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THE INFLAMMATORY RESPONSE IN STROKE

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Abstract

Recent work in the area of stroke and brain ischemia has demonstrated the significance of the inflammatory response accompanying necrotic brain injury. Acutely, this response appears to contribute to ischemic pathology, and anti-inflammatory strategies have become popular. This chapter will discuss the current knowledge of the contribution of systemic and local inflammation in experimental stroke. It will review the role of specific cell types including leukocytes, endothelium, glia, microglia, the extracellular matrix and neurons. Intracellular inflammatory signaling pathways such as nuclear factor kappa beta and mitogen-activated protein kinases, and mediators produced by inflammatory cells such as cytokines, chemokines, reactive oxygen species and arachidonic acid metabolites will be reviewed as well as the potential for therapy in stroke and hypoxic-ischemic injury.

1. Introduction

Stroke is one of the most frequent causes of death and disability worldwide, and has significant clinical and socioeconomic impact. Although different mechanisms are involved in the pathogenesis of stroke, there is increasing evidence showing that inflammation accounts for its progression, at least acutely (Barone and Feuerstein, 1999; Chamorro and Hallenbeck, 2006; Samson et al., 2005). A robust inflammatory reaction characterized by peripheral leukocyte influx into the cerebral parenchyma and activation of endogenous microglia follows focal cerebral ischemia (Becker, 1998; Davies et al., 1998; Hallenbeck, 1996; Morioka et al., 1993; Zheng and Yenari, 2004). Cessation of cerebral blood flow leads to energy depletion and necrotic neuron death, which can trigger immune responses ultimately leading to inflammatory cell activation and infiltration. Reperfusion of the occluded vessel, either due to compensation by the collateral circulation, or spontaneous or therapeutic recanalization leads to the generation of reactive oxygen species (ROS) either by reperfusion with oxygenated blood or production within brain and immune cells. ROS can then stimulate ischemic cells, even ischemic neurons, to secrete inflammatory cytokines and chemokines that cause, among other things, adhesion molecule upregulation in the cerebral vasculature and peripheral leukocyte recruitment, respectively. Once activated, inflammatory cells can release a variety of cytotoxic agents including more cytokines, matrix metalloproteinases (MMPs), nitric oxide (NO) and more ROS (Figure 1). These substances may induce more cell damage as well as disruption of the blood-brain barrier (BBB) and extracellular matrix ((Danton and Dietrich, 2003; Emsley and Tyrrell, 2002). BBB disruption can further potentiate brain tissue injury and contribute to

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secondary ischemic brain damage by permitting serum elements and blood to enter the brain (Rosenberg, 1999; Siesjo and Siesjo, 1996). Secondary damage develops as a consequence of brain edema, post-ischemic microvascular stasis and vasomotor/hemodynamic deficits leading to hypoperfusion and post-ischemic inflammation, thus involving activation of microglia and brain infiltration of peripheral inflammatory cells (Dirnagl et al., 1999; Siesjo and Siesjo, 1996). This type of migration of peripheral circulating leukocytes into the brain could produce an amplification of inflammatory signal cascades, which will enhance the damage. These processes are especially pronounced during reperfusion when previously occluded vessels are opened and lead to massive influx of ROS and leukocytes into injured brain. Blocking various aspects of the inflammatory cascade has shown to ameliorate injury from experimental stroke (Han and Yenari, 2003), although this has yet to be demonstrated at the clinical level (Becker et al., 2001).

During the past few years, progress has been made towards identifying the roles of important inflammatory signaling molecules, cells and proteins in the process of initiation and development of post-ischemic inflammation. This review focuses on current findings and provides an update on the understanding of post-ischemic inflammation.

2. Cellular response to ischemic stroke

Inflammation is characterized by the accumulation of inflammatory cells and mediators in the ischemic brain. After ischemia onset, inflammatory cells such as blood-derived leukocytes and microglia are activated and accumulate within the brain tissue subsequently leading to inflammatory injury. Increasing evidence shows that astrocytes may also act as inflammatory cells responding to ischemic stroke.

2.1. Leukocytes

4–6 h hours after ischemia onset, circulating leukocytes adhere to vessel walls, leading to migration and accumulation into ischemic brain tissue with subsequent release of proinflammatory mediators. These mediators lead to secondary injury of potentially salvageable tissue within the penumbra surrounding the infarct core. Neutrophils are generally the first leukocyte subtype recruited to the ischemic brain, and may potentiate injury by directly secreting deleterious substances or other inflammatory mediators (Hallenbeck, 1996). In transient ischemia, several studies have shown that infarct volume is significantly reduced when neutrophil infiltration is inhibited (Bowes et al., 1995; Chopp et al., 1996; Clark et al., 1995; Connolly et al., 1996; Garau et al., 2005; Yenari et al., 1998). Some mediators, while not directly cytotoxic, may be involved in the destruction of necrotic and neighboring viable tissue. Evidence that neutrophils potentiate ischemic injury include numerous studies documenting improved neurological outcome following neutrophil depletion and inhibition of adhesion molecules which facilitate neutrophil entry into injured brain (see reviews (Hartl et al., 1996; Zheng and Yenari, 2004). The roles of lymphocytes are generally intended to play a negative role in ischemic brain pathogenesis even though there is also conflicting data. Following permanent middle cerebral artery occlusion (MCAO) in rats, lymphocytes were elevated in the ischemic lesion after neutrophils (Li et al., 2005; Stevens et al., 2002). Preventing lymphocyte trafficking into ischemic brain ameliorated injury, suggesting that like neutrophils, lymphocytes also play a deleterious role (Becker et al., 2001). Clinical studies also show that lymphocytes have a strong pro-inflammatory and tissue-damaging properties, and the upregulation of circulating lymphocytes are correlated to an increased risk of stroke recurrence and death (Nadareishvili et al., 2004). However, in a study of cultured primary neurons, isolated neutrophils, but not lymphocytes potentiated neuronal injury due to excitotoxin exposure (Dinkel et al., 2004).

2.2. Microglia/Macrophages

Microglia, the resident macrophages of the brain, play a critical role as resident immunocompetent and phagocytic cells in the CNS (Kreutzberg, 1996), and serve as scavenger cells in the event of infection, inflammation, trauma, ischemia, and neurodegeneration (El Khoury et al., 1998; Thomas, 1992). Once activated, microglia can undergo morphologic transformation into phagocytes, making them virtually indistinguishable from circulating macrophages.

Microglial activation may be induced by cerebral ischemia, causing a release of a variety of substances many of which are cytotoxic and/or cytoprotective (Wood, 1995). Via CD14, microglia are activated, followed by stimulation of toll-like receptor 4 (TLR4) (Guha and Mackman, 2001; Saito et al., 2000). How microglia are activated following ischemia is not completely clear, but CD14 receptors have been documented in monocytes and activated microglia in brains of stroke patients (Beschorner et al., 2002). Furthermore, work in neonatal mice indicated that TLR4 was necessary for microglial activation following hypoxia/ischemia (Lehnardt et al., 2003).

Whether microglia/macrophages are necessarily damaging following brain ischemia is unclear, but a few lines of evidence suggest that activated microglia may contribute to injury. Edaravone, a novel free radical scavenger, significantly reduced the infarct volume and improved the neurological deficit scores for ischemic mice by reducing microglial activation (Zhang et al., 2005a). In spontaneously hypertensive rats with permanent MCAO, Gunther et al. (Gunther et al., 2005) found that repetitive hyperbaric oxygen (HBO) treatment obviously reduced the infarct volume by suppressing microglia activation. In transient MCAO, phagocytic microglial were documented in the cerebral cortex of the ischemic hemisphere (Yu et al., 2005; Zhang et al., 1997). Minocycline, a tetracycline family antibiotic, was shown to provide significant protection against brain ischemia by inhibiting of microglial activation and proliferation (Yrjanheikki et al., 1998; Yrjanheikki et al., 1999). Direct evidence supporting a damaging role following ischemic insults were demonstrated when microglia/macrophages were applied to neuron or oligodendrocyte cultures. Injury from various ischemia-like insults was increased in the presence of microglia/macrophages (Giulian et al., 1993; Lehnardt et al., 2003; Zhang et al., 1997). However, some studies indicate that microglia/macrophages or their secreted factors may actually protect cells (Watanabe et al., 2000). No effect on infarct size was seen after depleting peripheral macrophages using liposome-encapsulated clodronate (Schroeter et al., 1997). However, this latter study did not deplete brain macrophages and may suggest that brain, rather than circulating macrophages are important in ischemic pathogenesis.

2.3. Astrocytes

Aside from traditional inflammatory cells, astrocytes are known to express different kinds of inflammatory mediators (Benveniste, 1998; Che et al., 2001). Following ischemia, brain astrocytes are activated resulting in increased glial fibrillary acidic protein (GFAP) expression and a so-called “reactive gliosis,” characterized by specific structural and functional changes (Pekny and Nilsson, 2005). Astrocytes also participate in brain inflammation by expressing major histocompatibility complex (MHC) and costimulatory molecules, developing Th2 (anti-inflammatory) immune responses and suppressing interleukin-12 (IL-12) expression, though this has yet to be demonstrated in ischemia models (reviewed by(Dong and Benveniste, 2001). Astrocytes are also capable of secreting inflammatory factors such as cytokines, chemokines and inducible nitric oxide synthase (iNOS) (Dong and Benveniste, 2001). Following 10 minutes of transient global ischemia, iNOS expression was found in reactive astrocytes of hippocampus but not in uninjured hippocampal astrocytes (Endoh et al., 1994). Furthermore, inducible nitric oxide synthase (iNOS) in astrocytes has been shown to potentiate

ischemia-like injury to neurons (Hewett et al., 1996). Recently studied protein, tumor necrosis factor-like weak inducer of apoptosis (TWEAK), a member of the tumor necrosis factor superfamily, is thought to be produced by neurons, astrocytes and endothelial cells (Donohue et al., 2003; Yepes et al., 2005), and can stimulate proinflammatory molecule production by interaction with its Fn14 receptor found on astrocytes(Saas et al., 2000). Expression of TWEAK and Fn14 has been documented in a murine model of stroke, and a soluble decoy to Fn14 markedly reduced infarct volume (Yepes et al., 2005). These data may suggest that while astrocytes normally play important roles in neuron maintenance and function, activated astrocytes have the potential to pose harm to ischemic brain.

3. ADHESION MOLECULES

Adhesion molecules play a pivotal role in the infiltration of leukocytes into the brain parenchyma after stroke and may represent important therapeutic targets (see recent review by (Sughrue et al., 2004). Three major steps, rolling and adhesion and transendothelial migration of leukocytes, are involved in the access of leukocytes to the brain through the endothelial wall. Activated leukocytes, especially neutrophils, result in further damage of ischemic lesions through reperfusion or secondary injury mechanisms (Guha and Mackman, 2001). The interaction between leukocytes and the vascular endothelium is mediated by three main groups of cell adhesion molecules: selectins (P-selectin, E-selectin, and L-selectin), the immunoglobulin superfamily (intercellular adhesion molecules, e.g. ICAM-1, 2 and vascular cell adhesion molecule-1, or VCAM-1) and integrins (CD11a–c) (DeGraba, 1998; Emsley and Tyrrell, 2002). Several reports have shown that inhibiting leukocyte adhesion by targeting various adhesion molecules, thus preventing leukocytes from entering ischemic brain, results in reduced neurologic injury (Clark et al., 1995; Clark et al., 1997). Furthermore, animals deficient in adhesion molecules have reduced infarct volume after transient focal cerebral ischemia (Connolly et al., 1997; Kitagawa et al., 1998; Soriano et al., 1999). Although several adhesion molecules have been documented in both permanent and transient MCAO, (Haring et al., 1996; Suzuki et al., 1998; Zhang et al., 1996), inhibiting these targets only appears to be effective when reperfusion occurs (Clark et al., 1997; Prestigiacomo et al., 1999; Zhang et al., 1995a).

3.1. Selectins

Selectins mediate cell-cell adhesion, and rolling of leukocytes on the endothelium of postcapillary venules. Three kinds of selectins have been identified: E-selectin, P-selectin and L-selectin (Carlos and Harlan, 1994; Hallenbeck, 1996; Kim, 1996). They are expressed on the outer cell membrane immediately upon cell activation by stimulants such s thrombin or histamine. While E- and P-selectin are involved in leukocyte rolling and recruitment during the early stages of activation, L-selectin acts as a guide for unstimulated leukocytes (Bargatze et al., 1994).

The expression of P- and E-selectins have been documented in different experimental stroke models and their upregulation appears to be involved in promoting ischemic inflammatory responses and increases injury due to ischemic stroke (Huang et al., 2000b; Huang et al., 1999). In animal studies, mice overexpressing P-selectin had exacerbation of infarcts, whereas treatment with antibodies or inhibitors against P- and E-selectin was associated with improved neurological outcome (Huang et al., 2000b; Mocco et al., 2002). The effects of P-selectin in ischemic stroke appear different in focal and global ischemia. In focal cerebral ischemia, neutrophils accumulated in the ischemic cortex of wildtype mice more abundantly than in P-selectin knockout mice (Connolly et al., 1997). Moreover, P-selectin deficient mice demonstrated smaller infarct volumes and improved survival compared with wildtype mice. Functional blockade of P-selectin in using a monoclonal antibody also improved early reflow and stroke outcome, with reduced cerebral infarction even when the blocking antibody was

administered after ischemia onset. However, P-selectin may play a different role in global cerebral ischemia. Antibody blockade of P-selectin, while reducing leukocyte rolling, paradoxically reduced survival (Lehmberg et al., 2006). The reasons for these contrasting outcomes remain unclear, but suggests that the inflammatory response and its significance after focal and global ischemia may be quite different.

The role of L-selectin in brain ischemia is less clear. Although L-selectin mediates leukocyte transmigration, does not appear to significantly influence stroke outcome. Treating rabbits exposed to transient focal brain ischemia with an L-selectin antibody did not affect stroke outcome (Yenari et al., 2001). However, fucoidin, an inhibitor of both P- and L-selectin, significantly reduced infarct size and improved neurological function in experimental stroke in rats, but these observations could have been due to inhibition of P-selectin rather than L-selectin (Ruehl et al., 2002).

Recent work has also shown that exposing animals to E-selectin intranasally can induce immune tolerance to brain antigens, and consequently reduce the extent of injury (Chen et al., 2003b) and even prevent their occurrence (Takeda et al., 2002). Since E-selectin is exclusively upregulated in stimulated endothelium, tolerance to E-selectin could lead to suppression of immune responses and prevent peripheral leukocyte trafficking into the brain. Thus, it is conceivable that intranasal E-selectin might lead to the development of a vaccine against stroke.

3.2. Immunoglobulin superfamily

Members of the immunoglobulin superfamily include 5 molecules: ICAM-1 and ICAM-2, VCAM-1, platelet-endothelial cell adhesion molecule-1 (PECAM-1), and the mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1). ICAM-1 (also referred to as CD54) is constitutively present in low levels on cell membranes of endothelial cells, leukocytes, epithelial cells, and fibroblasts. Its expression increases upon stimulation by cytokines. ICAM-2 (CD102) is an endothelial cell membrane receptor that does not increase after stimulation, whereas VCAM-1 (CD106) is induced by TNF-α and IL-1. PECAM-1 (CD31) is involved in the attachment of endothelial cells to each other, and leukocyte transmigration across the endothelium. MAdCAM-1, acting as an endothelial cell ligand for leukocyte homing receptors L-selectin and alpha4beta7 integrin, is an adhesion protein expressed on endothelium in mucosal tissues that has been shown to play an important role in the selective homing of lymphocytes to intestinal mucosa and associated lymphoid tissue.

Among all of the 5 immunoglobulin members, ICAM-1 and VCAM-1 have been the most extensively investigated in cerebral ischemia. Prior work has shown increased expression of ICAM-1 in ischemic brain within hours after stroke onset, peaking at about 12–24 h, and precedes leukocyte infiltration (Wang and Feuerstein, 1995; Wang et al., 1994; Zhang et al., 1995b). Several studies have now shown that blocking ICAM-1 with antibodies (Bowes et al., 1993; Chopp et al., 1996; Kanemoto et al., 2002) or inhibiting ICAM-1 mRNA with antisense oligonucleotides (Vemuganti et al., 2004) improves outcome from experimental stroke. Similarly, mice deficient in ICAM-1 had smaller infarcts compared to wildtype mice (Connolly et al., 1996; Kitagawa et al., 1998). Not only inhibitors of ICAM-1 but also nitric oxide donors prevented the ischemia/reperfusion (I/R)-induced increase in ICAM-1 mRNA after ischemia/reperfusion and also led to neuroprotection (Khan et al., 2006). In diabetic rats, ICAM-1 expression was higher after ischemia compared to non-diabetic rats, suggesting that ICAM-1 may, in part, explain why stroke is exacerbated under conditions of hyperglycemia (Ding et al., 2005).

The role of VCAM-1 in stroke is less clear. While increases in VCAM-1 mRNA after cerebral ischemia have been observed (Blann et al., 1999), others have failed to observe such significant changes (Vemuganti et al., 2004). In a study of global cerebral ischemia in rats, ONO-1078, a

potent leukotriene receptor antagonist, improved neurological deficits and reduced neuron death by inhibiting the ischemia-induced upregulation of VCAM-1 in the hippocampus of ischemic rats (Zhang and Wei, 2003). One study showed that unfractionated heparin led to reduced infarct size in experimental stroke, and was associated with a reduced inflammatory response including decreased VCAM-1 expression (Cervera et al., 2004). However, another study showed that treatment with anti-VCAM-1 antibodies did not have any effect on stroke outcome suggesting that VCAM-1 may not play a significant role in ischemic brain injury (Justicia et al., 2006).

At the clinical level, increased sICAM-1 and sVCAM-1 have been documented in the plasma and cerebral spinal fluid of subjects with recent cerebral ischemic patients, and correlated to stroke severity (Ehrensperger et al., 2005; Selakovic et al., 2003; Simundic et al., 2004). VCAM-1 expression has been observed in autopsied brains of stroke victims within cerebral vessels and astrocytes (Blann et al., 1999). However, a phase III clinical trial of anti-ICAM therapy for stroke, indicated that anti-ICAM therapy with enlimomab was not an effective treatment for ischemic stroke. In fact, treatment significantly worsened outcome(Enlimomab, 2001). However, the interpretation of this study may have been confounded by the use of a murine antibody in humans, with subsequent neutrophil and complement activation (Vuorte et al., 1999).

3.3. Integrins

As a family of adhesion molecules, integrins consist of a common β subunit and a variable α subunit (Albelda, 1991). There are three subfamilies for the β subunits, denoted β1–3. Members of the β1 subfamily bind collagen, laminin and fibronectin and are involved in the structure of the extracellular matrix, whereas β2 integrins (CD18) are involved in leukocyte cell adhesion. β3 integrins, also known as the cytoadhesins, include the platelet glycoprotein IIb/IIIa (αIIb/β3) and the vitronectin receptor (αv/β3), factors involved in clot generation and stabilization.

Leukocyte integrins, the transmembrane cell surface proteins, are activated by chemokines, cytokines, and other chemoattractants. In order for leukocytes to bind to activated endothelium, integrins must be expressed on the cell surface so as to recognize endothelial cell adhesion molecules (Smith, 1993). Binding to receptors of the immunoglobulin gene superfamily, β2 integrins contain a common β2 chain with one of 3 distinct α chains (CD11a, CD11b, or CD11c). The CD11a/CD18 integrin is referred as LFA-1, whereas CD11b/CD18 is also called Mac-1. Of the α chains, CD11b has been the most studied in stroke models. Leukocytes and monocytes also express the α4β1 (very late antigen-4, VLA-4, CD49d) integrin, which binds to VCAM-1 and ligands of the subendothelial matrix (Frijns and Kappelle, 2002).

In an in vitro study, hypoxia caused an increase of neutrophil CD11b expression compared to normoxia, and this injury was protected by aprotinin by reducing the upregulation of neutrophil CD11b (Harmon et al., 2004). Treatment with 3-aminobenzamide (3-AB), a PARP inhibitor, appeared to protect by reducing expression of CD11b and other pro-inflammatory molecules (Koh et al., 2004).

Blocking CD11b (Chen et al., 1994) as well as CD18 (Bowes et al., 1995) or both (Jiang et al., 1995; Yenari et al., 1998) reduces injury from experimental stroke and is associated with decreased neutrophil infiltration. Similarly, mice lacking CD18 exhibited reduced leukocyte adhesion to endothelial cell monolayers, and improved cerebral blood flow and less neurological injury and neutrophil accumulation when subjected to experimental stroke (Prestigiacomo et al., 1999). Blocking integrins essential for lymphocyte and monocyte trafficking may also limit damage due to reperfusion injury. Antibodies against VLA-4 given 2 h after a 3 h period of temporary MCAO followed by reperfusion decreased infarct size (Becker et al., 2001).

To date, few clinical studies examined the potential of anti-integrin therapies in acute stroke patients. In one study, a humanized CD11/CD18 antibody (LeukArrest) was given to patients within 12 h symptom onset (Becker, 2002). Another trial was a phase IIb dose escalation study of a non-antibody peptide, recombinant neutrophil inhibiting factor (rNIF) in stroke patients (Acute Stroke Therapy by Inhibition of Neutrophils or ASTIN) administered within 6 h of symptom onset (Krams et al., 2003). Both studies were terminated prematurely due to a lack of effect on predetermined endpoints. Although both compounds appeared to be effective in rodent stroke models (Jiang et al., 1995; Yenari et al., 1998), lack of an obvious effect in humans could be due to study design not in line with laboratory data (such as late treatment or lack of documented reperfusion in humans) or the inherent heterogeneity of clinical stroke. Another possibility is that changes in neutrophil integrins are different in acute ischemic stroke patients compared to rodents. For example, CD11b is actually decreased in human stroke (Caimi et al., 2001), but increased after experimental stroke in rats (Campanella et al., 2002). Therefore, some anti-adhesion approaches may not be appropriate in humans. Regardless, it is clear that more work and possibly improved trial design are needed.

4. INFLAMMATORY MEDIATORS

4.1. Cytokines

Cytokines are upregulated in the brain after a variety of insults including stroke, and are expressed not only in cells of the immune system, but production by resident brain cells, including glia and neurons, have been observed (Liu et al., 1994; Sairanen et al., 2001). The most studied cytokines related to inflammation in stroke are interleukin-1 (IL-1), TNF-α, interleukin-6 (IL-6), interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) (Han and Yenari, 2003). Among those cytokines, IL-1 and TNF-α appear to exacerbate cerebral injury; however, IL-6, IL-10 and TGF-β may be neuroprotective (Allan and Rothwell, 2001).

IL-1—IL-1's two isoforms, IL-1α and IL-1β and its endogenous inhibitor, IL-1 receptor antagonist (IL-1ra) have been the most studied in experimental stroke. IL-1beta mRNA elevations have been documented within 15–30 min after ischemia (Buttini et al., 1994) with increased protein a few hours later (Davies et al., 1999). Follwoing 20 min transient global cerebral ischemia in rats followed, IL-1beta mRNA and protein expression were increased not only during early reperfusion (1 h), but also at later times (6–24 h) indicating biphasic expression (Haqqani et al., 2005). Consistent with a potential damaging effect, increased brain damage occurred when IL-1beta was administered to rats (Yamasaki et al., 1995), and mice deficient in IL-1 had smaller infarcts compared to wildtype. Overexpression or treatment with IL-1ra reduced infarct size (Mulcahy et al., 2003; Yang et al., 1997), while IL-1ra deficient mice exhibited a dramatic increase in ischemic damage (Pinteaux et al., 2006). Moreover, basal and NMDA- or AMPA-induced cells death was significantly higher in glial-neuronal co-cultures from IL-1ra KO than from WT mice, strongly suggesting that endogenous IL-1ra produced by microglia is neuroprotective in cerebral ischemia. IL-1 has two receptors, IL-1R1 and IL-1R2, but only the former is involved in signal transduction (Rothwell and Luheshi, 2000). Inactivating or knocking out the IL-1R1 decreased the extent of damage caused by a hypoxic-ischemic (H/I) insult and preservea neurological function (Basu et al., 2005).

TNF-α—TNF-α is also upregulated in the brain after ischemia with similar expression patterns as IL-1beta. Initial increases are seen 1–3 h after ischemia onset (Liu et al., 1994), and, like IL-1beta, has a biphasic pattern of expression with a second peak at 24–36 h (Murakami et al., 2005; Offner et al., 2006). TNF-α expression was initially observed in neurons (Liu et al., 1994), then later in microglia and some astrocytes (Uno et al., 1997) as well as in the peripheral immune system (Offner et al., 2006). TNF-α appears to have pleiotropic functions in the ischemic brain (Hallenbeck, 2002). Inhibition of TNF-α reduces ischemic brain injury (Yang

et al., 1998), while administration of recombinant TNF-α protein after stroke onset worsens ischemic brain damage (Barone et al., 1997). However, TNF-α may also protect the brain under certain circumstances. TNF-α appears to be involved in the phenomenon of ischemic tolerance (Ginis et al., 2002), and mice deficient in TNF receptors have larger infarcts ((Bruce et al., 1996). The reasons for this disparity might be due to different pathways through which TNF-α signals. There are at least two TNF-α receptors: TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2). Most effects induced by TNF-α are mediated by TNFR1, which contains a death domain (DD) that interacts directly with TNFR1 and may act as a bifurcation point for signaling related to cell death or cell survival. Ischemic preconditioning caused upregulation of neuronal TNFR1, and intracerebral administration of TNFR1 antisense oligodeoxynucleotide, which caused a reduction in TNFR1 expression, inhibited the ischemic preconditioning-induced protective effect, suggesting that TNFR1 upregulation is implicated in ischemic tolerance (Pradillo et al., 2005). Increased expression of TNFR1 mRNA in the ipsilateral cortex was noted slightly during ischemia and was significantly increased at 12 h after reperfusion in tMCAO (Yin et al., 2004). A clinical study also showed that TNFR1 concentration increased in patients with acute ischemic stroke (Fassbender et al., 1997). By signaling through the Fas-associated death domain (FADD) and caspase-8, TNF- α may lead to apoptosis, whereas reacting with TNF-receptor associating factor 2 and receptor-interacting protein may lead to anti-inflammatory and anti-apoptotic functions (reviewed by (Hallenbeck, 2002). Whether and how this applies in brain ischemia has yet to be clearly elucidated.

Other inflammation related cytokines—IL-6 is largely thought of as a pro-inflammatory cytokine, but whether it plays a significant role in ischemic stroke is far from clear. IL-6 deficient mice have similar sized infarcts compared to wildtype suggesting that it does not participate in ischemic pathogenesis (Clark et al., 2000). However, other studies suggest either a beneficial (Herrmann et al., 2003) or detrimental role (Smith et al., 2004). Clinical studies in stroke patients showed that serum concentrations of IL-6 had the strongest independent predictive value for in-hospital mortality (Rallidis et al., 2005). In a double blind clinical trial on patients with acute stroke, IL-6 concentration was much lower in rhIL-1ra, a neuroprotective drug, treated patients, who showed a better outcome compared with placebo treated group (Emsley et al., 2005).

IL-10, an anti-inflammatory cytokine, acts by inhibiting IL-1 and TNF-α and also by suppressing cytokine receptor expression and receptor activation. It is synthesized in the central nervous system (CNS) and is upregulated in experimental stroke (Strle et al., 2001). Both exogenous administration (Spera et al., 1998) and gene transfer of IL-10 (Ooboshi et al., 2005) in cerebral ischemia models appear to have beneficial effects. Patients with acute ischemic stroke have an elevated numbers of peripheral blood mononuclear cells secreting IL-10 (Pelidou et al., 1999) and elevated concentrations in cerebrospinal fluid (Tarkowski et al., 1997). Furthermore, subjects with low IL-10 levels have an increased risk of stroke (van Exel et al., 2002).

Expression of TGF-β1 has been reported in microglia and astrocytes, with low levels in neurons (Flanders et al., 1998). Overexpression of TGF-β1 using an adenoviral vector protected mouse brains from ischemic stroke and reduced the accompanying inflammatory response (Pang et al., 2001). A recent study showed that cultured neurons may be protected from ischemia-like insults by microglia-secreted TGF-β1 (Lu et al., 2005). Because TGF-β exhibits prominently in the recovery phase of some CNS diseases, it is proposed that TGF-β may contribute to the recovery of ischemic stroke (Benveniste, 1998).

4.2. Chemokines

Chemokines are a family of regulatory polypeptides with roles in cellular communication and inflammatory cell recruitment in host defense, such as regulating the migration of leukocytes in inflammatory and immune responses. Expression of chemokines following focal ischemia is thought to have a deleterious role by increasing leukocyte infiltration (Emsley and Tyrrell, 2002). Based on the positions of cysteine residues (C), chemokines can be divided into four groups: C, CC, CXC, and CX3C, with which chemokines act through specific and shared receptors belonging to the superfamily of G-protein-coupled receptors (Bajetto et al., 2001). Increasing data showed that a variety of chemokines such as monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α) are induced in the animal models of focal cerebral ischemia (Chen et al., 2003a). Consistent with a deleterious role, their inhibition or deficiency is associated with reduced injury (Garau et al., 2005), whereas (Chen et al., 2003a) found that over-expression of MCP-1 in the brain obviously exacerbated ischemic injury, which is correlated with recruitment of inflammatory cells.

Fractalkine, a neuronally expressed chemokine, acts through its G-protein-coupled receptor CX3C. Following ischemia, its expression has been localized to viable neurons in the infarct periphery as well as some endothelial cells. Interestingly, expression of its receptor, CX3CR1 was observed only on microglia/macrophages suggesting that fractalkine is involved in neuron-microglial signaling (Tarozzo et al., 2002). Furthermore, fractalkine deficient mice have smaller infarct sizes and lower mortality after transient focal cerebral ischemia, suggesting that fractalkine somehow exacerbates cell death (Soriano et al., 2002).

In addition to chemotactic properties, chemokines were found to directly affect BBB permeability. The addition of MCP-1 enhanced 17-fold the permeability of an in vitro BBB (cocultures of endothelial cells and astrocytes) model and caused alterations in tight junction (TJ) proteins, suggesting that MCP-1 may play a role in ‘opening’ the BBB (Stamatovic et al., 2005).

With recent interest in the area of cell based therapy for stroke, chemokines may also play an important role in honing stem cells to regions of injury (Newman et al., 2005). MCP-1 and SDF-1 and/or their receptors have been observed at the interface of ischemic tissue and cell transplants (Kelly et al., 2004). MCP-1 and other chemokines seem to be involved in marrow derived stromal cell migration into ischemic brain (Wang et al., 2002a; Wang et al., 2002b). Manipulation of these signals may be important in the successful application of such therapies.

4.3. Arachidonic Acid metabolites

Downstream of immune cell activation, the arachidonic acid (AA) cascade is initiated via the release of phospholipase A_2 (PLA_2) (Stanimirovic and Satoh, 2000). Energy failure due to cessation of blood flow can result in calcium accumulation in brain cells. This high concentration calcium activates PLA_2 which hydrolyses glycerophospholipids to release AA. Following transient MCAO, PLA_2 activity significantly increased (Adibhatla et al., 2006). As potent mediators, AA metabolites contribute to post-ischemic brain inflammation and circulatory disorders (Sanchez-Moreno et al., 2004). Consistent with a damaging role of this pathway, PLA_2 deficient mice had smaller infarcts and developed less brain edema with fewer neurological deficits than their wild type littermates (Bonventre et al., 1997). AA is metabolized through two different pathways via cyclooxygenase (COX) or lipoxygenase (LOX). (Figure 2).

4.3.1 Cyclooxygenase pathway—Arachidonic acid released from brain phospholipids during ischemia/reperfusion is converted to prostaglandin H_2 (PGH_2) by cyclooxygenase (COX). There are two isoforms of COX. COX-1 is constitutively expressed in many cells types,

including microglia and leukocytes during brain injury (Schwab et al., 2002). COX-1 deficient mice have increased vulnerability to brain ischemia, and would support a protective role possibly due to an effect on maintaining cerebral blood flow (Iadecola et al., 2001b). However, conflicting data exist. In transient global cerebral ischemia, pharmacologic inhibition of COX-1 with valeryl salicylate increased the number of healthy neurons in the hippocampal CA1 (Candelario-Jalil et al., 2003). These discrepancies may be due to differences in the immune responses between focal and global cerebral ischemia models.

COX-2, a rate-limiting enzyme for prostanoid synthesis, is upreglated and present at border of the ischemic territory following ischemia (Nogawa et al., 1997). In postmortem specimens of ischemic stroke patients, COX-2 is upregulated not only in regions of ischemic injury (Iadecola et al., 1999), but also regions remote from the infarct area (Sairanen et al., 1998). The roles of various COX metabolites are protean, but accumulated data suggest that those downstream of COX-2 are likely deleterious. Recent work has shown that prostaglandin E (2) EP1 receptors may be the downstream effectors responsible for neurotoxicity in ischemic stroke (Kawano et al., 2006). Several studies have now shown that treatment with COX-2 inhibitors improve neurological outcome after stroke (Nogawa et al., 1997; Sugimoto and Iadecola, 2003). Furthermore, COX-2 deficient mice have reduced injury after N-methyl-D-aspartate (NMDA) exposure (Iadecola et al., 2001a), whereas COX-2 overexpression exacerbates brain injury (Dore et al., 2003). Interestingly, COX-2 mediates its toxic effect through PGE_2 rather than ROS, even though COX-2 can generate both (Manabe et al., 2004).

4.3.2 5-Lipoxygenase pathway—Compared to the COX pathway, there is limited knowledge about the role of the lipoxygenase pathway in brain ischemia. AA can be converted to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) by 5-lipoxygenase (5-LOX) which is metabolized to leukotriene A4 (LTA4), a precursor of cysteinyl leukotrienes (cysLTs). LTC4 is a potent chemoattractant that has been implicated in the BBB dysfunction, edema and neuronal death after ischemia/reperfusion. During brain ischemia/reperfusion, biphasic AA and LTC4 elevations have been documented and appear to correspond to biphasic patterns of BBB disruption (Rao et al., 1999). 5-LOX has also been documented in autopsied ischemic human brains, with 5-LOX localizing to perivascular monocytes (Tomimoto et al., 2002). Pretreatment with a 5-LOX inhibitor, AA861 resulted in significant attenuation of LTC4 levels and reduction in brain edema and cell death (Baskaya et al., 1996). Furthermore, OGD-induced PC12 cell death was attenuated by 5-LOX inhibitor caffeic acid (Song et al., 2004). However, 5-LOX deficient mice had similar infarct sizes 6 days after both permanent and transient MCAO to wild type mice (Kitagawa et al., 2004). These conflicting observations may reflect the different times when assessments were made, but clearly, more work is needed in this area.

4.4. Nitric Oxide/Nitric Oxide Synthase

Nitric oxide (NO) is an important signaling molecule involved in physiological processes such as neuronal communication, host defense, and regulation of vascular tone. This relatively stable gas readily diffuses into cells and cell membranes where it reacts with molecular targets. Three nitric oxide synthases (NOS) isoforms exist; endothelial NOS (also known as type III, NOS-III and NOS-3), neuronal NOS (also known as type I, NOS-I and NOS-1), and inducible NOS (also known as type II, NOS-II and NOS-2). Among these three isoforms, iNOS is especially relevant to inflammatory cells and may contribute to ischemic injury via NO. In fact, iNOS expression is thought to be restricted to cells involved in inflammatory responses such circulating leukocytes, microglia and astrocytes. In the brain, ischemia-induced upregulation of iNOS mRNA and protein is associated with increases in iNOS enzymatic activity and NO production (Iadecola et al., 1995a; Iadecola et al., 1995b). NO may cause DNA damage in cerebral ischemia through the formation of peroxynitrite (Cui et al., 2000; Cui et al., 1999; Huang et al., 2000a). Pharmacological inhibition of iNOS reduces infarct volume by about

30% (Iadecola et al., 1995b), and iNOS-null mice have smaller infarcts and better neurologic outcomes than wild-type control animals (Zhao et al., 2000). Consistent with a damaging role, protection by hypothermia is associated with reduced microglial generation of both NO and iNOS (Han et al., 2002), and ischemic brain protection by estrogen and progesterone appears to be through modulating postischemic iNOS expression (Coughlan et al., 2005; Park et al., 2006)

4.5. Reactive Oxygen Species

Generation of reactive oxygen species (ROS) by inflammatory cells occurs via several enzyme systems. Superoxide is generated via COX, xanthine dehydrogenase, xanthine oxidase and NADPH oxidase, whereas myeloperoxidase (MPO) and monoamine oxidase (MAO) generate hypochlorous acid and H_2O_2. Among all the oxidants in the brain parenchyma after MCAO, superoxide anion is a major one, causing direct injury to ischemic brain or by reacting with NO to generate peroxynitrite (Chan, 2001).

NADPH oxidase (NOX) is a multicomponent enzyme that consists of two membrane bound subunits, gp91 and p22, and three cytosolic subunits, p67, p47 and p40 plus Rac, a small GTPase (Groemping and Rittinger, 2005). Other NOX isoforms have been recently characterized, but for the scope of this review, we will focus on the most studied NOX, NOX2 (phagocytic NOX) (Lambeth, 2004). With appropriate stimuli, the cytosolic subunits translocate to the membrane where they interact with the membrane bound subunits to transfer electrons from NADPH to oxygen to form superoxide. Largely thought to be exclusively produced by cells of the immune system, it is a major and significant source of inflammatory cell generated superoxide. Prior work has shown that mice deficient in the gp91 subunit of NOX2 have smaller infarcts than wild type mice (Walder et al., 1997). Recent work has shown that microglia potentiate injury to the blood brain barrier due to superoxide produced by NOX2 in brain ischemia models (Yenari et al., 2006).

Myeloperoxidase (MPO), an enzyme in leukocytes such as neutrophils and monocytes, is linked to inflammation, and is thought to mediate bactericidal killing through H_2O_2 and hypochlorous acid. MPO activity is normally used as a marker of polymorphonuclear neutrophil infiltration, and its upregulation in blood may predict the early risk of infarction. MPO has been documented in both permanent and transient MCAO (Garau et al., 2005). However, after focal cerebral ischemia, infarct size was increased in MPO deficient mice (Takizawa et al., 2002), suggesting a beneficial role. MPO deficient mice also had increased products of nitrosylation within the ischemic brain and suggested that MPO‘s protective effect may be due to its ability to scavenge nitrotyrosine (a by product of peroxynitrite reactions) in the presence of glutathione (Takizawa et al., 2002). Therefore, it is possible that MPO may actually limit the extent of ROS-mediated tissue injury.

4.6. Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are proteases that can break down extracellular proteins, such as collagen, and are involved in extracellular matrix remodeling as well as the neuroinflammatory response. Follwoing tPA treatedment, components of the BBB were disrupted following MMP-9 activation (Kelly et al., 2006). MMPs are normally found in the cytosol in a pro- or inactivated state, but are cleaved by proteases such as plasmin or other MMPs to their active state (Rosenberg, 2002). As a major source of the MMPs following ischemia, microglia are also necessary to stimulate astrocytes to generate active MMPs (Rosenberg et al., 2001).

In experimental stroke models, MMP inhibition reduces infarct size, brain edema and hemorrhage (Pfefferkorn and Rosenberg, 2003). Mice deficient in MMP-9 had smaller infarcts

compared to wildtype controls (Asahi et al., 2000); however, such an effect was not observed in MMP-2 deficient mice (Asahi et al., 2001), suggesting that MMP-9 appears to play a more significant role in stroke compared to MMP-2. Peripheral inflammatory cell, rather than brain derived MMP-9 may contribute significantly to ischemic brain injury as mice transplanted with bone marrow from MMP-9 deficient mice suffer less injury and less BBB disruption than mice transplanted with marrow containing intact MMP-9 (Gidday et al., 2005). Current work also showed that MMPs may be involved in endogenous mechanisms of neurogenic migration because a broad spectrum MMP inhibitor GM6001 was found to significantly decrease the migration of doublecortin-positive cells that extend from the SVZ into the striatum in transient focal cerebral ischemia in mice (Lee et al., 2006).

Interestingly, MMPs seem to play a different role in the later phases of cerebral ischemia, and may participate in plasticity and recovery. For instance, MMPs are known to associate with factors involved in angiogenesis such as vascular endothelial growth factor (VEGF). In one study, treatment with the MMP inhibitor FN-439 7 d post MCAO suppressed neurovascular remodeling, increased ischemic brain injury and impaired functional recovery at 14 days. This was also associated with reduced VEGF signaling resulting from MMP inhibition (Zhao et al., 2006).

5. TRANSCRIPTIONAL REGULATION OF INFLAMMATION

It is now well recognized that cerebral ischemia upregulates gene expression. Activation of several transcription factors has been documented in experimental stroke models. Some of these transcription factors are particularly involved in the inflammatory response, and will be discussed here.

5.1. Nuclear factor κB (NF-κB)

NF-κB, involved in the regulation of inflammation (Baeuerle and Henkel, 1994), is a dimeric transcription factor consisting of subunits of the Rel family, which includes five Rel forms: Rel (cRel), RelA (p65), RelB, NF-κB1 (p50 and its precursor p105) and NF-κB. The most common form of NF-κB is a heterodimer composed of Rel A (p65) and p50. NF-κB is normally located in the cytoplasm bound to its endogenous inhibitor protein, known as IκB, a family of proteins consisting of IκB-α, IκB-β, IκB-γ and IκB-ε. Phosphorylation of IκB-α at serines 32 and 36 by an upstream IκB kinase (IKK) leads to IκB phosphorylation, ubiquitination and degradation in the 26S proteasome. This liberates NF-κB and allows it to translocate to the nucleus, and bind to κB sites, specific domains within the promoters of downstream genes to activate their transcription. Many genes involved in inflammation contain functional κB sites, such as tumor necrosis factor-α (TNF-α), intercellular adhesion molecule-1 (ICAM-1), cyclooxygenase-2 (COX-2), iNOS and interleukin-6 (IL-6). Han et al., (Han et al., 2002) found that IKK and NF-κB activation were correlated to the anti-inflammatory effect of mild hypothermia following experimental stroke. However, the function of NF-κB in stroke is still controversial (Cechetto, 2001). Mice deficient in NF-κB's p50 subunit are protected from experimental stroke (Schneider et al., 1999), consistent with a death-promoting role of NF-κB in focal ischemia. Similar observations were made by inhibiting activation of NF-κB with the treatment of S-nitrosoglutathione (GSNO), an NO modulator (Khan et al., 2005). After deleting IkappaB kinase complex IKK, the central component of NF-kappaB activation, inhibition of IKK activity markedly reduced infarct size in a mouse model of stroke (Herrmann et al., 2005). In contrast, constitutive activation of IKK2 enlarged the infarct size (Herrmann et al., 2005). In global ischemia, neuronal damage was significantly attenuated by employing the nuclear factor-kappa B decoy oligodeoxynucleotides into rat brain neurons through the carotid artery (Ueno et al., 2001). However, rats given diethyldithiocarbamate (DDTC), a NF-κB inhibitor, had enhanced neuronal DNA fragmentation and larger infarct sizes compared to

controls, suggesting a beneficial role (Hill et al., 2001), and. The reasons for these discrepancies are not clear, but could be due to the cell type in which NFkB is activated, the experimental model studied, or a lack of specificity of pharmacological inhibitors.

5.2. Mitogen-activated protein kinase (MAPK)

Mitogen-activated protein kinases play an important role in transducing stress-related signals by a cascade of intracellular kinase phosphorylation and transcription factor activation that regulate inflammatory gene production among other functions (For reviews, see (Barone and Feuerstein, 1999); (Irving and Bamford, 2002)). During cerebral ischemia, three interlinked signaling pathways have been documented: the stress-activated protein kinases/c-Jun N-terminal kinases (SAPK/JNK), the p38 MAPKs and extracellular signal-regulated kinases (ERKs) (Irving and Bamford, 2002; Irving et al., 2000; Sugino et al., 2000). p38 MAPK promotes the stabilization and enhanced translation of mRNAs encoding proinflammatory proteins (Kyriakis and Avruch, 2001). In forebrain ischemia, MLK3-MKK4-JNK activation was rapidly increased with peaks both at 30 min and 3 days of reperfusion (Zhang et al., 2005b). Intracerebroventricular infusion of POSH (plenty of SH3s) antisense oligodeoxynucleotides (AS-ODNs) not only significantly decreased POSH interactions with MLK3, MKK4 and phospho-JNKs, but also attenuated the activation of the JNK signalling pathway as well as significantly increased the neuronal density in the CA1 region. This type of protective effect of POSH AS-ODNs on ischemic injury might be through a mechanism of inhibition of the MLK3-MKK4-JNK signalling pathway and c-Jun activation, which strongly suggests the involvement of MAPK. After inducing ischemia in vitro with an anaerobic chamber, introduction of bone marrow stromal cells activated mitogen-activated protein kinase, subsequently exerted protection to post-ischmic injury (Gao et al., 2005). In permanent MCAO, CDP-choline, a major neuronal membrane lipid precursor, showed a key role in recovery after ischaemic stroke by a notable reduction in the phosphorylation of MAP-kinase family members, ERK1/2 and MEK1/2, as well as Elk-1 transcription factor. Following forebrain ischemia in rodents, phosphorylated p38 MAPK was detected in the hippocampus within neuron- (Sugino et al., 2000) and microglia-like (Walton et al., 1998) cells, suggesting its role in the endogenous inflammatory response. Furthermore, p38 MAPK inhibitors have been shown to reduce brain injury and neurological deficits in focal cerebral ischemia as well as ischemia-induced cytokine expression (Barone and Feuerstein, 1999).

5.3. Activator Protein-1 (AP-1)

AP-1 is a heterodimer comprised of bZIP transcription factors (e.g., c-Jun and JunD), activating transcription factor 2 (ATF2) and c-*Fos*. Upstream activation of AP-1 components is mediated through the JNK/SAPK cascade. c-*Fos* was found to be up regulated as early as 30 minutes after stroke onset (Lu et al., 2004). The Fos protein contains a DNA binding region and a leucine zipper. The leucine zipper forms an α-helix which can align with other proteins (such as Jun) containing like structures to form dimers. These dimers bind to specific DNA regions known as the AP-1 domain, which regulates the expression of a number of target genes (collectively referred to as late response genes). Combinations of *c-Fos* and *c-Jun* family proteins form different dimers consisting of various subunits depending on the circumstances. The composition of the dimer may determine whether the late response gene is turned on or off (Morgan and Curran, 1991). Inhibition of p38 MAP kinase resulted in the attenuation of c-fos and c-jun mRNA and AP-1 DNA binding by lipopolysaccharide (LPS) (Simi et al., 2000), and subsequently led to neuroprotection in cerebral ischemia. ATF2 is a member of the cAMP response element binding protein (CREB) subfamily of bZIP transcription factors. AP-1 heterodimers containing ATF transcription factors can bind both to the TPA (12-O-tetradecanoylphorbol-13-acetate) responsive element (TRE) and to the cAMP response element (CRE) (Karin et al., 1997). In human umbilical vein endothelial cells (HUVECs), a dose-dependent lowering of mRNA expression of VCAM-1 and ICAM-1 was observed by

inhibiting AP-1 DNA binding activities (Zhou et al., 2005). Recent evidence also showed that selective induction of DeltaFosB, an AP-1 (activator protein-1) subunit, can promote the proliferation of quiescent neuronal precursor cells, thus enhancing neurogenesis after transient forebrain ischemia (Kurushima et al., 2005).

6. CONCLUSION

Inflammation is increasingly recognized to be the key element in pathological progression of ischemic stroke. Whether inflammation is destructive or beneficial may depend on how severe the ischemia is and the stages of ischemia in which inflammatory responses contribute. Likely, early inflammatory responses may potentiate ischemic injury, while late responses may be important in recovery and repair. Future work should address the optimal timing of inflammation modulating interventions as well as elucidating how the immune system moves from damaging to protective/restorative responses.

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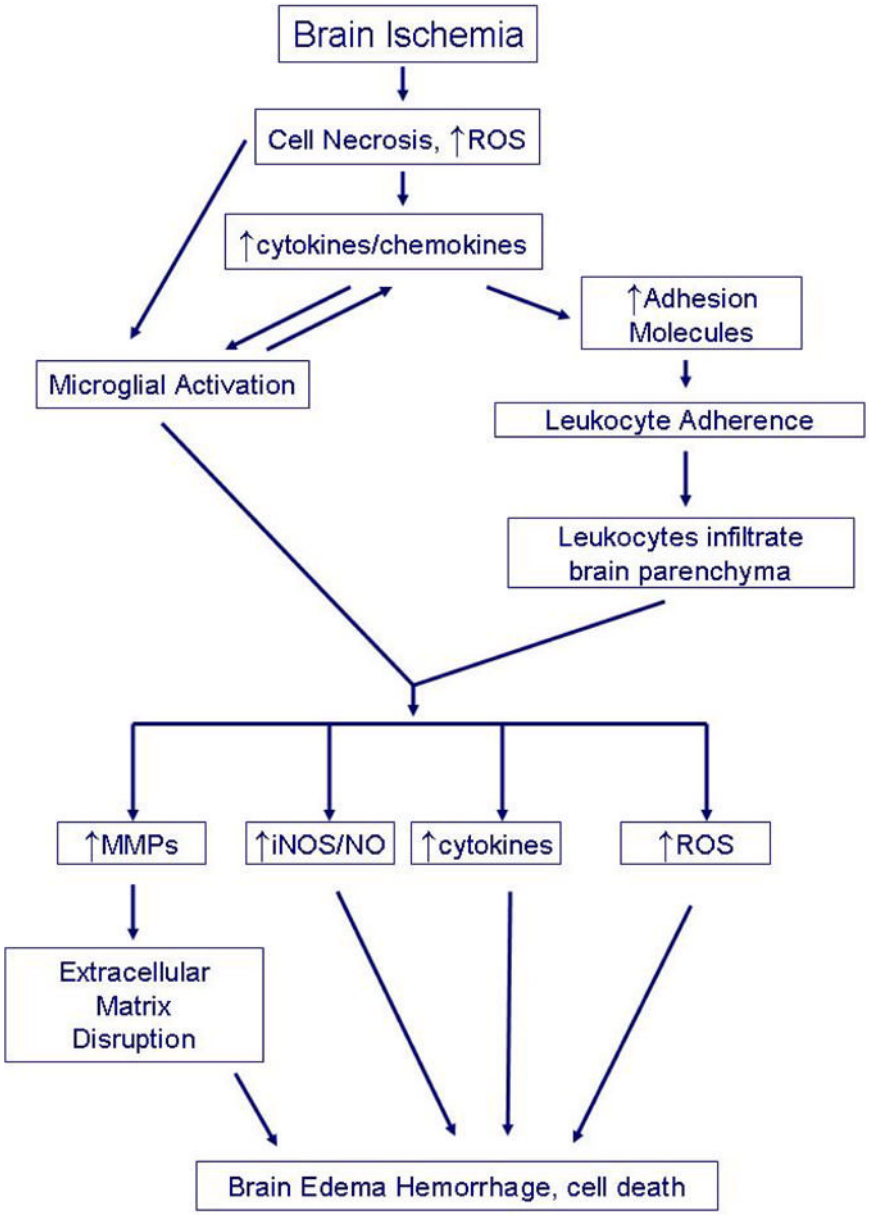

Figure 1. Inflammation following stroke

Brain ischemia is triggers inflammatory responses due to the presence of necrotic cells, generation of reactive oxygen species (ROS) and production of inflammatory cytokines even within neurons. These initiators lead to microglial activation which produce more cytokines causing upregulation of adhesion molecules in the cerebral vasculature. Chemokines lead to inflammatory cell chemotaxis to ischemic brain. Adhesion molecules mediate adhesion of circulating leukocytes to vascular endothelia and infiltration into the brain parenchyma. Once in the brain, activated leukocytes and microglia produce a variety of inflammatory mediators such as matrix metalloproteinases (MMPs), inducible nitric oxide synthase (iNOS) which generates nitric oxide (NO), cytokines and more ROS which lead to brain edema, hemorrhage and ultimately, cell death. MMPs are thought to mediate extracellular matrix disruption, a key event in brain edema and hemorrhage.

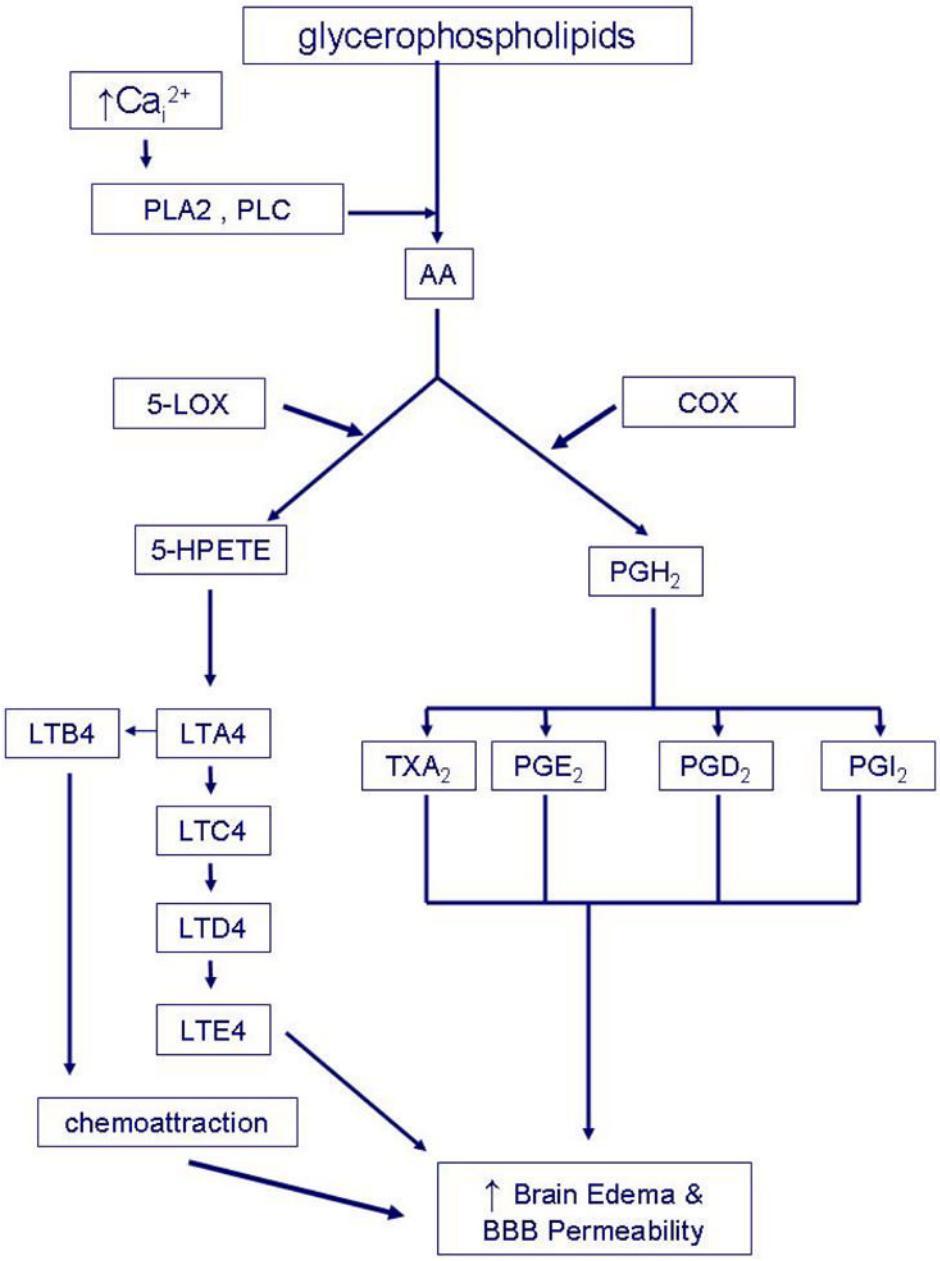

Figure 2. Ischemic activation of the arachidonic acid cascade

In the setting of cerebral ischemia, excess intracellular calcium (Ca_i^{2+}) activates various lipases, including phospholipase A2 (PLA2) and phospholipase C (PLC) which breakdown both intracellular and membrane phospholipids and release arachidonic acid (AA). Both the cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) pathways are activated. The COX pathway converts AA to prostaglandin H2 (PGH2), a precursor prostaglandin. PGH2 is then metabolized to various eicosanoids, including prostacyclin (PGI2), thromboxane A2 (TXA2), prostaglandin E2 and prostaglandin D2. Eicosanoid family members have been shown to exert potent effect on brain vasomotor regulation and increase microvascular and BBB permeability. In the brain, they can act as neutrophil chemoattractants. AA can be also converted to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) by LOX-5. 5-HPETE is then metabolized to leukotriene A4 (LTA4) and B4 (LTB4). LTA4 is a precursor of cysteinyl leukotrienes

(cysLTs). cysLTs are converted sequentially to leukotriene C4 (LTC4), leukotriene D4 (LTD4), leukotriene E4 (LTE4). Leukotrienes play multiple roles to mediate events such as chemoattraction, brain edema and BBB permeability.