

Systemic inflammatory response following acute traumatic brain injury

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1. ABSTRACT

The early, delayed, and systemic effects of acute traumatic brain injury (TBI) are the result of inflammatory mediators which initiate systemic inflammatory response syndrome (SIRS), subsequent complement deficits and coagulopathy. Once SIRS is triggered by acute inflammation, it can detrimentally self-propagate. Systemic inflammation causes tissue damage leading to further inflammation and damage, leaving the body in a vicious cycle of hyperinflammation. Therefore, important inflammatory mediators like interleukin (IL)-1 beta, IL-6 and tumour necrosis factor (TNF) alpha, are targeted in compensatory anti-inflammatory response syndrome (CARS) in an attempt to control the development of SIRS. The hypothalamus-pituitary (HPA)-axis and sympathetic nervous system (SNS) efferent limbs in CARS provide negative feedback for the production of inflammatory mediators. However, in the case of acute TBI, the activation of CARS often leads to the complication of immunosuppression which may result in multi-organ dysfunction syndrome (MODS) and mortality. In light of this, the activation of the SIRS following acute TBI does not bode well. If left uncontrolled, multiple systems will be implicated making it difficult to remedy.

2. INTRODUCTION

Traumatic brain injury (TBI) is one of the major causes of morbidity and mortality among young adults (1). It is damage to the brain from an external mechanical force causing temporary or permanent neurological dysfunction such as impairment of cognitive, physical and psychosocial functions (2). TBI can be subcategorised under immediate mechanical injury and delayed chemical injury.

Primary injury involves direct mechanical tissue stretching and tearing from the traumatic event itself (3). Necrosis of torn and overstretched cells is also involved. Haemorrhage may also be included due to the vascular damage which would lead to increased intracranial pressure (ICP), and ischemia. Ischemia itself results from the increased pressure and distortion of microvasculature (4) from trauma.

Delayed damage occurs a few hours to weeks after the initial injury and it involves biochemical and molecular changes in the immediate and distant tissues (5). It results from leukocyte migration to the wound area, their factor production, toxin release from blood breakdown products and necrosis, and activation of serum components.

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Severe TBI also causes multiple organ dysfunction or failure. Therefore, the complications of TBI are not only restricted to neurological consequences, but also include gastrointestinal and cardiovascular complications such as hepatic dysfunction, bowel incontinence, dysphagia and gastroparesis, hypertension, deep venous thromboses and pulmonary emboli (6, 7).

The inflammatory response elicited by trauma is a key component of TBI. Trauma causes not only neuroinflammation in the brain, but also leads to systemic inflammatory response. Inflammatory mediators such as cytokines, excitatory amino acids and free radicals, including nitric oxide (NO), appear to be implicated in secondary brain injury development (8). This review attempts to elucidate the mechanisms of systemic inflammatory response following TBI in the hope that they may lead to identifying some potential targets for therapeutic intervention.

3. IS THE BRAIN AN IMMUNE PRIVILEGED ORGAN?

The brain is immersed in the cerebrospinal fluid and is separated from other tissues by a natural brain-blood-barrier (BBB). About ten years ago, most researchers still regarded the brain as an 'immune privileged' organ, which was not largely affected by systemic inflammatory and immune responses (8). This view has since been challenged.

It is evident that the brain differs significantly from other tissues in response to pathogenic stimulus. Infection or trauma elicits modest and delayed leukocyte recruitment in the brain, albeit this recruitment occurs rapidly in many systemic organs. While leukocyte invasion may be delayed in response to inflammatory stimulus, brain microglia and macrophages can be activated and they release inflammatory mediators within minutes or hours (9, 10). Most importantly, there is now extensive evidence that the brain does exhibit key features of inflammation such as glial activation, major histocompatibility complex (MHC) expression, synthesis of inflammatory mediators and complement activation (11, 12). Furthermore, the neuroinflammatory response after TBI contributes to the development of BBB breakdown, cerebral oedema and neuronal cell death (13, 14). An increasing number of studies have also shown that inflammation within the central nervous system (CNS) contributes to many acute and chronic degenerative disorders and possibly some psychiatric diseases.

4. NEUROINFLAMMATORY RESPONSE IN CNS

Inflammation is a complicated process which involves numerous damage signals, cellular responses (15) and alterations in the microenvironment (16). Its role in the central nervous system may be structure or region specific (17). Its local function is to protect tissues and organs from invading pathogens across epithelial barriers. The immunological defences involved can be grouped under adaptive or nonadaptive immune defences. Adaptive

defences involve gene rearrangements that require time to mature for the production of highly specific T and B cells capable of recognising foreign antigens. Nonadaptive immune defences on the other hand are determined by the genome, rapidly activated and broadly microbicidal. Some require no modification while others require activation by foreign antigens (18).

In the process of local inflammation, an intrinsic defence is set up by cells surrounding the wound site immediately after injury. Leukocyte infiltration then occurs, filling the site with a plug of hematogenously derived material (15). Leukocyte factor release eventually results in reactive gliosis, neurite damage, necrosis and cavitation.

Following a trauma to the adult mammalian CNS, a complex cellular response occurs. The wound becomes filled with haematogenous derived material, forming a plug, including monocytes, which migrate from the blood into the damaged neural tissue where they transform into macrophages. Reactive gliosis is initiated in the surrounding neural tissue, which spreads along the edges of the wound by the proliferation and migration of glial cells (19, 20). Some inflammatory mediators have shown to be locally released after injury and to interact to control the cellular changes that occur. The influx of inflammatory cells to the site of injury may be regulated by the levels and distribution of inflammatory factors expressed in the injured CNS (15). The CNS is suspected to mount an early intrinsic inflammatory response after injury as elevation of IL-1 and tumour necrosis factor (TNF)-alpha levels in and around the injury site has been detected before leukocyte infiltration (21).

Microglia, which are residential cells in the CNS and a class of mononuclear phagocytes (22, 23), have been cited as the possible sensors of brain injury (24) and cytokine producers (25). They are activated and increase in cell numbers upon injury and resemble blood macrophages in their ability to secrete factors (26), scavenge, engulf and clear cellular debris in and around the wound site (27). In pathophysiological conditions, microglia and blood-derived macrophages are activated by CNS trauma or concomitant infection, and are aggregated rapidly at the site of insult. The presence of damaged cells and debris causes ramified resting microglia to transform into rounded migratory macrophages, so-called reactive or activated microglia. Activated microglia produce both cytokines and trophic factors that can exert double effects on neighbouring cells. Its secretion of IL-1 (28), an immunomodulator, leads to the stimulation of astroglial growth in vitro, astrogliosis in vivo (29, 30), and neovascularisation at trauma sites (31). At least two other astroglia stimulating growth factors other than IL-1 are secreted by microglia (26). Chondroitin sulphate proteoglycan, an extracellular matrix molecule, is also included in the list of suspected microglia secreted factors (32).

Following the peak production of IL-1, astrogliosis, involving cellular hypertrophy and hyperplasia, takes place, suggesting that the secretory

activity of mononuclear phagocytes affect the astrocytes (24). The increase in activated astrocytes may be beneficial for damaged neurons as they are involved in the mediation of neurotrophic effects (25), regulation of neurotransmitter levels, repair of the extracellular matrix, and control of the blood-CNS interface and transport processes. They also provide trophic support to damaged cells (15) by producing neurotrophins and pleiotrophins (33), and isolating the injury site. This isolation is achieved through conversion of normal basal lamina to ectopic basal lamina (34, 35) in order to protect surrounding tissue. The reactive astrocyte response is also accompanied by the induction and upregulation of many proteins like growth factors nerve growth factor (NGF) (36), fibroblast growth factor (FGF), neurotrophin-3 (NT-3), ciliary neurotrophic factor (CNTF), cytokines IL-1, IL-6, interferon (IFN), TNF and glial markers (37), glial fibrillary acidic protein (GFAP) (15). It is also suggested that some astrocytes produce inhibitory extracellular matrix molecules like proteoglycan (38-40) which inhibit axonal regeneration (39). The heterogeneity of proteoglycan production in astrocytes may account for astrocyte migration and adhesive changes (41-43).

Proteoglycan upregulation depends on the inflammatory response resulting from the injury and cannot be induced just by the presence of injured, dying or degenerating axons (44). It also takes place in a very restricted pattern, mirroring the distribution of hemorrhagic necrosis, astrocytes (38, 40), microglia, activated macrophages (45, 46), and BBB leakage. Proteoglycan also defines the borders of developing acellular cysts (32, 47) and interfaces between activated macrophages within developing necrotic cavities and surrounding astrocytes (32).

Cavities are formed due to astrocyte migration, as their dramatic movements may lead to rapid dysfunction of axons, thereby leaving them vulnerable to inflammatory damage. Stretching forces generated by the displacement/ or distortion may also contribute directly to damage of axons (48). No axonal regeneration occurs as the cellular terrain of glial cell matrix molecules for growth vanishes (49). It has also been suggested that reactive astrocytes are a barrier to axonal regeneration and remyelination, and they may secrete toxic substances that destroy their neighbouring neurons (50, 51). Cavitation can furthermore result from extrinsic factors like macrophage infiltration and inflammation (24, 52) or extravasation of serum components (53) that cause progressive necrosis (54-56). Intense inflammatory responses may in addition, induce the expansion of the cavity to many times its original size. Experimental cavities were repopulated after 2 weeks with astrocytes and endothelial cells; however, no axon growth was observed (48).

Extrinsic inflammatory cells infiltrate the central nervous system only after a significant delay, with the earliest being neutrophils and T-cells (24, 52, 57-59). Increased neutrophil adhesiveness, involving intercellular cell adhesion molecules (ICAM) and selectin upregulation (60) on endothelial cells, and cluster of differentiation-11/cluster of differentiation-18 (CD11/CD18) (61) and

integrins (62) on activated leukocytes, is a critical step in the permeability changes leading to neutrophil adherence to endothelial cells and extravasation across the BBB into the brain parenchymal tissue.

Upon activation, neutrophils generate and release numerous active substances like proteolytic enzymes (elastase, cathepsin G), reactive oxygen species (oxygen radicals, lipid peroxidation products) and vasoactive substances (leukotrienes, eicosanoids, platelet activating factor), which have damaging effects (61). The cytokines TNF-alpha, IL-6 and IFN-gamma secreted by polymorphonuclear leukocytes (PML) may also play a role in the brain damage.

Invading macrophages may also impair nervous system function through cytokine secretion and cytotoxin production (51, 63). They clear cellular debris and produce cytokines similar to that of microglia after costimulation of their macrophage mannose receptors and beta-glucan sites of the complement receptor 3 (CR3) integrin receptors (64). This coactivation can be achieved by substances like complement protein inactivated C3b (iC3b), erythrocytes, factor X, fibrinogen, lysosomal enzymes, pathogens and tissue plasminogen activator, which are potentially found in areas of trauma (65, 66). Its neurotrophic, proinflammatory cytokine and proteoglycan synthesis (45, 46) also results in astrogliosis (67, 68) and eventually cavitation (48).

Extravasated serum components that are not normally present in the central nervous system may also induce cell reaction. Thrombin for example can trigger astrocyte gliosis (69, 70). The C-reactive protein, a component of the innate immune system, is able to recognise foreign pathogens and phospholipids of damaged cells (71), and activate the complement system by binding one of its ligands. It can also initiate the elimination of target cells through interaction with the humoral and cellular defence systems (71). Several acute phase proteins (APPs), of which some are classic complement components, can similarly initiate or sustain inflammation.

The complement system may also cause tissue injury if activated inappropriately. It is an important innate defence mechanism that includes the attraction and activation of phagocytes, opsonisation, plasma protein exudation at the inflammatory site, lysis and phagocytosis of cells. The lysis of cells is achieved through the formation of the macromolecular complex (MAC) consisting of the complement proteins C5b to C9, which generates transmembrane pores through the cell membrane (72), allowing the escape of cellular contents. MAC may also contribute to the establishment of brain edema by inducing erythrocyte lysis and neurotoxic haemoglobin release (73). Neuronal injury and BBB disruption may also result from MAC insertion into neurons, astrocytes and endothelial cells. This damage to cell membranes induces an upregulation in tissue factor (factor III) activity, enhancing the extrinsic coagulation pathway and eventually increasing production of toxic thrombin (72). Cytokines can also cross the BBB through damaged endothelia or by active transport when the BBB is disrupted by a pathological condition (8).

Therefore TBI not only generates inflammatory response within the brain, but also leads to systemic inflammatory response through the action of mediators.

Another one of the key mediators produced following TBI is NO. It is believed to play a dual role, depending on the type and level of NO synthase (NOS) isoform, from which it is produced and its cellular environment (74). Endogenous NO is generated in physiological and pathophysiological conditions from L-arginine by a family of three distinct isoforms of NO synthase: constitutive Ca²⁺-dependent NOS (cNOS), including neuronal NOS (nNOS) and endothelial NOS (eNOS), or inducible Ca²⁺-independent NOS (iNOS) (75). While NO normally functions as a physiological neuronal mediator, excess production of NO by inappropriate induction of NOS protein in the brain may be involved in glutamate neurotoxicity and is responsible for neuronal death (76). It is suggested that increased levels of NO may contribute to pathophysiology following TBI (77, 78). NO is inherently reactive and cytotoxic; its effect is exerted through multiple mechanisms. It is postulated that NO mediates cellular toxicity by modulating membrane fluidity or by attacking critical cellular targets, thereby causing cellular destruction. NO can directly damage DNA (79) and inhibit DNA replication by inactivating ribonucleotide reductase (80). Furthermore, NO can inhibit the glycolytic enzyme by ADP ribosylation (81). NO may also act to inhibit mitochondrial respiration by inactivating the iron-sulfate centers of several essential enzymes and mitochondrial electron transport complex I and II (82, 83). It has been shown that NO reacts with superoxide to form a more deleterious oxidant, peroxynitrite (ONOO⁻) which is a powerful oxidant with a relatively long half-life and more toxic than NO (84). Peroxynitrite can mediate a variety of destructive interactions including oxidation, lipid peroxidation, DNA strand breakage, and nitration of cystine and tyrosine residues on proteins (84-87). Peroxynitrite has additionally been shown to induce cortical cell death *in vitro*, while the administration of peroxynitrite scavengers inhibited cell death (88). It has also been shown that inhibition of iNOS synthesis by NOS inhibitors significantly improved the outcomes of TBI (77, 89), providing further support for the role of NO in cell death.

5. SYSTEMIC INFLAMMATORY RESPONSE FOLLOWING ACUTE TRAUMATIC BRAIN INJURY

Acute TBI causes the increase of inflammatory mediators in circulation, leading to activation of the systemic inflammatory response, which when deregulated leads to complications of hyperinflammation followed by immunosuppression, multi-organ dysfunction syndrome (MODS) and even death.

The systemic response to trauma can be differentiated into the early and delayed phase. The early phase consists of the cardiovascular response, which is usually immediate, to compensate for haemodynamic changes from haemorrhage. The delayed phase on the other

hand consists of immunological and metabolic changes, of which onset can take from hours to days. It is the delayed phase, which produces longer-lasting effects, plays an important role in secondary effects of acute traumatic brain injury.

5.1. Systemic changes following acute TBI and SIRS

The response of the whole body inflammation is designated the systemic inflammatory response. Ideally, inflammation should be contained locally, thus systemic inflammation is a sign of an ineffective immune response, producing the systemic inflammatory response syndrome (SIRS), which was introduced by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference in 1992. The statement introduced hypothesized that SIRS is triggered by localized or generalized infection, trauma, thermal injury, or sterile inflammatory processes, e.g., acute pancreatitis. SIRS is considered to be present when patients have more than one of the following clinical findings: Body temperature higher than 38°C or lower than 36°C; Heart rate higher than 90/min; Hyperventilation evidenced by respiratory rate higher than 20/min or PaCO₂ lower than 32 mmHg; White blood cell count higher than 12,000 cells/μl or lower than 4,000/μl (90). The specific criteria proposed in the 1992 consensus definitions are widely considered to be too nonspecific in diagnosing a cause of the syndrome or in identifying a distinct pattern of host response (91).

SIRS is an initial hyperinflammatory response to trauma, resulting in increased levels of inflammatory mediators in the circulation (92, 93). The entry of cytokines from the site of local injury into the circulation is a key initiator of SIRS. Firstly, the acute phase response (94), a normal event in inflammation, is activated. Cytokines, mediators of the immune response, are initially released to promote healing at the site of injury and combat invading foreign bodies; however, when deregulated, their action becomes destructive. The massive increase of such inflammatory mediators in the systemic circulation can cause damage to end organs, increasing the risk of MODS (94).

From systemic inflammation, hyperinflammation develops, followed by immunodepression, which impairs host defences further. Other effects produced by systemic inflammation are the activation of the complement and coagulation systems.

At present, investigators have found that some biochemical factors such as IL-6, macrophage inflammatory protein-1 (MIP-1) and C-reactive protein (CRP) were elevated in patients, meeting the 1992 SIRS criteria (95). After trauma, systemic levels of proinflammatory mediators are increased. There is an increase in IL-6 in plasma (96-98) and cerebrospinal fluid (CSF); it is the only cytokine consistently augmented in tissue damage and is linked to the severity of the injury (99). It is furthermore correlated to the risk of post-trauma complications and infectious complications (100). Haemorrhage is also able to increase IL-6 levels, but it is not as strong a stimulus as tissue damage (101, 102).

TNF-alpha and IL-1 beta levels were also elevated after trauma but they were not correlated with IL-6. TNF-alpha was only produced after haemorrhage (98, 101). Although increased, IL-1 beta levels are not correlated with outcomes of complication (98). IL-8 and monocyte chemoattractant protein (MCP-1) levels were also increased and they are associated with ischemia (103). Anti-inflammatory mediators, tumour growth factor-beta (TGF-beta) and IL-10, were similarly elevated post-trauma (93, 104). On the other hand, concentrations of IL-2 were found to be decreased post-injury (94, 105).

Acute phase proteins (APP), such as CRP, increased after trauma. The increase in IL-6 precedes the increase in APP (97), suggesting that IL-6 stimulates APP release. APP is also increased by the stimulation of IL-1 and TNF-alpha. They are produced by the liver in response to the above mentioned circulating inflammatory mediators. The roles of APPs are protective; they are involved in the inactivation of proteases, scavenging of free-radicals and also healing.

With the support of further epidemiologic data, there is great potential to use purely biochemical and/or immunological, rather than clinical, criteria to identify the inflammatory response. This notion takes into consideration of the possibility that inflammation is present when the circulating concentrations of IL-6, procalcitonin, or CRP are increased (106). No large prospective studies currently support such a conclusion.

The SIRS following intracerebral proinflammatory activity, is an important trigger of post-traumatic cerebral damage and systemic complications according to the secondary injury concept. Regardless of TBI, severe trauma and multiple trauma are associated with BBB dysfunction and activation of peripheral neutrophils (107). Intracranial inflammatory responses following TBI may in turn cause the systemic proinflammatory response that can be explained by the diffusion of intracranially generated cytokines through the hyperpermeable BBB into the blood (108, 109).

The BBB forms a border between blood circulation and brain tissue. It consists of three layers: the capillary endothelial cells, the underlying basal lamina, and astrocyte end-feet, forming a tight contact with the basal membrane of the microvascular endothelium. One of the BBB functions is to prevent overshooting inflammatory activity within the brain. The intact tight BBB normally cannot be easily penetrated by neutrophils or blood components. During inflammatory reactions, the neutrophil activity involving protease-mediated disruption of interendothelial cell contacts and secretion of oxygen radicals would lead to severe BBB dysfunction entailing cerebral complications (110).

The mechanism underlying the inflammatory reaction following TBI, leading to SIRS is highly complex. However, the interaction between activated neutrophils and the vascular endothelium involving neutrophil adhesion and

subsequent transendothelial migration plays a crucial role in the pathophysiology of SIRS, and is closely related to endothelial dysfunction associated with a loss of functional intercellular contact sites. In conjunction with neutrophil activation, a dramatic release of neutrophils from the third space, especially the bone marrow, occurs after trauma. The neutrophil activation process involves complement and complement-independent mechanisms.

5.2. Hyperinflammation

The priming of polymorphonuclear cells (PMNs) is important to producing hyperinflammation, as well as mediating the development of systemic inflammation from a local site of injury. This is achieved systemically by the increased levels of inflammatory mediators. IL-6 sensitises PMNs to mediators (111), strengthening the inflammatory processes. IL-6 increases PMN release of platelet activating factor (PAF), which is involved in the priming of PMNs (112). The combination of IL-6 and PAF primes PMNs, increasing their cytotoxic capabilities (113, 114). PMN-elastase, proteases and oxygen radicals are the agents behind the PMN-mediated microvascular damage. TNF and eicosanoids in circulation also prime PMNs, increasing their free radical producing capacity, and hence the amount of tissue damage (60, 115).

IL-6 has other roles in hyperinflammation. It delays the apoptosis of PMNs, extending their period of activity in addition to their increased cytotoxic potential. IL-6 may also be involved in the non-neutrophil-mediated inflammation, increasing endothelial injury without PMN action (116).

5.3. Immunosuppression

The brain and the immune system are functionally linked through neural and humoral pathways. Severe TBI can lead to immune system dysfunction. Decreased immune competence or immunosuppression with severe infection has been demonstrated in human following brain injury. The immunosuppression also has been called "immune paralysis" or a "window of immunodeficiency" or "the compensatory anti-inflammatory response syndrome" by some researchers (117-119). It is the main factor which causes the increased susceptibility to infection of patients with severe TBI. The TBI patients with immunosuppression have increased numbers of monocytes with a persistent decrease in HLA-DR and HLA-DQ antigen expression (120). These cells also are characterized by functional disorders such as decreased ability to generate reactive oxygen species and proinflammatory cytokines (121,122). The exact mechanism of immunosuppression following TBI is not fully understood. Inhibition of antigen-specific T-lymphocyte proliferation and reduction of cytokine-induced macrophage activation by IL-10 and transforming growth factor have been suggested to cause immunosuppression following TBI (123, 124). The stress-induced glucocorticoid, catecholamine release and administration of exogenous catecholamines, such as vasopressors and inotropes can alter T- and B-lymphocyte activity (117, 125).

5.4. Neuroimmune regulation of systemic inflammation

Communication between the CNS and systemic immune systems is through the neuroimmune system, which provides coordination of the overall proinflammatory and anti-inflammatory immune responses, by the CARS (126).

IL-1 beta, IL-6 and TNF-alpha, present in the circulation, are the major cytokines which stimulate CARS (126). The intracerebrovascular injection of prostaglandin E2 (PGE2) has shown to have neuroendocrine functions, increasing adrenocorticotrophic hormone (ACTH) and glucocorticoid (GC) levels (127). Following trauma, PGE2 levels are increased, by release from damaged skin cells and macrophages, which is associated with a decrease in T-cell activity. Therefore, PGE2 has been suggested as a candidate for the induction of CARS.

The organum vasculosum laminae terminalis in the brain lacks the BBB, and so can allow entry of inflammatory mediators from the circulation to the preoptic area (POA) (126). The levels of these mediators are sensed in the POA causing the release of corticotrophin-releasing factor (CRF), which then activates the effector limbs of the neuroimmune system.

There are two efferent limbs of the neuroimmune system (126), the HPA-axis, involving the secretion of GC, and the SNS, which forms an anatomical link between the CNS and systemic lymphoid organs, leading ultimately to the increase in IL-10. These efferent pathways are anti-inflammatory and act as negative feedback to control the strength of the systemic inflammatory response.

Figure 1 summarizes CARS event following acute TBI.

5.5. The HPA-axis

CRF released stimulates the release of ACTH from the adenohypophysis, into the systemic circulation, which in turn activates the adrenal cortex, increasing the levels of immunosuppressive GCs (126). GCs can decrease the production of proinflammatory cytokines (128, 129), as well as increase the release of TGF-beta and IL-10 (107), which are anti-inflammatory. GCs also decrease the MHC class II expression on antigen presenting cells (APCs), decreasing the presentation of foreign antigens to activate the immune system. Other lymphocyte functions are also impaired, and the Th2 response is enhanced, changing the cytokine profile of the immune response, increasing IL-4 and IL-10, to decreasing the cytotoxic activities of the lymphocytes, which may result in a deflection of the immune response (130-133). Studies have shown that GCs also increase the production of APPs (133), which are protective in inflammation.

5.6. The sympathetic nervous system (SNS)

The SNS, forming the second effector limb, is also activated by CRF, increasing the release of catecholamines from the spleen, pancreas, lungs and the diaphragm into the circulation (134, 135, 136). Catecholamines have direct effects on circulating monocyte

activity, increasing their release of IL-10 and decreasing TNF-alpha release, so as to prevent hyperinflammation (137, 138, 139).

5.7. Effect of CARS on monocytes

Monocytes have a central role in inflammation and so are targeted in CARS. Both GC and beta-adrenergic receptors are expressed on the surface, which are linked to secondary signalling pathways within the cell. When GC is bound, the production of proinflammatory cytokines, such as IL-1, IL-6, IL-12, TNF-alpha (140, 141), is suppressed along with the expression of MHC class II (142, 143), reducing systemic inflammatory responses. When catecholamines bind to the beta-adrenergic receptor, production of the proinflammatory TNF-alpha is reduced, while those of anti-inflammatory IL-10 and TGF-beta are increased (143). Therefore, CARS leads to the deactivation of monocytes.

Increased IL-6 levels are associated with decreased T-cell and B-cell populations. The increased production of TGF-beta by monocytes has been implicated as the mediator of this effect of IL-6 on lymphocyte proliferation, providing support for this neuroimmune system (144).

5.8. Effects of acute TBI

CARS is usually stimulated to prevent the progression to SIRS. In acute traumatic brain injury, the locally produced proinflammatory cytokines released into the brain parenchyma may diffuse to the POA and activate CARS prematurely, causing the compensatory events for hyperinflammation in an understimulated systemic environment, resulting in unnecessary immunosuppression. In addition to that, the increased ICP from trauma can lead to activation of the SNS (126), activating both efferent pathways of CARS.

The BBB is a physiological and anatomical barrier between the brain and the rest of the body, protecting the local environment of the brain from systemic changes. However, the BBB is compromised in acute TBI (145), allowing the movement of locally produced proinflammatory mediators into the systemic circulation. This increases the levels of IL-1, IL-6 and TNF-alpha in the absence of systemic injury, and can generate SIRS. In the case where CARS is activated with a massive SIRS, mixed antagonistic response syndrome (MARS) develops (126). SIRS leads to hyperinflammation while CARS leads to immunosuppression, and unless a balance is achieved, the body experiences both syndromes in alternating phases. However, in cases of brain trauma, the local effects of CARS overwhelm SIRS, resulting in a dominant immunosuppression (126).

5.9. Activation and reduction of complement

The complement cascade is activated via the alternative pathway (61) after acute traumatic brain injury and contributes to brain oedema (72). Complement fixing of damaged tissue post-trauma (60) can activate neutrophils, possibly contributing to the activation of SIRS. The consumption of complement in acute inflammation can

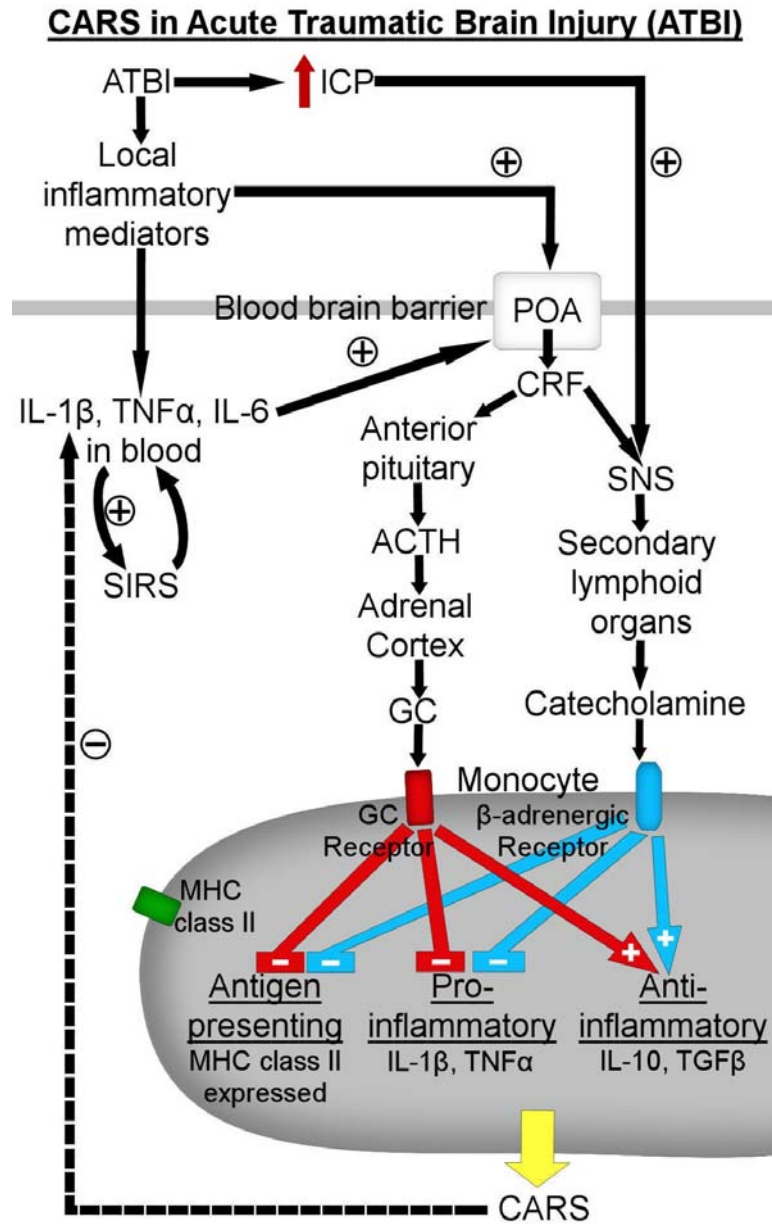


Figure 1. Schematic diagram of CARS in acute TBI. Inflammatory mediators released following TBI initiate SIRS which causes systemic tissue damage. The HPA-axis and SNS efferent limbs in CARS provide negative feedback for the production of inflammatory mediators. However, the activation of CARS often leads to the complication of immunosuppression and may consequentially lead to MODS and mortality.

deplete plasma complement systemically. The extent of complement reduction is dependent on the severity of tissue damage from trauma (146, 147). Systemic levels can return to normal in 4-6 days, if damage is moderate (148). If inflammation is prolonged, the depletion can lead to immunosuppression and deregulated systemic inflammation associated with complications of acute respiratory distress syndrome (ARDS) and MODS (149, 150). In view of this, the degree of complement activation, the ratio of C3a to C3, can be used to predict mortality after trauma (150).

5.10. Coagulation

Pathophysiological changes in coagulation occur after trauma (151), due to the activation of tissue factors by inflammatory mediators such as TNF (152, 153). Reciprocally, the clustering of tissue factors induce the increase of TNF (154).

TNF stimulates the procoagulant pathway of endothelial cells (155) by inhibiting the protein C anticoagulant pathway. Thrombomodulin (155, 156) and endothelial protein C receptor (EPCR) expression is down-

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regulated and EPCR shedding from the cell surface is increased (153), further inhibiting the anti-coagulation pathway. Thrombin itself also increases expression of P-selectin and synthesis PAF by endothelial cells (157).

Coagulopathy results from complicated interactions in the pathway. In systemic inflammation, tissue damage can activate the haemostatic process by damaging the endothelial surface, exposing the subendothelial surface, which activates coagulation, aggravating the procoagulative state produced by the inflammatory mediators. Apoptosis during inflammation causes externalization of phosphatidylserine on cells which also promotes coagulation (158). Intravascular coagulation can impede the delivery of oxygen through blood vessels, so hypoxia can result in severe cases, causing further inflammation (151). Multiple thrombi can form depending on the severity of the damage, consuming platelets and coagulation factors. Consumption coagulopathy may result and may even lead to disseminated intravascular coagulation (DIC) if there is serious deregulation of the coagulant pathway.

5.11. Multiorgan dysfunction syndrome (MODS)

MODS is a high mortality complication of trauma and systemic inflammation (159, 160). The causes may be infectious or non-infectious. It is the altered systemic inflammatory and immunological functions of that are causative of MODS. The initial phase is shock (161), followed by organ dysfunction, and the final phase is late organ dysfunction due to generalized inflammation of the organ. Generalized inflammation is associated with tissue damage and is a product of the excessive systemic response (162, 163). It is the overwhelming levels of inflammatory mediators that cause cellular dysfunction and ultimately organ failure.

To better understand its pathogenesis, MODS has been described in the “two-hit” theory. The “first-hit” is the initial trauma that leads to the activation and priming of the immune system, which may be asymptomatic. The “second-hit”, is another insult that can be mild, but greater amounts of inflammatory mediators are released, due to the primed immune system causing hyperinflammation and further tissue damage. Plasma elastase concentrations are associated with increased tissue damage. It is positively correlated to the development and intensity of ARDS and MODS (61). However it has also been suggested that the immunosuppressed state rather than hyperinflammation leads to MODS (164). Similarly, DIC is a contributor to MODS (165). Therefore, the precise cause of MODS is still debatable.

6. Role Of Mediators In Systemic Inflammatory Response Following TBI

The initiation of SIRS is induced by mediators produced during local inflammation. These mediators have both local and systemic effects and are normal components of the immune system. Nevertheless, if control of their

regulatory mechanisms is lost, they can switch from being protective to destructive.

6.1. Cytokines

Cytokines are one of the largest groups of mediators. Some cytokines that are involved in the inflammatory response are IL-1 beta, IL-2, IL-6, IL-8, IL-10, IL-11 and TNF-alpha.

IL-1 beta is proinflammatory and is released from macrophages and monocytes (166) and contributes to the initiation and control of the acute phase response (99, 167). It may be required to stimulate the production of IL-6 (168). It also increases the expression of leukocyte adhesion molecules. IL-1 beta has furthermore been shown to mediate damage to the BBB. In contrast, IL-1 beta may also preserve the CNS by producing protective factors for neurones and glial cells (21). Its other systemic responses include tachycardia, hypotension and the induction of fever. Anorexic behaviour and muscle wasting have also been associated with IL-1 beta (169). IL-1 beta may exhibit autoregulation of its own receptors (170).

In brain injury, activated microglia release IL-1 beta, which play diverse roles in inflammatory response following trauma through corresponding IL-1 receptor (type1). It can enhance activation of iNOS and generation of growth factors, modulate glutamate release and neuronal responses to N-methyl-D-aspartic acid and glycine, and strengthen gamma-aminobutyric acid inhibitory effects (9). It can additionally induce fever reaction through a change in hypothalamic thermoregulation. Until now, numerous regulatory effects of IL-1 beta on brain and systemic damage, infection and inflammation have been found.

IL-2 is similarly immunostimulatory and is produced by activated T-cells and natural killer (NK) cells (167, 171). It causes the proliferation of T-cells and B-cells, and is involved in the diffuse inflammatory response. However its levels are rapidly depressed after trauma, hence it is rarely detected (172).

Th2 cells also produce IL-6, which is also synthesised by antigen presenting cells and other somatic cells. Elevated levels may persist up to 21 days after trauma (100). IL-6 is one of the important mediators involved in post-trauma immunosuppression. It is also the dominant cytokine in inflammation, producing the acute phase response (173). It stimulates thrombocytosis in inflammation (71) and in brain trauma; it is associated with gliosis and parenchymal damage (174, 175). IL-6 is involved in regulating the levels of other cytokines. Furthermore, it contributes to the IL-1 beta-induced production of IL-1 receptor antagonist (176) and possibly inhibits expression of TNF-alpha (172). IL-11, produced by stromal cells, has similar effects as IL-6 (177).

More and more research has demonstrated that IL-6 and IL-6 receptor levels are markedly upregulated in the brain tissue, in the CSF, and in the serum of patients with TBI (143). IL-6 may be generated in the brain, and then enters blood circulation through the damaged BBB,

affecting other organ functions (178). It has also been confirmed that IL-6 is an inducer of NGF. Thus IL-6 is regarded as a protective inflammatory cytokine.

TNF-alpha is a proinflammatory and procoagulative cytokine (39, 60, 179), hence it is associated with the development of SIRS and DIC. It is released by macrophages and monocytes in damaged tissue (15, 166). Haemorrhage, not tissue damage, induces TNF-alpha release (101, 180), but without correlation with the severity of haemorrhage. However, patients who had septic complications after trauma had higher levels of TNF-alpha (181, 182). Together with IL-1 beta, it is associated with mediating BBB injury and the induction of iNOS mRNA (25). It also activates apoptosis of neurones and oligodendrocytes (24, 183, 184).

In TBI, resident macrophages, astrocytes and microglia can produce TNF-alpha in the central nervous system. TNF-alpha plays both deleterious and protective roles through different TNF receptor (TNFR) in the pathogenesis of TBI. TNF-alpha induces neuronal apoptosis by activating TNFR1 to aggregate brain tissue damage (178). In contrast, TNF-alpha can also promote growth and proliferation of neurons and oligodendrocytes through TNFR2 (185).

IL-8 is a chemoattractant and is associated with brain inflammation, damage and autoimmunity (186). It is upregulated in cerebral endothelial cells by IL-1 beta and has shown to have an effect on BBB permeability, infarct size and oedema after brain trauma (103). It is one of the important mediators in the transmigration of adhering leukocytes on the BBB (103).

Lastly IL-10 is a pleiotropic cytokine produced by monocytes, macrophages, keratinocytes, B-cells and Th2-cells (187). It is immunosuppressive (126), playing a role in CARS, and has inhibitory effects on macrophages, cytotoxic T-cells and NK cells (187).

The beneficial role of IL-10 has been confirmed in many inflammatory or trauma animal models. Administration of IL-10 in animals suffering from experimental TBI clearly demonstrated the suppressed synthesis of proinflammatory cytokines such as TNF and IL-1, reduced activation of glial cells and an improvement of the damage outcome (188). Some research also indicated that the level of IL-10 was elevated in the cerebrospinal fluid of patients with TBI (143).

6.2. Coagulation Factors

Mediators of the coagulation system are also affected after TBI, which can change the systemic balance between the procoagulant and anticoagulant states. Antithrombin III (ATIII), protein C (PC) and protein S (PS) are important serum components that are potent inhibitors of the clotting cascade (189).

ATIII is produced by the liver and has the functions of inactivating thrombin and inhibiting certain serin-proteases like IXa, Xa, XIa, XIIa, plasmin, kallikrein

and trypsin. It is also rapidly depleted during DIC, signalling a defect in plasma anticoagulant activity (189) or in serious cases, chronic or acute acquired liver failure (190).

PC is a vitamin K-dependant plasma protein that is also depleted during DIC (191). It contributes to the inactivation of factors Va and VIIIa, and fibrinolysis enhancement by neutralisation of plasminogen-activator-inhibitor type 1 (PAI1). It is similarly synthesised in the liver and a drop in levels is observed only in liver failure or acute defibrination (192, 193). A drop in activity may also result from cytokine action on PC and thrombomodulin expression at endothelial sites (39, 194).

PS is likewise vitamin-K dependant, facilitating the binding of activated PC to platelet membranes. Forty percent of its proteins circulate freely as cofactors of PC (192), while the rest are bound to C4b binding protein (C4bBP), an APP, and are rendered inactive (195).

Thrombin and the coagulation cascade are major role players in early brain oedema formation after intercranial haemorrhage (196). The infiltration of thrombin into the brain parenchymal tissue results in BBB disruption (197) and inflammation (69). Production of thrombin may also result from interactions around the haematoma formed (72). Thrombin can furthermore increase the expression of endothelial P-selectin and activate synthesis of platelet activating factor (PAF) (153).

Platelet activating factor is produced by endothelial cells from diverse vascular sources (198). It is then incorporated by the cellular membrane and carries out its functions on the cell surface (199). It activates attached leukocytes through P-selectin (114), which is also expressed on the cell surface, allowing further adhesion that is mediated by ICAM-1 (200). Neutrophil adhesion mediated by PAF is induced by hypoxia, and the tethered neutrophils are primed for increased production, and release of free radicals and arachidonic acid (114). Both free radicals and arachidonic acid eventually induce BBB breakdown.

6.3. Complement components

Anaphylatoxins that are generated after activation of the complement cascade are also important mediators of delayed injury. The C3a, C4a and C5a proteins produced may cause increased vascular permeability by degranulating mast cells and leukocytes. The proteins may additionally stimulate a dose dependant synthesis and release of TNF-alpha and IL-1 in inflammatory cells (201, 186, 202). This release may lead to a positive feedback, resulting in more proinflammatory cytokine release by activated macrophages (203), and may contribute to an early activation of a complex cascade, ending up with further cell damage and organ failure. Inflammatory cells like reactive astrocytes, microglia and endothelial cells also react to extremely low concentrations of C5a (concentration in the nanomolar range), with chemotaxis, and an upregulation of adhesion molecules (72) and the

receptor for C5a itself (204), contributing to systemic injury.

6.4. Growth factors

Neurotrophin and pleiotrophin upregulation coincides with trauma (205) and aids in the maintenance of neuronal survival and rebuilding of central nervous system cytoarchitecture respectively. The release of these growth factors must be exact in order to induce tissue-specific responses (15). The factors include basic fibroblast growth factor (bFGF), CNTF, NGF, platelet-derived growth factor (PDGF) and TGF-beta (15, 206, 207). Many of these neurotrophic factors are able to prevent neuronal death after TBI (208) by injury response regulation (19). TGF-beta, an agonist of IL-1 and TNF-alpha is able to activate negative feedback to limit inflammatory reaction. It is upregulated in acute TBI and is released by macrophages and microglia (10). It has been shown to increase the expression of tenascin in cell cultures (209) and may have protective properties in certain types of trauma (210). It is also involved in enhancing the production of other cytokines, the formation of scar tissue and the pathogenesis of CNS dysfunction (15). bFGF, a pleiotrophin produced by astrocytes (211, 212), and extracellular matrix during injury, contributes to astrogliosis and may also be part of efforts to seal and revascularise wounds (213). Lastly, CNTF is a survival factor that has potent effects on oligodendroglial cells and their progeny (21). It is required for the maturation of oligodendrocytes, promoting their synthesis of myelin proteins (184, 214) and protecting them from apoptosis (183, 184). It is suggested that IL-1 beta may be responsible for the regulation of CNTF (137) after injury.

6.5. Chemokines

Chemokines are also important mediators produced by leukocytes and endothelial cells during injury. They are highly basic and interact with acidic extracellular components, attracting inflammatory cells from circulation into the wound site (15). Some chemokines include growth-related oncogene (GRO), macrophage inflammatory protein-2 (MIP-2), MCP-1 and MIP-1 beta. GRO and MIP2 are both produced by activated macrophages and are involved in neutrophils infiltration. Sources of MCP-1 are monocytes, microglia (215), astrocytes (216), perivascular mononuclear cells (217, 218) and its expression and production are modulated by TNF-alpha and TGF-beta (219, 220), and PDGF (221) respectively. MCP-1 is chemotactic for monocytes (222), and induces release of histamine from basophiles (223). MIP-1 beta can be localised near injury and in necrotic tissue as it recruits inflammatory cells like neutrophils and macrophages to the site of injury (224). It is released by myeloid and lymphoid cells, and increases endothelial adherence of CD4+ T-cells (225).

6.6. Nitric Oxide (NO)

Following TBI, NOS is also activated by inflammation, which is initiated by both primary and secondary injuries. NO regulates the dilation of blood vessels and acts as chemotoxin during inflammatory processes. Proinflammatory cytokines can induce iNOS,

thereby promoting persistent iNOS over-activation for several days after injury (78, 226). iNOS is mainly expressed in macrophages, microglia and infiltrating neutrophils recruited from the blood, and thus has a substantially greater capacity to synthesize NO (226). During the course of the pathophysiological process triggered by TBI, NO accumulates in the brain immediately after injury, as well as several hours or days later. NO and the NOS pathways are involved, both positively and negatively, in the secondary injury cascade following injury.

7. CONCLUSIONS

Trauma causes not only neuroinflammation in the brain, but also can initiate SIRS which causes systemic tissue damage. Subsequently, CARS can occur in attempt to control the development of SIRS. The HPA-axis and SNS efferent limbs in CARS provide negative feedback for the production of inflammatory mediators via the altered activity of monocytes. However, the activation of CARS often leads to the complication of immunosuppression. The persistent immunosuppression may result in MODS and high mortality rate. The various inflammatory mediators play a pivotal role in the activation, development and prognosis of the SIRS following acute TBI. A fuller understanding of the above pathophysiological processes will undoubtedly help to develop early diagnosis and potential therapeutic strategies and decrease the mortality rate for the TBI patients with the SIRS.

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Abbreviations: CNS: central nervous system; TBI: traumatic brain injury; SIRS: systemic inflammatory response syndrome; HPA: hypothalamus-pituitary; SNS: sympathetic nervous system; CARS: compensatory anti-inflammatory response syndrome; NO: nitric oxide; IL: interleukin; TNF: tumour necrosis factor; MODS: multi-organ dysfunction syndrome; ICP: intracranial pressure; BBB: brain-blood-barrier; MHC: major histocompatibility complex; NGF: nerve growth factor; FGF: fibroblast growth factor; NT: neutotrophin; CNTF: ciliary neurotrophic factor; IFN: interferon; GFAP: glial fibrillary acidic protein; ICAM: intercellular cell adhesion molecules; CD: cluster of differentiation; PML: polymorphonuclear leukocytes; CR: complement receptor; iC3b: complement protein inactivated C3b; APP: acute phase proteins; MAC: macromolecular complex; NOS: NO synthase; cNOS: constitutive Ca2+-dependent NOS; nNOS: neuronal NOS; eNOS: endothelial NOS; iNOS: inducible Ca2+-independent NOS; ADP: adenosine diphosphate; ONOO-: peroxynitrite; MIP: macrophage inflammatory protein; CRP: C-reactive protein; CSF: cerebrospinal fluid; MCP: monocyte chemotactic protein; TGF: tumour growth factor; APP: acute phase protein; PMN: polymorphonuclear cell; PAF: platelet activating factor; HLA: human leukocyte antigen; PGE2: prostaglandin E2; ACTH: adrenocorticotrophic hormone; GC: glucocorticoid; POA: preoptic area; CRF: corticotrophin-releasing factor; MARS: mixed antagonistic response syndrome; ARDS: acute respiratory distress syndrome; EPCR: endothelial protein C receptor; DIC: disseminated intravascular coagulation; NK: natural killer; TNFR: TNF receptor; ATIII: antithrombin III; PC: protein C; PS: protein S; PAI1: plasminogen-activator-inhibitor type 1; C4bBP: C4b binding protein; bFGF: basic fibroblast growth factor; PDGF: platelet-derived growth factor; GRO: growth-related oncogene

Key Words: Traumatic brain injury, Inflammatory mediators, Systemic inflammatory response syndrome, Multi-organ dysfunction syndrome, Review

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