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Review article

Environmental hormesis and its fundamental biological basis: Rewriting the history of toxicology

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ABSTRACT

It has long been debated whether a little stress may be “good” for you. Extensive evidence has now sufficiently accumulated demonstrating that low doses of a vast range of chemical and physical agents induce protective/beneficial effects while the opposite occurs at higher doses, a phenomenon known as hormesis. Low doses of environmental agents have recently induced autophagy, a critical adaptive response that protects essentially all cell types, as well as being transgenerational via epigenetic mechanisms. These collective findings highlight a generalized and substantial ongoing dose-response transformation with significant implications for disease biology and clinical applications, challenging the history and practice of toxicology and pharmacology along with an appeal to stake holders to reexamine the process of risk assessment, with the goal of optimizing public health rather than simply avoiding harm.

1. Dose response models

The dose response is the pillar of toxicology and medicine and fundamental in agriculture, biology, ecology and physiology. The most significant historical model is the Threshold dose response, which was later complemented by the Linear Non-Threshold (LNT) single-hit model and widely applied for cancer risk assessment by worldwide regulatory authorities (Calabrese, 2017a, 2017b).

An old, but at the same time “rediscovered” dose-response model, is hormesis, a biphasic dose response relationship characterized by a low dose stimulation and a high dose inhibition (Fig. 1). While the hormetic model has a long history, it was only brought into the mainstream of toxicological thought over the last 2 decades (Calabrese, 2014; Calabrese and Baldwin, 2000a, 2000b; Luckey, 1980; Stebbing, 1987, 1982). These developments revealed the wide occurrence of hormesis for a vast array of endpoints from a highly diverse set of biological models, at different levels of biological organization, induced by hundreds of chemicals from diverse chemical classes and environmental stimuli, with a maximum stimulation commonly being less than two-fold the control response (Agathokleous, 2018, 2017; Agathokleous et al., 2018; Belz and Piepho, 2017; Calabrese, 2013, 2017c; Calabrese and Blain, 2011; Calabrese and Mattson, 2017; Cedergreen, 2008; Cedergreen et al., 2009; Kim et al., 2018; Valacchi et al., 2005; Vargas-Hernandez et al., 2017). Of further biological and evolutionary significance is that the quantitative features of hormetic responses are independent of biological model, level of biological organization, stressor, and mechanism (Calabrese, 2013; Calabrese and Mattson, 2017; Calabrese et al., 2017, 2016; Cornelius et al., 2013; Dattilo et al., 2015; Pennisi et al., 2017). Hormesis (Fig. 2) provides the first quantitative description of biological plasticity and one that is fundamental to all biological systems (Agathokleous, 2018; Calabrese, 2014; Calabrese and Blain, 2005, 2011, 2009; Calabrese and Mattson, 2017; Calabrese et al., 2012; Vaiserman, 2011).

In light of progressive and novel hormetic dose response developments this study seeks to depict recent groundbreaking advances, which challenge a wide range of scientific disciplines to better understand, use, and apply the hormesis concept in research, policy, and in the enhancement of human welfare and biosphere sustainability.

2. Autophagy and preconditioning

Recent developments show autophagy activation in the framework

Abbreviations: AMP, adenosine monophosphate; ER, endoplasmic reticulum; ROS, reactive oxygen species; UPR, unfolded protein response

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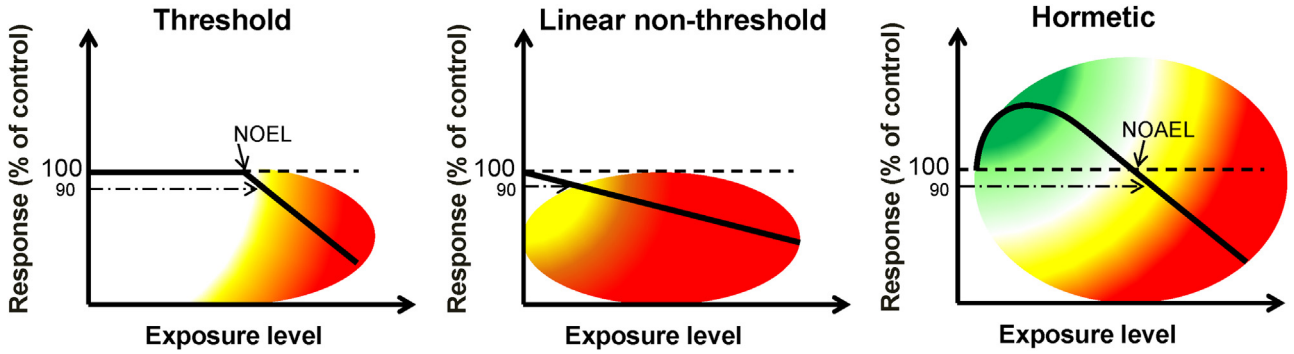

Fig. 1. Hypothetical lines, with zero or non-zero curvature, illustrating threshold, linear non-threshold (LNT), and hormetic dose-response models. No-observed-effects-level (NOEL) and no-observed-adverse-effects-level (NOAEL) indicate the toxicological threshold above which adverse effects occur. The LNT models suggest that adverse effects are starting to occur after a zero exposure level.

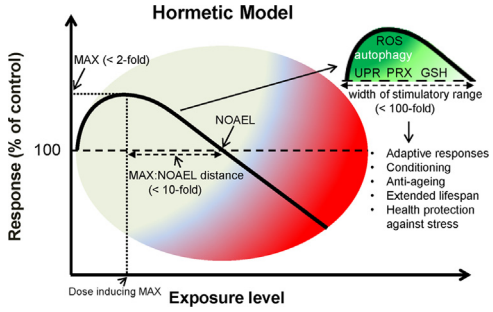

Fig. 2. Hypothetical hormetic dose-response relationship along with quantitative characteristics. Stimulatory effects occur in the low-dose region at the left of the no-observed-effects-level (NOAEL), whereas adverse effects occur in the high-dose region at the right of the NOAEL. The maximum stimulation (MAX) is commonly lower than 200% of the control response, the width of stimulatory response is commonly less than 100-fold, and the MAX: NOAEL distance is commonly less than 10-fold (Calabrese and Blain, 2011). Complex adaptive responses occur in the low-dose region, where, among others, reactive oxygen species (ROS) production, peroxiredoxin PRDX-2 (PRX) signaling, unfolded protein response (UPR) pathway, and autophagy are activated, and glutathione (GSH) levels are decreased, thus, inducing anti-ageing effects, extended lifespan and protection against a subsequent more massive stress (Castillo-Quan et al., 2016; De Haes et al., 2014; Hunt et al., 2011; Kozlowski et al., 2014; Kyriakakis et al., 2017; Mesquita et al., 2010; Pearce et al., 2014; Ristow et al., 2009; Ristow and Zarse, 2010; Schmeisser et al., 2011; Shi et al., 2015; Urban et al., 2017; Wei and Kenyon, 2016; Yizhak et al., 2013).

of hormesis and merit special attention due to its significant implications. These findings indicate that moderate endoplasmic reticulum (ER) stress acts as preconditioning agent which enhances the unfolded protein response (UPR) pathway and autophagy[1] in the nematode *Caenorhabditis elegans* (Kozlowski et al., 2014; Kyriakakis et al., 2017). Consistent with an hormetic perspective prolonged activation of moderate ER stress can lead to induction of mitochondrial apoptosis (Dufey et al., 2015; Guha et al., 2017; Urra et al., 2013). Further supportive studies suggest that curcumin (diferuloylmethane), curcumin derivatives, or other compounds with similar mode of action, applied in the framework of hormesis, can enhance autophagy and promote health against a broad spectrum of diseases (Rainey et al., 2015; Zhou et al., 2014). Additional remarkable findings show that, in addition to chemical compounds, environmental stimuli also induce autophagy in *C. elegans* (Kumsta et al., 2017; Kumsta and Hansen, 2017) enhancing survival transgenerationally (Kishimoto et al., 2017). A recent paper also reports that starvation-dependent *miR-980* regulation of Rbfox1/A2bp1 promoted formation of ribonucleoprotein granule and cell survival in *Drosophila*; autophagy marker Atg8 level was up-regulated and apoptosis marker Caspase3 level was down-regulated in cells with Rbfox1 overexpression (Kucherenko and Shcherbata, 2018). These changes reflect hormetic processes centered on autophagy.

Autophagy, which is a critical maintenance process through which cells recycle damaged protein and organelles (e.g., mitochondria), has a central role in aging with potential therapeutic applications (Mattson and Magnus, 2006) for many diseases such as cancer, Parkinson's disease, and other age-related diseases (Byun et al., 2017; Kyriakakis et al., 2017; Levy et al., 2017; Matus et al., 2012; Rainey et al., 2015; Zhang et al., 2017). Autophagy, whose discovery was rewarded with a Nobel Prize in 2016, displays its functional significance in marked conformity with the quantitative features of the hormetic dose response (Bergamini et al., 2007; Calabrese and Blain, 2011; Calabrese and Mattson, 2017; Martinet et al., 2009; Yen and Klionsky, 2008).

While the link of autophagy to hormesis is the most novel development in the relevant scientific disciplines, numerous basic processes are nonetheless also activated by low level stressors (e.g. nutrient or energy restriction), such as altered mitochondrial function and reduced growth factor signaling. These processes and their links to hormesis have been extensively documented and reviewed (Calabrese et al., 2016, 2017; Cornelius et al., 2013; Kolb and Eizirik, 2011; Rattan, 2004, 2006; Ristow and Schmeisser, 2011; Ristow and Zarse, 2010). It is now well recognized that autophagy and a series of other biological/physiological processes are activated by low level stress. However, do these processes reflect prosurvival/beneficial responses?

3. Extended lifespan

Indeed, recent developments show that exposure to low doses of a wide range of stressor agents promotes health and extend longevity of animal models. For example, low doses of metformin, widely used for treating type II diabetes mellitus extended the life span of *C. elegans* via upregulation of redox processes through the mediation of peroxiredoxin PRDX-2 (De Haes et al., 2014), and that of male mice via stimulation of adenosine monophosphate (AMP)-activated protein kinase activity and antioxidant protection (Martin-Montalvo et al., 2013). Reactive oxygen species (ROS), and other endogenously produced compounds such as H_2S, can activate adaptive pathways essential for maintaining health, with the potential to protect against environmental challenges and extend longevity (Miller and Roth, 2007; Najafi et al., 2018; Wei and Kenyon, 2016). Low level enhanced production of ROS also extended lifespan in *C. elegans* adults treated with low doses of lonidamine (Schmeisser et al., 2011) and naphthoquinones (Hunt et al., 2011). Diethyl maleate at low and moderate doses also extended lifespan and tolerance of *C. elegans* against oxidative stress, in contrast to opposite effects at higher doses (Urban et al., 2017). This is also the case for lithium, which induced hormesis and extended the lifespan of female and male *Drosophila* (Castillo-Quan et al., 2016). An enhanced

[1] UPR is a cellular stress response with is related to endoplasmic reticulum stress.

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