SAH and inflammation: Inflammatory Mechanisms after SAH (EBI and or Vasospasm)

XINGANG SUN[1], IVAN STEVE GODJE GODJE[2], HUIYU HU[2], XUEHONG CHU[2], and LIJUAN ZHU[2]

[1]Shanxi Medical University Second Affiliated Hospital
[2]Shanxi Medical University

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Abstract

Despite breakthroughs in care and treatment, the consequences of a subarachnoid hemorrhage (SAH) are still associated with morbidity and mortality. Early brain injury is still a major source of clinical deterioration in people with SAH. When a patient suffers a SAH, they are more likely to develop long-term neurological problems, which can be life-threatening. According to recent research, the management and remission of SAH are dependent on inflammatory mechanisms. The development of problems after SAH has recently been linked to inflammation. Many investigations have failed to show how inflammatory mechanisms affect SAH patients' prognosis and outcome. SAH procedures and management will be improved by better understanding the various inflammatory pathways that occur after SAH. It was the goal of this review to outline some of the most important inflammatory pathways that emerge after SAH and to provide a general understanding of SAH.

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First author: XIN-GANG SUN

Corresponding Author: XIN-GANG SUN

Department of Neurology, the Second Affiliated Hospital of Shanxi Medical University, Taiyuan, CHINA

Order of Authors:

IVAN STEVE GODJE GODJE

HUI-YU HU

XUE-HONG CHU

LI-JUAN JU

ABSTRACT

Despite breakthroughs in care and treatment, the consequences of a subarachnoid hemorrhage (SAH) are still associated with morbidity and mortality. Early brain injury is still a major source of clinical deterioration in people with SAH.

When a patient suffers a SAH, they are more likely to develop long-term neurological problems, which can be life-threatening. According to recent research, the management and remission of SAH are dependent on inflammatory mechanisms. The development of problems after SAH has recently been linked to inflammation. Many investigations have failed to show how inflammatory mechanisms affect SAH patients' prognosis and

outcome. SAH procedures and management will be improved by better understanding the various inflammatory pathways that occur after SAH. It was the goal of this review to outline some of the most important inflammatory pathways that emerge after SAH and to provide a general understanding of SAH.

Keywords : inflammation, EBI (early brain injury), cerebral vasospasm, subarachnoid hemorrhage, secondary brain injury.

INTRODUCTION : Acute subarachnoid hemorrhage (SAH) is a dangerous illness that affects many organ systems in addition to the brain (Cardentey-Pereda & Pérez-Falero, 2002).

Subarachnoid hemorrhage (SAH) accounts for around 5% of all strokes (Hong, Tosun, Kurland, Gerzanich, Schreibman & Simard, 2014), with more than 30% of patients dying as a result of the first or subsequent bleeding (Ostrowski, Colohan & Zhang, 2006). Brain injury that occurs immediately after bleeding is well understood and occurs as a result of a rise in intracranial pressure and a subsequent fall in cerebral perfusion. Brain injury that occurs later has a variety of causes and may necessitate a variety of treatment options because of the different time windows of varying duration (Schneider, Xu & Vajkoczy, 2018). The fact that some SAH patients improve while others continue to deteriorate after their initial spasm is also puzzling (Miller, Turan, Chau & Pradilla, 2014). Early brain injury (EBI) is primarily responsible for the poor outcome of subarachnoid hemorrhage (SAH), which is intimately linked to inflammation (Sun, Duan, Jing, Wang, Hou & Zhang, 2019). In individuals with subarachnoid hemorrhage (SAH), neuroinflammation is directly linked to functional prognosis. Microglia are myeloid cells that make up the CNS's innate immune system. In response to damage or disease processes in the CNS, they become highly engaged. The use of brain injury biomarkers could be useful not only for diagnosing and identifying intracranial lesions, but also for assessing severity, prognosis, and therapeutic efficacy (Mrozek, Dumurgier, Citerio, Mebazaa & Geeraerts, 2014).

SAH-related brain injury has been shown to be protected by inflammation as a defensive mechanism. In the event of a stroke, blood components such as red blood cells (RBCs), leukocytes (including macrophages), and plasma proteins (including Endothelin-1) enter the brain instantly. There is an inflammatory response as soon as there is blood present in the parenchyma. Inflammatory cells are mobilized and activated during this time period. The early inflammatory cells in reaction to the extravascular blood component are believed to be microglia and astrocytes.

Inflammatory mechanisms following SAH :

Following SAH, researchers began to look for probable links between cerebral vasospasm and inflammatory alterations in the CSF, because at the time, this condition was considered to be the primary, if not the only, cause of secondary brain injury. SAH-related secondary brain injury can result from a variety of factors, including traumatic brain injury (TBI) and SAH. It has been established in both human and animal research that inflammatory processes can occur in the central nervous system in conjunction with, contribute to, or even initiate programmed cell death (Minami, Tani, Maeda, Yamaura & Fukami, 1992). The first findings on systemic inflammation appeared around the end of the 1990s and the beginning of the 2000s, and they outlined a peripheral immune modulation after SAH (Yoshimoto, Tanaka & Hoya, 2001)

Inflammation was merely accounted to occur alongside, or aggravate cerebral vasospasm, rather than being comprehended as an unique pathomechanism, when cerebral vasospasm was thought to be the only-or at least biggest-contributor to subsequent brain injury following SAH (Schneider, Xu & Vajkoczy, 2018). With more recent studies, it is believed that not only cerebral vasospasm is a main interest when talking about secondary brain injury but also, early brain injury is an important condition. Around this same time, in early 2000, many mechanisms were studied to show effects of many substances on SAH (Fassbender et al., 2000).

Although cellular components reach the subarachnoid region from within the blood arteries, both cellular and molecular factors operate on the vascular walls, raising the question of whether CSF inflammation is an outside-in or inside-out event (Schneider, Xu & Vajkoczy, 2018).

Endothelium pathways

Serotonin:

Numerous studies have shown that serotonin (5-hydroxytryptamine, 5-HT) generated by active platelets and neurons causes cerebral vasospasm in patients with SAH (Heros & Zervas, 1983; Khey, Huard & Mahmoud, 2020). SAH patients' cerebrospinal fluid has been shown to cause considerable constriction of isolated arteries, which may be prevented by the 5-HT antagonist ketanserin. Additionally, tests of cerebral fluid demonstrated elevated 5-HT levels during the acute, but not chronic, spasm phase of SAH, while sustained exposure of arteries to 5-HT results in desensitization (Szabò, Emilsson, Hardebo, Nystedt & Owman, 1992). Additionally, it has been claimed that SAH may result in a boost of the expression of 5-HT receptors (Ansar, Vikman, Nielsen & Edvinsson, 2007; Hansen-Schwartz, 2004; Hansen-Schwartz, Hoel, Xu, Svendgaard & Edvinsson, 2003) . Additionally, it was suggested that activating 5-HT1B receptors activates the PLA2 (phospholipase A2) enzyme. The eicosanoid 20-HETE is then synthesized via PLA2 and works to amplify vasoconstriction (Cambj-Sapunar, Yu, Harder & Roman, 2003) . Several studies have shown that 5-HT receptors like 5-HT1B and 5-HT2A are up-regulated after SAH, possibly via the MAPK-ERK1/2 pathway, hinting that 5-HT receptors may be responsible for excessive vasoconstriction (Ansar & Edvinsson, 2008; Ansar & Edvinsson, 2009; Ansar, Svendgaard & Edvinsson, 2007) . More than a few studies have shown that inhibiting 5-HT or degenerating axons that contain 5HT do not relieve experimentally induced vasospastic rats (Khey, Huard & Mahmoud, 2020). The authors concluded that the disparity may be explained by the cerebral arteries receiving insufficient 5-HT antagonist and 5-HT.

Thrombin and Endothelin-1:

Thrombin:

Vasospasm may be caused in part by thrombin, according to some research (Zhang et al., 2001). Serine protease thrombin helps the coagulation process by degrading fibrinogen and generating fibrin. Before, Argatroban was discovered to improve neurological outcomes by reducing BBB rupture and brain edema, as well as having anti-cell death and anti-inflammatory effects that correspond to early brain injury after SAH (Sugawara, Jadhav, Ayer, Chen, Suzuki & Zhang, 2009). The discovery that thrombin has a role in a wide range of CNS pathologies suggests a therapeutic breakthrough (Krenzlin, Lorenz, Danckwardt, Kempski & Alessandri, 2016). Evidence from both in vivo and in vitro experiments showed that high levels of thrombin in the brain parenchyma can be harmful (Buisson, Nicole, Docagne, Sartelet, Mackenzie & Vivien, 1998; Jiang, Wu, Keep, Hua, Hoff & Xi, 2002; Lee, Drury, Vitarbo & Hoff, 1997; Vu, Hung, Wheaton & Coughlin, 1991; Xi, Keep, Hua, Xiang & Hoff, 1999). Thrombin, which also leads to ischemic brain injury, causes early brain edema after intracerebral hemorrhage (Lee, Drury, Vitarbo & Hoff, 1997; Vu, Hung, Wheaton & Coughlin, 1991). As a result, the role of thrombin activation in the pathophysiology of SAH is yet unknown.

Endothelin-1:

Endothelin is a long-acting, highly powerful vasoconstrictor found throughout the brain. Endothelin helps to the maintenance of CBF by working through its receptors, ETA and ETB, and is regarded as a major auto regulating peptide (Graves & Kreipke, 2015). ET-1 is a peptide that is generated and released by the vascular endothelium in response to substances like reactive oxygen species (ROS), cytokines, and thrombin. ET-1 is also known to be produced by leukocytes and macrophages (Fassbender et al., 2000). Although endothelin-1 is widely acknowledged as a strong vasoconstrictor, its precise role in autoregulation appears to be more elusive. Adults with elevated ET-1 levels in the CSF after TBI had poor clinical outcomes, including death, permanent vegetative state, or severe debility, according to data acquired by (Maier, Lehnert, Laurer & Marzi, 2007) Endothelin-1 has been associated to reduced CBF and poor prognosis post damage in several animal models of TBI. According to the findings of the following studies (Armstead & Kreipke, 2011; Beuth, Kasprzak, Kotschy, Woźniak, Kulwas & Sniegocki, 2001; Kreipke, Morgan, Roberts, Bagchi & Rafols, 2007; Lampl, Fleminger, Gilad, Galron, Sarova-Pinhas & Sokolovsky, 1997; Salonia et al., 2010; Sato & Noble, 1998), TBI disrupts autoregulatory systems by increasing endothelin-1-mediated vasoconstriction. Further studies revealed that, while the drug significantly reduced vasospasm, it did not result in significant improvements in the patient's condition, showing that vasospasm may not be the primary cause of poor

outcome after subarachnoid hemorrhage but early brain injury may also be a factor. To clarify the precise role of ET-1 in the development of EBI after SAH, more research is needed.

Platelet Activating Factor

Platelet activating factor is a protein present in a variety of cells throughout the body that participates in the activation of platelet, leukocyte, and PLA2, which results in inflammatory and thrombotic mechanisms. Many cell types produce platelet-activating factor (1-O-hexadecyl-2-acetyl-sn-glycero-3-phosphocholine [PAF]), a powerful lipid autocoid. When injected in vivo, PAF has a strong effect on brain arteries and metabolism. PAF has direct neuronal actions in vitro, such as suppression of acetylcholine release. Excessive PAF production has been demonstrated in pathogenic nervous system conditions such as neurotrauma and stroke (Yue & Feuerstein, 1994) . PAF synthesis and release may be enhanced in SAH as a result of activated immune cells and endothelial cells driven by thrombin and IL-1 (Khey, Huard & Mahmoud, 2020). PAF produces tissue edema by increasing vascular permeability in peripheral tissues, boosting platelet production of granule-based enzymes, and increasing superoxide and arachidonate metabolism in neutrophils, culminating in neurotoxicity and brain damage following an ischemic stroke (Bladowski, Gawrys, Gajecki, Szahidewicz-Krupska, Sawicz-Bladowska & Doroszko, 2020; Lindsberg, Hallenbeck & Feuerstein, 1991; Zimmerman, McIntyre, Mehra & Prescott, 1990).

TREM-1 factor:

Triggering receptors expressed on myeloid cells-1 is a key inflammatory amplifier that interacts with a number of TLR pathways depending on the severity of the inflammatory condition (He, Yang, Wang, Jia, Xie & Zhou, 2019; Youssef et al., 2009). According to Sun et al's research, TREM-1 was first revealed to be produced in the context of SAH and has been linked to the pathogenesis of BBB disruption. This is one of EBI's most serious pathological symptoms (Sun, Duan, Jing, Wang, Hou & Zhang, 2019; Sun, Ma, Jing, Wang, Hao & Wang, 2017a; Sun, Ma, Jing, Wang, Hao & Wang, 2017b). According to a new research, TREM-1 is necessary for SYK mobilization and downstream activation of CARD9/NF-$\varkappa$B and NLRP3/caspase-1 in microglia following stroke (Xu et al., 2019a) . TREM-1 inhibition by LP17 significantly reduced the severity of EBI, and the protective effects were attributed to reduction of downstream p38MAPK/MMP-9 activation and hence ZO-1 preservation (Sun, Duan, Jing, Wang, Hou & Zhang, 2019). TREM-1 activation can be inhibited by fusion proteins or synthetic inhibitory peptides, which can reduce the production of pro-inflammatory mediators and leukocyte recruitment (Boufenzer et al., 2015; Schenk, Bouchon, Seibold & Mueller, 2007). Neuroinflammation has been linked to post-stroke impairment in the past (Yirmiya & Goshen, 2011). According to the findings of (Xu et al., 2019a) , inhibiting TREM-1 improves long-term neurobehavioral deficits in the hippocampus following ischemic stroke by boosting cell proliferation and synaptic plasticity. According to the evidence described above, TREM-1 may have a role in the inflammatory pathways that contribute to EBI after SAH.

Microglial polarization:

Microglial polarization appears to play a significant part in the pathogenic processes of neuroinflammation following subarachnoid hemorrhage, according to increasing data (Gao et al., 2021). Microglia responds quickly to a variety of brain injuries by modifying the shape and polarization of their cytoplasmic structures. After a SAH, neuroinflammation develops over time and plays a role in both EBI and the long-term decline in cognitive function. As resident immune cells, microglia coordinates neuroinflammation differently in neurological disorders with varying degrees of polarization (Zheng, Lyu, Lam, Lam, Poon & Wong, 2020). After SAH, activated microglia are thought to polarize into two phenotypes: classic M1 (pro-inflammatory) and alternative M2 (anti-inflammatory), depending on the stimulus (Li & Barres, 2018). Lipopolysaccharide (LPS) and the pro-inflammatory cytokine interferon-γ (IFN-γ) traditionally stimulate microglia to the M1 phenotype through the release of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6 and When microglia are stimulated by IL-4 or IL-13, they adopt an alternative M2 phenotype and express anti-inflammatory molecules such as transforming growth factor beta and IL-10 (Zheng, Lyu, Lam, Lam, Poon & Wong, 2020). According to (Liu et al., 2020), Hb-induced microglial pro-inflammatory polarization

was inhibited more effectively by the RvD1-ALX/FPR2 connection, potentially by negatively modulating the signaling activities of IRAK1/TRAF6/NF-ϰB or MAPKs. Similarly, (You et al., 2016) indicated that, Rapamycin and AZD8055 may promote a selective modification of microglia polarization to the M2 phenotype for SAH therapy by inhibiting the mTOR pathway. RhMFG-E8 treatment reduces the microglial inflammatory response, which is linked to the M2 microglial shift and may have direct neuroprotective effects, and it may include the integrin 3/SOCS3/STAT3 signaling pathway (Gao et al., 2021). (Wei et al., 2017) study, showed that Erythropoietin reduces EBI after SAH by regulating microglia polarization through the EPOR/JAK2-STAT3 pathway. The above facts suggest that, modulating M1 and M2 microglial polarization could be a promising neuroprotective strategy. Further studies are needed to better understand the application of microglial modulation in SAH.

Toll-Like Receptors

Toll-like receptors are pathogen-detection and clearance receptors. Toll-like receptors (TLRs) are essential regulators of innate immunity and are involved in the initiation of the inflammatory response in the event of infection. TLRs initiate a series of signaling cascades in leukocytes in response to DAMPs or pathogen-associated molecular patterns (PAMPs), resulting in enhanced cytokine production and activation (Okada & Suzuki, 2017; Tang, Kang, Coyne, Zeh & Lotze, 2012). TLR4 activation by DAMPs such as OxyHb metabolites and fibrinogen, which are produced during aneurysm rupture, has been linked to the pro-inflammatory state that follows SAH (Khey, Huard & Mahmoud, 2020). TLR4 or its related pathways were inhibited with a variety of medicines in experimental SAH, which reduced vasospasm, provided neuroprotection, and offered anti-inflammatory effects (Chang, Wu & Kwan, 2014; Liu, Yang, Pan, Liu & Ma, 2016). Fluoxetine was discovered to reduce neuroinflammation and improve neurological function in SAH rats. TLR4/MyD88/NF-ϰB signaling pathway is one of the probable pathways involved (Liu et al., 2018). TLR4-deficient mice had reduced infarct volumes and improved neurological and behavioral outcomes, according to a research (Caso, Pradillo, Hurtado, Lorenzo, Moro & Lizasoain, 2007). TLR4 knockout mice had lower levels of mediators linked to brain injury, including stroke-induced IRF-1, iNOS, and cyclooxygenase 2. In the brains of TLR4-deficient rats, IFN- and the lipid peroxidation marker malondialdehyde were found to be lower. After an artificial stroke, the researchers found that in TLR4-deficient rats, the matrix metalloproteinase 9 expression which helps to cause brain injury was attenuated (Caso, Pradillo, Hurtado, Lorenzo, Moro & Lizasoain, 2007). TLR4 signaling appears to control the severity of ischemia-induced neuronal damage, suggesting that TLR4 could be a target for SAH prevention and treatment (Caso, Pradillo, Hurtado, Lorenzo, Moro & Lizasoain, 2007). TREM-1 was found to be dynamically raised in the brain after eSAH, especially in microglia and vascular endothelial cells, implying that it may improve EBI through interacting with the TLR4 pathway (Sun et al., 2021).

Figure1

MAPK Pathway

MAPKs are a type of threonine and serine protein kinase that has many functions in cell biology. MAPK pathways are initiated when TLR, TNF, and IL receptors, as well as receptor tyrosine kinases, are activated (RTK). The three major MAPK families in humans are extracellular signal-regulated kinase 1 and 2 (ERK1/2), p38 MAPK, and C-Jun N-terminal kinase (JNK) (Khey, Huard & Mahmoud, 2020). The majority of prior investigations used MAPK inhibitors or inhibitors of their upstream signaling molecules and demonstrated that MAPK inhibition prevented vasospasm (Suzuki, Hasegawa, Kanamaru & Zhang, 2011) conducted an experiment and concluded that. (Maddahi, Povlsen & Edvinsson, 2012) found that IL-1, IL-6, MMP-9, and pERK1/2 protein expression levels in cerebral arteries increased with time, with an early peak at roughly 6 h and a late peak at 48 to 72 h post-SAH. The elevated expression of TNF in cerebral arteries began at 24 hours and continued until 96 hours. In addition, the animals developed sensorimotor and spontaneous behavioral abnormalities as a result of SAH. They went on to say that SAH causes early activation of the MEK-ERK1/2 pathway in cerebral artery walls, which is linked to proinflammatory cytokines and MMP-9 upregulation. U0126 (selective inhibitor) suppressed the MEK-ERK1/2(mitogen-activated protein kinase kinase-extracellular signal-regulated kinases 1/2) pathway 6 hours after SAH, reducing the activation

of cytokines and MMP-9 in cerebral arteries and improving neurological outcome. In canine and rabbit models, blocking the p38 MAPK pathway was found to be efficient in lowering inflammatory cytokine production, including IL-1, IL-1, IL-8, and TNF-α. In addition, as compared to the control group, the scientists saw a decrease in vasospasm (Pan et al., 2013; Sasaki et al., 2004). By activating p38MAPK/MMP-9 and degrading ZO-1, TREM-1 may play a crucial role in the development of EBI following SAH. According to the authors, TREM-1 inhibition alleviated the severity of SAH-induced EBI, establishing a novel method for EBI treatment (Sun, Duan, Jing, Wang, Hou & Zhang, 2019).

NΦ-ϰB

When cells are exposed to damaging stimuli, the protein NF-ϰB is immediately activated and has been linked to a wide range of inflammatory illnesses. Inflammation and innate immunity are both affected by this protein complex, which controls DNA transcription. The NF-ϰB pathway is activated by TLRs, TNF receptors, and IL receptors recognizing different PAMPS and DAMPS (Okada & Suzuki, 2017). Because it regulates the development of a vasoconstrictor, NF-ϰB signaling and its downstream cytokine products are crucial to the pathophysiology of SAH. Using various drugs to inhibit NF-ϰB activity, several authors have observed improved neurological scores, decreased neuronal death, reduced BBB permeability, and lower inflammatory cytokines following SAH. (Chang, Wu, Lin, Hwang & Kwan, 2012; Liu, Yang, Pan, Liu & Ma, 2016; Zhang et al., 2015) , Future research on NF-ϰB is promising, and the usefulness of employing this molecule as a therapeutic target in the treatment of SAH in humans needs to be determined. In the study by Liu et al. (Liu et al., 2016) Matrine was found to reduce EBI in rats following subarachnoid hemorrhage by inhibiting NF-ϰB via PI3K/Akt and inducing HO-1 via Keap1/Nrf2.

Table 1

Eicosanoid Reactions and NLRP3 Inflammasome:

Eicosanoids

Eicosanoids are bioactive signaling lipids generated from arachidonic acid and related polyunsaturated fatty acids (PUFAs) that govern a wide range of homeostatic and inflammatory processes associated with a variety of illnesses (Dennis & Norris, 2015). One of the most well-known routes involved in inflammation is the eicosanoid pathway. Inflammatory processes are the body's physiological response to numerous stressors such as trauma, infections, or immunological reactions. These processes are distinguished by the activation of cellular and humoral mediator systems, as well as the production of a wide range of inflammatory mediators such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). Increased amounts of these mediators can cause changes in microvascular tone and permeability, as well as activation of eicosanoid production pathways (Homaidan, Chakroun, Haidar & El-Sabban, 2002). The availability of free AA is critical for eicosanoid production. When tissues are exposed to physiological or pathological stimuli such as growth factors, hormones, or cytokines, AA is generated from membrane phospholipids by the action of phospholipase A2 (PLA2) enzymes and can then be converted into different eicosanoids. The three principal enzymes capable of metabolizing AA are P-450 epoxygenase, cyclooxygenases (COXs), and lipoxygenases (LOXs) (Harizi, Corcuff & Gualde, 2008). Following PLA2 cleavage, the freed AA is processed by three different mechanisms: cyclooxygenase (COX), lipoxygenase (LOX), and the P450 family (CYP). The COX system produces prostaglandins (PG) and thromboxanes (TX), while the LOX system produces leukotrienes (LT), hydroxyeicosatetraenoic acids (HETE), and lipoxins (LX). Finally, the CYP pathway produces epoxyeicosatrienoic acids (EET) and heterecosatrienoic acids (HETE). Although free arachidonic acid is required for the majority of eicosanoid metabolism, it is typically kept in esterified form. Phospholipase A2 (PLA2) enzymes are essential for boosting free arachidonic acid levels for metabolism and eicosanoid production under normal physiological settings, but especially after inflammatory cell activation. PLA2 isoforms comprise various cystosolic, calcium dependent, and secretory isoforms, in addition to phospholipases A1, B, C, and D. Phospholipase activity can be influenced by calcium, phosphorylation, and agonists that bind to G-protein coupled receptors. These enzymes are generally involved in the physiological remodeling of cellular membranes, with free fatty acids being extracted via phospholipase activity and subsequently recycled with

another free fatty acid. Nonetheless, decreases in the cell's ability to sustain normal metabolic function, as well as the resulting drop in ATP levels, might result in the failure to recycle membrane phospholipids. Modification of membrane phospholipids is likely to affect a variety of cellular processes, including the capacity to accumulate excitotoxic amino acids. It was discovered in this study that selective phospholipase inhibitors limit the release of free fatty acids from in vivo rat brain. Following this inhibition, the severity of cortical damage after focal ischemia, forebrain ischemia, and cerebral trauma is reduced. Infarct volumes were similarly shown to be smaller in mice with PLA2 deletion (Phillis & O'Regan, 2003). Further research is needed to completely understand the role of Eicosanoids in events following SAH.

The NLRP3 inflammasome

The NLRP3 inflammasome is involved in caspase-1 activation and the release of proinflammatory cytokines IL-1β/IL-18 in response to infection and cellular damage (Kelley, Jeltema, Duan & He, 2019). In response to an attack, pattern-recognition receptors (PRRs) activate the innate immune system, which is the body's initial line of defense. Even though NLRP3 inflammasome activation is still poorly understood, there are several factors at play, including pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and a second signal that stimulates the assembly of NLRP3, ASC, and pro-caspase-1 into the NLRP3 inflammasome complex via multiple ROS-producing pathways (Abais, Xia, Zhang, Boini & Li, 2015). When these patterns are activated, it sets off a cascade of events that clears the infection and repairs any harm it has caused. Inflammasome activation results in the release of cytokines such as IL-1β and IL-18, as well as the generation of pyroptosis, an inflammatory form of cell death (Kelley, Jeltema, Duan & He, 2019; Sharma & Kanneganti, 2016). Studies have shown that pathogen-derived ligands include nucleic acids, microbial wall components, and toxitoxins activate NLRP3. NLRP3 has also been shown to be activated by environmental crystalline contaminants such silica, asbestos, and alum (Man & Kanneganti, 2015). When SAH boosted TREM-1 expression, NLRP3 inflammasome components (NLRP3, ASC), cleaved caspase-1, mature IL-1β, and mature IL-18 were all elevated into their active forms as well (Xu et al., 2021). Multiple studies have shown that SAH activates the NLRP3 inflammasome, which has been shown to be inhibited in those who have had the condition, For example, in both the early and delayed phases after SAH. (Dodd, Noda, Martinez, Hosaka & Hoh, 2021) found NLRP3 mediated neuroinflammation to be associated with cerebrovascular impairment. EBI and DCI therapies could benefit from the use of MCC950 and other NLRP3 inhibitors. (Xu et al., 2019b) found that following SAH, the levels of APJ and AMPK rose. Despite the fact that endogenous APJ and AMPK were increased, this was not enough to reduce NLRP3 inflammasome activity or inflammatory cytokines in the body, as previously described. Exogenous apelin-13 increased AMPK levels, which prevented the NLRP3 inflammasome from activating and decreased Bip, cleaved caspase-1, IL-1β, TNF-α, MPO, and ROS levels while simultaneously boosting AMPK levels. To make matters worse, the AMPK inhibitor upregulated the production of NLRP3, cleaved caspase-1, IL-1β, TNF-α, MPO, and ROS in addition to negating the good effects of anti-inflammatory and anti-oxidative stress, which made conditions to further worsen. Microglial modulation has been linked to favorable effects on the cerebrovascular system in studies by (Dodd, Noda, Martinez, Hosaka & Hoh, 2021), however these studies have not demonstrated that NLRP3 suppression alleviates cerebrovascular dysfunction through this mechanism. NLRP3-mediated neuroinflammation is frequently attributed to microglia as the primary cause (Luo, Reis & Chen, 2019).

Keap1-Nrf2-ARE

One of the most essential defense systems against oxidative and/or electrophilic stressors is the Keap1–Nrf2–ARE Kelch-like ECH-Associating protein 1 nuclearfactor erythroid 2 related factor 2-antioxidant response element, which is linked to inflammatory disorders. In response to ROS exposure, it activates a cytoprotective mechanism. The Nrf2-ARE transcriptional pathway regulates genes that encode proteins involved in the detoxification and elimination of reactive oxygen species (ROS) and electrophiles (Nguyen, Nioi & Pickett, 2009). The Keap1–Nrf2–ARE pathway is important for cell protection against oxidative and electrophilic stress. The ability of Nrf2–ARE activators to boost a battery of critical cell-protective genes involved in reducing oxidative damage and inflammation may be exploited in the development of antioxidant, anti-

inflammatory, and anticancer medicines (Lu, Ji, Jiang & You, 2016). The study of (Shang et al., 2013) achieved two goals. It first identified the timing of Keap1 inhibition and Nrf2 activation in rats during the early stages of ICH. Nrf2 is an important endogenous regulator of cellular oxidative stress resistance. Intravenous treatment of a Nrf2 activator (BARD) significantly raised Nrf2 and HO-1 expression earlier, thereby protecting neurons from IRI. Taken together, their findings revealed that Nrf2 activators may be neuroprotective in patients with IRI (Takagi et al., 2014). In the (Zhao et al., 2007) study, activation of Nrf2 by SF was related with enhanced expression of many antioxidative enzymes known to play essential roles in oxidative stress defense, including catalase, SOD, NAD(P)H dehydrogenase, quinone-1, and glutathione S-transferase. Nrf2 deficiency contributes to ROS-induced DNA damage and death largely in neurons in the early stages of ICH, according to (Wang et al., 2007) Activating Nrf2 prevents leukocytes from entering the injury site and preventing excessive free radical damage to the brain tissue. Despite the fact that more research with selective Nrf2 inducers and inhibitors is needed, the data suggest that Nrf2 could be a therapeutic target for the treatment of ICH. (Zhang et al., 2019) found that MitoQ promotes mitophagy and reduces mitochondrial oxidative stress-related neuronal apoptosis in EBI after SAH via the Keap1/Nrf2/PHB2 pathway, which is linked to improved short- and long-term neurological impairment. MitoQ could thus be used as an antioxidant therapy for EBI as well as a treatment for delayed neurological impairments following SAH. SalA (10 and 50 mg/kg/day) administered intraperitoneally was shown to protect EBI following SAH, at least in part due to its antioxidative, anti-inflammatory, and antiapoptotic properties. The following is the evidence that led to this conclusion: At 48 hours following a SAH in a rat model, SalA dramatically alleviated neurological impairments, reduced brain edema and BBB permeability, decreased inflammation factors, and repressed oxidative stress and cortical neuron death. Furthermore, SalA reduced MDA and ROS production produced by SAH while increasing GSH concentration and GSH-Px activity. These findings suggested that treating rats with SalA would be an effective way to protect their brains from EBI after SAH (Gu et al., 2017). SAH treatment may one day be based on this promising new discovery, but further studies are needed to confirm it.

High mobility group box 1 (HMGB1)

The HMGB1 protein is a pro-inflammatory cytokine with pro-inflammatory properties that acts as an initiator of neuroinflammation. It has been associated with traumatic brain injury (TBI) and acute brain injury (EBI) in the aftermath of a subarachnoid hemorrhage (SAH) (Paudel, Angelopoulou, Piperi, Othman & Shaikh, 2020). After SAH, HMGB1 expression rises, and it plays a role in the disease's development (Murakami, Koide, Dumont, Russell, Tranmer & Wellman, 2011). The activation of Janus kinases 2 (JAK2)/Signal transducer and activator of transcription by HMGB1 causes SAH-induced EBI (STAT3). In nuclei, HMGB1 is involved in chromatin structure preservation, transcription activity modulation, and DNA repair. HMGB1, on the other hand, is considered a typical damage-associated molecular pattern (DAMP) since it is translocated and released extracellularly from a range of brain cells, including neurons and microglia, and hence contributes to the pathophysiology of many CNS diseases (Nishibori, Wang, Ousaka & Wake, 2020). HMGB1 has been demonstrated to promote inflammatory cascades by binding to TLR4/TLR2 and RAGE, leading in activation of NF-ϰB, IL-6, IL-8, TNF-, MyD88, iNOS, ERK1 and ERK2 (Park et al., 2003). Extracellular HMGB1 release could play a key role in activating the early inflammatory responses by stimulating numerous receptors, resulting in BBB breakdown (Nishibori, Wang, Ousaka & Wake, 2020). HMGB1 induced vascular smooth muscle cells (VSMCs) and regulated VSMC phenotypic transition during SAH via interacting with IFN-γ (Wang, Zhang, Liang, Wu, Zhong & Sun, 2019). After treatment with anti-HMGB1 mAb, the vascular remodeling and VSMC phenotypic shift found in SAH were reported to be reduced, principally by reversing SAH-induced up-regulation of HMGB1, microglial activation, and brain edema. HMGB1 was once assumed to be a negative cytokine, but it has now been revealed to enhance the inflammatory response in acute stroke patients. On day 14 following SAH, however, (Tian et al., 2017) found that HMGB1 expression was considerably higher than in the sham group. This finding suggested that HMGB1 may play a role in the healing of brain injury following SAH. The pro- and anti-inflammatory effects of HMGB1 demonstrate the protein's complexity and role in circumstances following SAH, implying that more research is needed to validate its involvement in occurrences like EBI.

JAK/STAT (Janus-kinase/signal activator and transducer of transcription pathways)

These are a collection of intracellular processes that regulate gene expression. It's one of the most essential signaling channels for transmitting cytokine-induced signals from the cell surface. Inflammation of the central nervous system is also influenced by this route. STAT is phosphorylated by JAK when it is activated, and then it translocates into the nuclease to modify the expression of a specific gene. Depending on the STAT isoform, various anti-inflammatory, pro-inflammatory, proliferative, or apoptotic proteins can be expressed. The JAK-STAT pathway's dysregulation in inflammation and neurodegenerative illnesses makes it a key player in the majority of brain diseases. STAT1 activity has been linked to a decrease in cell viability in the brain, whereas STAT3 is thought to be a pro-survival factor (Planas, Gorina & Chamorro, 2006). Many investigations have shown that after SAH, STAT1 and STAT2, as well as their activators JAK1 and JAK2, are active (Osuka et al., 2006; Samraj, Müller, Grell & Edvinsson, 2014). (Gorina, Petegnief, Chamorro & Planas, 2005) discovered that anti-inflammatory cytokines such as IL-10 activated STAT3 but not STAT1, whereas pro-inflammatory signals such as IFN-γ (interferon) activated both STAT1 and not STAT3, and IL-6 activated both STAT1 and STAT3. Tyrphostin, a JAK2 inhibitor, was discovered to be involved in the reported activation of STATs following IL-6 and IFN-γ, but not following IL-10 (AG490). Oxidative stress, which is produced in the ischemic brain and contributes to ischemic brain damage, can also activate STATs. The Gorina, Petegnief, Chamorro, and Planas investigation went on to show that JAK2/STAT1 activation causes cell death, which is consistent with the notion that STAT1 is activated in neurons after ischemia and plays a role in ischemic brain injury (Takagi, Harada, Chiarugi & Moskowitz, 2002). According to Osuka et al., after SAH, IL-6 expression causes JAK1-STAT3 phosphorylation, which leads to the overexpression of COX-2, which is responsible for the synthesis of PGI, an enzyme recognized for reducing vasospasm by promoting vasodilation and inhibiting platelet aggregation. STAT1 and STAT3 are activated by oxidative stress and certain cytokines through a JAK2-dependent pathway (Planas, Gorina & Chamorro, 2006). A number of pro-inflammatory cytokines, including IL-10, activate STAT3, although others, such as interferon, induce STAT1 phosphorylation through the JAK2 pathway (Regis, Pensa, Boselli, Novelli & Poli, 2008). Melatonin therapy activates JAK1 and enhances the phosphorylation of STAT3, according to(Li, Yang, Sun & Hang, 2019). This effect is abolished by a JAK1 antagonist, demonstrating that JAK activation is implicated in Melatonin's protective benefits against EBI after SAH. Nonetheless, when discussing events following SAH, the role of the JAK/STAT system remains a subject of many unknowns, necessitating more research in this field.

NITRIC OXIDE PATHWAY

The enzyme nitric oxide synthase (NOS) catalyzes the interaction of L-arginine with molecular oxygen to make L-citrulline and NO. There are three forms of NOS that have been found so far: they constitutively expressed, Neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS) (Kleinert, Schwarz & Förstermann, 2003). NO, which is mostly produced by iNOS, can be detrimental and pro-inflammatory in high doses. However, the activities of nitric oxide are mostly influenced by the cellular context, NO concentration (depending on distance from the NO source), and the initial priming of immune cells, rather than the enzymatic source (Guzik, Korbut & Adamek-Guzik, 2003). The brain's NO levels rise dramatically as a result of vertebral ischemia. This is attributed to increased iNOS expression in reactive astrocytes and neutrophils invading the ischemic brain 6–12 hours after the injury, as well as increased eNOS and nNOS expression in the arteries and parenchyma within an hour of the lesion (Iadecola, 1997; Kader, Frazzini, Solomon & Trifiletti, 1993; Zhang et al., 1994). NO has pro-inflammatory and cytotoxic effects at high doses, but it is known to have anti-inflammatory and vasodilator characteristics under certain situations (Coleman, 2001; Sharma, Al-Omran & Parvathy, 2007). L-arginine treatment during the acute period improved symptoms in people with mitochondrial myopathy, encephalopathy, and stroke-like episodes (Koga et al., 2018). During an inhaled NO experiment, peripheral vascular resistance was lowered in a child with traumatic brain injury, despite no changes in middle cerebral artery blood flow, jugular bulb oxygen saturations, or intracranial pressure (Vavilala, Roberts, Moore, Newell & Lam, 2001). According to the researchers, the NO donor had no effect on cerebral blood flow, cerebral perfusion pressure, or cerebral steal in these people (Willmot, Ghadami, Whysall, Clarke, Wardlaw & Bath, 2006). These disparities in results could explain NO toxicity

or insufficient NO exposure, which could be explained by differences in NO concentration. More research is needed to determine the role of NO in SAH, which is currently up for contention.

Limitations

After describing the aforementioned inflammatory pathways in response to SAH and their impact on EBI, it's crucial to point out the review's shortcomings. The majority of the evidence included in this study regarding the inflammatory pathways following SAH was based only on in vitro and animal research. When it comes to experimental SAH, several methods have been used to simulate SAH for research aims. Two of the most commonly used models are blood injection and endovascular perforation. The blood injection model is less accurate than the endovascular perforation model in simulating SAH because it does not involve perforation of the cerebral artery. As a result, there may be discrepancies in experimental outcomes due to the different models, which we failed to account for in this review. When establishing the pathways, there was no distinction made between the molecular expression components of the pathways and the neurologic effects. Secondary brain injury may emerge from the activation of several different inflammatory pathways following SAH, although the severity of each pathway's ability to control inflammation has not been studied in detail in this review. After SAH, there was no distinction made in the inflammatory response time since it may be critical in the development of SAH problems in individuals who survive the first bleed. We highlight the majority of inflammatory pathways, however we understand that there may be more inflammatory pathways after SAH. The majority of the pathways included in the research did not take into account the different grades of SAH severity.

Conclusion

Multiple modes of action are implicated in the etiology of SAH, making it a difficult disease to understand. SAH-induced inflammation appears to be a complicated process. There have been numerous inflammatory pathways explored in SAH, with varying degrees of evidence to support each one. SAH-induced inflammation is mostly controlled by TLR, as described in the above processes and pathways. Antioxidants and TLR inhibitors that target these mediators may not only prevent the activation of downstream inflammatory pathways, but may also improve the prognosis for SAH patients. However, because to the intricacy of SAH, inflammation may not be the only aspect to consider; other events may either enhance or aggravate the symptoms after SAH. There have been several recent studies suggesting that inflammation is the most essential factor to consider in the prevention and treatment of issues that may arise after SAH, such as EBI. Recently, new studies have revealed how TREM-1 inhibition could improve the prognosis of EBI as a secondary brain injury after SAH. Thus more investigations should be carried in the mechanism of TREM-1. Despite the fact that inflammatory pathways offer a wide range of potential targets, further study is needed to determine the importance of these pathways in SAH. To assess the clinical relevance of this discovery, additional clinical trials will be required in the near future.

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