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REVIEWS

Review

Hormesis in Health and Chronic Diseases

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'What doesn't kill you makes you stronger'. Hormesis, the paradoxical beneficial effects of low-dose stressors, can be better defined as the biphasic dose–effect or time–effect relationship for any substance. Here we review hormesis-like phenomena in the context of chronic diseases for many substances, including lifestyle factors and endocrine factors. Intermittent or pulsatile exposure can generate opposite effects compared with continuous exposure. An initial exposure can elicit an adaptive stress response with long-lasting protection against subsequent exposures. Early-life stress can increase resilience in later life and lack of stress can lead to vulnerability. Many stressors are naturally occurring and are required for healthy growth or homeostasis, which exemplifies how 'illness is the doorway to health'.

Highlights

Biphasic dose–effect and time–effect relationships are prevalent for many environmental and endocrine factors.

Intermittent (pulsatile) exposure can have opposite effects as continuous (sustained) exposure.

Early-life stress can increase resilience and lack of stress can lead to vulnerability.

The nervous, endocrine, and immune systems are highly adaptive and responsive to stress.

Introduction

Hormesis was originally defined as a phenomenon in which exposure to a harmful substance gives beneficial effects to living organisms when the dose of the harmful substance is small. Radiation hormesis was among the first documented examples. Although high-dose radiation promotes mutagenesis and carcinogenesis, low-dose ionizing radiation such as X-rays has been shown to suppress tumor development [1]. Many chemical carcinogens, such as DTT or α-benzene hexachloride, when given at a low dose can protect against DNA damage and cytotoxic effects induced by subsequent exposures at a much higher dose [2]. As illustrated in the aphorism 'what doesn't kill you makes you stronger', this original idea of hormesis involves an adaptive response on the initial exposure and therefore can be referred to as 'stress-response' hormesis [3]. There are three components in this scenario: the initial stress exposure that 'tries to kill you', the subsequent stress exposure that you are more resilient against, and a time interval in between. If the initial low-dose exposure protects against subsequent exposure to the higher dose of the same substrate, it is a 'single-mode' stress response. If the initial low-dose exposure protects against a different substance, it is a 'cross-mode' stress response. If the time interval between the two exposures involves a developmental process, it is a 'developmental' stress-response hormesis.

The issue with this original definition is that 'harmfulness' or 'stress' is not an intrinsic feature for any substance. It is the dose, and the time of the exposure, that determines toxicity. Many substances discussed in the context of hormesis are naturally occurring substances that the body is exposed to during evolution. Therefore, our bodies are likely to have evolved mechanisms to respond to, adapt to, or even rely on the stressors for healthy growth and homeostasis. Similarly, what is 'beneficial' is also context dependent. A beneficial effect of calorie restriction on glucose metabolism can come with a sacrifice in muscle mass or bone mineral density [4]. A thrifty phenotype can be beneficial when food is scarce but can be detrimental when food is in excess. Therefore, a more reasonable definition of hormesis seems to be the biphasic dose–effect or time–effect relationship for any substance [5,6], which defines a broad sense of hormesis. The biphasic time–effect can be mechanistically related to stress-response hormesis.

Hormesis can be counterintuitive but not entirely surprising. If 'too much of a good thing is a bad thing', a little bad thing can be good. The golden-mean doctrine in philosophy suggests a Goldilocks zone for everything. A bell-like biphasic curve, therefore, is expected for the dose–effect or time–effect relationship for any substance (Figure 1A). A dose–effect relationship consistent with the original definition of hormesis appears only after we artificially define the baseline (Figure 1B). The transformation of an adverse effect into a favorable effect exemplifies how 'illness is the doorway to health' as articulated in the philosophy of Yin and Yang.

Hormesis induced by environmental chemicals and radiation has been nicely reviewed in the field of toxicology with the functional readout mainly on cell viability, cell proliferation, enzyme activity, or

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gene expression [6]. In this review, we focus on lifestyle factors (Boxes 1 and 2) and endocrine factors (Table 1) in the context of chronic diseases with the emphasis on *in vivo* studies in mammals. The underlying molecular mechanisms are unclear for most hormesis phenomena (see Outstanding Questions).

Stress-Response Hormesis

Single-Mode and Cross-Mode Stress Responses

Many xenobiotic chemicals induce the expression of detoxification enzymes, which is protective against subsequent higher-dose exposures [7]. Some xenobiotic chemicals can directly serve as ligands for nuclear receptors such as the constitutive androstane receptor (CAR) or pregnane X receptor (PXR). Other xenobiotic chemicals can indirectly activate other transcription factors, such as nuclear factor erythroid 2-related factor 2 (Nrf2), through altering the intracellular redox status or a variety of stress-response signaling pathways. Activation of these transcription factors upregulates the expression of genes that encode enzymes in xenobiotic metabolism. These enzymes are classified into three phases, comprising phase I enzymes such as cytochrome P450 family enzymes, phase II enzymes such as glutathione-based conjugation enzymes, and phase III enzymes such as ATP-binding cassette transporters, which are collectively responsible for detoxification and excretion of the xenobiotic chemicals from the body. Thus, priming the body with a low-dose xenobiotic chemical can confer protection against subsequent exposures to the same chemical [7]. This adaptive response in xenobiotic metabolism constitutes a classic example of single-mode stress-response hormesis.

If the initial exposure confers protection against a different substance, it is referred to as cross-mode hormesis. In the abovementioned example of xenobiotic-mediated upregulation of detoxification enzymes, a combination of detoxification enzymes induced by one chemical can protect against

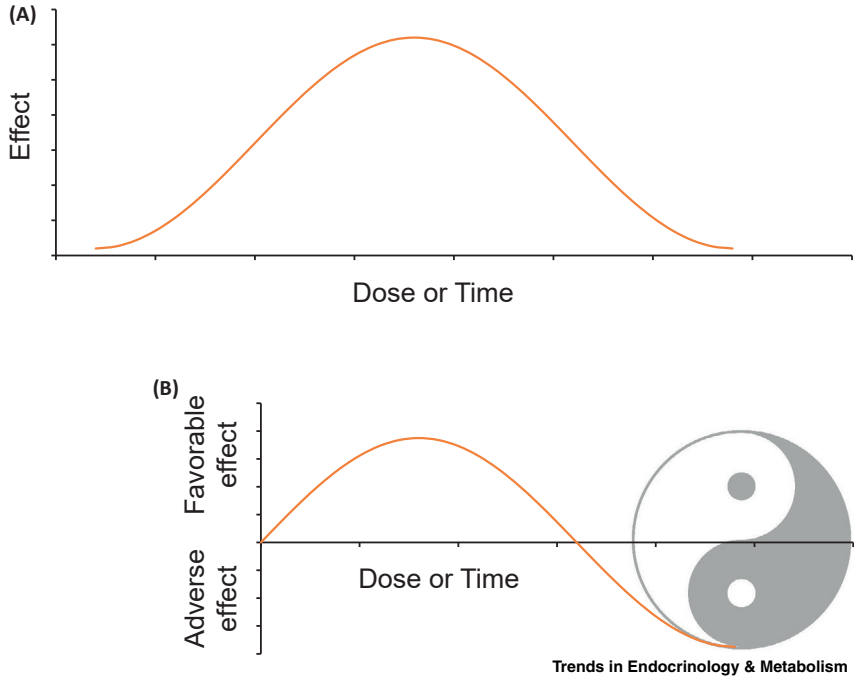

Figure 1. Illustration of Nonmonotonic Dose–Effect or Time–Effect Relationship.
(A) Bell-like curve depicting the optimal dose or time of an exposure. Time not only refers to the total duration but also includes the temporal pattern as defined by frequency and interval. (B) An artificial setting of the baseline leads to a biphasic curve aligned with the classic definition of hormesis: low-dose beneficial effects of harmful substances. The transformation of the adverse effect to the favorable effect exemplifies how 'illness is the doorway to health' as articulated in the ancient philosophy of Yin and Yang.

Box 1. Hormetic Effects of Lifestyle Factors

Cigarette Smoke

Cigarette smoke can cause lung diseases. However, epidemiological studies also reveal a correlation between smoking and a lower incidence of Parkinson's disease [108]. Specifically, a longer duration of smoking, not higher intensity, is correlated with a lower risk of Parkinson's disease [109]. Nicotine can be neuroprotective through nicotinic acetylcholine receptors that modulate neuroinflammation [110]. A major component of cannabis, delta-9-tetrahydrocannabinol (THC), can disrupt short-term memory. However, THC can improve neurocognitive functions in old animals when administered at low concentrations. THC promotes hippocampal neurogenesis and slows the neurodegenerative processes in animal models of Alzheimer's disease, which is associated with ameliorated inflammation and improved memory [111].

Alcohol Consumption

Heavy alcohol consumption can cause alcoholic fatty liver and alcoholic cardiomyopathy. However, compared with abstainers, moderate alcohol consumption is associated with reduced mortality and lower risk of cardiovascular diseases, although there is controversy regarding methodologies [112,113]. Moderate alcohol consumption is associated with beneficial alterations in blood lipid profile, platelet function, fibrinolytic activity, insulin sensitivity, myocardial blood flow, and cardiomyocyte survival signaling pathways, which can contribute to the lower risk of coronary events [113]. Moderate alcohol consumption can also be protective against cognitive dysfunction [114], although it is more controversial with the mechanism less well defined [115].

Exercise

Moderate levels of exercise reduce the levels of proinflammatory cytokines and stimulate the production of anti-inflammatory cytokines in healthy individuals [116]. Exercise activates the sympathoadrenomedullary and hypothalamus–pituitary–adrenal axes, leading to the release of catecholamines [117,118], which regulates inflammatory cytokines through the β2-adrenoceptor [119]. Intense exercise, however, can induce the release of proinflammatory cytokines and inhibit anti-inflammatory production [116]. Sedentary diabetic rats subjected to an acute intense swimming exercise showed aggravated inflammatory profiles and oxidative stress [120]. Metabolic derangements in obese rats impaired the negative feedback mechanisms between interleukin (IL)-6 and noradrenaline and excess high-intensity exercise can worsen the dysregulation, inducing proinflammatory effects [121]. Such a shifted balance between pro- and anti-inflammatory cytokines can cause excessive tissue damage and inflammatory diseases such as osteoarthritis [122].

Conversely, the role of inflammation in muscle tissue repair is also biphasic in the context of exercise. On the one hand, a low degree of inflammation seems to be required for the recovery of exercise-induced muscle microtrauma [123]. Post-exercise treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) can suppress satellite cell proliferation and reduce muscle protein synthesis [124]. On the other hand, intense exercise can cause muscle damage, as characterized by the disruption of myofibers and release of myocellular proteins. This leads to an inflammatory response and cytokine discharge, which can, in turn, worsen muscle performance [125]. Exercise also has biphasic effects on neurocognition. In a rat model of brain ischemia, a low-intensity exercise (LI) group, but not a high-intensity exercise (HI) group, performed better in spatial memory test compared with mice in a sedentary group. The HI group exhibited higher blood corticosterone levels, implicating a higher stress response. Expression levels of BDNF, synapsin-I, and PSD-95 in the hippocampus were increased only in LI rats, indicating that LI led to better synaptic plasticity [126].

many other chemicals. Such cross-mode hormesis is the basis of chemoprevention, an approach to use low-toxicity chemicals to induce adaptive protective responses against many other carcinogenic chemicals [3]. Cross-mode hormesis exists in many situations. For example, exposure of cells to mild heat stress can make them more protected from oxidative stress or toxins such as cyanide [8]. Similarly, exposure to a low-dose mitochondrial uncoupling agent, 2,4-dinitrophenol, can make cells less vulnerable to being killed by ischemia [9]. This cross-mode aspect of hormesis may contribute to the broad benefits of exercise and dietary restriction [10] (Boxes 1 and 2). Below we examine a few other common stressors.

Reactive Oxygen Species (ROS)

Oxidative stress refers to the high level of ROS that causes damage to DNA, protein, or other cellular components. The free radical theory of aging suggests that oxidative stress causes aging [11]. As

Box 2. Hormetic Effects of Fasting

Prolonged fasting or starvation causes muscle wasting and impairs cardiac function [127], while mild caloric restriction (CR) or intermittent fasting (IF) can have beneficial effects. Calorie restriction to 20% of *ad libitum* for 8 weeks in mice caused remarkable myocardial fibrosis with increased expression of caspase-1, IL-1β, and IL-18 compared with *ad libitum* control. By contrast, calorie restriction to 40% of *ad libitum* did not cause myocardial fibrosis and reduced expression of caspase-1, IL-1β, and IL-18 [128]. Mechanistically, one would assume that reduced calorie intake underlies fasting-induced metabolic benefits under overnutrition. However, it is not always the case. Time-restricted fasting, by restricting the feeding time within 8–12 h per day, does not change the total calorie intake in mice but can have many beneficial effects, including improved glucose tolerance, suppressed insulin resistance, and ameliorated dyslipidemia [129]. IF can also promote adipose thermogenesis by upregulating vascular endothelial growth factor (VEGF) expression and remodels adipose macrophages associated with adipose tissue browning [130].

Fasting can also facilitate cancer treatment. In preclinical mouse cancer models and patient xenograft models, fasting (six cycles of 1 day feeding, 1 day fasting) can inhibit the development of both B cell and T cell acute lymphoblastic leukemia (ALL) but not acute myeloid leukemia. This is associated with upregulated expression of the leptin receptor (LepR) and its downstream signaling, potentially due to a compensatory expression elevation triggered by reduced circulating leptin levels. The activated LepR signaling upregulated the PRDM1 gene, a known tumor suppressor, which contributed to the ALL inhibition effect [131]. In addition to the direct effect on tumor cells, fasting can affect immune cells and facilitate their recognition and the clearance of tumor cells. When combined with chemotherapy, fasting-mimicking diet (FMD) increased the level of bone marrow lymphoid progenitor cells and promoted the accumulation of $CD8^+$ tumor-infiltrating lymphocytes in the tumor bed and thus reduced the tumor progression of breast cancer and melanoma. FMD downregulated the expression of heme oxygenase-1 (HO-1) in breast tumors, which decreased regulatory T cells and facilitated the targeted attack of cancer cells [132]. Reduced circulating glucose, increased ketone bodies, and altered hormonal signals during fasting can also limit glucose availability to cancer cells, which may contribute to the anticancer effects of fasting [133].

some DNA repair mediators are downregulated in aged organisms, DNA damage induced by oxidative stress can be left unrepaired, leading to genome instability. However, low-level ROS can function as signal molecules to initiate biological processes without the above detrimental effects and therefore can be beneficial [12]. For example, the increased oxidative stress caused by depletion of mitochondrial superoxide dismutase extended lifespan in *Caenorhabditis elegans* [13]. Treatment with paraquat, a superoxide generator, at a low dose can also increase the lifespan, while high-dose paraquat was deleterious [14]. Randomized clinical trials have shown that antioxidants, such as vitamin C and vitamin E, do not prolong lifespan in human [15,16] and can potentially increase the risk for cancer and diabetes [17].

In addition to the level, the subcellular location also determines the role of ROS. While cytosolic ROS tend to shorten lifespan, mitochondrial ROS (mtROS) can extend the lifespan [18,19]. For example, skin wounding triggers local production of mtROS. Lowering mtROS levels by mitochondrial superoxide-specific antioxidants blocked actin-based wound closure. Paraquat, a pro-oxidant that induces mitochondrial superoxide, promoted actin-based wound closure. Mutations of superoxide dismutase in worms elevated mitochondrial superoxide, promoted wound closure, and enhanced survival. Mechanistically, mtROS was increased by wound-triggered calcium influx, which locally inhibited Rho GTPase activity via a redox-sensitive motif [20]. A similar role of mtROS was documented in mammalian skeletal muscle cells. Injury increased mitochondrial calcium uptake through the mitochondrial calcium uniporter, which transiently increased mtROS. The mitochondrial respiratory chain inhibitor rotenone and antimycin A increased injury-triggered mtROS production and showed beneficial effects on plasma membrane repair in a dose-dependent manner. Mechanistically, mtROS locally activated GTPase RhoA, triggered F-actin accumulation at the site of injury, which facilitated membrane repair. Quenching mtROS using mitoTEMPO in myofibers during eccentric exercise prevented injury-triggered RhoA activation and actin polymerization, leading to increased damage to myofibers and a greater loss of force [21]. Therefore, mtROS not only play a role in extending longevity but are also

Table 1. Biphasic Dose–Effect or Time–Effect of Endocrine Factors

Hormone	Target	Effect	Refs
PTH	Bone	Constant high-level exposure causes bone loss, while intermittent exposure increases bone mass	[65,66]
	Insulin secretion	Low dose stimulates glucose-induced insulin release, while high-dose inhibits it	[67,68]
Glucocorticoid	Muscle	Chronic treatment exacerbates muscle atrophy, while intermittent weekly treatment enhances muscle repair and improves muscle contractile function	[69,70]
	Cognitive function	Chronic high-level exposure is associated with increased risk of cognitive decline, while acute exposure improves memory consolidation but inhibits memory retrieval	[72–74]
Thyroid hormone	Heart	Hyperthyroidism increases the risk of coronary heart disease, pulmonary hypertension, and atrial fibrillation; hypothyroidism causes left ventricular diastolic dysfunction and increases carotid intima–media thickness	[76]
	Metabolism	Thyroid hormone increases catabolism and energy expenditure; however, T3 level is positively correlated with unfavorable metabolic parameters in some populations	[77,78]
Adiponectin	Metabolism	Adiponectin improves glucose tolerance and endothelial function while reducing inflammation and atherosclerosis, but adiponectin level is positively associated with mortality in coronary heart disease; adiponectin may exacerbate chronic inflammatory conditions	[80]
Estrogen	Tumor cell proliferation	Estrogen stimulates tumor cell proliferation at low doses but promotes cell apoptosis at high doses	[81,82]
	Cardiovascular system	Low dose activates, while high dose inhibits, plasminogen activator in aortic endothelial cells	[84]
	Bone	Estrogen stimulates endochondral bone formation at the start of puberty but induces epiphyseal closure at the end of puberty; in treating Turner syndrome, intermittent low-dose estrogen induces maximal ulnar growth, while high-dose estrogen fails to stimulate ulnar growth	[86,87]
Progesterone	Memory	Progesterone, when administrated shortly before test, potentiates estradiol-induced effects on extinction recall or spatial memory; however, when administrated 1 day before the test, progesterone abolishes the estradiol effects	[89,90]
	Immune response	Long exposure time is associated with poor immune responses to genital herpes; short treatment is protective against HSV challenge	[91]
GH and IGF-1	Lifespan	Both low and high IGF-1 levels are associated with increased mortality; GH can increase muscle mass, reduce adiposity, and improve bone density; however, deficiencies in GH/IGF-1 signaling pathways increase lifespan and healthspan	[92,95,99]
Insulin	Blood glucose	Insulin lowers blood glucose levels in diabetes patients; however, suppressing hyperinsulinemia can improve insulin sensitivity and extend lifespan in diet-induced obesity	[101,102]
Irisin	Bone	Low-dose weekly treatment increases bone density; however, irisin deficiency also suppresses OVX-induced bone resorption	[106]

required for wound repair. This biphasic dose–effect of ROS and other substances in mitochondria is referred to as mitohormesis [22].

ROS not only serve as an intracellular signal but can also mediate intercellular communications. ROS generated by neutrophils play a vital role in promoting liver repair [23]. On tissue injury, neutrophils are recruited to the injured site, contributing to liver repair by causing the phenotypic conversion of macrophages from a proinflammatory stage to a proregenerative stage. ROS from neutrophils act as a mediator for the process because reducing neutrophil ROS by either depletion of neutrophils or genetic perturbation of neutrophil NADPH oxidase 2 (Nox2) blocked the macrophage phenotypic conversion. Conversely, transferring wild-type neutrophils, but not Nox2-knockout neutrophils, can rescue the hepatic damage in neutrophil-depleted mice and promote the macrophage phenotypic conversion [23]. Thus, ROS are critical intercellular signaling molecules that mediate the resolution of inflammation.

Hypoxia

Obstructive sleep apnea (OSA) is a risk factor for cardiovascular and liver diseases. Intermittent hypoxia (IH) is a major component of OSA and contributes to the hepatic, metabolic, and vascular effects of OSA. Nocturnal IH is independently associated with metabolic dyslipidemia and steatosis. IH (1-min cycle, Fi_{O2} 5–6% for 30 s, Fi_{O2} 20.9% for 30 s, for 9 h) can also cause insulin resistance in lean mice [24]. Chronic IH (1-min cycle, Fi_{O2} 6–7% for 30 s, Fi_{O2} ~21% for 30 s) during the light phase (9 a.m. to 9 p.m.) for 4 weeks exacerbates insulin resistance and glucose intolerance in diet-induced obesity [25].

Paradoxically, IH shows benefits in some conditions by facilitating the adaptation to reduced oxygen. Exposure to a daily IH cycle for 4 days, each comprising 2 min at 6–8% O_2 followed by 3 min of reoxygenation for five times, can protect the heart against ischemia–reperfusion injury [26]. IH also increases exercise tolerance in elderly men [27] and improves myocardial perfusion in patients with severe coronary heart disease [28]. Mechanistically, IH improves nitric oxide (NO) bioavailability and storage [29]. Decreased O_2 levels can lead to less oxidization of NO to NO_2^- and NO_3^-, allowing more NO release from hemoglobin [30]. In addition, hypoxia can induce the expression of NO synthase through hypoxia-inducible factor HIF-1 [31]. IH (9.5–10% O_2, 5–10 min, 5–8 times/day, for 20 days) suppressed hypertension in spontaneously hypertensive rats. Endothelial function was sustained in the IH group but decreased in the control group. This was associated with enhanced capacity of aortic rings to store NO and increased NO availability in vascular walls [32]. In a mouse model of metabolic syndromes, short-term IH (1-min cycle, Fi_{O2} 5% for 30 s, Fi_{O2} 21% for 30 s, 8 h/day) increased insulin and leptin levels and prevented endothelial dysfunction caused by a high-fat diet. IH restored mitochondrial complex I activity and slightly increased complex II and IV activity, which may help to boost mitochondrial oxidative-phosphorylation and reduce liver lipid accumulation [33].

NO

NO can lead to mutagenesis and cell death at high concentrations through inhibiting DNA synthesis, disrupting cell membrane integrity, arresting the cell cycle, causing DNA strand break, and apoptosis [34]. Excess NO also impairs mitochondrial function and affects metabolic processes in neurons, contributing to neurodegenerative diseases [35]. However, NO at low concentrations modulates glutamatergic neurotransmission [36]. Depletion of neuronal NO synthase impaired cognitive performance and synaptic plasticity [37]. In the cardiovascular system, NO promotes new vessel formation, limits vessel constriction, suppresses inflammation, and promotes blood flow [38].

Amyloid-β Peptide (Aβ)

Excessive Aβ deposits cause synaptoxicity and memory dysfunction [39]. Beyond this amyloid hypothesis, emerging evidence suggests that Aβ and its precursor protein APP have physiological functions at low concentrations in the healthy brain [40,41]. APP is involved in cell proliferation and differentiation, neurite outgrowth, cell adhesion, and synaptogenesis [40]. In contrast to the detrimental effects at nanomolar concentrations, picomolar concentrations of $Aβ_{42}$ enhance hippocampal long-term

potential (LTP) formation by increasing acetylcholine and the activation of nicotinic acetylcholine receptors [42,43], which suggests a positive role of Aβ in synaptic plasticity. Infusion of mice with low-dose Aβ in the hippocampus improved fear memory [42]. Conversely, APP-knockout mice showed impaired LTP and memory [44]. Aβ oligomers can also bind to the glycoproteins of the herpesvirus capsid, resulting in the entrapment of virus particles and protection of the brain from *Herpesviridae* infection [45]. The biphasic dose–response effects of Aβ might contribute to the failure of Aβ-targeting drugs in clinical trials in treating Alzheimer's disease.

Developmental Stress-Response Hormesis

During stress-response hormesis, the initial exposure can occur at an early developmental stage. A classic example is the hygiene hypothesis, in which a lack of early childhood exposure to infectious agents and parasites can suppress the natural development of the immune system and increase susceptibility to allergic diseases [46]. The stress-inoculation hypothesis is a counterpart of the hygiene hypothesis in psychology. It suggests that mild or intermittent stress exposure early in life induces resilience to subsequent stress in adults [47].

The stress-inoculation hypothesis is supported by many animal studies. In one study, male mice were subjected to a variety of stress manipulations such as maternal separation, early weaning, reduced nesting, isolation, handling, restraining, and daily swim stress in early life and were then tested for depression- or anxiety-like behaviors in adulthood following exposure to chronic social-defeat stress. Some of the manipulations mitigated the deleterious consequences of adult stress [48]. Similarly, manipulations of female mice with early handling or limited nesting in early life can make them more resistant to similar aversive conditions in adult, as measured by anxiety, depression, or sociability behaviors [49]. Rats exposed to physical stress during early adolescence showed increased anxiety behaviors in adulthood, while midadolescence stress paradoxically reduced anxiety-like behaviors in adulthood. These results suggest that the timing of adolescent adversity is essential to long-term outcomes [50]. In another study, early-life stress of reduced bedding in mice led to resistance to social-interaction deficits after chronic social-defeat stress. It also mitigated acute restraint and tail-shock stress-induced impairments in hippocampal synaptic plasticity, an effect abolished by adrenalectomy [51]. Short-term separation stress in early life altered histone modifications and the expression of genes involved in dopamine receptor signaling in the brain, a distinct effect from long-term separation stress, suggesting the potential involvement of dopamine signaling and epigenetic changes in the underlying mechanisms [52]. Signaling pathways of other neurotransmitters or neuropeptides were also implicated in the process, including arginine vasopressin (AVP) and oxytocin [53].

The stress-inoculation theory also has support from human studies. Threat-related amygdala reactivity can be measured using task-based functional MRI (fMRI) in humans and is a biomarker of vulnerability to stress-related depression or anxiety [54]. In a study with adolescents, increased amygdala reactivity to an interpersonal threat was positively associated with better familial affective responsiveness, especially in adolescents reporting lower recent stressful life events [55]. The finding is in line with studies examining parenting style and the mental wellbeing of adolescents. Parental overprotection refers to a restrictive or indulgent parenting style when it comes to protecting the child from potential harm or risk. Parental overprotection is positively associated with later psychopathology, including dysfunctional attitudes, depression or anxiety disorders, and suicide intent [56,57]. Conversely, stress inoculation training (SIT) is a type of psychotherapy using intermittent exposure to mild stress to improve patients' ability to deal with stress. SIT can reduce anxiety and depression for cancer patients and veterans with post-traumatic stress disorder or traumatic brain injury [58,59]. The paradoxical beneficial effect of early-life stress makes sense from an evolutionary perspective, considering that the brain needs stimulation from the environment for proper mental development at a young age. What we assume to be a stressor can be perceived as a positive stimulation by the brain. The brain responds to a variety of stressors in a similar way as to the enriched-environment (EE) positive stimuli known to enhance synaptogenesis and intellectual development [60].

The resilience conferred by early-life stress is likely to represent an adaptation to the altered environment and is often a trade-off between different traits. Exposure of female zebra finches to time-restricted feeding and daily corticosterone injection from a young age reduced breeding performance during early adulthood but led to better breeding performance than the control when birds were bred in old adulthood [61]. Birds exposed to short episodes of mild heat stress in early life showed ameliorated oxidative damage in adulthood when given heat stress compared with the control group without the early-life priming. Interestingly, birds that had early-life heat stress, but did not experience it again later in life, had a shorter lifespan than any other group [62]. Females blackbirds show decreased breeding success but increased lifespan with increasing exposure to lead, but not cadmium [63]. These studies suggest that some stress can cause a rebalance of the trade-off between fecundity and longevity.

The trade-off can be either beneficial or harmful, depending on whether the late-life environment matches the early-life stress. If the outcome is harmful, it falls into the 'Developmental Origins of Health and Disease' (DOHaD) paradigm. A classic example of the later is the thrifty phenotype hypothesis, in which undernutrition during the fetal or infant stage rebalances the metabolism towards a thriftier phenotype that favors energy storage, which increases the risk of developing obesity, diabetes, and other metabolic syndromes in later life when food becomes plentiful [64]. Therefore, developmental stress-response hormesis and the DOHaD paradigm are two sides of the same coin.

Biphasic Dose–Effect or Time–Effect of Endocrine Factors

Parathyroid Hormone (PTH)

Many endocrine factors show dose-dependent or time-dependent opposite effects, which falls within the broad definition of hormesis. Here, time not only refers to the total duration of the exposure but also includes the temporal pattern. Intermittent or bipolar treatment can produce the opposite effects as chronic continuous treatment. PTH causes bone loss at a constantly high level as in chronic hyperparathyroidism. However, intermittent exposure to PTH or its paralog at a rate of once per day increases bone mass [65]. Such an intermittent-exposure strategy has been approved as a therapy for osteoporosis. The underlying mechanism is not completely understood. PTH promotes two opposite processes: bone formation by osteoblasts and bone reabsorption by osteoclasts, but with seemingly different kinetics [66]. Even within one cell type, PTH can have opposite effects. For example, in osteoblast cells PTH inhibits apoptosis but also inhibits differentiation [66]. PTH also affects other cell types, including bone lining cells, osteoblast progenitor cells, osteoclast cells, lymphocytes, and macrophages. A variety of intracellular molecular signaling pathways, presumably downstream of the cell membrane receptors for PTH, are being characterized in different cell types on PTH treatment [66]. However, what seems lacking is a detailed characterization of the kinetics of the cellular phenotypic changes in response to PTH with different temporal patterns. PTH also shows biphasic dose-dependent effects on insulin secretion from pancreatic islet cells. Low-dose PTH stimulates glucose-induced insulin release, while high-dose PTH inhibits it [67]. The PTH level for the maximal stimulatory effects is dependent on the extracellular calcium level. High-dose PTH reduces the intracellular ATP level and increases the resting intracellular calcium level, which contributes to impaired insulin release [68].

Glucocorticoid

Intermittent weekly glucocorticoid treatment can produce the opposite effect as chronic daily glucocorticoid treatment on muscle atrophy. In an acute focal muscle injury model in mice, pulsatile weekly treatment with glucocorticoids reduced injury area, macrophage infiltration, and injury-associated fibrosis, which improved muscle performance recovery [69]. However, chronic daily glucocorticoids worsened muscle performance. In mouse models of muscular dystrophy, daily glucocorticoids exacerbated muscle atrophy, while weekly glucocorticoids ameliorated it [69,70]. The expression of several genes in muscle atrophy was upregulated in skeletal muscles on daily glucocorticoid treatment but was downregulated on weekly treatment. The effect of glucocorticoids on cognitive function is also biphasic [71]. Chronic high levels of glucocorticoids are associated with increased risk of cognitive decline and neurodegeneration [72]. However, the acute rise of glucocorticoids improves

memory consolidation in multiple models [73]. This positive effect of glucocorticoids on memory consolidation is accompanied by an adverse effect on memory retrieval [74]. Electrophysiological recording assessing long-term potentiation in a rat CA1 population showed a positive correlation between low-level glucocorticoids and primed burst potentiation, but a negative correlation at high levels [75]. Thus, dosage, duration, and temporal pattern collectively determine the outcome of glucocorticoids on cognitive function by acting on multiple stages of memory processing.

Thyroid Hormone

Thyroid hormone is a classic example of biphasic dose–effect, as both hyperthyroidism and hypothyroidism are medical conditions. Thyroid hormone has cardioprotective potential because it inhibits apoptosis, activates mitochondrial metabolism, decreases fibrosis, and increases neoangiogenesis. Therefore, thyroid hormone replacement therapy could be used for myocardial infarction to induce positive cardiac remodeling. However, hyperthyroidism increases the risk of coronary heart disease, atrial fibrillation, and pulmonary hypertension. Conversely, hypothyroidism causes left ventricular diastolic dysfunction and increases carotid intima–media thickness [76]. Thyroid hormone increases catabolism and energy expenditure and therefore is presumably negatively correlated with metabolic syndromes characterized by overnutrition. However, blood triiodothyronine (T3) and thyroid-stimulating hormone (TSH) levels in euthyroid human subjects are positively associated with metabolic syndromes such as higher body mass index and blood lipid or glucose levels [77,78]. It is speculated that the elevated T3 can be a failed compensatory mechanism aiming to maintain metabolic health under overnutrition [79]. It is also possible that the dose–effect curve of thyroid hormone on each component of the metabolic syndrome is biphasic, and certain unfavorable metabolic parameters can shift the dose–effect curve in a way that favors detection of only one side of the curve.

Adiponectin

Adiponectin has an elusive relationship with mortality, known as the 'adiponectin paradox' [80]. Adiponectin improves glucose tolerance, reduces inflammation, improves endothelial functions, and inhibits atherosclerosis. However, blood levels of adiponectin – both total adiponectin and the high-molecular-weight isoform – are positively associated with mortality across many clinical conditions, such as coronary heart disease. One obvious explanation is that the elevated adiponectin is a compensatory response to potential adiponectin resistance in the situation of deteriorated health, although this hypothesis has not been rigorously tested. It is also possible that adiponectin has biphasic effects on some of the physiological processes. This possibility is supported by observations that adiponectin may exacerbate inflammation in chronic inflammatory conditions such as colitis, rheumatoid arthritis, or Crohn disease [80]. It is unclear what determines such a switch from anti-inflammatory to proinflammatory effects for adiponectin.

Estrogen

Estrogen has biphasic effects on cell proliferation and tumor growth. It stimulates tumor cell proliferation at low doses but promotes cell apoptosis at high doses [81]. In mouse models of prostate cancer and breast cancer, exposure to low-dose 17β-estradiol (E2) led to larger tumors than placebo, while exposure to high-dose E2 led to smaller tumors [81,82]. Mechanistically, low-dose E2 decreases KLF5-dependent proapoptotic FOXO1 transcription through ERβ, which inhibits apoptosis and promotes tumor growth. High-dose E2 activates extrinsic and intrinsic apoptosis pathways through a variety of mechanisms [82,83]. In the cardiovascular system, low-dose E2 activates plasminogen activator in aortic endothelial cells while high-dose E2 inhibits plasminogen activator [84], which may contribute to the increased risk of myocardial infarction or ischemic stroke in young women who receive higher doses of estrogen as oral contraception [85]. Estrogen also has biphasic effects on bone remodeling. During bone development, both estrogen and androgen stimulate endochondral bone formation at the start of puberty but induce epiphyseal closure at the end of puberty [86]. In treating Turner syndrome, intermittent low-dose estrogen induces maximal ulnar growth, while high-dose estrogen fails to stimulate ulnar growth [87].

Progesterone

Progesterone has a biphasic time–effect on estrogen-dependent regulation of memory. Intracranial infusion of progesterone in young ovariectomized mice increased dorsal hippocampal p42 ERK after 5 min but decreased its phosphorylation after 15 min and, intriguingly, had no apparent effect after 30 min [88]. Estradiol facilitates extinction recall, an effect potentiated by progesterone if progesterone administration occurred 6 h before extinction training. However, when given 24 h before the extinction training, progesterone abolished the estradiol effect on extinction recall [89]. Similar time-dependent biphasic effects were found for spatial memory in estradiol-treated ovariectomized rats; progesterone augmented the beneficial effect of estradiol on spatial memory when administered 90 min before the test, but reversed estradiol's effects when administered 24 h before the test [90]. The biphasic effect of progesterone on the immune system is also time dependent. Longer exposure time with a long-acting progestin formulation was associated with poor innate and adaptive immune responses to genital herpes simplex virus (HSV). By contrast, mice immunized shortly after progesterone treatment were protected against HSV challenge [91].

Growth Hormone (GH) and Insulin-Like Growth Factor 1 (IGF-1)

GH shares a common ancestry with insulin/ IGF-1. Epidemiological studies suggest that the relationship of IGF-1/GH levels with healthy aging is biphasic. Both low and high circulating IGF-1 levels are associated with increased mortality in the general population [92] or increased cancer mortality in older men [93,94]. Interventional studies also revealed a perplexing relationship between GH/IGF-1 and aging. On the one hand, GH administration in some elderly individuals can increase muscle mass, reduce adiposity, and improve bone mineral density, demonstrating antiaging benefits [95]. On the other hand, mice with deficiency in GH, the GH receptor, GH-releasing hormone (GHRH), the GHRH receptor, IGF-1, the IGF-1 receptor, the insulin receptor, insulin receptor substrate, or downstream molecules such as mammalian target of rapamycin (mTOR) or p70 ribosomal protein S6 kinase 1 (S6K1) have increased lifespan or healthspan [95–97]. The underlying mechanisms include improved antioxidant defenses, reduced inflammation, reduced insulin levels, reduced cell senescence, altered mitochondrial function and energy metabolism, and enhanced stress resistance [95]. Enhanced insulin sensitivity is particularly interesting, as mice with transgenic overexpression of a GH receptor antagonist showed increased adiposity but improved glucose tolerance on a high-fat diet [98]. Humans with genetic deficiencies in the GH/IGF-1 signaling pathway are characterized by proportional short stature, central obesity, and delayed puberty, but are generally healthy and protected from aging-related diseases such as cancer, diabetes, and atherosclerosis [95,99]. Thus, the general retardation of growth and reproduction seems to be a sacrifice for the longevity benefits [100]. It may be possible to get the best from both sides through careful timing of the intervention (i.e., reducing the GH/IGF-1 signaling pathway only after midlife). The trade-off between survival and fecundity, or between two other distinct physiological processes, can potentially explain many paradoxical hormesis phenomena.

Insulin

Insulin is widely used to lower blood glucose levels in diabetes patients. However, suppressing hyperglycemia can improve glucose control and protect against obesity, which implicates a potential biphasic effect of insulin in metabolic disorders. Insulin is encoded by two genes, *Ins1* and *Ins2*, in mice. Female $Ins1^{-/-}$; $Ins2^{+/-}$ mice showed reduced hyperinsulinemia compared with the control $Ins1^{-/-}$; $Ins2^{+/+}$ mice after high-fat diet feeding, which was associated with attenuated weight gain, lower glucose levels, improved insulin sensitivity, and extended lifespan [101,102]. These results suggest that hyperglycemia contributes to insulin resistance in diet-induced obesity. Pharmacological reduction of insulin secretion also lowers body weight in obese people [103]. However, on the leptin-deficient $Lep^{ob/ob}$ background, loss of two or three insulin alleles reduced body fat but resulted in exacerbated glucose intolerance compared with the control $Ins1^{+/+}$; $Ins2^{+/-}$; $Lep^{ob/ob}$ mice [104]. These results suggest that reduced adiposity can be separated from improved glucose control. It also suggests that leptin is required for the effect on glucose control.

Irisin

Irisin is a myokine secreted as a cleaved product of fibronectin type III domain-containing protein 5 (FNDC5) from skeletal muscle in response to physical exercise [105]. The effect of irisin on bone is biphasic. Recombinant irisin, given at a low dose weekly in mice, increased cortical bone mineral density and positively modified bone geometry, upregulated pro-osteoblastic genes in bone marrow, increased the activity of osteoblasts, and reduced osteoclast numbers [106]. Consistently, irisin upregulated sclerostin in an osteocyte-like cell line and in mice. However, FNDC5-null mice were resistant to ovariectomy (OVX)-induced trabecular bone loss and displayed a marked reduction in bone resorption [107]. Deficiency of FNDC5 suppressed bone resorption by reducing osteoclast numbers and bone erosion, which ameliorated OVX-induced bone loss. Thus, although irisin could be a therapeutic target for osteoporosis, its other effects on bone remodeling should also be considered.

Outstanding Questions

When we measure an effect of an exposure, what exactly is the baseline?

What are the molecular and cellular changes, on a fine timescale, on an acute exposure to an environmental or endocrine factor?

What causes the opposite effects of intermittent (pulsatile) versus continuous (sustained) exposures at the same dosage?

What are the mechanisms, epigenetic or nonepigenetic, underlying resilience induced by early-life stress?

Concluding Remarks

The golden-mean principle in philosophy suggests an optimal dose, duration, temporal pattern, or spatial distribution for any exposure for a given effect. Any deviation from this Goldilocks condition, in either direction, results in suboptimal or harmful effects, which generates a biphasic or nonmonotonic curve. In this broadest sense, everything can be hormesis. More often, we use 'hormesis' to refer to paradoxical low-dose beneficial effects of stressors. It might seem paradoxical because of our preconception regarding what constitutes 'stress' or 'benefit'. It can also be counterintuitive because we are often cognitively biased towards the monotonic cause–effect relationships. For example, we are used to expecting opposite outcomes from gain-of-function and loss-of-function manipulations. We describe many molecular signaling events in a monotonic manner. Looking at biological processes through the lens of hormesis could help to explain or reconcile many paradoxical phenomena, particularly the opposite effects of the same substance, regardless of whether it is 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. Compared with the dose, the temporal pattern and duration of the exposure are underappreciated factors in determining the net outcome. Intermittent exposure often generates opposite effects compared with continuous exposure.

Our bodies are highly adaptive. On the one hand, exposure to a stressor can induce stress responses that are protective against subsequent exposures as if the body anticipates more stress. On the other hand, constant high-level exposure can increase tolerance to avoid overstressing the system. Such adaptations are essential because the environmental changes can be unpredictable and the body needs to adjust the trade-off among different functions such as fecundity versus longevity or energy conservation versus expenditure. The endocrine, nervous, and immune systems are particularly amenable to these adaptations because these systems directly sense the environmental changes and communicate the perceived change to the rest of the body. These adaptations can be so common and successful during evolution that body becomes reliant on certain stress stimulations for 'training' purposes during healthy development and homeostasis. Removing the stressors, especially during early life, deprives the body of this training opportunity and can reduce resilience, as exemplified by the hygiene hypothesis and the stress-inoculation theory.

Acknowledgments

We owe apologies to colleagues whose work we failed to cite. We prefer to cite recent original research articles on mammals. We thank Dr Mitchell Lazar for critical reading of the manuscript and helpful discussions. We thank Thomas Fair for assisting with the table. We thank National Institutes of Health (NIH) grants DK111436 and ES027544 for supporting the related work in our laboratory. T.Y. is supported by a postdoctoral fellowship from the Children's Nutrition Research Center. We are also thankful for support or pilot funds from the Baylor College of Medicine Cardiovascular Research Institute, the Dan L. Duncan Comprehensive Cancer Center (P30CA125123), the Texas Medical Center Digestive Diseases Center (P30DK056338), and the SPORE program in lymphoma (P50 CA126752) at Baylor College of Medicine and the Gulf Coast Center for Precision Environmental Health (P30ES030285).

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