Adaptive Response to Environmental Stress

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Exposure of living organisms to environmental stress triggers defensive responses resulting in the activation of protective processes. Whenever exposure occurs at low doses, defensive effects overwhelm the adverse effects of the exposures; this adapative situation is referred as ‘hormesis’. Environmental, physical and nutritional hormetins lead to the stimulation and strengthening of the maintenance and repair systems in cells and tissues. Exercise, heat and irradiation are examples of physical hormetins, which activate heat shock-, DNA repair- and anti-oxidative-stress responses. The health promoting effect of many bio-actives in fruits and vegetables can be seen as the effect of mildly toxic compounds triggering this adaptive stimulus. Numerous studies indicate that living organisms possess the ability to adapt to adverse environmental conditions studies as examplified by the fact that DNA damage and gene expression profiling in populations living in the environment with high levels of air pollution do not correspond to the concentrations of pollutants. The molecular mechanisms of the hormetic response include modulation of (a) transcription factor Nrf2 activating the synthesis of glutathione and the subsequent protection of the cell; (b) DNA methylation; and (c) microRNA. These findings provide evidence that hormesis is a toxicological event, occurring at low exposures doses to environmental stressors, having benefit for the maintenance of healthy status.

Keywords: adaptive response ; preventive medicine ; microRNA machinery

1. Introduction

The exposure of living organisms to environmental stress triggers defensive responses resulting in the activation of protective processes. Whenever the exposure occurs at low doses, defensive effects overwhelm the adverse effects of the exposure; this adaptive situation is referred to as “hormesis”. Environmental, physical, and nutritional hormetins lead to the stimulation and strengthening of the maintenance and repair systems in cells and tissues. Exercise, heat, and irradiation are examples of physical hormetins, which activate heat shock-, DNA repair-, and anti-oxidative-stress responses. The health promoting effect of many bio-actives in fruits and vegetables can be seen as the effect of mildly toxic compounds triggering this adaptive stimulus. Numerous studies indicate that living organisms possess the ability to adapt to adverse environmental conditions, as exemplified by the fact that DNA damage and gene expression profiling in populations living in the environment with high levels of air pollution do not correspond to the concentrations of pollutants. The molecular mechanisms of the hormetic response include modulation of (a) transcription factor Nrf2 activating the synthesis of glutathione and the subsequent protection of the cell; (b) DNA methylation; and (c) microRNA. These findings provide evidence that hormesis is a toxicological event, occurring at low exposure doses to environmental stressors, having the benefit for the maintenance of a healthy status.

One of the research areas where the concept of hormesis is widely accepted and applied is in modulating ageing and longevity of cells and organisms [1], and is based on the fact that the adaptive behavior of biological systems in response to environmental or self-imposed mild stress(es) improves their functionality and survival. Physical, nutritional, and mental stresses or challenges which induce hormesis, termed hormesis, lead to the stimulation and strengthening of the maintenance and repair systems in the body [1]. Some examples of physical hormesis are exercise, heat, and irradiation, which activate anti-oxidative, heat shock, and DNA repair-stress responses, respectively [2]. A wide variety of non-chemical components in the food, such as flavonoids and polyphenols present in spices, herbs, and other sources, are examples of nutritional hormesis, which induce anti-oxidative, anti-inflammatory, and autophagy stress responses. Similarly, calorie restriction (CR) and intermittent fasting are also hormesis, which activate the autophagic and sirtuin-mediated stress responses [3].

CR appears to prolong life by modulating reactive oxygen species (ROS)-mediated oxidative damage through ROS formation, which is a highly regulated process controlled by a complex network of intracellular signaling pathways [3]. Furthermore, the nuclear factor erythroid 2-related factor (Nrf2) binding to antioxidant response elements (AREs), regulates the basal and inducible expression of glyoxylase 1 (Glo1), as well as of AKRs and ADH [4]. Reduced activity of Nrf2 and increased oxidative stress in aging and disease may predispose to dicarbonyl stress, which is beginning to

feature strongly as a driver of pathogenesis in aging-related disease. In a similar vein, intracellular nutrient and energy status, the functional state of mitochondria, and the concentration of ROS produced in mitochondria are involved in the regulation of lifespan across species by coordinating information and divergence of multiple branched signaling pathways, including vitagenes in preserving cellular homeostasis during stressful conditions [5]. Intense brain activity and focused attention comprise mental hormesis, which also induce various stress responses, including heat shock response. In a similar vein, intracellular nutrient and energy status, the functional state of mitochondria, and the concentration of ROS produced in the mitochondria are involved in the regulation of lifespan across species by coordinating information and divergence of multiple branched signaling pathways, including vitagenes in preserving cellular homeostasis during stressful conditions [5]. Intense brain activity and focused attention comprise mental hormesis, which also induce various stress responses, including heat shock response [5].

An important characteristic of hormesis for health is the simultaneous stimulation of many independent cellular functions/endpoints—each with its own set of quantitatively hormetic features. For example, enhancements of DNA repair, antioxidant defenses, autophagy, etc., whose actions are regulated by multiple interacting receptor/signaling pathways, ultimately produce a metabolically integrated and coherent cellular response [4]. More importantly, the hormetic response has specific characteristics which define both the quantitative features of biological plasticity and the potential for maximum biological performance, thereby estimating the limits to which numerous medical and pharmacological interventions may or may not affect humans [4]. Therefore, a combination of different hormesis can be the drugs for maintaining, improving, and recovering health during aging [1][2].

2. Biomarkers of Adaptive Responses in Human Health

WHO defined health as a state of complete physical, mental, and social well-being [6]. Today, there is a more dynamic definition of health, that is “the ability of an organism to adapt to the environment” [7].

Adaptive responses largely explain the health benefits of fruits and vegetables [8]. Indeed, many natural chemopreventive agents, are detoxified by the phase I/phase II metabolic reaction thus activating the involved enzymes and regulating pathways [9]. As an example, this situation typically occurs for indole-3-carbinole [10] and catechins [11]. However, nowadays it is increasingly recognized that also environmental toxicants frequently display an hormetic response. This has immense consequences in risk assessment [12]. We now understand some molecular mechanisms of this hormetic response. Incubation of lung epithelial cell with a low concentration of acrolein leads to activation of the transcription factor Nrf2 [13]. This activates the synthesis of glutathione and the subsequent protection of the lung cells to a high concentration of acrolein [14]. Moreover, a low dose of silver nanoparticles has been shown to activate Nrf2 and thus to hormesis [15].

This background knowledge on the mechanistic aspects of hormesis enables us to define specific biomarkers to follow this process [16].

Accordingly, hermetic biomarkers depend on the specific mechanisms triggered by the hormetic condition considered and may be either genetic, epigenetic, or metabolic. Genetic biomarkers include the decrease of genotoxic damage as evaluated by DNA adducts or cytogenetic biomarkers [17]. Epigenetic biomarkers mainly include miRNA due to their specific and important role in triggering and regulating the early stages of the adaptive response [18].

3. Conclusions

The existence of the hormetic effect in environmental toxicology has remarkable consequences in preventive medicine and environmental hygiene. Since hormesis occurs only at low exposure doses, there is no doubt that all the ongoing efforts to reduce pollutants in the environment are absolutely worthy to be pursued. However, the final goal is not the environmental zero dose, that is often an utopic goal for many pollutants generated from natural sources or existence means that, at least for the environmental toxicants for which this event is well established, low doses can be tolerated. The quantification of this “low dose” is extremely difficult because of the inter-individual variability in sensitivity to health effects of environmental pollutants. Indeed, fragile subjects (e.g., aged subjects, children, fetuses) having poor inducibility of their defensive mechanisms activated by hormesis, can receive health risk by lower exposure doses than doses tolerated by other subjects.

Accordingly, hormesis has relevance in preventive medicine as a tool that is able to enhance endogenous defenses by correct nutrition (chemopreventive functional foods) and healthy lifestyle (e.g., physical activity). This approach, paralleled by the progressive decrease of the amount of pollutants in the environment will allow the avoidance of health risk well before the reaching of a zero dose of pollutants in the environment.

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