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Hormesis defines the limits of lifespan

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ABSTRACT

This commentary provides a novel synthesis of how biological systems adapt to a broad spectrum of environmental and age-related stresses that are underlying causes of numerous degenerative diseases and debilitating effects of aging. It proposes that the most fundamental, evolutionary-based integrative strategy to sustain and protect health is based on the concept of hormesis. This concept integrates anti-oxidant, anti-inflammatory and cellular repair responses at all levels of biological organization (i.e., cell, organ and organism) within the framework of biphasic dose responses that describe the quantitative limits of biological plasticity in all cells and organisms from bacteria and plants to humans. A major feature of the hormetic concept is that low levels of biological, chemical, physical and psychological stress upregulate adaptive responses that not only precondition, repair and restore normal functions to damaged tissues/organs but modestly overcompensate, reducing ongoing background damage, thereby enhancing health beyond that in control groups, lacking the low level "beneficial" stress. Higher doses of such stress often become counterproductive and eventually harmful. Hormesis is active throughout the life-cycle and can be diminished by aging processes affecting the onset and severity of debilitating conditions/diseases, especially in elderly subjects. The most significant feature of the hormetic dose response is that the limits of biological plasticity for adaptive processes are less than twice that of control group responses, with most, at maximum, being 30–60 % greater than control group values. Yet, these modest increases can make the difference between health or disease and living or dying. The quantitative features of these adaptive hormetic dose responses are also independent of mechanism. These features of the hormetic dose response determine the capacity to which systems can adapt/be protected, the extent to which biological performance (e.g., memory, resistance to injury/disease, wound healing, hair growth or lifespan) can be enhanced/extended and the extent to which synergistic interactions may occur. Hormesis defines the quantitative rules within which adaptive processes operate and is central to evolution and biology and should become transformational for experimental concepts and study design strategies, public health practices and a vast range of therapeutic strategies and interventions.

1. Introduction

Multiple theories have been offered to explain the ageing process. However, current thoughts generally assert that senescence results from various extrinsic events that lead progressively to cell damage and death and/or that endogenous metabolism generation of vast quantities of oxyradicals/cell/day related to the genome-based theory. It is widely agreed that aging is a combination of several theories, the free radical and mitochondrial theories presumably being the most important, while others may play a definite, although less critical, role (Lopez-Otin et al.,

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2023; Lopez-Otin and Kroemer, 2021). Although several lines of evidence suggest that accumulation of oxidative molecular damage is a primary causal factor in senescence, it is increasingly evident that the mitochondrial genome may play a key role in aging and neurodegenerative diseases (Ristow, 2014). Mitochondrial dysfunction is characteristic of several neurodegenerative disorders, and evidence for mitochondria being a site of damage in neurodegenerative disorders is partially based on decreases in respiratory chain complex activities in Parkinson's disease, Alzheimer's disease, and Huntington's disease (Calabrese et al., 2010). Such defects in respiratory complex activities, possibly associated with oxidant/antioxidant balance perturbation, are thought to underlie defects in energy metabolism and induce cellular degeneration. Efficient functioning of maintenance and repair processes is crucial for both survival and the physical/psychological quality of life/health spans. This is accomplished by an evolutionary-based complex network of adaptive and longevity assurance processes, that are integrated within a very defined dose-response framework referred as hormesis, a highly specialized biphasic dose response relationship.

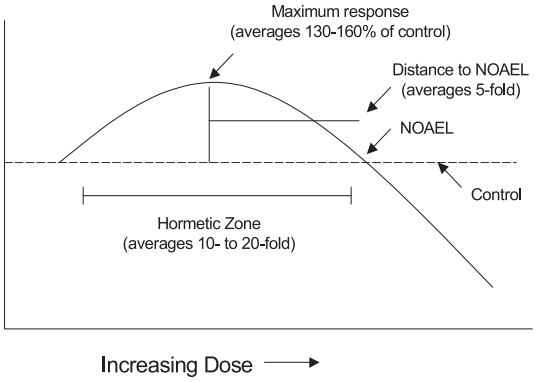
The present paper provides an integrative assessment of how biological systems, from bacteria to humans, have evolved a common and highly conserved general strategy to adapt to the vast range of anticipated and unanticipated threats to health and life from the extraordinary range of biological, chemical and physical stressors confronting living systems (Calabrese and Baldwin, 2003; Calabrese and Mattson, 2017). It is argued herein that all life evolved a common system of integrative adaptive responses that operate within and define the limits of biological plasticity and whereby such responses are universally mediated by the quantitative features of the hormetic dose response. It will be shown that vast networks of integrative and complementary mechanisms mediate these adaptive responses with particular focus on the challenges of human aging, lifespan extension potential, and the occurrence of neurodegenerative and other chronic diseases. Yet all such adaptive processes manifest their protective functions within the quantitative features of the hormetic dose response. The hormesis concept is central to biology, public health and medicine and should become their fundamental framework for understanding how biological systems respond to endogenous and environmental stresses and threats and how such knowledge can enhance biological performance, the human health span and longevity.

2. Hormesis: Life cycle and inflammaging

Human aging is characterized by a chronic, low-grade inflammation, and this phenomenon has been termed as "inflammaging" (Franceschi et al., 2000). Although intermittent increases in inflammation are critical for survival during physical injury and infection, recent research has revealed that certain social, environmental and lifestyle factors can promote systemic chronic inflammation (SCI) that can, in turn, lead to various conditions/diseases that collectively represent the leading causes of disability and mortality worldwide, such as cardiovascular disease, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease and autoimmune and neurodegenerative disorders. Inflammation is an evolutionarily conserved process characterized by the activation of immune and non-immune cells that protect the host from bacteria, viruses, and toxins by eliminating pathogens and promoting tissue repair and recovery. Depending on the degree and extent of the inflammatory response, including whether it is systemic or local, metabolic and neuroendocrine changes can occur to conserve metabolic energy and allocate more nutrients to the activated immune system. Specific biobehavioral effects of inflammation thus include a constellation of energy-saving behaviors commonly known as "sickness behaviors," such as sadness, anhedonia, fatigue, reduced libido and food intake, altered sleep and social-behavioral withdrawal, as well as increased blood pressure, insulin resistance and dyslipidemia. These behavioral changes can be critical for survival during times of physical injury and microbial threat. Shifts in the inflammatory response from short- to long-lived can cause a breakdown of immune tolerance and lead to major alterations in all tissues and organs, as well as normal cellular physiology, which can increase the risk for various non-communicable diseases in both young and older individuals (Furman et al., 2019).

3. Hormesis: an integrative adaptive evolutionary response strategy

Hormesis is an evolutionary-based adaptive strategy that mediates how cells, organs and organisms adapt to stress (Calabrese, 2008; Calabrese and Baldwin, 2000a; Calabrese and Baldwin, 2000b–f, 2002; Mattson, 2008). The hormetic phenomenon displays a biphasic dose response that is characterized by a low dose stimulation and a high dose inhibition (Fig. 1). The most unique feature of the hormetic dose response is that it has a modest stimulatory amplitude, with a maximum stimulatory response of 30–60 % greater than the control group (Calabrese and Blain, 2005, 2011; Calabrese et al., 2019). The maximum hormetic stimulation amplitude range reflects the limits of biological plasticity for integrative biological endpoints such as cell proliferation, growth, fecundity, memory, lifespan and others (Calabrese and Mattson, 2011, 2017). Hormetic dose responses are reported in all life forms, from bacteria to humans and for all cell types. The quantitative features of the hormetic dose response are independent of the biological model, cell type, endpoint, inducing agent and mechanism (Calabrese, 2008). Of considerable interest is that hormetic dose responses have been reported throughout the life cycle, starting soon after fertilization within the very early embryonic inner cell mass stage, through normal development and maturation and during the elderly stages of life (Calabrese et al., 2020; Calabrese, 2016a). The quantitative features of the hormetic dose response can be affected by numerous factors, including genetic background. age, health status, diet, and disease processes (Calabrese, 2008). The scientific assessment of hormesis can be complex and challenging since it typically requires the use of robust/rigorous study designs with many treatment groups in order to properly characterize the nature of the dose response across the low to high dose continuum. This experimental approach may also require a repeat measures component such as when the hormetic response occurs as an overcompensation response to an initial disruption in homeostasis/modest toxicity (Calabrese, 1999, 2016b,c). The above noted modest stimulatory response may require the use of enlarged sample sizes in order to achieve adequate statistical power. Likewise, it is critical that historical biological variability in the control group is well documented since it is important to reliably detect responses in the low dose stimulatory zone. Furthermore, given the modest magnitude of the hormetic stimulation, it is often necessary to replicate the experiment several times to ensure consistency and reliability of the findings. There is a heightened demand to identify



Dose-response curve depicting the quantitative features of hormesis

Fig. 1. Dose-response curve depicting the quantitative features of hormesis.

hormetic mechanisms and to use receptor and pathway inhibitors that can block hormetic responses, confirming the mechanistic basis of the hormetic process (Calabrese, 2013; Calabrese and Kozumbo, 2021b). This complex series of steps is often necessary to establish the biological foundations of the hormesis concept and to show its generality within numerous biological systems. These exceptional experimental demands in the assessment of hormetic dose responses have provided a firm foundation for its application to all stages of the life cycle, from early development through adult maturation and the process of progressive aging to an advanced elderly state (Calabrese, 2016a; Calabrese et al., 2020). While there is an extremely robust literature on hormetic dose responses, in general, this is not the case for targeted and systematic assessment of hormesis throughout the life cycle. This is due to the fact that hormesis has been a progressively expansive area of research only over the past two decades. In addition, the strong majority of experimental studies with hormetic dose responses have utilized cell culture studies since they are far less expensive and time consuming and can use more concentrations/doses.

4. Hormesis and lifespan extension

In the late 1980s, the concept of hormesis and its relevance to longevity mechanisms first became proposed as the mechanism by which lifespan could be extended (Boxenbaum et al., 1988). This was based on considerable research showing that low doses of ionizing radiation could extend the lifespan of insect and rodent models (Calabrese and Baldwin, 2000a). However, this became transformed further by a series of robust discoveries that caloric restriction could reliably extend lifespan in rodent models. The dose response findings for radiation (Calabrese and Baldwin, 2000f) and caloric restriction (Turturro et al., 1998, 2000) were biphasic, supporting an hormetic dose response model (Calabrese and Baldwin, 2002). Further, Masoro (1998) also showed that caloric restriction induced lifespan extension involved a stress response via increasing corticosterone concentrations, suggesting that the lifespan extension is a stress related hormetic process. Since the early 2000s, there has been a proliferation of research articles focused on finding ways to extend lifespan, mostly via pharmaceutical and dietary supplement means. These findings were soon mechanistically and dose response-wise integrated within with the hormetic dose response concept, especially by notable researchers such as (Masoro, 1998, 2000, 2007), Thomas Johnson (Cypser and Johnson, 2002, 2003; Cypser et al., 2006) and (Rattan, 1998, 2000), who became editor in chief of the journal Biogerontology. As a result of these research developments and leadership, the hormesis concept quickly became integrated into the scientific framework and lexicon of the fields of aging and biogerontology which has strongly influenced the directions of this area to the present and had a profound impact on related biological / biomedical areas of research.

The strong majority of these studies has involved the use of invertebrate models, especially the nematode, *C. elegans*, due to its short half-life (i.e., 20–25 days), ease of rearing, similarity to human relevant receptors and pathways for key endpoints, along with a spate of genetic mutants that permit the step by step dissection of the complex components of multiple lifespan extension and stress resistance mechanisms. Several hundred agents have been shown to enhance longevity in the nematode, *C. elegans*, and to a lesser extent in the fruit fly. These enhancements have been typically linked to specific pathways (insulin/insulin growth factor (IIS)/AMPK and transcription factors (e.g., DAF-16/NrF2, SIRT-1, HSP-1) and a series of genes (sod-3, catalase, glutathione transferase, metallothionein, heat shock proteins, phase 2 xenobiotic detoxification processes) (Martel et al., 2020). It is important to note that the numerous lifespan extending agents display similar quantitative features of the dose response, with all showing the general hormetic-based capacity to enhance longevity at low doses while reducing lifespan at higher doses (Calabrese and Blain, 2005, 2011; Calabrese, 2016b).

The mechanism research has strongly focused on how these interventions extend life but rarely address how the inhibition occurs. This is in contrast for many other endpoints where biological/biomedical pathway mechanisms have been identified for both the low dose stimulatory and high dose inhibitory components of the hormetic dose response (Calabrese, 2013). What pathways, transcription factors and genes are involved depend upon the agent being studied and perhaps other factors such as diet and age. In some circumstances the pathway and transcription factor appear to act an independent functioning unit. However, in other circumstances multiple pathway/transcription factor units may become activated and at times there is considerable cross-talk between two or more pathways and transcription factors depending on the agent. Likewise, the specific genes that become activated and the degree of activation can vary considerably depending on the transcription factor, inducing agent, dose and age tested. Furthermore, the different transcription factors (e.g., DAF-16, Nrf2) have the capacity to activate some of the same genes (Rattan, 1998; Martel et al., 2020). Despite such complexities and molecular mechanistic options, the most striking and consistent observation is that the plethora of lifespan extension agents conform to the quantitative features of the hormetic dose response regardless of the pathway, transcription factor and gene products. That is, the maximum hormetic responses are invariably reported to be about 30–60 % greater than control group values. Thus, the response of essentially all the positive tested lifespan enhancing agents falls within the relatively narrow and modest dimensions of the hormetic dose response, which itself describes the limits of biological plasticity. This is also the case whether one is testing single agents, multiple combined agents, or highly complex mixtures (e.g., moringa that contains multiple lifespan enhancing components) (Calabrese et al., 2023; Mattson, 2008). The hormetic framework therefore provides the biological boundaries within which the lifespan-extension adaptive responses operate. More importantly, these same hormetic dose responses apply to all integrative endpoints (e.g. cell proliferation, memory, stress responses, wound healing, fecundity) in all biological systems. These findings suggest that the search for the “perfect” lifespan extension dietary supplement may not be a realistic one as the likely best that could be expected is a response that will conform to the limits of biological plasticity as described by the hormetic dose response. This raises the question of whether one could adopt a type of science-guided process for supplement selection with the targets being a healthy lifespan and maximum lifespan extension. For example, one might reason that one could take three different supplements with each extending lifespan via activation of a different pathway/transcription factor, perhaps hypothesizing that these exposures could be additive or even possibly synergistic. Alternatively, one might consider a single agent that activates the same three lifespan enhancing pathways/transcription factors, creating its own version of additive and/or synergistic responses. However, as suggested above, the effects of each approach on lifespan are generally quantitatively similar in these scenarios. This situation could become more complex and nuanced if one were to now employ an additional series of stressors such as different types of infection, heat, chemical stresses, surgery, life threatening diseases (e.g., heart attacks and strokes). In general, the range of stress conditions assessed by C elegans is limited to mostly heat and chemical aspects (e.g., hydrogen peroxide, paraquat, rotenone) and not the range of the above noted human conditions. However, while all lifespan extending agents may respond in a similar and hormetically-based quantitative fashion in longevity studies, some combination of agents may become optimal in more complex longevity-stress resistance patterns, yet still conforming to the 30–60 % hormesis “Rule”. Of considerable importance to the longevity issue is the generally reported marked drop off in the capacity to activate transcription factors in adulthood especially in the elderly. While age dependent decreases in activation of transcription factor-mediated hormetic effects is a critical issue, it has not received adequate study. Multiple studies indicate hormetic responses in *C. elegans* lifespan studies show the capacity to induce these longevity enhancing effects

even well into adulthood (Wiegent et al., 2009; Xiong et al., 2018). Likewise, studies with rodent models have shown the capacity to repair previously degraded adaptive hormetic pathways in elderly animals via dietary and or exercise intervention combinations (Calabrese, 2016b).

Humans studies with recovered stroke subjects over 90 years of age indicated that recurrent strokes could be profoundly diminished with the intervention of hormetic-based conditioning treatments that systematically blocked blood flow via the use of inflated blood pressure cuffs (Meng et al., 2015; Calabrese et al., 2020; Calabrese, 2021a,b; Calabrese, 2022a). Thus, the issue of aging and hormetic mechanism activation is a critical one that needs considerably more study. Consistent with this notion, many of the *C elegans* studies have shown that both median and maximum lifespans are significantly enhanced in an hormetic manner (Martel et al., 2020). While the mechanistic basis for median and maximum lifespan extension is often assumed to be the same this remains to be clarified. Nonetheless the quantitative features of the lifespan extension are similar for the median and maximum estimates. While numerous hormetic acting lifespan extending agents and protocols can extend both median and maximum lifespans, it is not clear how general this conclusion is, although there are examples in which only the median lifespan is extended (Martel et al., 2020).

5. Take away message

The key takeaway message is that the hormetic dose response is central to all aspects of biology, including longevity. Hormesis provides the quantitative rules by which the process of adaptation and lifespan extension works. While the field of aging research has long been dominated by an hormetic perspective, a detailed assessment of the literature indicates that the hormetic concept was broadly adopted as the means by which low doses of stressor agents upregulate a potential mixture of integrative adaptive mechanisms that affect a modest extension of lifespan. What has been generally missing is an appreciation that the magnitude of this response is restricted by the limits of biological plasticity which is described by the quantitative features of the hormetic dose response. This is a general strategy and is the case for single agents, combination of agents, complex mixtures, as well as synergistic responses in the hormetic stimulatory zone. The quantitative features of the hormetic response is its most distinguishing characteristic and is independent of biological model, cell type, endpoint, inducing agent and mechanism. It is the major controlling framework with which drugs and supplements that enhance biological performance work. This knowledge is critical for it enhances the capacity to create insightful study hypotheses, study designs, which include sample size, number of doses, dose spacing, and the need for replication and other key parameters. These concepts are particularly important to enhance the success of randomized clinical control studies which so commonly appear to result in false negative results (Calabrese, 2022a,b; Calabrese and Kozumbo, 2021b; Calabrese et al., 2023).

6. Conclusions

The present paper provides a fundamental framework for understanding how all biological systems, including humans, adapt to endogenous and environmental stresses. These adaptations are evolutionarily-based and are mediated within the limits of biological plasticity, which is described by the quantitative features of the hormetic dose response. This concept is central to efforts to extend both the health span as well as longevity, both median and maximum potential increases.

These fundamental principles provide the theoretical, experimental and therapeutic strategies for the assessment and treatment of a vast range of human diseases as well as enhancing public health. While the hormesis concept has gained considerable acceptance within the biomedical community, especially within ageing research and applications, neuroprotection, exercise and cardiovascular applications much more progress is necessary in order to broaden this message and concept to other biomedical and therapeutic areas as well as public health and environmental regulatory agency domains. While the biomedical domain has now come to broadly recognize the occurrence and significance of hormetic-biphasic dose responses (Calabrese et al., 2010; Calabrese, 2021a; Calabrese and Kozumbo, 2021b; Calabrese, 2022a; Calabrese et al., 2023) it tends to fail to appreciate that this is a fundamental and universal concept acting across all life forms. This limiting perspective is largely due to the high degree of specialization within disciplines, and is in striking contrast to that which occurred in aging/biogerontology, neuroscience and related domains. We contend that major advances in public health and medicine depend upon the broader and more integrative understanding of the hormesis concept.

Some Remaining Questions:

Why are the limits of biological plasticity for integrative biological responses confined to the 30–60 % "Hormesis Rule'? This is a profoundly important evolutionary based question that should receive considerable attention. Since chemical agents that can extend longevity in an hormetic manner may have profoundly different tissue distributions and half-lives within mammalian systems, it will be important to assess hormetic effects within targeted organs as well as on the overall integrative endpoint of longevity. The occurrence of profoundly differing tissue distributions may offer a scientific based approach for developing a composite type of hormetic agent mixture that optimizes health benefits.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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