

REVIEW ARTICLE

Hormesis in Health and Disease: Molecular MechanismsAnna Meiliana^{1,2,*}, Andi Wijaya^{1,2}¹Postgraduate Program in Clinical Pharmacy, Padjadjaran University, Jl. Eijkman No.38, Bandung, Indonesia²Prodia Clinical Laboratory, Jl. Cisangkuy No.2, Bandung, Indonesia

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Abstract

BACKGROUND: Hormesis was initially defined as a phenomenon where a small dose of harmful agent exposure to living organisms gives beneficial effects. The dose and time of this ‘tress’ exposure has become the object of investigation across the broad range of biomedical studies.

CONTENT: Hormesis characterized by the biphasic dose-effect or time-effect relationship for any substance. Some hormetic mechanisms performed biological plasticity, involve oxidative damage which instead induce antioxidant enzyme production in various cells. Early-life stress can increase resilience in later life and lack of stress can lead to vulnerability. Many stressors like dietary factors and natural environmental toxins can be occupied for healthy growth or

homeostasis, which exemplifies how illness is the doorway to health.

SUMMARY: Hormesis reconcile many paradoxical phenomena exert opposite effects of the same substance, either a xenobiotic or an endogenous substance, a hormone or a metabolite, a genetic manipulation or an epigenetic alteration, an experimental intervention or a natural event. Human bodies are highly adaptive. A resilient body would be resulted after the ‘training’. In this review, we will elucidate the hormesis’ definition, mechanisms and pathways, and also how hormesis impacts in human health and lifespan.

KEYWORDS: biphasic, cell signaling, dose response, hormesis, preconditioning

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Introduction

‘What doesn’t kill you makes you stronger’. The ear-friendly aphorism illustrated the original idea of hormesis, which involved an initial exposure to induce an adaptive response before it can be referred to as ‘stress-response’ hormesis.(1) At a glance hormesis seems like counterintuitive, but in a deeper philosophical thinking, if ‘too much of a good thing is a bad thing’, a little bad thing can be good. At a precise dose and time, we can transform an adverse effect into a favorable effect, as articulated in the philosophy of Yin and Yang that ‘illness is the doorway to health’.

The hormesis scenario involves three factors: first, the initial stress exposure that ‘tries to kill you’; second, the following exposure which you are more resilient against; and third, the time interval between those two.

The initial dose low-dose exposure may protect against the following exposure of the same substrate in a higher dose (‘single mode’ stress-response), against a different substance (‘cross-mode’ stress-response), or may develop a process in the interval time (‘developmental’ stress-response).(2) A classic example of single-mode stress-response hormesis is priming the body with an initial low dose of xenobiotic chemical to induce the expression of detoxification enzymes, which can confer protection against subsequent exposures to the same chemical in a higher dose. Some xenobiotic chemicals serve directly as ligands for nuclear receptors such as the constitutive androstane receptor (CAR) or pregnane X receptor (PXR). Some other indirectly activate other transcription factors, for example altering the intracellular stress-response signaling pathways such as redox status, to activate the nuclear factor erythroid 2-related factor 2 (Nrf2). The transcription factors activation

will upregulate the genes that encode the enzymes for xenobiotic metabolism in three phases. Phases I including cytochrome p450 family enzymes, phase II is glutathione-based conjugation enzymes, and phases III is adenosine triphosphate (ATP)-binding cassette transporters. Those three phases collectively detox and secrete the xenobiotic from the body.(3)

The dose response concept is central to biology, medicine, and public health. It represents the biological integration of how living systems at all levels of organization (from the cell, more complex organisms, human being) respond, adapt or fail to adapt to endogenous agents, metabolic stress, and externally dynamic threats/stressors. (4-6) The substance's dose-effect or time-effect relationship was presented in a bell-like biphasic curve, either U-shape or inverted U-shape (2,7), describe the portion of the dose-response immediately below the threshold which is related to performance, contrast to the portion of the dose-response above the threshold, which have the potency of toxic interactive effects. Hormetic dose-response can occur as a direct stimulation response, a modest overcompensation response after an initial disruption in homeostasis, or as a response to an 'adapting' or 'pre-conditioning' dose followed by an extensive challenging dose.(8)

In the broadest sense, everything can be hormesis. The term often used to describe a paradoxical low-dose beneficial effects of stressors. The paradox arises due to our own preconception about what is good and bad, and we often cognitively biased towards the monotonic cause-effect relationships. The hormetic dose-response model is apparently the most fundamental and very common in the biological and biomedical sciences, across biological model, endpoint measured and chemical class and physical agent. (7) In this review, we will elucidate the hormesis definition, mechanisms and pathways, and also how hormesis impacts in human health and lifespan.

Defining Hormesis

The term hormesis first coined in 1943 by Chester Southam and John Ehrlich after their observation on low concentration Red Cedar tree extract benefit in enhancing the metabolism of fungal species.(9) The definition later been revived by Edward Calabrese.(10) Many variants have been grown of its exact meaning. In general, the term hormesis related to the dose-response relationships of treatments, including chemical, thermal, or radiological which are beneficial at a low level but harmful at a higher level. However, some

studies involve brief stress exposure to induce mechanisms that protect against stress. This form of hormesis refer as 'stress-response hormesis' to distinguish it from hormesis in the broader sense.(1) For example, a brief exposure to very high levels of oxygen increase life span in the nematode *Caenorhabditis elegans*.(11)

The most consistent and reliable character of the hormetic dose-response is its biphasic feature, *i.e.*, a low dose stimulation zone, followed by a higher dose with inhibitory response (Figure 1). The maximum magnitude of the stimulatory response is typically modest, being only about 30-60% above that of the control response. The strong majority of stimulatory responses are less than twice the control value.(7) The Hormesis concept suggested that dose responses in the low dose zone were not only not linear but possibly not even a threshold but probably biphasic (*i.e.*, J-shaped or inverted U-shaped depending on the endpoint graphed).

Figure 2 proposed the nomenclature for hormesis that recognizes the classic hormetic-like biphasic dose-response relationships, and the temporal hormesis which also include the duration of exposure.(12,13) The classic definition of hormesis is more common in the fields of radiation biology/health physics and ecological and human toxicology. Adaptive response of temporal hormesis could result from direct stimulation hormesis (DSH), or as the compensatory biological processes after initial disruption in homeostasis or overcompensation stimulation hormesis (OCSH)).(10)

Calabrese and Baldwin (10,14) defined hormesis as an adaptive biphasic response, *i.e.*, OCSH. Therefore, the adaptive response of hormesis can be low, no response at an intermediate level, then a second response at a high level of deviation from homeostasis, described in a U- or J-shaped response.(10) In other words, a low to moderate

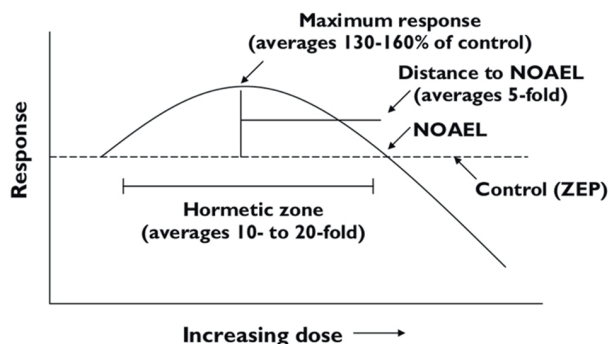


Figure 1. Dose-response curve showing the quantitative features of hormesis. NOAEL: No-observed-adverse-effect level; ZEP: Zero equivalent point.(7) (Adapted with permission from John Wiley and Sons).

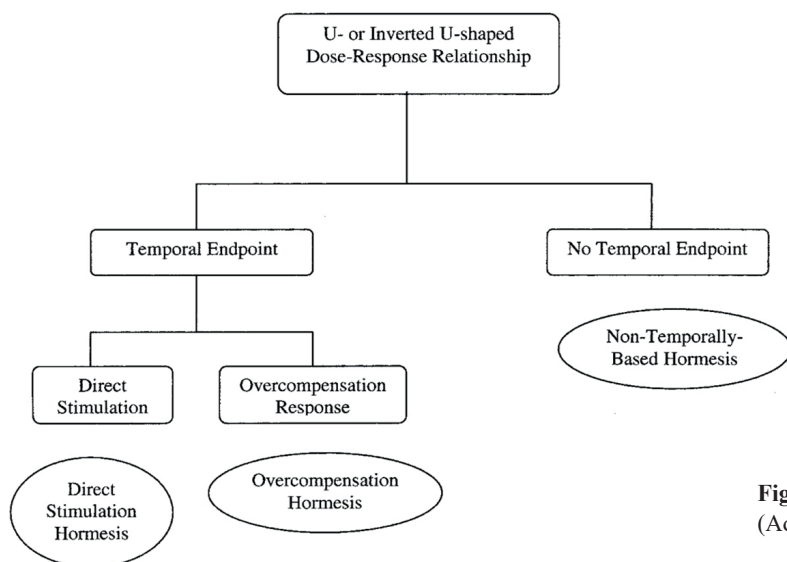


Figure 2. Schematic of hormetic nomenclature.(10)
(Adapted with permission from SAGE Publication).

levels of acute stress alerts multicellular organisms, disrupt and trigger a slight overcompensation before it return to homeostasis. The natural explanation for the biphasic response is either ignores the conventional dose response, or due to a different mechanism for the response.(10,15,16)

Hormetic Mechanisms

The hormetic dose/concentration response relationship has attracted many researchers from a broad range in biological and biomedical disciplines, seen from the markedly increased peer-reviewed scientific literatures over the past two decades (10,17,18), bring up hormesis as a highly generalizable, independent of biological model, endpoint measured, inducing agent and level of biological organization (*e.g.*, cell, organ, organism).(19)

It's not easy to provide one clear mechanism on hormesis, since more than 100 agents and signaling pathways involved in almost 400 dose/concentration responses from a wide range of chemical classes, with a broad range of endpoints. However, a general mechanism must underlie those all. Vast range of mechanisms mediate hormetic responses 400 different hormetic dose response relationships at the level of receptor and cell signaling pathways.(19,20) Hormetic-like biphasic dose/concentration responses occur by a single agonist which act via two different receptor subtypes, that antagonistic mediated the stimulatory and inhibitory pathways.(21) Receptor with high affinity to the agonist but have lower capacity (fewer receptors) mediate the stimulation, and receptor with lower affinity but have a greater capacity mediate the inhibitory response.(22-25) From this concept, numerous receptors that mediated

biphasic dose/concentration responses were identified since 1980s with many examples that conformed to the hormetic dose/concentration response quantitative features.(23,24) The mechanism involving a complex and integrative array of signal transduction pathways. A part of these pathways, the relationship to the cell membrane and membrane receptors, and the inter-connections among the signaling pathways described in Figure 3.(26) Hormesis employed the same mechanisms to yield a response, either mediated by cell signaling or by any receptor. The experiment on finding which pathway is mediating the hormesis response performed by blocking a specific cell signaling pathway and see if it prevents the hormetic stimulation.

There are three types of hormetic dose/concentration response mechanisms for signaling pathways, based on their pathways for stimulation and inhibition. First, low dose stimulation and higher dose inhibition were mediated by the same receptor; second, the receptor only mediated the stimulation and the inhibition mediated by another subtype of receptor; or third, the stimulation and inhibition do not share the same family of receptor, or happen in different mechanisms. Despite these differences in mechanistic strategies the quantifiable features of the dose/concentration responses are similar, suggesting a similar functional and adaptive strategy.(19) A lot of hormetic dose response with end point of cell proliferation was mediated via mitogen activated protein kinase (MAPK)-extracellular-signal-regulated kinase (ERK)1/2 cell signaling pathway (Figure 4), counted about 14 different cell types, except V79 cells in which p38 was essential whereas ERK1/2 involvement was absent. Meanwhile, when the same cell type have the hormetic dose responses for cell migration, it is typically mediated via a different cell signaling pathway such as p38

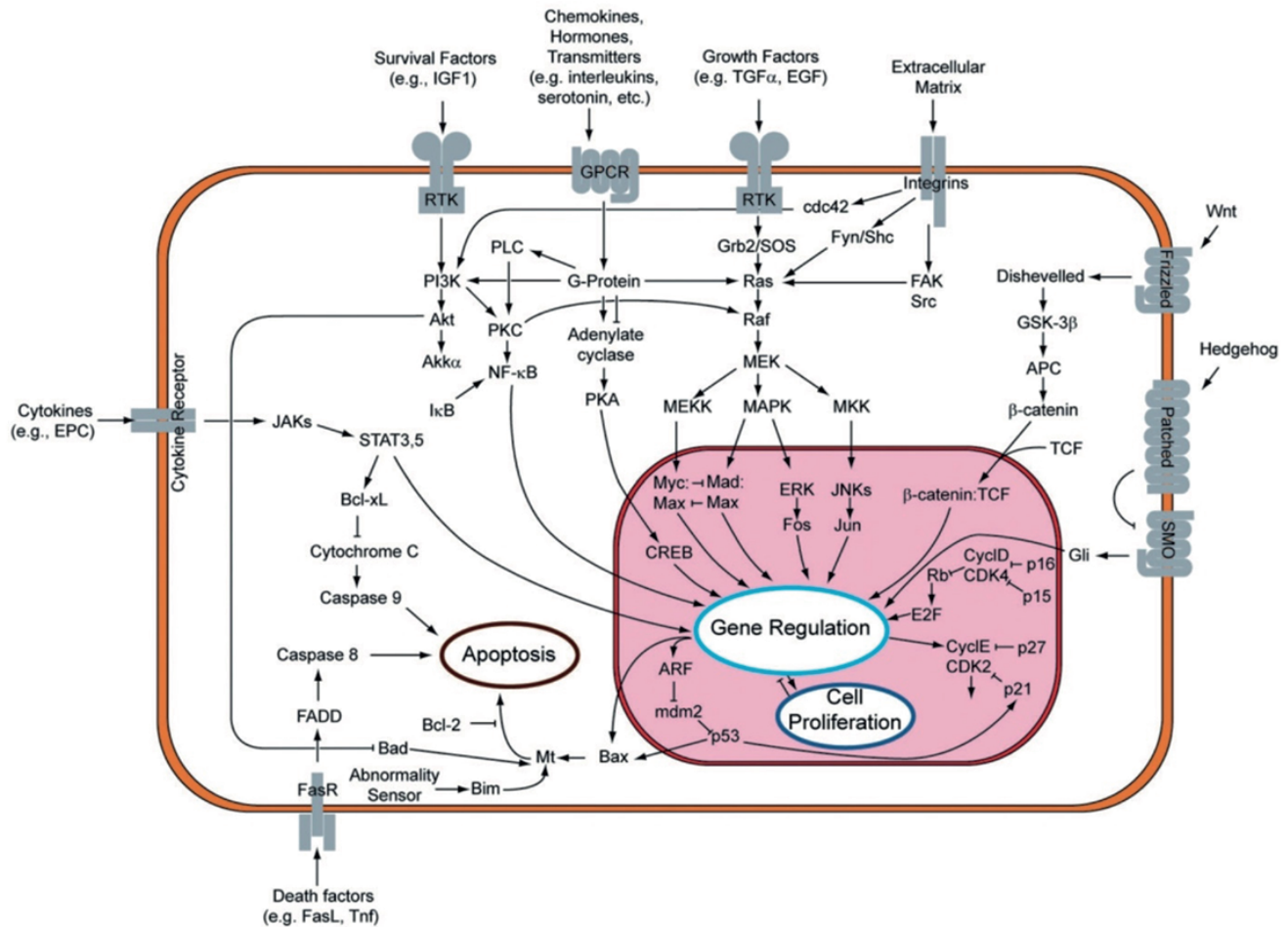


Figure 3. Signal transduction pathways.(26) (Adapted from Wikimedia Commons).

(e.g., rat aortic smooth muscle), c-Jun N-terminal Kinase (JNK) or ovarian tumor cell lines (28), and microglia (29). Thus, advance researches is needed focused on hormetic dose response quantitative features mechanisms, and how modifying dose could modulate it in a biological switching context.

Hormesis and Biological Plasticity

Phenotypic plasticity represents changes in an organism’s observable properties such as behavior, morphology, and physiology, in response to the environment challenges. It is a fundamental adaptive feature, which has been extensively assessed within an ecological evolutionary framework. Phenotypic plasticity is the basic concept in biology, and applied in many broader subjects including evolutionary biology, genetics, ecology, neurosciences, developmental biology, stem cell biology and biogerontology, among others which concern about phenotypical adaptation to heterogeneous environments as described in Figure 5.(30-33)

In the principals, hormesis represents a central evolutionary strategy that is constrained by the limits of biological plasticity, where a high dose of stressors damaged a biological system, while a low dose of the same substance yield in a positive response in several physiologic functions from cell growth to cognition, thus hormesis can be seen as a component of biological plasticity.(35,36) Hormesis dose response model is the quantitative features of plasticity. (34) Generally, the degree of phenotypic adaptive change and type of phenotypic alternative can vary depends on environmental conditions.(36) The phenotypic adjustments induced by hormesis could be long lasting, and probably irreversible. This adjustment might regards as a mechanism of survival in organism, and one potential mechanism involving transmission of chromatin modifications through mitosis (somatic memory) and meiosis (trans-generational memory).(37)

In many biomedical disciplines such as radiation biology, toxicology and environmental mutagenesis, the phenomenon of preconditioning and adaptive responses involving a low dose exposures of numerous agents (radiation, heavy metals, hepatotoxins such as carbon

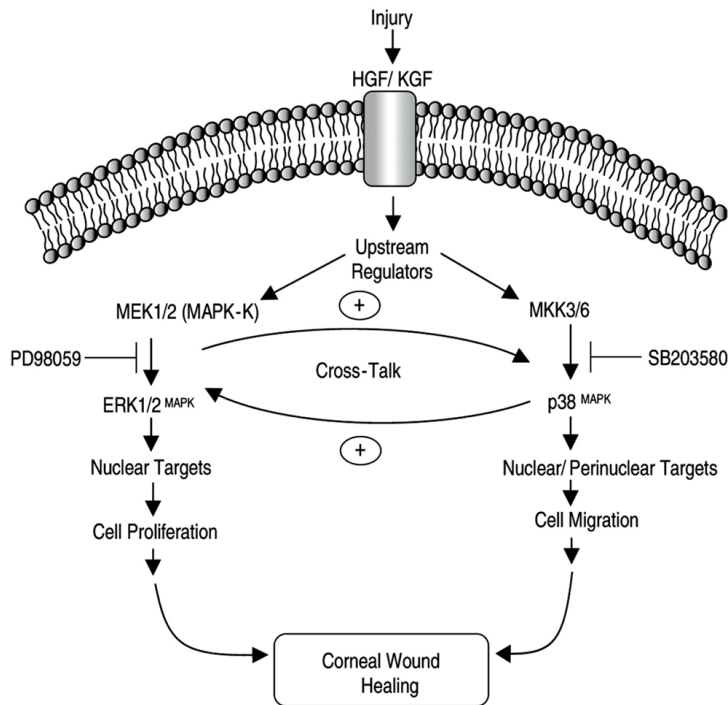


Figure 4. Schematic representation of activation of corneal epithelial wound healing by MAPK.(27) (Adapted with permission from American Society for Biochemistry and Molecular Biology).

tetrachloride, numerous oxidants, hypoxia) and stressful procedures to protect against a subsequent and more massive exposure.(38) The prior exposure aims to produce an environmentally induced phenotype alteration with an enhanced adaptive response to the subsequent higher dose. Different magnitude of the pre-conditioning dose result in altered phenotype created. When the higher dose was exposed, and the phenotype response generally follows an inverted U-shaped dose response, that indicates that the change in plasticity is both qualitatively and quantitatively described by the hormetic dose response.

The point where the dose response crossed from stimulation to inhibition is called the Zero Equivalent Point

(ZEP) or threshold (Figure 1). The stimulatory response is believed to be at the below threshold dose, *i.e.*, when the organism acquired an altered/new adaptation phenotype. Then, the quantitative features in hormetic stimulatory zone represent a quantitative index of phenotypic plasticity, or a measure of biological performance, usually in average maximum response being about 30-60% greater than the control.(39,40) The models are remarkable consistent in different substances and endpoints, suggest a similar plasticity strategies and constraints are the rule throughout the biological sciences. Therefore, assessing the hormetic dose response could revealed the quantitative features of biology plasticity and clarify the basic biological concepts.

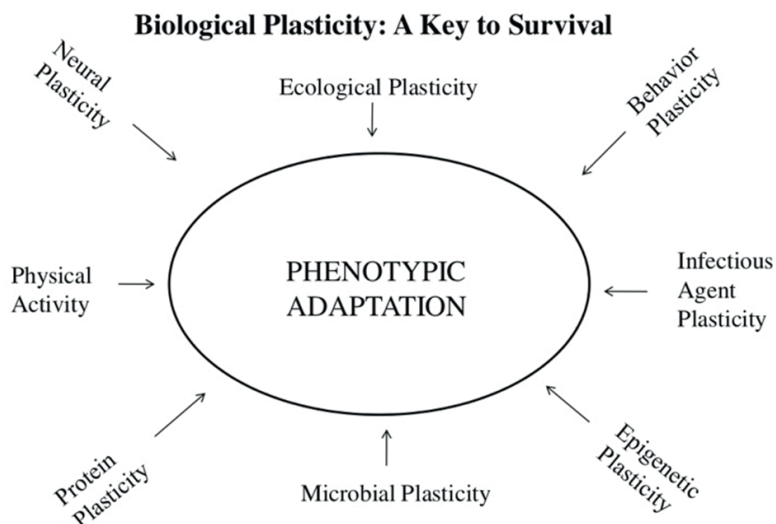


Figure 5. Biological plasticity: A key to survival.(34) (Adapted with permission from Springer Nature).

(34) The hormesis-induced phenotypic responses do not manifest only at the molecular level but even substantial for life-history or demographic traits.(37)

One clear example is the macrophages polarization. Over the past two decades, studies recognize that macrophages can be reprogrammed toward pro-oxidative (called M1 macrophages) or anti-inflammatory forms (called M2 macrophages). A recent study hypothesized that macrophage reprogramming with polarization to M1 or M2 macrophage forms may be mediated via concentration gradients of signaling agents utilizing many substances, and that conforms to an hormetic dose response.(41)

Signaling Pathways: Mechanisms of Protection in Pre- and Post-conditioning

Preconditioning is an exposure of a sub-lethal physiologic stress to an organ, in order to confers subsequent protection from lethal injury by the prolonged exposure of same stressor. The term and concept of preconditioning later expanded rapidly with various modifiers for specific application such as ischemic preconditioning (IPC), hypoxic preconditioning and remote preconditioning. Hence, preconditioning concept developed into a different temporal exposure conditions where a low dose of stress administered in order to enhance repair and recovery processes after exposure of a more challenging stress, resulting in the term post-conditioning. (38,42-44). Both pre- and post-conditioning phenomena were biphasic dose responses with quantitative features similar to hormesis.(38,45) The adaptive phenomena as the specific manifestation to hormesis could present as an auto-protection, pre- and post-conditioning, and radiation- and chemical-induced adaptive responses.(46)

Hypoxia is one of the most frequently encountered stresses in health and disease. Previous studies demonstrated that hypoxia could be beneficial or harmful depend on the duration, frequency, and severity of hypoxic episodes. Obesity has been a growing problem worldwide, due to its cardiovascular morbidity and mortality.(47,48) Metabolic Syndrome (MS), a group of metabolism abnormality including central obesity, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, hypertension and hyperglycemia, is the most frequent clinical and metabolic consequence of obesity among others.(49,50) Furthermore, overweight and obesity is the essential risk factor for obstructive sleep apnea (OSA). Indeed, two-thirds of MS patients experience moderate to severe OSA, and the frequent association between OSA and obesity

obscures the independent OSA contribution in metabolic and vascular dysfunction.(51,52) OSA itself is recognized to be an independent risk factor for cardiovascular (53) and liver diseases (54). Intermittent hypoxia (IH) is the major component in OSA that is responsible to hepatic, glucose and lipid metabolism impairment, liver and vascular consequences of OSA.(54-57) In contrast, IH then proposed as a technique to improve physiological performance by utilizing the adaptation capability on ischemia-reperfusion preconditioning mechanisms, and shown to improve endothelial function in hypertension (58) and to limit infarct size (59). Thus, adaptation to IH could offer confer cardiovascular protection against more severe and sustained hypoxia, and other stresses such as ischemia. The results are different depend on the diversity and duration of reduced oxygen patterns applied, age, genotype variations, which determine the homeostatic response and decompensation. (60) The direct and cross benefit of IH was used as treatment and prevention of a variety of diseases, and to increase exercise training efficiency.

Hypoxia may affect nitric oxide (NO) production (Figure 6), NO tissue concentration, and nitric oxide synthases (NOS) expression by several mechanisms: (i) inadequate of O₂ as NOS substrate, limit NO production; (ii) O₂ act as NOS feedback inhibition; (iii) modulation of NO bioavailability; (iv) hypoxia inducible factor (HIF)-1 and other NOS transcription factors induced; (v) intracellular Ca²⁺ concentration and influx changed; (vi) NOS-regulating heat shock proteins (HSP) induced.(61) NO plays a pivotal role in adaptation to IH. It may be beneficial by increasing efficiency of vascular oxygen transport and energy supply (62,63), inducing protective antioxidant enzymes such as catalase and superoxide dismutase (59), and HSP (60), stabilizing cellular membranes, and restricting apoptosis (61).

NO synthesis moderate stimulation and NO overproduction restriction, either directly or via NO negative feedback originating from NOS and alternative sources are the key of NO-dependent adaptation to IH. In adapted condition, NO synthesis and availability was enhanced despite of the oxygen lack, and this will induce the expression of other protective factors in robust and sustained way. Therefore, IH could represent an efficient and economic strategy to prevent and treat hypoxic or ischemic damage in organs and cells without drugs, with a similar protection resulted by physical training. In this respect strategic modulation of NO metabolism is of specific interest.(61) Some protocols were developed utilizing IH to improve cardio performance, induce neo-angiogenesis

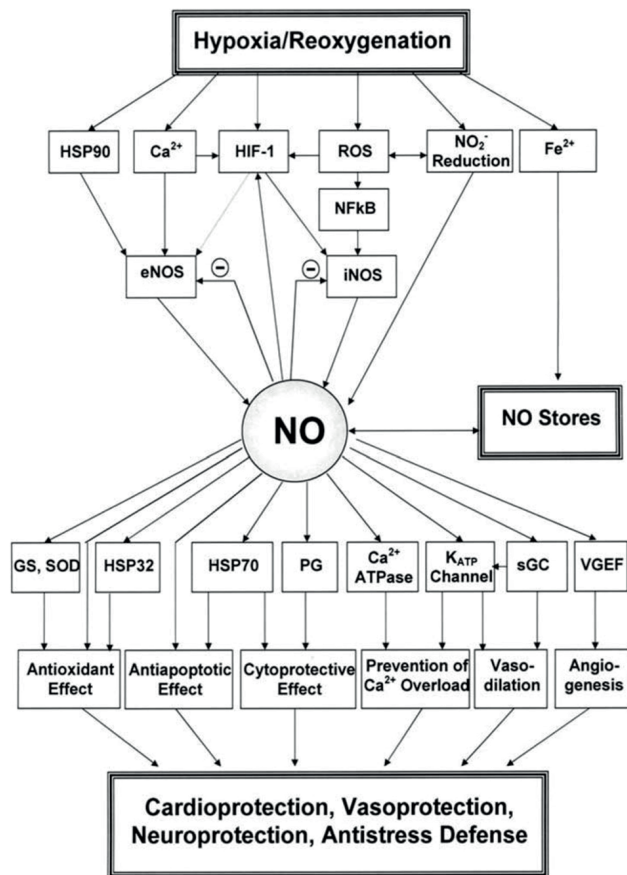


Figure 6. NO-dependent mechanisms in protective effects of adaptation to hypoxia.(60) (Adapted with permission from SAGE Publications).

and resist to ischemia-reperfusion injury, mediates by the phosphatidylinositol 3-kinase (PI3K)-Akt signaling. Such preconditioning maybe not reduce the incidence of myocardial ischemia-reperfusion injury, but at least reduce the myocardial damage severity.(59,64)

Ischemic conditioning performed by induced a transient, subcritical ischemia in a tissue to form endogenous protection. It is promising to protect ischemia-sensitive organs such as the heart, the brain, and spinal cord. Both pre- and post-conditioning give a similar level of neuroprotection. The effects can appear immediately after the sublethal stress, or with a delay of days, termed as early or late effects. The early effects may associate to post-translational modification of critical proteins (membrane receptors, mitochondrial respiratory chain), while the late effects come after gene up-or down- regulation. The transient ischemic attacks (TIA) could be relevant to brain ischemic preconditioning and may reduce the severity of subsequent strokes.(65)

Ischemic preconditioning (IPC) was first described in 1986, implemented as four 5 minutes cycles of coronary

occlusion, which was insufficient to cause myocardial necrosis, and continue with a prolonged (40 minutes) coronary occlusion and reperfusion which caused infarction. This resulted in a substantial reduction (75%) in the area of infarction in the subsequent exposure (66). The experiment in cerebral did in 4 years later using a brief (2 minutes) bilateral carotid occlusions, and could protect from neuronal death due to the subsequent 5 minutes bilateral carotid in gerbils.(67)

Ischemic pre- and postconditioning complex signaling pathways involve ligands released from ischemic myocardium, G-protein-linked receptors, membrane growth factor receptors, phospholipids, signaling kinases, NO, protein kinase C (PKC) and cGMP-dependent protein kinase or protein kinase G (PKG), mitochondrial ATP-sensitive potassium channels, reactive oxygen species (ROS), tumor necrosis factor (TNF- α and sphingosine-1-phosphate. The mitochondrial permeability transition pore (mtPTP) is probably the final effector, together with the signal to prevent pore formation. Many studies tried to produce a roadmap of this signaling, hope to reveal a point to intervene and could patients with acute myocardial infarction whose hearts are being reperfused.(62)

Scientists acknowledged IPC as the most powerful cardioprotective intervention to salvage ischemic myocardium, reduce infarct size, and protect the cardiac. Acute myocardial infarction (AMI) is caused by a coronary thrombus, which could be dissolved with a thrombolytic agent. the size of a myocardial infarction is not only determined by ischemic damage, but also by reperfusion itself which contribute up to 50% of the final infarct size. Current standard of treatment is revascularization therapy (62), such as mechanical postconditioning using short periods of ischemia immediately after reperfusion. Oxygen re-introduction leads to sudden changes in myocardial viability, mediated by a burst of ROS produced in the mitochondria. This led to membrane damage, ion pumps interference, and volume dysregulation. Another hypothesis was the invasion of leucocyte to the reperfused tissue and attack viable myocytes by releasing free radicals.

Preconditioning and adaptive responses are the manifestation of hormesis. The constraints of biological plasticity may be an obstacle in enhancing the hormetic stimulation amplitude. However, in the resilient phenotype, the duration may be extended to resolve this.(68,69) It is expected that efforts will be directed in these directions via metabolic engineering and other molecular approaches.(20)

Mitohormesis Promoting Health and Lifespan

The levels of molecular damage increase over time, contributes to the biological process of aging, and organism's pathology and mortality. The precise mechanisms underlying aging process and how to control its rate to increase lifespan was investigated using models such as *Saccharomyces cerevisiae*, *C. elegans*, *Drosophila melanogaster*, and *Mus musculus*. From a molecular genetic perspective, hormetic adaptive and defensive dose response involving an alteration of genes' expression, and result in stress resistance. Utilizing the hormetic principal, longevity may be increased after achieving a greater resistance to a range of stressors. The treatments applied in many studies involving insulin/IGF-1 signaling pathway manipulations, dietary restriction (food intake significant reduction without malnutrition), oxygen reduction, physical activity, etc (Figure 7).(70) The hormetic dose response has important implications for the fields of hazard assessment, risk assessment for carcinogens, endocrine disruption, for pharmaceuticals/natural products that enhance biological performance, and pre/post conditioning activities that upregulate adaptive mechanisms, enhancing resilience.

A brief thermal stress exposure is sufficient to induce thermotolerance in *C. Elegans* and cause small, but statistically significant increases in life span.(71) Apparently, the dose-response relationships for thermotolerance and longevity are very similar (68); after subjected to a mild

heat stress, the expression levels of the small heat-shock protein gene *hsp-16* in *C. Elegans* are predictive of both thermotolerance and life span.(72) Another study suggested an extension of lifespan in *C. Elegans* after glucose restriction, which induces hormesis via mitochondrial respiration and oxidative stress enhancement.(73,74) Seems that increased stress resistance will increased life span.(1)

ROS regards as toxic oxygen-containing molecules that induce molecular damage in the cell, and contribute to aging.(75,76) In contrary, mildly elevated ROS alter physiologic rates (77-79) and contribute to longevity in some organisms including *clk-1* worms (79-81). Treatment with the superoxide-generator paraquat induce oxidative damage (77,80,82) and decreased the levels of protein carbonylation (83,84), decreased lipofuscin accumulation (85), and decreased 4-Hydroxynonenal (4-HNE) (86,87), while increasing the levels of F3-isoprostanes (88) in the worms. Measurement of ROS level in *clk-1* worms using redox dyes showed increased level of ROS in whole worm extracts and in the heads of whole worms (82), but not in isolated mitochondria (80). This indicate that the worms have increased levels of ROS but decreased levels of at least some types of oxidative damage.

Oxidative damage is a result of the homeostasis between ROS production, ROS detoxification and repair, thus the result suggested that antioxidant defense or damage repair may be increased in the worms. The elevated ROS in *clk-1* worms upregulates multiple classes of antioxidant genes during adulthood, increased the level of catalase activity (89), while the increasing of superoxide dismutase (SOD) protein or mRNA showed different results (83,90-

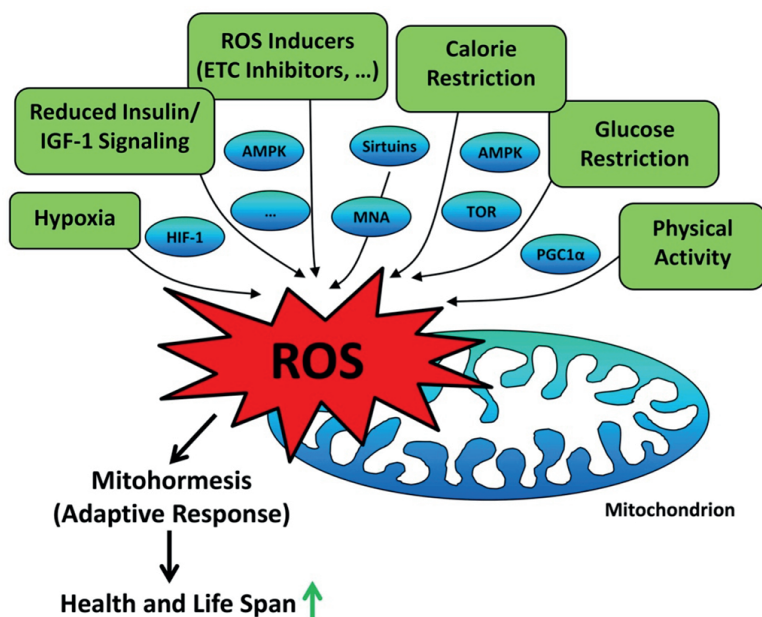


Figure 7. A non-exhaustive overview on lifespan-extending interventions linked to mitohormetic ROS signalling.(70) (Adapted with permission from SAGE Publication).

92). Increased levels of ROS in the mitochondria further increase clk-1 lifespan, while cytoplasmic ROS decrease it, but actually the specific compartment does not affect on lifespan. What counted to the longevity of clk-1 worms is both ROS-dependent and ROS-independent mechanisms on stress resistance.(93)

Besides their responsibility in conversing the bulk of nutritive energy, mitochondria play an important role in aging processes and the related diseases. Over 90% of all intracellular ROS was produced as the inevitable by-product of mitochondria oxidative phosphorylation (OxPhos) process, with conversion of 0.15-5 % of total oxygen consumed by resting cells (89-92). Thus, mitochondria are the main producers of energy and ROS within the cell, which majorly impact on cell's physiological and pathophysiological processes. Mitochondrial dysfunction increased oxidative stress and associated with many diseases such as diabetes, cancer and neurodegenerative disorders, including Alzheimer's and Parkinson's disease (94-97), and of course aging (97-99), whereas the role of ROS in this regard is still unclear. Hence, ROS in different levels may exert opposite effects on biological outcomes. At a high dose, ROS clearly induce detrimental effects on cellular integrity, while in low amounts ROS may exert specific functions in promoting general health, and specifically lifespan. By today, a range of stressors provide hormetic effects on aging process (10,11,18,100-102). The term of mitochondrial hormesis or mitohormesis later specified in 2006 (103), which used in setting for mitochondrial ROS (mtROS) as sublethal stressors promoting lifespan in a lower doses (73). Figure 8 showed how ROS transcriptionally influence stress resistance and lifespan.

Calorie restriction (CR) has been applied in study for aging since world war II, refers to dietary regimens that reduce 10-50% calorie intake without incurring malnutrition (104). CR induces metabolic adaptation and reduces regenerative diseases including cardiovascular diseases, cancer, and type 2 diabetes mellitus (T2DM) (105-109) as well as the factors involved in the before-mentioned diseases (110-112). CR is capable of inducing stress defense mechanisms which reflect mitohormetic responses, notably in ROS detoxification, involving radical-scavenging enzymes and phase I and II biotransformation response enzymes.(73,74,81,113-125)

Mitohormetic mechanism was showed in CR as hypothesized in some independent observations. Initial induction of mtROS by CR induces stress defense mechanisms and culminate in secondarily decreased of mtROS levels, in a time-resolved manner.(81) Some

misinterpretation happened to the subsequent decrease in ROS as being the primary result of CR, whereas it is an adaptive detoxifying mechanism, and CR is the essential trigger of mitohormetic mechanisms.(73,126)

Thioredoxin is another important factor regarding the effects of CR. It extends *C. elegans* lifespan under dietary deprivation and knockouts of eat-2, a genetic surrogate of nematodal CR.(127) The oxidoreductase thioredoxin roles in antioxidant response via Nrf2 binding at the antioxidants responsive elements (AREs), redox regulation, acts as electron donor for metabolic enzymes, and prevents aggregation of cytosolic proteins in the cell.(128,129) Nrf2 transcription factor activation from the leucine zipper family is indeed a crucial pathway to mediate mitohormesis. Nrf2 in a normal condition is insulated by its specific repressor Kelch-like ECH-Associated Protein 1 (KEAP1) in the cytoplasm. KEAP1 is an actin-binding protein, which also targets Nrf2 for proteasomal degradation.(130) The redox-sensitive cysteine residues in KEAP-1 sensors oxidants and electrophiles, leading to abrogation of the Nrf2/KEAP1

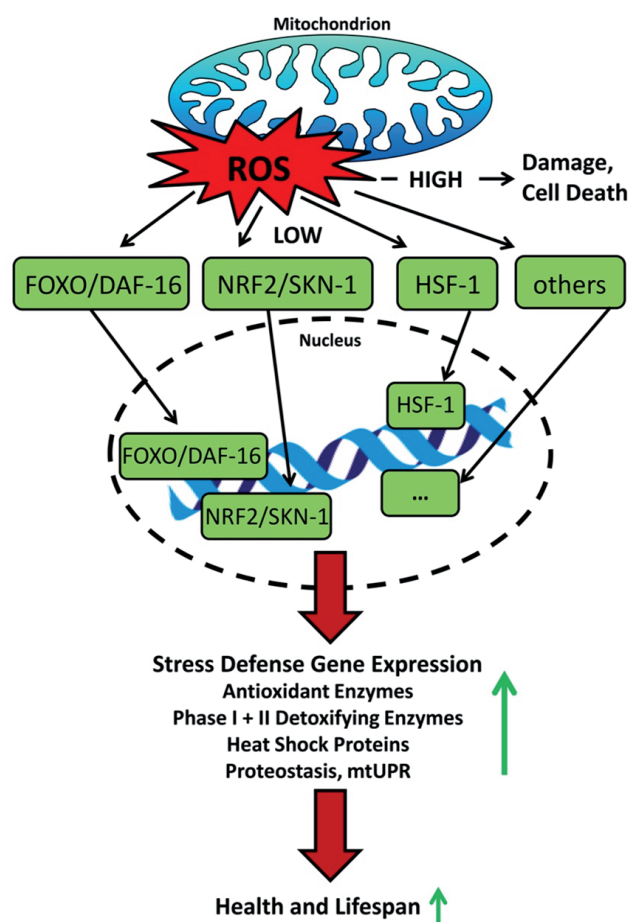


Figure 8. Overview on how ROS transcriptionally influence stress resistance and lifespan.(70) (Adapted with permission from SAGE Publication).

complex.(130,131) Nrf2 is shown to be activated by ROS (131,132), and binds to the DNA via AREs to coordinate the stress response by boosting the expression of antioxidant proteins, and phase I and II detoxification enzymes.(133)

Due to various interventions mechanisms, there are some other transcription factors which are important for lifespan extension including member of the Forkhead transcription factors (FOX) and heat shock factor 1 (HSF-1). FOXOs activate a number of target genes involved in cellular stress response. Oxidative stress induce mitohormesis and upregulates superoxide dismutase and catalase in FOXO-dependent pathway (134-136), while stress-response induced by CR is mediated by FOXAs (137,138). Overall, a number of important lifespan-regulating molecular pathways were unified in mitohormesis, and prospectively to become a common denominator in aging research.(70)

Dietary Factors, Hormesis and Health

Many studies demonstrated different dietary factors effect on health and longevity. Some of those showed incontrovertible evidences, while some other were inconclusive. Beyond of the food variety, the amount of calories consumed firmly showed an associated with the risk of many prominent age-related diseases.(139–141) Higher calories increase the risks of such metabolic and even neurodegenerative disorders. Regarding the dietary components, diet high in saturated fats, cholesterol and trans-fats may promote age-related disease (142,143), while simple sugars increase the risk of diabetes (144). Healthy diets recommendation including lots of vegetables and fruits (145), fish (146) and nuts (147).

Oxidative stress is often be blamed for ageing process and mortality. Therefore, modifying dietary factors might influence disease processes and longevity. Dietary energy restriction (DER), and substances contain in vegetables, fruits, nuts and fish oils exert anti-oxidative effects.(148) Animal and in vitro studies found that dietary factor induced specific adaptive stress response signaling pathways, *i.e.*, hormesis.(149) Another highly controlled studies on animals showed that DER either by controlled CR or intermittent fasting can increased animal cells to various types of stress. DER studies in human also resulted in counteract disease processes. Alternate day fasting reduced inflammation markers and oxidative stress and also improve symptoms in asthma subjects.(150)

DER regiment in animals change several biochemical and molecular which are consistent with the involvement

of hormesis mechanisms, propose the beneficial effects of DER for health. HSP level was increase in several different tissues, which serve a chaperone function that protects proteins against damage. For example, HSP-70 levels are increased in liver cells of rats treated on CR (151), while intermittent fasting increased HSP-70 and glucose-regulated protein 78 in rat's brain synapses (152).

Another cytoprotective benefit of DER is the upregulation of antioxidants. Diabetic rodents demonstrated increased levels of some antioxidant enzymes in their liver after DER maintenance (153), and reduced calorie diet result in increased vitamin E and coenzyme Q10, also higher plasma membrane redox enzyme activities, in brain cell membranes compared to control rats fed *ad libitum* (154). The increased antioxidant levels are consistent with reduced oxidative damage to proteins, lipids and DNA in various tissues of animals as a result of hormetic mechanisms on DER (155), which involve system adaptation on cellular energy regulation. For example, some proteins which involved in mitochondrial oxidative phosphorylation (138), glycolysis (148) and nicotinamide adenine dinucleotide (NAD)/NADH metabolism (166) regulation were upregulated in some cell types as respond to DER.

The current evidences for hormetic response due to environmental toxins in biological systems raise the possibility that the same mechanism also occurs by the induction from chemicals in foodstuffs (particularly plants), resulting from chemicals ingestion in doses within the hormetic range. Plants developed biosynthetic pathways and generate more than 100 biotoxins in its evolution in order to prevent microorganisms and insects from eating them.(164) The harmful chemicals usually concentrated in exposed vulnerable regions of the plant such as the skin of fruits and the growing buds. The phytochemicals can be toxic to mammalian cells in high concentrations, but in subtoxic doses, it may induce adaptive stress responses. Several studies performed on the hormetic actions of specific phytochemicals, such as high levels of isothiocyanates in broccoli which induced the expression of cytoprotective phase 2 proteins in liver, intestinal and stomach cells (167); curcumin contains in curry spices induce adaptive stress responses genes and protect cells in animal models of cataract formation, pulmonary toxicity, multiple sclerosis and Alzheimer's disease (168); resveratrol found in grape skin protect cells in models of myocardial infarction and stroke (169). Nrf-2 is involved in the hormetic signal transduction, by its binding to ARE upstream of genes and encodes cytoprotective antioxidant enzymes and phase-2 proteins.(170) Other pathways such in resveratrol, involving

Table 1. Summarized agents that induce hormesis-related to dietary and health.

Hormetin Agents	Food in Diet	Stress Pathway	Effect
Phytochemicals (isothiocyanates, curcumin)	Broccoli, curry spices	Activation of nuclear factor erythroid 2 (Nrf2)	Broccoli induced the expression of cytoprotective phase 2 proteins in liver, intestinal and stomach cells. Curcumin protects against cataract formation, pulmonary toxicity, multiple sclerosis and Alzheimer's disease.
Resveratrol	Grapes skin, red wine	Regulation of redox homeostasis, Activation of Nrf2 and sirtuin pathway, Blocking of nuclear factor κ B (NF- κ B)	Resveratrol protect cells in models of myocardial infarction and stroke.
Alcohol	Alcoholic drinks	Alterations in protein kinase C (PKC)	Moderate consumption of alcohol increase in HDL cholesterol, increased insulin sensitivity, anti-inflammatory effect, increase adiponectin, increase fibrinolysis, decrease in platelet aggregation, and coagulation and improved endothelial function.

activation of sirtuin – FOXO, and increase the expression of antioxidant enzymes, and cell survival-promoting proteins. (162) Some other phytochemicals may activate the hormetic transcription factors NF- κ B and CREB and induce genes encoding growth factors and anti- apoptotic proteins. (163,164)

Since the early recorded history, alcohol has been an integral part of human culture. Moderate alcohol consumption associated with beneficial health effects, but excess and binge drinking leads to increasing risk of cardiovascular diseases and mortality. (165-170) Thus, moderate amount of alcohol is protective against coronary artery disease (CAD), and the higher amount exert different effect. (171) Multiple studies observed a J- or U-shaped association between alcohol consumption and all-cause mortality. (169-175) The benefit of moderate alcohol consumption include an increase in HDL cholesterol, increased insulin sensitivity, favorable effects mediated by alterations in PKC, anti-inflammatory effect, increase adiponectin, increase fibrinolysis, decrease in platelet aggregation, and coagulation and improved endothelial function. (176-178) The complex metabolic pathways are interconnected on these mechanisms. The role of individual factors are not yet be elucidated, but some studies on the biphasic dose responses associated with increased expression of genes encoding cytoprotective proteins including antioxidant enzymes, protein chaperones, growth factors and mitochondrial proteins. Table 1 showed some summarized agents that induce hormesis-related to dietary and health. More research on how dietary factors exert dose response and kinetic characteristics in animals and humans will lead to a better understanding of hormesis and to improvements in dietary interventions for disease prevention and treatment. (149)

Conclusion

Human bodies are highly adaptive. Exposure to a stressor in adequate dose evidently can induce stress responses that are protective against the same stress exposure in higher levels. While constant high-level exposure induce tolerance to avoid overstressing the system. Our body needs to adjust to different functions from fecundity versus longevity until energy conservation versus expenditure. These adaptations are essential to protect us from unpredictable environmental changes. Our endocrine, nervous, and immune systems are capable to adapt, since these systems directly sense the environmental changes and communicate the perceived change to the rest of the body. A lot of adaptation occurred during evolution and the training formed the body that is more resistant to stress.

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