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Review article

Help-me signaling: Non-cell autonomous mechanisms of neuroprotection and neurorecovery

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ABSTRACT

Self-preservation is required for life. At the cellular level, this fundamental principle is expressed in the form of molecular mechanisms for preconditioning and tolerance. When the cell is threatened, internal cascades of survival signaling become triggered to protect against cell death and defend against future insults. Recently, however, emerging findings suggest that this principle of self-preservation may involve not only intracellular signals; the release of extracellular signals may provide a way to recruit adjacent cells into an amplified protective program. In the central nervous system where multiple cell types co-exist, this mechanism would allow threatened neurons to "ask for help" from glial and vascular compartments. In this review, we describe this new concept of help-me signaling, wherein damaged or diseased neurons release signals that may shift glial and vascular cells into potentially beneficial phenotypes, and help remodel the neurovascular unit. Understanding and dissecting these non-cell autonomous mechanisms of self-preservation in the CNS may lead to novel opportunities for neuroprotection and neurorecovery.

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Contents

Abbreviations: Aβ, β amyloid; BBB, blood brain barrier; BrdU, 5-bromo-2′-deoxyuridine; CSF, cerebrospinal fluid; CSF1, colony stimulating factor-1; CSF1R, colony stimulating factor-1 receptor; DAMPs, damage associated molecular pattern family; EPO, erythropoietin; FGF, fibroblast growth factors; IL, interleukin; LCN2, Lipocalin-2; LPS, lipopolysaccharide; MCPs, monocyte chemoattractant proteins; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; NPCs, neural progenitor cells; OGD, oxygen-glucose deprivation; 6-OHDA, 6-hydroxydopamine; SVZ, subventricular zone; TIA, transient ischemic attack; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor; ZO, zonula occludens.

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1. Introduction

Cellular function requires the ability to respond to an existing stimulus and then adapt for future stimuli. Within this broad definition of homeostasis lies the concept of tolerance and preconditioning against injurious stimuli. Preconditioning is a well-defined phenomenon whereby a first sublethal dose of an otherwise harmful stimulus results in tolerance to a second injury stimulus (Stevens et al., 2014). A large amount of data from both experimental models as well as clinical conditions exists for cerebral ischemia. Therefore, this review is focused on signaling cascades for ischemic brain injury.

Ischemic preconditioning in the brain was described in 1990, wherein an initial sublethal ischemic stress induced tolerance in the hippocampal CA1 against subsequent lethal ischemic injury in gerbil models of transient global ischemia (Kitagawa et al., 1990). Then this phenomenon was confirmed for transient global ischemia in the rat brain (Nishi et al., 1993) and other models of focal ischemia (Chen et al., 1996). Several retrospective studies have also suggested that transient ischemic attacks (TIAs) in humans are associated with improved clinical outcome after stroke, perhaps because TIAs are capable of inducing ischemic tolerance (Fu et al., 2008; Moncayo et al., 2000; Wegener et al., 2004; Weih et al., 1999). In the context of stroke, preconditioning induces a transient window of protection that requires gene activation and new protein synthesis (Dirnagl et al., 2009). This reprogrammed response forms the basis for endogenous neuroprotection and provides a conceptual framework for investigating the molecular mechanisms that protect the brain against ischemic injury (Chen et al., 1996; Kapinya et al., 2002; Koerner et al., 2007; Marsh et al., 2009; McCabe and Simon, 1993; Stenzel-Poore et al., 2003; Stevens et al., 2011; Truettner et al., 2002; Zimmermann et al., 2001).

At a cellular level, the ability of preconditioning to trigger endogenous protective mechanisms can be viewed within a conceptually cell autonomous model (Fig. 1A). The initial sublethal insult induces intracellular signaling pathways that serve to block the second lethal insult. However, cells do not exist in isolation and beyond a theoretical single cell response, the release of extracellular signals may provide a way to recruit adjacent cells into an amplified protective program (Fig. 1B). The initial sublethal insult induces a cascade of intracellular signals that provoke the release of extracellular mediators that affect an adjacent cell. Then this second cell responds by releasing another set of extracellular signals that block a lethal insult against the original cell. This non-cell autonomous model thus sets the stage for the concept of help-me signaling, wherein multiple cells interact to assemble an integrated adaptive and protective response after injury and disease.

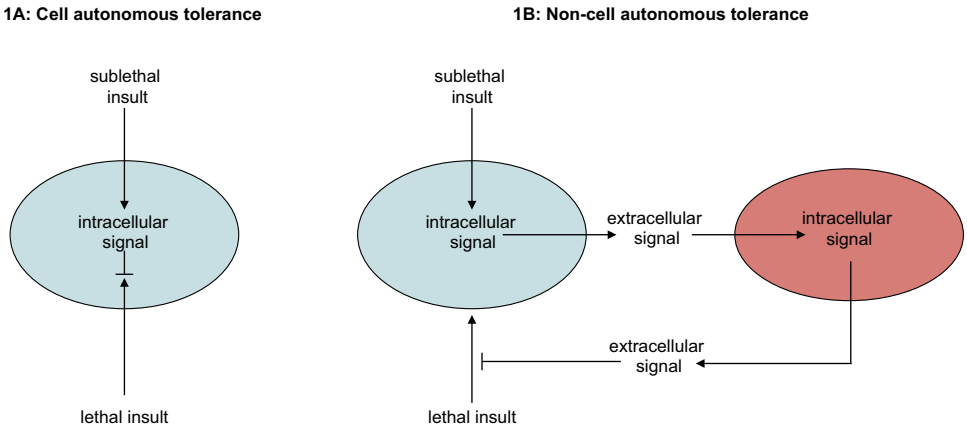

Fig. 1. Cell autonomous tolerance (A) and non-cell autonomous tolerance (B). (A) The initial sublethal insult induces intracellular signaling pathways that serve to block the second lethal insult. (B) The initial sublethal insult induces a cascade of intracellular signals that provoke the release of extracellular mediators that affect an adjacent cell. This second cell responds by releasing another set of extracellular signals that then block a lethal insult against the original cell.

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