Review

Hormesis in aging

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Abstract

Hormesis in aging is represented by mild stress-induced stimulation of protective mechanisms in cells and organisms resulting in biologically beneficial effects. Single or multiple exposure to low doses of otherwise harmful agents, such as irradiation, food limitation, heat stress, hypergravity, reactive oxygen species and other free radicals have a variety of anti-aging and longevity-extending hormetic effects. Detailed molecular mechanisms that bring about the hormetic effects are being increasingly understood, and comprise a cascade of stress response and other pathways of maintenance and repair. Although the extent of immediate hormetic effects after exposure to a particular stress may only be moderate, the chain of events following initial hormesis leads to biologically amplified effects that are much larger, synergistic and pleiotropic. A consequence of hormetic amplification is an increase in the homeodynamic space of a living system in terms of increased defence capacity and reduced load of damaged macromolecules. Hormetic strengthening of the homeodynamic space provides wider margins for metabolic fluctuation, stress tolerance, adaptation and survival. Hormesis thus counter-balances the progressive shrinkage of the homeodynamic space, which is the ultimate cause of aging, diseases and death. Healthy aging may be achieved by hormesis through mild and periodic, but not severe or chronic, physical and mental challenges, and by the use of nutritional hormesis incorporating mild stress-inducing molecules called hormetins. The established scientific foundations of hormesis are ready to pave the way for new and effective approaches in aging research and intervention.

1. Introduction

Two of the leading biogerontologists, Robin Holliday and Leonard Hayflick, have given almost identical titles to their latest articles, asserting that aging is no longer an unsolved problem in biology (Hayflick, 2007; Holliday, 2006a). This does not imply that every single detail of the phenomenology of biological aging, at all levels of organization, has been elucidated. What is underlined is that the biological basis of aging are now well understood, and general principles of aging and longevity are formulated which can be the basis for future research and intervention towards achieving a healthy old age. One of the main principles to emerge from biogerontological research is that the primary molecular phenotype of aging is the stochastic occurrence and accumulation of molecular damage leading to a progressive increase in molecular heterogeneity and functional impairment (Rattan, 2006). A failure of maintenance and repair pathways effectively determines the course of aging, origin of age-related diseases and eventual death

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(Holliday, 1995, 2000; Rattan, 2006; Rattan and Clark, 2005). Therefore, effective anti-aging strategies can be based in this principle in order to develop methods to prevent and/or to slow down the failure of maintenance. The aim of this article is to discuss one such strategy, hormesis, which makes use of the fundamental characteristic of all living systems—their homeostatic or homeodynamic ability.

2. Homeodynamics, aging, and hormesis

All living systems have the intrinsic ability to respond, to counteract and to adapt to the external and internal sources of disturbance. The traditional conceptual model to describe this property is homeostasis, which has dominated biology, physiology and medicine since 1930s. However, advances made in our understanding of the processes of biological growth, development, maturation, reproduction, and finally, of aging, senescence and death have led to the realization that homeostasis model as an explanation is seriously incomplete. The main reason for the incompleteness of the homeostasis model is its defining principle of "stability through constancy", which does not take into account the new themes, such as cybernetics, control theory, catastrophe theory, chaos theory, information and interaction networks, which comprise and underline the modern biology of complexity (Rattan, 2007). Since 1990s, the term homeodynamics is being increasingly used to account for the fact that the internal milieu of complex biological systems is not permanently fixed, is not at equilibrium, and is a dynamic regulation and interaction among various levels of organization (Yates, 1994).

Aging, senescence and death are the final manifestations of unsuccessful homeostasis or failure of homeodynamics (Holliday, 2007; Rattan, 2006). A wide range of molecular, cellular and physiological pathways of repair are well known, and these range from multiple pathways of nuclear and mitochondrial DNA repair to free radical counteracting mechanisms, protein turnover and repair, detoxification mechanisms, and other processes including immune response 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 (Holliday, 2007; Rattan, 2006). A progressive shrinking of the homeodynamic space is the hallmark of aging and the cause of origin of age-related diseases.

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 responses 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, including death.

Several meta-analyses performed on innumerable research papers published in the fields of toxicology, pharmacology and radiation biology have led to the conclusion that the most fundamental shape of the dose–response is neither threshold nor linear, but is U- or inverted U-shaped, depending on the endpoint being measured (Calabrese, 2006, 2004, 2005b; Calabrese and Blain, 2004; Calabrese and Baldwin, 2001a,b, 2003). This phenomenon of bi-phasic dose–response was termed as hormesis in 1940s (for historical development of the term, see Calabrese, 2002). The key conceptual features of hormesis are the disruption of homeodynamics, the modest over-compensation, the reestablishment of homeodynamics and the adaptive nature of the process. A wide variety of physical, chemical and biological agents exhibit hormetic dose–response, and these include heavy metals, pesticides, antibiotics, chemotherapeutic agents, ethanol, aldehyde, chloroform, pro-oxidants, vitamins, trace elements and ionizing radiation (Calabrese, 2004, 2005a,b; Calabrese and Baldwin, 2001a,b).

The paradigm for considering the applicability of hormesis in aging intervention is the well-documented beneficial effects of exercise which at a biochemical level results in the production of potentially harmful substances such as free radicals, acids and aldehydes (Alessio and Hagerman, 2006; McArdle et al., 2002; Singh, 2002). Thus, it is hypothesized that if biological systems are deliberately exposed to mild stress, so that their homeodynamic pathways of maintenance and repair are challenged and activated, this should lead to achieving beneficial hormetic effects, including health- and longevity-promoting effects. Hormesis in aging is, therefore, defined as the life supporting beneficial effects resulting from the cellular responses to single or multiple rounds of mild stress (Rattan, 2001a,b, 2004, 2005).

Since the harmful effects of severe stress have long over shadowed the beneficial hormetic effects of low-level stress, applying hormesis in aging research and therapy is a relatively recent development. However, the concept of

hormesis, by providing mechanistic explanations for the apparently paradoxical and non-linear effects of potentially damaging agents, has given rise to new lines of investigation in anti-aging research (Rattan, 2004, 2005).

What follows is a brief review of the published literature on various physical, chemical and biological conditions which are known to be potentially harmful at high doses, but which, at lower doses, have the effects of slowing down aging and/or prolonging the lifespan of cells and organisms. This is followed by a discussion of the possible molecular mechanisms involved in hormesis and of the issues remaining to be resolved in order for hormesis to be applied in human aging intervention, prevention and therapy.

3. Radiation hormesis in aging

Although earlier studies on checking the effects of irradiation on biological systems were mainly performed with a view to demonstrate its harmful effects, the observed bi-phasic – low-dose beneficial and high dose harmful – effects can best be understood by invoking hormesis as a plausible explanation.

Whereas high doses of radiation decrease lifespan, low-dose radiation (LDR) is often accompanied by enhanced lifespan, for example as observed in fruitflies (Lamb, 1964; Sacher, 1963) and in houseflies (Allen and Sohal, 1982). It has been argued that irradiation leads to female sterility and that the lifespan increase is thus an outcome of decreased fecundity. It was also shown that mutant females without ovaries did not exhibit increased lifespan after irradiation. The environmental conditions influenced the lifespan of male houseflies differently after an exposure to LDR (Allen and Sohal, 1982). The increased lifespan was observed only when animals were reared in groups, which promoted a high locomotor activity. However, if individually reared and assumed to have a low locomotor activity, flies did not show longer lifespans. Furthermore, irradiated flies had longer lifespan than controls only when the latter were kept on sub-optimal rearing conditions (for discussion see, Minois, 2000; Minois and Rattan, 2003). The long-term consequences of the X-irradiation of *Drosophila* eggs demonstrated longevity hormesis in male flies exposed to 0.5 and 0.75 Gy, who also had smaller amounts of DNA segments resulting from cleavage in S1 nuclease sensitive sites (Vaiserman et al., 2003).

Several studies have reported the hormetic effects of gamma rays on longevity in rats, mice and guinea pigs (Calabrese and Baldwin, 2000; Caratero et al., 1998). Suppression of thymic lymphoma induction and prolongation of lifespan associated with immunologic modification by chronic LDR in C57BL/6 mice have been reported (Ina and Sakai, 2005; Ina et al., 2005). In contrast to this, some earlier studies had failed to show an increase of lifespan after a LDR. For instance, deuteron-irradiated mice exhibit higher mortality rates and lower lifespan in both sexes than non-irradiated ones (Ordy et al., 1967). However, an exposure of the nematode *Caenorhabditis elegans* to 140-rad gamma irradiation did not extend their lifespan (Cypser and Johnson, 2002). In contrast, the adaptive response of human embryonic cells to low-dose gamma-radiation has been shown to increase the replicative lifespan up to 160% compared to non-irradiated cells (Watanabe et al., 1992). Similarly, human embryonic lung diploid fibroblasts MRC-5 sequentially irradiated with 1 Gy gamma rays had their replicative lifespan increased to some extent (Holliday, 1991). Hormetic effects of low-dose X-irradiation on the proliferative ability, genomic stability and activation of mitogen-activated protein kinase pathways have been reported for other human diploid cells (Suzuki et al., 1998a,b, 2001; Tsutsui et al., 1997).

In the case of human beings, although there are some claims that exposure to LDR has anti-aging and other health benefits such as cancer prevention, the demographic data are insufficiently precise to be conclusive (Parsons, 2003; Wyngaarden and Pauwels, 1995). For example, although better survival and other beneficial effects of low to intermediate doses of atomic bomb radiation on Hiroshima and Nagasaki survivors have been claimed (Hayakawa et al., 1989; Mine et al., 1990; Okajima et al., 1985), these results have been challenged by later analyses (Cologne and Preston, 2000). On the other hand, mortality rates of all workers in UK's Atomic Energy Authority were found to be lower than national rates (Atkinson et al., 2004). All cause mortality and all cause cancers (leukaemia and prostate cancer) were also significantly lower for nuclear workers than for non-radiation workers (Atkinson et al., 2004). Furthermore, application of low-dose total body irradiation in treatment of cancers, such as non-Hodgkin's lymphoma, is another example of radiation hormesis (Safwat, 2000).

Although the exact mechanisms of how LDR brings about beneficial and longevity-promoting effects are not fully understood, stimulation of various repair and maintenance pathways is indicative of hormesis. These include enhanced DNA repair, induced DNA methylation, increased antioxidative enzymes, and increased removal of damaged macromolecules (Eller et al., 1997; Feinendegen, 2005; Holliday, 1991; Pollycove and Feinendegen, 2001; Wolff, 1996). It will be useful to design and perform studies aimed specifically to test the anti-aging, anti-cancer and longevity-promoting hormetic effects of stress-inducing levels of irradiation.

4. Caloric restriction and hormesis

In more than 70 years of studying the effects of dietary caloric restriction (CR) on aging and longevity, CR is the most commonly used intervention that has shown to extend the lifespan and slow down the onset of a wide range of age-related changes in a variety of organisms, including yeast, insects, rats, mice, and monkeys. The universal applicability of CR as an anti-aging and lifespan extending intervention, especially in human beings, is a highly debated issue at present, based mainly on evolutionary arguments (Braeckman et al., 2006; Dirks and Leeuwenburgh, 2006; Goto, 2006; Holliday, 2006b; Ingram et al., 2006; Le Bourg, 2006; Le Bourg and Rattan, 2006; Masoro, 2006a,b; Mockett et al., 2006; Phelan and Rose, 2006; Shanley and Kirkwood, 2006; Weindruch, 2006; Yu, 2006).

However, some beneficial and health promoting effects of CR have been reported for human beings. For example, long-term CR is reported to be highly effective in reducing the risk for atherosclerosis in humans (Fontana et al., 2004), and ameliorates the decline in diastolic function in humans (Meyer et al., 2006). An unintentional CR imposed on the participants of the Biosphere-2 experiment in 1991 also gave some indication of the beneficial effects of CR, as measured by several physiologic, hematologic, hormonal and biochemical parameters (Walford et al., 2002). Similarly, unintentional chronic under nutrition and low body mass index have been shown to improve certain DNA-repair parameters in peripheral blood lymphocytes of human subjects (Raji et al., 1998).

A relatively short duration CR for six months has also been shown to have beneficial effects in humans by reducing the fasting insulin levels, body temperature and DNA damage (Heilbronn et al., 2006). Intermittent CR by periodic fasting has been shown to have a range of beneficial effects in rodents (Anson et al., 2003; Sharma and Kaur, 2005; Sogawa and Kubo, 2000). These observations make periodic CR more easily applicable and acceptable to human beings with several potential benefits, especially with respect to the prevention of neurodegenerative diseases with age (Arumugum et al., 2006; Martin et al., 2006). Our recent pilot studies on checking the effects of periodic partial (80%) fasting, once a week for 24 h, by serum reduction in serially passaged human skin fibroblasts have shown some anti-aging and lifespan extending effects (Rattan and Ali, 2007).

In order to understand the mechanisms for the wide range of beneficial biological effects of CR, hormesis has been suggested as a major explanation by considering CR as a low-intensity stressor (Masoro, 1998, 2007; Parsons, 2000; Yu and Chung, 2001). The main evidence in support of the view that CR is a low-intensity stressor is its association with the increase in plasma levels of glucocorticoid steroid stress hormones (reviewed in Masoro, 2007). Another requirement for the hormesis hypothesis to explain the effects of CR is that CR should work through one or more pathways involved in stress response, molecular damage prevention and turnover and metabolic regulation. There is significant evidence for the hormetic action of CR by promoting maintenance and repair pathways. Table 1 gives a summary of the main pathways shown to be involved in the hormetic response of CR in various organisms.

Table 1
Pathways involved in bringing about the hormetic effects of calorie restriction

Pathway	Organisms	References
Heat shock proteins	Rats, yeast	Aly et al. (1994), Colotti et al. (2005), Hahn et al. (2004), Harris et al. (2001), Heydari et al. (2000), Selsby et al. (2005), Shama et al. (1998)
Nucleotide excision repair	Rats	Guo et al. (1998)
Proteasome activity	Rats, yeast	Hahn et al. (2004), Selsby et al. (2005), Shibatani et al. (1996), Shibatani and Ward (1996)
Lysosomal autophagy	Rats	Bergamini et al. (2003), Cuervo and Dice (2000)
Antioxidant activities	Rats, mice, *Drosophila*	Semsei et al. (1989), Sohal and Weindruch (1996)
Insulin and glucose metabolism regulation	Mice	Anson et al. (2003), Duan et al. (2003a), Duan et al. (2003b)
Neurotrophic factors	Rhesus monkey	Maswood et al. (2004)
Metabolic shift involving sirtuins, histone deacetylation, etc.	Yeast, nematodes, *Drosophila*, rats	Cohen et al. (2004), Guarante and Picard (2005), Koubova and Guarante (2003), Nemoto et al. (2004), Rogina and Helfand (2004), Wood et al. (2004)
Mitochondrial uncoupling	Rats	Crescenzo et al. (2006), Liu et al. (2006)
Hormonal regulation	Rats, mice	Everitt (2003), Klebanov et al. (1995), Mobbs et al. (2001)

5. Exercise hormesis

The well-documented beneficial effects of exercise occur in a paradoxical background of biochemical framework. It is well known that exercise increases the production of potentially harmful substances such as reactive oxygen and nitrogen species, other free radicals, acids and aldehydes (Alessio and Hagerman, 2006; Ji, 2006; Ji et al., 2006; Radak et al., 2005; Radák et al., 1998). 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 (Ji, 2006). Prolonged exercise then leads to the formation and accumulation of acids and other metabolites, which are potentially powerful damaging agents. In order to understand the long-term beneficial effects of repeated moderate exercise, hormesis provides the best explanation.

Some of the main molecular pathways involved in bringing about the adaptive and hormetic effects of exercise are activation of nuclear factor NFκB signaling cascade involving various stress kinases and antioxidant genes (Ji, 2006; Wakatsuki et al., 2004), enhanced anti-inflammatory responses, enhanced DNA repair, and increased degradation of damaged proteins and other macromolecules by proteasomal and lysosomal pathways (Radak et al., 2005; Short et al., 2004). Another pathway which is active in realizing the hormetic effects of exercise is the stress response or heat shock protein (HSP) synthesis pathway in which the induction of various HSP, during and after exercise, has a variety of beneficial biological effects associated with it (Atalay et al., 2004; Gonzales and Manso, 2004; Lancaster et al., 2004; McArdle et al., 2004; Verbeke et al., 2001b). Increased levels of HSP provide several benefits including a protection against molecular damage occurrence and accumulation, which is a crucial aspect of aging.

6. Thermal hormesis

6.1. Heat stress in organisms

Temperature stress, especially heat stress (HS), is one of those stresses that have been used with a specific aim to test and apply hormesis. The reason for this is not only because HS is easy to implement and gives consistent results, but also because HS mainly acts through an evolutionarily highly conserved stress response pathway known as the heat shock response (Verbeke et al., 2001b). Effects of mild and sever HS have been tested on yeast, nematodes, fruitflies, and rodent and human cells. For example, a 2 h HS at 37 °C applied before the first division and after the fourth division extended the replicative lifespan of *Saccharomyces cerevisiae* by 10% (Shama et al., 1998). The same HS had no effect if applied later in life as well as if applied everyday. In the case of nematodes, wild-type and *age-1* mutant hermaphrodite *C. elegans* exposed for 3–24 h to 30 °C exhibited a significant increase in mean lifespan compared to controls (Johnson, 2002; Lithgow et al., 1995). Similarly, a 6 h exposure at 30 °C of wild-type worms induced a 12.5% increase in lifespan, but no effect was found after exposures of 2 or 4 h (Yokoyama et al., 2002). In a series of articles (Butov et al., 2001; Michalski et al., 2001; Yashin et al., 2001), the purpose of which was to model survival under stress, *C. elegans* worms were subjected to 35 °C HS of different durations. Those studies showed that HS not longer than 2 h produced an extension of lifespan of animals. In contrast, longer HS had either no effect or deleterious effects. In a study of multiple stresses in *C. elegans* an extension of lifespan after 1 and 2 h HS at 35 °C was reported (Cypser and Johnson, 2002, 2003). In another study performed on *C. elegans* it was observed that repeated mild heat treatments throughout life had a larger effect on lifespan compared to a single mild heat treatment early in life, and the effect was related to the levels of heat shock protein (HSP) expression (Olsen et al., 2006).

Virgin males of inbred lines of *D. melanogaster* exhibited an increase in mean lifespan and lower mortality rates during several weeks after a heat treatment of 36 °C for 70 min (Khazaeli et al., 1997). No beneficial effect of HS was reported in females or in mated flies. It has also been shown that wild-type *D. melanogaster* exposed 5 min a day, 5 days a week for one week to 37 °C live on average 2 days longer than the control flies (Le Bourg et al., 2001). Longer exposures had either no effect or negative effect on lifespan. In another study on *D. melanogaster*, exposure of young flies to four rounds of mild HS at 34 °C significantly increased the average and maximum lifespan of female flies and increased their resistance to potentially lethal heat stress (Hercus et al., 2003). Interestingly, the beneficial effects of HS in *Drosophila* do not entirely depend on a continuous presence of HSP, but are observed long after newly synthesized HSP had disappeared, indicating the involvement of a cascade of post-stress events in hormesis (Sørensen et al., 2003; Vermeulen and Loeschcke, 2007).

Studies have also been performed on the effect of subjecting transgenic *D. melanogaster* over-expressing the inducible HSP70, to 20 min at 36 °C in an incubator under saturated humidity (Minois et al., 2001; Minois and Vaynberg, 2002). In the control "parental" line, such an exposure significantly increased the lifespan of both virgin flies kept in groups and of mated flies. The effect was more pronounced in males than in females. In individually kept flies, the same trend was observed but was statistically not significant. No beneficial effect of this HS has been seen in the transgenic lines (Minois and Vaynberg, 2002). At least one study also reports the beneficial effects of cold stress-induced hardening in *Drosophila,* in terms of improved survival (Overgaard et al., 2005).

Irradiated and non-irradiated mice who were give intermittent cold-shocks showed lower rates of mortality in non-irradiated males as well as in both sexes in irradiated mice. Longer lifespans were observed in thermally stressed non-irradiated males and irradiated females. Finally, rats kept in water set at 23 °C, 4 h a day, 5 days a week had a 5% increase in average lifespan and diminished the occurrence of certain age-related diseases (Holloszy and Smith, 1986).

6.2. Heat stress in cells in culture

The hormesis hypothesis of the beneficial effects of mild HS has been tested on the Hayflick system of cellular aging of normal human cells in culture. Using a mild stress regimen of exposing serially passaged human fibroblasts to 41 °C for 1 h twice a week throughout their replicative lifespan *in vitro*, we have reported several anti-aging effects. These effects include the maintenance of youthful morphology, reduced accumulation of oxidatively and glycoxidatively damaged proteins, and increased resistance to ethanol, hydrogen peroxide and UV-A irradiation (Fonager et al., 2002; Rattan, 1998; Verbeke et al., 2000, 2001a, 2002). Possible mechanisms for the above hormetic effects of repeated mild HS in human fibroblasts include an increase in the activities of the proteasome, increased levels of various HSP, and increased antioxidative enzyme activities (Beedholm et al., 2004; Fonager et al., 2002). Furthermore, we have also shown that repeated mild HS at 41 °C, but not the relatively severe HS at 42 °C, increased the replicative lifespan, and elevated and maintained the basal levels of MAP kinases JNK1, JNK2 and p38 in human skin fibroblasts (Nielsen et al., 2006).

Recently, we have undertaken studies on the hormetic effects of repeated mild HS on normal human epidermal keratinocytes (NHEK), and the results obtained are very much similar to those for dermal fibroblasts (Rattan and Ali, 2007). As previously observed for human skin fibroblasts, NHEK also showed a variety of cellular and biochemical hormetic anti-aging effects on repeated exposure to mild HS at 41 °C. These effects included maintenance of youthful cellular morphology, enhanced replicative lifespan, enhanced proteasomal activity, and increased levels of HSP (Rattan and Ali, 2007). Additionally, we have also studied the effects of HS on Na,K-ATPase or the sodium pump. Mild HS significantly increased the content and activity of the pump in NHEK. Increased Na,K-ATPase activity is consistent with an overall increase in the metabolic rate of the cell. However, the molecular mechanisms and interactions which bring about the mild HS-induced increase in the amounts and activity of Na,K-ATPase, and its consequences on other biochemical pathways, in NHEK during aging are yet to be elucidated. Notably, comparable hormetic effects could not be seen in NHEK repeatedly exposed to 43 °C, which underlines the differences between the beneficial effects of mild stress and the harmful effects of severe stress. Other hormetic effects of mild HS on NHEK include increased differentiation of keratinocytes in the presence of calcium, and reduced cytotoxic effects of glucose and glyoxal (Berge et al., 2007). Similarly, vitamin-D-induced differentiation of telomerase-immortalized bone marrow stem cells into osteoblasts could be enhanced by pre-exposure to HS (Nørgaard et al., 2006).

As regards the molecular mechanisms through which the hormetic effects of mild HS are achieved, these remain to be elucidated. Although the general mechanisms of severe heat shock response are well understood (Feder and Hofmann, 1999; Sun and MacRae, 2005; Verbeke et al., 2001b), it is not clear whether there are any significant differences between mild heat stress which has hormetic effects, and severe heat stress, repeated exposure to which has deleterious effects (Park et al., 2005). It is likely that the physiological cost of stress in terms of energy utilization, molecular damage overload and metabolic shift determine the difference between the outcome of mild and severe stress. Also, it is yet to be understood how the transient appearance of HSP leads to biologically amplified hormetic effects at various other levels of cellular functioning, such as improved proteasome activity, enhanced resistance to other stresses, maintenance of the cytoskeletal integrity and others.

7. Nutritional hormesis and hormetins

Several dietary components, such as vitamins, antioxidants, trace elements, minerals, ethanol, and even herbicides and pesticides have been shown to have typical hormetic dose–response (Calabrese and Blain, 2004). All such compounds (natural or synthetic), which bring about biologically beneficial effects by acting through one or more pathways of maintenance and repair, and stress response, are termed as hormetins (Ali and Rattan, 2006).

In a recently published article Hayes has critically reviewed the hormetic effects of various vitamins and macro- and micro-minerals, including iron, iodine, fluorine, selenium and copper (Hayes, 2007). Additionally, the effects of zinc also show a typical hormetic dose–response, and its beneficial effects are considered to be achieved through stress response induced alterations in gene expression of various maintenance and repair pathways (Mocchegiani et al., 2000, 2006).

Dietary intake of moderate amounts of ethanol has been shown to have memory enhancing beneficial effects in mice (Ritzmann et al., 1994). The cardio-protective, antioxidative and other beneficial effects of wine are considered to be due to flavonoid and non-flavonoid components, such as resveratrol (Corder et al., 2006), which also have hormetic dose–response. Resveratrol is considered to be a product of sunlight- and microbial-stress-induced hormetic response (Lamming et al., 2004). Several studies have reported the anti-aging and longevity enhancing effects of resveratrol in nematodes, *Drosophila* and mice (Baur et al., 2006; Lamming et al., 2004; Rogina and Helfand, 2004; Valenzano et al., 2006; Wood et al., 2004). Since resveratrol's mode of action involves regulating various pathways of maintenance, repair, and metabolic rate, it qualifies to be called a hormetin.

Other potential hormetins are various antioxidants, including components of spices and other medicinal plants. Almost all antioxidants show hormetic dose–response and become pro-oxidants above certain doses. Furthermore, in some cases such as alpha lipoic acid and coenzyme Q10, it is their pro-oxidant activity in producing hydrogen peroxide, which induces defensive responses, which are the basis of their ultimately beneficial effects (Linnane and Eastwood, 2006). Certain mimetics of superoxide dimutase claimed to have anti-aging effects also appear to work through hormetic pathways by inducing oxidative stress response (Keany et al., 2004; Liu et al., 2003; Melov et al., 2000). It has also been argued that initial low-level deposition of A-beta protein, that eventually leads to Alzheimer's disease, may actually have some protective hormetic role for neurons (Rubinsztein, 2006). Even DNA damage products, for example thymidine dimers, have cytoprotective effects in the skin by inducing DNA repair pathways (Eller et al., 1997; Goukassian et al., 2004). Another secondary DNA damage product, N^6-furfuryladenine or kinetin – known to have anti-aging effects in human cells, and widely used as a component of several skin care cosmeceutical products (Rattan, 2002; Rattan and Clark, 1994) – may also work as a hormetin through stress-induced hormetic pathways (Barciszewski et al., 1999, 1996).

Components of various medicinal plants used frequently in the traditional Chinese medicine (TCM) and in the Indian Ayurvedic system of medicine are claimed to have anti-aging effects, which appear to be achieved through hormetic pathways. For example, celasterols and paeoniflorin present in some medicinal herbs used in TCM, have cytoprotective effects and induce HSP in human cells (Westerheide et al., 2004; Yan et al., 2004). Similarly, curcumin, which is the active component in the commonly used yellow food spice *Haldi* and is derived from the roots of *Curcuma longa*, is a co-inducer of HSP and has wide ranging biological effects depending on its dosage (Cronin, 2003; Dunsmore et al., 2001; Joe et al., 2004). Whereas curcumin doses above 10 μmol have been reported to have anti-inflammatory and anti-cancer effects in experimental studies (Moos et al., 2004; Rashmi et al., 2003), at lower doses (0.3 and 1 μmol) curcumin stimulates proteasome activity, enhances HSP induction after HS, and stimulates sodium pump activity effects (Ali and Rattan, 2006; Rattan and Ali, 2007).

Hormesis may also be an explanation for the health beneficial effects of numerous other foods and food components, such as garlic, Gingko, and other fruits and vegetables (Everitt et al., 2006; Ferrari, 2004; Fischer and Morley, 2002; Gurib-Fakim, 2006; Hayes, 2005, 2007; Moriguchi et al., 1996; Svendsen et al., 1994). Understanding the hormetic and interactive mode of action of natural and processed foods is a challenging field of research, and has great potential in developing nutritional and other life style modifications for aging intervention and therapies. For example, it may be possible to develop multi-hormetin formulations as anti-aging drugs and nutriceuticals whose mode of action is through hormetic pathways by mild stress-induced stimulation of homeodynamic processes.

8. Hypergravity and other stresses

8.1. Hypergravity

Hormetic effects of hypergravity have been studied in *Drosophila*. Whereas life long exposure to hypergravity decreases the lifespan in rodents and fruitflies, a 2-week exposure to 3 or 5 g at earlier stages in life, resulted in an increase of 15% in the lifespan of male but not of female *D. melanogaster* (Le Bourg et al., 2000; Minois, 2006). In addition to longevity, other physiological and behavioural parameters, such as fecundity, fertility, locomotor activity, antioxidant enzyme activity, HSP levels and heat resistance, have also been analyzed. Except for increased survival of hypergravity-exposed *Drosophila* under heat stress, no other clear cut patterns have been observed so far that can be associated with anti-aging effects of transient hypergravity (Le Bourg, 2005; Le Bourg and Fournier, 2004; Minois and Le Bourg, 1999). It is also not clear why the longevity-extending hormetic effects of hypergravity are restricted to male flies only. Studies on checking the anti-aging effects of hypergravity on various molecular biomarkers of aging, such as the level of macromolecular damage and other maintenance and repair pathways, are yet to be performed.

8.2. Other stresses

Some examples of other stresses that have been investigated with respect to their effects in aging and longevity include starvation, electromagnetic stress, and mechanical stress, but the results obtained are not consistent or well understood (for details see Minois, 2000; Minois and Rattan, 2003). In one such study, chronic low-frequency (10 Hz) electric stimulation of young and old male Brown Norwegian rats resulted in more than two-fold increase in the proportion of IIa slow muscle fibers and in the content of satellite cells (Putman et al., 2001). An example of low-level mechanical stress having beneficial hormetic effects is the study showing that 20 min burst of very low magnitude high frequency vibrations given to hind limbs of sheep increases the trabecular density by 34% in 1 year (Rubin et al., 2001). There is some indication that osteopontin synthesis in human dental osteoblasts is stimulated by low levels of mechanical stress (Liu et al., 2004). The effects of repeated physical injuries on lifespan extension have been studied for a marine oligochaete Paranais *litoralis*, capable of posterior regeneration, and of asexual reproduction (Martínez, 1996).

Another kind of stress that appears to have hormetic effects is the population density in early stages of life. For example, it has been shown in *Drosophila* that larval crowding can induce both nutritional limitation and high concentrations of waste products, and can thus be considered as a stress for the larvae. Several studies have reported that raising larvae in such conditions increased the lifespan of adult flies. For instance, an increase in lifespan with increased larval density, between 5 and 100 larvae per 5 cm^3 of food has been reported. Furthermore, it was reported that whereas the developmental time, starvation resistance, relative fat content and lifespan increased with larval density, viability was dramatically decreased (for details see Minois and Rattan, 2003). However, in a separate study it was shown that larval crowding had no negative effect on viability but could increase the lifespan in *D. melanogaster* (Sørensen and Loeschcke, 2001).

There are some studies attempting to check the hormetic effects of mental and psychological stress. Although the harmful effects of chronic and acute stress on life functioning, quality of life, and survival are well documented (Padgett and Glaser, 2003; Segerstrom and Miller, 2004), beneficial effects of periodic low-level mental stress are also being investigated. For example, C57BL6 young male mice exposed to stress by keeping them in a restrained space for 2.5 h increased the levels of stress hormone catecholamines and corticosterones and adrenal steroids, and enhanced their immunoprotection during surgery, vaccination or infection (Viswanathan and Dhabhar, 2005). Skin fibroblasts from Cushing syndrome patients, who have higher plasma levels of glucocorticoids, have longer replicative lifespan *in vitro* and have a better HSP stress response (Pratsinis et al., 2002; Zervolea et al., 2005). There are some preliminary studies which show that hormesis through mental challenge (Bierhaus et al., 2003) and through mind-concentrating meditational techniques (De Nicolas, 1998; Fábián et al., 2003, 2004; Selkoe, 1992) may be useful in stimulating stress response, and intercellular and intracellular debris-removal processes.

9. Hormesis potential, challenges and unresolved issues

Since hormetic effects of mild stress are normally observed to be quite moderate and not so dramatic, some people find it difficult to envisage the biological significance of hormesis in terms of its application in human aging

intervention and prevention (Thayer et al., 2006; Zapponi and Marcello, 2006). However, it should be pointed out that although the initial hormetic effects may be relatively small when studied at the level of an individual biochemical step, often the final biological outcome, such as overall stress-tolerance, functional improvement and survival, is much larger, synergistic and pleiotropic. This suggests that hormesis is involved in the biological amplification of adaptive responses leading to the improvement in overall cellular functions and performance. Exercise is a good example of the biological amplification of beneficial effects of mild stress where it is not only the specific muscle targets which gain benefit, but improvements in the immune system, cardiovascular system, sex hormones, libido and mood are also well documented (Kyriazis, 2003; Radak et al., 2005; Singh, 2002). A recent study performed on rats shows that exercise performed in a young age can have lifelong benefits on bone structure and strength (Warden et al., 2007).

At present we have little knowledge of the interactive molecular pathways which, through a process of biological amplification, result in the maintenance and/or improvement of the physiological functions. Furthermore, in the case of human beings, the role of the mental state and psychological challenge in modulating various physiological functions, such as the immune response, stress hormone synthesis, gene expression, cardiac output and muscle strength are only beginning to be addressed.

The main promise and potential of hormesis as a modulator of aging lies in its mode of action. Since hormetic effects occur by involving a series of molecular and physiological processes, the final target of hormesis is the overall homeodynamic machinery of the living systems. Although hormesis-inducing stress may be targeted at a single pathway, the cascade of biological effects and their amplification results in the modulation and strengthening of the total homeodynamic ability.

As discussed in the earlier sections above, the process of aging is primarily characterized by a progressive shrinking of homeodynamic space in terms of increased molecular heterogeneity, which leads to increased vulnerability, onset of diseases and eventual death. It is also important to realize that the dimensions of the homeodynamic space of an individual are determined by its interacting network of genes, milieu and chance (Rattan, 2006), which are the basis of the uniqueness of the individual. Several studies have been made and many are in progress in order to associate genetic variations (polymorphisms) with individual health status, probability of onset of various diseases and lifespan potential (Bessenyei et al., 2004; Christensen et al., 2006). Since the practical applications of mild stress-induced hormesis are critically dependent on individual variations in stress response, studies to establish the association between stress gene variants and stress response are highly important and informative (Altomare et al., 2003; Singh et al., 2006a,b, 2004). Such studies are also necessary to establish the scientific foundations of the so-called personalized medicine and personalized neutrigenomics (Dalton and Friend, 2006; Mutch et al., 2005).

This also leads to a few other important issues that remain to be resolved before hormesis can be successfully applied as an effective anti-aging, health-promoting and lifespan extending strategy. Some of these issues are:

- to establish molecular criteria for identifying hormetic effects of different stresses;
- to establish stress exposure regimens in terms of the intensity and frequency;
- to identify qualitative and quantitative differences in stress response pathways initiated by different stressors;
- to determine the interactive and pleiotropic effects of multiple stresses;
- to adjust the levels of mild stress for age-related changes in the sensitivity to stress; and
- to determine the biological and evolutionary costs of repeated exposure to stress.

Although resolution of these issues will requires much more research on hormesis than that being done at present, analyses of the published data and new experiments performed with a variety of biological systems using a range of physical, chemical and biological stressors have clearly put hormesis on a solid footing. In the context of modulating aging, repeated mild stress-induced hormesis increases the boundaries of the homeodynamic space thus giving cells and organisms wider margins for metabolic fluctuation and adaptation. Increased efficiency of maintenance and repair pathways, and decreased molecular heterogeneity are two of the major hallmarks of improved homeodynamics. Hormesis can slow down the rate and extent of shrinkage of the homeodynamic space, and can prevent the onset and/or decrease the intensity of age-related impairments and diseases. The scientific foundations of hormesis are now strong enough to build upon them.

Acknowledgements

References

Alessio, H.M., Hagerman, A.E. (Eds.), 2006. Oxidative Stress, Exercise and Aging. Imperial College Press, London.

Ali, R.E., Rattan, S.I.S., 2006. Curcumin's biphasic hormetic response on proteasome activity and heat shock protein synthesis in human keratinocytes. Ann. N.Y. Acad. Sci. 1067, 394–399.

Allen, R.G., Sohal, R.S., 1982. Life-lengthening effects of gamma-radiation on the adult housefly, *Musca domestica*. Mech. Ageing Dev. 20, 369–375.

Altomare, K., Greco, V., Bellizzi, D., Berardelli, M., Dato, S., DeRango, F., Garasto, S., Rose, G., Feraco, E., Mari, V., Passarino, G., Franceschi, C., De Benedictis, G., 2003. The allele (A)-110 in the promoter region of the HSP70-1 gene is unfavourable to longevity in women. Biogerontology 4, 215–220.

Aly, K.B., Pipkin, J.L., Hinson, W.G., Feuers, R.J., Duffy, P.H., Hart, R.W., 1994. Temporal and substrate-dependent patterns of stress protein expression in the hypothalamus of calorie restricted rats. Mech. Ageing Dev. 76, 1–10.

Anson, R.M., Guo, Z., de Cabo, R., Lyun, T., Rios, M., Hagepanos, A., Ingram, D.K., Lane, M.A., Mattson, M.P., 2003. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie restriction. Proc. Natl. Acad. Sci. U.S.A. 100, 6216–6220.

Arumugum, T.V., Gleichmann, M., Tang, S.C., Mattson, M.P., 2006. Hormesis/preconditioning mechanisms, the nervous system and aging. Age. Res. Rev. 5, 165–178.

Atalay, M., Oksala, N.K., Laaksonen, D.E., Khanna, S., Nakao, C., Lappalainen, J., Roy, S., Hanninen, O.O., Sen, C.K., 2004. Exercise training modulates heat shock protein response in diabetic rats. J. Appl. Physiol..

Atkinson, W.D., Law, D.V., Bromley, K.J., Inskip, H.M., 2004. Mortality of employees of the United Kingdom Atomic Energy Authority, 1946–97. Occup. Environ. Med. 61, 577–585.

Barciszewski, J., Rattan, S.I.S., Siboska, G., Clark, B.F.C., 1999. Kinetin—45 years on. Plant Sci. 148, 37–45.

Barciszewski, J., Siboska, G.E., Pedersen, B.O., Clark, B.F.C., Rattan, S.I.S., 1996. Evidence for the presence of kinetin in DNA and cell extracts. FEBS Lett. 393, 197–200.

Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., Prabhu, V.K., Allard, J.S., Lopez-Lluch, G., Lewis, K., Pistell, P.J., Poosala, S., Becker, K.G., Boss, O., Gwinn, D., Wang, M., Ramaswamy, S., Fishbein, K.W., Spencer, R.G., Lakatta, E.G., Le Couter, D., Shaw, R.J., Navas, P., Puigserver, P., Ingram, D.K., de Cabo, R., Sinclair, D.A., 2006. Reseveratrol improves health and survival of mice on a high-calorie diet. Nature 443.

Beedholm, R., Clark, B.F.C., Rattan, S.I.S., 2004. Mild heat stress stimulates proteasome and its 11S activator in human fibroblasts undergoing aging in vitro. Cell Stress Chaperon. 9, 49–57.

Bergamini, E., Cavallini, G., Donati, A., Gori, Z., 2003. The anti-ageing effects of calorie restriction may involve stimulation of macroautophagy and lysosomal degradation, and can be intensified pharmacologically. Biomed. Pharmacol. 57, 203–208.

Berge, U., Behrens, J., Rattan, S.I.S., 2007. Sugar-induced premature aging and altered differentiation in human epidermal keratinocytes. Ann. N.Y. Acad. Sci. 1100, 524–529.

Bessenyei, B., Marka, M., Urban, L., Zeher, M., Semsei, I., 2004. Single nucleotide polymorphisms: aging and diseases. Biogerontology 5, 291–300.

Bierhaus, A., Wolf, J., Andrassy, M., Rohleder, N., Humpert, P.M., Petrov, D., Fersti, R., von Eynatten, M., Wendt, T., Rudofsky, G., Joswig, M., Marcos, M., Schwaninger, M., McEwen, B., Kirschbaum, C., Nawroth, P.P., 2003. A mechanism converting psychosocial stress into mononuclear cell activation. Proc. Natl. Acad. Sci. U.S.A. 100, 1920–1925.

Braeckman, B.P., Demetrius, L., Vanflateren, J.R., 2006. The dietary restriction effects in *C. elegans* and humans: is the worm a one millimeter human? Biogerontology 7, 127–133.

Butov, A., Johnson, T.E., Cypser, J., Sannikov, I., Volkov, M., Sehl, M., Yashin, A.I., 2001. Hormesis and debilitation effects in stress experiments using the nematode worm *Caenorhabditis elegans:* the model of balance between cell damage and HSP level. Exp. Gerontol. 37, 57–66.

Calabrese, E., 2006. The failure of dose-response models to predict low dose effects: a major challenge for biomedical, toxicological and aging research. Biogerontology 7, 119–122.

Calabrese, E., Blain, R., 2004. The hormetic database: an overview. Toxicol. Appl. Pharmacol. 202, 289–300.

Calabrese, E.J., 2002. Hormesis: changing view of the dose-response, a personal account of the history and current status. Mutat. Res. 511, 181–189.

Calabrese, E.J., 2004. Hormesis: from marginalization to mainstream: a case for hormesis as the default dose-response model in risk assessment. Toxicol. Appl. Pharmacol. 197, 125–136.

Calabrese, E.J., 2005a. Cancer biology and hormesis: human tumor cell lines commonly display hormetic (biphasic) dose response. Crit. Rev. Toxicol. 35, 463–582.

Calabrese, E.J., 2005b. Horemtic dose-response relationship in immunology: occurrence, quantitative features of the dose response, mechanistic foundations, and clinical implications. Crit. Rev. Toxicol. 35, 89–295.

Calabrese, E.J., Baldwin, L.A., 2000. The effects of gamma rays on longevity. Biogerontology 1, 309–319.

Calabrese, E.J., Baldwin, L.A., 2001a. Hormesis: a generalizable and unifying hypothesis. Crit. Rev. Toxicol. 31, 353–424.

Calabrese, E.J., Baldwin, L.A., 2001b. U-shaped dose-responses in biology, toxicology, and public health. Annu. Rev. Public Health 22, 15–33.

Calabrese, E.J., Baldwin, L.A., 2003. Toxicology rethinks its central belief. Nature 421, 891–892.

Caratero, A., Courtade, M., Bonnet, L., Planel, H., Caratero, C., 1998. Effect of continuous gamma irradiation at a very low dose on the life span of mice. Gerontology 44, 272–276.

Christensen, K., Johnson, T.E., Vaupel, J.W., 2006. The quest for genetic determinants of human longevity: challenges and insights. Nat. Rev. Genet. 7, 436–448.

Cohen, H.Y., Miller, C., Bitterman, K.J., Wall, N.R., Hekking, B., Kessler, B., Howitz, K.T., Gorospe, M., de Cabo, R., Sinclair, D.A., 2004. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. Science 305, 390–392.

Cologne, J.B., Preston, D.L., 2000. Longevity of atomic-bomb survivors. Lancet 356, 303–307.

Colotti, C., Cavallini, G., Vitale, R.L., Donati, A., Maltinti, M., Ry, S.D., Bergamini, E., Giannessi, D., 2005. Effects of aging and anti-aging caloric restrictions on carbonyl and heat shock protein levels and expression. Biogerontology 6, 397–406.

Corder, R., Mullen, W., Khan, N.Q., Marks, S.C., Wood, E.G., Carrier, M.J., Crozier, A., 2006. Red wine procyanidins and vascular health. Nature 444, 566.

Crescenzo, R., Lionetti, L., Mollica, M.P., Ferraro, M., D'Andrea, E., Mainieri, D., Dulloo, A.G., Liverini, G., Iossa, S., 2006. Altered skeletal muscle subsarcolemmal mitochondrial compartment during catch-up fat after caloric restriction. Diabetes 55, 2286–2293.

Cronin, J.R., 2003. Curcumin: old spice is a new medicine. Altern. Complement. Ther. (February), 34–38.

Cuervo, A.M., Dice, J.F., 2000. Age-related decline in chaperone-mediated autophagy. J. Biol. Chem. 275, 31505–31513.

Cypser, J.R., Johnson, T.E., 2002. Multiple stressors in *Caenorhabditis elegans* induce stress hormesis and extended longevity. J. Gerontol. Biol. Sci. 57A, B109–B114.

Cypser, J.R., Johnson, T.E., 2003. Hormesis in Caenorhabditis elagans dauer-defective mutants. Biogerontology 4, 203–214.

Dalton, W.S., Friend, S.H., 2006. Cancer biomarkers—an invitation to the table. Science 312, 1165–1168.

De Nicolas, A.T., 1998. The biocultural paradigm: the neural connection between science and mysticism. Exp. Gerontol. 33, 169–182.

Dirks, A.J., Leeuwenburgh, C., 2006. Caloric restriction in humans: potential pitfalls and health concerns. Mech. Ageing Dev. 127, 1–7.

Duan, W., Guo, Z., Jiang, H., Ware, M., Li, X.J., Mattson, M.P., 2003a. Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. Proc. Natl. Acad. Sci. U.S.A. 100, 2911–2916.

Duan, W., Guo, Z., Jiang, H., Ware, M., Mattson, M.P., 2003b. Reversal of behavioral and metabolic abnormalities, and insulin resistance syndrome, by dietary restriction in mice deficient in brain-derived neurotrophic factor. Endocrinology 144, 2446–2453.

Dunsmore, K.E., Chen, P.G., Wong, H.R., 2001. Curcumin, a medicinal herbal compound capable of inducing heat shock response. Crit. Care Med. 29, 2199–2204.

Eller, M.S., Maeda, T., Magnoni, C., Atwal, D., Gilchrest, B.A., 1997. Enhancement of DNA repair in human skin cells by thymidine dinucleotides: evidence for a p53-mediated mammalian SOS response. Proc. Natl. Acad. Sci. U.S.A. 94, 12627–12632.

Everitt, A.V., 2003. Food restriction, pituitary hormones and ageing. Biogerontology 4, 47–50.

Everitt, A.V., Hilmer, S.N., Brand-Miller, J.C., Jamieson, H.A., Truswell, A.S., Sharma, A.P., Mason, R.S., Morris, B.J., Le Couteur, D.G., 2006. Dietary approaches that delay age-related diseases. Clin. Intervent. Aging 1, 11–31.

Fábián, T.K., Gáspár, J., Fejérdy, L., Kaán, B., Bálint, M., Csermely, P., Fejérdy, P., 2003. Hsp70 is present in human saliva. Med. Sci. Mont. 9, BR62–BR65.

Fábián, T.K., Toth, Z., Fejérdy, L., Kaán, B., Csermely, P., Fejérdy, P., 2004. Photo-acoustic stimulation increases the amount of 70 kDa heat shock protein (Hsp70) in human saliva. A pilot study. Int. J. Psychophysiol. 52, 211–216.

Feder, M.E., Hofmann, G.E., 1999. Heat-shock proteins, molecular chaperones, and the stress response. Annu. Rev. Physiol. 61, 243–282.

Feinendegen, L.E., 2005. Evidence for beneficial low level radiation effects and radiation hormesis. Brit. J. Radiol. 78, 3–7.

Ferrari, C.K.B., 2004. Functional foods, herbs and neutraceuticals: towards biochemical mechanisms of healthy aging. Biogerontology 5, 275–289.

Fischer, A., Morley, J.E., 2002. Antiaging medicine: the good, the bad, and the ugly. J. Gerontol. Med. Sci. 57A, M636–M639.

Fonager, J., Beedholm, R., Clark, B.F.C., Rattan, S.I.S., 2002. Mild stress-induced stimulation of heat shock protein synthesis and improved functional ability of human fibroblasts undergoing aging in vitro. Exp. Gerontol. 37, 1223–1238.

Fontana, L., Meyer, T.E., Klein, S., Holloszy, J.O., 2004. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc. Natl. Acad. Sci. U.S.A. 10, 6659–6663.

Gonzales, B., Manso, R., 2004. Induction, modification and accumulation of HSP70s in the rat liver after acute exercise: early and late responses. J. Physiol. 556, 369–385.

Goto, S., 2006. Health span extension by later-life caloric or dietary restriction: a view based on rodent studies. Biogerontology.

Goukassian, D.A., Helms, E., Van Steeg, H., van Oostrom, C., Bhawan, J., Gilchrest, B.A., 2004. Topical DNA oligonucleotide therapy reduces UV-induced mutations and photocarcinogenesis in hairless mice. Proc. Natl. Acad. Sci. U.S.A. 101, 3933–3938.

Guarante, L., Picard, F., 2005. Calorie restriction—the SIR connection. Cell 120, 473–482.

Guo, Z., Heydari, A., Richardson, A., 1998. Nucleotide excision repair of actively transcribed versus nontranscribed DNA in rat hepatocytes: effect of age and dietary restriction. Exp. Cell Res. 245, 228–238.

Gurib-Fakim, A., 2006. Medicinal plants: traditions of yesterday and drugs of tomorrow. Mol. Asp. Med. 27, 1–93.

Hahn, J.S., Hu, Z.W., Thiele, D.J., Iyer, V.R., 2004. Genome-wide analysis of the biology of stress responses through heat shock trasncription factor. Mol. Cell. Biol. 24, 5249–5256.

Harris, N., MacLean, M., Hatzianthis, K., Panaretou, B., Piper, P.W., 2001. Increasing *Saccharomyces cerevisiae* stress resistance, through the overactivation of the heat shock response resulting from defects in the Hsp90 chaperone, does not extend replicative life span but can be associated with slower chronological ageing of nondividing cells. Mol. Genet. Genomics 265, 258–263.

Hayakawa, N., Ohtaki, M., Ueoka, H., Matsuura, M., Munaka, M., Kurihara, M., 1989. Mortality statistics of major causes of death among atomic bomb survivors in Hiroshima Prefecture from 1968 to 1982. Hiroshima J. Med. Sci. 38, 53–67.

Hayes, D.P., 2005. The protective role of fruits and vegetables against radiation-induced cancer. Nutr. Rev. 63, 303–311.

Hayes, D.P., 2007. Nutritional hormesis. Eur. J. Clin. Nutr. 61, 147–159.

Hayflick, L., 2007. Biological aging is no longer an unsolved problem. Ann. N.Y. Acad. Sci. 1100, 1–13.

Heilbronn, L.K., L, d.J., Frisard, M.I., DeLany, J.P., Larson-Meyer, D.E.R.J., Nguyen, T., Martin, C.K., Volaufova, J., Most, M.M., Greenway, F.L., Smith, S.R., Deutsch, W.A., Williamson, D.A., Ravussin, E., 2006. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals. JAMA 295, 1539–1548.

Hercus, M.J., Loeschcke, V., Rattan, S.I.S., 2003. Lifespan extension of *Drosophila melanogaster* through hormesis by repeated mild heat stress. Biogerontology 4, 149–156.

Heydari, A.R., You, S., Takahashi, R., Gutsmann-Conrad, A., Sarge, K.D., Richardson, A., 2000. Age-related alterations in the activation of heat shock transcription factor 1 in rat heapatocytes. Exp. Cell Res. 256, 83–93.

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., 1995. Understanding Ageing. Cambridge University Press, Cambridge, UK.

Holliday, R., 2000. Ageing research in the next century. Biogerontology 1, 97–101.

Holliday, R., 2006a. Aging is no longer an unsolved problem in biology. Ann. N.Y. Acad. Sci. 1067, 1–9.

Holliday, R., 2006b. Food, fertility and longevity. Biogerontology 7, 139–141.

Holliday, R., 2007. Ageing: The Paradox of Life. Springer, Dordrecht, The Netherlands.

Holloszy, J.O., Smith, E.K., 1986. Longevity of cold-exposed rats: a reevaluation of the rate of living theory. J. Appl. Physiol. 61, 1656–1660.

Ina, Y., Sakai, K., 2005. Further study of prolongation of life span associated with immunologic modification by chronic low-dose-rate irradiation in MRL-lpr/lpr mice: effects of whole-life irradiation. Radiat. Res. 163, 418–423.

Ina, Y., Tanooka, H., Yamada, T., Sakai, K., 2005. Suppression of thymic lymphoma induction by life-long low-dose-rate irradiation accompanied by immune activation in C57BL/6 mice. Radiat. Res. 163, 153–158.

Ingram, D.K., Roth, G.S., Lane, M.A., Ottinger, M.A., Zou, S., de Cabo, R., Mattison, J.A., 2006. The potential for dietary restriction to increase longevity in humans: extrapolation from monkey studies. Biogerontology.

Ji, L.L., 2006. Oxidative stress and antioxidative defense: effects of aging and exercise. In: Alessio, H.M., Hagerman, A.E. (Eds.), Oxidative Stress, Exercise and Aging. Imperial College Press, London, pp. 85–108.

Ji, L.L., Gomez-Cabrera, M.C., Vina, J., 2006. Exercise and hormesis: activation of cellular antioxidant signaling pathway. Ann. N.Y. Acad. Sci. 1067, 425–435.

Joe, B., Vijaykumar, M., Lokesh, B.R., 2004. Biological properties of curcumin—cellular and molecular mechanism of action. Crit. Rev. Food Sci. Nutr. 44, 97–111.

Johnson, T.E., 2002. A personal retrospective on the genetics of aging. Biogerontology 3, 7–12.

Keany, M., Matthijssens, F., Sharpe, M., Vanfleteren, J., Gems, D., 2004. Superoxide dismutase mimetics elevate superoxide dismutase activity in vivo but do not retard aging in the nematode *Caenorhabditis elegans*. Free Radic. Biol. Med. 37, 239–250.

Khazaeli, A.A., Tatar, M., Pletcher, S.D., Curtsinger, J.W., 1997. Heat-induced longevity extension in *Drosophila*. I. Heat treatment, mortality, and thermotolerance. J. Gerontol. Biol. Sci. 52A, B48–B52.

Klebanov, S., Diais, S., Stavinoha, W.B., Suh, Y., Nelson, J.F., 1995. Hyperadrenocorticism, attenuated inflammation, and the life-prolonging action of food restriction in mice. J. Gerontol. Biol. Sci. 50, B79–B82.

Koubova, J., Guarante, L., 2003. How does calorie restriction work? Genes Dev. 17, 313–321.

Kyriazis, M., 2003. Practical applications of chaos theory to the modulation of human ageing: nature prefers chaos to regularity. Biogerontology 4, 75–90.

Lamb, M.J., 1964. The effect of radiation on the longevity of female *Drosophila subobscura*. J. Insect Physiol. 10, 487–497.

Lamming, D.W., Wood, J.G., Sinclair, D.A., 2004. Small molecules that regulate lifespan: evidence for xenohormesis. Mol. Microbiol. 53, 1003–1009.

Lancaster, G.I., Møller, K., Nielsen, B., Secher, N.H., Febbraio, M.A., Nybo, L., 2004. Exercise induces the release of heat shock protein 72 from the human brain in vivo. Cell Stress Chaperon. 9, 276–280.

Le Bourg, E., 2005. Hormetic protection of *Drosophila melanogaster* middle-aged male flies from heat stress by mildly stressing them at young age. Naturwissenchaften 92, 293–296.

Le Bourg, E., 2006. Dietary restriction would probably not increase longevity in human beings and other species able to leave unsuitable environments. Biogerontology 7, 149–152.

Le Bourg, E., Fournier, D., 2004. Is lifespan extension accompanied by improved antioxidant defences? A study of superoxide dismutase and catalase in *Drosophila melanogaster* flies that lived in hypergravity at young age. Biogerontology 5, 261–264.

Le Bourg, E., Minois, N., Bullens, P., Baret, P., 2000. A mild stress due to hypergravity exposure at young age increases longevity in *Drosophila melanogaster* males. Biogerontology 1, 145–155.

Le Bourg, E., Rattan, S.I.S., 2006. Can dietary restriction increase longevity in all species, particularly in human beings? Introduction to a debate among experts. Biogerontology 7.

Le Bourg, E., Valenti, P., Lucchetta, P., Payre, F., 2001. Effects of mild heat shocks at young age on aging and longevity in *Drosophila melanogaster*. Biogerontology 2, 155–164.

Linnane, A.W., Eastwood, H., 2006. Cellular redox regulation and prooxidant signaling systems. A new perspective on the free radical theory of aging. Ann. N.Y. Acad. Sci. 1067, 47–55.

Lithgow, G.J., White, T.M., Melov, S., Johnson, T.E., 1995. Thermotolerance and extended life-span conferred by single-gene mutations and induced by thermal stress. Proc. Natl. Acad. Sci. U.S.A. 92, 7540–7544.

Liu, D., Chan, S.L., de Souza-Pinto, N.C., Slevin, J.R., Wersto, R.P., Zhan, M., Mustafa, K., de Cabo, R., Mattson, M.P., 2006. Mitochondrial UCP4 mediates an adaptive shift in energy metabolism and increases the resistance of neurons to metabolic and oxidative stress. Neuromol. Med. 8, 389–414.

Liu, D., Vandahl, B.B., Birkelund, S., Nielsen, L.B., Melsen, B., 2004. Secretion of osteopontin from MG-63 cells under a physiological level of mechanical strain in vitro—a [35S] incorporation approach. Eur. J. Orthodont. 26, 143–149.

Liu, R., Liu, I.Y., Bi, X., Thompson, R.F., Doctrow, S.R., Malfroy, B., Baudry, M., 2003. Reversal of age-related learning deficits and brain oxidative stress in mice with superoxide dismutase/catalase mimetics. Proc. Natl. Acad. Sci. U.S.A. 100, 8526–8531.

Martin, B., Mattson, M.P., Maudsley, S., 2006. Caloric restriction and intermittent fasting: two potential diets for successful aging. Ageing Res. Rev. 5, 332–353.

Martínez, D.E., 1996. Rejuvenation of the disposable soma: repeated injury extends lifespan in an asexual annelid. Exp. Gerontol. 31, 699–704.

Masoro, E.J., 1998. Hormesis and the antiaging action of dietary restriction. Exp. Gerontol. 33, 61–66.

Masoro, E.J., 2006a. Caloric restriction and aging: controversial issues. J. Gerontol. A Biol. Sci. Med. Sci. 61, 14–19.

Masoro, E.J., 2006b. Dietary restriction-induced life extension: a broadly based biological phenomenon. Biogerontology 7, 153–155.

Masoro, E.J., 2007. The role of hormesis in life extension by dietary restriction. Interdiscip. Top. Gerontol. 35, 1–17.

Maswood, N., Young, J., Tilmont, E., Zhang, Z., Gash, D.M., Gerhardt, G.A., Grondin, R., Roth, G.S., Mattison, J., Lane, M.A., Carson, R.E., Cohen, R.M., Mouton, P.R., Quigley, C., Mattson, M.P., Ingram, D.K., 2004. Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease. Proc. Natl. Acad. Sci. U.S.A. 101, 18171–18176.

McArdle, A., Dillmann, W.H., Mestril, R., Faulkner, J.A., Jackson, M.J., 2004. Overexpression of HSP70 in mouse skeletal muscle protects against muscle damage and age-related muscle dysfunction. FASEB J. 18, 355–357.

McArdle, A., Vasilaki, A., Jackson, M., 2002. Exercise and skeletal muscle ageing: cellular and molecular mechanisms. Ageing Res. Rev. 1, 79–93.

Melov, S., Ravenscroft, J., Malik, S., Gill, M.S., Walker, D.W., Clayton, P.E., Wallace, D.C., Malfroy, B., Doctrow, S.R., Lithgow, G.J., 2000. Extension of life-span with superoxide dismutase/catalase mimetics. Science 289, 1567–1569.

Meyer, T.E., Kovács, S.K., Ehsani, A.A., Klein, S., Holloszy, J.O., Fontana, L., 2006. Long-term caloric restriction ameliorates the decline in diastolic functions in humans. J. Am. Coll. Cardiol. 47, 398–402.

Michalski, A.I., Johnson, T.E., Cypser, J.R., Yashin, A.I., 2001. Heating stress patterns in *Caenorhabditis elegans* longevity and survivorship. Biogerontology 2, 35–44.

Mine, M., Okumura, Y., Ichimaru, M., Nakamura, T., Kondo, S., 1990. Apparently beneficial effect of low to intermediate doses of A-bomb radiation on human lifespan. Int. J. Radiat. Biol. 58, 1035–1043.

Minois, N., 2000. Longevity and aging: beneficial effects of exposure to mild stress. Biogerontology 1, 15–29.

Minois, N., 2006. The hormetic effects of hypergravity on longevity and aging. Dose-response 4, 123–132.

Minois, N., Khazaeli, A.A., Curtsinger, J.W., 2001. Locomotor activity as a function of age and life span in *Drosophila melanogaster* overexpressing hsp70. Exp. Gerontol. 36, 1137–1153.

Minois, N., Le Bourg, E., 1999. Resistance to stress as a function of age in *Drosophila melanogaster* living in hypergravity. Mech. Ageing Dev. 109, 53–64.

Minois, N., Rattan, S.I.S., 2003. Hormesis in aging and longevity. In: Modulating Aging and Longevity. Kluwer Academic Publishers, Rattan, S.I.S. Dordrecht, pp. 127–137.

Minois, N., Vaynberg, S., 2002. Fecundity and life span in transgenic *Drosophila melanogaster* overexpressing hsp70. Biogerontology 3, 301–306.

Mobbs, C.V., G.A., B., Atkinson, R.L., Bartke, A., Finch, C.E., Maratos-Flier, E., Crawley, J.N., Nelson, J.F., 2001. Neuroendocrine and pharmacological manipulations to assess how caloric restriction increases life span. J. Gerontol. Biol. Sci. 56 (special no. 1), 34–44.

Mocchegiani, E., Muzzioli, M., Giacconi, R., 2000. Zinc, metallothioneins, immune responses, survival and ageing. Biogerontology 1, 133–143.

Mocchegiani, E., Rink, L., Blasco, M.A., 2006. Zinc and ageing (ZINCAGE project). Biogerontology 7, 305–306.

Mockett, R.J., Cooper, T.M., Orr, W.C., Sohal, R.S., 2006. Effects of caloric restriction are species-specific. Biogerontology.

Moos, P.J., Edes, K., Mullally, J.E., Fitzpatrick, F.A., 2004. Curcumin impairs tumour suppressor p53 function in colon cancer cells. Carcinogenesis 25, 1611–1617.

Moriguchi, T., Saito, H., Nishiyama, N., 1996. Aged garlic extract prolongs longevity and improves spatial memory deficit in senescence-accelerated mouse. Biol. Pharm. Bull. 19, 305–307.

Mutch, D.M., Wahli, W., Williamson, G., 2005. Nutrigenomics and nutrigenetics: the emerging faces of nutrition. FASEB J. 19, 1602–1616.

Nemoto, S., Fergusson, M.M., Finkel, T., 2004. Nutrient availability regulates SIRT1 through a orkhead-dependent pathway. Science 306, 2105–2108.

Nielsen, E.R., Eskildsen-Helmond, Y., Rattan, S.I.S., 2006. MAP-kinases and heat shock-induced hormesis in human fibroblasts during serial passaging in vitro. Ann. N.Y. Acad. Sci. 1067, 343–348.

Nørgaard, R., Kassem, M., Rattan, S.I.S., 2006. Heat shock-induced enhancement of osteoblastic differentiation of hTERT-immortlized mesenchymal stem cells. Ann. N.Y. Acad. Sci. 1067, 443–447.

Okajima, S., Mine, M., Nakamura, T., 1985. Mortality of registered A-bomb survivors in Nagasaki, Japan, 1970–1984. Radiat. Res. 103, 419–431.

Olsen, A., Vantipalli, M.C., Lithgow, G.J., 2006. Lifespan extension of *Caenorhabditis elegans* following repeated mild hormetic heat treatments. Biogerontology 7, 221–230.

Ordy, J.M., Samorajski, T., Zeman, W., Curtis, H.J., 1967. Interaction effects of environmental stress and deutron irradiation of the brain on mortality and longevity of C57BL/10 mice. Proc. Soc. Exp. Biol. Med. 126, 184–190.

Overgaard, J., Sørensen, J.G., Petersen, S.O., Loeschcke, V., Holmstrup, M., 2005. Changes in membrane lipid composition following rapid cold hardening in *Drosophila melanogaster*. J. Insect Physiol. 51, 1173–1182.

Padgett, R.W., Glaser, R., 2003. How stress influences the immune response. Trends Immunol. 24, 444–448.

Park, H.G., Han, S.I., Oh, S.Y., Kang, H.S., 2005. Cellular responses to mild heat stress. Cell. Mol. Life Sci. 62, 10–23.

Parsons, P.A., 2000. Caloric restriction, metabolic efficiency and hormesis. Hum. Exp. Toxicol. 19, 345–347.

Parsons, P.A., 2003. Energy, stress and the invalid linear no-threshold premise: a generalization illustrated by ionizing radiation. Biogerontology 4, 227–231.

Phelan, J.P., Rose, M.R., 2006. Caloric restriction increases longevity substantially only when the reaction norm is steep. Biogerontology 7, 161–164.

Pollycove, M., Feinendegen, L.E., 2001. Biologic responses to low doses of ionizing radiation: detriment versus hormesis. Part 2. Dose responses of organisms. J. Nucl. Med. 42, 26N–37N.

Pratsinis, H., Tsagarakis, S., Zervolea, I., Giannakopoulos, F., Stathakos, D., Thalassinos, N., Kletsas, D., 2002. Chronic in vivo exposure to glucocorticoids prolongs cellular lifespan: the case of Cushing's syndrome-patients' fibroblasts. Exp. Gerontol. 37, 1237–1245.

Putman, C.T., Sultan, K.R., Wassmer, T., Bamford, J.A., Skorjanc, D., Pette, D., 2001. Fiber-type transitions and satellite cell activation in low-frequency-stimulated muscles of young and aging rats. J. Gerontol. Biol. Sci. 56A, B510–B519.

Radak, Z., Chung, H.Y., Goto, S., 2005. Exercise and hormesis: oxidative stress-related adaptation for successful aging. Biogerontology 6, 71–75.

Radák, Z., Nakamura, A., Nakamoto, H., Asano, K., Ohno, H., Goto, S., 1998. A period of anaerobic exercise increases the accumulation of reactive carbonyl derivatives in the lungs of rats. Eur. J. Physiol. 435, 439–441.

Raji, N.S., Surekha, A., Subba Rao, K., 1998. Improved DNA-repair parameters in PHA-stimulated peripheral blood lymphocytes of human subjects with low body mass index. Mech. Ageing Dev. 104, 133–148.

Rashmi, R., Santhosh Kumar, T.R., Karunagaran, D., 2003. Human colon cancer cells differ in their sensitivity to cucumin-induced apoptosis and heat shock protects them by inhibiting the release of apoptosis-inducing factor and caspases. FEBS Lett. 538, 19–24.

Rattan, S.I.S., 1998. Repeated mild heat shock delays ageing in cultured human skin fibroblasts. Biochem. Mol. Biol. Int. 45, 753–759.

Rattan, S.I.S., 2001a. Applying hormesis in aging research and therapy. Hum. Exp. Toxicol. 20, 281–285.

Rattan, S.I.S., 2001b. Hormesis in biogerontology. Crit. Rev. Toxicol. 31, 663–664.

Rattan, S.I.S., 2002. N6-furfuryladenine (kinetin) as a potential anti-aging molecule. J. Anti-aging Med. 5, 113–116.

Rattan, S.I.S., 2004. Aging intervention, prevention, and therapy through hormesis. J. Gerontol. Biol. Sci. 59A, 705–709.

Rattan, S.I.S., 2005. Anti-ageing strategies: prevention or therapy? EMBO Reports, vol. 6. pp. S25–S29.

Rattan, S.I.S., 2006. Theories of biological aging: genes, proteins and free radicals. Free Radic. Res. 40, 1230–1238.

Rattan, S.I.S., 2007. Homeostasis, homeodynamics, and aging. In: Encyclopedia of Gerontology. Elsevier Inc., Birren, J. UK, pp. 696–699.

Rattan, S.I.S., Ali, R.E., 2007. Hormetic prevention of molecular damage during cellular aging of human fibroblasts and keratinocytes. Ann. N.Y. Acad. Sci. 1100, 424–430.

Rattan, S.I.S., Clark, B.F.C., 1994. Kinetin delays the onset of ageing characteristics in human fibroblasts. Biochem. Biophys. Res. Commun. 201, 665–672.

Rattan, S.I.S., Clark, B.F.C., 2005. Understanding and modulating ageing. IUBMB Life 57, 297–304.

Ritzmann, R.F., Glasky, A., Steinberg, A., Melchior, C.L., 1994. The interaction of ethanol with the cognitive enhancers tacrine, physostigmine, and AIT-082. J. Gerontol. 49, B51–B53.

Rogina, B., Helfand, S.L., 2004. Sir2 mediates longevity in the fly through a pathway related to calorie restriction. Proc. Natl. Acad. Sci. U.S.A. 101, 15998–16003.

Rubin, C., Turner, A.S., Bain, S., Mallinckrodt, C., McLeod, K., 2001. Low mechanical signals strengthen long bones. Nature 412, 603–604.

Rubinsztein, D.C., 2006. The roles of intracellular protein-degradation pathways in neurodegeneration. Nature 443, 780–786.

Sacher, G.A., 1963. Effect of X-rays on the survival of *Drosophila imagoes*. Physiol. Zool. 36, 295–311.

Safwat, A., 2000. The role of low-dose total body irradiation in treatment of non-Hodgkins lymphoma: a new look at an old method. Radiother. Oncol. 56, 1–8.

Segerstrom, S.C., Miller, G.E., 2004. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol. Bull. 130, 601–630.

Selkoe, D.J., 1992. Aging brain, aging mind. Sci. Am. 267, 135–142.

Selsby, J.T., Judge, A.R., Yimlamai, D., Leeuwenburgh, C., Dodd, S.L., 2005. Life long calorie restriction increases heat shock proteins and proteasome activity in soleus muscle of Fischer 344 rats. Exp. Gerontol. 40, 37–42.

Semsei, I., Rao, G., Richardson, A., 1989. Changes in the expression of superoxide dismutase as a function of age and dietary restriction. Biochem. Biophys. Res. Commun. 164, 620–625.

Shama, S., Lai, C.-Y., Antoniazzi, J.M., Jiang, J.C., Jazwinski, S.M., 1998. Heat stress-induced life span extension in yeast. Exp. Cell Res. 245, 379–388.

Shanley, D.P., Kirkwood, T.B., 2006. Caloric restriction does not enhance longevity in all species and is unlikely to do so in humans. Biogerontology.

Sharma, S., Kaur, G., 2005. Neuroprotective potential of dietary restriction against kainate-induced excitotoxicity in adult male Wistar rats. Brain Res. Bull. 67, 482–491.

Shibatani, T., Nazir, M., ward, W.F., 1996. Alteration of rat liver 20S proteasome activities by age and food restriction. J. Gerontol. Biol. Sci. 51A, B316–B322.

Shibatani, T., Ward, W.F., 1996. Effect of age and food restriction on alkaline protease activity in rat liver. J. Gerontol. Biol. Sci. 51A, B175–B178.

Short, K.R., Vittone, J.L., Bigelow, M.L., Proctor, D.N., Nair, K.S., 2004. Age and aerobic exercise training effects on whole body muscle protein metabolism. Am. J. Phsyiol. Endocrinol. Metab. 286, E92–E101.

Singh, A.M.F., 2002. Exercise comes of age: rationale and recommendations for geriatric exercise prescription. J. Gerontol. Med. Sci. 57A, M262–M282.

Singh, R., Kølvraa, S., Bross, P., Christensen, K., Gregersen, N., Tan, Q., Jensen, U.B., Eiberg, H., Rattan, S.I.S., 2006a. Heat-shock protein 70 genes and human longevity. A view from Denmark. Ann. N.Y. Acad. Sci. 1067, 301–308.

Singh, R., Kølvraa, S., Bross, P., Gregersen, N., Nexø, B.A., Frederiksen, H., Christensen, K., Rattan, S.I.S., 2004. Association between low self-rated health and heterozygosity for -110A-C polymorphism in the promoter region of HSP70-1 in aged Danish twins. Biogerontology 5, 169–176.

Singh, R., Kølvraa, S., Bross, P., Jensen, U.B., Gregersen, N., Tan, Q., Knudese, C., Rattan, S.I.S., 2006b. Reduced heat shock response in human mononuclear cells during aging and its association with polymorphisms on HSP70 genes. Cell Stress Chaperon. 11, 208–215.

Sogawa, H., Kubo, C., 2000. Influence of short-term repeated fasting on the longevity of female (NZB × NZW) F1 mice. Mech. Ageing Dev. 115, 61–71.

Sohal, R.S., Weindruch, R., 1996. Oxidative stress, calorie restriction, and aging. Science 273, 59–63.

Sørensen, J.G., Kristensen, T.N., Loeschcke, V., 2003. The evolutionary and ecological role of heat shock proteins. Ecol. Lett. 6, 1025–1037.

Sørensen, J.G., Loeschcke, V., 2001. Larval crowding in *Drosophila melanogaster* induces Hsp70 expression, and leads to increased adult longevity and adult thermal stress resistance. J. Insect Physiol. 47, 1301–1307.

Sun, Y., MacRae, T.H., 2005. The small heat shock proteins and their role in human disease. FEBS J. 272, 2613–2627.

Suzuki, K., Kodama, S., Watanabe, M., 1998a. Suppressive effects of low-dose preirradiation on genetic instability induced by X rays in normal embryonic cells. Radiat. Res. 150, 656–662.

Suzuki, K., Kodama, S., Watanabe, M., 2001. Extremely low-dose ionizing radiation causes activation of mitogen-activated protein kinase pathway and enhances proliferation of normal human diploid cells. Cancer Res. 61, 5396–5401.

Suzuki, M., Yang, Z., Nakano, K., Yatagai, F., Suzuki, K., Kodama, S., Watanabe, M., 1998b. Extension of in vitro life-span of gamma-irradiated human embryo cells accompanied by chromosome instability. J. Radiat. Res. 39, 203–213.

Svendsen, L., Rattan, S.I.S., Clark, B.F.C., 1994. Testing garlic for possible anti-ageing effects on long-term growth characteristics, morphology and macromolecular synthesis of human fibroblasts in culture. J. Ethnopharm. 43, 125–133.

Thayer, K.A., Melnick, R., Huff, J., Burns, K., Davis, D., 2006. Hormesis: a new religion? Environ. Health Perspect. 114, A632–A633.

Tsutsui, T., Tanaka, Y., Matsudo, Y., Hasegawa, K., Fujino, T., Kodama, S., Barrett, J.C., 1997. Extended lifespan and immortalization of human fibroblasts induced by X-ray irradiation. Mol. Carcinog. 18, 7–18.

Vaiserman, A.M., Koshel, N.M., Litoshenko, A.Y., Mozzhukhina, T.G., Voitenko, V.P., 2003. Effects of X-irradiation in early ontogenesis on the longevity and amount of the S1 nuclease-sensitive DNA sites in adult *Drosophila melanogaster*. Biogerontology 4, 9–14.

Valenzano, D.R., Terzibasi, E., Genade, T., Cattaneo, A., Domenici, L., Cellerino, A., 2006. Resveratrol prolongs lifespan and retards the onset of age-related markers in a short-lived vertebrate. Curr. Biol. 16, 296–300.

Verbeke, P., Clark, B.F.C., Rattan, S.I.S., 2000. Modulating cellular aging in vitro: hormetic effects of repeated mild heat stress on protein oxidation and glycation. Exp. Gerontol. 35, 787–794.

Verbeke, P., Clark, B.F.C., Rattan, S.I.S., 2001a. Reduced levels of oxidized and glycoxidized proteins in human fibroblasts exposed to repeated mild heat shock during serial passaging in vitro. Free Radic. Biol. Med. 31, 1593–1602.

Verbeke, P., Deries, M., Clark, B.F.C., Rattan, S.I.S., 2002. Hormetic action of mild heat stress decreases the inducibility of protein oxidation and glycoxidation in human fibroblasts. Biogerontology 3, 105–108.

Verbeke, P., Fonager, J., Clark, B.F.C., Rattan, S.I.S., 2001b. Heat shock response and ageing: mechanisms and applications. Cell Biol. Int. 25, 845–857.

Vermeulen, C.J., Loeschcke, V., 2007. Longevity and the stress response in *Drosophila*. Exp. Gerontol. 42, 153–159.

Viswanathan, K., Dhabhar, F.S., 2005. Stress-induced enhancement of leukocyte trafficking into sites of surgery or immune activation. Proc. Natl. Acad. Sci. U.S.A. 102, 5808–5813.

Wakatsuki, T., Schlessinger, J., Elson, E.L., 2004. The biochemical response of the heart to hypertension and exercise. Trends Biochem. Sci. 29, 609–617.

Walford, R.L., Mock, D., Verdery, R., MacCallum, T., 2002. Calorie restriction in biosphere 2: alterations in physiologic, hematologic, hormonal, and biochemical parameters in humans restricted for a 2-year period. J. Gerontol. Biol. Sci. 57A, B211–B224.

Warden, S.J., Fuchs, R.K., Castillo, A.B., Nelson, I.R., Turner, C.H., 2007. Exercise when young provides lifelong benefits to bone structure and strength. J. Bone Miner. Res. 22, 251–259.

Watanabe, M., Suzuki, M., Suzuki, K., Nakano, K., Watanabe, K., 1992. Effect of multiple irradiation with low doses of gamma-rays on morphological transformation and growth ability of human embryo cells in vitro. Int. J. Radiat. Biol. 62, 711–718.

Weindruch, R., 2006. Will dietary restriction work in primates? Biogerontology 7, 169–171.

Westerheide, S.D., Bosman, J.D., Mbadugha, B.N.A., Kawahara, T.L.A., Matsumoto, G., Kim, S., Gu, W., Devlin, J.P., Silverman, R.B., Morimoto, R.I., 2004. Celastrols as inducers of the heat shock response and cytoprotection. J. Biol. Chem. 279, 56053–56060.

Wolff, S., 1996. Aspects of the adaptive response to very low doses of radiation and other agents. Mutat. Res. 358, 135–142.

Wood, J.G., Rogina, B., Lavu, S., Howitz, K.T., Helfand, S.L., Tatar, M., Sinclair, D.A., 2004. Sirtuin activators mimic caloric restriction and delay ageing in metazoans. Nature 430, 686–689.

Wyngaarden, K.E.V., Pauwels, E.K.J., 1995. Hormesis: are low doses of ionizing radiation harmful or beneficial? Eur. J. Nucl. Med. 22, 481–486.

Yan, D., Saito, K., Ohmi, Y., Fujie, N., Ohtsuka, K., 2004. Paeoniflorin, a novel heat shock protein-inducing compound. Cell Stress Chaperon. 9, 378–389.

Yashin, A.I., Cypser, J.R., Johnson, T.E., Michalski, A.I., Boyko, S.I., Novoseltsev, V.N., 2001. Ageing and survival after different doses of heat shock: the results of analysis of data from stress experiments with the nematode worm *Caenorhabditis elegans*. Mech. Ageing Dev. 122, 1477–1495.

Yates, F.E., 1994. Order and complexity in dynamical systems: homeodynamics as a generalized mechanics for biology. Math. Comput. Model 19, 49–74.

Yokoyama, K., Fukumoto, K., Murakami, T., Harada, S., Hosono, R., Wadhwa, R., Mitsui, Y., Ohkuma, S., 2002. Extended longevity of *Caenorhabditis elegans* by knocking in extra copies of hsp70F, a homolog of mot-2 (mortalin)/mthsp70/Grp75. FEBS Lett. 516, 53–57.

Yu, B.P., 2006. Why calorie restriction would work for human longevity. Biogerontology.

Yu, B.P., Chung, H.Y., 2001. Stress resistance by caloric restriction for longevity. Ann. N.Y. Acad. Sci. 928, 39–47.

Zapponi, G.A., Marcello, I., 2006. Low-dose risk, hormesis, analogical and logical thinking. Ann. N.Y. Acad. Sci. 1076, 839–857.

Zervolea, I., Pratsinis, H., Tsagarakis, S., Karavitaki, N., Stathakos, D., Thalassinos, N., Kletsas, D., 2005. The impact of chronic in vivo glucocorticoid excess on the functional characteristics of human skin fibroblasts obtained from patients with endogeneous Cushing's syndrome. Eur. J. Endocrinol. 152, 895–902.