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Review article

Astrocytes and ischemic tolerance

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ABSTRACT

A mild non-lethal ischemic episode can induce resistance to a subsequent severe ischemic injury in the brain. This phenomenon is termed ischemic tolerance or ischemic preconditioning, and is an endogenous mechanism that can provide robust neuroprotection. Because of its neuroprotective effects against cerebral ischemia or stroke, ischemic tolerance has been widely studied. However, almost all studies have been performed from the viewpoint of neurons. Accumulating evidence suggests that glial cells have various roles in regulation of brain function, including modulation of synaptic transmission, neuronal excitation, and neuronal structure. In addition, astrocytes are closely related to homeostasis, stability of brain function, and protection of neurons. However, glial cells have received only limited attention with regard to ischemic tolerance. Cross-ischemic preconditioning is a phenomenon whereby non-ischemic preconditioning such as mechanical, thermal, and chemical treatment can induce ischemic tolerance. Of these, chemical treatments that affect the immune system can strongly induce ischemic tolerance, suggesting that glial cells may have important roles in this process. Indeed, we and others have demonstrated that glial cells, especially astrocytes, play a pivotal role in the induction of ischemic tolerance. This glial-mediated ischemic tolerance provides a robust and long-lasting neuroprotection against ischemic injury. In this review, we discuss the mechanisms underlying glial-mediated ischemic tolerance, as well as its potential benefits, problems, and therapeutic application.

Contents

1. Introduction 00
2. Mechanisms of cerebral ischemic tolerance 00
3. Innate immune system and microglial-mediated cerebral ischemic tolerance 00
4. Astrocyte-mediated ischemic tolerance 00
4.1. Essential role of astrocytic activation for induction of ischemic tolerance 00
4.2. Mechanisms underlying astrocyte-mediated ischemic tolerance 00
5. Concluding remarks 00
Declaration of interest 00
Acknowledgements 00
References 00

1. Introduction

Stroke or cerebral ischemic injury is a leading cause of death and disability worldwide. Reducing the length of ischemia by restoring blood flow is the most important treatment for stroke. However, progressive neuronal degeneration can still occur well after restoration of cerebral blood flow. This delayed injury involves several proinflammatory mediators or excitatory transmitters, including cytokines, glutamate, nitric oxide, free radicals, and prostaglandins (Ikeda-Matsuo et al., 2006; Lucas et al., 2006). However, pharmacological treatments targeting these pathways are only partially effective, with hundreds of clinical trials testing neuroprotective agents failing to show therapeutic effect against ischemic stroke (O'Collins et al., 2006; Tymianski, 2013). Thus, there is increasing interest in understanding the mechanisms of endogenous neuronal protection as potential neuroprotective strategies.

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Ischemic preconditioning (PC) or 'ischemic tolerance' was first reported in the heart over 30 years ago (Murry et al., 1986). This phenomenon is an endogenous protective mechanism whereby a mild ischemic episode (i.e., PC) can produce resistance to a subsequent more severe ischemic insult (Stenzel-Poore et al., 2003). Since its first discovery, PC had been found to induce tolerance in a range of organs including the lung (Soncul et al., 1999), kidney (Bonventre, 2002), liver (Yadav et al., 1999), skeletal muscle (Pang et al., 1995), intestine (Hotter et al., 1996), and brain, the most vulnerable organ to ischemia (Kirino et al., 1991; Kitagawa et al., 1990). In addition, these protective effects were observed in both animal experiments (Kirino et al., 1991; Kitagawa et al., 1990) and in the clinical setting (Weih et al., 1999).

Ischemic tolerance has several different aspects, but can be broadly divided into two types based on timing of onset; i.e., rapid- or early-tolerance and delayed-tolerance. Rapid-tolerance is a classical tolerance that is observed immediately after PC, whereas delayed-tolerance involves a slow-onset over 1–3 days after PC, but which lasts longer. Although most stimuli include both rapid- and delayed-tolerance, rapid-tolerance is mainly induced by modulation of neurotransmitters such as adenosine and $\gamma-$amino butyric acid (GABA), and by their receptor-mediated rapid signaling cascades such as phosphorylation, while delayed-tolerance is mediated by synthesis of proteins that induce protective effects. Rapid-tolerance is used therapeutically in cardiac and brain surgery, and has been the major focus of experimental studies in cardiology (Stokfisz et al., 2017). However, the neuroprotective effect of delayed-tolerance is stronger and more robust, and there is increasing interest in delayed-tolerance in the field of neuroscience.

It has also become apparent that there are various types of ischemic tolerance depending on the induction methods. For example, remote-tolerance is induced by a PC treatment at a remote site from the CNS. For example, hind limb PC induces ischemic tolerance in the CNS (Ren et al., 2008). Cross-tolerance is a phenomenon where ischemic tolerance can be induced by a non-ischemic PC such as hyperthermia, hypothermia, or chemical treatments (Kirino, 2002; Stetler et al., 2014). Although the causes of diseases vary markedly, neuronal injury in the brain has overlapping mechanisms related to inflammation, excitotoxicity, and apoptosis. Thus, cross-tolerance has been considered to be applicable to the clinical setting.

The mechanisms of ischemic tolerance in the CNS are complex and have not been fully elucidated. Nevertheless, many molecules and signaling cascades have been reported as important sensors, transducers, and effectors for ischemic tolerance (Abbott et al., 2006; Stetler et al., 2014). Although many of these have been investigated from the point of view of neuronal autonomous mechanisms, ischemic tolerance can be induced by multistep mechanisms through multiple cell types including neurons, astrocytes, microglia, and vesicular cells. Indeed, cross-tolerance studies indicate that many chemicals that control immune cells can also induce cerebral ischemic tolerance (Pardon, 2015), suggesting a potential mechanistic role of immune responses.

The brain consists of both neurons and non-neuronal cells such as glia and vascular endothelial cells, of which microglia and possibly astrocytes are considered important in regulating innate immunity in the CNS. Importantly, glial cells are highly sensitive to environmental changes, and thus can be influenced by even a mild insult such as brief ischemia or PC, which may result in marked effects on neuronal function, survival, and ischemic tolerance. Accumulating evidence suggests that neurons, glia, and vascular cells are interconnected to provide a wide control over brain function (Araque et al., 2001; Haydon, 2001; Koizumi et al., 2003), and there is increasing interest in a more 'gliocentric' understanding of the brain. Nevertheless, the glial contribution to ischemic tolerance remains poorly understood. Thus, as there are many comprehensive reviews on cerebral ischemic tolerance, herein we focus on the role of glial cells, particularly astrocytes, and summarize recent progress on glial-mediated ischemic tolerance.

2. Mechanisms of cerebral ischemic tolerance

Cerebral ischemic tolerance was first described by Kitagawa et al. in 1990 (Kitagawa et al., 1990), where a brief period of global ischemia protected hippocampal neurons from a subsequent severe global ischemic insult. Transient focal ischemic PC was then reported to be neuroprotective against subsequent global severe global ischemic damage in the ischemic zone, as well as in ipsilateral hippocampal neurons (Kirino, 2002). Further, cerebral ischemic tolerance was demonstrated to be induced by non-ischemic PC such as hypoxia (Gidday et al., 1994), as well as other physical, chemical, or pharmacological treatments (termed cross-tolerance). In addition, unlike tolerance seen in other tissues or organs, cerebral ischemic tolerance is induced by characteristic mechanisms such as spreading depression (Kobayashi et al., 1995), epilepsy (Sasahira et al., 1995), and brief stimulation of glutamatergic signals (Himori et al., 1991). Thus, the mechanisms underlying cerebral ischemic tolerance are complex and involve a wide range of molecules, cells and systemic responses.

Numerous studies have examined the mechanisms that underlie cerebral ischemic tolerance (Abbott et al., 2006 Dirnagl et al., 2009; Stetler et al., 2014). Ischemic tolerance is induced in a stepwise process, involving sensing of PCs, their transduction, and neuroprotection. As shown by Dirnagl et al., a range of sensors, transducers, and effectors are involved in these processes (Dirnagl et al., 2009). For example, adenosine receptors, $GABA_A$ receptors, N-methyl-D-aspartate (NMDA) receptors, toll-like receptor (TLR)s, K_{ATP}, and hypoxia inducible factor (HIF) have been reported as sensors; MAPK, protein kinase C (PKC), phosphoinositide 3(PI3)-kinase, nuclear factor-kappa B (NFκB), Akt, cAMP response element binding protein (CREB), and HIF (also a sensor) have been reported as transducers; and superoxide dismutase, Bcl-2, erythropoietin (EPO), vascular endothelial growth factor (VEGF), insulin-like growth factor, nerve growth factor, and brain-derived neurotrophic factor (BDNF) have been reported as effectors. Activation of CREB mediates Bcl-2 (Meller et al., 2005) or BDNF (Terasaki et al., 2010) expression in neurons, and accumulation and translocation of HIF induces VEGF, EPO, and insulin-like growth factor expression in neurons. Mitochondrial K_{ATP} in neurons is a key molecule that controls subsequent energy homeostasis. Thus, these receptors, transducers, and effectors overlap in a complex manner, and multiple steps, molecules, cells (organs), or systems are involved in the mechanism of cerebral ischemic tolerance.

3. Innate immune system and microglial-mediated cerebral ischemic tolerance

Mild ischemia (Stenzel-Poore et al., 2003) or hypoxia (Baranova et al., 2007) is the most common PCs for induction of cerebral ischemic tolerance. However, as described, cross-tolerance can cause a similar extent of ischemic tolerance as ischemic PC. For example, physical PC such as hyperthermia (Chopp et al., 1989), hypothermia (Yunoki et al., 2003), or hyperbaric oxygen (Li et al., 2008a) can induce ischemic tolerance. In addition, chemicals or pharmacological treatments (chemical PC) such as volatile anesthetic agent isoflurane (Zheng and Zuo, 2004), 3-nitropropionic acid (Horiguchi et al., 2003), the anti-oxidative molecule resveratrol (Raval et al., 2006), lipopolysaccharide (LPS) (Nawashiro et al., 1997; Tasaki et al., 1997), and several proinflammatory cytokines (Castillo et al., 2003; Nawashiro et al., 1997; Ohtsuki et al., 1996) induce strong resistance against subsequent lethal cerebral

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