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Preconditioning provides neuroprotection in models of CNS disease: Paradigms and clinical significance

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ABSTRACT

Preconditioning is a phenomenon in which brief episodes of a sublethal insult induce robust protection against subsequent lethal injuries. Preconditioning has been observed in multiple organisms and can occur in the brain as well as other tissues. Extensive animal studies suggest that the brain can be preconditioned to resist acute injuries, such as ischemic stroke, neonatal hypoxia/ischemia, surgical brain injury, trauma, and agents that are used in models of neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. Effective preconditioning stimuli are numerous and diverse, ranging from transient ischemia, hypoxia, hyperbaric oxygen, hypothermia and hyperthermia, to exposure to neurotoxins and pharmacological agents. The phenomenon of "cross-tolerance," in which a sublethal stress protects against a different type of injury, suggests that different preconditioning stimuli may confer protection against a wide range of injuries. Research conducted over the past few decades indicates that brain preconditioning is complex, involving multiple effectors such as metabolic inhibition, activation of extra- and intracellular defense mechanisms, a shift in the neuronal excitatory/inhibitory balance, and reduction in inflammatory sequelae. An improved understanding of brain preconditioning should help us identify innovative therapeutic strategies that prevent or at least reduce neuronal damage in susceptible patients. In this review, we focus on the experimental evidence of preconditioning in the brain and systematically survey the models used to develop paradigms for neuroprotection, and then discuss the clinical potential of brain preconditioning.

Contents

Abbreviations: MCAO, middle cerebral artery occlusion; 2VO, two vessel occlusion; 3-NPA, 3-Nitropropionic acid; 4VO, four vessel occlusion; BCCAO, bilateral common carotid artery occlusion; CSD, cortical spreading depression; 6-OHDA, 6-hydroxydopamine; Aβ, amyloid-beta; AD, Alzheimer's disease; ATA, atmospheres absolute; BBB, blood brain barrier; DA, dopamine; HBO, hyperbaric oxygen; HI, hypoxia/ischemia; HMGB1, high-mobility group protein box-1; HSP, heat shock proteins; LPS, lipopolysaccharide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mtK_{ATP} channel, mitochondrial adenosine triphosphate-sensitive potassium channel; NMDA, N-methyl-D-aspartate; NOS, nitric oxide synthase; OGD, oxygen/glucose deprivation; PD, Parkinson's disease; ROS, reactive oxygen species; SBI, surgical brain injury; TBI, traumatic brain injury; TH, tyrosine hydroxylase; TLR, toll-like receptor; MSCs, mesenchymal stem cells.

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1. Introduction

Until now, few pharmacological agents have been successfully translated to human acute brain injury (*e.g.*, stroke or traumatic brain injury (TBI)) and other neurodegenerative diseases, even though many molecules have initially appeared promising in animal models. Although the reason for these failures is unclear, we believe that understanding the means and mechanisms of stimuli that trigger an endogenous and pluripotent neuroprotective response in the brain will aid in the translation of interventions to prevent and/or limit many human disorders. As long ago as the 16th century, the toxicologist Paracelsus observed, "The dose makes the poison." A corollary is that subtoxic doses of cellular stress can lead to the generation of a protective state, termed "preconditioning." Preconditioning has been most commonly employed in studies of ischemia. In stroke models, sublethal ischemic episodes reduce the size of an infarct in response to a subsequent longer duration ischemic challenge (Kirino et al., 1991; Kitagawa et al., 1990; Liu et al., 1992). Consistently, evidence suggests that transient ischemic attacks may precondition humans against stroke (Moncayo et al., 2000; Weih et al., 1999). Such preconditioning can be elicited throughout the body, but it is of particular clinical interest in brain where the majority of neurons cannot regenerate and strokes can leave humans severely disabled.

The purpose of this review is to demonstrate that preconditioning is actually a widely applicable phenomenon that can be applied to many disease states in addition to ischemia. Neurodegenerative diseases in particular involve a lengthy prodromal phase during which there may be subtoxic stress caused by a wide variety of events, some of which are similar to subtoxic insults prevalent in the brain of individuals suffering from ischemic stroke. In a widely cited review, it was argued that preconditioning is stereotypical in nature, that is, it follows a similar pattern in both cause and effect (Dirnagl et al., 2003). If true, many findings from stroke models might be generalized to other disease models, including models of neurodegeneration. This is of obvious clinical importance because it would broaden the array of possible therapeutic targets for a multiplicity of diseases.

In order to review both the basic scientific literature as well as clinical applications, this review will explore the various preconditioning protocols currently used. In a second review we will focus on the underlying cellular mechanisms identified to date. In this review, we will detail the preconditioning paradigms to induce brain tolerance against ischemic stroke and other acute brain injuries as well as neurodegenerative states that have been employed in animal models by categorizing the preconditioning stimuli.

2. Relevant models of CNS diseases

In order to conceptualize the neural diseases that have appeared to be sensitive to preconditioning-induced protection, we will first describe the model systems of the major disease states within this section. The major models will be briefly described, not as a conclusive survey, but rather as a foundation upon which one can understand the disease context in which various preconditioning stimuli were found to be protective.

2.1. Global/focal ischemia

Ischemic brain injuries, resulting either from global or focal decreases in perfusion, are one of the most common causes of death and the leading cause of adult disability worldwide. Although many neuroprotective drugs have been shown to reduce infarction and improve neurological functioning in animal models of stroke, only tissue plasminogen activator (tPA) has been successfully translated into clinical application. The negative results of these attempts have prompted research of endogenous modulators of neuroprotection as an alternative approach to therapy. Such endogenous modulators mediate the ischemic tolerance phenomenon, which was first identified in brain in the early 1990s and shown to have a neuroprotective role in cerebral ischemia (Kitagawa et al., 1990, 1991).

The primary model of stroke used in basic research targets the region of the middle cerebral artery, an area highly sensitive to thrombotic occlusion in humans. The rodent model of middle cerebral artery occlusion (MCAO) can be performed by insertion of

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