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HORMESIS CAN AND DOES WORK IN HUMANS

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□ If we accept the validity of the general concept of physiological hormesis as being the phenomenon of achieving health beneficial effects by exposure to mild stress, then hormesis is being applied already and successfully to humans. The evidence for this is the well-demonstrated health benefits of regular and moderate exercise. Mild stress-induced activation of one or more intracellular pathways of stress response are central to this. Experimental studies performed on human cells in culture exposed to mild heat shock and other stresses provide biochemical and molecular evidence in support of the application of hormesis to human systems. Although several issues remain to be resolved by more research with respect to the extent and duration of hormetic exposure, making use of the cellular stress response pathways can facilitate discovering novel hormetins for human applications.

Keywords: stress, hormetin, cultured cells, fibroblasts, stem cells, nutrition

INTRODUCTION

If the general concept of physiological hormesis as being the phenomenon of achieving health beneficial effects by exposure to mild stress is accepted, then hormesis is being applied already and successfully to humans. The evidence for this is the well demonstrated health benefits of regular and moderate exercise. These benefits range from improved physique and enhanced pulmonary-cardio stamina to a delay or prevention of onset of age-related metabolic diseases, and to an increase in the mental, hormonal and emotional functionality. The expectation that such an increase in the general well being and the quality of life also leads to increased health-span and total lifespan is its logical extension, with emerging epidemiological data in its support (Khaw *et al.*, 2008; Landi *et al.*, 2008; Yates *et al.*, 2008; Fisher-Wellman and Bloomer, 2009). The beneficial effects of exercise can best be understood within the framework of stress-induced hormesis. This is because exercise increases the production of potentially harmful substances, such as reactive oxygen species (ROS), reactive nitrogen species (RNS), other free radicals, acids and aldehydes. The most significant physiological change that occurs during exercise is up to 20-fold enhanced mitochondrial respiration and oxidative phosphorylation leading to increased metabolic rate and its poten-

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tially damaging byproducts (Goto *et al.*, 2007; Radak *et al.*, 2008; Rattan, 2008a, b; Goon *et al.*, 2009).

The question, therefore, is not whether hormesis is applicable as an aging intervention, but how to apply it in the context of our present understanding of aging and its consequent age-related diseases. In order to do so, it maybe useful to recapitulate what has been understood so far in biogerontology with respect to the general principles of aging and longevity, which form the basis of applying hormesis as an intervention.

AGING AS A PROGRESSIVE SHRINKAGE OF THE HOMEODYNAMIC SPACE

Aging, senescence and death are the final manifestations of unsuccessful homeostasis or failure of homeodynamics (Rattan, 2006). A wide range of molecular, cellular and physiological pathways of repair are well known, and these include multiple pathways of nuclear and mitochondrial DNA repair, free radical counteracting mechanisms, protein turnover and repair, detoxification mechanisms, and other processes including immune- and stress-responses. All these processes involve numerous genes whose products and their interactions give rise to a "homeodynamic space" or the "buffering capacity", which is the ultimate determinant of an individual's chance and ability to survive and maintain a healthy state (Rattan, 2006; Holliday, 2007). A progressive shrinking of the homeodynamic space, mainly due the accumulation of molecular damage, is the hallmark of aging and the cause of origin of age-related diseases (Rattan, 2008c).

HORMETIC MODULATION OF AGING IN HUMAN CELLS

A critical component of the homeodynamic property of living systems is their capacity to respond to stress. In this context, the term "stress" is defined as a signal generated by any physical, chemical or biological factor (stressor), which in a living system initiates a series of events in order to counteract, adapt and survive. While a successful and over-compensatory response to low doses of stressors improve the overall homeodynamics of cells and organisms, an incomplete or failed homeodynamic response leads to the damaging and harmful effects of stress. It is this homeodynamic space as a whole or the individual components of the homeodynamic machinery, which are the targets of hormetic interventions.

Aging modulatory effects of hormesis have been reported for various human cell types *in vitro*. For example, using a regimen of repeated mild heat shock at 41°C, for 1 hr twice a week, given to cultured normal human skin fibroblasts, keratinocytes, endothelial cells, and telomerase-immortalised bone marrow mesenchymal stem cells, we have reported a variety of hormetic effects. These effects include slowing down of cellular aging, some extension of replicative lifespan, maintenance of youthful

morphology, reduction in the levels of oxidatively- and glycoxidatively-damgaed proteins, stimulation of proteasomal activities, increased levels of chaperones, enhancement of stress tolerance, and improvement in differentiation, wound healing and angiogenesis (Rattan *et al.*, 2009). Other hormetic conditions, which have been shown to have some anti-aging effects in human cells, are irradiation, mechanical stretching and electromagnetic field shock (Holliday, 1991; Perez *et al.*, 2008; Rattan, 2008b). Thus, the proof of the principle regarding the applicability of hormesis as a modulator of aging in human cells is well demonstrated. However, further short term and long term studies, using a wide variety of human cell types, and a combination of stressors, are required in order to establish the universality of the phenomenological and mechanistic aspects of this issue.

INDIVIDUALISTIC NATURE OF AGING AND PERSONALIZED HORMESIS

A crucial aspect of aging is the individualistic nature of age-related changes. The rate and progress of aging differs among individuals, among different parts of the individual, and among different tissues, cell types and molecular types within. A combination of genes, milieu and chance or stochastic events is what effectively determines the duration and quality of life (Rattan, 2007). As is being increasingly realized for any kind of biomedical, therapeutic and interventionary approaches personalized strategies will have to be developed in the case of hormesis too (Bains, 2008). Some of the main factors that will have to be considered for this include genetic polymorphism, and epigenetic factors involving pre- and post-natal exposures to stress, nutritional and lifestyle habits, and disease- and infection-history of the individual. Additionally, varied response of different cell types to single or multiple stressors as a function of age will also be a critical factor to be taken into consideration. The knowledge about all such factors will be essential for applying appropriate hormetic challenge at appropriate time and age at an appropriate level and combination.

DISCOVERING NOVEL HORMETINS

A hormetin is defined as any condition that may be potentially hormetic in physiological terms, by invoking one or more pathways of stress response (SR) within a cell. Table 1 gives a list of the main and immediate molecular SR pathways, that are integral to the organismic property of homeodynamics. Based on the involvement of one or more molecular SR, higher order responses (cellular, organ level and body level) are manifested, which include down-stream expression of numerous genes, and the resultant cellular and physiological phenotypes, such as apoptosis, inflammation, and hyperadrenocorticism.

TABLE 1: Main molecular level stress responses in a cell.

Response	Stressors	Effectors	References
Heat shock response	Heat, heavy metals, antibiotics, protein denaturation	Heat shock proteins, proteasome and other proteases	(Liberek *et al.*, 2008)
Unfolded protein response	Unfolded and misfolded proteins in endoplasmic reticulum	Chaperones, co-chaperones	(Yoshida, 2007)
Antioxidant response	Free radicals, reactive oxygen species, pro-oxidants	Nrf-2, heme-oxygenase, FOXO	(Ishii *et al.*, 2002)
NF-κB inflammatory response	Pathogens, allergens, damaged macromolecules	cytokines, nitric oxide synthase	(Medzhitov, 2008)
Autophagic response	Food starvation, hypoxia, damaged organelles	Lysosomes	(Yen and Klionsky, 2008)
DNA-repair response	Radiation, oxidants, free radicals	DNA-repair enzymes	(Hakem, 2008)
Sirtuin response	Energy depletion	Sirtuins	(Longo, 2009)

Not all pathways of SR respond to every stressor, and although there may be some overlap, generally SR pathways are quite specific. The specificity of the response is mostly determined by the nature of the damage induced by the stressor and the variety of downstream effectors involved. For example, cytoplasmic induction of protein denaturation by heat, heavy metals and antibiotics will initiate the so-called heat shock response by inducing the synthesis of heat shock proteins, followed by the activation of proteasome-mediated protein degradation (Verbeke *et al.*, 2001; Liberek, *et al.*, 2008). But, unfolded proteins in the endoplasmic reticulum (ER) will induce unfolded protein response (UPR), and will initiate the induction of synthesis of a totally different set of proteins and their downstream effectors (Banhegyi *et al.*, 2007; Yoshida, 2007). Furthermore, often the source of activation (stressor) cannot be easily identified, and may involve more than one stressor and their effectors. Examples of such SR include early inflammatory SR and neuroendocrinal SR, which lead to the synthesis and release of interleukins and corticoid hormones, respectively. Similarly, pathways involving NF-kB, Nrf2, FOXO, sirtuins and heme-oxygenase activation may involve more than one type of stressors and stress signals, including pro-oxidants, free radicals, ROS, and nutritional components.

The seven major pathways of SR listed above can be used as the screening platform for discovering, testing and monitoring the effects of novel hormetins. Such hormetins may be categorized as: (1) physical hormetins, such as exercise, heat and radiation; (2) biological and nutritional hormetins, such as infections, micronutrients, spices and other sources; and (3) psychological hormetins, such as mental challenge and focused attention or meditation.

Finally, although the precise mode and extent of application of hormesis for maintaining and/or improving human health and longevity still needs resolving several important issues discussed above, many of the commonly issued public health recommendations involving lifestyle modifications make use of hormetic principles knowingly or unknowingly. What is important and demands serious and urgent attention of scientists and science-policy makers is recognizing that hormesis can be a powerful public health tool that can help to maintain health and extend healthspan and longevity.

REFERENCES

Bains, W 2008. Truly personalised medicine: self-experimentation in medical discovery. Med. Hypoth. 70: 714-718

Banhegyi, G, Baumeister, P, Benedetti, A, Dong, D, *et al.* 2007. Endoplasmic reticulum stress. Ann N Y Acad Sci 1113: 58-71

Fisher-Wellman, K and Bloomer, RJ 2009. Acute exercise and oxidative stress: a 30 year history. Dyn Med 8: 1

Goon, JA, Aini, AH, Musalmah, M, Anum, MY, Nazaimoon, WM and Ngah, WZ 2009. Effect of tai chi exercise on DNA damage, antioxidant enzymes, and oxidative stress in middle-age adults. J Phys Act Health 6: 43-54

Goto, S, Naito, H, Kaneko, T, Chung, HY and Radak, Z 2007. Hormetic effects of regular exercise in aging: correlation with oxidative stress. Appl Physiol Nutr Metab 32: 948-953

Hakem, R 2008. DNA-damage repair; the good, the bad, and the ugly. Embo J 27: 589-605

Holliday, R 1991. A re-examination of the effects of ionizing radiation on lifespan and transformation of human diploid fibroblasts. Mutat. Res. 256: 295-302

Holliday, R 2007. Ageing: the paradox of life. Dordrecht, The Netherlands., Springer.

Ishii, T, Itoh, K and Yamamoto, M 2002. Roles of Nrf2 in activation of antioxidant enzyme genes via antioxidant responsive elements. Methods Enzymol 348: 182-190

Khaw, KT, Wareham, N, Bingham, S, Welch, A, Luben, R and Day, N 2008. Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. PLoS Med 5: e12

Landi, F, Russo, A, Cesari, M, Pahor, M, Liperoti, R, Danese, P, Bernabei, R and Onder, G 2008. Walking one hour per day prevented mortality among older persons: results from ilSIRENTE study. Prev. Med. doi:10.1016/j.ypmed.2008.06.020

Liberek, K, Lewandowska, A and Zietkiewicz, S 2008. Chaperones in control of protein disaggregation. EMBO J. 27: 328-335

Longo, VD 2009. Linking sirtuins, IGF-I signaling, and starvation. Exp Gerontol 44: 70-74

Medzhitov, R 2008. Origin and physiological roles of inflammation. Nature 454: 428-435

Perez, FP, Zhou, X, Morisaki, J and Jurivich, D 2008. Electromagnetic field therapy delays cellular senescence and death by enhancement of the heat shock response. Exp. Gerontol. 43: 307-316

Radak, Z, Chung, HY, Koltai, E, Taylor, AW and Goto, S 2008. Exercise, oxidative stress and hormesis. Ageing Res Rev 7: 34-42

Rattan, SIS 2006. Theories of biological aging: genes, proteins and free radicals. Free Rad. Res. 40: 1230-1238

Rattan, SIS 2007. The science of healthy aging: genes, milieu, and chance. Ann N Y Acad Sci 1114: 1-10

Rattan, SIS 2008a. Hormesis in aging. Ageing Res. Rev. 7: 63-78

Rattan, SIS 2008b. Hormetic modulation of aging in human cells. In: Mild stress and healthy aging: applying hormesis in aging research and interventions. (Eds) Le Bourg, E. and Rattan, S. I. S., Dordrecht, The Netherlands, Springer: 81-96.

Rattan, SIS 2008c. Increased molecular damage and heterogeneity as the basis of aging. Biol. Chem. 389: 267-272

Rattan, SIS, Fernandes, RA, Demirovic, D, Dymek, B and Lima, CF 2009. Heat stress and hormetin-induced hormesis in human cells: effects on aging, wound healing, angiogenesis and differentiation. Dose-response 7: 93-103

Verbeke, P, Fonager, J, Clark, BFC and Rattan, SIS 2001. Heat shock response and ageing: mechanisms and applications. Cell Biol. Int. 25: 845-857

Yates, LB, Djoussé, L, Kurth, T, Buring, JE and Gaziano, JM 2008. Exceptional longevity in men. Arch. Intern. Med. 168: 284-290

Yen, WL and Klionsky, DJ 2008. How to live long and prosper: autophagy, mitochondria, and aging. Physiol. 23: 248-262

Yoshida, H 2007. ER stress and diseases. FEBS J. 274: 630-658