



Hormesis in toxicology

Description

Hormesis is a characteristic of many biological processes, namely a biphasic or triphasic response to exposure to increasing amounts of a substance or condition. Within the hormetic zone, the biological response to low exposures to toxins and other stressors is generally favorable. The term “hormesis” comes from Greek *hórmēsis* “rapid motion, eagerness”, itself from ancient Greek *hormáein* “to set in motion, impel, urge on”, the same Greek root as the word hormone. The term ‘hormetics’ has been proposed for the study and science of hormesis.

In toxicology, hormesis is a dose response phenomenon to xenobiotics or other stressors characterized by a low-dose stimulation, with zero dose and high-dose inhibition, thus resulting in a J-shaped or an inverted U-shaped dose response (e.g. the arms of the “U” are inhibitory or toxic concentrations whereas the curve region stimulates a beneficial response.) Generally speaking, hormesis pertains to the study of benefits of exposure to toxins such as radiation or mercury (perhaps analogous to health paradoxes such as the smoker’s paradox, although differing by virtue of dose-dependent effects). Microdosing, and to some extent homeopathy, are often regarded as applications of hormesis.

In physiology and nutrition, hormesis can be visualized as a hormetic curve with regions of deficiency, homeostasis, and toxicity. Physiological concentrations deviating above or below homeostasis concentrations adversely affects an organism, thus in this context, the hormetic zone is synonymously known as the region of homeostasis. In pharmacology the hormetic zone is similar to the therapeutic window. Some psychological or environmental factors that would seem to produce positive responses have also been termed “eustress”.

In the context of toxicology, the hormesis model of dose response is vigorously debated. The biochemical mechanisms by which hormesis works (particularly in applied cases pertaining to behavior and toxins) remain under early laboratory research and are not well understood. The notion that



hormesis is an important policy factor for chemical risk regulations is not widely accepted.



Further References

Calabrese, E. J., & Baldwin, L. A.. (2002). Defining hormesis. Human and Experimental Toxicology

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"Much confusion surrounds the concept of hormesis and what its biological meaning represents. this paper provides a definition of hormesis that addresses its historical foundations, quantitative features, and underlying evolutionary and toxicologically based mechanistic strategies. hormesis should be considered an adaptive response characterized by biphasic dose responses of generally similar quantitative features with respect to amplitude and range of the stimulatory response that are either directly induced or the result of compensatory biological processes following an initial disruption in homeostasis. given the limited magnitude of the stimulatory response (i.e., usually 30-60% greater than controls at maximum), heightened study design and replication requirements are often necessary to ensure reliable judgments on causality. even though hormesis is considered an adaptive response, the issue of beneficial/harmful effects should not be part of the definition of hormesis, but reserved to a subsequent evaluation of the biological and ecological context of the response."

Mattson, M. P.. (2008). Hormesis defined. Ageing Research Reviews

Plain numerical DOI: 10.1016/j.arr.2007.08.007

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"Hormesis is a term used by toxicologists to refer to a biphasic dose-response to an environmental agent characterized by a low dose stimulation or beneficial effect and a high dose inhibitory or toxic effect. in the fields of biology and medicine hormesis is defined as an adaptive response of cells and organisms to a moderate (usually intermittent) stress. examples include ischemic preconditioning, exercise, dietary energy restriction and exposures to low doses of certain phytochemicals. recent findings have elucidated the cellular signaling pathways and molecular mechanisms that mediate hormetic responses which typically involve enzymes such as kinases and deacetylases, and transcription factors such as nrf-2 and nf- κ b. as a result, cells increase their production of cytoprotective and restorative proteins including growth factors, phase 2 and antioxidant enzymes, and protein chaperones. a better understanding of hormesis mechanisms at the cellular and molecular



levels is leading to and to novel approaches for the prevention and treatment of many different diseases."

Ullman, D.. (2021). Exploring Possible Mechanisms of Hormesis and Homeopathy in the Light of Nanopharmacology and Ultra-High Dilutions. Dose-Response

Plain numerical DOI: 10.1177/15593258211022983

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"Serially diluted succussed solutions of a suitable drug/toxic substance can exhibit physicochemical and biological properties even far beyond avogadro's limit defying conventional wisdom. they can show hormesis, and homeopathy uses them as medicines. many studies confirm that they can have an impact on gene expression different than controls. water in the exclusion zone phase can have memory but for a short period. however, the nanoparticle as the physical substrate can hold information. nanoparticle and exclusion zone duo as nanoparticle-exclusion zone shell can provide a prolonged memory. the nanoparticle-exclusion zone shell model may be an important step toward explaining the nature and bioactivity of serially diluted succussed solutions used as homeopathic medicines. this model may also provide insight into the workings of hormesis. hormesis is the primary phenomenon through which homeopathic phenomenon may have evolved exhibiting the principle of similars. hahnemann exploited it to establish homeopathy. the nanoparticle-exclusion zone shells present in the remedy, selected on the principle of similars, can be patient-specific nanoparticles in a symptom syndrome-specific manner. they can carry the drug-specific information for safer clinical applications in an amplified form for high yielding. it suggests homeopathy is a type of nanopharmacology."

Calabrese, E. J.. (2014). Hormesis: A fundamental concept in biology. Microbial Cell

Plain numerical DOI: 10.15698/mic2014.05.145

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"This paper assesses the hormesis dose response concept, including its historical foundations, frequency, generality, quantitative features, mechanistic basis and biomedical, pharmaceutical and environmental health implications. the hormetic dose response is highly generalizable, being independent of biology model (i.e. common from plants to humans), level of biological organization (i.e. cell, organ and organism), endpoint, inducing agent and mechanism, providing the first general and quantitative description of plasticity. the hormetic dose response describes the limits to which integrative endpoints (e.g. cell proliferation, cell migration, growth patterns, tissue repair, aging processes, complex behaviors such as anxiety, learning, memory, and stress, preconditioning responses, and numerous adaptive re-sponses) can be modulated (i.e., enhanced or diminished) by pharmaceutical, chemical and physical means. thus, the hormesis concept is a fundamental concept in biology with a wide range of biological implications and biomedical applications."

Calabrese, E. J.. (2020). Hormesis and ginseng: Ginseng mixtures and individual constituents commonly display hormesis dose responses, especially for neuroprotective effects



. Molecules

Plain numerical DOI: 10.3390/molecules25112719

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"This paper demonstrates that ginseng mixtures and individual ginseng chemical constituents commonly induce hormetic dose responses in numerous biological models for endpoints of biomedical and clinical relevance, typically providing a mechanistic framework. the principal focus of ginseng hormesis-related research has been directed toward enhancing neuroprotection against conditions such as alzheimer's and parkinson's diseases, stroke damage, as well as enhancing spinal cord and peripheral neuronal damage repair and reducing pain. ginseng was also shown to reduce symptoms of diabetes, prevent cardiovascular system damage, protect the kidney from toxicities due to immune suppressant drugs, and prevent corneal damage, amongst other examples. these findings complement similar hormetic-based chemoprotective reports for other widely used dietary-type supplements such as curcumin, ginkgo biloba, and green tea. these findings, which provide further support for the generality of the hormetic dose response in the biomedical literature, have potentially important public health and clinical implications."

Mcclure, C. D., Zhong, W., Hunt, V. L., Chapman, F. M., Hill, F. V., & Priest, N. K.. (2014). Hormesis results in trade-offs with immunity. *Evolution*

Plain numerical DOI: 10.1111/evo.12453

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"Many have argued that we may be able to extend life and improve human health through hormesis, the beneficial effects of low-level toxins and other stressors. but, studies of hormesis in model systems have not yet established whether stress-induced benefits are cost free, artifacts of inbreeding, or come with deleterious side effects. here, we provide evidence that hormesis results in trade-offs with immunity. we find that a single topical dose of dead spores of the entomopathogenic fungus, metarhizium robertsii, increases the longevity of the fruit fly, drosophila melanogaster, without significant decreases in fecundity. we find that hormetic benefits of pathogen challenge are greater in lines that lack key components of antifungal immunity (dif and turandot m). and, in outbred fly lines, we find that topical pathogen challenge enhances both survival and fecundity, but reduces ability to fight off live infections. the results provide evidence that hormesis is manifested by stress-induced trade-offs with immunity, not cost-free benefits or artifacts of inbreeding. our findings illuminate mechanisms underlying pathogen-induced life-history trade-offs, and indicate that reduced immune function may be an ironic side effect of the "elixirs of life. © 2014 the author(s)."

Zimmermann, A., Bauer, M. A., Kroemer, G., Madeo, F., & Carmona-Gutierrez, D.. (2014). When less is more: Hormesis against stress and disease. *Microbial Cell*

Plain numerical DOI: 10.15698/mic2014.05.148

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"All living organisms need to adapt to ever changing adverse conditions in order to survive. the phenomenon termed hormesis describes an evolutionarily conserved process by which a cell or an entire organism can be preconditioned, meaning that previous exposure to low doses of an insult protects against a higher, normally harmful or lethal dose of the same stress-or. growing evidence suggests that hormesis is directly linked to an organ-ism's (or cell's) capability to cope with pathological conditions such as aging and age-related diseases. here, we condense the conceptual and potentially therapeutic importance of hormesis by providing a short overview of current evidence in favor of the cytoprotective impact of hormesis, as well as of its underlying molecular mechanisms."

Calabrese, E. J., & Mattson, M. P.. (2017). How does hormesis impact biology, toxicology, and medicine?. *Npj Aging and Mechanisms of Disease*

Plain numerical DOI: 10.1038/s41514-017-0013-z

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"Hormesis refers to adaptive responses of biological systems to moderate environmental or self-imposed challenges through which the system improves its functionality and/or tolerance to more severe challenges. the past two decades have witnessed an expanding recognition of the concept of hormesis, elucidation of its evolutionary foundations, and underlying cellular and molecular mechanisms, and practical applications to improve quality of life. to better inform future basic and applied research, we organized and re-evaluated recent hormesis-related findings with the intent of incorporating new knowledge of biological mechanisms, and providing fundamental insights into the biological, biomedical and risk assessment implications of hormesis. as the literature on hormesis is expanding rapidly into new areas of basic and applied research, it is important to provide refined conceptualization of hormesis to aid in designing and interpreting future studies. here, we establish a working compartmentalization of hormesis into ten categories that provide an integrated understanding of the biological meaning and applications of hormesis."

Calabrese, E. J.. (2018). Hormesis: Path and progression to significance. *International Journal of Molecular Sciences*

Plain numerical DOI: 10.3390/ijms19102871

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"This paper tells the story of how hormesis became recognized as a fundamental concept in biology, affecting toxicology, microbiology, medicine, public health, agriculture, and all areas related to enhancing biological performance. this paper assesses how hormesis enhances resilience to normal aging and protects against a broad spectrum of neurodegenerative, cardiovascular, and other



diseases, as well as trauma and other threats to health and well-being. this paper also explains the application of hormesis to several neurodegenerative diseases such as parkinson's and huntington's disease, macrophage polarization and its systematic adaptive protections, and the role of hormesis in enhancing stem cell functioning and medical applications."

Category

1. General

Tags

1. Homeostasis
2. Hormesis

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