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The Future of Aging Interventions

Aging Intervention, Prevention, and Therapy Through Hormesis

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The phenomenon of hormesis is represented by mild stress-induced stimulation of maintenance and repair pathways resulting in beneficial effects for the cells and organisms. Anti-aging and life-prolonging effects of a wide variety of the so-called stressors, such as pro-oxidants, aldehydes, calorie restriction, irradiation, heat shock, and hypergravity, have been reported. Molecular mechanisms of hormesis due to different stresses are yet to be elucidated, but there are indications that relatively small individual hormetic effects become biologically amplified resulting in the collective significant improvement of cellular and organismic functions and survival. Accepting that some important issues with respect to establishing the optimal hormetic conditions still need to be resolved by future research, hormesis appears to be a promising and effective approach for modulating aging, for preventing or delaying the onset of age-related diseases, and for improving quality of life in old age.

THE phenomenon in which adaptive responses to low doses of otherwise harmful conditions improve the functional ability of cells and organisms is known as *hormesis* (1–5). A wide variety of physical, chemical, and biological agents exhibit hormetic effects, including heavy metals, pesticides, antibiotics, chemotherapeutic agents, ethanol, aldehydes, chloroform, pro-oxidants, hypergravity, and ionizing radiation. Several meta-analyses performed on thousands of 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 U-shaped or inverted U-shaped, depending on the end point being measured (1–3).

The key conceptual features of hormesis are the disruption of homeostasis, the modest overcompensation, the reestablishment of homeostasis, and the adaptive nature of the process (1). Traditionally, homeostasis is defined as the maintenance of a constant internal state for efficient functioning and performance of the organism. However, convincing arguments have been put forward to replace the term homeostasis with *homeodynamics*, taking into account the dynamic nature of living processes in an ever-changing life line (6). 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. Thermoregulation, detoxification, cell proliferation/apoptosis, DNA repair, heat shock protein synthesis, protein turnover, and antioxidative responses are some of the crucial homeodynamic responses (5,7). Often, these mechanisms are common to several stresses as well as different species, and have been given a collective term ''the general-adaptive syndrome,'' by virtue of which biological survival is possible (8).

Aging, on the other hand, is characterized by a decrease in adaptive abilities due to progressive failure of maintenance (7,9,10). Therefore, it is opined that if cells and organisms are exposed to brief periods of *mild* stress so that their stress response-induced gene expression is up-regulated and the related pathways of maintenance and repair are stimulated, one should observe anti-aging, health-improving, and longevity-promoting hormetic effects. The paradigm for 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 various harmful substances such as free radicals, acids, and aldehydes (11,12).

Since the harmful effects of severe stress have long shadowed the hormetic effects of low-level stress, applying hormesis in aging research and therapy is a relatively recent development (5,13–15). What follows is a brief review of the published literature on various hormetic agents that have been shown to slow down aging and prolong the life span of cells and organisms [for other recent reviews, see (13,15)]. This is followed by a discussion of the possible molecular mechanisms involved in hormesis and of the issues remaining to be resolved before hormesis can be applied in human aging intervention, prevention, and therapy.

Irradiation

Radiation hormesis was one of the first to be studied in relation to aging and longevity (16). Whereas high doses of

irradiation decrease life span (17), low doses of irradiation enhance mean life span in *Drosophila melanogaster* (17,18) and *Musca domestica* (19). It has been argued that irradiation leads to female sterility and that the life span increase is thus an outcome of decreased fecundity (17). It was also shown that mutant females without ovaries did not exhibit increased life span after irradiation. The environmental conditions influenced the life span of male house flies differently after exposure to a low dose of irradiation (19). The increased life span 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 life spans. Furthermore, irradiated flies had longer life spans than controls only when the latter were kept on suboptimal rearing conditions (15). An increase in the life span of gamma ray-exposed female mice has also been reported (20). Hormetic effects of low-dose irradiation on the proliferative ability, genomic stability, and activation of mitogen-activated protein kinase pathways have been reported for human diploid cells (21–23). In contrast to this, some studies have failed to show an increased life span after low-dose irradiation. For instance, deuteron-irradiated mice exhibit higher mortality rates and lower life span in both sexes than nonirradiated ones (15). There is also a report of lack of life span extension in *Caenorhabditis elegans* after gamma irradiation at 104 rad (24).

Temperature

Temperature stress is extensively used in the study of hormesis, not only because it is easy to implement and gives consistent results, but also because heat stress mainly acts through an evolutionarily highly conserved stress response pathway known as the heat shock (HS) response (25). Wild-type and *age-1* mutant hermaphrodite *C. elegans* exposed for 3–24 hours to 30°C exhibited a significant increase in mean life span compared with controls (26). Similarly, a 6-hour exposure at 30°C of wild-type worms induced a 12.5% increase in life span, but no effect was found after exposures of 2 or 4 hours (27). In a series of articles (28–30), 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 no longer than 2 hours produced an extension of life span in animals. In contrast, longer HS had either no effect (3-hour HS) or deleterious effects (exposures longer than 3 hours). In a study of multiple stresses in *C. elegans*, an extension of life span after 1 and 2 hours HS at 35°C was reported (24). Longer HS had either no effect (3 hours) or deleterious effects (4 hours and more). The same effects of different HS were observed on thermotolerance (survival time at 35°C).

Virgin males of inbred lines of *D. melanogaster* exhibited a 2-day increase in mean life span and lower mortality rates during several weeks after a heat treatment of 36°C for 70 minutes (31). 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 minutes a day, 5 days a week for 1 week to 37°C live, an average of 2 days longer than the control flies (32). Longer exposures had either no effect or negative effect on life span. In our recent studies on *D. melanogaster*, exposure of young flies to four rounds of mild HS at 34°C significantly increased the average and maximum life span of female flies and increased their resistance to potentially lethal heat stress (33).

Studies also have been performed on the effect of subjecting transgenic *D. melanogaster*, over-expressing the inducible Hsp70, to 20 minutes at 36°C in an incubator under saturated humidity (15,34). In the control ''parental'' line, such an exposure significantly increased the life span 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 (15).

Other examples of the effects of thermal stress on longevity include the following. A 2-hour HS at 37°C applied before the first division and after the fourth division extended the replicative life span of *Saccharomyces cerevisiae* by 10% (35). The same HS had no effect if applied later in life as well as if applied every day. Irradiated and nonirradiated mice, intermittently cold-shocked, showed lower rates of mortality in nonirradiated males as well as in both sexes in irradiated mice. Longer life spans were observed in thermally stressed nonirradiated males and irradiated females. Finally, rats kept in water set at 23°C, 4 hours a day, 5 days a week, had a 5% increase in average life span (15). In addition, this treatment seemed to diminish the occurrence of certain age-related diseases.

During the last few years, research done in our laboratories has shown hormetic effects of mild HS on human skin fibroblasts. Using a mild stress regime of exposing serially passaged human fibroblasts to 41°C for 1 hour twice a week throughout their replicative life span in vitro, we have reported several beneficial anti-aging effects. These effects include the maintenance of youthful morphology, reduced accumulation of oxidatively and glycoxidatively damaged proteins (14,36–38), increased levels of various HS proteins, increased antioxidative abilities, increased resistance to ethanol, hydrogen peroxide, and ultraviolet-A irradiation (39), and increased activities of the proteasome and its 11S activator (40). An important aspect of these studies is the observation that anti-aging and beneficial effects of repeated mild heat stress on human cells were observed without inducing additional cell proliferation. It appears that the progression of cellular aging in vitro in terms of accumulation of molecular damage can be slowed down without escaping the regulatory mechanisms of cell cycle checkpoints.

Hypergravity

Life-long exposure to hypergravity has been shown to slightly decrease the life span in different species studied, i.e., rodents and fruit flies (15). In contrast, a 2-week exposure to 3 or 5 *g* at the beginning of imaginal life resulted in an increase of 15% in the life span of male but not of female *D. melanogaster* (13). The life span increase was larger than the one observed after HS. Those results have been replicated in a more thorough study conducted in two different laboratories (in France and Belgium) with slightly different conditions and in two different strains of flies (41). The French study reported that group- or individually reared male flies

kept for 2 weeks at 3 or 5 *g* exhibited an increased life span. This was also the case for males subjected for 3 weeks to 3 *g*, but not to 5 *g*, and individually reared males exposed for 3 weeks to either 3 *g* or 5 *g*. No effect of hypergravity was observed in females, when longer or intermittent exposures were used. The Belgian laboratory showed that the beneficial effect of hypergravity was observed at least up to 7.38 *g* and in a range of exposure between 14 and 24 days (41).

Other Stresses

A study of the life span of X-ray-irradiated rats subjected to starvation for 9 days, desiccation for 6 days, or forced swimming showed that all groups of stressed irradiated males lived longer than unstressed irradiated rats (13,15). In females, two of the three stressed groups exhibited a longer life span than unstressed irradiated females, but all irradiated groups had shorter life spans than nonirradiated females. Ordy and colleagues (42) have not only studied the effects of deuteron irradiation and cold shock, but also exposed irradiated and nonirradiated mice to electric shock for 1 hour each day, from 90 days of age onwards for the next 1 to 20 months, either alone or combined with cold shock. Electric shocks decreased mortality rates and increased life span in nonirradiated females. No significant effect was observed in the other groups. The combination of electric and cold shocks decreased the mortality rates in all groups and increased life span more or less strongly, except in irradiated males in which life span was shortened. Chronic low-frequency (10 Hz) electric stimulation of young and old male Brown Norwegian rats resulted in more than a twofold increase in the proportion of IIa slow muscle fibers and in the content of satellite cells (43).

Larval crowding can induce both nutritional limitation and high concentrations of waste products. Larval crowding can thus be considered as a stress for the larvae. Several studies have reported that raising larvae in such conditions increased the life span of adult flies. For instance, an increase in life span with increased larval density, between 5 and 100 larvae per 5 cm^3 of food, has been reported (15). It has also been reported that, whereas the developmental time, starvation resistance, relative fat content, and life span increased with larval density, viability was dramatically decreased from 91% at density 50 to 59% at density 350 (15). The increase of the life span in those conditions might thus be due to a selection process at the larval stage. However, it has been shown that larval crowding without an effect on viability can increase life span in *D. melanogaster* (44).

The effects of repeated physical injuries on life span have been studied for a marine oligochaete, *Paranais litoralis*, capable of posterior regeneration, and of asexual reproduction (45). Worms were bisected on a segment immediately anterior to the fission zone (growth zone generating offspring in asexual reproduction) either once at 10, 30, or 50 days of age, or three times during the life span at 10, 30, and 50 days of age. The results showed that worms bisected once exhibited only a slight increase in life span, but the extension of life span was increased with the age at bisection. However, worms bisected three times have a significantly longer life span than controls (45). Similarly, mechanical stimulation by very low magnitude, high frequency vibrations have been shown to increase the density of trabecular bone in adult sheep (46). Hormetic effects of moderate exercise are also well documented, and their molecular basis in terms of alterations in gene expression and antioxidant levels are being elucidated (11,12,47–49). Anti-aging and life-prolonging effects of calorie restriction observed in rodents and other species are also considered to be an example of hormesis due to low-level chronic stress (50–52).

Application of Hormesis and Unresolved Issues

Since hormetic effects of mild stress are normally observed to be quite moderate in experimental systems, it may be difficult to envisage the biological significance of hormesis in terms of its application in human aging intervention and prevention. However, it should be pointed out that, although the 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 higher and more significant than expected (3,39). 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 that gain benefit, but improvements in the immune system, cardiovascular system, sex hormones, libido, and mood are also well documented (11,53). At present, we have very little knowledge of the interactive biochemical pathways that, through a process of biological amplification, result in the maintenance and improvement of the physiological functions. In the case of human beings, the role of the mental state and psychological stress 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 (54,55).

There are, however, several issues that remain to be resolved before hormesis can be widely used for modulating aging and preventing the onset of age-related impairments and pathologies. Some of these issues are as follows:

1. To establish biochemical and molecular criteria for determining the hormetic levels for different stresses (including psychological stress);
2. To establish the optimal hormetic regime in terms of the intensity, frequency, and recovery periods;
3. To identify differences and similarities in stress response pathways initiated by different stressors;
4. To quantify the extent of various stress responses;
5. To determine the interactive and pleiotropic effects of various stress response pathways;
6. To adjust the levels of mild stress for age-related changes in the sensitivity to stress; and
7. To determine the biological and evolutionary costs of repeated exposure to stress.

Resolution of these issues requires much more research on hormesis than that at present. The ''proof of the principle'' has already been provided by experiments with a wide variety of

biological systems and by using a range of physical, chemical, and biological stressors. Two of the main lifestyle interventions, exercise and calorie restriction, both of which bring their beneficial and anti-aging effects through hormesis (11,12,50–52), are being widely recognized and increasingly practiced as effective means of achieving a healthy old age. Within the next 10 years, one could also expect the availability of certain neutraceutical and pharmacological hormetic agents to mimic HS response and calorie restriction. For example, bimoclomal, a nontoxic, hydroxylamine derivative with HS protein-inducing activity and cytoprotective effects is under Phase II clinical trials (56–59). Similarly, various chemical mimetics of calorie restriction, such as 2-deoxy-D-glucose and its analogs (60), and resveratrol (61), which is a polyphenol found in red wine, are being tested for their use as anti-aging agents in the near future.

Another small molecule, N^6-furfuryladenine or kinetin, which has been shown to have significant anti-aging (62,63) and antithrombotic (64) effects in human cells, is considered to work both as an antioxidant (65,66), and possibly as a hormetic agent (63,67). Although at present the use of kinetin has been limited to being a cosmeceutical ingredient in a range of cosmetics products, the use of kinetin as a hormetic neutraceutical agent is under investigation.

In the case of irradiation as a hormetic agent, epidemiologic studies of the public, medical cohorts, and occupational workers confirm that low doses of radiation are associated with reduced mortality from all causes, decreased cancer mortality, and reduced mutation load observed in aging and cancer (68). Increasing use of low-dose total body irradiation as an immunotherapy for cancer (69) also has its basis in hormesis, which, in the not-so-distant future, will be developed into a safe and preventive strategy against a variety of age-related diseases. Hormesis through mental challenge (54) and through mind-concentrating meditational techniques (70,71) may be useful in stimulating intercellular and intracellular debris-removal processes and thus preventing the neuronal loss that leads to the onset of age-related neurodegenerative diseases.

Thus, applying hormesis in slowing down aging from within, in preventing the onset of age-related diseases, and in maintaining the physical and mental abilities in terms of healthy old age is a real present-day possibility, but which requires refinement and optimization for different hormetic agents.

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