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Endocrine function in naturally long-living small mammals

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ABSTRACT

The complex, highly integrative endocrine system regulates all aspects of somatic maintenance and reproduction and has been widely implicated as an important determinant of longevity in short-lived traditional model organisms of aging research. Genetic or experimental manipulation of hormone profiles in mice has been proven to definitively alter longevity. These hormonally induced lifespan extension mechanisms may not necessarily be relevant to humans and other long-lived organisms that naturally show successful slow aging. Long-lived species may have evolved novel anti-aging defenses germane to naturally retarding the aging process. Here, we examine the available endocrine data associated with the vitamin D, insulin, glucocorticoid and thyroid endocrine systems of naturally long-living small mammals. Generally, long-living rodents and bats maintain tightly regulated lower basal levels of these key pleiotropic hormones than shorter lived rodents. Similarities with genetically manipulated long-lived rodent models of aging suggest that evolutionary well-conserved hormonal mechanisms are integrally involved in lifespan determination.

1. Introduction

For thousands of years, the process of aging has been attributed to a progressively larger deficit of some vital regulatory substances with advancing years. Within the past two centuries, the decline in hormone levels has been touted as responsible for the age-related deterioration in physiological function and greater frailty (for historical reviews see Haber, 2004). In mammals, these pleiotropic hormones work together in a highly integrated manner to exert control over energy and ion balance, and affect metabolism, growth, repair and reproductive function. Not surprisingly, given the continued quest for human immortality, hormone replacement therapy (HRT) is often proposed as a reliable method of slowing aging (Olshansky et al., 2001; Horani and Morley, 2004). However, HRT has, at best, yielded equivocal results, and even though it may restore hormone levels to those of young healthy adults, it does not avert aging. Indeed, HRT may even accelerate the aging process and lead to increased incidence of many age-associated diseases such as cancer and cardiovascular ailments (Rossouw, 2002; Manson et al., 2003).

1.1. Role of endocrines in lifespan extension

Contrary to proposals espoused by "anti-aging HRT" advocates, genetic and experimental manipulations in animal aging models reveal that those individuals with naturally low levels of key hormones (e.g., growth hormone) live longer than those with higher, albeit "normal" levels (for review see Bartke, 2007; Brown-Borg, 2007). A deficiency in pituitary hormones, and growth hormone in particular, is strongly implicated in lifespan extension. Mice homozygous for *Pit 1* show attenuated aging, live approximately 40% longer than wild-type, and have lower growth hormone and IGF-1 levels than wild-type (Flurkey et al., 2001). Conversely, mice over-expressing bovine growth hormone appear to age faster and show greater incidence of age-associated pathologies (Bartke, 2003).

The life-extending effects of dietary restriction (DR) also are attributed, in part, to low basal hormone levels and reduced daily fluctuations in insulin, insulin-like growth factor (IGF), thyroid hormone and sex steroids and the concomitant decline in metabolism (Longo and Finch, 2003; Masoro, 2005). A fundamental, but still unanswered, question is whether or not naturally long-living species have low or sustained high levels of hormones.

1.2. Long-living small mammals

For our size, humans are exceptionally long-living relative to most other species, surviving five times longer than predicted by

Abbreviations: HRT, hormone replacement therapy; NMR, naked mole-rat; MLSP, maximum lifespan; LQ, longevity quotient; BMR, basal metabolic rate.

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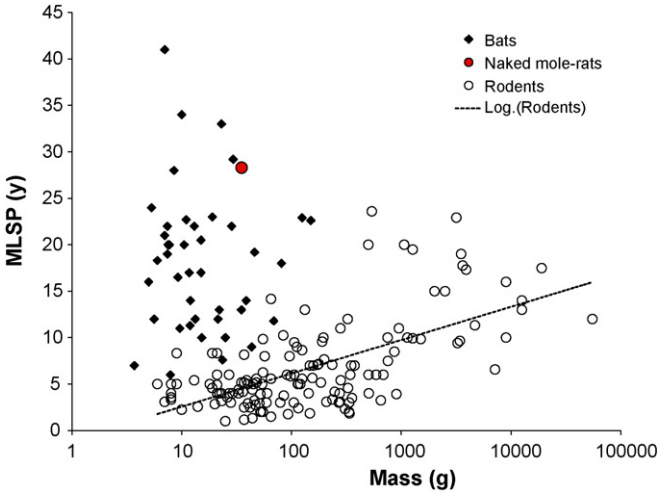

Fig. 1. Maximum lifespan as a function of body mass of small mammals. Please note that most bat species are long-lived while only a few rodent species acquire similar longevity. Most of these long-living rodents are burrow dwelling rodents, like mole-rats and squirrels.

size (Hulbert et al., 2007). Paradoxically, traditional animal models used in aging research are primarily chosen because they age extremely rapidly and are short-lived (Miller and Nadon, 2000), even though the principal aim of most of these studies is to discover mechanisms that will allow us to ultimately further retard human aging. These short-lived animal models may reveal lifespan extension mechanisms not necessarily relevant to organisms (like us) that naturally age slowly. Rather, long-lived species may have evolved novel anti-aging characteristics that are present throughout life, and germane to naturally retarding the aging process, thereby maintaining the low age-specific mortality that allows slow-aging organisms to achieve their impressive longevity.

Among mammals, maximum species lifespan potential (MLSP) scales with body mass. This allometric relationship holds true for rodents as well (Fig. 1; de Magalhaes et al., 2007). The larger rodent species such as squirrels, marmots, porcupines and mole-rats frequently attain maximum lifespans, exceeding 20 years (Fig. 1; Weigl, 2005), while most mouse-sized rodents in captivity live no more than four years. Surprisingly, the longest living rodent defies this allometric relationship and is a small mouse-sized (35 g) hystricognath, the naked mole-rat (*Heterocephalus glaber*). This species in captivity shows attenuated age-related declines in reproduction, physiological and biochemical function, maintaining good health until very near the end of their long >28.3 years lifespan (O'Connor et al., 2002; Buffenstein, 2005, 2008; Csiszar et al., 2007). Other reportedly long-living rodents such as certain squirrel species, porcupines and deer mice live approximately double that predicted by body mass. The naked mole-rat, like humans, lives five times longer than predicted allometrically using the equations of de Magalhaes et al. (2007). Volant mammals (e.g., bats) are generally excluded from the data used to determine the mammalian allometric relationship as this distinct phylogenetic order are all extremely long-lived with several small species (e.g., *Myotis lucifugus* 11 g) living in excess of 30 years (Fig. 1; de Magalhaes et al. (2007).

In this paper, we report on the very sparse literature addressing the comparative biology of hormone profiles pertinent to aging in long-living small mammals, and assess these limited data in the light of what is known about hormone profiles associated with extended lifespan in mutant mice models. A list of the main animals discussed in this review and their phenotypic characteristics is provided in Table 1. Most of these data were collated to address

Table 1
Some phenotypic characteristics of long-living small mammals

	MICE	Ames, Snell	Dietary restriction	Deer mouse	Golden mantle sq.	Damara mole-rat	Egyptian fruit bat	Naked mole-rat	Little brown bat
Body mass	25	9	17	20	250	180	21	35	11
MLSP	3	4	4	8	10	16	23	28	34
Body temperature (°C)	37 Normal	35.5 Reduced labile	36 Reduced	36 Reduced labile	36 Reduced labile	34 Reduced	35 Reduced	32 Reduced labile	33 Reduced labile
BMR, mass specific	Normal	Reduced	Normal	Reduced	Reduced	Reduced	Reduced	Reduced	Reduced
Gestation length (days)	19	–	–	24	30	85	120	77	55
Fasting glucose	Normal	Reduced	Reduced	Normal	Normal	Reduced	Reduced	Reduced	Normal
GTT	Normal	Abnormal	Normal	Normal	NAD	Abnormal	Abnormal	Abnormal	NAD
Insulin	Normal	Reduced	Reduced	Normal	Normal	Reduced	Reduced	Reduced	Normal
Thyroid	Normal	Reduced	Reduced	Normal variable	Normal variable	Reduced	NAD	Reduced	Normal variable
Vitamin D	Normal	NAD	NAD	NAD	NAD	Reduced	Reduced	Reduced	NAD
Main Glucocorticoid	Corticost.	Corticost.	Corticost.	Corticost.	Cortisol	Cortisol	Cortisol	Cortisol	Cortisol

Data are complied from multiple sources: mice, Ames and Snell dwarf mice and dietary restriction data are taken from Longo and Finch (2003). Comparative species information was taken from de Magalhaes et al. (2005), Bauman (1990), Bauman et al. (1987), Buffenstein et al. (1994, 2001), Cavaleros et al. (2003), Faulkes and Bennett (2001), Hulbert (2000), Korine et al. (2004), Kwiecinski et al. (2001), Masoro (1988), Ogunsua et al. (1969), Reeder et al. (2004), Stone and Wiebers (1966), Tracy et al. (2007), Widmaier and Kunz (1993). NAD - no available data; corticost - corticosterne. See text for details.