

Review Article

Brain ischemic tolerance and inflammation reaction

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Abstract: Brain ischemic tolerance is a phenomenon that a prior sublethal harmful stimulus could promote the tolerance to subsequent deadly ischemic injuries. It is well established that inflammatory reaction plays a key role in the period of pre- and post-stroke. However, the exact mechanism between brain ischemic tolerance and inflammatory reaction during the stroke period is not well clarified until now. In this review, we summarized the related mechanisms of the influence of inflammatory reaction for brain ischemic tolerance. If the detailed mechanism of inflammatory reaction for stroke is elucidated clearly, the stroke patients will gain benefits from the therapy method in regulating inflammatory reaction in the period of stroke treatment.

Keywords: Inflammation reaction, stroke, cytokine, toll-like receptors

Introduction

Stroke has become the first reason of death in china where has at least seven million patients suffering stroke [1]. Recurrent stroke is more destructive and lethal compared to the first, accounting for 25-30% of preventable stroke [2]. Ischemic tolerance describes a phenomenon that a prior sublethal harmful stimulus could promote the ability of resistance to subsequent deadly ischemia. This adaptive response is now known to be an evolutionarily conservative defense mechanism, discovered in a widely various species [3]. A number of related studies have shown that exercise training, electro-acupuncture and normobaric hyperoxia may induce brain ischemic tolerance via the augment of angiogenesis, regulation of the inflammatory response, down-regulation of glutamate over-activation, improvement of blood brain barrier (BBB) and mediation of apoptosis [4]. Different study data shows that 23% to 65% of patients suffer from the development of infection after stroke [5]. Inflammatory reaction and substantial innate immune responses induced by stroke in the brain areas are assembled. However, the relationship between antigen presentation and functional and brain ischemic tolerance is still unclear until now [6].

Inflammatory reaction and brain injury following ischemic stroke

Inflammatory response is important for the pathogenesis of brain ischemic stroke [7], and is known to play a key role in the process of the recovery and repair after injury [8]. Clinical studies show that the sensibility of the patients to ischemic stroke and the following prognosis could be influenced by systemic inflammation. However, restraint of inflammatory responses could deteriorate issue repair and long-run functional rehabilitation after ischemic stroke [7]. It is well known that post-stroke inflammatory response contributes to blood-brain barrier disorder, poor functional recovery and neurovascular injury in both clinical and animal studies. Precious reports indicate that post-ischemic inflammation is also necessary for the brain remodeling and repair [8]. Inflammatory response not only aggravates secondary brain damage in the sharp stage of ischemic stroke but also advantageously redounds to ischemic issue repair after stroke [7]. The characteristic for inflammation in acute ischemic stroke (AIS) includes a series of chemokines, cytokines and Damage-Associated Molecular Patterns (DAMPs) delivered by the cells which aggravate the tissue damage both in the acute and chronic periods [9].

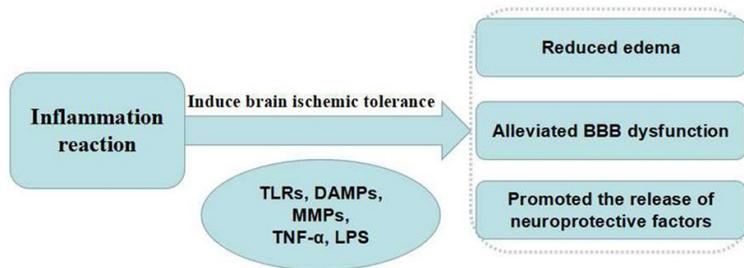


Figure 1. Inflammation reaction may induce brain ischemic tolerance via a series of inflammation-mediated factors, such as TLRs, DAMPs, MMPs, TNF- α , LPS, ultimately reducing cerebral edema, alleviating BBB dysfunction and promoting the release of neuroprotective factors.

Immune response in both central and peripheral immune system during stroke

Ischemic tolerance has involved in a subtle activation of the immune response, including cytokine signaling pathways and toll-like receptors (TLRs) [10]. Immune and inflammatory responses obviously regulate the pathophysiological actions in the process of acute stroke. In the early stage of stroke, protein factors, for instance cytokines, chemokines, danger-associated molecular patterns (DAMPs), and related factors, are delivered from the brain ischemic area into the systemic circulation [11]. The brain ischemic areas communicate with peripheral organs via the sympathetic and parasympathetic embranchments of the autonomic nervous system. Those related various signals not only activate brief immune cells of the brain, but also elicit potent immune responses of the periphery. Peripheral immune cells then move toward the ischemic brain and release additional chemokines, cytokines, and other related molecules, inducing further devastative or patronal effects in the brain ischemic area. It is well established that bidirectional interaction between the peripheral immune system and the ischemic brain modulates the progression of ischemic stroke pathology and injured tissue restoration [11].

The effect of cytokines on the outcome of brain injury

It is debated that cytokines are beneficial to the outcome of brain injury. The TNF-receptor knock-out mice (p75 and p55 knock-out) exhibits increased sensitivity to ischemia injury, and repeated administration IL-1 can induce the condition of ischemic tolerance [12]. Reduced inflammatory responses and brain edema are

connected with altered levels of cytokines and angiogenic factors in preconditioned brains after MCAO [13]. In addition, proinflammatory cytokines heighten sympathetic nerve system activity and excite the hypothalamic-pituitary-adrenal axis [14].

Cytokines, such as IL-1 β and TNF- α , are released in the early hypoxia, inducing either local or systemic inflammatory response, relating with cell death [15].

Early after ischemia, cytokines and activated metalloproteases (MMPs), which are released by perivascular astrocytes, contribute to vasogenic oedema and blood-brain barrier (BBB) disruption [10]. Therefore, in this period, the ability of cytokines is to worsen brain injury [12]. At later stages of ischemia, perivascular astrocytes involve in neurotrophic factors release, BBB regeneration and extracellular glutamate uptake [10]. Lacking monocyte chemoattractant protein-induced protein 1 (MCP-1) aggravates ischemic brain injury and MCP-1 participates in ischemic stroke tolerance via preconditioning of Lipopolysaccharide (LPS) [16].

In humans, IL-10 may produce a beneficial effect in ischemic stroke. Modulation of cerebral inflammation may improve stroke outcome and enhance mechanisms of restoring through nasal vaccination with myelin Ags which increase IL-10 in the brain [17]. Microglia may prompt the mitigation of inflammation, by releasing IL-10 and tumor growth factor (TGF)- β , and delay the prothetic processes by growth factors production and phagocytic activity [10].

Tumor necrosis factor-alpha (TNF- α), as an important pro-inflammatory cytokine, is released in brain following ischemia. TNF- α protects brain against from ischemic damage and plays a key role in the signaling pathways which induce brain ischemic tolerance [18]. The in vivo study indicates that transforming growth factor beta 1 (TGF-beta 1) mediates the brain ischemic tolerance caused by lipopolysaccharide (LPS) preconditioning [19]. CCL2 (MCP-1) in one of the leukocyte-derived pro-inflammatory chemokines and is also immediately activated by hypoxia-induced transcription. The early release of CCL2 from neurons, the late release

of CCL2 from cerebral endothelial cells, and CCL2-regulated effects on circulating CCR2+ monocytes, seem to be necessary to induce ischemic tolerance to focal stroke following HPC, demonstrating a new way for CCL-2 in endogenous neurovascular protection [20].

The role of toll-like receptors in the process of brain ischemic tolerance

The preconditional intervention for minor cerebral ischemia or the pretreatment on TLR ligands might mitigate brain ischemic damage via modulating the TLR signaling pathway after ischemic stroke, leading to TLR ischemic tolerance [21]. TLR ligands systematical administration initiates a phenomenon of tolerance to succedent ischemic damage. Inhibition of pro-inflammatory mediators and up-regulated expression of a series of anti-inflammatory molecules could jointly induce mighty neuroprotection [22]. Experiment results indicate that pretreatment with diverse Toll-like receptor (TLR) agonists successfully attenuate ischemic injury, partially by genomic reprogramming of the organism's reaction to stroke. This treatment reduces the inflammatory reaction to stroke and simultaneously promotes the release of neuroprotective factors and anti-inflammatory cytokines [23]. In addition, recent studies indicate that intervention with TLR ligands following cerebral ischemia may also mitigate ischemic injury by modulating the TLR signaling pathway, displaying an obvious treatment effect against brain ischemia [21]. Activation of TLR can be induced by a series of pretreatment stimulation, an event that ahead of ischemia and finally results in TLR reprogramming. Therefore, genomic reprogramming of TLR signaling pathway might be a consolidating tenet of tolerance to brain ischemia [22]. It is indicated that astrocytic TLR3 signaling can regulate brain ischemic tolerance. This reprogramming of astrocytes TLR3 signaling via IPC can play a key role in suppressing inflammatory reaction following ischemia and thus protect against cerebral ischemic injury. The mechanism may be due to activate the TLR3/TRIF/IRF3 signaling pathway [24].

Cerebral ischemic tolerance caused by hypoxia preconditioning may be due to a possible mechanism of initiating TLR4 signal pathway and then suppressing inflammatory reaction caused by asphyxial cardiac arrest (ACA) [25]. Furthermore, minor activation of TLR4 via pre-

treatment with low-dose lipopolysaccharide (LPS) ahead of brain ischemia obviously ameliorates outcome of cerebral damage via reprogramming the TLR4 signaling reaction to damage. It is indicated that TLR4 signaling may lead to an endogenously neuroprotective effect [26]. The results characterize a series of crucial mediators of the TLR4 signaling events related to neuroprotection. LPS pretreatment reprogrammes TLR4 signaling responding to brain ischemia via inhibiting NF κ B activity, increasing IRF3 activity, and prompting anti-inflammatory/type I IFN gene expression. Interestingly, this protective phenotype is not required to the inhibition of pro-inflammatory molecules. Moreover, the result pinpoints an important role of TRIF-IRF3 signaling as the key mechanism of neuroprotective effect for stroke [26]. Additionally, It is indicated that innate immunity and TLR4 signaling might take part in ischemic tolerance and the protective mechanisms of post conditioning [27].

In conclusion, inflammation reaction influenced the brain damage before and after stroke occurrence via a serious of inflammation mediating factors, as shown in **Figure 1**. If the exact mechanism could be clarified, the possible medication therapy target or new treatment methods might be contrived to provide benefits for stroke patients.

Disclosure of conflict of interest

None.

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