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COMMENTARY

Can FSH influence longevity?

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Summary

It was recently reported that the extragonadal actions of follicle-stimulating hormone (FSH) include regulation of brown and white adipose tissue function and thermogenesis. Based on these findings and on our evidence for reduced FSH levels and enhanced thermogenesis in long-lived growth hormone (GH)-deficient mice and GH-resistant mice, we suggest that FSH may have a role in the control of aging and longevity. We speculate that alterations in FSH secretion may represent one of the mechanisms of trade-offs between reproduction and aging.

Key words: Aging; life span; longevity; longevity regulation; mice; molecular biology of aging.

Recent evidence for extragonadal actions of follicle-stimulating hormone (FSH), including effects on the function of both brown and white adipose tissue (Liu *et al.*, 2017), raises the intriguing possibility that FSH may be involved in the control of aging. If confirmed, this novel action of FSH would enhance our understanding of mechanisms and trade-offs involved in the control of healthspan and longevity of homeothermic organisms.

Follicle-stimulating hormone is produced by the anterior pituitary gland and acts as one of the master regulators of reproductive functions in both females and males. Recent work indicates that FSH also acts within nonreproductive tissues, including bone (Sun *et al.*, 2006). In a paper recently published in *Nature* (Liu *et al.*, 2017), Liu *et al.* provide elegant evidence that FSH also influences adipose tissue functions; specifically, blocking FSH actions with a specific antibody-stimulated thermogenesis in both brown and white adipose tissues (BAT and WAT), reduced adiposity, and increased bone mass in laboratory mice. These findings imply that the well-documented postmenopausal increase in FSH secretion is likely among the causes for increased adiposity, reduction in bone mass, and alterations in energy metabolism at this stage of life history. One could also suspect that the gradual age-related increase in FSH levels in men has similar consequences.

Extrapolating from the findings of Liu *et al.* (2017), we suggest that the physiological changes resembling the benefits of blocking FSH action may also occur in response to a modest reduction in FSH levels in animals genetically predisposed to extreme longevity. This would imply that FSH may have a role in the control of aging. Our hypothesis that FSH may have a role in the control of aging stems from observations in two types of mice in which reduction in FSH levels, activation of BAT, browning of WAT, and increased energy expenditure are associated with major extensions of healthspan and longevity. In *Prop1*^{df} mutants with a genetic defect in the differentiation of somatotroph, lactotroph, and thyrotroph cell lineages in the anterior pituitary, the expression of the FSH-β subunit gene, the pituitary FSH content, and the plasma FSH levels are significantly reduced (Tang *et al.*, 1993). A similar reduction in plasma FSH levels occurs in both sexes of mice with deletion of the growth hormone receptor (GHR) gene (Chandrashekar *et al.*, 2004, 2007). In both *Prop1*^{df} (Ames dwarf) and GHR−/− (Laron dwarf) mice, BAT is enlarged and highly active (Li *et al.*, 2003; Darcy *et al.*, 2016), subcutaneous WAT exhibits characteristics of 'beiging' (unpublished data) and metabolic rate (measured by the rate of oxygen consumption per unit of body mass) is increased during both active (dark) and resting (light) phases of the diurnal cycle (Westbrook *et al.*, 2009). Moreover, their respiratory exchange ratio is reduced, implying a shift in mitochondrial function toward greater utilization of fatty acids as metabolic fuel (Westbrook *et al.*, 2009). Both Ames dwarf and GHR−/− mice are remarkably long-lived, with increases in longevity ranging from some 20% to over 60% depending on the diet, gender, and genetic background of the animal (Brown-Borg *et al.*, 1996; Coschigano *et al.*, 2003; Bartke *et al.*, 2013). The enhancement of longevity in these mice is associated with maintenance of youthful levels of cognitive and neuromuscular function, and other phenotypic characteristics into advanced age (Bartke *et al.*, 2013), delayed onset, and reduced incidence of cancer and other age-related pathological changes (Ikeno *et al.*, 2009; Bartke *et al.*, 2013), and a reduced rate of aging (Koopman *et al.*, 2016). We have previously proposed that the activation of BAT and increased metabolic rate in these long-lived mice represent responses to increased radiational heat loss in these diminutive animals (Westbrook, 2012; Darcy *et al.*, 2016). However, results of GH replacement therapy in *Prop1*^{df} mice indicate that their metabolic characteristics and extended longevity can be at least partially uncoupled from body size (Sun *et al.*, 2017). Extrapolating from the recent findings of Liu *et al.* (2017), we now hypothesize that reduced FSH levels in these animals may produce (or contribute to) their unique metabolic profile, and also likely to their extended longevity.

If confirmed, the effects of reduced FSH levels in these animals would represent a novel mechanism of trade-offs between their fertility and longevity. Both sexes of GHR−/− mice and male Ames dwarfs are fertile, but their sexual maturation is delayed and fecundity is reduced (Bartke *et al.*, 2013). Important trade-offs between reproduction and aging have been studied and discussed for decades (Bartke *et al.*, 2013), but our understanding of the underlying mechanisms is very limited, and in mammals, virtually nonexistent. Thus, combining the results of FSH blockage reported by Liu *et al.* (2017), Sun *et al.* (2017) with the available information on endocrine and metabolic characteristics of two types of long-lived mice produces a novel mechanistic insight into the complex interaction of sexual maturation, reproductive effort, fecundity, aging, and lifespan.

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Conflict of interest

None declared.

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