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COMMENTARY

From biology of reproduction to biology of aging

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Readers of *Aging Pathobiology and Therapeutics* may have come across our work in the field of aging biology, particularly studies of the relationships between pituitary growth hormone (GH) and longevity. Personal reflections below explain "how we got there" and how work on this topic has evolved in our laboratory during the last 30 years.

The beginning: prolactin and reproduction

I was introduced to reproductive endocrinology in a graduate course at Kansas University in 1963. Soon, the results of my dissertation research led me into this field. With the guidance of one of my professors, Jerome Yochim, I found that two types of genetically dwarf mice (now known as Snell dwarf and Ames dwarf) were prolactin (PRL) deficient. Treatment with PRL reversed the sterility of females and, somewhat unexpectedly, stimulated fertility of males [1]. A few years later I obtained support from the National Science Foundation (NSF), and subsequently from the National Institutes of Health (NIH), for studies of the role of PRL in male reproduction. In this work, we used PRL-deficient dwarf mice, hypophysectomized animals and animals with hyperprolactinemia (hyperPRL) induced by transplantation of anterior pituitaries under the kidney capsule or by treatment with synthetic estrogen. Reports from other labs that hyperPRL in women and men can have major impact on reproductive functions generated much interest in the role of PRL in reproductive endocrinology and our lab benefited from this development.

While continuing work on hyperPRL, we became interested in the role of PRL in seasonal reproduction, and particularly in its role in mediating the effects of photoperiod on the hypothalamic-pituitary-testicular axis [2]. For this work we used golden (Syrian) hamsters which undergo dramatic seasonal shifts between gonadal activity and quiescence, a stark contrast to the relatively constant testicular function in adult mice and rats. I remember working on seasonal reproduction as some of the most exciting and satisfying studies we ever did. In retrospect, I think that some of this satisfaction came from the degree of my involvement in this work: doing most of the surgical procedures, working side by side with fellows and students, and catching a few hours of sleep between collections of samples during an "all through the night" experiment.

More reproductive biology

While the role of PRL in male reproduction continued to be one of our key interests, we also worked on other topics. When Burt Caldwell and his colleagues at the Worcester Foundation for Experimental Biology developed a radioimmunoassay for testosterone (T) and provided us with an antibody, we were able to measure T levels in small samples of plasma and in seminiferous tubule fluid collected after ligation of the efferent ducts. Mary Harris used this approach to relate local levels of T to spermatogenesis and to elucidate the mechanism of action of T precursors (pregnenolone and progesterone) on spermatogenesis in hypophysectomized rats [3]. Susan Dalterio decided to study the effects of psychoactive and non-psychoactive cannabinoids on reproductive development and function [4]. Her work produced exciting (including some unexpected) results and generated much interest, with several of her papers appearing in Science and her being asked to testify before the United States Congress. We also were able to address other topics in reproductive biology including impact of exposure to novel female or male animals of the same species, presumably mediated by pheromones, on plasma T levels [5]. This time, the interest of some Congress members in our work was more than slightly disconcerting to us and to our Program Officers.

Giant mice and accelerated aging

In the 1980s, several laboratories produced transgenic

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mice expressing high levels of growth hormone (GH). Tom Wagner, one of the pioneers of this technology, noticed that giant GH transgenic mice from some of the lines he produced had various reproductive deficits. On suggestion of Dharam Dhindsa, our Project Officer at NICHD, he decided to collaborate with us to elucidate the mechanisms of these deficits. This work resulted in demonstration that disruption of female fertility in GH transgenic females was due to defects in luteal function [6]. In the course of this work, we noticed that these "super mice" were visibly deteriorating during the second half of the first year of their life, that is at an age when their genetically normal (wild-type) siblings were healthy and robust. Working together with Rick Steger, a colleague interested in neuroendocrinology, we examined multiple characteristics of these animals and concluded that many of the differences between transgenic and normal mice resemble effects of aging and may represent acceleration of the aging process [7]. Our suggestion that supraphysiological GH levels accelerate aging was counterintuitive in that it was already well established that circulating GH levels decline with age and this decline was thought to be responsible for many age-related changes in body composition and function. This conundrum is not easily explained and existence of seemingly contradictory findings in this area likely explains why we were not able to secure funding for studying mechanisms of accelerated aging in GH transgenic animals. We continued to be interested in mechanisms of reduced longevity of GH transgenics, and recent analysis of transcriptomic profiles in these animals by Singh *et al*. suggests that ectopic overexpression of GH may indeed accelerate biological aging, at least in the liver [8]. Findings in GH transgenic mice prompted us to join forces with Rich Falvo and Ezio Giacobini, our Southern Illinois University School of Medicine colleagues sharing our newly developed interest in aging, to organize the International Symposium on Neurobiology and Neuroendocrinology of Aging. This symposium was held in Bregenz, Austria in 1992. Two years later we organized the second symposium in this series at the same site and these symposia continue to be held every other year until now with the leadership eventually passing from Rich Falvo and me to Holly Brown-Borg.

How long do Ames dwarf mice live?

This question came up during a coffee break conversation with Holly Brown-Borg and her husband Kurt when they were working in our laboratory in Carbondale, Illinois in the early 1990s. Holly and Kurt knew that Ames dwarf mice lack not only PRL, but also GH, and that I have been working with these animals for many years. They were wondering if I knew anything about their aging and how this could relate to what we saw as symptoms of accelerated aging in GH transgenics. I had to admit that I had no data on aging of the Ames dwarfs except that they seemed to continue to "look good" well into what is middle age in mice. Moreover, I had no idea how long they live. We decided to get this information by setting aside a group of weanling Ames dwarfs along with age- and sex-matched wild-type siblings of these mutants and following their survival. Two years later most of the normal (wild-type) controls were gone, while most of the dwarfs were still alive. When this study was finished, the average lifespan of the Ames dwarfs was 1,206 days for females and 1,076 days for males, with one animal surviving over four years while the average lifespan of the controls was 718 days for females and 723 days for males. Holly reported these results in a letter to Nature in 1996 [9]. As we were not working in the field of aging, we did not realize that extension of longevity by mutation (usually loss of function) of a single gene was shown in numerous studies in yeast, worms, and flies, and there was an ongoing discussion among researchers in this field whether these findings are likely to apply also to more complex organisms, especially mammals. Thus, our data provided an answer to this question.

While we were (and still are) excited by finding this remarkable extension of longevity and by the publicity and recognition that this work received, I feel I need to mention similar or closely related findings of others. When we wrote our paper, we were not aware that a 1972 study of osteoarthritis in Snell dwarf mice by R. Silbergerg *et al*. referred to these animals as long-lived and although no longevity data were provided or referenced, it included data from individual mice aged over three years [10]. While we were determining the longevity of Ames dwarfs, Kevin Flurkey was studying the same issue in Snell dwarfs and independently obtained evidence of extended longevity: first in females and later on in males after housing them with normal female rather than normal male siblings [11]. I remember how happy we were when we talked on the phone and discovered the agreement of our findings. Arthur Everitt reported in 1980 that hypophysectomized rats given cortisone acetate replacement therapy outlived sham operated controls [12].

Effects of calorie restriction in GH-deficient and GH-resistant mice. Becoming a biology of aging lab

Finding extended longevity of Ames dwarf mice prompted us to undertake a series of studies aimed at identifying mechanisms linking GH deficiency to what we suspected was delayed and/or slower aging. We also started working with GH-resistant GH receptor knockout (GHRKO) mice derived from breeders kindly provided by John Kopchick. With help of George Roth and Mark Lane we started working with calorie restriction and Julie Mattison took a lead in these studies [13]. Our visiting Argentinian collaborators helped us in assessment of glucose homeostasis [14]. Michael Bonkowski continued calorie restriction studies [15]. Michal Masternak was measuring expression of PPARs [16] and Oge Arum studied healthspan-related traits [17]. Multiple collaborations have developed and included assessment of pathology by Yuji Ikeno [18]

and studies of cellular stress resistance in the Rich Miller laboratory [19]. Thus, we became a biology of aging lab.

While we were immersed in the studies of aging in GH-deficient and GH-resistant mouse mutants, we were, of course, wondering which of our findings may apply to our own species and why some of what we saw in mice appeared opposite to what was being said about GH and human aging. From a talk by John Parks at the annual meeting of the Endocrine Society I learned about the existence of "little people" in Croatia, about the fact that their small stature is due to mutation of Prop1, the same gene which is mutated in Ames dwarf mice, and that some of them reached very advanced age [20]. At a later meeting of the same organization, I met Manuel Aguiar-Oliveira who was studying a large population of individuals with hereditary isolated GH deficiency (IGHD) in Brazil who have never been treated with GH. We were amazed to realize how closely the phenotype of these individuals resembled that of the long-lived GH-deficient mice we were studying [21]. Members of this population of people with IGHD have no extension of average longevity, but are completely or partially protected from several aging-related diseases and can survive to very old age. Resembling the characteristics of "healthy aging" in these individuals, people with GH-resistance due to a mutation of the GH receptor who were studied by Jaime Guevara-Aguirre and Valter Longo in Ecuador, were found to be protected from cancer and diabetes [22]. Studies of genetic and endocrine correlates of familial longevity provided examples of a reciprocal relationship between GH signaling and human lifespan [23, 24].

Current research topics

Much of current work in our laboratory evolved from our earlier studies of the effects of GH replacement therapy in Ames dwarf mice. We have shown that six weeks of GH treatment started at one or two weeks of age was sufficient to partially or completely normalize ("rescue") many of the aging-related traits of these mutants and to shorten their longevity [25]. Ames dwarf mice treated with GH in these studies grew at a nearly normal rate as long as the treatment was continued but thereafter their growth slowed down and their adult body weight was much lower than the weight of their normal siblings. Findings in GH-treated dwarf mice add to the evidence from numerous experimental and demographic studies that interventions and conditions experienced during early postnatal life can shape adult health and trajectory of aging. They also support the reciprocal relationship between the rate of development and longevity as suggested by the ecological concept of the "pace-of-life". Interestingly, pace-of-life (unlike adult body size) is inversely related to longevity not only in comparisons of short- and long-living individuals from the same species but also in comparisons of different species of animals with a huge range of lifespans. Ongoing studies led by my colleague, Rong Yuan, examine the effects of dietary and pharmacological interventions during early life on adult health, aging-related traits and longevity of normal (wild-type) animals. In this work, we emphasize relatively mild interventions that could be incorporated in human lifestyle and compounds already approved for human use. Because of Rong's interest in the relationship of the age of puberty to IGF-1 levels and longevity, we are evaluating the effects of various potentially anti-aging interventions on sexual maturation. Thus, studies of reproductive parameters have "re-emerged" in our laboratory.

Other work includes collaboration with Erin and Kevin Hascup on aging-related characteristics of mouse models of Alzheimer's disease and effects of various environmental and surgical interventions in these animals and other collaborative and pilot studies on relationships of GH signaling, cancer, and blood pressure.

Declarations

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