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Review article

# Preconditioning in neuroprotection: From hypoxia to ischemia

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ABSTRACT

Sublethal hypoxic or ischemic events can improve the tolerance of tissues, organs, and even organisms from subsequent lethal injury caused by hypoxia or ischemia. This phenomenon has been termed hypoxic or ischemic preconditioning (HPC or IPC) and is well established in the heart and the brain. This review aims to discuss HPC and IPC with respect to their historical development and advancements in our understanding of the neurochemical basis for their neuroprotective role. Through decades of collaborative research and studies of HPC and IPC in other organ systems, our understanding of HPC and IPC-induced neuroprotection has expanded to include: early- (phosphorylation targets, transporter regulation, interfering RNA) and late- (regulation of genes like EPO, VEGF, and iNOS) phase changes, regulators of programmed cell death, members of metabolic pathways, receptor modulators, and many other novel targets. The rapid acceleration in our understanding of HPC and IPC will help facilitate transition into the clinical setting.



**Contents**



*Abbreviations:* ALD, aldolase; Akt, protein kinase B; ATF3, activating transcription factor 3; BAIPC, bilateral arm ischemic preconditioning; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CPB, cardiopulmonary bypass; ERK, extracellular signal-regulated kinase; EPO, erythropoietin; Glut-1, glutamate transporter-1; Glut-3, glutamate transporter-3; GSH-PX, glutathione peroxidase; HBO-PC, hyperbaric oxygen preconditioning; HIF-1, hypoxia-inducible transcription factor 1; HPC, hypoxic preconditioning; HSPA5, heat-shock protein A5; ICAS, intracranial atherosclerotic stenosis; IPC, ischemic preconditioning; I/R, Ischmia/reperfusion; LDH, lactate dehydrogenase; LiHPC, local in situ hypoxic preconditioning; LPO, lactoperoxidase; LRIPC, limb remote ischemic preconditioning; MAPK, mitogen activated protein kinase; MCAO, middle cerebral artery occlusion; NO, nitric oxide; PC, preconditioning; pCREB, phosphorylated cAMP response element-binding; PFK, phosphofructokinase; PHD, prolyl hydroxylase; PI3-K, phosphatidylinositol 3-kinase; PKC, protein kinase C; RelPC, remote ectopic ischemic preconditioning; RIPC, remote ischemic preconditioning; ROS, reactive oxygen species; SIAS, symptomatic intracranial arterial stenosis; siRNA, small interfering RNAs; SOD, superoxide dismutase; STEMI, ST-segment elevation MI; TIA, transient ischemic attack; UCHL1, ubiquitincarboxy-terminal hydrolase isozyme L1; VEGF, vascular endothelial growth factor; wb-HPC, whole body HPC.

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## 1. Introduction

A decrease in oxygen concentration that comprises the cell's intrinsic ability to sustain life is termed hypoxia. In comparison, scarcity of oxygen due to restriction of the blood supply to tissue is designated ischemia. Although the terms are often used interchangeably, ischemia is characterized not only by hypoxia, but also by insufficient nutrient supply due to decreased perfusion. Nevertheless, both of these are important problems that arise commonly in clinical settings.

Sublethal hypoxic or ischemic events can improve the tolerance of not only cells or tissues, but also entire organs and even the organism itself, to subsequent hypoxia or ischemia. This phenomenon is referred to as hypoxic or ischemic preconditioning (HPC or IPC respectively). The terms preconditioning (PC) and tolerance were first used in this context in the 1960s (Janoff, 1964). Current understanding of PC and tolerance were built throughout subsequent investigations and follow this basic premise: the stress induced by HPC triggers an adaptive response involving multiple genes, which ultimately counteracts the effects of pathways that cause cell death (Feng and Bhatt, 2015). With respect to nomenclature, both HPC and IPC are often referred to collectively under the heading of HPC, since both include hypoxia. In all, HPC and IPC have been well documented in relation to the heart and brain by a plethora of studies, as discussed below.

The basic physiology of oxygen delivery forms the framework of our discussion. To begin, a continuous oxygen and glucose supply is necessary to maintain the viability and function of the brain. Most notably, the entire central nervous system (CNS) is highly sensitive to changes in oxygen concentration due to a high intrinsic oxygen consumption rate (Luo et al., 2011). Therefore, during hypoxic episodes, the brain utilizes key adaptive mechanisms that allow it to survive and maintain homeostasis. In addition, with systemic hypoxia, other organ systems (such as the skin) conserve their use of the scarce oxygen supply to allow for the demands of life-supporting organs, such as brain and heart.

A key focus of research on HPC is the plasticity of the brain, which confers a lifelong ability to modify function and organization according to challenges posed by the external or internal environment. Hypoxic tolerance is though to stimulate brain plasticity through a combination of energy conservation and enhanced homeostatic control directed at subsequent hypoxic insults. This latter phenomenon is referred to as modulation. During HPC, modulation works hand in hand with plasticity and functions to sustain it. This occurs primarily at the cellular level and is discussed in detail below. Of clinical significance, the mechanisms underlying plasticity and modulation can point to novel strategies for the prevention and treatment of hypoxic and ischemic injury (Lu et al., 1999, 2005; Wang et al., 2007).

The body's ability to adapt to hypoxia has been rigorously investigated. For example, many studies have been done on acclimation to high altitude and the effects of chronic hypoxia. This has led to a systems-based level of understanding of the physiological responses to hypoxia. However, the time course and severity of hypoxia in these settings differs from that in pathological processes, so the adaptative response may not be identical. Therefore, understanding the cellular mechanisms of hypoxic tolerance requires more than extrapolating from more physiological conditions, and may yield unique therapeutic targets.

In myocardial ischemia, the ischemic insult triggers biochemical alterations involving the release of molecules that stimulate a signaling cascade allowing the ischemic myocyte to withstand a subsequent episode of ischemia more robustly and for longer than normal myocytes. This scenario provides a rationale for pharmacological preconditioning, in which a drug that activates the same signaling pathways, rather than ischemia itself, induces preconditioning (Kloner and Jennings, 2001).

This progress-review article aims to succinctly integrate the significant research over the past decade our colleagues have done in laboratories around the world. Our goal is to not include all that is known regarding HPC since many excellent and comprehensive reviews are already available (Lutz, 1992; Perez-Pinzon et al., 1993; Hochachka et al., 1999; Mortola, 1999, 2004; Singer, 1999, 2004; Mitchell and Johnson, 2003; Lutz and Nilsson, 2004; Gidday, 2006; Luh and Yang, 2006; Ramirez et al., 2007; Storey, 2007; Hyder et al., 2010; Nayak et al., 2011; Vande Loock et al., 2012; Zhao et al., 2013a, 2013b; Hess et al., 2015a, 2015b). Rather we seek to provide a conceptual framework that will help to identify promising avenues of research that may yield therapeutic advances.

## 2. Hypoxic preconditioning (HPC): history and neuroprotective role

Traditional knowledge of systemic respiratory and cardiovascular responses does not fully explain adaptation to hypoxia at the level of tissues and cells. Long before the term HPC was introduced, Haldane noted this difficulty in relation to what he called the physicochemical brain (Haldane, 1927). An "acquired tolerance of tissue-cells to hypoxia" was thought to have developed through evolution. Later, this was termed a "tissue-cell adaptation to hypoxia" (Lu, 1963). Subsequently, animal models of hypoxia were developed to explore HPC from the vantage point of behavior, neurophysiology, neurochemistry, neuromorphology, and molecular biology.

Studies on HPC's neuroprotective role began as early as 1986 when HPC was identified in the central nervous system (Schurr et al., 1986). Early human studies on hypoxia were not too much, and focused primarily on highland natives exposed to a low oxygen atmosphere and demonstrated no increased capacity for their homeostasis beyond their successfully adaptation to atmospheric hypoxia (Clinton et al., 1946; Houston and Riley, 1947). Early animal studies showed similar adaptations to low ambient oxygen levels. In one such study, day-3 newborn animals showed a minimal blood pressure decrease (dropping to only 67% the normal value)