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BELLE Article:

Principles and practice of hormetic treatment of aging and age-related diseases

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Aging is characterized by stochastic accumulation of molecular damage, progressive failure of maintenance and repair, and consequent onset of age-related diseases. Applying hormesis in aging research and therapy is based on the principle of stimulation of maintenance and repair pathways by repeated exposure to mild stress. Studies on the beneficial biological effects of repeated mild heat shock on human cells in culture, and other studies on the anti-aging and life-prolonging effects of

prooxidants, hypergravity, irradiation and ethanol on cells and organisms suggest that hormesis as an anti-aging and gerontomodulatory approach has a promising future. Its clinical applications include prevention and treatment of diabetes, cataract, osteoporosis, dementia and some cancers.

Key words: prooxidants, ethanol, gerontomodulatory approach

Introduction

The highly complex biological phenomenon of aging is now considered as being epigenetic and stochastic in origin. The three main principles of biological aging and longevity are: the life history principle, the mechanistic principle and the non-genetic principle. Briefly, according to these principles, aging is, first and foremost, an emergent phenomenon seen primarily in protected environments, which allow survival beyond the natural lifespan in the wild. Second, the biochemical and molecular basis of aging reside in the mechanisms of progressive failure of homeostasis or homeodynamics, which leads to the accumulation of damage in nucleic acids, proteins and lipids. This results in the impairment in functional ability at all levels of organization thereby increasing the possibilities of a plethora of diseases and eventual death of the organism. Third, the

non-genetic principle of aging rules out any genetic program for aging, and the genes that do influence aging and longevity are those that have evolved in accordance with the life history of a species. Identification of genes so far have shown that these cover a wide range of biochemical pathways, such as insulin metabolism, kinases and kinase receptors, transcription factors, DNA helicases, telomerase, membrane glucosidases, GTP-binding protein-coupled receptors, cholesterol metabolism, heat shock protein (HSP) genes, cell cycle arrest pathways and others.^{1,2} Such genes are known as virtual gerontogenes.³

Aging: therapy or prevention?

Occurrence of aging during extended period of survival and the onset of one or more diseases before eventual death appear to be the 'normal' sequence of events. This viewpoint makes modulation of aging different from the treatment of one or more specific diseases. In the case of a disease, such as a cancer of any specific kind, its therapy means the removal and

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elimination of the cancer cells and restoration of the affected organ/tissue to its original disease-free state. Attaining such an 'age-free' state is not a realistic possibility. Similarly, although piecemeal replacement of non-functional or half-functional body parts with natural or synthetic parts made of more durable material may provide a temporary solution to the problems of age-related impairments, it does not modulate the underlying aging process as such.²

Scientific and rational anti-aging strategies aim to slow down aging, to prevent and/or delay the physiological decline and to regain lost functional abilities. Hormesis offers a promising approach in aging intervention and prevention, and is based on making use of an organism's intrinsic homeodynamic property of self-maintenance and repair. Since aging is characterized by a decrease in the adaptive abilities due to progressive failure of homeodynamics, it has been hypothesized that if cells and organisms are exposed to brief periods of stress so that their stress response-induced gene expression is upregulated and the related pathways of maintenance and repair are stimulated, one should observe anti-aging and longevity-promoting hormetic effects.⁴

During the last few years, research done in our labs has shown the hormetic effects of mild stress. We have demonstrated the hormetic effects of repeated mild stress on human cells undergoing aging in culture. Using a mild stress regime of exposing human skin fibroblasts to 41°C for 1 h twice a week throughout their replicative lifespan *in vitro*, several beneficial and anti-aging effects have been observed. These effects include reduced accumulation of oxidized proteins, increased levels of various HSPs, increased proteasome activities and enhanced stress resistance to other stresses, for example, UV, ethanol and sugars.^{5,6}

Other chemical, physical and biological treatments have been used to unravel various pathways of maintenance and repair whose sustained activities improve the physiological performance and survival of cells and organisms. Stresses that have been reported to delay aging and prolong longevity in various systems (e.g., yeast, *Drosophila*, nematodes, rodents and human cells) include temperature shock, irradiation (UV-, gamma- and X-rays), heavy metals, pro-oxidants, acetaldehyde, alcohols, hypergravity, exercise and caloric restriction (CR).⁷⁻⁹ Hormesis-like beneficial effects of chronic but mild undernutrition have been reported for human beings.¹⁰ For example, it was reported that peripheral blood lymphocytes isolated from people with low body mass index, representing a group with natural intake of restricted food calories, had higher DNA repair capacity and higher levels of DNA polymerase-beta, which were

also maintained during aging.¹⁰ Intermittent fasting has been reported to have beneficial effects on glucose metabolism and neuronal resistance to injury.¹¹

The proof of the hormetic principle being applicable to aging intervention has now been provided by experiments with a wide variety of biological systems and by using a range of physical, chemical and biological stressors. Two of the main lifestyle interventions, exercise and reduced food intake or CR, both of which bring their beneficial and anti-aging effects through hormesis,¹²⁻¹⁶ are being widely recognized and increasingly practiced as an effective means of achieving a healthy old age. Clinical applications of exercise-mediated hormesis in prevention or slowing down of the progress of age-related diabetes 2, osteoporosis and sarcopenia are being tested.^{12,17-19} Improvement in the biochemical response of the heart, strengthening of the immune system by biological (mild infection), physical and mental stress and challenge, and the possibility of stimulating protein turnover pathways to prevent the accumulation of abnormal proteins leading to neuronal degeneration and dementia are some of the other clinical avenues under investigation.²⁰⁻²⁴

From the health care point of view, one can also expect the availability of certain nutraceutical and pharmacological hormetic agents to mimic the heat shock response and CR. For example, bimosclomal, a non-toxic, hydroxylamine derivative with HSP-inducing activity and cytoprotective effects is under clinical trial.^{25,26} Celastrol, a quinone methide triterpene,²⁷ and paeoniflorin,²⁸ which are active components of certain Chinese medicinal herbs, are other HSP-inducing hormetic agents under test for their cytoprotective effects. Similarly, curcumin, an Indian yellow spice, has also been shown to have cytoprotective effects through its hormetic action in co-stimulating the synthesis of HSP.²⁹ Various chemical mimetics of CR, such as 2-deoxy-D-glucose and its analogs,³⁰ and resveratrol, which is a polyphenol found in red wine, are being tested for their use as anti-aging hormetic agents.³¹⁻³³

Another small molecule, N⁶-furfuryladenine or kinetin, has been shown to have significant anti-aging^{34,35} and anti-thrombotic³⁶ effects in human cells. Kinetin is considered to work both as a direct antioxidant^{37,38} and as a hormetic agent by inducing the synthesis of other protective enzymes and HSP.^{35,39,40} Recently reported anti-aging effects of another cytokinin zeatin may also operate through hormetic pathways.⁴¹ Although at present the use of kinetin has been limited to being a cosmeceutical ingredient in a range of cosmetics products, its usefulness as a hormetic nutraceutical agent is under investigation. In experimental hairless mice system,

topical application of DNA-damage product thymidine dinucleotides (pTT) has hormetic effects in the prevention of UV-induced mutations and photocarcinogenesis by activating the expression of a tumor-suppressive gene p53.^{42,43}

Although at present there are only a few studies performed which utilize mild stress as a modulator of aging and longevity, hormesis can be a useful experimental approach in biogerontology and geriatric medicine. However, there are a few issues that remain to be resolved before hormetic approaches can be used widely as a clinical tool to affect aging and to prevent the onset of age-related impairments and pathologies. Some of these issues are: (1) to establish biochemical and molecular criteria for determining the hormetic levels for different stresses; (2) to identify differences and similarities in stress response pathways initiated by different stressors; (3) to quantify the extent of various stress responses; (4) to determine the interactive and pleiotropic effects of various stress response pathways; (5) to adjust the levels of mild stress for age-related changes in the sensitivity to stress; (6) to determine the biological and evolutionary costs of repeated exposure to stress; (7) to determine the biological significance of relatively small hormetic effects, which may or may not have large beneficial effects during the entire lifespan. Resolution of these issues requires much more research on hormesis than is being carried out at present.

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