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Review

Preconditioning is hormesis part II: How the conditioning dose mediates protection: Dose optimization within temporal and mechanistic frameworks

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ABSTRACT

In Part I, hormetic doses of a variety of agents stimulated adaptive responses that conditioned and protected cells against the subsequent toxicity resulting from a second, higher dose (called a challenging dose) of the same or different agents. Herein (Part II), the optimal conditioning (hormetic) doses of many agents are documented, cellular mechanisms and temporal profiles are examined from which the conditioning (hormetic) responses are elicited, and the optimal conditioning doses are compared to the levels at which optimal protection occurs in response to the toxic challenge dose. Entry criteria for study evaluation required a conditioning mechanism-induced endpoint response, an hormetic/biphasic dose response for the protective response following the challenging dose, and a mechanistic assessment of how the conditioning dose afforded protection against a toxic challenging dose. The conditioning dose that demonstrated the largest increase in a mechanism-related conditioning (hormetic) response (i.e., prior to administration of the challenging dose) was the same dose that was optimally protective following the challenging dose. Specific receptor antagonists and/or inhibitors of cell signaling pathways which blocked the induction of conditioning (hormetic) effects during the conditioning period abolished the protective effects following the application of a challenge dose, thus identifying a specific and essential component of the hormetic mechanism. Conditioning responses often had sufficient doses to assess the nature of the dose response. In each of the cases these mechanism-based endpoints displayed an hormetic dose response. The present analysis reveals that hormetic biphasic dose responses were associated with both the conditioning process and the protective effects elicited following the challenging dose. Furthermore, based on optimal dosage, temporal relationships and the known mediating actions of receptor-based and/or cell signaling-based mechanisms, the protective effects were shown to be directly linked to the actions of the conditioning (hormetic) doses. These findings indicate that the biological/biomedical effects induced by conditioning represent a specific type of hormetic dose response and thereby contribute significantly to a generalization of the hormetic concept.

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1. Introduction

Preconditioning in the biological and biomedical sciences is a phenomenon in which a prior exposure to an appropriate low dose of a toxic agent or stress reduces toxicity from a subsequent harmful exposure (i.e., challenging dose) of the same, a related, or an unrelated toxic/stressor agent. The term preconditioning first significantly entered the medical lexicon in 1986 when Murry et al. [1] demonstrated that a prior modest ischemic stress significantly reduced cardiac damage from a subsequent highly damaging ischemic stress using the dog model. These findings were substantially replicated and then generalized to other organs and animal models, other inducing agents, and endpoints [2,3]. Amidst the rapid and robust expansion of this concept the term preconditioning became widely accepted and used with various modifiers such as ischemic preconditioning, hypoxic preconditioning and remote preconditioning, adding appropriate specificity to diverse inducing experimental protocols. The concept of preconditioning was later extended to different temporal exposure conditions in which the low dose stress was administered after the more substantial stress exposure (i.e., challenging dose), resulting in the term post-conditioning [4–7].

While the terms pre- and post-conditioning have dominated the biomedical and clinical literature, the preconditioning concept had a considerably earlier origin tracing as far back as 1928 in which a prior low dose of ionizing radiation was protective with plants against a subsequent more harmful exposure [8]. Ito and Sawauchi [9] reported a similar response in 1966 concerning the effects of a pretreatment with cadmium. In the early 1970s a similar phenomenon was reported in which a prior low dose of CCl_4 protected against a subsequent highly toxic dose of the same agent, receiving the description autoprotection or heteroprotection when two different agents were used [10]. By the mid-1970s the term adaptive response emerged to describe the situation where a prior exposure to a chemical mutagen reduced damage from a subsequent exposure to a much higher dose of the same agent [11]. This concept was later extended to include both ionizing radiation and mutagenicity and was referred to as the radiation adaptive response [12]. The preconditioning concept was extended by others who demonstrated that low concentrations of paraquat induced a preconditioning protection response in E. coli that was mediated by superoxide dismutase [13]. The same group later reported paraquat preconditioning also decreased DNA damage induced in E. coli by a subsequent UV challenging dose via the induction of DNA repair [14].The concept of preconditioning therefore has a long history of close to a century. As a result of multiple independent discoveries in different research areas, this concept has received various descriptor terms for phenomena that appear to have similarities in their temporal sequencing and final outcome.

Over the course of several decades, research on acquired radioresistance, autoprotection, adaptive response and preconditioning was principally conducted to assess its occurrence in diverse biological models and different organs, magnitude of responses, the temporal features of protection, including its windows of occurrence, mechanistic foundations and dose optimization. However, early studies emerged, such as the 1966 report of Ito and Sawauch [9], suggesting that the pre- and post-conditioning phenomena were biphasic dose responses with quantitative features similar to that reported for hormesis [5]. Other similar observations soon led to the hypothesis that adaptive phenomena in general (i.e., autoprotection, pre- and post-conditioning, and radiation- and chemical-induced adaptive responses) were specific manifestations of hormesis [5]. Since that initial proposal, subsequent findings have provided considerable support to this hypothesis [15].

Despite many newly derived findings alluding to the convergence of these phenomena (i.e., adaptive response, pre- and post-conditioning and hormesis [15]), an integrative assessment is both lacking and needed to help clarify and unify these concepts. To accomplish this objective, dose-response data were acquired from both the low-dose conditioning phase and the subsequent high-dose challenge phase of many two phase experiments. These data were then used (1) to explain mechanistically and temporally how a low (hormetic) dose could condition cells to resist toxic insults from a subsequent high challenge dose and (2) to directly link optimal conditioning (hormetic) doses to optimal levels of protection during the challenge phase. The evidence from this study strongly indicates that adaptive responses of various types and pre- and post-conditioning responses are all manifestations of and variations on a fundamental unifying concept known as hormesis.

2. Methodology

This paper assesses preconditioning within the following framework-based criteria:

(1) A dose-response context;
(2) A mechanistic basis of the protective responses;
(3) The effect of the prior exposure (i.e., priming/conditioning doses) measured during the conditioning dose period with and without the subsequent toxic/challenging exposure;
(4) Whether the priming/conditioning dose also displays an hormetic dose response for the induction of adaptive response(s) parameters measured; if so, does the same dose also affect the optimal protection following the massive toxic/challenging exposure.
(5) If the optimal response for the conditioning dose and the protective effect following the challenging dose treatments occur at the same dose, a further assessment determined whether the protection observed after the challenging dose could be prevented by blocking the conditioning response at the optimal dose.

A review of the literature was undertaken using the databases Pub Med and Web of Knowledge/Science, employing the key words preconditioning; ischemic preconditioning; hormesis; hormetic; biphasic dose response; bimodal dose response; U-shaped dose response; and ischemic tolerance as starting terms. After the collection and evaluation of articles; relevant references were identified via cross-referencing. Literature searches were also performed on key investigators who had been identified using Pub Med and the Web of Knowledge/Science. Articles displaying hormetic-like dose responses consistent with the criteria of Calabrese and Blain [16–18] were retained for further evaluation within a dose-response; temporal and mechanistic context. The present findings are based both on the integrated endpoint responses to conditioning doses and on response(s) to the subsequent challenging dose. Table 1 provides a listing of 43 references containing dose-responses that satisfied the entry and evaluative criteria.