding with specific membrane receptors. Also included is IL-1 receptor antagonist (IL-1ra), which is a glycosylated secretory protein of 23 kDa counteracting the action of IL-1.²² Interleukin-1 is an important initiator of the immune response, playing a key role in the onset and development of a complex hormonal and cellular inflammatory cascade. Elevated IL-1 β has been detected in the CSF and brain parenchyma within the early hours after brain injury in both humans and rodents.^{23,24}

Treatment of TBI rats with either endogenous IL-1ra or soluble IL-1 receptors conferred no improvement in motor outcome.²⁵ Nonetheless, IL-1 has been documented to play a role in neuronal degeneration. Neuronal damage was reported to be attenuated when recombinant IL-1ra was injected intracerebroventricularly following ischemic or traumatic injury in rats.^{26,27} In accordance with these findings, preclinical animal experiments testing immunosuppressive drugs such as minocycline or erythropoietin after TBI attributed the neuroprotective mechanisms of these compounds to the reduction of brain IL-1 synthesis.^{4,28,29}

Interleukin-6

Interleukin-6 (IL-6) is a multifunctional cytokine that plays an important role in host defense,³⁰ with major regulatory effects upon the inflammatory response.³¹ It belongs to the neuropoietin family of cytokines,³² and has both direct and indirect neurotrophic effects on neurons.³³ In TBI patients, IL-6 has been reported to be highly elevated in CSF and to a lesser extent in serum; serum concentrations were associated with increased acute phase proteins (C-reactive protein, fibrinogen, and α 1-antitrypsin) and with severe BBB dysfunction.³⁴

Interleukin-6 has also been detected in brain tissue in several experimental models of TBI.^{24,35,36} Studies using

GFAP-IL-6 transgenic mice to elucidate IL-6 function after brain injury demonstrated that the enhanced cytokine production after cryolesion confers neuroprotection.³⁷ Concordantly, in experiments using the same injury model mice deficient for IL-6 exhibited increased oxidative stress, decreased cell survival, and delayed wound healing,³⁸ indicating that IL-6 is required for repair.

Interleukin-10

As a noncovalently linked homodimer of 35 to 40 kDa,³⁹ interleukin-10 (IL-10) is produced by microglia and astrocytes in the CNS and in the periphery by lymphopoietic cells.⁴⁰⁻⁴² Its neuroprotective characteristics include suppression of microglia and astroglia activation, as well as decreased production of proinflammatory cytokines^{43,44} and reactive oxygen species.⁴⁵ Thus, it has been proposed that IL-10 treatment improves outcome in neuropathology. Indeed, after TBI in rats, systemic administration of IL-10 improved neurological recovery⁴³ and significantly attenuated the expression of proinflammatory cytokines including IL-1 in the injured hippocampus. Nonetheless, no protection was seen after IL-10 administration in piglets subjected to hypoxic-ischemic insult.⁴⁶

In humans, high levels of IL-10 have been measured in the CSF of children with brain injury; surprisingly, this increase has been correlated with adverse outcome.⁴⁷ Increased production of IL-10 in human CSF of adult TBI patients corresponded to decreases in tumor necrosis factor levels; however, no correlation was found between IL-10 and outcome.⁴⁵

Tumor necrosis factor- α

Tumor necrosis factor- α (referred to simply as TNF) plays a central role in initiating and regulating the cytokine cascade during an inflammatory response. It is produced as a membrane-bound 26-kDa precursor molecule that is cleaved by the TNF converting enzyme to produce a 17-kDa active cytokine.⁹ Because of the low levels of TNF expression in the healthy brain, it has been difficult to determine its precise role in physiological conditions. In inflammatory or disease states, TNF along with several other proinflammatory mediators and neurotoxic substances is produced predominantly by activated microglia.

Although brain-derived TNF is synthesized mostly by glial cells in response to pathological stimuli, neuronal production has also been demonstrated.⁴⁸ Although TNF and IL-1 interact with receptors that are structurally unrelated, both cytokines share a significant overlap in functional and postreceptor intracellular cascades. The potent neurotoxic effects of IL-1 have been shown to be synergistically enhanced in the presence of TNF, suggesting that these crucial cytokines mediate post-traumatic inflammation and secondary brain damage.^{49,50}

Glial cells secrete both TNF and IL-1, which in turn, activate these cells in an autocrine manner to induce further cytokine production and astrogliosis.

Early transient mRNA expression of TNF, IL-1, and IL-6 in the injured rat brain has been shown to precede the appearance of respective cytokine bioactivity following closed head injury.⁵¹ In addition, the upregulation of IL-1 and TNF mRNA occurred prior to the time of leukocyte infiltration to the injured site,⁵² suggesting that resident brain cells have the capacity to produce cytokines independent of peripheral immune cell activation. In a diffuse axonal injury rat model, activated endogenous microglia and astrocytes have been shown to release IL-1 and TNF at 1 h and gradually declining within 24 h.⁵³

The role of TNF in CNS inflammation is controversial. Studies on rat models of focal TBI have demonstrated that TNF is upregulated in the brain within a few hours of trauma.^{35,36,54} The contribution of TNF to tissue damage has been reported in animal studies, whereby recombinant TNF injected into the brain induced cerebral inflammation, breakdown of the BBB, and intracranial leukocyte recruitment.^{55,56}

Shohami et al.⁵¹ analyzed three different compounds, dexanabinol (HU-211), TNF-binding protein and pentoxifylline (PTX), for their effectiveness in inhibiting TNF transcription and bioactivity following closed head injury in rats. All three agents significantly improved neurological outcome in closed head injury animals, and administration of recombinant TNF reversed the beneficial effects. In addition, these treatments reduced post-traumatic BBB dysfunction and brain edema. From this study it was concluded that TNF plays a major role in neurotoxicity after TBI and that its inhibition within the first 24 h ameliorates outcome.

Almost a decade after these initial studies in rats, the efficacy of HU-211 was tested in a phase III clinical trial on head trauma patients. This trial included 860 patients with severe TBI randomized into placebo group or HU-211 treatment with a single intravenous dose within the first 6 h of injury.⁵⁷ At study completion, no differences were detected in outcome, as measured by the 6-month Glasgow Outcome Scale.

The controversy surrounding the role of TNF in TBI arose with studies using TNF and TNF receptor knockout mice. Deletion of TNF expression in knockout mice led to milder deficits in the acute phase after injury, but only limited neurological improvements in the long term.⁵⁸ Experiments from our laboratory on mice deficient for both TNF and lymphotoxin (TNF/LT double knockout) subjected to closed head injury resulted in a higher mortality rate, despite the degree of BBB dysfunction, infiltrating leukocytes and numbers of apoptotic cells being similar to that observed in control animals. Neurological outcome between 1 and 72 h after injury

was comparable; by 7 days, however, the TNF/LT double knockout mice tended to have improved compared to controls.⁵⁹ Lastly, others showed that mice deficient for TNF or TNF receptors displayed exacerbated tissue and BBB damage, as well as impaired neurological recovery after injury.^{58,60} Together, these findings suggest that the function of TNF may differ in the acute and the delayed phase after TBI. Initially, TNF seems to act as a potent immune mediator, but later as a protective neurotrophic factor that is required for repair.

Fas ligand

Fas ligand (FasL), a 40-kDa type II transmembrane protein, belongs to the TNF family of proteins.⁶¹⁻⁶³ Within the CNS, FasL and Fas are expressed on both fetal and adult astrocytes.⁶⁴ Following CNS injury, these proteins are also synthesized by neurons and microglia in rodents⁶⁵⁻⁷⁰ and were found elevated for several days after trauma in the CSF of severe head injury patients.^{71,72} Analysis of rat brain homogenates following controlled cortical impact demonstrated upregulation in Fas and its ligand from 15 minutes to 72 h;⁶⁵ however, immunoreactivity was still evident at day 14. Furthermore, TUNEL-labeling (i.e., terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end-labeling) colocalizes with NeuN and Fas/FasL immunoreactivity on mouse brain sections following TBI.⁶⁶ Together, these data implicate Fas and its ligand in neuronal cell apoptosis. Thus, it is conceivable that inhibition of Fas or its ligand (or inhibition of both) may be neuroprotective.

Although apoptosis and inflammation were previously considered to be independent molecular cascades, there is evidence to suggest a close link between cell death and cytokines, particularly related to the molecular structure and role of the Fas–FasL and TNF–TNF receptor protein systems (see review by Stoica and Faden, this issue). For example, both Fas and TNF receptor, p55, are type I transmembrane members of the TNF–NGF receptor superfamily and share homologous sequences in the extracellular regions.^{62,63,66} Besides being a mediator of apoptosis, Fas displays some neuroimmunomodulatory functions. In fact, Fas ligation on monocytes and macrophages induces proinflammatory cytokine production, resulting in potent neutrophil chemoattractant bioactivity.⁷³ Likewise, the cytokines IL-1, IL-6, TNF, and interferon γ have the ability to enhance constitutive Fas and FasL expression in cultured human astrocytes.⁶⁴ Together, these studies substantiate the complex and interconnected relationship between inflammation and pathways of cell apoptosis, indicating that further research is required to fully elucidate the molecular mechanisms involved in neuronal cell death secondary to TBI.

Interleukin-8/macrophage inflammatory protein-2

The chemokine IL-8, corresponding to the rodent homolog macrophage inflammatory protein-2 (MIP-2), was

originally described as a chemotactic and activating factor for neutrophils,⁷⁴⁻⁷⁶ but has also been implicated in the activation of basophils, T cells, and monocytes.⁷⁷ Aloisi et al.⁷⁷ reported that IL-8 is released by cytokine-stimulated human astrocytes, suggesting that these cells promote the recruitment of circulating blood cells into brain inflammatory sites.

Interleukin-8 has been defined as a potential contributor to secondary brain damage, in that previous studies established an association between increased mortality and higher CSF IL-8 levels in children with severe head injury.⁷⁸ In addition, our group showed that maximal concentrations of IL-8 in human CSF were associated with severe BBB disruption; however, the ability of IL-8 to stimulate nerve growth factor production from cultured mouse astrocytes implies some neurotrophic properties of this chemokine.⁷⁹

Monocyte chemoattractant protein

The monocyte chemoattractant protein MCP-1 (also known as CCL2) is a member of the C-C chemokine family that attracts monocytes both *in vitro* and *in vivo*.⁸⁰ Glabinski et al.⁸¹ identified the upregulation of MCP-1 transcripts before the appearance of inflammatory cells within the brain tissue, suggesting that resident glial cells are an early source of MCP-1. Expression of MCP-1 and its receptor CCR2 is rapidly increased in a wide range of cell types after acute brain injury.^{82,83} Astrocytes, and to a lesser extent macrophages or fully reactive microglia, have been found to express MCP-1 following ischemia⁸⁴ and mechanical injury,⁸¹ and CCR2 colocalized with activated microglia,⁸⁵ neurons, and astrocytes.⁸² In addition to monocyte recruitment, there is direct evidence for the involvement of MCP-1 in driving acute inflammatory responses within the CNS, as well as indications that it may contribute to the pathogenesis of brain lesion development.⁸⁵⁻⁸⁷

In addition to MCP-1, the concentration of the chemokines MIP-1 α , MIP-2, and KC has been reported to increase following TBI in mouse brain.⁴ Together, these results highlight the contribution of chemokines in the development of secondary brain injury mediated by the accumulation of active leukocytes that perpetuate inflammatory and neurotoxic cascades.

ANTI-INFLAMMATORY INTERVENTIONS AFTER TBI

Research on therapeutic neuroprotection is currently expanding, with the focus mainly on pharmacological intervention aimed at manipulating secondary injury processes, in hope of improving the outcome of TBI patients. The ability of several agents to attenuate biochemical neurotoxicity and secondary cell death has been well established in numerous animal models of stroke, brain

injury, and spinal cord injury. In human clinical trials, however, the results for such neuroprotective strategies have been inconclusive.

Over the last decade, several groups have focused on the development of novel therapeutics to specifically target inflammation. We have already referred to the use of cannabinoids (pentoxifylline and dexanabinol) with the purpose of inhibiting cerebral inflammation in experimental TBI (see also the TNF section). Other studies have tested corticosteroids; however, this approach has since been abandoned, because clinical trials had to be discontinued because of an increased mortality rate in the treatment group.⁸⁸

Currently, the use of nonsteroidal, anti-inflammatory compounds in TBI models are being investigated, but to date the results obtained are ambiguous.⁴ Chronic treatment with ibuprofen improved functional and histopathologic outcome in a mouse model of Alzheimer's disease.⁸⁹⁻⁹¹ Its use in a TBI model, however, failed to confer neuroprotection.⁹² In fact, the outcome of injured animals treated with chronic ibuprofen was significantly worse, compared with placebo animals. In addition, there was no difference in the extent of tissue atrophy of the cortex or hippocampus between treated and nontreated animals. Together, these findings suggest that the use of high doses of anti-inflammatory agents for a prolonged period of time after TBI may abolish the essential neuroprotective properties conferred by post-traumatic cytokine production.

Another common nonsteroidal, anti-inflammatory compound is minocycline, a tetracycline derivative. It has been consistently shown to be beneficial in various models of CNS injury and disease by reducing both immunological and apoptotic pathways.⁹³⁻⁹⁵ Attenuation of the pericontusional lesion volume has been reported following minocycline treatment in a mouse model of TBI²⁹ and in a rat model of transient middle cerebral artery occlusion.⁹⁶ Nonetheless, controversy surrounds the effects minocycline exerts after brain injury. Using a mouse model of focal TBI, our group has shown that minocycline improved neurological outcome and pericontusional lesion volume only transiently, with no differences to vehicle controls by day 4.⁴ Neither the density of apoptotic cells nor neutrophils differed with time or minocycline treatment; however, the amount of activated microglia and macrophages decreased in the injured cortex, as did the levels of cytokines IL-1 and IL-6. More recent preliminary experiments have shown that reduced doses of minocycline administered for a longer period of time result in sustained neurological recovery over a 6-week period (personal communication, N. Bye, 2009). This supports the concept that mild immunosuppression is more effective in attenuating the detrimental effects of neuroinflammation, but simultaneously maintaining its neuroprotective properties.

Altogether, these studies suggest that inhibiting inflammation after TBI is a challenge, for which the specific action of each compound (specific target or general immunosuppressive) as well as doses (high vs low) and the duration of therapy (acute vs prolonged or chronic) must be taken into account.

CONCLUSIONS

This review has highlighted not only the complexity of inflammatory cellular and molecular cascades elicited after TBI, but also their controversial action. The inconsistency of the results obtained with animal models reflects their dependency on specific experimental paradigms, which may explain the negative outcomes of clinical trials. The physiological and biochemical responses to TBI, including inflammation, may differ based on the species or strain, as well as the injury models, used in the laboratory. Furthermore, each study assessed outcome by using distinct behavioral tests, thus making comparison of findings a major challenge. Differences in the pathology of diffuse *versus* focal injury must be taken into consideration before we can fully comprehend the actual role of these cellular and molecular components. Despite such experimental heterogeneity, the common consensus remains: inflammation possesses both beneficial and detrimental properties, for complete ablation of cytokines or cytokine receptors exacerbates tissue and neurological damage after TBI. The development of novel treatments following TBI should aim at minimizing secondary injury by modifying, rather than eliminating the inflammatory response, while creating optimal conditions for regeneration.

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