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Abstract	<p>Mild stress-induced hormetic stimulation of protective mechanisms in cells and organisms can result in potential antiaging 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 defense 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 counterbalances the progressive shrinkage of the homeodynamic space that 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.</p>	
Keywords (separated by '-')	Antiaging - Homeostasis - Longevity - Skin - Stress	

Hormesis and Aging

Suresh I.S. Rattan and Dino Demirovic

Abstract Mild stress-induced hormetic stimulation of protective mechanisms in cells and organisms can result in potential antiaging 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 defense 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 counterbalances the progressive shrinkage of the homeodynamic space that 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.

Keywords Antiaging · Homeostasis · Longevity · Skin · Stress

Introduction

Because the harmful effects of severe and chronic stress have long overshadowed the beneficial hormetic effects of low-level stress, the application of hormesis in aging research and therapy is a relatively recent development. The paradigm for considering the applicability of hormesis in aging intervention is the well-documented beneficial effect of moderate exercise, which at a biochemical level results in the

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46 production of potentially harmful substances such as free radicals, acids, and alde-
 47 hydres. Thus, it was hypothesized that if aging systems are deliberately exposed
 48 to mild stress, this should lead to achieving beneficial hormetic effects, including
 49 health- and longevity-promoting effects. Hormesis in aging is therefore defined as
 50 the life-supporting beneficial effects resulting from the cellular responses to single
 51 or multiple rounds of mild stress (Rattan, 2001a, b, 2004, 2005).

52 Here we review and analyze the published literature on various physical, chemi-
 53 cal, and biological conditions that are known to be potentially harmful at high doses
 54 but that at lower doses have the effects of slowing down aging and/or prolonging the
 55 lifespan of cells and organisms. Table 1 lists the main stresses that have been shown
 56 to have aging- and longevity-modulatory effects in various systems.

57
 58 **Table 1** Various Types of Stresses Tested for Their Antiaging Effects

59	Physical stress
60	Thermal
61	Hypergravity
62	Radiation
63	Exercise
64	Biological stress
65	Dietary restriction
66	Dietary components
67	Natural hormetins
68	Chemical stress
69	Minerals
70	Heavy metals
71	Pro-oxidants
72	Synthetic hormetins

73 However, it is important to point out that so far only a few studies have been
 74 performed with the specific aim of testing the applicability of hormesis in aging, for
 75 example, those using thermal stress and hypergravity as hormetic agents. For most
 76 other studies that have been interpreted to involve hormesis as the mode of action of
 77 the stressful conditions used in those experiments, these conclusions are generally
 78 derived in retrospective analyses. Such studies include the effects of radiation, exer-
 79 cise, pro-oxidants, nutritional components, and food restriction. However, to fully
 80 appreciate the rationale for using hormesis as a modulator of aging and longevity,
 81 we first provide a brief overview of the biological understanding of aging, which
 82 is considered to be no longer an unresolved problem in biology (Hayflick, 2007;
 83 Holliday, 2006).

84 85 **Recapitulating the Biological Basis of Aging**

86 Biogerontology—the study of the biological basis of aging—has unveiled mysteries
 87 of aging by describing age-related changes in organisms, organs, tissues, cells, and
 88 macromolecules. The large body of descriptive data has led two of the pioneers of
 89
 90

91 modern biogerontology, Leonard Hayflick and Robin Holliday, to declare that aging
92 is no longer an unsolved problem in biology (Hayflick, 2007; Holliday, 2006). This
93 declaration does not mean that there are no remaining descriptive data on aging and
94 that every piece of information about aging in every biological system has been
95 gathered. The bold assertion by Hayflick and Holliday underlines the fact that the
96 biological basis of aging is well understood and a distinctive framework has been
97 established that will not be altered significantly with additional descriptive data.
98 Based on the large body of descriptive data, certain general principles of aging and
99 longevity can be clearly formulated, and these can be the basis for translational
100 research and interventions toward achieving a healthy old age (Table 2).

101 **Table 2** General Principles of Aging and Longevity Derived from Modern Biogerontological
102 Research

-
- 104 • *Life history principle*: Aging is an emergent phenomenon seen primarily in protected
105 environments that allows survival beyond the natural lifespan of a species, termed “essential
106 lifespan” (ELS) (Rattan, 2000a, b; Rattan and Clark, 2005).
 - 107 • *Differential principle*: The progression and rate of aging is different in different species, in
108 organisms within a species, in organs and tissues within an organism, in cell types within a
109 tissue, in subcellular compartments within a cell type, and in macromolecules within a cell.
 - 110 • *Mechanistic principle*: Aging is characterized by a progressive accumulation of molecular
111 damage in nucleic acids, proteins, and lipids. The inefficiency and failure of maintenance,
112 repair, and turnover pathways is the main cause of age-related accumulation of damage.
 - 113 • *Nongenetic principle*: There is no fixed and rigid genetic program that determines the exact
114 duration of survival of an organism, and there are no “gerontogenes” whose sole function is
115 to cause aging and to determine precisely the lifespan of an organism.
-

116 Thus, aging has many facets, and almost all the experimental data suggest that
117 aging is an emergent, epigenetic, meta-phenomenon that is not controlled by a single
118 mechanism. Although individually no tissue, organ, or system becomes functionally
119 exhausted even in very old organisms, it is their combined interaction and interde-
120 pendence that determines the survival of the whole. A combination of genes, milieu,
121 and chance determines the course and consequences of aging and the duration of
122 survival of an individual (Rattan, 2007b).

123 There is much supporting evidence for the theory that the survival and longevity
124 of a species are a function of the ability of its maintenance and repair mechanisms to
125 keep up with damage and wear and tear. All living systems have the intrinsic ability
126 to respond to, counteract, and adapt to external and internal sources of disturbance.
127 The traditional conceptual model to describe this property is homeostasis, which has
128 dominated biology, physiology, and medicine since the 1930s. However, advances
129 in our understanding of the processes of biological growth, development, matura-
130 tion, reproduction, and aging, senescence, and death have led to the realization that
131 the homeostasis model as an explanation is seriously incomplete. The main reason
132 for the incompleteness of the homeostasis model is its defining principle of “sta-
133 bility through constancy,” which does not take into account the new themes, such
134 as cybernetics, control theory, catastrophe theory, chaos theory, information, and
135 interaction networks, that comprise and underlie the modern biology of complexity

(Rattan, 2007a). Since the 1990s, the term homeodynamics has been 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 and stress responses. All of these processes involve numerous genes whose products and interactions give rise to the “homeodynamic space” or “buffering capacity that 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 age-related diseases.

Figure 1 is a pictorial representation of the concept of homeodynamic space and the consequences of its shrinkage during aging. In a normal, healthy, young individual, the complex network of maintenance and repair systems (MRS) constitutes a functional homeodynamic space. Because no MRS can be 100% efficient 100% of the time, even in a young system, there is a probability of incomplete homeodynamics, giving rise to a zone of vulnerability, manifested in age-independent diseases and mortality. However, a progressive accumulation of molecular damage and its effects on the interacting molecular networks leads to the reduction in the functional homeodynamic space and effectively increases the vulnerability zone, thus allowing for the occurrence and emergence of age-related diseases. Alzheimer’s disease, cancer, cataract, diabetes type 2, osteoporosis, Parkinson’s disease, sarcopenia, and other age-related diseases are the result of an individual’s reduced homeodynamic space.

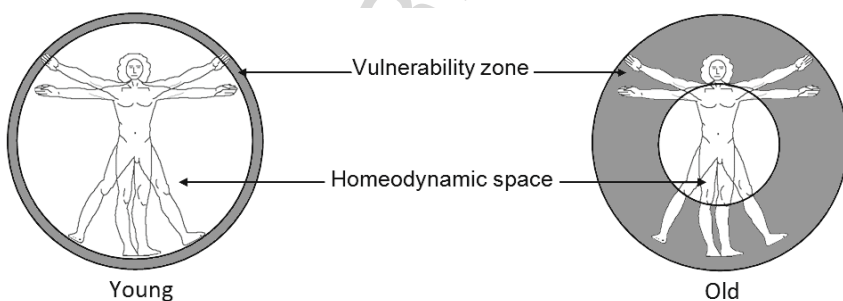


Fig. 1 Pictorial representation of the concept of homeodynamic space, whose progressive shrinkage due to the accumulation of molecular damage leads to an increase in the area of vulnerability zone in the elderly, and hence to the occurrence and emergence of age-related diseases

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) that in a living

181 system initiates a series of events to enable the organism to counteract, adapt, and
182 survive. Although a successful and over-compensatory response to low doses of
183 stressors improves the overall homeodynamics of cells and organisms, an incom-
184 plete or failed homeodynamic response leads to the damaging and harmful effects
185 of stress, including death. It is this homeodynamic space as a whole or the individ-
186 ual components of the homeodynamic machinery that are the targets of hormetic
187 interventions.

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190 **Thermal Hormesis in Aging**

191

192 *Thermal Hormesis in Organisms*

193

194 Temperature stress, especially high-temperature-induced heat shock (HS), has been
195 widely used with the specific aim of testing and applying hormesis in aging research
196 and interventions. One of the main reasons for choosing HS as a hormetic agent is
197 that HS acts through an evolutionarily highly conserved stress response pathway,
198 known as the heat-shock response, the molecular basis of which is well understood
199 (Sun and MacRae, 2005; Verbeke et al., 2001b). Effects of mild and severe HS
200 have been tested on yeast, nematodes, fruit flies, and rodent and human cells. For
201 example, wild-type and *age-1* long-lived mutant hermaphrodite *Caenorhabditis ele-*
202 *gans* exposed for 3 to 24 hours to 30°C exhibited a significant increase in mean
203 lifespan compared to controls (Johnson, 2002; Lithgow et al., 1995). Similarly, a
204 6-hour exposure at 30°C of wild-type worms increased their lifespan, but no effect
205 was found after exposures of 2 or 4 hours (Yokoyama et al., 2002). Furthermore,
206 studies of *C. elegans* subjected to 35°C HS for different durations showed that HS
207 not longer than 2 hours resulted in an extension of lifespan (Butov et al., 2001;
208 Michalski et al., 2001; Yashin et al., 2001). In a study of multiple stresses in
209 *C. elegans* an extension of lifespan after 1 and 2 hours of HS at 35°C was reported
210 (Cypser and Johnson, 2002, 2003). In another study performed on *C. elegans* it was
211 observed that repeated mild HS throughout life had a larger effect on lifespan than
212 a single mild HS early in life, and the effect was related to the levels of heat-shock
213 protein (HSP) expression (Olsen et al., 2006).

214 In the case of fruit flies, virgin males of inbred lines of *Drosophila melanogaster*
215 exhibited an increase in mean lifespan and lower mortality rates during several
216 weeks after a heat treatment of 36°C for 70 min (Khazaeli et al., 1997). It has also
217 been shown that wild-type *D. melanogaster* exposed to 37°C for 5 minutes a day,
218 5 days a week for 1 week lived on average 2 days longer than the control flies (Le
219 Bourg et al., 2001). Longer exposures had either no effect or a negative effect on
220 lifespan. In another study on *D. melanogaster*, the exposure of young flies to four
221 rounds of mild HS at 34°C significantly increased the average and maximum lifes-
222 pan of female flies and increased their resistance to potentially lethal HS (Hercus
223 et al., 2003). Of interest, the beneficial effects of HS in *Drosophila* did not entirely
224 depend on the continuous presence of HSP but were observed long after newly
225 synthesized HSP had disappeared, indicating the involvement of a cascade of
poststress events in hormesis (Sørensen et al., 2008). Furthermore, the hormetic

226 effects of HS appear to occur to different extents in male and female *Drosophila*,
227 which may be due to the fact that females have to trade off stress resistance and
228 reproduction (Sørensen et al., 2008).

229 Studies have also been performed on the effect of subjecting transgenic
230 *D. melanogaster* overexpressing the inducible HSP70 to 20 minutes at 36°C (Minois
231 et al., 2001; Minois and Vaynberg, 2002). In the control “parental” line, such expo-
232 sure significantly increased the lifespan of both virgin flies kept in groups and mated
233 flies. In individually kept flies, the same trend was observed but was statistically
234 not significant. No beneficial effect of such HS has been seen in the transgenic
235 lines, which may be suggestive of upper limits of modulating HS responses (Minois
236 and Vaynberg, 2002). In addition to the high temperature, there is some evidence
237 demonstrating that cold shocks at young age increased the longevity and survival of
238 *Drosophila* at high temperature and increased longevity of *Drosophila* after cold
239 stress-induced hardening (Le Bourg, 2008; Overgaard et al., 2005). In the case
240 of mammals, irradiated and nonirradiated mice that were given intermittent cold
241 shocks showed lower rates of mortality in the irradiated mice. Longer lifespans were
242 observed in thermally stressed nonirradiated males and irradiated females (Minois,
243 2000). Similarly, rats kept in water set at 23°C, 4 hours a day, 5 days a week, had a
244 5% increase in average lifespan and diminished occurrence of age-related diseases
245 (Holloszy and Smith, 1986).

246
247

248 ***Thermal Hormesis in Human Cells Undergoing Aging in Vitro***

249

250 A series of studies performed in our labs tested the hormesis hypothesis of the ben-
251 efcial effects of mild HS, using the Hayflick system of cellular aging of normal
252 human cells in culture. Employing a mild stress regimen of exposing serially pas-
253 saged human skin fibroblasts to 41°C for 1 hour twice a week throughout their
254 replicative lifespan, we found several antiaging effects, which are listed in Table 3.

255 The choice of the repeated mild heat shock (RMHS) regimen was based on
256 several pilot experiments performed for selecting conditions in which 30% of the
257 maximal HS response was elicited without affecting cell growth and survival (Kraft
258 et al., 2006; Rattan, 1998). This does not imply that these are the ideal hormetic
259 conditions for these cells. Other combinations of dose and duration may well have
260 similar or even better effects, but that issue remains to be investigated. Furthermore,
261 we also showed that repeated mild HS at 41°C, but not the relatively severe HS at
262 42°C, increased the replicative lifespan and elevated and maintained the basal lev-
263 els of MAP kinases JNK1, JNK2, and p38 in human skin fibroblasts (Nielsen et al.,
264 2006).

265 To confirm the wider applicability of mild HS-induced hormesis in other human
266 cell types, we also performed studies on normal human epidermal keratinocytes
267 (NHEKs) and obtained results that were very similar to those for dermal fibroblasts.
268 NHEK also showed a variety of cellular and biochemical hormetic antiaging effects
269 on repeated exposure to mild HS at 41°C. These effects included maintenance of
270 youthful cellular morphology, enhanced replicative lifespan, enhanced proteasomal

Table 3 A Summary of Results of Studies on the Antiaging Hormetic Effects of Repeated Mild Heat Shock on Human Skin Fibroblasts in Vitro

Characteristic	Hormetic Effect	Reference
Cellular phenotype		
Cell size	Reduced enlargement	(Rattan, 1998)
Cell morphology	Reduced irregularization	(Rattan, 1998)
Proliferative lifespan	20% increase	(Nielsen et al., 2006)
Wound healing	30% increase	(Rattan et al., 2009)
Cell physiological phenotype		
H ₂ O ₂ decomposing ability	50%–140% increase	(Fonager et al., 2002)
Survival after H ₂ O ₂ exposure	10%–18% increase	(Fonager et al., 2002)
Survival after ethanol exposure	10%–40% increase	(Fonager et al., 2002)
Survival after ultraviolet A exposure	5%–17% increase	(Fonager et al., 2002)
Molecular damage		
Glucation, furasine level	50%–80% reduction	(Verbeke et al., 2001a)
Glycooxidation level	10%–30% reduction	(Verbeke et al., 2001a)
Carboxymethyl-lysine-rich protein level	20%–85% reduction	(Verbeke et al., 2001a)
Lipofuscin pigment level	6%–29% reduction	(Verbeke et al., 2001a)
Protein carbonyl level	5%–40% reduction	(Verbeke et al., 2001a)
Reduced glutathione level	3-fold increase	(Verbeke et al., 2001a)
Oxidized glutathione level	2-fold reduction	(Verbeke et al., 2001a)
Induction of sugar-induced protein damage	10-fold reduction	(Verbeke et al., 2002)
Molecular mechanisms		
HSP27 level	20%–40% increase	(Fonager et al., 2002)
HSC70 level	20% increase	(Fonager et al., 2002)
HSP70 level	7- to 20-fold increase	(Fonager et al., 2002)
HSP90 level	50%–80% reduction	(Fonager et al., 2002)
Proteasome activities	40%–90% increase	(Beedholm et al., 2004)
11S activator content	2-fold increase	(Beedholm et al., 2004)
11S activator binding	2-fold increase	(Beedholm et al., 2004)
JNK1, JNK2 and p38 level	45%–70% increase	(Nielsen et al., 2006)

activity, and increased levels of HSPs (Rattan and Ali, 2007). In addition, we also studied the effects of HS on Na,K-ATPase and the sodium pump, whose content and activity were increased significantly after mild HS (Rattan and Ali, 2007). However, the molecular mechanisms and interactions that bring about the mild HS-induced increase in the amounts and activity of Na,K-ATPase and their consequences on other biochemical pathways 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.

316 We also observed that mild HS enhances the ability of serially passaged ker-
317 atinocytes to enter into differentiation in the presence of calcium, as measured
318 by the levels of differentiation markers involucrin, p38, and HSP27 (Berge et al.,
319 2008). Another cell type in which we tested whether differentiation can be improved
320 hormetically by RMHS is the telomerase-immortalized bone marrow mesenchymal
321 stem cell-line hTERT-MSC. Single or multiple exposures to mild HS significantly
322 enhanced the vitamin D-induced differentiation of hTERT-MSC into osteoblasts,
323 as measured by determining the levels of osteoblastic markers alkaline phosphatase
324 and mineralized matrix (Nørgaard et al., 2006). Although the mechanistic aspects
325 of the hormetic effects of HS on the differentiation of human cells are yet to be elu-
326 cidated, such studies pave the way for developing novel means for the maintenance
327 and improvement of differentiation abilities of various cell types and thus prevent-
328 ing age-related alterations that lead to impairments such as thinning and excessive
329 wrinkling of the skin and loss of bone mass leading to osteoporosis.

330 Other hormetic effects of mild HS on human cells that we have observed are
331 improved wound healing and enhanced angiogenesis *in vitro* (Rattan et al., 2009).
332 For example, HS-conditioned medium collected from one set of cultures after
333 6 hours post-HS at 41°C for 1 hour enhanced wound healing by 17% to 38% in
334 a separate set of cells. This increase in wound healing by HS-conditioned medium
335 was accompanied by a 68% increase in mobility and migration of cells and by about
336 54% enhanced elongation of individual cells. These studies indicate that mild HS
337 induces the synthesis of one or more gene products secreted by the cells in the
338 culture medium. Furthermore, these molecules can stimulate wound healing either
339 as direct stimulants or as inhibitors of the negative modulators of wound healing,
340 such as the plasminogen activator inhibitor PAI-1 (Kortlever and Bernards, 2006).
341 However, the full range of secreted proteins, including HSPs, that may be responsi-
342 ble for enhanced wound healing and other biological effects are yet to be identified.
343 We are analyzing various other molecular markers of cell migration, such as
344 paxillin, talin, and focal adhesions, to elucidate the mechanisms of mild HS-induced
345 improvements in wound healing.

346 Improved angiogenesis *in vitro* is another hormetic effect of mild HS that
347 we have observed. Preexposure of normal human umbilical vein endothelial cells
348 (HUVECs) to 1 hour of HS at 41°C or 42.5°C, followed by different periods of
349 recovery at 37°C, had hormetic effects with respect to angiogenesis. Of interest,
350 whereas the general extent and quality of the tubes formed by cells preexposed to
351 41°C were better than those in the controls, a preexposure at 42.5°C resulted in a
352 relative worsening of tube structures, indicating that only mild stress has hormetic
353 effects (Rattan et al., 2009). We are now attempting to elucidate whether the extent
354 of hormetic effects of mild HS on angiogenesis are related to the levels of vari-
355 ous HSPs synthesized during this period and what other pathways are involved in
356 this. For example, there is some evidence that HSP90 stimulates tube formation by
357 HUVEC via its role in enhancing the expression of the nitric oxide synthase (NOS)
358 gene and the production of nitric oxide (Sun and Liao, 2004).

359 The molecular mechanisms through which the hormetic effects of mild HS are
360 achieved remain to be elucidated. Although the general mechanisms of severe HS

361 response are well understood, it is not clear whether there are any significant dif-
362 ferences between mild HS, which has hormetic effects, and severe HS, which has
363 deleterious effects (Park et al., 2005). It is likely that the physiological cost of
364 stress in terms of energy utilization, molecular damage overload, and metabolic
365 shift determines the difference between the outcomes of mild and severe stress. In
366 addition, it is yet to be understood how the transient appearance of HSPs leads to
367 biologically amplified hormetic effects at various other levels of cellular function-
368 ing, such as improved proteasome activity, enhanced resistance to other stresses,
369 and maintenance of the cytoskeletal integrity.

372 **Hypergravity Hormesis in Aging**

374 Antiaging and life-prolonging hormetic effects of hypergravity have been studied
375 in *Drosophila*. Whereas lifelong exposure to hypergravity decreases the lifespan in
376 rodents and fruit flies, a 2-week exposure to 3 or 5 g at earlier stages in life resulted
377 in an increase of 15% in the lifespan of male but not of female *D. melanogaster*
378 (Minois, 2006). In addition to longevity, other physiological and behavioral param-
379 eters, such as fecundity, fertility, locomotor activity, antioxidant enzyme activity, HSP
380 levels, and heat resistance, have also been analyzed. Except for increased survival of
381 hypergravity-exposed *Drosophila* under heat stress, no other clear-cut patterns have
382 been observed that can be associated with antiaging effects of transient hypergravity
383 (Le Bourg, 2008). It is also not clear why the longevity-extending hormetic effects
384 of hypergravity are restricted to male flies. Studies on checking the antiaging effects
385 of hypergravity on any of the molecular biomarkers of aging, such as the level of
386 macromolecular damage and other maintenance and repair pathways, have yet to be
387 performed.

390 **Radiation Hormesis in Aging**

393 *Radiation Hormesis in Insects*

395 One of the earliest studies to show the life-prolonging effects of irradiation were
396 performed on the flour beetle, *Tribolium confusum*, in which repeated exposure of
397 beetles to low-dose radiation (LDR) of X-rays reduced their death rates as com-
398 pared with those of unexposed organisms. Similar observations on the life-extending
399 effects of γ -rays and X-rays on flour beetles were later reported by others (for ref-
400 erences, see Rattan, 2008). Other insects used for similar studies are the housefly,
401 *Musca domestica*, and the fruitfly, *Drosophila*. For example, whereas high doses
402 of radiation decreased the lifespan, LDR extended the lifespan of fruit flies and of
403 houseflies (Rattan, 2008). It has been argued that irradiation leads to female steril-
404 ity and that the lifespan increase was an outcome of decreased fecundity. It was
405 also shown that mutant females without ovaries did not exhibit increased lifespan

406 after irradiation. The long-term consequences of the X-irradiation of *Drosophila*
407 eggs demonstrated longevity hormesis in male flies exposed to 0.5 and 0.75 Gy,
408 which also had smaller amounts of DNA segments resulting from cleavage in S1
409 nuclease-sensitive sites (Vaiserman et al., 2003; 2004a; Vaiserman et al., 2004b).
410 One explanation given for the life-extending effects of LDR in insects is that irradi-
411 ation induces stable epigenetic DNA modifications and enhanced DNA repair
412 capacity (Vaiserman, 2008).

413

414

415 ***Radiation Hormesis in Rodents and Other Animals***

416

417 Several studies have reported the hormetic effects of γ -rays on longevity in rats,
418 mice, and guinea pigs (Calabrese and Baldwin, 2000; Caratero et al., 1998).
419 Suppression of thymic lymphoma induction and prolongation of lifespan associ-
420 ated with immunological modification by chronic LDR in C57BL/6 mice have
421 been reported (Ina and Sakai, 2005; Ina et al., 2005). In contrast, some earlier
422 studies had failed to show an increase of lifespan after LDR. For instance, deuter-
423 on-irradiated mice exhibit higher mortality rates and lower lifespan in both sexes than
424 nonirradiated ones (Ordy et al., 1967).

425 There are some data available on the effects of LDR on the survival and longevity
426 of the nematode *C. elegans*. For example, an increase in the survival of *C. ele-*
427 *gans* was sometimes observed after intermediate levels of irradiation (Johnson and
428 Hartman, 1988). However, pretreatment with ultraviolet or ionizing radiation did
429 not promote subsequent resistance or increased longevity of the worms exposed to
430 other hormetic stresses, such as heat, hyperbaric oxygen, and pro-oxidants (Cypser
431 and Johnson, 2002).

432

433

434 ***Radiation Hormesis in Humans***

435

436 The adaptive response of human embryonic cells to low-dose γ -radiation has been
437 shown to increase the replicative lifespan significantly (Watanabe et al., 1992).
438 Similarly, human embryonic lung diploid fibroblasts sequentially irradiated with
439 1 Gy γ -rays had their replicative lifespan increased to some extent (Holliday, 1991).
440 Hormetic effects of low-dose X-irradiation on the proliferative ability, genomic
441 stability, and activation of mitogen-activated protein kinase pathways have been
442 reported for other human diploid cells (Suzuki et al., 1998a, 2001; Suzuki et al.,
443 1998b; Tsutsui et al., 1997).

444 In the case of humans, there are some claims that exposure to LDR has antiag-
445 ing and other health benefits such as cancer prevention, but the demographic data
446 are insufficient and inconclusive (Parsons, 2003; Wyngaarden and Pauwels, 1995).
447 For example, although better survival and other beneficial effects of low to inter-
448 mediate doses of atomic bomb radiation on Hiroshima and Nagasaki survivors have
449 been claimed (Hayakawa et al., 1989; Mine et al., 1990; Okajima et al., 1985),
450 these results were challenged by later analyses (Cologne and Preston, 2000). On the

451 other hand, mortality rates of all workers in the U.K. Atomic Energy Authority were
452 found to be lower than national rates (Atkinson et al., 2004). All-cause mortality
453 and all-cause cancers (leukemia and prostate cancer) were also significantly lower
454 for nuclear workers than for nonradiation workers (Atkinson et al., 2004). In an ear-
455 lier study analyzing the varying levels of environmental radiation and incidence of
456 cancer in different parts of India, it was reported that the cancer risk was invariably
457 less in regions such as Kerala where the background radiation level is higher due
458 to rich coastal thorium-monazite deposits (Nambi and Soman, 1987). Recent anal-
459 yses of a series of 15-country international cohort studies of nuclear workers and
460 of people living near nuclear reactors also indicates that radiation effects are not
461 linear in terms of survival and incidence of cancer and other diseases, and that these
462 effects may be further accentuated as a function of age, health status, and lifestyle
463 variations (Cardis et al., 2007; Vrijheid et al., 2007).

464 Application of low-dose (1.2–1.8 Gy) total body irradiation (TBI) in the treat-
465 ment of cancers, such as non-Hodgkin's lymphoma, is considered to be an example
466 of radiation hormesis (Safwat, 2008). This is due to the fact that low-dose TBI
467 did not kill cancer cells directly, but enhanced their removal by the immune
468 system by increasing the proportion of cytotoxic T-lymphocytes, helper-inducer
469 T-lymphocytes, and helper T-lymphocytes while decreasing the proportion of the
470 suppressor-inducer T-lymphocytes and suppressor T-lymphocytes (Safwat, 2008).
471 Although the exact mechanisms of how LDR brings about beneficial and longevity-
472 promoting effects are not fully understood, there is evidence that LDR stimulates
473 various repair and maintenance pathways as the cellular response to counteract
474 the damage induced by radiation. These pathways include enhanced DNA repair,
475 induction of DNA methylation, increased levels of antioxidative enzymes, and
476 increased removal of damaged macromolecules (Rattan, 2008). It will be useful to
477 design and perform studies aimed specifically to test the antiaging, anticancer, and
478 longevity-promoting hormetic effects of stress-inducing levels of irradiation.

481 **Calorie Restriction and Hormesis**

483 Calorie restriction (CR) is the most commonly used intervention that has shown
484 to extend the lifespan and slow down the onset of a wide range of age-related
485 changes in a variety of organisms, including yeast, insects, rats, mice, and mon-
486 keys. Beneficial effects of other CR regimens, such as 25% and 8.5% chronic CR
487 (Gomez et al., 2007) and intermittent CR (once or twice a week), have also been
488 reported in animal studies (Anson et al., 2003; Martin et al., 2006). In the case of
489 humans, some beneficial and health-promoting effects of CR have been reported.
490 For example, long-term CR is reported to be highly effective in reducing the risk
491 for atherosclerosis in humans (Fontana et al., 2004) and ameliorates the decline in
492 diastolic function in humans (Meyer et al., 2006). An unintentional CR imposed on
493 the participants of the Biosphere 2 experiment in 1991 also gave some indication of
494 the beneficial effects of CR, as measured by several physiological, hematological,
495

496 hormonal, and biochemical parameters (Walford et al., 2002). Similarly, unintentional
497 chronic undernutrition and low body mass index have been shown to improve
498 certain DNA repair parameters in peripheral blood lymphocytes of human subjects
499 (Raji et al., 1998).

500 A relatively short-duration CR for 6 months has also been shown to have beneficial
501 effects in humans by reducing fasting insulin levels, body temperature, and
502 DNA damage (Heilbronn et al., 2006). Intermittent CR by periodic fasting has been
503 shown to have a range of beneficial effects in rodents (Anson et al., 2003; Sharma
504 and Kaur, 2005; Sogawa and Kubo, 2000). These observations make periodic CR
505 more easily applicable and acceptable to humans, with several potential benefits,
506 especially with respect to the prevention of neurodegenerative diseases with age
507 (Arumugum et al., 2006; Martin et al., 2006). We have reported antiaging and
508 lifespan-extending effects in serially passaged human skin fibroblasts by periodic
509 partial (80%) fasting (once a week for 24 hours) by serum reduction, resulting in
510 enhanced autophagy (Moore, 2008; Rattan, 2007b).

511 Hormesis has been suggested as a major explanation for the antiaging effects of
512 CR by considering CR as a low-intensity stressor (Masoro, 2007). The evidence
513 in support of the view that CR is a low-intensity stressor is its association with
514 the increase in plasma levels of glucocorticoid steroid stress hormones (reviewed
515 in Masoro, 2007). Another requirement for the hormesis hypothesis to explain the
516 effects of CR is that CR should work through one or more pathways involved
517 in stress response, molecular damage prevention and turnover, and metabolic
518 regulation. There is significant evidence for the hormetic action of CR through
519 the promotion of maintenance and repair pathways, which include increase in
520 nucleotide excision repair, increase in the level of chaperones, increase in the level
521 of proteasomal activities, enhancement of lysosomal autophagy, reduction in mitochon-
522 drial free radical generation and increase in mitochondrial uncoupling, and a
523 shift in the metabolic regulation involving sirtuins and insulin-dependent pathways
524 (Bonelli et al., 2008; Masoro, 2007; Rattan, 2008).

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527 **Exercise Hormesis**

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529 Some of the main molecular pathways involved in bringing about the adaptive and
530 hormetic effects of exercise are activation of the nuclear factor NF- κ B signaling
531 cascade involving various stress kinases and antioxidant genes (Ji, 2008), enhanced
532 anti-inflammatory responses, enhanced DNA repair, and increased degradation of
533 damaged proteins and other macromolecules by proteasomal and lysosomal path-
534 ways (Radak et al., 2005; Short et al., 2004). Another pathway that is active in
535 realizing the hormetic effects of exercise is the stress response or HSP synthesis
536 pathway, in which the induction of various HSPs during and after exercise has a
537 variety of beneficial biological effects (Atalay et al., 2004; Lancaster et al., 2004).
538 Increased levels of HSPs provide several benefits, including protection against
539 molecular damage occurrence and accumulation, which is a crucial aspect of aging
540 (Radak et al., 2008a, b).

Nutritional Hormesis and Hormetins

Several dietary components, such as vitamins, antioxidants, trace elements, minerals, and ethanol, have been shown to have typical hormetic dose response (Calabrese, 2004; Mattson, 2008). All such compounds (natural or synthetic) that bring about biologically beneficial effects by acting through one or more pathways of maintenance and repair and of stress response are termed *hormetins* (Ali and Rattan, 2006; Rattan, 2008). The hormetic effects of various vitamins and macro- and microminerals, including iron, iodine, fluorine, selenium, and copper, have been reviewed (Hayes, 2007). In addition, the effects of zinc also show a typical hormetic dose response, and its beneficial effects are achieved through stress response-induced alterations in gene expression in various maintenance and repair pathways (Mocchegiani et al., 2006).

Dietary intake of moderate amounts of ethanol has been shown to have memory-enhancing beneficial effects in mice (Ritzmann et al., 1994). In the case of humans, consumption of moderate amounts of alcohol, combined with other positive lifestyle factors, has been associated with fourfold reduction in mortality (Khaw et al., 2008). The cardioprotective, antioxidative, and other beneficial effects of wine are considered to be due to flavonoid and nonflavonoid components, such as resveratrol (Corder et al., 2006), which also have a 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 antiaging and longevity-enhancing effects of resveratrol in nematodes, *Drosophila*, and mice (Baur et al., 2006; Rogina and Helfand, 2004; Valenzano et al., 2006; Wood et al., 2004). Because resveratrol's mode of action involves regulating various pathways of maintenance, repair, and induction of HSP synthesis, it is another example of a hormetin (Putics et al., 2008).

Other compounds that qualify to be called 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 α -lipoic acid and coenzyme Q10, it is their pro-oxidant activity in producing hydrogen peroxide that induces defensive responses (Linnane and Eastwood, 2006). Certain mimetics of superoxide dismutase claimed to have antiaging 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). 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, N⁶-furfuryladenine or kinetin, which is known to have antiaging effects in human cells and is widely used as a component of several skin care cosmetic products, may also work as a hormetin through stress-induced hormetic pathways (Berge et al., 2008).

Components of various medicinal plants used frequently in traditional Chinese medicine and in the Indian Ayurvedic system of medicine are claimed to have antiaging effects, which appear to be achieved through hormetic pathways. For example, celasterols and paeoniflorin present in some medicinal herbs used in Chinese

586 medicine have cytoprotective effects and induce HSP in human cells (Westerheide
587 et al., 2004; Yan et al., 2004). Similarly, curcumin, which is the active component in
588 the commonly used yellow food spice from the roots of *Curcuma longa*, is a coin-
589 ducer of HSP and has wide-ranging biological effects depending on its dose (Cronin,
590 2003; Dunsmore et al., 2001; Joe et al., 2004). Whereas curcumin doses greater than
591 10 μ mole have been reported to have anti-inflammatory and anticancer effects in
592 experimental studies (Moos et al., 2004; Rashmi et al., 2003), at lower doses (0.3
593 and 1 μ mole) curcumin stimulates proteasome activity, enhances HSP induction
594 after HS, and stimulates sodium pump activity (Ali and Rattan, 2006; Rattan and
595 Ali, 2007). Several pharmaceuticals that also have typical hormetic dose-response
596 effects (Calabrese, 2008) may be other examples of hormetins.

597 Hormesis may also be an explanation for the health beneficial effects of numer-
598 ous other foods and food components, such as garlic, ginkgo, and other fruits and
599 vegetables (Everitt et al., 2006; Ferrari, 2004; Gurib-Fakim, 2006; Hayes, 2005,
600 2007). Understanding the hormetic and interactive mode of action of natural and
601 processed foods is a challenging field of research and has great potential for develop-
602 ing nutritional and other lifestyle modifications for aging intervention and therapies.
603 For example, it may be possible to develop multihormetin formulations as antiag-
604 ing drugs and nutraceuticals whose mode of action is through hormetic pathways by
605 mild stress-induced stimulation of homeodynamic processes.

607 Other Stresses

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610 Some examples of other stresses that have been investigated with respect to
611 their effects in aging and longevity include starvation, electromagnetic stress, and
612 mechanical stress, but the results are not consistent or well understood. For example,
613 the effects of repeated physical injuries on lifespan have been studied for a marine
614 oligochaete, *Paranais litoralis*, capable of posterior regeneration and of asexual
615 reproduction (Martínez, 1996). Chronic low-frequency (10 Hz) electric stimulation
616 of young and old male brown Norwegian rats resulted in more than twofold increase
617 in the proportion of type IIa slow muscle fibers and in the content of satellite cells
618 (Putman et al., 2001). Similarly, a long-wavelength, low-energy, and nonthermal
619 electromagnetic frequency (50 MHz/0.5 W) enhanced cellular defenses of human T-
620 cells and various aging characteristics in human fibroblasts (Perez et al., 2008). An
621 example of low-level mechanical stress having beneficial hormetic effects was found
622 in a study showing that a 20-minute burst of very low magnitude high-frequency
623 vibrations given to the hind limbs of sheep increased the trabecular density by 34%
624 in 1 year (Rubin et al., 2001). There is some indication that osteopontin synthesis
625 in human dental osteoblasts is stimulated by low levels of mechanical stress (Liu
626 et al., 2004).

627 Another kind of stress that appears to have hormetic effects is the population
628 density in early stages of life. For example, it has been shown in *Drosophila* that
629 larval crowding can induce both nutritional limitation and high concentrations of
630 waste products and can thus be considered as a stressor for the larvae. Several studies
reported that raising larvae in such conditions increased the lifespan of adult flies.

631 For instance, an increase in lifespan with increased larval density between 5 and 100
632 larvae per 5 cm³ of food has been reported (Minois and Rattan, 2003). It has also
633 been reported that whereas the developmental time, starvation resistance, relative
634 fat content, and lifespan increased with larval density, viability was dramatically
635 decreased from 91% to 50%–59% at density 350 (Minois and Rattan, 2003). The
636 increase of the lifespan in those conditions might thus be due to a selection process
637 at the larval stage. However, it has been shown that larval crowding without an effect
638 on viability can increase lifespan in *D. melanogaster* (Sørensen and Loeschcke,
639 2001).

640 There are some studies attempting to check the hormetic effects of mental and
641 psychological stress. Although the harmful effects of chronic and acute stress on life
642 functioning, quality of life, and survival are well documented (Padgett and Glaser,
643 2003; Segerstrom and Miller, 2004), beneficial effects of periodic low-level mental
644 stress are also being investigated. For example, C57BL6 young male mice exposed
645 to stress by keeping them in a restrained space for 2.5 hours showed increased lev-
646 els of stress hormone catecholamines and corticosterones and adrenal steroids and
647 enhanced immunoprotection during surgery, vaccination, or infection (Viswanathan
648 and Dhabhar, 2005). Skin fibroblasts from Cushing's syndrome patients, who have
649 higher plasma levels of glucocorticoids, have longer replicative lifespan in vitro and
650 have a better HSP stress response (Pratsinis et al., 2002; Zervolea et al., 2005). There
651 are some preliminary studies that show that hormesis through mental challenge
652 (Bierhaus et al., 2003) and through mind-concentrating meditational techniques may
653 be useful in stimulating the stress response.

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657 **Hormesis Potential, Challenges, and Unresolved Issues in Aging**

658

659 Because hormetic effects of mild stress are normally observed to be quite moderate,
660 sometimes it is difficult to envisage the biological significance of hormesis in terms
661 of its application in human aging intervention and prevention (Thayer et al., 2006;
662 Zapponi and Marcello, 2006). However, it should be pointed out that although the
663 initial hormetic effects may be relatively small when studied at the level of an indi-
664 vidual biochemical step, often the final biological outcome, such as overall stress
665 tolerance, functional improvement, and survival, is much larger, synergistic, and
666 pleiotropic. This suggests that hormesis is involved in the biological amplification
667 of adaptive responses leading to the improvement in overall cellular functions and
668 performance. Exercise is a good example of the biological amplification of benefi-
669 cial effects of mild stress, where not only do the specific muscle targets benefit, but
670 also improvements in the immune system, cardiovascular system, sex hormones,
671 libido, and mood are well documented. A recent study performed on rats showed
672 that exercise performed at a young age can have lifelong benefits on bone struc-
673 ture and strength (Warden et al., 2007). This indicates that even moderate hormetic
674 strengthening of homeodynamic networks can have much larger beneficial effects in
675 terms of maintenance of functionality and prevention or delay of onset of age-related
frailty.

676 The main promise and potential of hormesis as a modulator of aging lie in its
677 mode of action. Because hormetic effects occur by involving a series of molecular
678 and physiological processes, the final target of hormesis is the overall homeody-
679 namic machinery of the living systems. Although hormesis-inducing stress may be
680 targeted at a single pathway, the cascade of biological effects and their amplifica-
681 tion result in the modulation and strengthening of the total homeodynamic ability.
682 Furthermore, hormesis-induced increase in the prevention and removal of molecular
683 damage will affect the rate of aging by slowing down the rate of shrinkage of the
684 homeodynamic space and by reducing the increase in the size of the vulnerability
685 zone (see Fig. 1).

686 As discussed earlier, the process of aging is primarily characterized by a
687 progressive shrinking of homeodynamic space in terms of increased molecular het-
688 erogeneity, which leads to increased vulnerability, onset of diseases, and eventual
689 death. It is also important to realize that the dimensions of the homeodynamic space
690 of an individual are determined by an interacting network of genes, milieu, and
691 chance, which are the basis of the uniqueness of the individual (Calabrese, 2008;
692 Rattan, 2006). Several studies have been made and many are in progress to asso-
693 ciate genetic variations (polymorphisms) with individual health status, probability
694 of onset of various diseases, and lifespan potential (Christensen et al., 2006; Rattan
695 and Singh, 2008). Because the practical applications of mild stress-induced horme-
696 sis are critically dependent on individual variations in stress response, studies to
697 establish the association between stress gene variants and stress response are highly
698 important and informative (Singh et al., 2004). Such studies are also necessary to
699 establish the scientific foundations of so-called personalized medicine and person-
700 alized nutrigenomics (Calabrese, 2008; Dalton and Friend, 2006; Mutch et al.,
701 2005).

702 Finally, there are some other important issues that remain to be resolved before
703 hormesis can be successfully applied as an effective antiaging, health-promoting,
704 and lifespan-extending strategy. Some of these issues are as follows:

- 705 • Establishing stress exposure regimens in terms of intensity and frequency
- 706 • Adjusting the levels of mild stress for age-related changes in the sensitivity to
707 stress
- 708 • Establishing molecular criteria for identifying hormetic effects of different
709 stresses
- 710 • Identifying qualitative and quantitative differences in stress response pathways
711 initiated by different stressors
- 712 • Determining the interactive and pleiotropic effects of multiple stresses
- 713 • Determining the biological and evolutionary costs of repeated exposure to stress
714

715 In the context of modulating aging, repeated mild stress-induced hormesis
716 increases the boundaries of the homeodynamic space, thus giving cells and organ-
717 isms wider margins for metabolic fluctuation and adaptation. Slowing the shrinkage
718 of the homeodynamic space hormetically will reduce the increase in the probabili-
719 ty of occurrence and emergence of various diseases in old age and thus extend the
720 health span.

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