Pharmacological Research 110 (2016) 242–264

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

# Preconditioning is hormesis part I: Documentation, dose-response features and mechanistic foundations

Edward J. Calabrese*

*Department of Environmental Health Sciences, Morrill I, N344, University of Massachusetts, Amherst MA 01003, United States*

ARTICLE INFO

*Article history:*
Received 23 November 2015
Received in revised form
18 December 2015
Accepted 19 December 2015
Available online 3 January 2016

*Keywords:*
Preconditioning
Postconditioning
Hormesis
Dose-response
Biphasic
Adaptive response

ABSTRACT

This article provides the first extensive documentation of the dose response features of pre- and postconditioning. Pre- and postconditioning studies with rigorous study designs, using multiple doses/concentrations along with refined dose/concentration spacing strategies, often display hormetic dose/concentration response relationships with considerable generality across biological model, inducing (i.e., conditioning) agent, challenging dose treatment, endpoint, and mechanism. Pre- and postconditioning hormesis dose/concentration-response relationships are reported for 154 diverse conditioning agents, affecting more than 550 dose/concentration responses, across a broad range of biological models and endpoints. The quantitative features of the pre- and postconditioning-induced protective responses are modest, typically being 30–60% greater than control values at maximum, findings that are consistent with a large body (>10,000) of hormetic dose/concentration responses not related to pre- and postconditioning. Regardless of the biological model, inducing agent, endpoint or mechanism, the quantitative features of hormetic dose/concentration responses are similar, suggesting that the magnitude of response is a measure of biological plasticity. This paper also provides the first documentation that hormetic effects account for preconditioning induced early (1–3 h) and delayed (12–72 h) windows of protection. These findings indicate that pre- and postconditioning are specific types of hormesis.



**Contents**



* Corresponding author. Fax: +1 413 545 4692.
*E-mail address:* edwardc@schoolph.umass.edu

http://dx.doi.org/10.1016/j.phrs.2015.12.021
1043-6618/

## 1. Introduction

Preconditioning received considerable attention in 1986 when Murry et al. [1] reported that a modest prior ischemic stress reduced heart tissue damage by about 75% in the dog model subsequently subjected to a prolonged ischemia. These findings were replicated, soon generalized by many research groups to other species, and applied to other organs such as the brain, lungs, liver, kidneys and skin. The type of conditioning agent was also generalized to include a variety of physical agents, mechanical approaches, as well as physiological, dietary, and pharmacological means. The preconditioning process via mechanical approaches was subsequently induced remotely, that is, at a distance from the affected organ, and designated remote preconditioning. Research was also directed to in vitro, ex vivo and in vivo experimental approaches with considerable emphasis on the mechanistic basis of preconditioning and on complementary translational clinical epidemiological studies. The conditioning dose was also effective in preventing damage from the challenging dose when given after this treatment, a phenomenon now called postconditioning [2,3]. Since the original publication of Murry et al. [1] there have been over 30,000 papers cited in the Web of Science on ischemic preconditioning alone. The protections induced by the various pre- and postconditioning approaches have led to a broad general perspective that pre- and postconditioning represents an adaptive process with potentially profound clinical [4–9] and public health implications [10–12]. This research wave has spawned numerous efforts to translate the beneficial effects of the pre- postconditioning from the laboratory to the clinic and to the population at large via public health programs/activities (e.g., exercise and various fasting regimes).

## 2. Historical foundations

While the findings of Murry et al. [1] stimulated a massive biomedical research effort on preconditioning, the same preconditioning concept was independently reported by others in various fields considerably prior to the key 1986 publication. The first apparent reporting of the preconditioning concept (termed radiopraxis) was by the well-known French embryologist Paul Ancel [13] who published the results of 48 experiments in which a prior dose of X-rays enhanced the growth of lentil plants and protected them from injury resulting from a subsequent and more massive challenging X-ray dose. Their research approach was sophisticated, independently evaluating variations in the magnitude of the conditioning and challenging doses, as well as the temporal inter-relationship between these two treatment parameters. Considerations such as sample size and inter-subject variation were also evaluated experimentally. Despite its strong study design features and findings supporting preconditioning, this paper was only cited four times throughout the remainder of the 20th century [14–17].

During the mid decades of the 20th century, the concept of preconditioning (e.g., radiopraxis) was also referred to as "acquired radioresistance" by Bloom [17], who cited Ancel and Lallemand [13] but also other researchers as far back as Regaud and Nogier [18]. These earlier researchers reported a lower therapeutic effectiveness of X-rays for the treatment of myxosarcoma due to an acquired tolerance following multiple X-ray treatments. Other examples of such acquired X-ray tolerance were reported [19–30]. In general, these researchers induced a tolerance to subsequent higher doses of X-rays by a prior lower dose. The magnitude of protection was limited, but potentially notable, such as increasing $LD_{50}$'s by nearly 100% [21]. During this series of reports the term "conditioning" dose was introduced by Rugh and Wolff [29] who used it in the title as "Fetal Conditioning".

In a remarkable paper for its era, Pape [24] presented what might be the first detailed representation of preconditioning experimental findings to show an hormetic dose response using plants and seven conditioning doses of ionizing radiation prior to a challenging dose. The striking hormetic-like biphasic dose response displayed quantitative features similar to that observed in subsequent studies of hormesis. Likewise, the recovery response seen in Pape [24] is fully consistent with that reported here.

The topic of preconditioning was extended beyond ionizing radiation starting in the late 1950s with application to hypoxia, heavy metals and heptatotoxic chemical challenges. For example, researchers at the University of Kansas reported that rats that survived one exposure to anoxia were able to survive a much longer anoxic duration than non-adapted controls [31–33]. During 1963 Lu et al. [34] independently reported that a prior hypoxic stress can protect against a subsequent more massive hypoxic challenging dose. A year later the first use of the term preconditioning (as compared to "conditioning") was made by Janoff [35] on research with lysosomes. The field of chemical toxicity also incorporated the concept of preconditioning in the 1960s with research on heavy metals [36] and later with hepatotoxicity using chlorinated solvent toxins such as $CCl_4$ [37–40]. In the latter case the term autoprotection was used, but this concept was fundamentally the same as acquired resistance. By the mid-1970s, Samson and Cairns [41] reported that a low dose of the mutagen DMN protected against a subsequent higher dose of that agent reducing its capacity to induce mutations, calling this an adaptive response. The chemical mutation adaptive response concept was then extended to the capacity of low doses of ionizing radiation to protect against damage from a subsequent more substantial exposure to ionizing radiation [42]. These findings revealed that the major conceptual breakthrough by Murry et al. was preceded by a series of independent discoveries of the preconditioning concept, with multiple terms being used to describe it.

The strong majority of contemporary published papers on the preconditioning concept has employed an optimal dose for maximizing the adaptive response for temporal and mechanistic understandings and for potential clinical applications. No systematic effort has addressed the dose response features of the preconditioning phenomenon including its quantitative features such as the dose-dependence of the magnitude/amplitude and width of the protective responses, and how these parameters may vary by endpoint, model, age, gender, pre-existing diseases, conditioning and challenging agents and mechanisms. Knowledge of such dose response features may have therapeutic relevance as they could affect clinical efficiency and safety evaluations.

The only publication that addressed dose response for preconditioning in a broad conceptual manner was Calabrese et al. [43] who suggested that pre- and postconditioning experimental studies, when employing an adequate number of doses and an appropriate dose range and spacing, appeared to conform to the quantitative features of the hormetic dose response. However, since this earlier report was based on relatively few studies, the present paper has significantly extended this earlier proposal by obtaining, evaluating and integrating extensive experimental findings of pre- and postconditioning studies. The results of this assessment confirm that pre- and postconditioning represents a specific type of hormetic dose response. This research assessed pre- and postconditioning papers that included mechanistic evaluations as well as those that were principally descriptive. Both mechanistic and non-mechanistic papers were analyzed separately and combined for analysis when appropriate and informative. A further goal of this paper was to compare the pre- and postconditioning hormesis papers with nearly 10,000 hormetic dose responses in the hormesis database [44–46]. A companion paper assessed how the condition-