Cell Metabolism
Minireview

Stress-Response Hormesis and Aging: "That which Does Not Kill Us Makes Us Stronger"

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DOI 10.1016/j.cmet.2008.01.001

Hormesis refers to the beneficial effects of a treatment that at a higher intensity is harmful. In one form of hormesis, sublethal exposure to stressors induces a response that results in stress resistance. The principle of stress-response hormesis is increasingly finding application in studies of aging, where hormetic increases in life span have been seen in several animal models.

What Is Hormesis?

The term hormesis comes from the field of toxicology, and there are several variants of its exact meaning. In its broadest (and older) sense, it describes the dose-response relationships of treatments (e.g., chemical, thermal, or radiological) that are beneficial at a low level but harmful at a higher level (Figure 1) (for a detailed review, see Calabrese et al., 1999). Beneficial effects observed include increased growth rate, fecundity, and stress resistance. Given the toxicological axiom "the dose determines the poison," this sort of dose-response relationship can apply to agents that are not commonly considered toxic as well as those that are. For example, oxygen sustains life at atmospheric levels but is noxious at much higher levels.

However, there is a narrower sense in which hormesis is more often understood in recent studies, which can be illustrated as follows. Brief exposure to very high levels of oxygen can be beneficial, for example, increasing life span in the nematode *Caenorhabditis elegans* (Cypser and Johnson, 2002). Here, hormesis appears to involve induction by stress of mechanisms that protect against stress. We shall refer to this form of hormesis as "stress-response hormesis" to distinguish it from hormesis in the broader sense. The principle of stress-response hormesis is nicely captured by the well-known maxim of the nineteenth-century German philosopher Friedrich Nietzsche: "That which does not kill us makes us stronger."

The principle of stress-response hormesis can be seen in action in many contexts. As a classical example, low levels of insecticides can induce chemical resistance by increasing xenobiotic detoxification (Calabrese et al., 1999). Various other phenomena involve stress-response hormesis, though they are not typically described as such. For example, induction of drug-metabolizing enzymes by xenobiotic chemicals can provide protection against carcinogenesis (so-called chemoprotection) (Talalay et al., 2003), and innate and acquired immunity involves pathogen-stimulated resistance.

Hormesis: An Interesting History

Over the years, the concept of hormesis has been influential in a number of unusual contexts, including quack medicine and the popular imagination. Ideas about the benign effects of low levels of toxins have their origins in the late nineteenth century and the Arndt-Schulz "law," which postulated that all poisons are stimulatory in low doses. Proponents of homeopathy used this idea to justify their medical practice of administering compounds at very low concentrations. It has been argued that its association with homeopathy brought the concept of hormesis into disrepute (Calabrese et al., 1999). More recently, controversial claims about the health benefits of radiation hormesis were rejected in a major review by the US National Research Council (National Research Council, 2006).

Hormesis also has an unusual place in cinematic history. During the 1950s, reports on the capacity of ionizing radiation to stimulate growth inspired the genre of so-called "nuclear monster" movies, which included *Godzilla* (1954) and *Attack of the 50 Foot Woman* (1958). Typical of this genre was *Them!* (1954), in which ants exposed to radiation from atomic bomb tests grow to gigantic proportions and terrorize residents of New Mexico. (Contemporary publicity material promises "A horror hoard of crawl-and-crush giants crawling out of the earth from mile-deep catacombs!") Beyond this checkered past, the principle of stress-response hormesis has found a new lease of life in a novel context: the biology of aging.

Hormesis and Aging

From a molecular genetic perspective, stress-response hormesis corresponds to the induction by stressors of an adaptive, defensive response, particularly through alteration of gene expression. For example, thermal stress induces a heat-shock response involving increased expression of heat-shock proteins (chaperonins). These lead to protection against heat-induced molecular damage, particularly partial denaturation of proteins, by promoting the restoration of protein function via molecular chaperone activity.

The biological process of aging, while not fully understood, is clearly associated with an increase over time in levels of molecular damage, which contributes to increasing pathology and mortality at an organismal level. A powerful approach to investigating the mechanisms underlying aging and controlling its rate is the use of treatments that increase life span in laboratory model organisms (e.g., the budding yeast *Saccharomyces cerevisiae*, *C. elegans*, the fruit fly *Drosophila melanogaster*, and the mouse *Mus musculus*). Such treatments include manipulations of the insulin/IGF-1 signaling pathway and dietary restriction, the controlled reduction of food intake without malnutrition (Kenyon, 2005).

Increased longevity can be associated with greater resistance to a range of stressors. For example, long-lived *C. elegans*

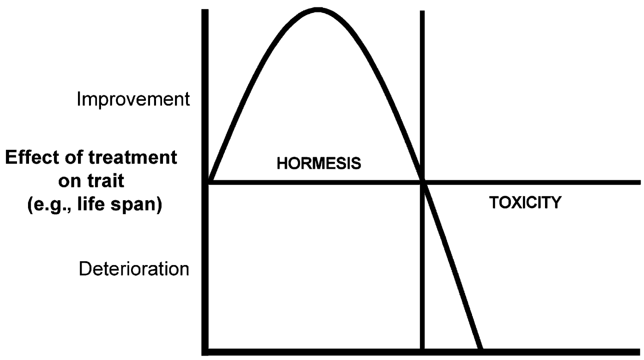

Figure 1. Dose-Response Curve of a Treatment with a Hormetic Effect
Low doses result in enhanced function, whereas higher doses result in dysfunction.

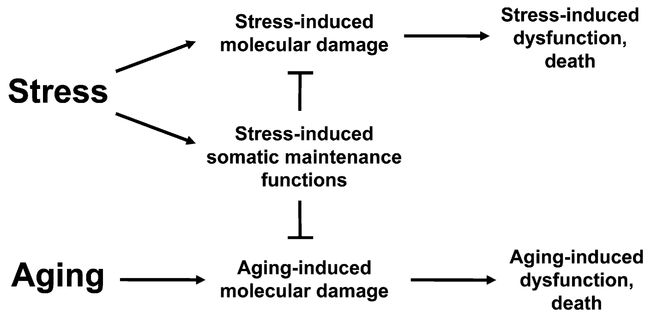

Figure 2. Possible Mechanism of Stress-Response Hormesis
Both stressors and aging cause molecular damage, leading to dysfunction and death. Stressors can also induce a stress response leading to enhanced somatic maintenance (e.g., via molecular chaperones and detoxification enzymes) and resistance to stress. This response can also cause some resistance to aging, suggesting that some overlap exists between the forms of molecular damage that result from some types of stress and those occurring during aging.

insulin/IGF-1 signaling mutants are resistant to thermal and oxidative stress (Lithgow and Walker, 2002). One possibility is that the increased longevity of these organisms is the result of increased expression of genes contributing to cellular maintenance processes, thereby protecting against the molecular damage that causes aging. Consistent with this, *C. elegans* insulin/IGF-1 signaling mutants show increased expression of a range of heat-shock proteins and antioxidant and drug-metabolizing enzymes (Lithgow and Walker, 2002; McElwee et al., 2007). Whether induction of each of these classes of enzyme is sufficient to increase life span remains largely undemonstrated. However, overexpression of individual heat-shock proteins can be sufficient to increase life span, at least in an insulin/IGF-1 signaling mutant (Walker and Lithgow, 2003). Long-lived mutant flies with reduced insulin/IGF-1 signaling also show some resistance to oxidative stress (Clancy et al., 2001). However, flies that are long lived as a result of dietary restriction do not show any general increase in stress resistance (Burger et al., 2007). It is therefore important to establish whether the stress resistance associated with extension of life span by altered insulin/IGF-1 signaling is causal or simply correlated.

If induction of stress resistance increases life span and hormesis induces stress resistance, can hormesis result in increased life span? Here the answer is definitively yes. For example, in *C. elegans*, brief thermal stress sufficient to induce thermotolerance also causes small but statistically significant increases in life span (Lithgow et al., 1995). Significantly, the dose-response relationships for thermotolerance and longevity are very similar (Cypser and Johnson, 2002); furthermore, in *C. elegans* populations subjected to mild heat stress, expression levels of the small heat-shock protein gene *hsp-16* in individual worms are predictive of both thermotolerance and life span (Wu et al., 2006). These results further support the view that increased stress resistance causes increased life span. Other sorts of stress-response hormesis can also increase life span. For example, brief exposure to hyperbaric oxygen or juglone (a compound that generates reactive oxygen species) can increase life span (Cypser and Johnson, 2002), perhaps through induction of antioxidant enzymes, although this remains to be demonstrated. A hypothetical view of the action of stress-response hormesis on aging is shown in Figure 2.

This application of hormesis has implications for drug design, opening the possibility of chemical inducers of hormesis ("hormetins") with a range of therapeutic applications, including protection against aging-related disease. The animal model studies described above also raise further questions, such as: What are the processes that hormesis stimulates that increase life span? Are all effects on aging attributable to induction of chaperonins, or is induction of other biochemical processes important? Is selective induction of expression of other maintenance processes possible and sufficient to protect against aging? Other processes that are candidate effectors in the impact of hormesis on aging include antioxidant defense, biotransformation (xenobiotic metabolism), metal trafficking (e.g., metallothioneins and ferritins), and innate immunity, all of which appear to be induced in long-lived mutants.

Dietary Restriction, Insulin/IGF-1 Signaling, and Hormesis

One possibility raised by studies of hormesis is that the increase in life span in animals subjected to dietary restriction or in insulin/IGF-1 signaling mutants results from hormesis. In fact, in each case there is evidence consistent with this. For example, rats subjected to dietary restriction show elevated plasma levels of the stress hormone corticosterone relative to ad libitum-fed controls and are resistant to carcinogenesis (e.g., phorbol ester-induced skin papillomas). Whether the increased levels of corticosteroids cause the increase in life span remains unclear. However, it has been shown that if dietarily restricted rats are adrenalectomized, their tumor resistance is abrogated (Masoro, 1998). These findings provide support for the possibility that dietary restriction is a stressful condition and results in stress-response hormesis and that this response contributes to increased longevity (Masoro, 1998).

It has recently been suggested that extension of life span by one type of dietary restriction, glucose restriction, in *C. elegans* involves hormesis through an increase in mitochondrial respiration and oxidative stress (Schulz et al., 2007). However, rodents subjected to dietary restriction show lower levels of oxidative damage and lower expression of oxidative defense systems

(Pamplona and Barja, 2007), suggesting that some effects of dietary restriction may not be evolutionarily conserved.

Could hormesis be involved in the altered longevity of insulin/IGF-1 signaling mutants? Hypothetically, abnormalities in insulin/IGF-1 signaling could lead to a stressed metabolic state, resulting in stress-response hormesis. The increase in life span resulting from reduced insulin/IGF-1 signaling involves activation of the FOXO transcription factor DAF-16 (Kenyon, 2005). Insulin/IGF-1 receptor-activated kinases inactivate DAF-16 by phosphorylation, such that lowered insulin/IGF-1 signaling leads to activation of DAF-16, which contributes to the increase in longevity. Mutation of the *daf-16* gene fully suppresses the altered longevity of insulin/IGF-1 signaling mutants, and mutation of the *daf-18* PTEN phosphatase also suppresses insulin/IGF-1 signaling-mediated increases in life span. Interestingly, extension of life span via hormesis, whether induced by heat or oxidative stress, is suppressed by mutation of *daf-16* or *daf-18* (Cypser and Johnson, 2003). This is at least consistent with the possibility that lowered insulin/IGF-1 signaling causes stress-response hormesis, but further work will be required to determine whether this is really true. Ultimately, this will require identifying the genes and processes that are regulated by insulin/IGF-1 signaling that produce such large effects on aging rate and establishing whether the same factors mediate the effects of hormesis.

Here it is worth noting that the effects of dietary restriction on *C. elegans* life span are, according to most studies, not *daf-16* dependent, arguing that any role for hormesis in this context must rely on different molecular mechanisms. Interestingly, in *Drosophila*, extension of life span by altered insulin/IGF-1 signaling, but not by dietary restriction, is associated with increased resistance to bacterial infection, again arguing for different mechanisms (Libert et al., 2008). Possibly, the mechanisms by which dietary restriction extends life span are different in different kinds of organisms, with mammals showing a greater effect of hormesis. Alternatively, other types of hormesis may be important in both rodents and the two invertebrates.

Hormesis and Biotransformation

The biotransformation system, the effector of drug/xenobiotic metabolism, is very susceptible to hormetic induction. This is a complex system of enzymes, including cytochrome P450 oxidases and glutathione S-transferases, involved in both detoxification and excretion of a wide range of biologically undesirable organic compounds, including damaged cellular constituents, drugs, and other environmental xenobiotics (Gibson and Skett, 2001). Induction of biotransformation provides protection against molecular damage and can be achieved by administration of xenobiotics at nontoxic levels. This has been shown to provide effective protection against molecular damage-induced pathologies, including carcinogenesis and light-induced damage in retinal epithelial cells (reviewed in Talalay et al., 2003). This therapeutic, referred to as chemoprotection, is a form of chemical stress-response hormesis.

One interesting possibility is that in long-lived animals (e.g., dietarily restricted animals or insulin/IGF-1 signaling mutants), disturbances in physiology may cause internal chemical stress that results in chemical hormesis of this type and increased life span. A recent study of mice is consistent with this possibility. In recent years, a range of long-lived mutant mice have been identified that have common abnormalities affecting growth hormone (GH) and/or IGF-1 signaling. These include the Little mouse, which has a defect in the GH-releasing hormone receptor (*Ghrhr*) gene and is therefore GH deficient and, consequently, a dwarf. Studies of hepatic gene expression in Little mice show increased expression of biotransformation genes and imply abnormalities in bile acid metabolism (Amador-Noguez et al., 2007). Bile acids are oxidation products of cholesterol that contribute to biliary function. These mice have been shown to be resistant to xenobiotic toxicity, i.e., there is some correlation between resistance to xenobiotic compounds and longevity. Furthermore, induction of biotransformation proved to be attributable to increased levels of bile acids in this mutant, acting via a nuclear hormone receptor, the farnesoid X receptor (FXR) (Amador-Noguez et al., 2007). Thus, chemical hormesis leads to induced biotransformation and xenobiotic resistance, although the importance of this in longevity assurance remains undemonstrated. Interestingly, long-lived insulin/IGF-1 signaling mutant *C. elegans* and *Drosophila* also show evidence of elevated expression of genes involved in xenobiotic metabolism (McElwee et al., 2007).

Environmental Stressors: Good or Bad?

An intriguing implication of the study by Amador-Noguez et al. (2007) relates to the role of bile acids in wild-type mice that, at normal circulating levels, continually stimulate low-level expression of biotransformation genes via FXR. Thus, normal levels of stressors may be important for setting the "tone" of the stress-resistance processes. This is consistent with the broader view that the best route to optimal health involves not the elimination of all stressors from our environment but their reduction to optimal levels. If true, this would have major implications for public health policy.

Whether it is better to eliminate or optimize levels of an environmental stressor will, of course, vary with the stressor concerned. For example, elimination of ionizing radiation seems to be the best course. Other stressors may have hormetic benefits that are far outweighed by their dangers. An example here is cigarette smoke, which is highly protective against Parkinson's disease (Quik, 2004). This is probably because nicotine has neurotrophic effects but might also be because it induces biotransformation enzymes that detoxify compounds that promote this disease.

For other stressors, a better course of action may be optimization rather than elimination. Fruits and vegetables contain a wide range of mildly stressful electrophilic compounds that stimulate phase 2 xenobiotic metabolism and oxidative stress resistance (Talalay et al., 2003). These include sulforaphane, an isothiocyanate isolated from broccoli, and resveratrol, a stilbene phytoalexin abundant in grape skins. The presence of such compounds may contribute to the beneficial effects of eating fruits and vegetables. In terms of immunity, the hygiene hypothesis proposes that recent increases in the incidence of allergies and asthma are due to insufficient exposure to pathogens during childhood (Martinez, 2001). Tests of this hypothesis imply that exposure to bacterial endotoxins in house dust is particularly important. Similarly, the physiological stress of exercise has an optimal point (e.g., for developing muscle strength and improving cardiovascular health), beyond which detrimental effects can be experienced (e.g., attrition of cartilage in joints, leading to arthritis). Another possible example here is alcohol consumption. Epidemiological data show that, relative to abstainers, moderate drinkers have reduced mortality risk, especially from coronary heart disease (Marmot, 2001). However, it is not known whether this effect involves stress-response hormesis.

In summary, the study of stress-response hormesis and the induction by stressors of biochemical processes that protect against stress is providing new insights into the mechanisms that protect against a range of pathological processes, including aging. It also suggests that improvements in public health may be achieved through optimization of environmental stressors, perhaps including dietary supplements to induce appropriate forms of chemical hormesis.

ACKNOWLEDGMENTS

We thank the Wellcome Trust for support.

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