COMMENTARY

Somatotropic axis

Aron Walker

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INTRODUCTION

Mice with genetic Growth Hormone (GH) deficiency or resistance live much longer than their normal siblings under identical conditions with unlimited food access. These mutants' extended longevity is associated with an increase in their health span (period of life free of disability and disease) as well as delayed and/or slower ageing. Importantly, GH and GH-related traits have been linked to the regulation of ageing and longevity in both unaltered mice and other mammalian species, including humans. Evidence suggests that suppressed GH signaling has an impact on ageing via multiple interacting mechanisms and involves trade-offs between growth, reproduction, and longevity. Slow postnatal growth, delayed sexual maturation, and other life history traits of long-lived GH-related mutants.

These characteristics are consistent with a slower pace of life, which is a well-documented characteristic of wild animal species that live for a long time in their natural environment. Slower pace of life (or at least some of its features) appear to be associated with increased longevity both within and between species. This association is unexpected and may appear counter intuitive, because the relationships between adult body size (a GH-dependent trait) and longevity are opposite rather than similar within and between species. To elucidate the mechanisms of these relationships, studies of energy metabolism and nutrient-dependent signaling pathways at various stages of life will be required.

Longevity varies greatly between species, as measured by average, median, or maximal lifespan. This variability has a huge range, ranging from hours and days to hundreds of years. Maximum longevity in mammals ranges from two to three years in some small rodents to well over a hundred years in some whale species. Larger animals, such as mice and humans, live longer lives in general, but there are many exceptions. Primates, such as monkeys, great apes, and humans, for example, live longer than carnivores or ungulates of the same body size. Furthermore, rodents that spend their entire lives underground, as well as various species of bats, outlive other small mammals. In laboratory populations of house mice, genetic suppression of GH signaling results in a remarkable increase in longevity (Mus musculus).

This was demonstrated in mice with mutations that interfered with the development and function of GH-producing cells in the pituitary or with hypothalamic control of GH release, as well as in mice with targeted disruption ("knock out") of the gene coding for GH receptor, which results in complete resistance to GH actions. In these animals, severe (almost complete) suppression of GH signals results in dramatic changes in many phenotypic characteristics. Slower postnatal growth, delayed maturation, reduced adult body size, and changes in body proportions are all symptoms of dwarfism, which is characterized by increased adiposity.

Growth hormone transgenic mice have accelerated postnatal growth, increased adult body size, and a shorter lifespan because their circulating GH levels are chronically elevated above the normal range. Interestingly, these animals have reproductive characteristics that are diametrically opposed to those seen in long-lived dwarf mice, including early puberty, increased litter size, increased fecundity at a young age, and accelerated reproductive ageing.

Authors recently noted that exceptionally long-lived rodents with a slow pace of life are also distinguished by the retention of juvenile traits throughout life, a phenomenon known as "pedomorphy." This could be interpreted as another example of maturation versus ageing trade-offs. Reduced plasma levels of insulin-like growth factor-1 (IGF-1, a key mediator of GH actions), insulin, inflammatory markers, and lipids are associated with increases in plasma adiponectin levels, insulin sensitivity, thermogenic activity of brown adipose tissue, oxygen consumption per unit body mass, and utilization of fatty acids as metabolic fuel in long-lived dwarf mice. The majority of these traits are likely mechanisms of extended longevity, but they can also be interpreted as markers of a younger biological age. Both of these interpretations are generally consistent with the evidence of these mutants' delayed and/or slower ageing, as well as findings in other species and types of long-lived mice. A relatively brief period of GH replacement therapy in the early postnatal life of long-lived hypopituitary Prop1df (Ames dwarf) mice can largely or completely eliminate (normalize or "rescue") most of the phenotypic alterations.

Managing Editor, Journal of Reproductive Biology and Endocrinology, UK.

Correspondence: Aron Walker, Managing Editor, Journal of Reproductive Biology and Endocrinology, UK. E-mail :aronwalker@yahoo.com

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Importantly, this GH intervention shortens the lifespan of Ames dwarf mice. These findings are interpreted as evidence that the longevity-associated characteristics of Ames dwarf mice, as well as their extended lifespan, are mechanistically (causally) related to GH deficiency in these mutants, and that GH signals during the period of rapid peri-pubertal growth are important determinants of adult phenotype and ageing trajectory.

Given the evidence linking pace of life to longevity in both inter- and intra-species comparisons, it is worth considering whether pace of life influences ageing in humans. The answer appears to be affirmative, though the evidence is largely indirect and open to alternative interpretations. Humans, in comparison to other mammalian species, have a slower pace of life and a longer lifespan, as stated earlier in this article. Growth hormone-related mutations that slow the pace of life and increase longevity in laboratory mice have also been identified in humans and have been linked to a variety of aging-related traits, including the risk of chronic disease. Individuals with GH receptor gene mutations and resulting GH resistance (Laron Syndrome) are almost completely deaf.

Authors studied a Brazilian population of people with Isolated Gh Deficiency (IGHD) caused by a mutation in the GHRH receptor gene, and they discovered that they have a lower risk of atherosclerosis, better insulin sensitivity, less fatigue, and more hair pigmentation. Furthermore, IGHD patients in this cohort appear to be more resistant to infections by an endemic parasite, Leishmania, and to cope better with Covid-19 infections. These characteristics, however, appear to have little, if any, impact on their longevity. The average lifespan of humans with these or other GH-related mutations is unknown and somewhat controversial, with an emerging consensus that these people have a normal life expectancy.

Early puberty (a feature of an accelerated pace of life) has been linked to poor adult health outcomes in the general population. It's worth wondering if the recent trend of nutritionally-driven acceleration of sexual maturation has anything to do with the stalling and/or likely reversal of historical trends of progressive increase in longevity. The nutritional, public health, medical, and socioeconomic factors that are likely to have an impact on these trends are beyond the scope of this brief article. The discovery of the mechanisms underlying the relationships between pace of life and longevity will aid in the development of practical interventions to promote healthy ageing.