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NUTRITIONAL HORMESIS AND AGING

Daniel P. Hayes □ The Brooklyn Hospital Center, Brooklyn, New York

□ Nutritional hormesis has the potential to serve as a pro-healthy aging intervention by reducing the susceptibility of the elderly to various chronic degenerative diseases and thereby extending human healthspan. Supportive evidence for nutritional hormesis arising from essential nutrients (vitamins and minerals), dietary pesticides (natural and synthetic), dioxin and other herbicides, and acrylamide will be reviewed and discussed.

Keywords: aging, hormesis, pesticides, herbicides, dioxin, acrylamide, vitamin D

INTRODUCTION

In response to the questions at hand whether hormesis is applicable as a pro-healthy aging intervention in mammals and human beings, and how: yes, hormesis is applicable as a pro-healthy aging intervention and nutritional hormesis provides a means of achieving this goal. In this context hormesis is defined as a process in which a low dose of a nutritional stressful stimulus activates an adaptive response that increases resistance to moderate or severe stress. Evidence suggests that no single mechanism explains hormetic responses, with some ten different mechanisms (including inducible repair, gene upregulation, apoptosis, etc.) being listed by Hoffmann (2009). Among stressors which may induce hormetic effects in humans are exercise, ethanol, pharmacological agents and dietary restriction (both every-day caloric restriction and intermittent fasting). Supportive evidence from laboratory and human studies for the positive and important role of nutritional hormesis as an aging intervention will be discussed. The evidence arises from the following nutritional stressors: essential nutrients (vitamins and minerals), dietary pesticides (natural and synthetic), dioxin and other herbicides, and acrylamide.

ESSENTIAL NUTRIENTS (VITAMINS AND MINERALS)

Vitamin and minerals are hormetic essential nutrients that are necessary to maintain and promote human health. Deprivation levels of these essential nutrients produce adverse effects such as loss of function or overt disease, while excessive levels of some nutrients also lead to adverse effects such as hypervitaminosis, tissue mineralization, and electrolyte imbalance.

Address correspondence to Daniel P. Hayes, The Brooklyn Hospital Center, 121 DeKalb Avenue, Brooklyn, New York 11201; Phone: 212 676-1558; Fax: 212 676-1548; E-mail: dhayes@health.nyc.gov.

Intermediate nutrient levels are both required and beneficial with the organism then being in a state of homeostasis (operationally defined as the dose range that results in neither deficiency nor toxicity.) The 17th edition of The Merck Manual of Diagnosis and Therapy (Beers and Berkow 1999) describes these effects and discusses and contrasts deficiencies, dependencies, and toxicities of 5 vitamins, and deficiencies and toxicities of 6 macrominerals and 5 microminerals. Eaton and Klaassen (2001) in their "Principles of Toxicology" chapter of a major toxicological reference, Casarett and Doull's Toxicology: the Basic Science of Poisons, depict the individual dose-response relationship for an essential substance required for normal physiological function and survival such as an essential vitamin or mineral nutrient as being U-shaped with the biphasic nature of response being subdivided into low-dose and high-dose regions where the toxicity response differentially occurs (the arms of the U), plus a region of no toxicity (the trough of the U). Many additional examples of essential trace elements (i.e., micronutrients) producing U-shaped responses on physiologic functioning – ranging from impairment at deficient intakes to optimal functioning at intermediate intakes, and toxicity at excessive intakes – have also been given by Mertz (1981).

Over the past three to four decades, convincing evidence has emerged that vitamin D generates positive and important biological responses in the immune, heart-cardiovascular, muscle, pancreas and brain systems, as well as involvement in cell cycle control and thus of cancer disease process (Norman 2008). Reasons have also been advanced which strongly suggest that vitamin D provides protection against low-level radiation damage (Hayes 2008a). In addition, the positive and important role of vitamin D in the aging process, through its exertion of salutary control/amelioration of various human maladies contributing to aging, has also been discussed (Hayes 2009). There is substantative evidence that vitamin D acts as a hormetic agent. Laboratory studies attest to vitamin D-induced biphasic dose-responses (Aubin and Heersche 1997). Cited by Stumpf (2006) as exemplifying hormesis in humans is the fact that low doses of vitamin D have stimulatory effects promoting epidermal wound healing in contrast to high doses inhibiting psoriasis. A longitudinal nested case-control epidemiological study of prostate cancer risk showed intriguing biphasic U-shaped vitamin D dose-response (Tuohimaa et al. 2004).

DIETARY PESTICIDES (NATURAL AND SYNTHETIC)

Naturally occurring pesticides that are rodent carcinogens are ubiquitous in fruits, vegetables, herbs and spices, and dwarf the contribution of synthetic chemical pesticides in the human diet. Even though only a small proportion of natural pesticides have been tested for carcinogenicity, circa year 2003 half of those tested (38/72) have been found to be

rodent carcinogens (Gold et al. 2003). Epidemiological and other studies support the protective role of fruits and vegetables against cancer, including prospective epidemiological studies of atomic bomb radiation survivors (Hayes 2005). Hormesis has been suggested to explain the paradox that plant foods containing carcinogens also protect against cancer with the plant diet bringing together many different toxic chemicals that when ingested at low doses stimulate the chemo-defense system and enhance host resistance (Parsons 2000; Rico 2002). There is also evidence that some synthetic chemical pesticides that enhance tumor formation at high doses may affect a reduction in tumor incidence at lower doses. For example, biphasic dose-responses have been reported in DDT laboratory rat studies (Sukata et al. 2002; Kushida et al. 2005).

DIOXIN AND OTHER HERBICIDES

Evidence that hormesis may be an important factor in herbicide use has been presented (Duke et al. 2006). There is great interest in the seventy-five phenoxy acid compounds which constitute the group labeled dioxins (polychlorinated dibenzo-p-dioxins). The most acutely toxic of the polychlorinated dibenzo-p-dioxin isomers is considered to be 2,3,7,8-tetrachlorodibenzo-p-dioxin, hereafter TCDD. Since dioxin is found in trace amounts in some herbicides, autoexhaust, and the incineration process, humans could be exposed to it just by eating meat, fish, eggs or diary products. While declared a human carcinogen by both the International Agency for Research on Cancer (IARC) and the United States Environmental Agency (EPA), a critical review of these declarations has concluded that "the long-term accumulation of negative, weak, and inconsistent findings suggests that TCDD eventually will be recognized as not carcinogenic for *humans* (italics mine)" (Cole et al. 2003). The largest, longest, and most detailed dioxin laboratory experiment entailed a 2-year TCDD study of white rats carried out by Kociba et al. (1978) which formed the basis of the EPA declaring dioxin a human carcinogen. But the Kociba study also showed that dioxin has an anticancer effect at low doses: reducing tumor incidences in various organs, showing striking U-shaped dose-response relations when all tumors were combined, and displaying a modest decrease in female liver tumors which was the critical target organ for the EPA cancer risk assessments (Cook 1994). Striking hormetic effects have been reported in a TCDD study of Sprague-Dawley rats (Fan et al. 2006).

Hormetic effects have been reported from various TCDD epidemiological studies. Various case-control studies have reported biphasic soft tissue sarcoma dose-responses for low body burdens of dioxin and three related polychlorinated biphenyl compounds (Tuomisto et al. 2004, 2005). These results were reported to support similar hormetic biphasic dose-responses in animal studies. Long-term monitoring of the victims of

major dioxin industrial accidents at Saveso, Italy in 1976 and at Monsanto Chemical's Nitro, West Virginia plant in 1949 failed to reveal any deleterious effects other than temporary chloracne (a severe acne-like skin disorder), and short-term reversible nerve dysfunction (Cole et al. 2003). It has also been reported that both the chemical plant worker mortality data underlying the 1990 National Institute of Occupational Safety and Health (NIOSH) Report on Dioxin and the Saveso cancer data showed hormetic J-shaped responses (Kayajanian 1999, 2002). A major quantitative study's evaluation of long-term mortality of workers previously exposed to substantial dioxin levels at the Dow Chemical Company (the producer of the herbicide Agent Orange) revealed that both all cancers combined and lung cancers were at or below expected levels, with very low rates for those who developed chloracne (Bodner et al. 2003). Agent Orange used in the Vietnam War was the name for a mixture of the TCDD-containing herbicide 2,4,5-T and the nondioxin herbicide 2,4-D (which itself evinces hormesis in oyster growth, Davis and Hidu 1969). Associations between TCDD and all-site cancer and prostate cancer in members of the Operation Ranch Hand cohort who handled Agent Orange were only reported after stratification based on years of service (before 1969, when the TCDD levels on Ranch Hand veterans were highest) and days of spraying (Michalek and Pavuk 2008). The findings of elevated levels of other toxic chemicals in the Vietnamese environment, including dibenzofurans and pesticides, as well as an association between time spent in Southeast Asia and cancer, suggest that focusing only on Agent Orange exposure with respect to health in Vietnam veterans is no longer appropriate (Schecter et al. 2009).

ACRYLAMIDE

Acrylamide occurs as a natural product of cooking with high levels being detected in widely consumed food items. It has been classified as a group 2A carcinogen (probably carcinogenic to humans). Hormetic effects have been reported: "unexpectedly an inverse trend was found for large bowel cancer with a 40% reduced risk in the highest compared to lowest quartiles of known acrylamide intake" (Mucci et al. 2003a), and a decreased risk of colorectal and kidney cancers with increasing acrylamide dose (Mucci et al. 2003b).

DISCUSSION AND CONCLUSIONS

Evidence for nutritional hormesis arising from essential nutrients (vitamins and minerals), dietary pesticides (natural and synthetic), dioxin and other herbicides, and acrylamide have been reviewed and discussed. The evidence is an operational definition of Paracelsus' dictum that the efficacy of toxic chemicals depends on dosage which in no ways negates the historic misuse and dangers of many of these things. Nutritional

hormesis could very well be applicable as a pro-health intervention by extending human healthspan. An example of this arises from the hormetic agent vitamin D which has been posited to play a productive and positive role by reducing susceptibility in the elderly to various chronic degenerative diseases (Hayes 2009).

Throughout the world there is increasing awareness of the importance of nutrition to human well-being. Advancement of the facts and ideas presented here would not only contribute to human well-being but also to an appreciation and acceptance of the hormesis paradigm by the public. More extended discussions of this topic are available (Lindsay 2005; Hayes 2007, 2008b).

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