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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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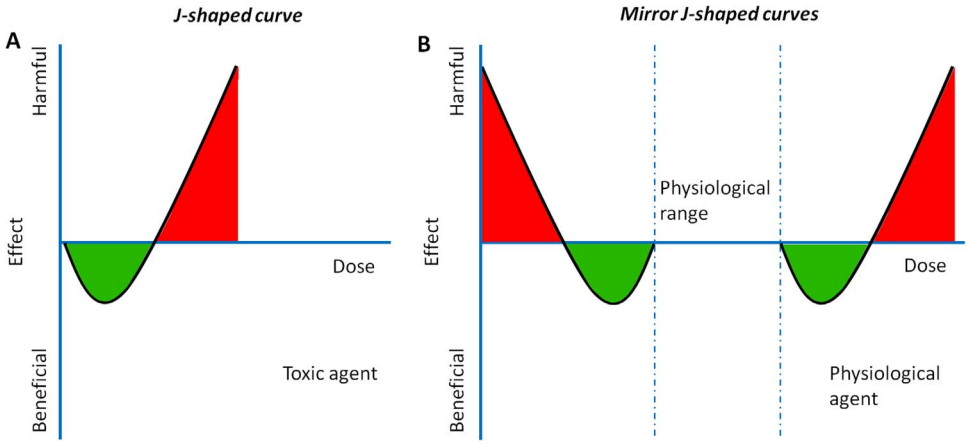

Fig. 1. Hormetic dose-response curves. (A) Typical J-shaped curve of hormesis induced by toxic agents. At low doses some toxins exhibit beneficial effects (green), while detrimental effects (red) occur at high doses. (B) Physiological agents induce hormesis-like response when acting outside their physiological 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

hypoglycemic episodes (please see below).

High glucose causes wide range of disorders associated with non-enzymatic glycation of biomolecules, increased osmotic load and oxidative stress due to increased production of ROS by mitochondria and NADPH oxidase [40,41]. However, a study by Riddle et al. analyzing data from the ACCORD study showed that patients receiving standard treatment (not aimed at intensive glycemic control) displayed lower risk of all-cause mortality when average HbA1c was slightly greater (7–8%) than the normal level (< 6%) [9] The HbA1c is a clinical measure of glycemia in the past 8–12 weeks and greater values indicate greater glycemia. Unlike severe diabetes that aggravates myocardial infarction [42] and increases long-term mortality rate in patients following myocardial infarction [43], these outcomes are beneficially affected by mild diabetes [42,44,45]. Our studies have shown that acute high glucose abrogates anesthetic preconditioning in animal and cell culture models [41,46,47]. However, depending on the dose and experimental settings, high glucose can also induce preconditioning, which likely underlies favorable outcomes of moderately higher HbA1c in ACCORD trial. For example, preconditioning with high glucose (25 mM for 3 days) improved resistance of isolated neonatal cardiomyocytes to hypoxia (induced by 2.3% O_2, glucose-free solution with 10% deoxyglucose and 3 mM amobarbital) [48]. In this study the improved stress resistance was linked to the upregulation of PKC-δ and attenuated calcium overload. Another study showed that high glucose induced translocation (activation) of α, δ, ε and ς isoforms of PKC [49]. This is in agreement with our study showing that anesthetic preconditioning translocates PKC-ε to mitochondria, thereby delaying mPTP opening and protecting cardiomyocytes from oxidative stress [50].

It has been demonstrated that high glucose induced proliferation of mesangial cells [51], pancreatic cancer cell lines [52] and breast cancer cell line (in combination with leptin) [53]. Proliferation of pancreatic cancer cell lines BxPC-3 and Panc-1 depended on the induction of EGF expression and transactivation of its receptor [52]. Proliferation of breast cancer cell line MCF-7 induced by high glucose and leptin was achieved through accelerated cell cycle and mediated by upregulation of cyclin-dependant kinase 2 and cyclin D1. In non-diabetics, anabolic effects of hyperglycemia can be mediated in part by stimulation of secretion of regulatory hormone insulin [54].

3.2. Non-linear response to oxygen

Low oxygen levels diminish ATP production, which leads to cell injury. Conversely, prolonged mild hypoxia and brief severe hypoxia seem to have beneficial effects. As reviewed by Burtscher, epidemiological data from different countries such as Switzerland, USA, Greece or Andes, show that high altitudes decreased specific mortality rates from coronary heart disease, stroke and certain types of cancer mostly in an altitude-dependant manner [55]. At very high altitudes (> 3000 m), the trend was reversed and mortality started to increase in part due to chronic mountain sickness. Hypoxia appears to be the major beneficiary factor of high altitude in addition to increased vitamin D production and lesser air pollution. It activates transcription factor HIF1 [56] and its target genes, which promote angiogenesis, inhibit apoptosis and cause adaptation of energy metabolism to anaerobic conditions [57]. Rats exposed to moderate altitude (2000 m) exhibited an increase in the length of leukocyte telomeres and increase in the expression of telomerase reverse transcriptase, suggesting increased life span of these and other cells [58]. In addition, hypoxia delayed aging and extended the life span of vascular smooth-muscle cells also by increasing telomerase activity [59].

Chronic hypoxia can decrease myocardial infarct size [56] and improve postischemic recovery in animals [60]. Heart contractility in adult mice was increased by chronic intermittent hypoxia (4 weeks, nadir O_2 of 5–6% at 60 cycles/h for 12 h) [61]. Heart biopsies from infants with cyanotic (hypoxemic) congenital heart defects displayed upregulation of cytoprotection mediators, PKC-ε, p38, JUN [62], as well as iNOS [63]. Intermittent, brief and pronounced hypoxia, which can be observed in hypoxic or ischemic preconditioning elicits endogenous cytoprotective mechanisms against prolonged ischemia-reperfusion injury [64]. Hypoxic preconditioning activates signaling cascade and recruits effectors of cytoprotection similar to other types of preconditioning, like K_{ATP} channels, ROS, NO, PKC, ERK and p38, as reviewed in [22]. Many cell types may proliferate under the influence of hypoxia, including neural stem cells [65], renal clear cell carcinoma [66] and T-cell acute lymphoblastic leukemia [67], where HIF1α played an important role.

Hyperoxia and oxygen toxicity due to oxidative stress occur when breathing oxygen at high partial pressures. Finite normobaric and hyperbaric hyperoxia can induce preconditioning in various experimental models [13,68], and it has been especially investigated in neuroscience [69,70]. A study showed that hyperoxic preconditioning (100% O_2) protected mesenchymal stem cells from subsequent hypoxia and downregulated caspases 1, 3, 6, 7 and 9 [71]. Elicited mediators of cytoprotection were Akt, NF-κB and Bcl2. In general, hyperoxia retards the growth of cells. However, hyperoxia can increase proliferation of mesenchymal cell from lung explants cultures via IGF1 and its receptor [72].

3.3. Non-linear response to osmolarity

Regulation of normal osmolarity of 300–310 mOsm/L is necessary for the maintenance of cell volume, where hyposomolarity and hyperosmolarity cause cell swelling and shrinkage, respectively, and cell death in extreme cases. Hypotonic shock can increase life span of yeast cells [73]. Hypoosmolarity-induced (225 mOsm/L) hepatocyte swelling was shown to stimulate cell proliferation that paralleled the effects of insulin [74]. The underlying pathway triggered by cell swelling included activation of EGF receptor, ERK1/2, p38, integrins and c-Src kinase. HaCaT keratonocyte line also responded with proliferation to brief hypotonic stress (174 mOsm/L), which was preceded by increase in cytosolic calcium that likely served as a trigger for this non-linear response [75]. Increased proliferation of prostate cancer cells caused by hypoosmotic stimulation depended on the release of ATP and its binding to purinergic receptor [76]. This initiated signaling cascade involving ERK1/2, p38 and PI3K.

Studies showed that hypertonic stress by NaCl, glucose, xylitol, sorbitol or and glycerol increased the life span of *Saccharomyces cerevisiae* [77,78]. In fact, Kaeberlein demonstrated biphasic response of yeast to varying glucose concentrations, where concentrations both greater and lower than normal glucose concentration (as in mirror J-shaped curves) increased the life span [78]. Authors verified that the protective effect of high glucose was indeed due to the hypertonic stress. They also showed that signaling pathway involved recruitment of Sir2p which also mediates non-linear actions of calorie restriction, further indicating that various hormetic stimuli share common pathways. Hypertonic solutions can induce preconditioning of the heart [79], liver [80] and brain [81] and protect from ischemia-reperfusion. Isolated and artificially perfused hearts of spontaneously hypertensive rats exhibited lower creatine kinase release and better recovery of diastolic function after exposure to 360 mOsm/L solution (extra NaCl) just before ischemia [79]. Neuroprotective effects of hypertonic mannitol solutions in patients with acute ischemic stroke have been described [82]. Hypertonic NaCl or KCl solutions exhibited preconditioning effect by inducing inhibitors of inflammation [83]. Anti-inflammatory effects of hypertonic preconditioning were also attributed to protection of hepatocytes, which was manifested by reduced sequestration of neutrophils and reduced generation of TNF-α [80]. Hypertonic preconditioning improves osmotic tolerance of mouse brain tissue through downregulation of aquaporine 4, which decreases water transfer and lipopolysaccharide-induced brain edema [84]. Cell proliferation and angiogenesis in supraoptic nucleus of the brain was

observed in rats drinking 2% saline for 9 days [85]. Moreover, human induced pluripotent stem cell are induced into proliferation and cytoskeleton remodeling as a response to hyperosmotic environment [86].

3.4. Non-linear response to calcium

Calcium plays many physiological roles, from activation of coagulation cascade, down to intracellular signaling, etc. Beneficial effects of hypocalcemia are reflected in experiments where brief calcium depletion-repletion episodes (calcium preconditioning) induced protection from massive depletion-repletion of calcium (calcium paradox) [87]. Disruption of the cell membrane, calcium overload, depletion of high-energy phosphates and oxidative stress were hallmarks of calcium paradox [87]. Calcium preconditioning involved a release of adenosine as a mediator of cardioprotection [87], which is common for other types of preconditioning. It has been shown that mesencephalic astrocyte-derived neurotrophic factor is another mediator of calcium preconditioning. It was secreted from cultured ventricular myocytes and HeLa cells upon depletion of calcium from the endo/sarcoplasmatic reticulum [88]. Nifedipine, a calcium channel blocker, can elicit preconditioning of isolated rat and human pancreatic islets [89]. In calcium preconditioning, brief episodes of extracellular calcium depletion may upregulate calcium transport into the cytosol [90]. During episodes of brief calcium repletion this may result in mild calcium overload that triggers preconditioning via activation of PKC [27,90].

It is well documented that cellular calcium overload initiates death pathways with the prominent role of the mPTP opening [50] and activation of various proteases [91]. Increase in intracellular calcium is observed in different types of preconditioning and application of exogenous calcium also triggers preconditioning. For example, Kouchi et al. showed a reduction of infarct size in rabbits *in vivo* by preconditioning with high calcium that was quantitatively similar to ischemic preconditioning, and was mediated by mitochondrial K_{ATP} channels [92]. Preconditioning by infusion of high calcium solution protected isolated pig retinal ganglion cells from excitotoxicity [93]. A transient rise in intracellular calcium as mediator of preconditioning was demonstrated in several models, including preconditioning of hematopoietic stem/progenitor cells with granulocyte-derived cationic peptide LL-37 [94] or preconditioning of canine and rat hearts [95]. The key mediator involved in preconditioning with high calcium is PKC, similar to preconditioning with calcium depletion [96]. Another mediator of calcium preconditioning is mPTP [97] and its inhibition appears downstream of PKC activation [50]. Studies showed that high calcium stimulated proliferation of osteoblasts [98] and MCF-7 breast cancer cell lines via upregulation of TRPC1 and activation of ERK1/2 [99].

3.5. Non-linear response to thermal energy

Normal body temperature is required for optimal maintenance of chemical reactions and structure of biomolecules. Extreme temperatures impair structure and function of biomolecules and cause cell death. It has been shown that brief episodes (1 h/day at 0 °C in two cycles lasting 5 days) of exposure to cold at young age of *Drosphila melanogaster* flies increased their life span and resistance to cold and heat [100]. Conversely, exposure to cold episodes of adult rats showed only a trend for increase in life span (968+/−141 vs 923+/−159 days in control) [101]. However, unlike the study with flies, rats were exposed to cold at adult age and throughout the lifetime, and the episodes were much longer (4 h/day at 23 °C). Absence of statistically significant increase in life span in that study could be explained by overstimulation by stress of less reactive adult animals. A pronounced stimulation of body response in the rat study is suggested by observation that food intake in rats increased by as much as 44%, while body weight decreased. Beneficial effects of moderate hypothermia was also observed in studies where brief cold exposure induced preconditioning and protection from ischemia-reperfusion of neurons in cerebrum [102] and retinal ganglion cells [103]. Analysis of 5453 cases in Singapore showed that post-resuscitation hypothermia improved survival of patients having cardiac arrest [104].

Hyperthermic shock can increase the life span of *Saccharomyces cerevisiae* [77]. Hyperthermic preconditioning in a form of brief exposure to heat protects astrocytes [105], spinal cord [106], heart [107], lungs [107], small intestine [107], skeletal muscle [107] kidney [108], liver [109], etc. Wound healing capacity of skin fibroblasts is improved following repeated mild heat stress [110]. HIF1α was shown to mediate protective effects of hyperthermic preconditioning [106], together with induction of heat shock proteins, PKC, MAPKs, NO, K_{ATP} channels and neural peptides, as reviewed in [107]. A hot spring bathing and whole body hyperthermia have been shown to improve cardiovascular functions and to reduce inflammation in patients with chronic heart failure [111].

3.6. Non-linear response to body mass/calorie intake

Calorie intake is necessary for daily energy production. Analysis of the data from the United States nationally representative NHANES I (1971–1975) and NHANES II (1976–1980), with follow-up through 1992, and from NHANES III (1988–1994), with follow-up through 2000 revealed that overweight (BMI 25–30) was associated with reduced mortality [86094 deaths less than in normal BMI group (18.5–25); 95% CI, −161223 to −10966] [10]. Extreme body weights BMI > 30 and < 18.5 were associated with increased mortality. The latter group encompassed all underweight people and may have obscured potential beneficial effects of moderate underweight. The ARIC study analyzing 13941 African-American and Caucasian adults in USA who self-reported their weight at the age of 25, found a tendency for all-cause mortality hazard ratio to be < 1 in individuals with BMI < 18.5 [112]. Conversely to NHANES data, this study found a progressive increase in hazard ratio for mortality with increase in BMI almost in all analyzed subgroups.

A collaborative analyses of 57 prospective studies in 900000 adults recruited at the average age of 46 showed the U-shaped curve with the lowest number of deaths in BMI group 22.5–25 [113]. This and other studies in older populations showing increased mortality with low-normal or moderate-low BMI values probably reflect the same effect as observed in old rats and hypothermia, i.e. that in older population moderate stress may turn into noxious stimulus due to limited reactivity, instead of eliciting beneficial effects. Conversely, in younger population, as in ARIC study [112], a possible non-linear action of low BMI, (which potentially could have been even greater if only moderate-low BMI was analyzed), induced beneficial adaptive responses due to normal reactivity. This is in line with NHANES data that demonstrated the greatest benefit of moderate overweight in younger population (age 25–59 years).

Calorie restriction is one of the most studied treatments that may promote longevity in a variety of organisms, from yeasts to mammalias with sirtuins being identified as key mediators of adaptive response [114]. In mice, calorie restriction also decreased tumor incidence and increased proliferation of T-lymphocytes obtained from the spleen [114]. In human subjects calorie restriction increased muscle mitochondrial biogenesis and efficiency [115], which could be associated with a decrease in oxidative stress [116].

4. Beneficial effects of exercise mediated through finite disarrangement of physiological agents

Exercise is perceived as one of crucial factors that can positively modify various diseases, improve functional capacity of different organs, like brain [21], and promote longevity [21,117]. Exercise can stimulate cell proliferation, for example neurons in dentate gyrus [118], cells in intervertebral disc [119], skeletal satellite cells [120] and

others. It seems that beneficial effects of exercise encompass multiple mechanism and pathways, including sirtuins, MAPK signaling, ERK1/2, p38, AMPK, Akt, JNK, HIF1 and others, as reviewed in [21].

A plethora of positive effects of exercise could arise in part from inducing hormesis-like response by finite disarrangement of many of the abovementioned physiological agents, which occurs during exercise. A study by Ahlborg et Felig examined the effects of bicycle exercise at a 58% maximal oxygen uptake on various physiological parameters in healthy volunteers [121]. They found a drop in the femoral vein oxygen saturation from 71% at rest to 29% after 120-min exercise, which corresponded to a decrease of pO_2 from 35 mmHg to 18 mmHg, respectively. Such decreases in pO_2 indicates tissue hypoxia. Exercise caused hypoglycemia in these subjects (4.1 mM after 40 min and 3.6 mM after 120 min of exercise). This was accompanied by an increase in arterial concentration of lactate, epinephrine and norepinephrine by 2, 3.5 and 7.5 fold, respectively. Exercise also increases body temperature [122], plasma osmolarity [123] and cytosolic calcium [124], which all may contribute to hormesis-like response.

5. Reactive oxygen species and cytosolic calcium as common mediators of hormetic stimuli

Overproduction of ROS and cytosolic accumulation of calcium occur following various stressors, including toxic hormetins and deviation of physiological agents from the normal range. ROS and calcium can activate cytoprotective pathways and effectors that may protect from virtually any stressor that increases ROS and calcium. This is probably a basis for hormesis-like actions of physiological agents and cross-resistance to different types of stress (Fig. 2).

Cellular calcium overload occurs in different types of injury such as ischemia-reperfusion [27] or cyanide poisoning [125]. In many of these

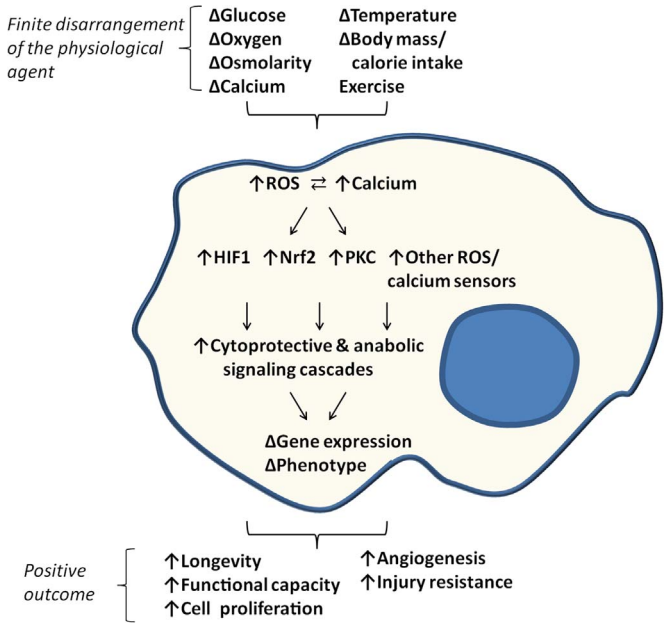

Fig. 2. Common pathways and outcomes of hormesis-like response induced by disarrangement of physiological agents. Finite deviation of physiological agents (glucose, oxygen, etc.) outside the normal range causes stress, which in most cases encompasses increase in ROS production and/or cytosolic calcium. Both ROS and calcium overload are potent stressors that trigger adaptive signaling cascades, starting with HIF1, Nrf2, PKC and others. If the increase in ROS and calcium (i.e. stress) is moderate and the adaptation capacity of cell/organism is sufficient, signaling pathways alter gene expression and phenotype, causing a broad range of beneficial effects, which may be manifested by improved fitness, longevity, etc., depending on the specific stimulus and context within the cell. Many toxic agents cause injury by increasing ROS production and cytosolic calcium, which may lead to activation of the same pathways and explain common hormetic effects of toxic and physiological agents.

pathological conditions, especially ischemia, calcium overload occurs as a secondary event due to a failure in energy metabolism and impaired function of ATP-dependant calcium pumps or opening of voltage-dependant calcium channels caused by membrane depolarization [126]. However, a rise in cytosolic calcium is crucial for activation of cytoprotective machinery [127]. Increase in cytosolic calcium was observed in various types of preconditioning, including ischemic (67) and hypoxic preconditioning [128]. It was also found following disorders of physiological agents: low- [129] and high glucose [130], hyperoxia [131], hypo- [75,76] and hyperosmolarity [132], hypo- [133] and hyperthermia [122] and during exercise [124]. Downstream mediators of protective calcium signaling involve PKC [27], Akt [127] and MAP kinase ERK (p42/44) [127].

Similar to calcium, overproduction of ROS is common for various hormetins occurring secondary to altered cellular metabolism. This includes cyanide [134], ischemia-reperfusion [135] and others. ROS are signaling molecules in various types of preconditioning [135], which can be also elicited by direct H_2O_2 treatment [136]. Elevated ROS production was detected in most of the abovementioned disarrangements of physiological agents, including low- [136] and high glucose [40], hypo- [22] and hyperoxia [13], hypo- [137] and hyperosmolarity [41,77,138], high calcium [139], hypo- [140] and hyperthermia [77,107], overfeeding [141] and exercise [21].

Among other mechanisms, high glucoses enhances mitochondrial ROS production by promoting mitochondrial fission [142], by enhancing electron flux and leak along the respiratory chain [40]. High calcium can also enhance mitochondrial respiration and ROS generation by stimulating several key enzymes of oxidative phosphorylation [143] and activating NADPH oxidase [139]. ROS can support calcium overload by activating ryanodine receptor [143]. This may create a positive feedback loop between ROS production and calcium overload augmenting cell injury, but also a hormetic stimulus. Seemingly paradoxically, hypoxic preconditioning also relies on generation of ROS as suggested by observations that ROS scavengers like SOD abrogated this form of preconditioning [22]. Reinehr et al. demonstrated that hyperosmotic stress in hepatocytes depended on ROS production by NADPH oxidase that was activated via phosphorylation by PKC-ζ and acid sphingomyelinase [138]. Enhanced cellular metabolism is likely responsible for elevated ROS production in hyperthermia [107]. Hypothermia may also increase ROS generation as shown in the experiment with isolated rat hearts perfused with cold solution at 27 °C [140]. Lastly, exercise can acutely increase ROS production in skeletal and cardiac muscle [144] and increase expression of SOD2 [21].

ROS activate several downstream targets with HIF1α and PKC being among the most important in the context of hormesis [28,145]. It is estimated that approximately 500 proteins have cysteine residues that are sensitive to redox signaling and potentially regulated by ROS [145]. HIF1 recruits different mediators of cytoprotection, including, heme oxygenase-1, iNOS, erythropoietin, hexokinase 1,2, anti-apoptotic BNIP3 and others [57]. PKC is activated by ROS via redox-sensitive cystein residues in its regulatory domain [146]. It is crucial for activation of pro-survival pathways [28].

Disruption of cellular redox homestasis via oxidative stress or antioxidants may activate vitagenes, which represent group of genes that act in order to preserve cellular function. Vitagenes encode variety of cytoprotective proteins, such as heat shock proteins and sirtuins [23]. Such cellular stress response exhibits antioxidant actions by thioredoxins, glutathione or bilirubin, latter produced by hem oxygenase enzymes [23]. Vitagenes have been associated with life-extending treatments that, among other things, reduce damaging effects of excessive oxidative stress. It is possible that the induction of vitagenes via generation of ROS may underlie some of the abovementioned beneficial effects of finite disarrangements of physiological agents and nutrients. Several studies support such claim. For example, it has been demonstrated that redox-sensitive transcription factor Nrf2, a major regulator of vitagen expression, is activated during hyperglycemia [147],

Table 1
Summary of described non-linear responses to physiological agents.

Physiological agent	Beneficial effect	Organism/organ/cell	Reference number
↓glucose	1) ↑longevity	1) human	1) [8]
	2) ↑resistance to hypoglycemia	2) brain	2) [34]
↑glucose	1) ↑longevity	1) human	1) [9]
	2) ↑resistance to ischemia	2) cardiomyocytes, heart	2) [42,44,45]
	3) ↑resistance to hypoxia	3) cardiomyocytes	3) [48]
	4) ↑cell proliferation	4) mesangial cells, pancreatic cancer cells, breast cancer cells	4) [51–53]
↓oxygen	1) ↑longevity	1) leukocytes, vascular smooth muscle cells	1) [58,59]
	2) ↓specific disease mortality	2) human	2) [55]
	3) ↑resistance to ischemia	3) heart	3) [22,56,60,64]
	4) ↑functional capacity	4) heart	4) [61]
	5) ↑cell proliferation	5) neural stem cells, renal clear cell carcinoma, T-cell acute lymphoblastic leukemia	5) [65–67]
↑oxygen	1) ↑resistance to ischemia	1) spinal cord,brain, heart, kidney	1) [13,68–70]
	2) ↑resistance to hypoxia	2) mesenchymal stem cells	2) [71]
	3) ↑resistance to toxicity by chemotherapeutics	3) kidney	3) [68]
	4) ↑cell proliferation	4) mesenchymal cells	4) [72]
↓osmolarity	1) ↑longevity	1) yeast	1) [73]
	2) ↑cell proliferation	2) hepatocytes, keratonocyte line, prostate cancer cells	2) [74–76]
↑osmolarity	1) ↑longevity	1) yeast	1) [77,78]
	2) ↑resistance to ischemia	2) heart, liver, brain	2) [79,80,82]
	3) ↑resistance to LPS-induced edema	3) brain	3) [73]
	4) ↑angiogenesis	4) brain	4) [85]
	5) ↑cell proliferation	5) induced pluripotent stem cells	5) [86]
↓calcium	1) ↑resistance to ischemia	1) heart	1) [88,90]
	2) ↑resistance to hypoxia	2) pancreatic islets	2) [89]
	3) ↑resistance to calcium paradox	3) heart	3) [87]
↑calcium	1) ↑resistance to ischemia	1) heart	1) [92]
	2) ↑resistance to excitotoxicity	2) retinal ganglion cells	2) [93]
	3) ↑cell proliferation	3) osteoblasts, breast cancer cell line	3) [98,99]
↓temperature	1) ↑longevity	1) fly	1) [100]
	2) ↑resistance to cold	2) fly	2) [100]
	3) ↑resistance to heat	3) fly	3) [100]
	4) ↑resistance to ischemia	4) brain, retinal ganglion cells	4) [102,103]
↑temperature	1) ↑longevity	1) yeast	1) [77]
	2) ↑cardiovascular function	2) heart	2) [111]
	3) ↑resistance to ischemia	3) heart, lungs, small intestine, skeletal muscle	3) [105–109]
↓body mass/ calorie intake	1) ↑longevity	1) human, mouse	1) [112,114]
	2) ↓tumor incidence	2) mouse	2) [114]
	3) ↑cell proliferation	3) T-lymphocytes	3) [114]
	4) ↑mitochondrial biogenesis & efficiency	4) skeletal muscle	4) [115]
↑body mass/ calorie intake	1) ↑longevity	1) human	1) [10]
exercise	1) ↑longevity	1) human	1) [21,117]
	2) ↑functional capacity	2) brain	2) [21]
	3) ↓tumor incidence	3) human	3) [21]
	4) ↑cell proliferation	4) neurons	4) [118–120]

hyperthermia [148], hyper- [149] and hypoxia [150], or it mediates cytoprotection against calcium overload [151]. Carefully designed studies, taking into account non-liner behavior of physiological agents and ROS are required for better insight into molecular pathways mediating their beneficial effects.

6. Discussion and conclusions

The data provided in this article suggest that finite disarrangements of important physiological agents elicit adaptive response that not only mitigates the specific stress, but also activates non-related beneficial effects, like cell proliferation and migration, wound healing, increase in functional capacity and delay in ageing that promotes longevity. Such response is similar to hormesis, described by a plethora of beneficial effects elicited by low doses of toxins. We have provided examples for hormesis-like actions of major nutrients, physiological substances and thermal energy that are indispensable for normal functioning of the living entity and operate within the normal range (Table 1). In contrast to classical J-shaped curve for toxins, beneficial effects of the physiological agents include two J-shaped curves, each occurring on upward and downward deviation from the normal range, i.e. the mirror J-shaped curves. Historically the term hormesis is associated with toxins, however such beneficial response could be extended to physiological agents that exhibit similar non-liner actions and induce plethora of beneficial effects when acting outside the normal range in a limited fashion. Elaborated mirror J-shaped type of response adds to complexity of physiological non-linear reactivity in disease/health states. Increased ROS production and elevated cytosolic calcium, and possibly other mediators, are likely common elements in beneficial signaling activated by toxic agents or finite disarrangement of the physiological agents.

Data suggest that hormesis-like response can be induced by brief and severe or longer but moderate disarrangement of physiological agents. Younger organisms with greater reactivity tend to benefit more from such stress [100,112]. Therefore, the dosage of stress on one hand and the reactivity of the living entity on the other hand seem to be key determinants whether the outcome would be beneficial or detrimental. Such moderate perturbations in homeostasis, induced by fluctuations of key physiological agents in a stressful environment, may upregulate adaptive programs, increasing functional capacity and mitigating stress exerted per one functional unit over long period of time. Activation of beneficial response involves specific and general adaptation. The former refers to adaptation to the specific stressor, such as adaptation to high osmolarity by synthesis of endogenous osmolytes. General adaptation refers to switching on common stress response pathways, a pro-survival program, such as activation of PKC or HIF1. Common elements

in signaling of pro-survival pathways and for example cell proliferation are likely responsible for improvement of overall functional capacity following finite disarrangements of physiological gents. It remains to be investigated whether different physiological agents induce identical beneficial effects, as well as their potency, contribution of co-stimuli (e.g. induction of hormonal response) and reactivity of the living organism, i.e. the cellular context.

Adaptation to disarrangement of the physiological agents (hormesis-like response) appears crucial for functioning of various living entities, from bacteria [152] to vertebrates [50]. It is also hierarchically conserved from the level of the single cell [19] up to the entire organism [8]. The elaborate approach to this complex non-linear response is important for designing studies and interpretation of seemingly paradoxical observations. For example, opposite reports on the effect of diabetes on cardiovascular function could be explained by protective effects of preconditioning and hormesis-like response triggered by mild hyperglycemia and detrimental effects of severe hyperglycemia. Even more intriguing and perhaps counterintuitive are results from large clinical trials. They suggest that mild hypoglycemia [8] or mild hyperglycemia [9] in diabetics (ACCORD trial), and moderate overweight [10] (NHANES I-III) actually reduce the overall risk of death. Here we provide potential explanation that non-linear actions of glucose and calorie intake may have caused unexpected beneficial effects in these trials.

Exploiting the benefits of non-liner response by physiological agents could be important for various aspects of research and medicine. This includes regenerative medicine and conditioning of transplanted cells. Conversely, in a tumor we could try to block hormesis-like response by physiological agents, which is likely activated by fluctuations in a supply of nutrients due to a specific nature of tumor vasculature. Hence, a flawed cytoarchitecture of the tumor may also be its advantage. Future studies with more elaborate dose-response analyses will provide better characterization of potential non-linear behavior of these and other physiological agents.

Exploring mechanisms and exploiting benefits of non-linear response to physiological and other agents is a promising tool in fighting disease, improving functional capacity and fitness, and promoting longevity.

Declaration of interest statement

Authors declare no conflict of interest.

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