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Hormesis in aging: approaching cautiously

SIS Rattan

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I am grateful for the comments to my lead paper "Applying hormesis in aging research and therapy." It is encouraging to note that, unlike researchers in some other fields of biology, accepting the existence of hormesis as a valid biological phenomenon is not problematic for biogerontologists. The basic principle of "survival instinct" in terms of biological responses to stress and the upregulation of maintenance and repair pathways, based on which hormesis is expected to function, is almost universally accepted. However, it is in the details of the applicability of hormesis in research and therapy that important issues emerge, and a cautious approach is advocated. These issues can be grouped in three main categories: (1) genes and their mechanisms of action; (2) environmental manipulation of gene expression; and (3) cost benefits in evolutionary terms.

Genes and aging

Dr Hayflick has rightly reasserted the need of making a distinction between longevity determination and aging. Whereas the growth, development, maturation, and reproductive history of an organism is under strict genetic regulation, and which effectively determines the natural or essential life span required for the propagation of the species, the progress of aging is a stochastic process. It is implicit in this view that the genes only determine longevity, but not aging. Therefore, in a strict evolutionary sense it is meaningless to use the term gerontogene. However, for practical purposes it may be appropriate to invoke this term in order to focus any discussion about the gene-based biochemical processes involved in aging and to describe genes whose altered activity influences aging and longevity. That is why I had proposed the term "virtual" gerontogenes for maintaining this distinction. Distinguishing between public and private genes, and between major and minor genes, as discussed by Dr Jazwinski, is a further refinement of these ideas. An ever-growing list of putative longevity assurance genes or gerontogenes requires their further categorization with respect to their modes of action, interspecies correlation, and evolutionary divergence.

Drs Cypser and Johnson, and Dr Lithgow have discussed in detail the implications of single-gene mutations in model systems, which extend life span and generally, but not always, increase stress resistance. There is still a lot to be learnt about the biochemical and molecular mechanisms of gene mutations, which extend the lifespan of an organism most commonly by a loss of function of that particular gene while enhancing other abilities including stress tolerance. Combining genetic analysis with mild stress-induced genomic and proteomic alterations are necessary to build a solid foundation for the application of hormesis in anti-aging therapies.

Environmental manipulation

Manipulating environmental conditions, such as temperature, nutrition, gaseous composition, radiation, and natural and synthetic toxins and pollutants is intrinsic to hormesis. Almost all the respondents to my lead paper have raised the important issue of synergistic, additive or antagonistic effects of manipulating one condition with respect to the others. For example, Dr Toussaint and his colleagues have tried to make a distinction between stress and stimulation within the concept of the stability of far-from-equilibrium open systems, which allow to sort the various global cellular responses to stress into four classes. In the context of aging, this is a crucial factor that whereas a certain level of exposure may be "mild" stress at one age, the same may be categorized as "severe" stress at later ages. This is a concern raised also by Drs Minois, Le Bourg, and Van Voorhies. There is no resolution of this concern at present. Extensive research on age-related physiological, biochemical, and molecular changes in responsiveness to various physical, chemical, and biological stressors is required to tackle this issue. This will also be

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important to determine hormetic levels of various stressors applicable at different ages. Dr Forbes in her commentary too has identified certain practical limitations of prescribing stress as an anti-aging treatment.

Evolutionary implications

Drs Hercus and Loeschcke have raised an important biological concern as regards the implications of hormesis with respect to the concept of fitness. Associations or interactions between traits, and the interactions between genotypes and the environment make the interpretation of hormetic effects even more difficult. They have also argued that from an evolutionary point of view the extended longevity cannot be considered as beneficial without considering the potential negative effects of the mild stress on fitness components. Furthermore, as pointed out by Dr Forbes, there are difficulties of predicting precisely the conditions under which hormesis will or will not occur. A concern raised by Dr Minois that wild organisms, including humans, that face environmental changes and various forms of stress on a regular basis may not be amenable to further hormesis is countered by the fact that moderate exercise has been shown to have hormetic and beneficial effects.

It is therefore clear that applying hormesis in aging research and therapy requires a cautious approach. We do not yet have all the answers, but the seven issues listed in my lead paper and the 10 commentaries covering molecular, biochemical and evolutionary concerns can surely help to set a framework for discussion and experimentation. This special issue of the BELLE Newsletter is the right step in that direction.

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