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Review article

Non-linear actions of physiological agents: Finite disarrangements elicit fitness benefits

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ABSTRACT

Finite disarrangements of important (vital) physiological agents and nutrients can induce plethora of beneficial effects, exceeding mere attenuation of the specific stress. Such response to disrupted homeostasis appears to be universally conserved among species. The underlying mechanism of improved fitness and longevity, when physiological agents act outside their normal range is similar to hormesis, a phenomenon whereby toxins elicit beneficial effects at low doses. Due to similarity with such non-linear response to toxins described with J-shaped curve, we have coined a new term "mirror J-shaped curves" for non-linear response to finite disarrangement of physiological agents. Examples from the clinical trials and basic research are provided, along with the unifying mechanisms that tie classical non-linear response to toxins with the non-linear response to physiological agents (glucose, oxygen, osmolarity, thermal energy, calcium, body mass, calorie intake and exercise). Reactive oxygen species and cytosolic calcium seem to be common triggers of signaling pathways that result in these beneficial effects. Awareness of such phenomena and exploring underlying mechanisms can help physicians in their everyday practice. It can also benefit researchers when designing studies and interpreting growing number of scientific data showing non-linear responses to physiological agents.

1. Introduction

Homeostasis/homeodynamics critically depends on the constant supply/exchange of the important (vital) physiological agents and nutrients within the normal (physiological) range. These physiological agents include molecules (e.g. glucose), energy (e.g. heat) or forces exerted upon the cell or organism (e.g. osmolarity/osmotic pressure). Deviation from the normal range of physiological agents disrupts homeostasis, causing stress and potentially injury. Regulatory mechanisms may be activated in parallel in the attempt to mitigate the specific stress and maintain homeostasis. However, finite disarrangements of many physiological agents can also trigger beneficial responses that are unrelated to the specific stressor, such as increased cell proliferation, which may translate into increased functional capacity, fitness and ultimately longevity.

The underlying mechanism of improved fitness and longevity when physiological agents act outside their normal range appears to be similar to hormesis, a phenomenon whereby toxins elicit beneficial effects at low doses [1]. Such toxic agents exert moderate stress at low doses that activates adaptive responses, which not only improve their handling [1], but also induce non-related potentially beneficial effects such as cell hypertrophy, proliferation and migration, increased functional capacity, longevity, and others [2]. For an elaborate review pertaining to the nature of hormesis please see following articles [1,3,4]. Non-linear response to toxins is described as J- or U-shaped. Based on the shape of dose-response curve, the term hormesis was extended to all agents exhibiting characteristic biphasic response (low dose-stimulation, high dose-inhibition). Stress induced by toxins and disarrangement of physiological agents is commonly associated with the overproduction of reactive oxygen species (ROS) or intracellular calcium overload. These molecules are potent triggers of various signaling pathways that on one hand increase resistance to stress, and on the other can regulate different functions like cell proliferation [5–7].

Induction of hormesis-like response by finite disarrangement of physiological agents may explain seemingly counterintuitive results from basic and clinical studies. Some of these include reduction in overall mortality of certain groups of diabetic patients with episodes of hypoglycemia [8] or hyperglycemia [9], or lower overall mortality of moderately obese people [10]. The purpose of this review is to provide evidence and mechanisms for the novel concept of hormesis-like response occurring when physiological agents (like glucose or osmolarity) act outside their normal range. Such response exceeds mere adaptation

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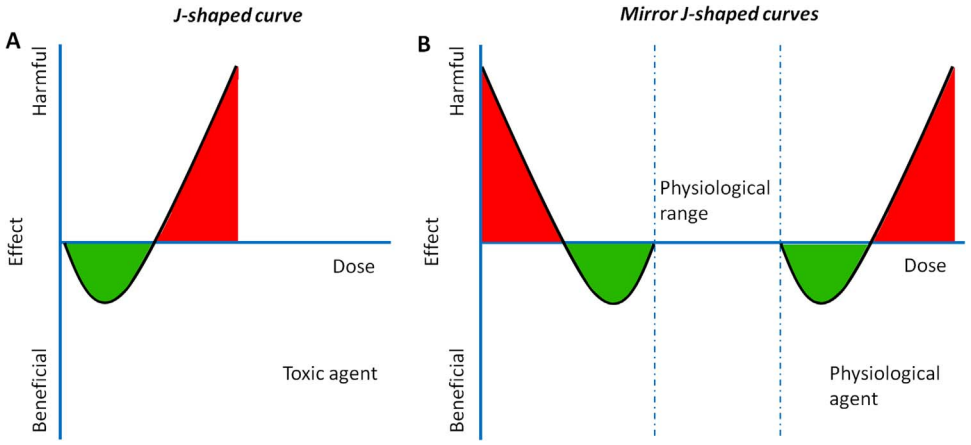

Fig. 1. Hormetic dose-response curves. (A) Typical J-shaped curve of hormesis induced by toxic agents. At low doses some toxins exhibit beneficial effects (green), while detrimental effects (red) occur at high doses. (B) Physiological agents induce hormesis-like response when acting outside their physiological range, as shown by the proposed mirror J-shaped curves. At slightly lower or higher doses than the normal range (green), physiological agents trigger response that produces beneficial effect that exceeds sole adaptation to the stress and produces broader positive effects, such as increased functional capacity and/or fitness. A greater deviation from the physiological range harms the cell/organism. Altogether this represents a non-linear response. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

to mitigate the stress, and produces broader beneficial effects depending on the specific agents and the cellular context. We propose the term "mirror J-shaped curves" for this non-linear response to finite disarrangement of physiological agents starting at both ends of the normal range (Fig. 1). Results from the great number of clinical and basic studies suggest that non-linear response to physiological agents reflects a universal mechanism improving fitness and promoting longevity of living organisms.

2. Mechanisms and pathways of hormesis

The receptor(s) and signal transduction cascade(s) of many hormetic agents have been identified. Please see other articles for comprehensive review on signaling pathways and effectors of hormesis [2,3,11]. Hormetic stimuli (also called hormetins) activate relatively ubiquitous defense programs in different organs [12]. In general, the defense programs act to reduce the stressor (e.g. upregulation of SOD [13,14] or stimulation of microsomal P450 enzymes for detoxification of alcohol [15]), repair damage (e.g. upregulation of heat shock proteins [14] or DNA repair enzymes [16]), remove damaged elements and cells that produce secondary mediators of injury (e.g. autophagy of damaged mitochondria [2,17] or proteosomal degradation of irreparably damaged proteins [18]), block cell death pathways (e.g. inhibition of mitochondrial permeability transition pore opening [19] or upregulation of antiapoptotic proteins [20]), and others.

Cellular adaptation to stress encompasses activation of various signaling pathways and effectors of cytoprotection, including PI3K/Akt pathway, ERK1/2, K_{ATP} channels, HIF1, induction of vitagenes and many others [14,21–23]. Since cytoprotective and anabolic signaling pathways share common mediators in cells, hormetins can also induce cell proliferation, for example via activation of MAPK/ERK1/2 pathway [24], which is also active in cell migration [25] in addition to activation of JNK, PI3K/Akt or p38 [26]. Overlap in signaling cascades among preconditioning, cell proliferation, migration, etc., may explain why hormetins induce not only cytoprotection, but also an increase in functional capacity and growth, ultimately translating to increased fitness and longevity. Cytoprotection induced by ischemic or pharmacological preconditioning depends on the activation of specific receptors and associated signaling cascades (e.g. adenosine and A1 receptors) [27]. However, preconditioning also depends on signaling initiated by ROS or calcium overload with PKC being directly activated by both [27,28]. Modification of energy metabolism and mitochondrial function is important for hormesis, as it maintains ATP production via anaerobic glycolysis and other processes regulated by AMPK [29]. It also attenuates mitochondrial ROS production and calcium overload via mild mitochondrial depolarization [19]. Hormesis is often regarded as adaptive hormesis since is provides adaptation to disrupted homeostasis produced by a certain toxin [30]. However, hormesis exceeds mere adaptation to mitigate the effects of the specific stressor (e.g. ROS upregulate antioxidants [13]). It also produces unrelated beneficial events (e.g. arsenite induces fibroblast proliferation [31]), likely by activating common signaling cascades (please see below), ultimately translating into increase in functional capacity and longevity.

The majority of endogenous and non-toxic hormetins described so far include signaling molecules, cytokines and hormones, such as norepinephrine, nitric oxide, or IL-8 [3]. Their dose-response curve is also (single) J-shaped. The increase in functional capacity elicited by these hormetins depends on activation of their receptor (e.g. norepinephrine and β-adrenergic receptors) and the effects are relatively specific for that agent, i.e. receptor. This includes activation of distinct signal transduction cascade (here cAMP, PKA, etc.) and effectors (here muscle hypertrophy) [32]. Overstimulation of the receptor can induce secondary pathological processes that are relatively common for different types of injury. In this example, β-adrenergic receptor overstimulation may cause cellular calcium overload, cell injury and death [33].

3. Non-linear response to physiological agents

3.1. Non-linear response to glucose

Cells utilize glucose for energy metabolism and for making structural molecules. Blood glucose concentration between 4.4 and 6.1 mM is considered normal in humans. Severe hypoglycemia (being defined as glucose < 2.8 mM or requiring specific intervention and being associated with specific mortality) increases mortality according to the ACCORD trial [8]. Conversely, retrospective analysis of data from 10251 participants with type II diabetes mellitus in the ACCORD study suggested protective effects of mild hypoglycemia (2.8–3.9 mM) [8]. Namely, in a specific subgroup of patients with ≥1 severe hypoglycemic episodes, mild hypoglycemia was associated with lower risk of death (HR 0.68, 95% CI 0.36–1.24). Authors argued that this observation is caused by "preconditioning" effect of mild hypoglycemia that increased adaptive responses and improved resistance to subsequent episodes of severe hypoglycemia. Indeed, Puente et al. demonstrated in Sprague-Dawley rats that three episodes of moderate hypoglycemia reduced brain injury and defects in spatial learning and memory caused by subsequent severe hypoglycemia [34]. Possible mechanisms of brain protection by hypoglycemic preconditioning include enhanced uptake of glucose [35] and other substrates [36] during prolonged hypoglycemia, and GABA-induced decrease in neuronal activity and excitotoxicity [37]. In addition to direct preconditioning/non-linear response to low glucose, hypoglycemia may elicit cytoprotection also by upregulating regulatory hormones, like catecholamines, which can induce preconditioning by activating adrenergic receptors and PKC [38] or glucocorticoids and their receptors [39]. Protective effects of calorie restriction could be mediated in part by accompanying