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Hormesis within a mechanistic context

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This paper provides an assessment of the mechanistic foundations of hormesis and how such understandings evolved over the course of the past century. Particular emphasis is placed on recent developments particularly with respect to receptor-based and cell signaling-based pathways. Of particular importance is that the quantitative feature of the hormetic dose response are independent of mechanism. *Homeopathy* (2015) **104**, 90–96.

Keywords: Hormesis; Dose–response; Biphasic; U-shaped; Adaptive response

Introduction

The hormetic dose response has generated considerable interest within the scientific and medical communities over the past two decades. This is supported by the fact that the terms hormesis or hormetic have shown a large increase in the number of citations in the Web of Knowledge/Science database during this time period. For example, during the entire decade of the 1980s these two terms were collectively cited about 10–15 times per year. However, in 2013 alone they were collectively cited nearly 6000 times. There are now more than 2000 peer-reviewed scientific papers on hormesis with nearly 35,000 collective citations of these terms during this time based on the Web of Science/Knowledge. The term hormesis was first reported in the scientific literature in 1943 by Southam and Ehrlich[1] based on observations of extracts of the red cedar tree on the growth of a large number of fungal species. Prior to the creation of the hormesis term, such biphasic dose responses were more commonly referred to as examples of the Arndt–Schulz Law or Hueppe's Rule.[2–4] The original hormesis concept, although not the term, can be directly traced back to several publications of (Hugo Schulz in the 1880s).[5–9]

The history of hormetic-like biphasic dose responses is a long, controversial and important one. The present issue of Homeopathy provides a detailing of this history[10] while the present paper represents an assessment of the pharmacological and toxicological literature concerning hormetic mechanisms.

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Hormetic mechanisms – historical perspectives

The topic of hormetic mechanisms is part of the history of hormesis and spans well over one hundred years. What constitutes a mechanistic explanation of biological processes underlying the hormesis concept is also an evolving entity. Hormesis is not a concept or hypothesis that originated or evolved with a clear and precise meaning. The mechanistic assessment of hormesis must be viewed within the framework of the definition of this dose–response concept. That is, the mechanism of hormesis must be directly related to what is attempting to be explained.

The first step in addressing the mechanisms of hormesis is therefore to provide a definition of hormesis. The definition of scientific terms such as hormesis can be made over a several levels of biological inquiry. For example, hormesis can be seen within a descriptive mode, such as a dose response with certain quantitative and temporal features. It has also been defined within ecological and evolutionary contexts, such as a type of adaptive response induced by low doses of stressors. Hormesis may therefore be defined as a biphasic dose response phenomenon that is characterized by a low dose stimulation and a high dose inhibition.[11] The stimulatory aspect of this biphasic dose response can be derived from either a direct stimulation (Figure 1) or via an overcompensation response following a disruption in homeostasis (Figure 2).[3] The biphasic dose response can also occur within a preconditioning, post-conditioning or peri-conditioning mode.[12,13] In this case, the hormetic effect is evaluated within the context of the conditioning dose. That is, a low dose of a chemical or physical stressor given hours or several days prior to a more massive and toxic dose of the same or related stressor agent often markedly reduces the toxicity of the massive exposure. However, the protective response typically

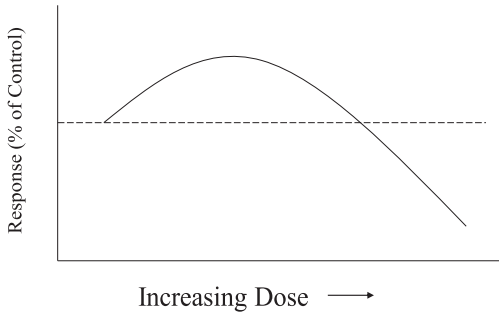

Figure 1 Hormetic dose–response: Direct stimulation with response reported at only one time point.

follows an hormetic dose response when tested over a broad range of pre-conditioning doses (Figure 3).[14] The quantitative features of the hormetic dose response are such that the magnitude of the stimulatory response is modest, typically not exceeding twice the control group value (Figure 4).[15–17] While most of the hormetic dose responses have been seen within an adaptive framework, there is substantial evidence that the hormetic dose response could also result in responses that are undesirable and/or harmful (e.g. enhancing the proliferation of tumor cells, harmful bacteria, enlargement of organs such as the prostate, etc.).[3] Thus, the hormetic response may be adaptive or maladaptive depending on the specific circumstances, including responses affected by interindividual variability. The key underlying feature of this definition therefore is the conformity to the quantitative features of the biphasic dose response relationship.

Overcompensation stimulation hormesis

The first clear articulation that hormetic dose responses might occur via an overcompensation stimulation was given by Townsend who was working under the direction of Professor Pfeffer in Germany at the Botanical Institute in Leipzig from 1896 to 1897. Townsend assessed the extent to which an injury induced upon one part of a plant will influence growth of the injured and an non-injured sections of the plant. In his research, Townsend[18] induced plant stress/damage using a range of different physical in-

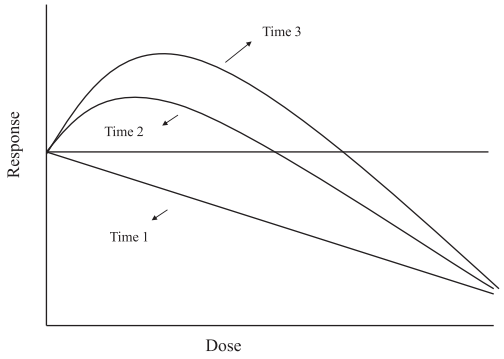

Figure 2 Hormetic dose response: Overcompensation stimulation incorporating multiple time points.

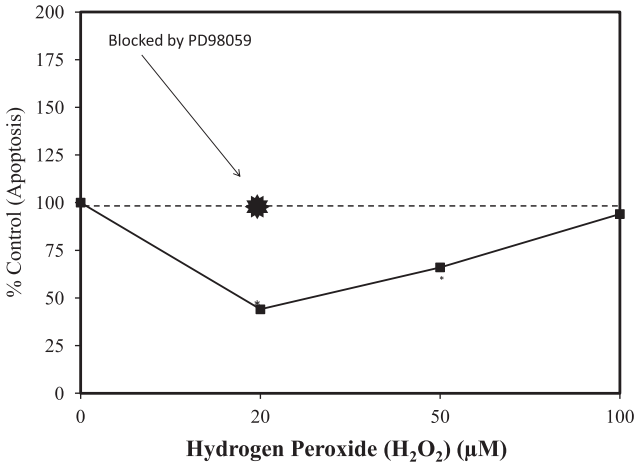

Figure 3 Effect of H_2O_2 pretreatment (20–100 μM, 24 h) on apoptosis induced by a subsequent high dose (500 μM) H_2O_2 treatment on mesenchymal stem cells from femurs and tibias of Sprague–Dawley male rats. The ERK1/2 inhibitor blocked (✹) protection against apoptosis by H_2O_2 (20 μM) by blocking stromal cell derived factor-1α.

juries or via exposure to a chemical stressor, ether. With respect to the ether experiments high doses resulted in a significant decrease in growth over a 7 day period. However, at the lowest doses there was a distinct enhancement of growth. The growth period was assessed over four specific time intervals (i.e., 24, 48, 72, and 192 h). While the low dose treatment affected a 25% reduction in growth at the 24 h time observation, these plants displayed a marked stimulatory response by 72 h, being about two fold greater than the control group. However, at the 192 h interval, the growth differential had declined to only 12.3% greater than the controls. The findings with the ether experiments were consistent with those using physical agents. According to Townsend, "if the injury is slight, a sign of acceleration in the rate of growth will be apparent from 6 to 24 h, and will continue for approximately 1 to several days. If the injury is severe, the acceleration of growth will be preceded by a period of retardation of growth of longer duration depending upon the nature of the induced injury and upon the condition of the plant injured."

The overcompensation basis for the stimulatory response of Townsend was extended by others, including

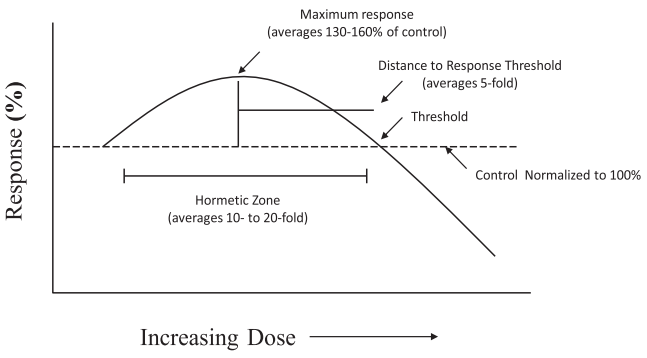

Figure 4 Dose-response curve depicting the quantitative features of hormesis.