Interventions in Aging and Age-Associated Pathologies by Means of Nutritional Approaches

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ABSTRACT: So-called antioxidant strategies have not been shown convincingly to be effective in increasing life spans of animals. Thus, the general consensus of experimental gerontology in the last century was that the only reproducible means of prolonging survivals of animals is the calorie restriction paradigm. As a challenge against this dogma, we attempted to examine the effect of two potent antioxidants, one tetrahydrocurcumin (a biotransformed metabolite of curcumin contained in turmeric of Indian curry) and the other green tea polyphenols.

KEYWORDS: antioxidant; aging; mice; tetrahydrocurcumin; green tea polyphenol

INTRODUCTION

The "Free Radical Theory of Aging" (FRTA) initially proposed half a century ago by Harman[1] has been increasingly supported in recent years. However, while there have been a number of studies demonstrating a significant effect of antioxidant treatment in preventing experimentally induced pathologies that are believed to be at least partially caused by oxygen-induced tissue damage, so-called antioxidant strategies have not been shown convincingly to be effective in increasing life spans of animals.[2] Accordingly, the general consensus of experimental gerontology in the last century was as follows: "The only reproducible means of prolonging survival of animals is the calorie restriction paradigm."

As a challenge to this dogma, we attempted to examine the effect of two potent antioxidants, one tetrahydrocurcumin (TC), a biotransformed metabolite of curcumin contained in turmeric of Indian curry, and the other green tea polyphenols (PPs).

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MATERIALS AND METHODS

Male C57L/6JNia mice (Harlan Sprague Dawley) began to receive treatments at the age of 13 months. In the TC experiment, animals received TC-containing pellets (0.2%) or standard pellets (MF, Oriental Limited, protein 24%). In the experiment with PPs, animals received normal diets (MF) and normal drinking water or water containing green tea water extract product (Sunphenon 100S, Taiyokagaku, Yokkaichi, Japan) containing various PPs (>70%) at a concentration of 80 mg/L, both pasteurized by γ-ray irradiation. Survival of animals were examined until deaths of these animals.

RESULTS

Average life span (days) in TC fed mice was 11.7% longer (882.2 ± 154.6, mean ± SD) than in control mice (797.6 ± 151.2, both $n = 50$) ($P < .01$). The 10% longest survival was also significantly greater (+6.5%, each $n = 5$, $P < .05$) in TC fed animals. The increase in average life expectancy after 24 months of age, calculated by including mice that died before 24 months as negative days, was 125.9%. In mice fed PPs, the average life span increased by 6.4% (801.1 ± 121.5 vs. 852.7 ± 88.2, control vs. PP fed mice, each $n = 50$, $P < .01$). The increase in average life expectancy after 24 months was 72.6%.

Body weights of TC fed animals were slightly (4–6%), but significantly ($P < .05$) lower compared with corresponding values in control mice in the first 6 months of treatments. Thereafter, the difference was totally lost. In PP fed mice, average body weights were almost identical to those in control mice throughout the observation periods.

DISCUSSION

Since the proposal of FRTA by Harman, several attempts have been reported primarily on mice in order to prolong the life spans of animals by feeding animals with different kinds of antioxidants. These earlier attempts used mostly antioxidant preservatives, some of which turned out to be carcinogenic (for review, see Ref. 3). Apparently, a safer and more practical approach to intervene in aging based on antioxidant strategies is needed. Since antioxidants contained in foods (vegetables and fruits) are largely harmless, nutritional antioxidants (so-called nutriceuticals) may justify a further study of this approach. However, most past attempts, including that by Lipman and co-workers,[2] by nutritional means have failed in achieving a statistically significant prolongation of life spans of animals.

In contrast, as shown in the present study, some nutriceuticals appear to have potential of significantly increasing life spans of animals. In the case of TC in the present study, very minor, but significant differences in average body weight are observed between control and TC fed animals. It is conceivable that these differences in body weight have been caused by a slightly lower food intake in TC fed animals, leading to an unintended dietary restriction. However, the difference between the two groups is only 4–6% and also only in the first 6 months of the treatment. In past references, we have been unable to find a study showing a positive effect of dietary

restriction on survival of animals that had body weights with such minor differences from control animals.

Accordingly, we judge that the difference in survival between control and TC fed animals was not solely due to the very minor dietary restriction, but that TC feeding significantly affected survival of animals, although an additive (or synergistic) effect of very moderate dietary restriction cannot be excluded. In the case of PPs, body weights were practically identical for both groups, excluding the above possibility, although the effect was milder with PPs compared with TC feeding. Both nutriceuticals have been shown to be effective in preventing a number of experimentally induced age-associated disorders, including cancer, atherosclerosis, and others.[4–10] Furthermore, the advantage of these agents is their lower toxic nature to humans, which has been confirmed in human experimentation over thousands of years.

Since these agents are known to be effective in preventing atherosclerosis that does not involve wild-type rodents, but is the number-one killer of elderly humans, it is expected that supplementation of these agents may be effective for prolonging the life span (at least health span) of humans possibly more effectively than observed in rodents.

CONCLUSIONS

Nutritional approaches in prolonging the health span (if not life span) of humans may be more promising than believed before and deserve further extensive study using nutriceuticals possessing antioxidant properties.

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