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REVIEW

Post-conditioning hormesis creates a "subtraction to background" disease process: biological, aging, and environmental risk assessment implications

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Abstract
The interaction of background disease processes with environmental induced diseases has long been an issue of considerable interest and debate with respect to its impact on risk assessment. Whether and to what extent these processes should be considered independent or additive to background has been the principal focus of debate. The concept of hormesis, a biphasic dose response characterized by a low dose stimulation and a high dose inhibition, as framed within the context of post-conditioning, reveal the occurrence of a third type of "background" possibility, that of "subtraction to background". This novel application of the hormesis concept, which is framed within the biological context of post-conditioning adaptive processes, offers considerable implications for the assessment of aging and environmental risk assessment.

Keywords Hormesis · Hormetic · Preconditioning · Post-conditioning · Biphasic · U-shaped · Additive to background

Introduction

While the concept of preconditioning is now approaching a century since it was first reported by Ancel and Lallemand (1928), it has only been since the 1970's that this concept received a significant renewed interest following the seminal papers of Samson and Cairns (1977) and Olivieri et al. (1984) on the capacity of low doses of chemical mutagens/carcinogens and ionizing radiation to markedly diminish harmful effects of subsequent more massive/challenging doses of the agent or related agents. Despite the importance of these two papers, the field of preconditioning exponentially expanded following the extraordinary paper of Murray et al. (1986) which reported that ischemia stress given 24 h prior to inducing a massive myocardial infarction in dogs reduced the heart damage by up to 70% - 80%. This lead to the rapid confirmation of these findings and their generalization to other biological models and other organs with a plethora of experimental approaches and protocols including that of post-conditioning. Subsequent findings have honed in on mechanistic understanding and in the translation of these remarkable findings for human clinical applications and public health protection/enhancement practices (Sharma et al. 2008; Zhang et al. 2015).

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Post-conditioning hormesis: Concept and applications

A crucial extension of the preconditioning concept involved the discovery that a similar magnitude of protection could be affected by administration the conditioning stimulation after the challenging dose within a prescribed time window. Both pre- and post-conditioning consistently displayed a biphasic dose response with quantitative features fully consistent with the hormesis dose response (Calabrese 2016a, b). Hormesis is a biphasic dose response that was first reported by Schulz (1887, 1888) concerning the effects of a wide range of disinfectants on yeast metabolism over a century ago. The hormetic dose response has been extensively documented in the biological and biomedical literature and shown to be highly generalizable, being independent of biological model, endpoint, inducing agent and mechanism (Calabrese and Blain 2005, 2011; Calabrese and Baldwin 2000a, b, c, d, e; Calabrese

2013a, b). Of particular significance is that the hormetic dose response displays a modest stimulation with most maximal responses being only 30–60% greater than control values. The hormetic response reflects the occurrence and extent of plasticity within biological systems independent of the level of biological organization (i.e., cell, organ, and organism) (Calabrese and Mattson 2011). In 2007 Calabrese et al. proposed that pre- and post-conditioning be considered as a type of hormetic dose response, a proposal that has been strongly supported in numerous subsequent publications (Calabrese 2016a, b) (Fig. 1).

While the concept of post-conditioning hormesis is typically considered within a biomedical/clinical framework, it may also have a key role in aging/biogerontology as well as in environmental health hazard and risk assessment. Within this context, most diseases (e.g., cancers, neurodegenerative diseases) display an ongoing, progressive, age-related background incidence. This is the case across a broad spectrum of biological models, ranging from plants to humans.

In the study of hormetic dose responses, it is common to observe that harmful agents may induce J-shaped dose responses, decreasing the background disease incidence at low doses while enhancing adverse effects beyond that seen in the control group as the dose increases (Fig. 2). Background disease incidence could have a broad range within a population from negligible to exceeding 50%, depending on the biological model, the disease condition, and the age at observation. This suggests that numerous disease processes are activated within individuals with differing rates of progression.

The occurrence of a significant background disease may be considered similar to harmful effects that follow a challenging dose in a conditioning experiment except its occurrence would generally be expected to occur more gradually. When an hormetic dose of a toxic and/or carcinogen agent is administered to a control group with a modest to high background disease incidence and the incidence of that disease is significantly diminished as compared to the unexposed control, this is an example of **post-conditioning hormesis**.

Typically, the concept of post-conditioning has been studied following the induction of acute disease symptoms such as after a heart attack, adverse cerebral event such as a stroke, or acute respiratory infection. It is proposed here, that the post-conditioning hormesis concept for ongoing background disease processes be considered similarly as those that occur in acute-induced damage frameworks (e.g., heart attacks), a concept which has not yet been addressed within the post-conditioning literature. Thus, the concept of post-conditioning hormesis is far broader than previously considered, with considerable public health implications. In effect, this type of hormetic post-conditioning phenomenon creates a type of "subtraction to background" concept. For the past nearly four decades regulatory agencies across the globe have assumed an additive to background assumption for carcinogens, assuring a linearity at low dose result (Anderson 1983). This post-conditioning hormesis mediated subtraction to background concept offers a new and challenging insight into how to estimate the effects of a broad spectrum of environmental stressor conditions and/or agents at low doses.

The evidence supporting chemical and radiation induced hormesis is substantial, with many thousands of examples in the peer-reviewed literature (Calabrese and Blain 2005, 2009, 2011). Hormetic dose responses are highly generalizable, be-

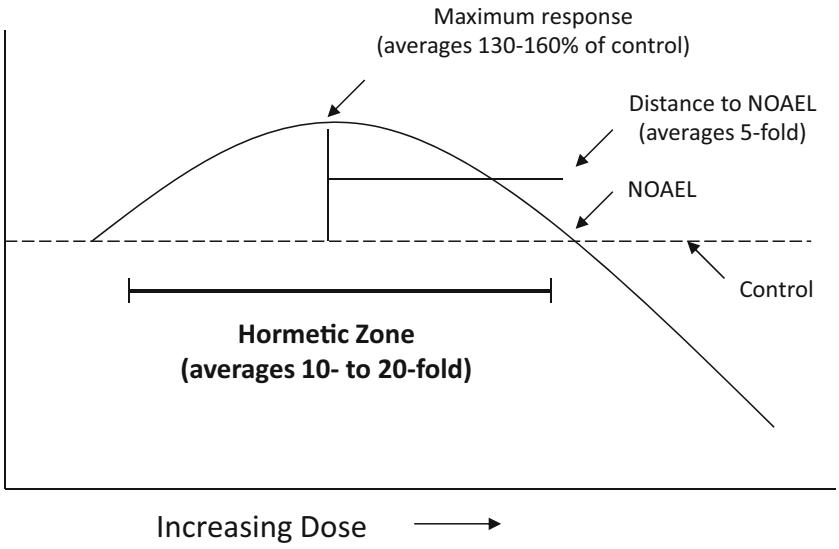

Fig. 1 Features of the hormetic dose response

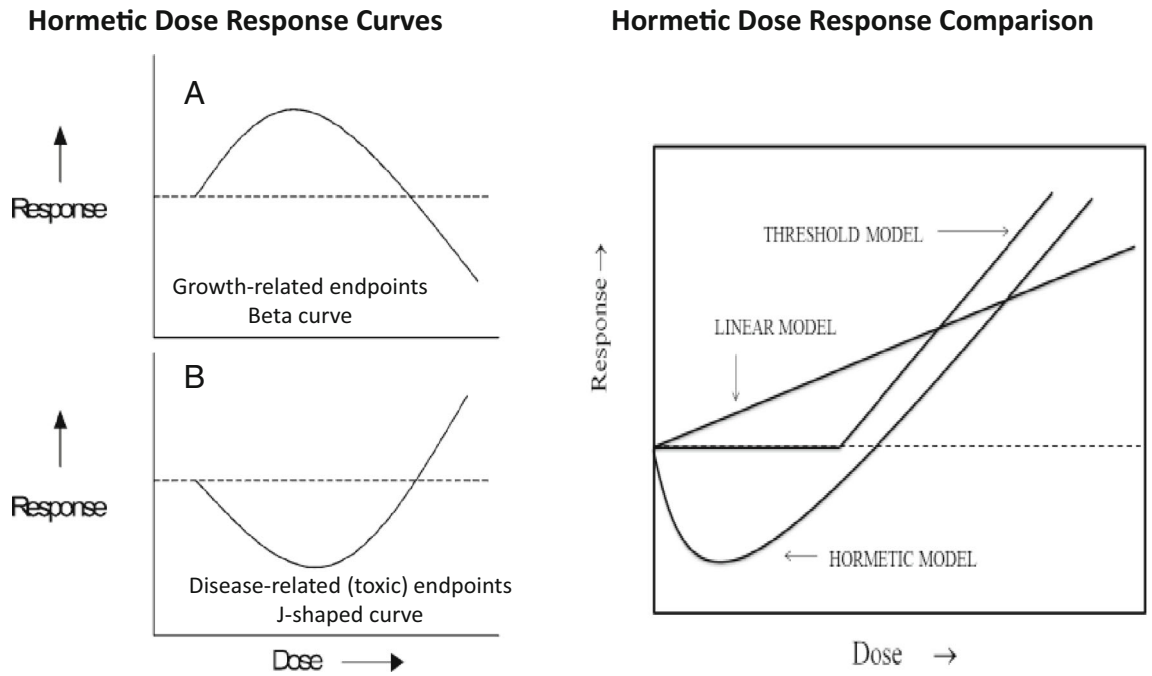

Fig. 2 Hormesis and its comparison to the threshold and linear dose-response models

ing independent of endpoint, including a broad spectrum of human conditions such as numerous neurodegenerative and cardiovascular diseases and cancers (Calabrese 2008). The quantitative features of the hormetic dose response are remarkably consistent, typically displaying a modest 30–60% increase over control values (Calabrese and Baldwin 2003). These widespread generalizable features of hormesis are readily applicable to pre- and post-conditioning processes (Sharma et al. 2008; Zhang et al. 2015; Calabrese 2016c).

The integration of hormesis within the concept of background disease incidence was initially proposed by Crump (1997). He explored its possible application to the additive to background assumption for cancer risk assessment. The present paper generalizes and extends the Crump proposal to a far broader array of age-related disease conditions, including cancer, by the application of the post-conditioning concept.

Conclusions

The application of the post-conditioning hormesis subtraction to background to disease processes should provide a conceptual and research based framework with in which a plethora of public health and other interventionary actions may be studied. It also provides regulatory agencies with the opportunity to enhance the accuracy of low dose cancer risk assessments based on improved biological plausibility.

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Compliance with ethical standards

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