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Item Type	article;article
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Download date	2024-08-14 23:21:13
Link to Item	https://hdl.handle.net/20.500.14394/20595

HORMESIS AS A PRO-HEALTHY AGING INTERVENTION IN HUMAN BEINGS?

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□ Hormesis is a phenomenon in which adaptive responses to low doses of otherwise harmful factors (also called mild stressors) make cells and organisms more robust. Aging is a complex and poorly understood process. This review explores the positive effects of hormesis on aging in animal models and human cell cultures, and discusses whether it might apply to humans. As an example, repeated mild heat stress confers anti-aging benefits to normal human cells in culture. Calorie restriction and xenohormetic compounds such as resveratrol, in large part via activation of sirtuins, decrease risk of common age-related conditions, such as cancer, cardiovascular disease, type 2 diabetes, and neurological diseases, so lengthening lifespan. Mild stressors and xenohormetic dietary components have diverse molecular targets and affect many pathways. Despite experimental advances in aging research, findings in humans are still quite limited. Moderate-intensity exercise, weight management and healthy diet ameliorate diseases of aging to increase lifespan and this could involve hormesis.

Key words: ageing; sirtuin activators; preinfarction angina; resveratrol; rapamycin.

INTRODUCTION

The process involved in aging has always been a popular topic. There is evidence that aging and age-related pathologies involves the progressive accumulation of molecular damage due to inefficiency and failure of maintenance, repair and turnover pathways (reviewed by Rattan 2008a). After a century of research, hormesis is now an accepted phenomenon. Hormesis is where low doses of external stressors that are noxious at higher levels can exert a beneficial effect on cells. Its most fascinating aspect, however, is in longevity research, where hormetic effects can involve modulation of the expression of genes related to maintenance and repair pathways, with resultant anti-aging and longevity-promoting effects (Rattan 2008a). Although studies in humans are restricted largely to epidemiologic observations, there has been a diversity of relevant evidence from research involving animal models and cultures of human cells (reviewed by Rattan 2008b). Historical observations on dietary constituents have suggested that certain substances, such as the red wine

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polyphenol resveratrol, might be capable of preventing numerous diseases of aging so as to increase lifespan. The present review examines whether hormesis could have positive effects on diseases of aging and on lifespan of a diversity of species. In particular, we discuss how this concept could be applied to human beings.

FINDINGS IN MODEL SYSTEMS

Although the aging process is not understood fully, it is undeniably associated with a gradual increase in molecular damage to cells (Gems and Partridge 2008). The mechanisms modulating aging and hormesis seem to be shared across different species (Le Bourg 2009). Interventions that increase lifespan in animal models have led to a better understanding of the mechanisms involved (Gems and Partridge 2008). The effect on lifespan of mild stressors, such as heat shock and cold, hypergravity, irradiation, controlled reduction of food intake (calorie restriction: CR), chemicals that are 'beneficial' (because of strong antioxidant effects) and low doses of certain toxic chemicals have been studied extensively in model organisms – *Caenorhabditis elegans* and *Drosophila melanogaster* (reviewed by Gems and Partridge 2008; Rattan 2008b; Le Bourg 2009). The molecular mechanisms involved in hormesis in these species are still not clear, however.

CR is probably one of the most well recognized hormetic phenomenon capable of increasing mammalian lifespan, but is also one of the most controversial (reviewed by Rattan 2008b; Le Bourg 2009). CR is able to prolong lifespan in diverse species of metazoans, including rodents (Wood *et al.* 2004) and rhesus monkeys (Colman *et al.* 2009). Where tested, the increase in lifespan involves the activation of the sirtuin class of nicotinamide adenine dinucleotide (NAD)⁺-dependent histone deacetylases (reviewed by Markus and Morris 2008; Morris 2008). Sirtuins, of which there are seven, regulate a number of intracellular pathways via the activation of transcription factors and enzymes responsive to nutrient availability. Sirt1 is the major sirtuin activated by both CR and resveratrol. The latter is a stilbene polyphenol found in diverse plants, such as grapes and other berry fruits, and mediates the beneficial effects of mild environmental stressors on lifespan and health (Markus and Morris 2008; Morris 2008; Marques *et al.* 2009). In a mouse model of obesity, resveratrol improved insulin sensitivity (Baur *et al.* 2006) and motor function (Lagouge *et al.* 2006). Its protection against atherosclerosis, cancer and diabetes, and increase in muscle endurance involves xenohormesis (Howitz and Sinclair 2008). Rapamycin, an inhibitor of TOR, positioned downstream of Sirt1, increases mouse lifespan (Harrison *et al.* 2009).

Regular physical exercise can be regarded as a mild stress and has well-known benefits as we age. Its hormetic effect involves attenuation of oxidative stress in non-muscular tissues of mice by the upregulation of

antioxidant mechanisms. Interestingly, beneficial effects are seen even when regular exercise is initiated late in life (Goto *et al.* 2007).

Increased lifespan and diverse anti-aging effects in response to repeated mild heat stress (RMHS) have been demonstrated in cultured normal human skin fibroblasts, keratinocytes and telomerase-immortalized bone marrow mesenchymal stem cells (reviewed by Rattan *et al.* 2009). An increase in and maintenance of numerous heat shock proteins (HSPs) are believed to be involved in the response to RMHS (Rattan *et al.* 2009). HSPs were, moreover, able to enhance wound healing in human skin fibroblasts, probably by inducing the synthesis of genes that can stimulate the healing process. RMHS also improved angiogenesis in aging human umbilical vein endothelial cells (Rattan *et al.* 2009).

CAN PRO-HEALTHY MILD STRESSES IN HUMAN BEINGS INCREASE LIFESPAN?

Most of the evidence points to factors that improve clinical conditions of aging, but not lifespan necessarily. At the moment, the implementation of lifestyle changes, such as physical exercise, weight reduction and dietary modifications, including dietary supplements, are still the best way to increase lifespan by decreasing the risk of premature death. For instance, the consumption of substances rich in antioxidants and flavonoids has been shown to be beneficial. There is scope for the development of more potent substances having the same beneficial effects. As part of this, the pathways mediating their actions need to be elucidated. Doses, duration of treatments and age at which benefits ensue have yet to be established. Some examples of the most successful mild stressors and the benefits they confer on aging will now be described.

Physical exercise

Moderate-intensity exercise stimulates the immune system, increasing resistance to infections and decreases the risk of other age-related diseases, including cancer (Radak *et al.* 2008). The release of neurotrophins and the modulation of redox homeostasis help to decrease the risk of Alzheimer's disease by increasing metabolic activity of neurons, as well as improving cardiovascular function (Radak *et al.* 2008). Physical exercise in young healthy men improves insulin resistance, decreasing risk for the development of type 2 diabetes, and was able to induce an adaptive response involving an increase in endogenous antioxidant capacity, termed "mitohormesis" (Ristow *et al.* 2009). Exercise, by generating ROS, induced various genes that encode proteins affecting insulin sensitivity and antioxidant defenses. These include transcriptional coactivators and transcription factors (such as peroxisome proliferator-activated receptor- γ) and some of their targets. Exercise-induced oxidative stress ameliorates

insulin resistance and, by an adaptive response, promotes endogenous anti-oxidant defenses, consistent with mitohormesis (Radak *et al.* 2008). Counterintuitively, daily consumption of antioxidant supplements (vitamins C and E) has been found to counteract such beneficial effects of exercise on metabolism (Ristow *et al.* 2009).

Sirtuin activators

Resveratrol and other, more potent, synthetic sirtuin activators that confer similar beneficial effects are in phase II trials for type 2 diabetes, colon and colorectal cancers, and Alzheimer's disease (reviewed by Marques *et al.* 2009).

Other environmental mild stressors

Ischemic preconditioning, represented by preinfarction angina in humans, increases the chance of surviving a cardiogenic shock. This was also observed in rodents. The effect decreased, however, with age, but could be restored with physical exercise and/or lowering of BMI (Le Bourg 2009).

The beneficial mild stressors mentioned above, if given in exaggerated amounts, can, however, result in negative effects on health and, consequently, on aging, an example being excessive physical exercise (Radak *et al.* 2008). Normal levels of stressors may, nevertheless, be important for the development of stress-resistance, so that reduction to their optimal levels or total elimination might have public health implications (Gems and Partridge 2008). The optimum beneficial dosage of each stressor is dependent on the genetic profile of the individual and its interaction with concomitant environmental factors.

CONCLUSIONS

Despite evidence of positive, hormesis-like effects in various species including humans, more research is needed in order to confirm and apply such possible benefits to humans. Future studies need to be directed not just at the cell as a whole, but at the dynamic functioning of sub-cellular compartments and their interactions. Clearly, many diverse interactions between different mild stressors, such as physical exercise and antioxidants, will need to be appreciated in order to gain a complete understanding of the hormetic response of cells and thus organisms. In a practical sense, it is hoped that gaining such an understanding will assist in improvements in health at the cellular and organismal level, so enhancing lifespan and reducing mortality and morbidity. The ability of organisms, including mammals, to be able to activate their own endogenous hormetic response pathways by utilizing hormetic chemicals in the food they consume, while quite remarkable, is nevertheless understandable in their adaptation to environmental changes.

Nevertheless, while appreciating certain aspects of the biological phenomenon of hormesis, the assumption that hormesis is generally adaptive could be an oversimplification of the complex biological processes involved. “Even if certain low-dose effects were sometimes considered beneficial, this should not influence regulatory decisions to allow increased environmental exposures to toxic and carcinogenic agents, given factors such as interindividual differences in susceptibility and multiplicity in exposures” (Thayer *et al.* 2005). Thus, as a general principle, the potential adverse consequences of instituting policies based on low-dose beneficial effects of actual or perceived stimuli that are at higher doses noxious means we must end with a note of caution pending the outcome of much more research in this fascinating area.

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