INFLAMMATION AND ANTI-INFLAMMATORY STRATEGIES IN STROKE

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ABSTRACT

Stroke is an important public health issue due to high rates of disability, morbidity/mortality and is now the third leading cause of death after heart disease and cancer affecting 15 million people worldwide each year. In spite of extensive research in the field of stroke during past decade the current therapeutic strategies have been largely unsuccessful. One possible explanation is that research and pharmacological management have focused on very early events in brain ischemia. Two important pathophysiological mechanisms involved during ischemic stroke are oxidative stress and inflammation. Brain tissue is not well equipped with antioxidant defenses, so reactive oxygen species and other free radicals/oxidants, released by inflammatory cells, threaten tissue viability in the vicinity of the ischemic core. Recent studies have shown that brain ischemia and trauma elicit strong inflammatory reactions driven by both external and brain cells. Clinical observations suggest that patients with stroke have higher plasma levels of inflammatory cytokines or soluble adhesion molecules and anti-inflammatory therapy is effective at reducing stroke incidence in not only animal models, but in humans as well. This suggests that inflammation might directly affect the onset of stroke. The recognition of inflammation as a fundamental response to brain ischemia provides novel opportunities for new anti-inflammatory therapies. Currently, little is known about endogenous counter regulatory immune mechanisms. Statins have been shown to decrease the stroke incidence via anti-inflammatory effects that are both dependent and independent of their cholesterol-lowering effects. Here in this review we will discuss the molecular aspects of oxidative stress and inflammation in ischemic stroke. We will also present the latest findings about the cellular and humoral aspects of immune and inflammatory reactions in the brain. This will
increase our understanding regarding neuro-injuries and role immune reactions play in the brain milieu. This all may have an impact on the potential therapeutic strategies that target neuro-inflammation and the innate immune system.

**Keywords:** Neuroinflammation, antioxidant, macrophages, Ischemia, cytokines, ischemic, statins, brain, immune reactions.

**INTRODUCTION**

Stroke is the third leading cause of death and a major cause of disability in industrialized countries. Ischemic stroke is the most common type of stroke, occurring in approximately 80% of all strokes. A less common type of stroke is hemorrhagic stroke, which occurs due to a subarachnoid hemorrhage and/or an intra-cerebral hemorrhage. Although different mechanisms are involved in the occurrence and development of stroke, inflammatory response is greatly involved in its sequence [1]. Cerebral ischemia initiates a cascade of detrimental events including glutamate associated excitotoxicity, membrane lipid degradation, DNA damage, formation of reactive oxygen species and acute inflammation, which lead to the disruption of cellular homeostasis (See Fig 1) and structural damage of ischemic brain tissue [2]When the brain blood flow is interrupted, it results in deprivation of oxygen and nutrients to the cells; this situation constitutes an ischemic stroke [3]. During ischemia, reactive oxygen (ROS) and nitrogen species can be generated in the ischemic penumbra but can also be produced during reperfusion injury [4-5]. Indeed, it is now established that albeit maintenance of partial or complete blood flow is essential for preserving cerebral tissue, it is during reperfusion when it paradoxically induces excessive generation of ROS, such as superoxide anion radical (O$_2^-$) hydroxyl radical (OH$^-$), hydrogen peroxide (H$_2$O$_2$), and nitric oxide (NO), which contribute to increased neuronal death by oxidizing proteins, damaging DNA, and inducing lipid peroxidation [6]. After focal ischemia, primary neuronal death appears rapidly in the core area and is followed by secondary death in the ischemic penumbra, which evolves from the delayed activation of multiple cellular death pathways. Inflammation is increasingly recognized to be the key element in pathological progression of ischemic stroke. Therefore, reducing oxidative stress and downregulating the inflammatory response are options that merit consideration as potential therapeutic targets for ischemic stroke.
Cerebral ischemia initiates a cascade of complex series of detrimental events including glutamate associated excitotoxicity, membrane lipid degradation, DNA damage, formation of reactive oxygen species and acute inflammation, which lead to the disruption of cellular homeostasis (See Fig 1) and structural damage, blood-brain barrier dysfunction and post ischemic inflammation leading ultimately to cell death of neurons, glia and endothelial cells of ischemic brain tissue. The degree and duration of ischemia determine the extent of cerebral damage.

Stroke induces production and release of cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β [IL-1β], interleukin-6 (IL-6), [7,8] and inducible nitric oxide synthase (iNOS), by a variety of activated cell types; endothelial cells, microglia, neurons, leukocytes platelets, monocytes, macro-phages and fibro-blasts[9]. Cerebral ischemia results in the loss of blood supply followed by a cascade of events including glutamate excitotoxicity, calcium overload, oxidative stress and inflammation, leading eventually to cell death by both necrosis and apoptosis. Many of the molecules involved in this complex series of biochemical events are potential therapeutic targets for the development of effective treatment for stroke [10-12]. Studies have shown that mechanisms including apoptosis, necrosis, inflammation, immune modulation and oxidative stress may lead to the development of the ischemic cascade. Recent advances in the stroke medicine have highlighted the role of acute transitory inflammation in the cellular pathology following ischemic stroke [13]. Inflammation plays a key role in cerebral ischemic injury [14-15]. Elevated levels of reactive oxygen species (ROS), generated

Fig.1 Ischemic cascade after stroke leading to cerebral damage
by the cessation of cerebral blood flow, stimulate cells to secrete cytokines and chemokines which subsequently cause the secondary ischemic damage [16]. It is imperative that acute inflammation might potentiate or perturb the already initiated excitotoxicity.

Over the past decade, remarkable advances have been made in understanding the basic molecular mechanisms underlying neuronal death. However, clinically effective neuro-protectants have not yet been discovered and no specific therapy for stroke is available at present. The body of experimental data supports the view that reducing OS should continue to be a potentially viable target for stroke therapy [17]. In addition, the inflammatory response requires consideration as a potential target of therapy for ischemic stroke [18]. Therefore, agents capable of modulating both elements will constitute promising therapeutic solutions [19–22].

**Immune reactions in brain after stroke**

Nervous and immune systems engage in a bidirectional communication that aims to maintain homeostasis in the whole body. Stroke (as any acute lesion of the CNS) can disturb this generally well balanced interaction/ homeostasis. After the stroke, ischemic brain tissue releases factors such as cytokines and neurotransmitters that can reach chemosensitive brain areas involved in immune control such as the hypothalamus, where they can in turn activate the sympathetic nervous system. Damage to cortical regions involved in immune regulation, such as the insula, can lead to loss of tonic inhibition and thus activation of hypothalamic areas [23-25]. Furthermore, inflammatory mediators can be released from the damaged brain tissue and enter the systemic circulation where they act on cells of the immune system in the blood and secondary lymphatic organs or, through the bloodstream, activate the brain via consensus. Besides immunomodulatory signaling specific to a brain lesion, stroke is a strong unspecific stressor (eg, sudden loss of relevant bodily functions, fear, or sense of emergency) and activates immunomodulatory systems such as the hypothalamic–pituitary axis and the sympathetic nervous system [26-27]. Within a few hours after the onset of cerebral ischemia, brain–immune system interactions can result in a downregulation of systemic immunity termed stroke-induced immunodepression (SIDS). Almost all immune cells have numerous noradrenaline receptors, which can be activated by circulating epinephrine produced by the adrenal medulla or via the dense innervation by postganglionic sympathetic fibers of lymphoid organs. Noradrenaline stimulates interleukin-10 production by blood monocytes. [28]. Overall, noradrenaline decreases the number and the activity of immune cells through its
pleiotropic effects. Glucocorticoids, which are produced as a result of stress induced stimulation of the hypothalamic–pituitary-axis, are also well known immunosuppressants. Since its description in clinical stroke, many studies have confirmed the existence of SIDS in experimental and clinical stroke and shown a strong correlation between immunodepression, sympathetic nervous system activation, and outcome [29-31]. For example, concentrations of metanephrine in the blood are as robust for prediction of clinical outcome as they are for stroke severity, [32] and markers of SIDS, such as decreased expression of HLA-DR on monocytes, predict risk of infection [33]. Nonetheless, immunodepression after stroke might also have an adaptive component. As a result of stroke, the blood–brain barrier is disrupted; CNS-specific antigens are exposed to the immune system and may enter the systemic circulation. Downregulation of the immune system could help prevent aggressive responses. Although the general response to stroke could be a decrease in the number of immune cells and subsequently of their function, further complexity ensues as some immune-cell subtypes could increase (e.g., regulatory T cells). Little is known about the consequences of these changes in circulating immune cells in the brain, but there are indications that they might be involved in brain protection and repair [34]. Immune responses against antigens are determined by the microenvironment of the tissue in which they occur. Co-stimulatory molecules are necessary for the priming of immune responses. Such molecules are weakly expressed in the healthy brain, but become upregulated after brain damage such as a stroke. Furthermore, systemic infection, which often occurs in patients after a stroke, leads to upregulation of co-stimulatory and MHC class I and II molecules in the periphery and the brain, thus facilitating activation of T cells and B cells against endogenous brain antigens [35]. As a result of systemic inflammation, for example, during infection cytokines are produced outside and within the brain and mediate aspects of sickness behavior [36]. Infection after a stroke might thus lead to an exacerbated proinflammatory phenotype. Within hours, stroke induces systemic immune changes that last for weeks [30] and can affect clinical outcomes. SIDS at least partly explains the high risk of infection in patients after a stroke, and might thus be indirectly responsible for the production of inflammatory and co-stimulatory mediators that in turn negatively affect the brain lesion. Whether these deleterious effects of brain–immune interactions after stroke are offset, at least partly, by their beneficial effect on brain repair or the restricted development of CNS integration is unclear till now.
Inflammatory Mechanism in the Brain

Inflammation plays an important role in the pathogenesis of ischemic stroke and other forms of ischemic brain injury. Experimentally and clinically, the brain responds to ischemic injury with an acute and prolonged inflammatory process, characterized by rapid activation of resident cells (mainly microglia), production of pro-inflammatory mediators, and infiltration of various types of inflammatory cells (including neutrophils, different subtypes of T cells, monocyte/macrophages, and other cells) into the ischemic brain tissue[2-4]. These all cellular events collaboratively contribute to ischemic brain injury. Inflammation is caused by complex interactions involving multiple cell types, multiple mediators and multiple cellular processes. It is not yet clear which anti-inflammatory targets will yield the greatest effect in preventing, reversing or delaying the ischemic stroke process.

Neuro-inflammatory mediators play a crucial role in the pathophysiology of brain ischemia, exerting either deleterious effects on the progression of tissue damage or beneficial roles during recovery and repair. Within hours after the ischemic insult, increased levels of cytokines and chemokines enhance the expression of adhesion molecules on cerebral endothelial cells, facilitating the adhesion and trans-endothelial migration of circulating neutrophils and monocytes. These cells may accumulate in the capillaries, further impairing cerebral blood flow, or extravasate into the brain parenchyma. Infiltrating leukocytes, as well as resident brain cells, including neurons and glia, may release pro-inflammatory mediators, such as cytokines, chemokines and oxygen/nitrogen free radicals that contribute to the evolution of tissue damage (See Fig 2). Inflammation may play an important role in acute ischemic stroke. Experimental and clinical data suggest that post-stroke inflammatory responses are complex cascade phenomena, which may have detrimental or beneficial effects on outcome. Inflammation is an important avenue of therapeutic research in acute stroke. A better understanding of the inflammatory pathophysiology may help to a better design of clinical trials. Cerebral ischemia results in a number of hemodynamic, biochemical and neurophysiology alterations. A series of complex acute, subacute and chronic events occur after the incidence of stroke and reperfusion. Ischemic injury involves energy failure, loss of cell ion homeostasis, acidosis, increased intracellular calcium excitotoxicity, free radical-mediated toxicity, and pathological permeability of the blood-brain barrier (BBB). Free radicals, specifically reactive oxygen species (ROS) that are generated soon after ischemia, as well as in later stages of ischemic reperfusion (e.g., by inflammatory cells), are the fundamental mediators of reperfusion injury [37-38]. Two important pathophysiological
mechanisms involved during ischemic stroke are oxidative stress and inflammation. Brain tissue is not well equipped with antioxidant defenses, so reactive oxygen species and other free radicals/oxidants, released by inflammatory cells, threaten the tissue viability in the vicinity of the ischemic core.

![Fig.2 Putative cascade of damaging events in focal cerebral ischemia.](image)

Very early after the onset of the focal perfusion deficit, excitotoxic mechanisms can damage neurones and glia lethally. In addition, excitotoxicity triggers a number of events that can further contribute to the demise of the tissue. Such events include peri-infarct depolarizations and the more-delayed mechanisms of inflammation and programmed cell death. The x-axis reflects the evolution of the cascade over time, while the y-axis aims to illustrate the impact of each element of the cascade on final outcome (courtesy of Dirnagl et al. 1999).

Although for many years the Central Nervous System (CNS) was considered an immune-privileged organ, it is now well accepted that the immune and the nervous system are engaged in bidirectional crosstalk. Moreover, mounting data suggest that in the brain, as in peripheral organs, inflammatory cells participate in tissue remodeling after injury. CNS is able to raise an immune response to the majority of threatening stimuli, whereby resident cells generate inflammatory mediators including cytokines, prostaglandins, free radicals, complementary chemokines, and adhesion molecules that recruit immune cells and activate glia and microglia [39-42]. Microglial cells are the resident macrophages of the brain and play a critical role as resident immunocompetent and phagocytic cells in the CNS. The role of microglia and proinflammatory cytokines in the CNS has been characterized in models of brain insults, such as experimental stroke, the most common form of ischemic injury [40]. As mentioned previously, cerebral ischemia triggers acute inflammation, which exacerbates primary brain damage. Although inflammation should be adaptive, the release of
proinflammatory cytokines has often been associated with harmful consequences to neurons and myelin [43]. The control of early CNS inflammation is a careful balancing act, as both too much and too little inflammation will lead to decreased or delayed recovery. Whether the inflammation is neurotoxic or protective may depend upon the context and the location of the inflammatory mediator in relation to an injury, and the timing of inflammatory response may determine the outcome [41]. For example, tumor necrosis factor alpha (TNF-α) upregulated in the proximity of an evolving lesion contributes to secondary infarct growth, whereas cytokine induction remote from the ischemic lesion confers neuroprotection [44]. TNF-α could enhance apoptotic processes through its action on its tumor necrosis factor type 1 receptor (TNFR1) in models of acute (ischemia, excitotoxicity). TNF-α and interleukin 1 beta (IL-1β) exert neurotoxicity in cerebral ischemia in the presence of elevated inducible nitric oxide synthase (iNOS), while in the absence of iNOS, both cytokines appear to contribute to neuroprotection and plasticity, highlighting the role of the context [45].

There is important recognition that protection of endothelial function and downregulation of vascular inflammation comprise part of neuroprotection phenomena and may possess added therapeutic benefit against stroke injury [46]. However, research on clinically effective neurovascular protective therapies for brain damage remains at an early phase [47]. Much attention has been focused on the role of NO in vessel protection from OS and inflammation [48]. Because OS coexists with inflammation and endothelial dysfunction, determining antioxidant status may be helpful in monitoring the progress of Nitric oxide donors (NOD) treatment. A variety of structurally different NOD, which release NO either as a free radical (NO\(^{•}\)) or as an NO ion (NO\(^{+}/NO^{−}\)), have shown to reduce OS/inflammation and to increase cerebral blood flow [49-51]; thus, these can be considered attractive candidates for therapeutic agents in experimental models of stroke. Currently, little is known about endogenous counter regulatory immune mechanisms. However, recent studies showing that regulatory T cells are major cerebroprotective immunomodulators after stroke hence, suggesting that targeting the endogenous adaptive immune response may offer novel promising neuroprotectant therapies.

Inflammation is intricately related to the onset of stroke and to subsequent stroke-related tissue damage. Inflammation within the arterial wall plays a vital role in promoting atherosclerosis [52-53]. Elevated stroke risk has been linked to high levels of serologic markers of inflammation such as C-reactive protein, interleukin-6, TNF-alpha, and soluble
intercellular adhesion molecule (sICAM) [54-55]. These events are promoted in part by the binding of cell adhesion molecules from the selectin and immunoglobulin gene families expressed on endothelial cells to glycoprotein receptors expressed on the neutrophil surface. As evidence, reduced ischemic infarction is observed in ICAM-1 knockout mice and infarction volumes are increased in mice that overexpress P-selectin [56-57]. In the early stage of cerebral ischemia, circulating leukocytes including neutrophils, macrophages, and lymphocytes migrate and adhere to the injured endothelial cells and infiltrate into the ischemic brain region via a dysfunctional blood–brain barrier [58]. Inflammatory response is also characterized by endogenous microglia activation following focal cerebral ischemia [59]. The infiltration of blood derived leukocytes and macrophages liberate toxic and inflammatory mediators involved in ano “reflow phenomenon” and amplify the ischemic brain injury [60]. Ischemic stroke-related brain injury itself triggers inflammatory cascades within the parenchyma that further amplify tissue damage [61]. As reactive microglia, macrophages, and leukocytes are recruited into ischemic brain, inflammatory mediators are generated by these cells as well as by neurons and astrocytes. Inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), interleukin-1 (IL-1), and monocyte chemo-attractant protein-1 (MCP-1) are key inflammatory mediators, as evidenced by attenuated ischemic injury in mutant mice with targeted disruption of these genes [62-63]. These complexities of interactions between multiple pathways will have to be carefully considered for optimal translation to the clinic.

**Proinflammatory Cytokines in Stroke**

The original notion that the brain represented an "immune-privileged" organ lacking the capability to produce an inflammatory response to an injury is no longer valid. Research during the last decade has shown that CNS can mount a well-defined inflammatory response to a variety of insults including trauma, ischemia, transplantation, viral infections, toxins as well as neurodegenerative processes. Most inflammatory reactions are mediated by cytokines which may potentiate ischemic brain injury. Cytokine responses in the initial phase of brain injury might have a role in aggravating brain damage [2-4]. However, in later stages, these molecular mediators might contribute to recovery or repair. In the brain there are different cell types capable to secrete cytokines such as; microglia, astrocytes, endothelial cells and neurons. In addition, it has been shown that peripherally derived cytokines are involved in brain inflammation. Thus, peripherally derived mononuclear phagocytes, T-lymphocytes, natural killer (NK) cells and PMN’s, produce and secrete cytokines and might contribute to
inflammation of the CNS. Proinflammatory cytokines, such as TNF-a, IL-1β, and IL-6, might act directly on neurons to induce apoptosis. Furthermore, factors such as TNF-α and IL-1β released by microglia can activate astrocytes, whereas factors released from astrocytes may lead to further activation of microglia (See figure 3). Cytokines are upregulated in the brain in response of a variety of stimulus including ischemia, being IL-1, interleukin-6 (IL-6), TNF-a, interleukin-10 (IL-10) and TGF-b, the most studied cytokines related to inflammation in stroke [39-42].

Fig. 3 Postischemic inflammatory responses.

Excitotoxicity and oxidative stress caused by the initial ischemic event activate microglia and astrocytes, which react by secreting cytokines, chemokines and matrix metalloproteases (MMP). These inflammatory mediators lead to an upregulation of cell adhesion molecules on endothelial cells, allowing blood derived inflammatory cells, mainly neutrophils, to infiltrate the ischemic brain area. Neutrophils themselves also secrete cytokines which cause a further activation of glial cells. These processes all result in neuronal cell death and enhance the damage to the ischemic brain.

Analysis of the temporal profile of mRNA expression of cytokines in ischemic rats, have revealed that the up-regulation of TNF-αmRNA is proportional to IL-1 and IL-6 up-regulation [64-65]. Initial increases are seen 1-3 h after ischemia onset [66], and have a two-phase pattern of expression with a second peak at 24-36 h [67-68]. In particular, the
importance of cytokines, especially TNF alpha and IL-1 beta, as well as adhesion molecules, has been emphasized in the propagation and maintenance of a CNS inflammatory response [69].

Post-ischemic reflow, reactive oxygen species (ROS) are generated, which then stimulates ischemic cells including neurons and astrocytes to secrete inflammatory cytokines, chemokines and adhesion molecule. Once the inflammatory cascade is activated, inflammatory cells can release a variety of cytotoxic agents including more cytokines, matrix metalloproteinases (MMPs), nitric oxide (NO) and induce more cell damage as well as disruption of the blood–brain barrier (BBB) and extracellular matrix[24-25]. Blocking various aspects of the inflammatory cascade was shown to attenuate ischemic brain injury from experimental stroke [70] although this has yet to be demonstrated clinically.

During cerebral ischemia, inflammatory cytokines interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF), are extremely up-regulated (up to 40- to 60-fold) at least in the brain within the first 24 h of experimental stroke model [71-72]. These cytokines are also increased in cerebrospinal fluid (CSF) and circulating blood after ischemic stroke in humans [73-75]. These three proinflammatory cytokines are able to affect the volume of the ischemic induced tissue damage in rodent experimental stroke [76]. Although IL-1β, IL-6, and TNFα are among the most investigated cytokines in CSF and blood in human stroke patients, their availability and mechanism of action in human brain in the early phase after experimental stroke remain unknown [77]. Besides these three cytokines, other factors such as IL-8, IL-10, CD40L, IFNγ, IL-1α, IL-17, and TGFβ also participate in the inflammatory response after ischemic stroke [78-79]. Understanding the cellular production of cytokines in normal brain, and the time profile and the cellular sources of these cytokines and the possibilities of their transport into the ischemic territory in the early phase after stroke onset is crucial to unveiling the mechanisms by which these cytokines potentially affect brain damage after ischemic stroke.

There exists a close relationship between pro-inflammatory cytokine release and post-stroke inflammatory injury [72]. Although many studies focus on the clinical significance of individual cytokine, each source of circulating cytokines is unclear. Study on the source of cytokines in peripheral blood is useful to better understand the function of cytokine both in peripheral and brain inflammation. There are three major hypotheses: (1) cytokines are released into circulating blood by inflammatory cells in ischemic brain tissue via an impaired
blood–brain barrier; (2) cytokines are secreted and released by activated leukocytes such as neutrophils, lymphocytes and monocytes; (3) cytokines are released by peripheral immune organs [80]. The detailed cytokine network during ischemia development calls for further investigation with animal experiments in vivo and in vitro. Therefore, the source of circulating cytokines needs to be further studied in the future.

Both clinical and animal studies revealed that these inflammatory events occurred prior to stroke onset. Plasma levels of soluble vascular cell adhesion molecule-1 (sVCAM-1), sICAM-1, sE-selectin, and MCP-1 were elevated in patients with essential hypertension in the absence of other diseases [81-82]. Anti-inflammatory strategies were shown to suppress the incidence of stroke in both human and animal models. These reports suggest that inflammation might be a risk factor for stroke. Inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, are secreted by activated microglial cells and macrophages in stroke lesions and induce the expression of chemokines, which recruit more circulating monocytes/macrophages into lesions and lead to further brain damage. However, the role of each cytokine in stroke is complicated (See Fig 4).

**Fig 4**Inflammatory mechanisms before and after stroke
(A) Inflammatory mechanisms that promote stroke: infection and inflammatory disorders can contribute to trigger cerebral ischaemia through pathophysiological processes such as vasculitis, changes of vascular reactivity, and especially atherosclerosis. (B) The acute phase of inflammation after stroke: ischemia causes cell death in the brain parenchyma and subsequent release of endogenous molecules termed damage-associated molecular patterns (DAMPs) from dying cells. DAMPs trigger a cascade of inflammatory events that contribute to the activation of resident cells (microglia and astrocytes) and recruitment of circulating leukocytes (neutrophils, macrophages, dendritic cells, and T lymphocytes). Production of inflammatory mediators exacerbates neuronal injury. Conversely, activated resident cells might produce trophic factors that promote tissue repair and recovery. A potential role of regulatory T cells in restricting brain ischemic injury has been proposed [Liesz A et al. 2009]

**Interleukin-1 (IL-1)**

Interleukin-1 is an important initiator of the immune response, playing a key role in the onset and development of a complex hormonal and cellular inflammatory cascade. IL-1-mediated inflammation contributes to the catastrophic events of acute ischemic diseases. These include myocardial infarction, stroke, liver and kidney failure as well as acute lung injury, each with rapid loss of function [8, 39, 42, 45, 62-63]. Recently, IL-1β has been considered a therapeutic target for stroke. Chronic increases in IL-1β expression in the brain led to leukocyte infiltration and increased MCP-1 and ICAM-1 expressions in a mouse model, which is a phenotype also seen in stroke lesions. In addition, a number of studies have demonstrated that inhibiting the release or action of IL-1 markedly reduced ischemic cerebral damage in animal models [64, 69,77]. IL-1α and IL-1β double knockout mice exhibited dramatically reduced ischemic infarct volume compared with wild-type mice. In a meta-analysis of animal model studies, IL-1 receptor antagonist (IL-1Ra), which represents the most advanced approach to modify IL-1 action, reduced infarct volume in models of focal cerebral ischemia [62, 83]. In humans, a phase II clinical trial of intravenous IL-1Ra compared with placebo in patients with acute stroke is currently underway [24-25]. Further, IL-1Ra gene polymorphism represents a risk factor for ischemic stroke [84]. These reports suggest that inhibition of IL-1β signals can prevent the onset of stroke. The neuroprotective effects attributed to IL-1β seem to be partially mediated by induction of neuronal growth factor (NGF). Treatment of traumatic brain injury in rats with either endogenous IL-1ra or soluble IL-1 receptors conferred no improvement in motor outcome [85]. Nonetheless, IL-1 has been documented to play a role in neuronal degeneration. However neuronal damage was
reported to be attenuated when recombinant IL-1ra was injected intracerebro-ventriculally following ischemic or traumatic injury in rats [86-87]. In accordance with these findings, preclinical animal experiments testing immunosuppressive drugs such as minocycline or erythropoietin after traumatic brain injury attributed the neuroprotective mechanisms of these compounds to the reduction of brain IL-1 synthesis. The endogenous, highly selective, IL-1 receptor antagonist (IL-1ra) protects against ischemic cerebral injury in a range of experimental settings, and IL-1ra causes a marked reduction of cell death when administered peripherally or at a delay in transient cerebral ischaemia. Interleukin-1 receptor antagonist (Anakinra) is the optimal IL-1-targeting agent for stroke because of its small size and proven ability to enter the brain and suppress inflammation in patients who have had a stroke.

**Tumor Necrosis Factor-α (TNF-α)**

In the CNS, the pro-inflammatory cytokine TNF-α is considered the principal mediator of neuro-inflammation that elicits a cascade of cellular events culminating in neuronal death. TNF-α orchestrates a diverse array of functions involved in immune surveillance and defense, cellular homeostasis, and protection against certain neurological insults [88]. TNF-α is upregulated in the brain after ischemia. In clinical studies it has been shown that TNF-α is upregulated in the brain tissue of patients with acute cerebral infarction [89], and appears sequentially in the infarction core and peri-infarct areas before it is expressed in the contralateral hemisphere and other remote brain areas [90]. Concentration of TNF-α in cerebrospinal fluid (CSF) are increased in patients with acute ischemic stroke [91], including those with pronounced white matter lesions [92]. Serum concentrations of TNF-α are also increased in most studies with acute ischemic stroke patients [91, 93] and raised TNF-α concentrations in plasma of patients suffering from lacunar infarctions are associated with early neurologic deterioration and poor functional outcome [94]. Increased serum and cerebrospinal fluid levels of TNF-α have been found in patients 24 hours, 1 week, and 2 weeks after stroke, and these increases correlate with infarct volume and severity of neurological impairment [95]. However, previous reports suggest that TNF-α has a dual role in brain injury [96]. Blockade of TNF-α actions reduced infarct volume after permanent middle cerebral artery occlusion in BALB/C mice with the dimeric type I soluble TNF receptor, which binds to TNF-α and antagonizes its action. In contrast, TNF-α pretreatment was neuroprotective against permanent middle cerebral artery occlusion in BALB/C mice with reduction of infarct size, macrophages, and CD11b-positive neutrophils [97-99]. In addition to these observations, pentoxifylline, an anti-inflammatory agent, attenuated damage
of stroke via the dual role of TNF-α. Pentoxifylline treatment increased serum levels of TNF-α, but not IL-1β and IL-6, and dosedependently prevented the occurrence of spontaneous brain damage by reducing macrophage infiltration into lesion in SHRSP, suggesting a protective role of TNF-α. On the other hand, pentoxifylline reduced brain edema in a rat model of transient focal cerebral ischemia through a decline in TNF-α production [100], suggesting a deleterious role of TNF-α.

Further TNF-α is strongly implicated in the pathophysiology of ischemia induced brain injury. TNF-α may cause secondary cerebral injuries through interference with astrocyte removal of extracellular glutamate, exacerbation of excitotoxicity, activation of microglia and induction of NF-κB-driven production of inflammatory cytokines and ROIs. Studies have also shown that the TNF-α levels directly correlate with the extent of brain damage following ischemia. Adenosine receptor agonists are potent inhibitors of TNF-α production, and adenosine A2A receptor agonist CGS 21680 decreases TNF-α production and neutrophil infiltration after experimental ischemia. Due to its short half-life and quick desensitization, other upstream targets are currently being explored. Although anti-TNF-α strategies have proved beneficial in other clinical settings such as inflammatory bowel disease, there are no clinical trials of anti-TNF-α agents in stroke. Further studies are required to clarify the role of TNF-α in stroke.

**Interleukin-6 (IL-6)**

IL-6 is a multifunctional cytokine that plays an important role in host defense, with major regulatory effects upon the inflammatory response. IL-6 belongs to the neuropoietin family of cytokines, and it has both direct and indirect neurotrophic effects on neurons [101]. IL-6 promotes astrogliosis, activates microglia, and stimulates the production of acute phase proteins. IL-6 is involved in the regulation of neuronal apoptosis and is up-regulated following cerebral ischemia [102]. Different studies suggest that IL-6 has detrimental effects in cerebral ischemia. Thus, raised plasma concentrations of IL-6 are a powerful predictor for early neurological deterioration [103] and are associated with greater infarct volumes and bad outcome. Furthermore, as demonstrated by our group, the association between IL-6 and early neurological worsening prevails without regard to the initial size, topography, or mechanism of the ischemic infarction [104-105]. Cerebral ischemia is a potential bioactivator of IL-6 mRNA, especially in middle cerebral artery occlusion (MCAO) in animal models. Intracerebroventricular injection of anti-inflammatory IL-6 has been associated with
significant reduction in ischemic damage. In a clinical study, circulating IL-6 levels were found to increase significantly, reaching a plateau between 10 h and 3 days, before returning to baseline by 7 days. It also correlated with volume of computed tomography of brain lesion, as well as, poor functional and neurologic outcome. Similar correlation in CSF studies has also been noted. However, IL-6 may also have a proinflammatory role, as in advanced atherosclerosis.

A prospective cohort study and systemic review revealed that plasma levels of IL-6 were associated with poor outcome after both ischemic and hemorrhagic strokes [106]; however, it was not clear whether IL-6 increased before or after stroke onset. Animal models showed less association between IL-6 and stroke. IL-6 could not induce adhesion molecules and MCP-1 mRNA expressions in cerebrovascular endothelial cells derived from SHRSP. Mice deficient in IL-6 showed similar stroke lesion volume and neurological function as control mice in an acute ischemic injury model [107-108]. Furthermore, IL-6 mediates anti-inflammatory effects in addition to its proinflammatory role [109]. Interleukin-6 produced locally by resident brain cells promotes post-stroke angiogenesis and thereby affords long-term histological and functional protection. IL-6 promotes early transcriptomic changes in angiogenesis-related gene networks after brain ischaemia, which leads to increased angiogenesis during the delayed phases after experimental stroke. IL-6 thereby affords long-term histological and functional protection.[110]. Therefore, its manipulation can have either detrimental or beneficial effects. Further studies are required to clarify the role of IL-6 in stroke.

Anti-inflammatory Strategies for stroke

The pathologic processes after ischemic stroke can be separated into acute (within hours), subacute (hours to days), and chronic phases (days to months). Clinical and experimental data show an acute and prolonged inflammatory response in the brain after stroke, and leukocyte recruitment is a hallmark feature of the prolonged inflammatory response that occurs over hours to days after cerebral ischemia. Current protocols of primary stroke management and secondary prevention focuses on modifiable vascular risk factors such as hypertension, smoking, carotid stenosis, atrial fibrillation, physical inactivity, diabetes mellitus, and dyslipidemia, with usage of drugs like antiplatelet agents, antihypertensive drugs, lipid-lowering agents, and anticoagulant drugs. A recent addition to this armamentarium was intravenous tissue plasminogen activator in cases of acute ischemic stroke, the efficacy of which is often limited by stroke severity, older age, systolic hypertension, location of arterial
occlusion, collateral blood supply, and time from stroke onset to treatment, and reperfusion-associated inflammation. The overall recanalization rate in thrombolytic therapy varies from 46.2% during the first 6–24 h of intravenous administration, to 63.2% in intra-arterial and 83.6% with mechanical reperfusion techniques [Stroke Trails Registry 2011]. Current understanding of various pathogenetic mechanisms of stroke has paved the path for newer therapeutic approaches.

There are several reports that treatment with drugs that have anti-inflammatory properties can prevent stroke not only in animal models, but also in humans. Numerous clinical trials have investigated the effects of anti-hypertensive molecules, GP IIa/IIIb inhibitors, or lotrafiban), antiplatelet agents (eg, aspirin, clopidogrel, Dipyridamole, ticlopidine, triflusal, anticoagulants (eg, low-molecular-weight heparins or warfarin), or lipid-lowering drugs (eg, Statins) on prevention of stroke occurrence or recurrence [Stroke Trails Registry 2011]. Several of these strategies (See table 1.1) are presently being used to target the immune system. The MOSES trial, [111] which tested the efficacy of an angiotensin type 1-receptor antagonist (eprosartan) versus a calcium-channel blocker (nitrendipine) in 1352 patients, showed that eprosartan reduced the risk of recurrent acute stroke by about 25%. Similarly, PROGRESS88 reported a 28% relative risk reduction (95% CI 17–38%; p<0.0001) in the primary endpoint of cardiovascular events in 6105 patients who were randomly assigned to perindopril or control. Multiple trials have shown that anti-hypertensive drugs targeting the renin-angiotensin system can reduce stroke incidence. Beyond pharmacological strategies targeting this system, there are other interesting attempts to manipulate the immune system targeting molecules involved in blood-pressure regulation. PMD311789 and Cyt006-AngQb90 vaccines directed against angiotensin I and angiotensin II, respectively, have been tested in phase 2 trials and were inferior in their effect on blood pressure compared with pharmacological inhibitors of the renin-angiotensin system. Nevertheless, strategies to improve the efficacy of such vaccines might confer substantial benefits for stroke prevention in the future by increasing the proportion of patients who are treated for hypertension, as these patients might more readily accept vaccination twice a year than pills every day. However, the long-term effects of such strategies remain unassessed [112].
Table 1: Clinical studies of agents targeting inflammatory pathways in acute ischemic stroke.

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<th>S. No</th>
<th>Neuro-protective agent</th>
<th>Mode of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Enlimomab</td>
<td>Anti-ICAM-1 monoclonal antibody</td>
<td>Enlimomab 2001</td>
</tr>
<tr>
<td>2</td>
<td>Cerovive (NXY-059)</td>
<td>Nitrone-based free radical trapping agent</td>
<td>Lyden PD et al. 2007, Shuyaib A et al. 2007</td>
</tr>
<tr>
<td>3</td>
<td>Recombinant human IL-1RA</td>
<td>Interleukin-1 receptor antagonist</td>
<td>Emsley HC et al. 2005</td>
</tr>
<tr>
<td>4</td>
<td>UK-279, 276</td>
<td>Neutrophil inhibitory factor</td>
<td>Krams M et al. 2003</td>
</tr>
<tr>
<td>5</td>
<td>Tirilazad</td>
<td>Lipid peroxidation inhibitor</td>
<td>Bath PM et al. 2001</td>
</tr>
<tr>
<td>6</td>
<td>Ginsenoside</td>
<td>Ca2+ channel antagonist</td>
<td>Liu X et al. 2009</td>
</tr>
<tr>
<td>7</td>
<td>Edaravone MCI-186</td>
<td>Free radical scavenger</td>
<td>Edaravone Study Group 2003</td>
</tr>
<tr>
<td>8</td>
<td>Acetaminophen (Paracetamol)</td>
<td>Anti-pyretic effect</td>
<td>Van Breda EJ et al. 2005</td>
</tr>
<tr>
<td>9</td>
<td>Minocycline</td>
<td>Anti-inflammatory</td>
<td>Lampl Y et al. 2007</td>
</tr>
<tr>
<td>10</td>
<td>ONO-2506 (Arundic Acid)</td>
<td>Astrocyte modulator</td>
<td>Pettigrew LC et al. 2006</td>
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</table>

Commonly used anti-inflammatory agents used in ischemic stroke prevention and treatment are the lipid-lowering agents-hydroxy-methylglutaryl coenzyme A reductase inhibitors (statins), Thiazolidinediones including rosiglitazone and pioglitazone, and antiplatelet agents like acetylsalicylic acid (aspirin). All of them possess anti-inflammatory effects in addition to their traditionally accepted actions.

Statins

Lipid-lowering effect of statins has already been established its efficacy by significantly reducing incidence of ischemic stroke in patients with coronary artery disease, both with and without elevated serum cholesterol concentrations [135]. Anti-inflammatory and/or neuroprotective properties of statins, have found its base in its ability to reduce CRP levels, especially ones with high CRP levels. Rosuvastatin treatment significantly delayed the onset of stroke and attenuated the transcription of inflammatory biomarkers [113]. Clinical studies using statins already use inflammatory events as endpoints for stroke prevention. In healthy persons without hyperlipidemia but with elevated high-sensitivity CRP levels, rosvastatin, which lowered high-sensitivity CRP as well as cholesterol levels, reduced the incidence of stroke and myocardial infarction by 50% relative to placebo [114]. A meta-analysis of statin trials showed that statins might reduce the incidence of all strokes by decreasing LDL-cholesterol without increasing the incidence of hemorrhagic stroke [115]. In addition to cholesterol dependent effects, cholesterol-independent effects of statins on stroke have also
been recognized [116]. However, statin treatment increases the risk of hemorrhagic stroke in patients with a history of cerebrovascular disease, even though it also clearly decreased the risk of ischemic stroke [117]. Therefore, patients undergoing statin treatment should be carefully monitored to avoid achieving very low level of cholesterols, which are known risks for hemorrhagic stroke [118].

**Thiazolidinediones**

Thiazolidinediones, including rosiglitazone and pioglitazone, are peroxisome proliferator activated receptor-\(\gamma\) (PPAR-\(\gamma\)) agonists used in the treatment of type 2 diabetes. A systemic review showed that Mediators of Inflammation rosiglitazone and pioglitazone were similarly effective in reducing infarct volume and protecting neurologic function in a rodent model of focal or global cerebral ischemia [119]. Pioglitazone delayed the onset of stroke by improving vascular endothelial dysfunction and brain inflammation in SHRSP. Pioglitazone suppressed macrophage infiltration, MCP-1 and TNF-\(\alpha\) gene expressions in the brain [120]. Rosiglitazone induced upregulation of CD36 in macrophages and enhanced the ability of microglia to phagocytose red blood cells, which helped to improve hematoma resolution, and improved functional deficits in an intracerebral hemorrhage mouse model [121]. In humans, the PROspective Pioglit Azone Clinical Trial InMacro Vascular Events (PROACTIVE) [122] showed that pioglitazone significantly reduced the risk of recurrent stroke in high-risk patients with type 2 diabetes [123]. On the other hand, one report showed that compared with pioglitazone, rosiglitazone was associated with an increased risk of stroke, heart failure, and all-cause mortality and an increased risk of the composite of acute myocardial infarction, stroke, heart failure, or all-cause mortality in patients of 65 years or older [124].

**Aspirin**

Apart from its well-established role in prevention of death, myocardial infarction, and stroke in high-risk patients, aspirin has a direct role in modifying CRP levels, thus raising the possibility of an anti-inflammatory action apart from its antiplatelet effect mediated via COX inhibition. Low-dose acetylsalicylic acid (aspirin) also delayed the onset of stroke in SHRSP via suppression of inflammation. Aspirin reduced salt induced macrophage accumulation and MMP-9 activity at the stroke-negative area in the cerebral cortex of SHRSP [127]. Frequent aspirin use might also confer a protective effect for risk of stroke in humans [128]. Based on the findings of the Second European Stroke Prevention Study (ESPS-2), and European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), a
combination of aspirin and extended-release dipyridamole was found superior to aspirin alone for reducing the occurrence of the primary combined end point of vascular death, nonfatal stroke, nonfatal myocardial infarction, and major bleeding complications, and found favour with the most recent American Heart Association guidelines. This was partly attributed to the anti-inflammatory actions of this combination therapy [125]. Further, it is also thought to block NF-κB, which is the transcription factor for a host of proinflammatory mediators of ischemia. Since NF-κB also has a role in resolution of inflammation, excessive modulation might create a problem during the recovery phase [126].

Other anti-Inflammatory Drugs
Terutroban, a specific thromboxane/prostaglandin endoperoxide receptor antagonist, decreased cerebral mRNA expressions of IL-1β, transforming growth factor-β, and MCP-1 and increased survival in SHRSP. These effects were similar to rosuvastatin and aspirin [129]. The Prevention of cerebrovascular and cardiovascular events of ischemic origin with terutroban patients with a history of ischemic stroke or transient ischemic attack (PERFORM) study was started in February 2006 [130]. Recently, it was reported that PERFORM study did not meet the predefined criteria for non-inferiority, but showed similar rates to terutroban and aspirin for the primary end point, such as a composite of fatal or nonfatal ischemic stroke, fatal or nonfatal myocardial infarction, or other vascular death [131].

Deep barbiturate coma, and recently described, NXY-059, the disulfonyl derivative of the radical scavenging spintrapped phenylbutyl nitrotrone, is reported to be neuroprotective in stroke [132-133]. These reports indicate that antiplatelet agents that have anti-inflammatory properties could suppress inflammation and prevent stroke onset.

So neuroprotective agents with anti-inflammatory action which include a diverse range of drugs are directed at restricting damage and salvaging the penumbral tissue. Though the small rim of penumbra acts as a barrier for the successful application of these drugs, their role can be vital in a setting where reperfusion obtained by combined thrombolysis and neuroprotective agent, is sufficient. These drugs act by modulating the excitatory amino acid system, controlling calcium influx, or can be metabolic activators, anti-edema agents, inhibitors of leukocyte adhesion, and free radical scavengers. Unfortunately, despite the safety and efficacy being proved by more than 100 clinical trials its translation into clinical practice remains awaited.
Inflammation and ischemic tolerance

Inflammatory and immune responses play important roles following ischemic stroke. Inflammatory responses contribute to damage and also contribute to repair. Injury to tissue triggers an immune response. This is initiated through activation of the innate immune system. In stroke there is microglial activation. This is followed by an influx of lymphocytes and macrophages into the brain, triggered by the production of pro-inflammatory cytokines. This inflammatory response contributes to further tissue injury. There is also a systemic immune response to stroke, and there is a degree of immunosuppression that may contribute to the stroke patient’s risk of infection. This immunosuppressive response may also be protective, with regulatory lymphocytes producing cytokines and growth factors that are neuroprotective. The specific targets of the immune response after stroke are not known, and the details of the immune and inflammatory responses are only partly understood. The role of inflammation and immune responses after stroke is twofold. The immune system may contribute to damage after stroke, but may also contribute to repair processes. The possibility that some of the immune response after stroke may be neuroprotective is exciting and suggests that deliberate enhancement of these responses may be a therapeutic option.

The suppression of inflammation appears to be the means by which ischemic preconditioning protects against stroke. It is known that a sub-lethal ischemic event confers protection against subsequent lethal ischemia, in various organs, including the brain [134]. In experimental studies, animals that have been subjected to preconditioning have reduced inflammation after a subsequent ischemic challenge and reduced expression of inflammatory molecules [135]. These changes are thought to be associated with changes in expression of genes such as hypoxia inducible factor 1 (HIF1) [136]. In summary, it appears that immune suppression after a preconditioning ischemic episode prevents the acute harmful immune response after a subsequent ischemic episode. There is evidence that inflammation participates in tissue damage in stroke, and this is brought about by the activation of the innate immune system. Immunosuppression after stroke has occurred may be too late to reduce this damage, although further work is required. After the acute injury of stroke, there appears to be a naturally occurring state of immunosuppression, during which infection can occur. This immunosuppression appears to be due, in part, to circulating T cells. There is evidence that the immune system, possibly through such T cells, but also by other types of T cells, may be able to assist in neural repair. There is some animal work that suggests that tolerization to brain antigens improves outcomes after stroke. Thus, immune and inflammatory responses
after stroke are both good and bad. Therapeutic possibilities based on this data include the early use of antibiotics to prevent infection (currently undergoing clinical trial), inhibition of the early inflammatory/immune response, although it is perhaps likely, that doing so after the stroke has occurred may be too late, and perhaps enhancing protective immune responses to speed neural repair.

**DISCUSSION**

Understanding the interaction between the CNS and the immune system will provide greater insight into several different pathologies that involve CNS inflammation and the increase in the number of potential pharmacological targets. The various mechanisms involved in tissue injury during ischemia and neuroprotection are: depletion of cellular energy store due to failure of mitochondria, loss of membrane ion pump function and its deleterious effects, release of excitatory neurotransmitters, production of oxygen free radicals/reactive oxygen species and apoptosis. Knowledge of these mechanisms is vital in order to salvage brain tissue undergoing ischemic damage. Neuroprotective drugs that scavenge reactive oxygen species, inhibit apoptosis, or inhibit excitotoxic neurotransmitters, if used during the ongoing phase of ischemic injury may help to achieve the goal of neuroprotection.

The great variability in the observed effects elicited by NOD, from neuroprotection to toxicity, could be due to the great diversity in doses used in the experiments, which in fact are mainly distant from the existing physiological concentrations. Clarity about the NO concentrations that exists physiologically is essential for developing a quantitative understanding of NO signaling, for performing experiments with NO that emulate reality, and for knowing whether or not NO concentrations become abnormal in disease states. Several independent lines of evidence suggest that NO operates physiologically at concentrations that are orders of magnitude lower than the near-micromolar order once considered correct. Therefore, therapeutic use of these molecules must be performed carefully, because they can be beneficial for one tissue or cell type and harmful for others. Given their short therapeutic window, NOD appears appropriate for use during neurosurgical procedures involving transient arterial occlusions or in very early treatment of acute ischemic stroke. At present, translation from in vitro to in vivo preclinical stroke models requires further research, as clearly as that required for the case for translation from in vivo animal models to the clinical condition of drugs for treatment of acute ischemic stroke, which requires overcoming phase III trials in patients.
Cerebral ischemia triggers a very important inflammatory response, which has been associated to an increase in brain damage and poor outcome in stroke patients. After arterial occlusion, the up-regulated expression of cytokines including IL-1, IL-6 and TNF-α act upon the vascular endothelium to increase the expression of intercellular adhesion molecule–1, P-selectin, and E-selectin, which promote leukocyte adherence and accumulation. Integrins then serve to structurally modify the basal lamina and extracellular matrix. These inflammatory signals then promote leukocyte transmigration across the endothelium and mediate inflammatory cascades leading to further cerebral infarction. Inflammatory interactions that occur at the blood-endothelium interface, involving cytokines, adhesion molecules, chemokines and leukocytes, are critical to the pathogenesis of tissue damage in cerebral infarction. Exploring these pathophysiological mechanisms underlying ischemic tissue damage may direct rational drug design in the therapeutic treatment of stroke. Therefore, anti-inflammatory therapies should be considered to reduce brain damage.

Evidence of epidemiological association of inflammatory markers, particularly C-reactive protein, has accrued, but the independence of inflammation from more conventional risk indicators is under question. Other inflammatory markers are associated with intermediate phenotypes such as hypertension. Tissue inflammation in atherosclerotic plaque is of probable relevance in identifying recently symptomatic carotid disease. Both humoral and cellular inflammations are evident following stroke, with evidence that these responses may exacerbate tissue injury. Blockade of interleukin-1, or of neutrophil chemotaxis, has reduced infarct volume in models of stroke but has yet to show benefit in clinical trials. Other anti-inflammatory strategies are promising. Inflammation is implicated in several aspects of acute ischemic stroke. It remains to be established whether the inflammatory response is a truly independent risk factor in general, or whether specific anti-inflammatory interventions are beneficial either in prevention or acute treatment.

**CONCLUSION**

The complex pathophysiology stroke encompasses various excitotoxicity mechanisms, inflammatory pathways, oxidative damage and ionic imbalances. Despite significant therapeutic advances in the form of carotid endarterectomy, thrombolytics, anticoagulant therapy, antiplatelet agents, neuroprotective agents, and treating associated risk factors such as hypertension and dyslipidemia have failed to reduce the burden of stroke. Current understanding of inflammation and ischemia has caused a paradigm shift in the perspective of
stroke pathogenesis and outcome. It has also opened newer avenues in stroke management and prevention strategies, beyond the realms of antithrombotics. Though one needs to keep abreast with recommended protocols for stroke management, knowledge of the underlying pathogenetic process, aided by laboratory investigations and imaging, may usher in more therapeutic options. Well-designed clinical trials of novel therapeutic agents and strategies will be able to substantiate or refute their clinical usefulness, and confirm the possibility of being incorporated into evidence-based practice guidelines.

Furthermore, the latest advances in the immunomodulation field, together with the advances on the knowledge of the ischemic tolerance phenomenon and the role of innate immunity in such phenomenon could open a possibility for the application of immunomodulatory therapies prior to a stroke insult to prepare the organism to stand better the inflammatory response when stroke occurs. In summary, inflammation has been associated to an increase in brain damage in stroke patients. Furthermore, inflammation is necessary to activate repairing mechanisms. Therefore, it is necessary a strictly control the inflammatory response after stroke to reduce brain damage without inhibition of the repairing mechanisms.

Several complex and overlapping pathways underlie the pathophysiology of cell death after ischemic stroke. While pharmaceutical agents can inhibit these pathways at various levels, resulting in effective neuroprotection in experimental models, no single agent intended for neuroprotection has been shown to improve outcome in clinical stroke trials. Refinements in patient selection, brain imaging, and methods of drug delivery, as well as the use of more clinically relevant animal stroke models and use of combination therapies that target the entire neurovascular unit, are warranted to make stroke neuroprotection an achievable goal. Ongoing trials assessing the efficacy of thrombolysis with neuroprotective agents and strategies aimed at extending the therapeutic window for reperfusion therapy promise to enhance the known benefits of reperfusion therapy. Most investigators agree that genomics and proteomics are the most promising recent developments impacting the future of stroke prevention, diagnosis, treatment, and outcome. Although many challenges lie ahead, an attitude of cautious optimism seems justified at this time.

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The authors declare no conflict of interest.

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