Dose-Response: An International Journal

Volume 8 | Issue 1 Article 10

3-2010

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Dose-Response, 8:41–47, 2010
Formerly Nonlinearity in Biology, Toxicology, and Medicine

ISSN: 1559-3258
DOI: 10.2203/dose-response.09-024.Yashin

International Dose-Response Society
www.Dose-Response.org

HORMESIS AGAINST AGING AND DISEASES: USING PROPERTIES OF BIOLOGICAL ADAPTATION FOR HEALTH AND SURVIVAL IMPROVEMENT

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□ The idea of using hormesis for postponing aging and improving human health has been recently discussed in scientific literature. This paper shows that redundancy in renewal capacity, some portion of which become activated and manifested in hormesis effects, may originate as a result of interaction between living organisms and their environment. It is shown that such redundancy may normally exist for organisms in the wild, and not only in domesticated and laboratory animals. Further development of the hormesis idea requires: (i) investigating regularities of response to multiple stimuli; (ii) studying slow-time responses (e.g., physiological adaptation) to repeated stimuli; (iii) studying connection between slow and fast (e.g., developing at the cellular and sub-cellular levels) stress responses; (iv) translating knowledge accumulated in studies of animal model systems to humans; (v) evaluating unrealized potential for improving health and longevity using hormetic mechanisms. The use of mathematical and computer modeling for translating experimental knowledge about hormesis effects to humans, as well as connection between studying hormetic mechanisms and analyses of the age trajectories of physiological and biological indices affecting U-shapes curves of morbidity-mortality risks using longitudinal data on aging, health, and longevity are discussed.

Key words: aging, hormesis, allostatic adaptation, modeling, longitudinal data, morbidity-mortality risks

INTRODUCTION

Studying factors and mechanisms affecting human aging may result in findings, capable of making substantial improvements in public health. The progress can be reached through the development and wide use of holistic approaches to medical treatment which diminish aging rate. These approaches are likely to be substantially more efficient than those currently used in health care (Miller, 2009). Recent studies of mechanisms involved in stress response indicated an opportunity for diminishing the aging rate using hormesis effects (Le Bourg and Rattan, 2008). The hormesis hypothesis assumes existence of hidden defense capacities which become activated in response to "mild" stresses. These capacities enhance organisms' robustness and resilience properties allowing for improving the quality of repair, compensation, replacement of damaged units, and other renewal mechanisms, which work against aging and diseases. Although it is clear that hormesis is the property of organisms'

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biological adaptation, its origin, and anti-aging potential require additional studies. This paper discusses these and other questions, which could help us better understand how hormesis can be used for postponing aging and improving health. In particular, it shows how hormetic redundancy of organisms could be evolved in the wild as a result of interaction between organisms and their environment, and how studying hormesis effect can be performed using new approaches for analyses of human longitudinal data on aging, health, and longevity.

ORGANISM AND ITS ENVIRONMENT: UNEXPLORED POTENTIAL FOR AGING RESEARCH

Living organisms would not age, if any damaged unit was replaced or properly repaired, and consequences of malfunctioning were eliminated. The aging process develops when organism's renewal capacity is not enough to compensate an occurring damage. It can be slowed down either by reducing the rate of damage production, or by improving organism's renewal capacity. Such effects are observed in case of hormesis, which activates: DNA repair, compensation of proteins' damage, removal of toxic metabolic components, utilization of damaged non-repairable proteins, etc. This property of hormesis suggests an idea that the rate of aging process can be reduced using external signals, capable of activating additional (normally silent) defense mechanisms, or enhancing functions of the existing ones. How do these additional capacities originate, and what is their potential for postponing aging? Studying links between organisms and their environment, established during their joint evolution, may help in clarifying these issues. An important feature of such evolutionary development is that certain level of external challenging became a necessary condition of organisms' "normal" functioning. Such challenging activates defense mechanisms, which provide efficient protection not only from consequences of harmful external disturbances, but also from action of deleterious processes of internal origin (e.g. aging, disease development). Note that keeping all defense capacities activated during the entire life course involves metabolic cost. Therefore some of them are kept in a silent mode until appropriate "waking up" signal arrives. Taking into account that the number of different signaling pathways, which can be activated during an organism's life course, may be much smaller than that built in organisms' "evolutionary memory", one may hypothesize that hormetic anti-aging potential exceeds the effects observed in experimental studies of hormesis using one stimulus at a time. Evaluating such a potential requires understanding how many different defense mechanisms can be activated by one stimulus, how many different stimuli can activate the same defense mechanisms, how much the effect of multiple stimuli exceeds that of one, how much repeated stimuli increases the effect, are there ages when exposure

to stimuli is most efficient, what is individual variability in hormetic response, which factors are responsible for such variability, how hormetic mechanism changes with age, and what would be a metabolic cost associated with activating each additional defense mechanisms?

WHY DOES HORMESIS EXIST?

Hypothetical example below shows that "renewal redundancy" could be formed in a process of evolution of organism-environment interaction. It is reasonable to assume that organism's behavior affects environmental response, for example, by changing the mean value of stress distribution. An organism distinguishes among three ranges of stress values: small, which do not produce any response; high, which are lethal; and intermediate, which induce renewal response. If the renewal process fails – organism dies. The chances of successful renewal depend on how many renewal capacities are activated. The latter quantity is proportional to probability of having stress within the third (renewal) range. Thus, by changing its behavior an organism modifies two key variables, related to mortality outcome: the portion of activated renewal capacity, which affects chances of death from renewal failure, and the portion of lethal stresses. Organism chooses behavior (the mean value of stress) to minimize total mortality risk (the sum of mortality risks from lethal stresses and from renewal failure). The "renewal redundancy" arises because the mean value of stress with minimal total mortality, chosen by an organism, does not minimize mortality risk from the renewal failure. The diagram in Fig. 1 illustrates this situation.

THE U-SHAPE OF THE DOSE-RESPONSE CURVE

Hormesis effects are characterized by the biphasic dose-response curves. Its alternative characterization involves the U-shapes curves (e.g., morbidity-mortality risks), considered as functions of risk factors (stimuli). Although most traditional studies investigate an effect of one stimulus (risk factor) at a time, more advanced approaches capable of evaluating possible synergistic effects of many stimuli using parabolic risk functions in multidimensional risk (stimulus) space are now available (see Yashin *et al.*, 2007 and references in it). An important methodological advantage of these approaches is that they also allow for taking into account changes in physiological and biological homeodynamics (linked with changes in morbidity-mortality risks) developing in an aging organism. The multidimensional age trajectories in the stimuli (risk factors) space, which minimize risk function at each given age, characterize age dynamics of hormetic point (i.e., the magnitudes of stimuli, for which hormesis effect reaches its maximum). These approaches based on mathematical and computer modeling could be especially important for

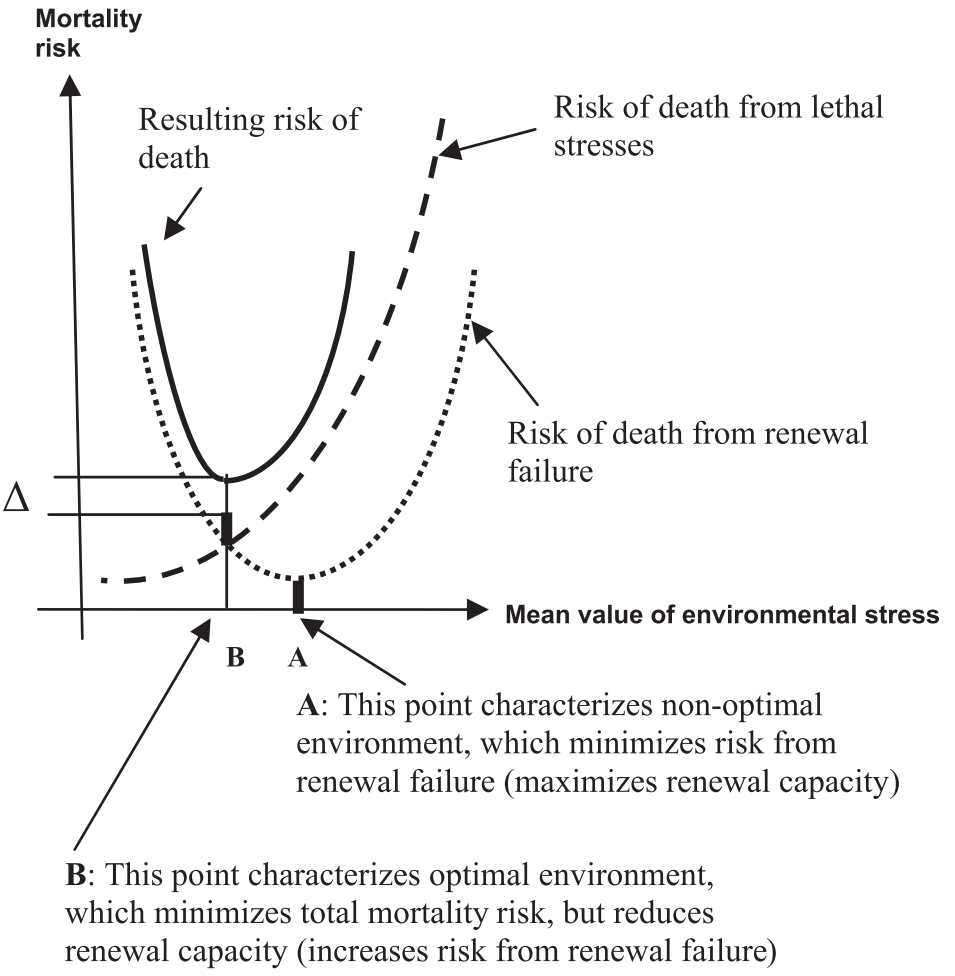

FIG. 1. Three curves at this diagram describe components of mortality risks as functions of mean value of environmental stress distribution. The dashed curve represents risk of death from lethal stresses. This risk increases monotonically because the proportion of lethal stresses (having high magnitude) is getting larger when the mean value of stress distribution increases. The second curve (the U-shaped dotted line) corresponds to mortality risk from the failure to eliminate the damage (renewal failure). The U-shape indicates that non-zero level of stresses is needed to minimize risk from renewal failure by keeping respective renewal capacities activated. The minimum value of this curve is reached at the point "A". The third curve (solid line) describes the risk of death resulted from adding the first two. This curve is also U-shaped, however, its minimum (point "B") is reached at the mean value of stress, which is lower than the point corresponding to maximum renewal capacity (point "A"). An organism chooses behavior which minimizes total mortality risk (solid line, point "B"). However, at point "B" an organism has non-minimal value of mortality risk from the renewal failure, which means that it has unused (inactivated) renewal capacities (reserves). To reduce mortality risk these capacities have to be activated without increasing risk of lethal environmental challenges (e.g., by developing proper (artificial) challenges). Symbol Δ in the diagram indicates potential for risk improvement using such artificial challenges.

translating knowledge about hormesis and its mechanisms accumulated in animal studies to humans, and for performing computational experiments (experiments "in silico"), which would supplement traditional experiments with animal model systems in evaluating response to multiple and repeated stimuli, testing biological hypotheses about mechanisms involved, etc. The use of computational experiments could be beneficial for studying hormetic mechanisms in humans, where direct experimenting is not always possible.

HORMESIS AS A FEATURE OF BIOLOGICAL ADAPTIVE MACHINERY

Researchers studying hormesis pay most attention to mechanisms enhancing cells' resistance to oxidative stress including enzymatic and non-enzymatic detoxification, production of heat shock and other stress proteins, removing damaged molecules, production of DNA repair enzymes by mild doses of stress, and others. Studies of the effects of caloric restriction (CR) and physical exercises indicate that in addition to such rapid cellular and sub-cellular adaptive responses, slow-time adaptation involving biological tissues, organs, and systems in response to persistent stimuli also takes place (Le Bourg and Rattan, 2006; Radak *et al.*, 2008; Gomez-Pinilla, 2007).

When stresses are mild the response contributes to improving capacities of defense mechanisms, which also works against aging and diseases. The results, however, could be detrimental when organisms adapt to stresses, which magnitude exceeds hormetic boundary. In such cases, the adaptation process, often called "allostatic adaptation" (McEwen and Wingfield, 2003), may shift the balance between damage production and damage removal towards additional damage production. Depending on the type of stress such shifting may differ in different organs and systems of the body, increasing morbidity (mortality) risks for diseases involving organs and systems where damage is most rapidly accumulating. The detrimental effects of such adaptation in humans are measured in terms of "allostatic load" represented by an index constructed from measured deviations of a number of physiological and biological indices from their normal values (Singer *et al.*, 2004). An alternative dynamic approach to measuring components of allostatic adaptation from available longitudinal data is developed by Yashin *et al.* (2007).

Thus, hormesis is a particular property of biological adaptive machinery, which properties are reflected in the biphasic dose-response curves, or in the U-shaped risk functions. The age-dependence of such curves can be studied using longitudinal data on physiological homeodynamics and health/well-being/survival status in humans. Many such data are now enriched by genetic information, providing possibility for studying genetic basis of hormetic response on different stimuli. Additional efforts are needed for studying connection between adaptive mechanisms acting

in different time scales, and using this connection to get benefits for health and survival by activating multi-scale hormetic mechanisms.

CONCLUSIONS

This paper supports the view that hormesis is a feature of biological multi-scale adaptive machinery, involving various tissues, organs, and systems of the body. This machinery mediates effects of external conditions on aging, health, and survival by activating, regulating, and coordinating functioning of adaptive defense mechanisms. The studies of adaptive response to external stimuli in humans indicate possibility of beneficial effects of minor stresses on health and longevity. However, since the most of knowledge about hormesis effect is accumulated in animal studies the translation of this experience to humans is necessary before any practical application of these ideas for improving human health. Experimental studies using laboratory animals still have high potential for proper quantification of hormesis effects, including effects of age, repeated and multidimensional stimuli, coordination of responses developing in different time scales, etc. For humans studying effects of hormesis on health and longevity involves evaluation of age-dependent morbidity-mortality risks considered as functions of stimuli and variables involved in adaptive response. Note, however, that many properties of adaptive processes producing hormesis effects in humans remain unknown. Some of them (e.g. slow-time adaptation due to allostatic response) can be studied using data collected in longitudinal studies of aging, health, and longevity. The comprehensive analyses of such data, using advanced methods discussed above, with a focus on beneficial effects of adaptive response will contribute to developing holistic approaches to improving human health and longevity.

ACKNOWLEDGEMENTS.

The research reported in this paper was supported by the National Institute on Aging grants R01AG027019, R01AG028259, and R01AG030612. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Aging or the National Institutes of Health.

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