Dose-Response: An International Journal

Volume 8 | Issue 1 Article 4

3-2010

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Peter A Parsons
La Trobe University, Bundoora, Victoria, Australia

Dose-Response, 8:4–9, 2010
Formerly Nonlinearity in Biology, Toxicology, and Medicine

ISSN: 1559-3258
DOI: 10.2203/dose-response.09-018.Parsons

International Dose-Response Society
www.Dose-Response.org

PROSPECTUS

SURVIVAL ACROSS THE FITNESS-STRESS CONTINUUM UNDER THE ECOLOGICAL STRESS THEORY OF AGING: CALORIC RESTRICTION AND IONIZING RADIATION

Peter A. Parsons □ La Trobe University, Bundoora, Victoria, Australia

□ Free living organisms typically occur in harsh environments challenged by abiotic stresses of varying intensities. Taking ionizing radiation and caloric restriction as examples, environmental variation from benign to extreme gives a fitness-stress continuum where energetic efficiency, a measure of fitness, is inversely related to stress level. Hormesis occurs in benign regions for these examples. In contrast aging emphasizes survival towards the limits of survival under accumulating stress from Reactive Oxygen Species, ROS. An energetic evolutionary approach underlies an ecological aging theory based principally upon survival, which incorporates hormesis. Multiple environmental agents contributing to hormesis should be considered by those attempting to improve the quality of life by delaying the onset of senescence, so enhancing survival. Caloric restriction has wider acceptance in this process than ionizing radiation.

Key words: energetic efficiency, environmental stress, hormesis, longevity, senescence, survival.

INTRODUCTION: WHAT IS FITNESS?

Environmental stresses are a feature of the habitats of all organisms on Earth. Resource depletion and hence inadequate nutrition are the norm so that organisms struggle to survive (White 2008). A general feature of exposure to abiotic stresses is an increase in energy expenditure. Variations in energy can be related to the level of cellular adenosine triphosphate (ATP) which is the universal energy currency for living cells. The metabolic organization of organisms should therefore follow quantitative rules derived from basic physical principals. In other words bioenergenetics, the study of energy flow through living systems, provides a context for evolutionary studies of organisms in their habitats. That is, how does variation in energy flow translate into fitness differences among genotypes?

Selection favors efficiency in the conversion of food into reproductive output. In this process, food input interacts with the environment to provide metabolic pools, which mainly involve ATP and other high-energy nucleotides. From such metabolic pools, resources are allocated to fitness-related entities including development and growth, maintenance, reproduction, foraging and ultimately survival.

Address correspondence to Peter A. Parsons, PO Box 906, Unley SA 5061, Australia; E-mail: pparsons@internode.on.net.

Commencing with the pivotal role of ATP synthesis, Torres (1991) defined fitness in terms of the distance of a given individual's thermodynamic parameters from its optimal value, an approach anticipated by Fisher (1930). While fitness is characteristically assessed at the organismic level for a range of traits such as fecundity, survival and longevity, energy provides a more fundamental foundation. A tendency towards increases energetic efficiency of organisms in their habitats represents an adaptive process which translates into increased fitness. In this context, stress is an energy drain which can be expressed by a loss of fitness so that energetic efficiency is reduced. Increased stress will therefore disturb the energy balance between input and output that organisms build up in their habitats.

THE FITNESS-STRESS CONTINUUM AND RADIATION HORMESIS

Variation in the severity of an environmental stress gives a non-linear fitness continuum from benign to extreme. Considering temperature, fitness should be maximal at intermediate temperatures between extremes of heat and cold. Physiologically this expectation is manifested by low metabolic rates at intermediate temperatures. Indeed, fitness maxima occur in regions of mild temperature fluctuations reflecting those of wild habitats; more extreme constant or wide fluctuations are disadvantageous. Since fitness in relation to stress level is non-linear, the linear no-threshold (LNT) premise is invalid, because all environmental agents have energetic costs. Especially in the toxicology literature, the term hormesis is used to describe such maxima; they are close to the origin for agents that are exceedingly toxic at high exposures.

An array of mild stresses including cold, heat, physical activity, irradiation and caloric restriction can induce longevity extensions (Calabrese and Baldwin 2000; Rattan 2004). Fitness maxima of hormetic zones therefore should reflect trade-offs among various metabolic components all directed towards high energetic efficiency.

Radiation hormesis is commonly observed in experimental organisms and in man at exposures substantially exceeding background radiation levels. Assume that energy and metabolic reserves such as heat shock proteins, hsps, are built up to counter the wide array of stresses to which organisms are exposed in natural habitats. Such adaptive responses could provide protection from low-level to moderate stresses such as ionizing radiation at non-catastrophic levels but at higher levels than background. That is, the hormetic response becomes part of a general stress response involving hsps and other metabolic adaptations across stress levels and environmental agents. Fitness interactions for combinations of stresses should therefore ameliorate the effects of individual stresses in isolation. Therefore the hormetic model can be extended to multiple environmental agents. Cross- protection among various environmental agents should then occur, so that hormesis depends upon the energetic consequences of the totality of interacting environmental stresses of natural habitats. Hormesis therefore is an expression of high energetic efficiency and hence high fitness that evolves in response to single and multiple environmental agents, and where energetic costs are not excessive (Parsons 2005, 2006, 2007a).

Such interactive effects are consistent with numerous observations of radiation hormesis in a wide variety of microorganisms, plants, invertebrates and vertebrates (especially our own species) far in excess of background exposures. Using measures of cancer mortality rates and mean lifespan in humans, Luckey (2006) concluded that 'no scientifically acceptable study' was found which showed that less than 100 mSv was harmful, and in fact radiation hormesis is the norm. By contrast the normal background exposure at sea level is around 1/40 of 100mSvy, that is 2.5 $mSvy^{-1}$. Radiation hormesis is apparently an expression of evolutionary adaptation of organisms to multiple abiotic stresses in the environments of organisms. Indeed, Luckey (2006) has commented that low dose irradiation may have a role as an agent of health, although this view does not have wide acceptance.

THE STRESS THEORY OF AGING

Genetically-determined resistance to a variety of stresses in many species, including yeast, nematodes and *Drosophila melanogaster*, is strongly correlated with longevity especially when measured by survival. The primary or operative factor is oxidative stress. In fact, similar gene expression patterns characterize aging and oxidative stress in *D. melanogaster*. Individuals with the potential for a long life should therefore carry genes for resistance to Reactive Oxygen Species, ROS, which are an inevitable consequence of life in a world rich in oxygen (Arking 1998).

Genes conferring high stress resistance should therefore promote substantial vitality, homeostasis, and energetic and metabolic efficiency. They underlie fitness to survive to old age in the face of multiple hazards within natural populations. Evolutionary changes in the rate of senescence and hence longevity should therefore depend on selection for stress resistance, which in *D. melanogaster* is a more effective procedure for increasing longevity than direct selection on longevity (Parsons 2005). Indeed survival from multiple stress (heat, oxidative, starvation) screening is an effective procedure for the isolation of longevity mutants (Wang *et al.* 2004). The rate of aging then depends upon the effectiveness of selection for energetic efficiency in the face of free radical stresses. Internal factors within organisms interact and overlap with external factors from the environment in this process.

The ecological stress theory of aging incorporates the environment of organisms (Parsons 1995, 2007a). For example, a highly significant association was found between heat-stress resistance and viability and longevity in *D. melanogaster* taken from the heat-stressed south-facing slope (SFS) of 'Evolution Canyon', Israel, when compared with flies from the more benign north-facing slope (NFS). Strong microclimate selection clearly occurs based upon oxidative stress as the primary determinant of the niche differences (Miyazaki *et al.* 2005).

Turning to humans, median lifespans in earlier times were in the 25-30 year range compared with values at least double those in well-nourished populations today, although from Greek and Roman times some individuals achieved extremely old ages. The lifespan extensions of the modern era permit the possibility that the relative fitnesses of traits can change with age, especially beyond reproduction. Various evolutionary theories of aging, which appear most applicable to the benign environments of such human populations, have been developed implicitly incorporating these complications (eg Arking 1998).

HORMESIS FOR CALORIC RESTRICTION

The energetic consequences of the ecological stress theory of aging imply that in the relatively benign environments of modern human populations, median lifespan should increase upwards by delaying the obvious onset of senescence, but with little effect on the potential maximum. In fact, the mitochondrial free-radical theory of aging favors an upper limit to the quantity of oxygen that cells can accommodate before irreversible change occurs. For example, in many modern human populations diets tend to be excessive so that the production of free radicals is elevated. Maximum energetic efficiency and fitness should therefore occur when diets are adequate but not excessive. This non-linear relationship between the energetic costs of diet and fitness is an example of caloric or nutritional hormesis.

Caloric restriction (CR) markedly extends the lifespan of rats, mice, *D. melanogaster* and other species, since age-associated physiological deterioration and disorders are delayed. Masoro (2007) argues that CR is a low-level stressor, which enhances the ability of organisms to cope with abiotic stresses in general. At times of CR-induced life extension, there is reduced endogenous generation of damaging agents, especially ROS, implying enhanced survival. Hormesis therefore follows as a consequence of the energetic (and metabolic) efficiency of evolutionary adaptation to the interacting stresses of CR-restricted environments in parallel with radiation hormesis. Hormesis from CR therefore has an important role in delaying aging and extending life.

SENESCENCE AND SURVIVAL

Towards stressed extremes where fitness is low, the premium is on individual survival at times of substantial potential mortalities under stress. Hormesis should be of little consequence especially where limits to adaptation are tested, even though the economical management of resources required under these circumstance implies strong selection for stress resistance and hence energetic efficiency.

Measures of survival are inherited more directly than lifespan, and should be highlighted. In fact, senescence, the decreasing effectiveness of mechanisms by which organisms avoid death or loss of fitness and hence survive in their environments, has a higher heritability than longevity (Williams 1999; Parsons 2007a). Survival to old age is therefore underwritten by high energetic efficiency implying high metabolic (emphasizing protein) homeostasis based upon genes for high stress resistance, enabling maximum tolerance to the stresses and rigors of free-living populations (eg Leopold and Perrimon 2007; Nicchitta 2009). Delays in various age-dependent mechanisms leading to frailty would be expected in individuals with a genetic architecture incorporating high stress resistance (Vaupel 1988). Indeed, there is some limited evidence for survival and longevity improvements at extreme ages. A dependence upon highly adaptive, oxidative-stress resistant and presumably somewhat homozygous genotypes underlying outlier phenotypes, has been put forward as one explanation (Parsons 2007b).

CONCLUSION

Hormesis is an expression of high fitness typically measured by survival in response to environmental agents where energetic costs are not high so that metabolic stability is high. Cross-protection across environmental agents enhances hormesis, including radiation and CR hormesis. Hormesis and aging should be considered as an integrated evolutionary system covering environments ranging from benign to extreme on a fitness-stress continuum. This is the ecological stress theory of aging and hormesis which has predictive power for organisms in their habitats, including those of favored humans of the modern era.

The multiple environmental stresses underlying hormesis therefore appear significant in terms of enhancing the quality of life of organisms. In the case of humans of the modern era, CR should attract more attention. Compared with hunter-gatherer societies, extremes of many abiotic stresses are ameliorated, thus potentially deferring the onset of obvious senescence.

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