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New roles of reactive astrocytes in the brain; an organizer of cerebral ischemia

Schuichi Koizumi*, Yuri Hirayama, Yosuke M. Morizawa

Department of Neuropharmacology, Interdisciplinary Graduate School of Medicine, University of Yamanashi, 1110 Shimokato, Chuo, Yamanashi 409-3898, Japan

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ABSTRACT

The brain consists of neurons and much higher number of glial cells. They communicate each other, by which they control brain functions. The brain is highly vulnerable to several insults such as ischemia, but has a self-protective and self-repairing mechanisms against these. Ischemic tolerance or preconditioning is an endogenous neuroprotective phenomenon, where a mild non-lethal ischemic episode can induce resistance to a subsequent severe ischemic injury in the brain. 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. Glial cells are structurally in close association with synapses. Recent studies have uncovered the active roles of astrocytes in modulating synaptic connectivity, such as synapse formation, elimination and maturation, during development or pathology. However, glia-mediated ischemic tolerance and/or neuronal repairing have received only limited attention. We and others have demonstrated that glial cells, especially astrocytes, play a pivotal role in regulation of induction of ischemic tolerance as well as repairing/remodeling of neuronal networks by phagocytosis. Here, we review our current understanding of (1) glial-mediated ischemic tolerance and (2) glia-mediated repairing/remodeling of the penumbra neuronal networks, and highlight their mechanisms as well as their potential benefits, problems, and therapeutic application.

1. Introduction

The brain is the most vulnerable organ to several diseases such as ischemia. Cerebral ischemia or stroke is a leading cause of death and disability worldwide. A quick restoring blood flow is the most important treatment for stroke, but progressive neuronal degeneration can still occur even after well restoration of cerebral blood flow, i.e., after supply of oxygen and energy. This delayed injury is thought to involve several proinflammatory mediators or excitatory transmitters, including cytokines, glutamate, nitric oxide, free radicals, and prostaglandins (Ikeda-Matsuo et al., 2006; Lucas et al., 2006), and thus, hundreds of chemicals targeting these pathways were developed. However, almost all were only partially effective, and hundreds of clinical trials for such pathways failed 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' and/or 'repairing' as potential strategies.

A mild non-lethal ischemic episode (preconditioning, PC) can produce resistance to a subsequent more severe ischemic insult. This phenomenon is called 'ischemic tolerance' or 'ischemic preconditioning' and, was first reported in the heart over 30 years ago (Murry et al., 1986). Since then, ischemic tolerance 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, one of the most vulnerable organs 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), and thus many of both basic and clinical researchers have studied this event.

It has also become apparent that there are various types of ischemic tolerance based on the induction methods. For example, cross-tolerance is a phenomenon where ischemic tolerance can be induced by a non-ischemic PC such as hypoxia, hyperthermia, hypothermia, or chemical treatments (Kirino, 2002) (Stetler et al.,

* Corresponding author.
E-mail address: skoizumi@yamanashi.ac.jp (S. Koizumi).

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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 is considered to be applicable to the clinical setting.

With regard to mechanisms of ischemic tolerance, 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), but ischemic tolerance in the CNS are complex and have not been fully elucidated. Because cerebral ischemic tolerance is believed to be caused by cell autonomous mechanisms of neurons, so far, many of these have been investigated from the viewpoints of neurons. However ischemic tolerance can be induced by multistep mechanisms through multiple cell types including neurons, glial cells (Trendelenburg and Dirnagl, 2005) (Hazell, 2007; McDonough and Weinstein, 2016; Weinstein et al., 2010)and vascular cells (Busija et al., 2016; Ozaki et al., 2016). In fact, 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 in the brain.

Among neurons and non-neuronal cells, microglia and possibly astrocytes are considered important in regulating innate immunity in the brain. Importantly, glial cells are highly sensitive to environmental changes (Shinozaki et al., 2014, 2017), and thus can be influenced by even a mild insult such as brief ischemia or PC. The brain consists of neurons and much higher number of glial cells, i.e., astrocytes, microglia and oligodendrocytes. Glial cells especially astrocytes have been previously known to serve the supportive roles in neural functions, such as ion homeostasis, neurotransmitter clearance and energy supply to neurons, and they are structurally in close association with synapses (Eroglu and Barres, 2010) (Freeman, 2010) (Fields et al., 2014; Khakh and Sofroniew, 2015). However, 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 has received only limited attention (Hazell, 2007; Trendelenburg and Dirnagl, 2005; Vangeison and Rempe, 2009; Weinstein et al., 2010) (McDonough and Weinstein, 2016). In addition, the glial contribution to fix the injured neurons also remains largely unknown. In this review, we focus on the role of glial cells, particularly reactive astrocytes, and summarize recent progress on glial-mediated ischemic tolerance as well as glia-mediated repairing/remodeling of the brain.

2. Cerebral ischemic tolerance

2.1. Neurogenic history of ischemic tolerance

The first finding of cerebral ischemic tolerance was reported by Kitagawa et al. (1990), where he demonstrated that a brief period of global ischemia protected hippocampal neurons from a subsequent severe global ischemic insult. After that, transient focal ischemic preconditioning 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). 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 more 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), and a range of sensors, transducers, and effectors are demonstrated to be involved in these processes in a complex manner (Dirnagl et al., 2009). Since there have already been many lines of reviews, we would not like to describe further about molecular mechanisms, but would like to mention that many of them are from neuronal viewpoints. Again, mechanisms underlying cerebral ischemic tolerance are highly complex, probably because the brain consists of many different types of cells, and they use a big variety of neurotransmitters, gliotransmitters, growth factors, chemokines and cytokines. Therefore, we would like to describe cerebral ischemic tolerance from the viewpoint of neuron-to-glia communications.

2.2. Microglia-mediated cerebral ischemic tolerance

A mild ischemia/hypoxia (Stenzel-Poore et al., 2003) (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), several proinflammatory cytokines (Castillo et al., 2003; Nawashiro et al., 1997; Ohtsuki et al., 1996) and lipopolysaccharide (LPS) (Nawashiro et al., 1997; Tasaki et al., 1997) induce strong resistance against subsequent lethal cerebral ischemia. Although these, herein we focus on chemicals or pharmacological treatments that cause inflammatory responses, as these pretreatments strongly and efficiently induce cerebral ischemic tolerance. These data also suggest that innate immune signals form an important mechanism of cerebral ischemic tolerance, which in the CNS, likely involves microglia and astrocytes.

The endotoxin LPS, a membrane component of Gram-negative bacteria, is often used to mimic the inflammatory responses in various experimental models. LPS acts on TLRs especially TLR4 mainly expressed on innate immune cells, and can trigger a wide range of inflammatory responses. Pretreatment of animals with LPS induces potent ischemic tolerance, which was dramatically inhibited in TLR4-deficient animals (Rama Rao and Kielian, 2015). A similar TLR4-mediated cross-tolerance was also observed following pretreatment with several other TLR4 agonists (Ejlerskov et al., 2015). In the CNS, TLR4 is highly expressed on microglia, suggesting microglial involvement in LPS-induced cross-tolerance. Microglia are highly sensitive to changes in the brain environment, and rapidly become activated (Shinozaki et al., 2014) (Shinozaki et al., 2017). Although ischemic PC is a non-lethal insult, it is sufficient to transform microglia into activated or ischemic tolerance-inducible phenotypes (Fig. 1). These findings strongly suggest that microglia may turn on the initial switch of induction of cerebral ischemic tolerance.

Using a middle cerebral artery occlusion (MCAO) model, we tested whether microglia are involved in cerebral ischemic tolerance. A brief transient MCAO, i.e., PC, was sufficient to activate microglia, which was followed by astrocytic activation 2–3 days after PC (Fig. 1). There was a positive correlation in the spatio-temporal pattern of microglial activation with induction of cerebral ischemic tolerance, although there were some discrepancies especially in its time-course (Hirayama et al., 2015). In that study, microglial activation was quick, and in the later stage of ischemic

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