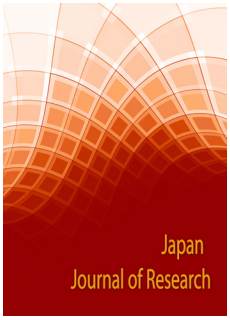
Japan Journal of Research

Mini Review



Growth hormone and aging: focus on healthspan

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- Received Date: 25 Jan 2020;
- Accepted Date: 03 Feb 2020;
- Publication Date: 13 Feb 2020.

Keywords

aging; growth hormone; healthspan

One of the most effective anti-aging interventions in mice is suppression of growth hormone (GH) signaling. Increased longevity of both females and males was reported in animals in which spontaneous mutations of Pit-1, Prop-1, or Ghrhr genes, or targeted disruption of Ghrh or Ghr produces states of GH deficiency or resistance [1-4]. Importantly, life-prolonging effects of suppressed GH-signaling are not limited to a particular strain, genetic background, or diet, and have been reproduced in independent studies in different laboratories [4,5]. Comparably large and consistent extension of longevity is difficult to produce by any means other than severe restriction of caloric intake during most of the lifespan.

Evidence for remarkable "anti-aging" effects of GH deficiency and resistance contrasts with the reports of detrimental effects of the corresponding syndromes in people, including increased cardiovascular risk factors [6,7] and with persistent (although generally poorly supported) claims that GH therapy can produce various rejuvenating effects in middle-aged and elderly humans. While some individuals with hypopituitarism due to Prop1 mutations reached advanced age [8], isolated deficiency (IGHD) was reported to reduce longevity [9]. Subsequent studies in larger cohorts of individuals with IGHD or GH resistance (Laron syndrome) showed various changes in most common causes of death, but no significant (negative or positive) effects on average longevity [10,11]. Intriguingly, a cohort of slightly over 100 individuals with IGHD in northeastern Brazil included one centenarian and one nonagenarian [4]. Possible relationship of GH signaling to late life mortality suggested by these observations appears consistent with relationship of stature to mortality in an unrelated large cohort of normal men [12]. Thus, we must conclude that the association of reduced GH signaling with remarkably extended longevity, which is consistently seen in laboratory stocks of mice is not seen in humans with IGHD or genetic GH resistance. However, there is increasing evidence that reduced GH signaling promotes healthy aging and increases healthspan in both mice and men.

Phenotypic characteristics of mice with various GH-related mutations indicative of the extension of healthspan include reduced incidence and delayed onset of neoplastic disease, reduced oxidative damage to macromolecules, reduced expression of inflammation markers, improved insulin sensitivity and management of blood glucose levels, maintenance of youthful levels of cognitive function into advanced age, reduced immune and collagen aging, and reduced cardiac fibrosis [1-5]. Recent studies provided evidence for additional indications of extended healthspan: improved capacity for DNA repair [13], reduced ovarian aging [14], and younger "biological age" assessed by age-related changes in hepatic DNA methylation [15,16]. Future studies should systematically assess time course of age-related changes in resilience and other measures of healthspan in these long-lived mutants and their normal (wild-type) siblings.

Association of reduced GH action with extension of healthspan in human subjects is suggested by the remarkable protections from age-related disease including cancer and diabetes in the Ecuadorian cohort of Laron dwarfs [10] and protection of Brazilian subjects with IGHD from atherosclerosis and cancers other than skin cancer [4,11,17]. Moreover, subjects with IGHD generally experience healthy aging and tend to look younger than their age. Importantly, Dr. Aguiar-Oliveira and his colleagues documented that subjects with IGHD from the cohort they had been following exhibit improved muscle strength, greater resistance to fatigue, reduced incidence of bone fractures, improved insulin sensitivity, and no graying of the hair, while memory, walking, postural balance, and risk of falls are not affected [4,11,17].

What are the implications of these findings? It can be concluded that the anti-aging effects of GH deficiency or resistance discovered in laboratory studies of mice can be seen also in humans, but the quantitative impact of these syndromes on the aging process is much smaller in our own species than in domesticated mice. Thus, healthspan is extended in both species, but longevity only in mice. What is responsible for this difference? We speculate that this may be due to a different pace-of-life in small rodents

Citation: Bartke A. Growth hormone and aging: focus on healthspan. Japan J Res. 2020;1(1):1-2

and large primates. In small rodents, suppression of the somatotropic axis changes characteristics associated with fast paces of life: fast growth, early puberty, high fecundity, and fast aging, to resemble the life course, growth, maturation, and reproductive strategy of species with slower pace-of-life, and, thus, extends longevity. In humans, the "pro-longevity" characteristics of slow pace-of-life are already present, and thus effects of reducing GH actions are more subtle. Obviously, other mechanisms and other characteristics of rodents and primates may also be involved in producing the observed species difference.

Another important implication of these findings is that the normal actions of physiological levels of GH are not optimal for healthy aging, and can be assumed to exert "pro-aging" actions. This may appear counterintuitive, but fits well with the well documented role of other anabolic/nutrient-responsive pathways (insulin/insulin-like growth factors, and mechanistic target of rapamycin) in the control of aging in many organisms, including mammals [18-22].

Conflict of interest

Andrzej Bartke has no conflict of interest to declare.

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