The major purpose of this book is to review the evidence supporting the concept that intrinsic cell survival programs can be activated by a variety of mildly noxious stimuli or pharmacologic agents to confer protection against the deleterious effects of ischemia/reperfusion (I/R). We begin with a discussion of the concept of hormesis (a term used most extensively in the toxicologic literature which refers to biphasic cellular responses that depend on concentration or intensity of a stimulus), review the seminal studies that led to the discovery of the cardioprotective effects of ischemic preconditioning, and outline its therapeutic potential (Chapter 1). This is followed by a summary of our current understanding of the mechanisms of I/R injury (Chapter 2), as this provides several points of intervention in limiting posts ischemic tissue injury that may be targeted by the adaptive programs invoked by conditioning stimuli. Chapters 3 and 4 focus on the mechanisms underlying ischemic pre-, post-, and remote conditioning, which establishes the mechanistic rationale for development of pharmacologic conditioning strategies that may mimic the remarkably powerful effects of ischemic conditioning (and are covered in Chapter 5). Lifestyle interventions, including exercise, caloric restriction, and consumption of alcoholic beverages and/or phytochemicals, that may induce hormetic responses will also be reviewed in this chapter. While the promise for conditioning as a therapeutic approach is enormous, there are obstacles to its practical application in patients, which are covered in Chapter 6. The final chapter (Chapter 7) examines the extension of our mechanistic understanding of the signaling pathways invoked by conditioning stimuli into the realm of gene therapy and to the preservation of stem cell viability in the harsh ischemic environment as natural translational outgrowths of preconditioning into therapeutics.
Cell Survival Programs and Ischemia/Reperfusion: *Hormesis, Preconditioning, and Cardioprotection*
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Cell Survival Programs and Ischemia/Reperfusion: 
Hormesis, Preconditioning, and Cardioprotection

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COLOQUIUM SERIES ON INTEGRATED SYSTEMS PHYSIOLOGY:
FROM MOLECULE TO FUNCTION TO DISEASE #44
ABSTRACT

The major purpose of this book is to review the evidence supporting the concept that intrinsic cell survival programs can be activated by a variety of mildly noxious stimuli or pharmacologic agents to confer protection against the deleterious effects of ischemia/reperfusion (I/R). We begin with a discussion of the concept of hormesis (a term used most extensively in the toxicologic literature which refers to biphasic cellular responses that depend on concentration or intensity of a stimulus), review the seminal studies that led to the discovery of the cardioprotective effects of ischemic preconditioning, and outline its therapeutic potential (Chapter 1). This is followed by a summary of our current understanding of the mechanisms of I/R injury (Chapter 2), as this provides several points of intervention in limiting postischemic tissue injury that may be targeted by the adaptive programs invoked by conditioning stimuli. Chapters 3 and 4 focus on the mechanisms underlying ischemic pre-, post-, and remote conditioning, which establishes the mechanistic rationale for development of pharmacologic conditioning strategies that may mimic the remarkably powerful effects of ischemic conditioning (and are covered in Chapter 5). Lifestyle interventions, including exercise, caloric restriction, and consumption of alcoholic beverages and/or phytochemicals, that may induce hormetic responses will also be reviewed in this chapter. While the promise for conditioning as a therapeutic approach is enormous, there are obstacles to its practical application in patients, which are covered in Chapter 6. The final chapter (Chapter 7) examines the extension of our mechanistic understanding of the signaling pathways invoked by conditioning stimuli into the realm of gene therapy and to the preservation of stem cell viability in the harsh ischemic environment as natural translational outgrowths of preconditioning into therapeutics.

KEYWORDS

ischemia, reperfusion, postischemic tissue injury, inflammation, hormesis, adaptive cytoprotection, ischemic tolerance, cell survival programs, cardioprotection, ischemic preconditioning, ischemic postconditioning, remote conditioning, pharmacologic preconditioning, lifestyle interventions, exercise, cardiovascular risk factors, gene therapy, stems cells, and regenerative medicine
Contents

Introduction ........................................................................................................................................ 1

1. Hormesis and Preconditioning Defined ...................................................................................... 3
   1.1 Hormesis: Definition and Characteristics ............................................................................. 3
   1.2 Ischemic Conditioning Is a Specific Type of Hormetic Response ........................................... 5
   1.3 Chemical Hormesis and Pharmacologic Conditioning .......................................................... 7

2. Mechanisms of Ischemia/Reperfusion Injury ............................................................................. 9
   2.1 General Features of Ischemia/Reperfusion (I/R) .................................................................... 9
   2.2 Ischemic Versus Reperfusion Components of Total Tissue Injury Induced by I/R ................. 11
      2.2.1 Mechanisms of Ischemic Injury ....................................................................................... 11
      2.2.2 Pathogenesis of Reperfusion Injury ............................................................................... 12
      2.2.3 Oxidative/Nitrosative Stress ............................................................................................ 12
      2.2.4 Inflammation Contributes to Reperfusion Injury ............................................................ 13
   2.3 Risk Factors for I/R ............................................................................................................... 15
   2.4 Why Pursue Preconditioning as a Therapeutic Option in I/R? ............................................ 15

3. Ischemic Preconditioning and Cardioprotection ..................................................................... 19
   3.1 Acute, Early Phase, or Classical IPC ..................................................................................... 21
   3.2 Late Phase or Delayed Ischemic Preconditioning — The Second Window of Protection ......... 27
   3.3 Innate Immunity and Preconditioning ............................................................................... 29
Hormesis refers to a pattern of cellular responses to stressors whereby a beneficial effect (improved health, stress tolerance, growth or longevity) results from exposure to low doses of agents or intensities of environmental factors that are otherwise toxic or lethal when given at higher concentrations or intensities. Although first described in 1946, hormetic responses were largely ignored in biomedical research until the discovery that transient heat stress invoked the appearance of a protected phenotype in cells, tissues, or organisms such that they were better able to withstand the harmful effects induced by otherwise lethal stressors. Interest in this area was boosted to new heights with the discovery that anteccedent exposure to short bouts of ischemia followed by reperfusion conferred cardioprotection in hearts subsequently exposed to lethal ischemia and reperfusion (I/R), and phenomenon termed ischemic preconditioning (IPC). Shortly after the initial description of IPC in 1986, it was recognized that IPC induced the appearance two phases of protection that are temporally and mechanistically distinct. An early phase of protection (early phase or acute IPC) arises within minutes of IPC, persists for 1–4 hrs, involves activation of pre-existing effector molecules to confer tolerance to lethal I/R, and then disappears. A second window of protection (SWOP or late phase IPC) reemerges 12–24 hrs after the cycles of preconditioning I/R and although less powerful than acute IPC, persists for 24–96 hrs, and relies on the expression of new gene products that limit the injury induced by lethal I/R. Subsequent to that came the discoveries that the heart (or other tissues) could be protected by subjecting distant site organs or tissues (e.g., the small intestine, kidneys, limbs) to IPC (which is referred to as remote, interorgan, or distant site ischemic preconditioning) or by using gradual and hemodynamically controlled reperfusion (multiple shorts bouts of I/R) to salvage previously ischemic but viable myocardium (a phenomenon designated as ischemic postconditioning or stuttering/staccato reperfusion).

Because the protective responses invoked by ischemic pre-, post- and remote conditioning are so powerful, occur in every species, tissue, and organ studied, target multiple deleterious sequelae to prolonged I/R, and have been demonstrated in humans, use of ischemic conditioning has been toutsed for its enormous potential to revolutionize therapeutic management of ischemic disease. However, the real promise lies in identification of new drug interventions that become appreciated from understanding the biochemical steps that are invoked by short bouts of conditioning ischemia.
In addition, several lifestyle interventions (e.g., exercise and dietary manipulations) may invoke tolerance to ischemia. Despite the promise of preclinical studies, the efficacy of many hormetic interventions has proven ineffective in the presence of cardiovascular risk factors and/or is adversely affected by coincident use of drugs commonly used to treat cardiovascular disease. Uncovering the mechanisms responsible for such impaired responses to preconditioning stimuli will be imperative to successful clinical application of hormetic interventions in relevant patient populations. Finally, identification of the end-effector molecules that mediate the beneficial actions of preconditioning stimuli has led to use of gene therapy approaches to upregulate their expression, thereby invoking a permanent preconditioned state. Hormetic stimuli have also been used to promote survival and engraftment of stem cells in ischemic tissues, owing to the ability of preconditioned stem cells to better withstand the harsh milieu of postischemic tissues. These topics will be discussed in detail in the following chapters of this book.
“Was mich nicht umbringt, macht mich stärker.” (“What does not destroy me, makes me stronger.”)

Friedrich Nietzsche, Götzen-Dämmerung oder Wie man mit dem Hammer philosophiert (“Twilight of the Idols or How One Philosophizes with a Hammer”), 1888

1.1 HORMESIS: DEFINITION AND CHARACTERISTICS

Cellular responses to stressors depend on their intensity, such that reactions to the same harmful stimulus can range from induction of stress resistance at sublethal doses to acceleration of cellular demise at high doses. Hormesis is the term that applies to these divergent responses and was first reported by C. Southam and J. Ehrlich in the journal *Phytopathology* in 1943. They showed that a compound in oak bark promoted fungal growth at low doses but strongly inhibited this response at higher doses. Since that time, the term hormesis has evolved to refer to the cellular processes that are invoked on exposure to low doses or intensities of stressful stimuli (e.g., chemical agents, pathologic perturbations, or environmental factors which damage cells at higher doses/intensities) and activate adaptive responses that increase the tolerance of the cell, tissue, or organism to moderate to severe levels of the same or other harmful stimuli on ensuing exposure [37, 51, 317]. This term has been most widely used in the fields of toxicology and radiation biology to describe biphasic dose–response relationships wherein low toxicant doses produce beneficial effects while high concentrations result in toxic responses to the agent under study. However, biphasic dose–response curves are also observed in other fields such as experimental psychology where it has been noted that mild emotional stress enhances cognitive performance while severe stress impairs intellectual task execution. Such observations emphasize that exposure to low doses of toxic agents or mildly noxious environmental stimuli disrupts normal homeostasis in cells, tissues, or organs and induces the expression of survival programs that enable the organism to better withstand the deleterious effects of subsequent exposure to harmful stressors at higher doses or intensities.

The discovery of heat shock proteins in the 1970s expanded the concept of hormesis into biomedicine, providing the framework for the notion that new therapeutic interventions based on