Sex differences in health and aging: a dialog between the brain and gonad?

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Abstract Women live longer than men in virtually all circumstances. However, a more common pattern among animals is that one sex lives longer under some conditions, the other lives longer under other conditions. In laboratory mice, interventions that extend longevity are surprisingly often sex-specific in their effects. Understanding these conditional sex differences could provide mechanistic insight into how longevity could be modulated in humans. One way that longevity can be consistently enhanced is by inhibiting reproduction or eliminating the capacity to reproduce. Thus, there appears to be a mechanistic link between gonadal activity and longevity. There also appears to be a mechanistic link between some types of neuroendocrine signaling and longevity. Combining these two observations suggest that communication between the brain and gonad is a ripe avenue for further exploring longevity-assurance mechanisms. Also, because the timing and activity of specific brain–gonad endocrine differs between the sexes, neuroendocrine linkages between the brain and gonad, particularly among the less obvious hormones such as activin and inhibin, could provide additional insight into mechanisms of sex differences in aging.

Keywords Sex differences · Tradeoffs · Hypothalamic–pituitary–gonadal axis · Reproduction · Aging

Sex differences in aging

One of the most robust features of human biology is women's superiority in survival and longevity (Austad 2011). Women have higher survival rates than men from birth throughout life. In fact, this female survival advantage begins prenatally, as female babies are better survivors than male babies when born prematurely (Draper et al. 2009; Zeitlin et al. 2008). Women survive better than men in good times and bad (Austad and Fischer 2016). For instance, in Iceland, life expectancy since 1840 has dipped as low as 19 years in times of epidemic disease outbreaks and recently has been as high as 82 years, but in every one of those years, female life expectancy was greater than male life expectancy. In modern, technologically developed countries, women die at lower age-adjusted rates of *almost* all leading causes of death. Women also survive better during extreme events such as severe famine or epidemic disease outbreaks (Zarulli et al. 2018).

Females outlive males in many, but not all, species—not even all mammals. For instance, males are clearly the longer-lived sex in guinea pigs, golden hamsters, and at least some bat species as well as several South American monkeys (Austad 2006). Among intact dogs, males are also slightly longer-lived than females (Hoffman et al. 2018). In other species, there may be no consistent longevity difference between the sexes, although there often are in individual studies. For instance, an analysis of 118 laboratory mouse longevity studies that used both sexes found that males lived nearly 50% longer than females in the most extreme

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study, yet females lived as much as 30% longer than males in another study. Overall, there was a continuum of differences between these extremes. Even within a single inbred mouse genotype, the commonly-used C57BL/6 mouse, considering 29 available studies, there was nearly as broad a range of survival differences among the sexes as in all the mouse genotypes combined. The conditions favoring survivor of one sex over the other in mice are unknown, but if they could be discovered it would go a long way to informing us about the reason for these differences (Austad 2011).

This latter pattern—condition-dependent survival advantage by one sex over the other—is also seen in other laboratory species such as the nematode, *Caenorhabditis elegans*, and the fruit fly, *Drosophila melanogaster*. Sometimes the conditions favoring the superior survival of one sex are known. In *D. melanogaster*, these differences depend on genotype, mating status, female fecundity, and the presence or absence of the opposite sex. Under some combination of these variables, males have been reported to live as much as 3.8 times longer than females and under other combinations females lived 2.3 times longer than males (Malick and Kidwell 1966). In *C. elegans*, individually housed males live 10–20% longer than hermaphrodites (the two worm sexes are males and hermaphrodites), but when groups of worms, either all male or mixed sex groups, are cultured together, the sex difference in survival disappears (McCulloch and Gems 2003).

Sex-specific interventions in mouse longevity

For decades, the only intervention that reliably lengthened life and extended health in laboratory rodents was dietary restriction and its effects seemed to affect both sexes approximately equally (Swindell 2012; Weindruch and Walford 1988). That was also true of the first genetic intervention that lengthened life and improved health in mice (discussed below) (Brown-Borg et al. 1996). There was little reason in those days to focus on how the sexes differed with respect to aging. However, as more and more genes extending mouse longevity were discovered, it began to emerge that sex specific effects were common (Austad and Fischer 2016). For instance, haploinsufficiency of the IGF-1 receptor increases longevity in female mice but not in males (Bokov et al. 2011; Holzenberger et al. 2003). On the other hand, haploinsufficiency of the insulin receptor

increases longevity in male mice but not in females (Nelson et al. 2012). It is not easy to imagine the mechanism(s) of genetically determined sex specificity as presumably if one copy of a gene is disabled; it will be equally disabled in both sexes. However, manifold of other genetic manipulations also displayed sex-specific effects. In addition to the studies noted above, female but not male lifespan was lengthened by knocking out IRS1 (Selman et al. 2008) or S6K1 (Selman et al. 2009) or by double haploinsufficiency of *mTOR* and *mlst8*, a component of both mTOR complexes (Lamming et al. 2012). As with the insulin receptor heterozygote, male, but not female, longevity has also been enhanced by disrupting protein kinase A (Enns et al. 2009) and overexpressing the protein deacetylase, Sirt6 (Kanfi et al. 2012).

In addition to these genetic manipulations, putative senescence-retarding drugs have also proven sex-specific remarkably often. This is somewhat easier to imagine than in the genetic manipulations as sex differences in pharmacokinetics are well known (Chen et al. 2018; Pestka et al. 2017). Still, the commonness of such effects in life-extending drugs administered to mice is rather stunning. For instance, in the National Institute on Aging's Interventions testing program, which evaluates drugs for their impact on mouse longevity at three independent sites has found that of six drugs that extended life in mice, 4 (aspirin, nordihydroguaiaretic acid (NDGA), 17- α -estradiol, and Protandim®) did so only in males and one (acarbose) had a much larger effect in males than females (Austad and Fischer 2016). The sixth drug, rapamycin, which was the one with the largest effect on longevity, sex specificity appears to be dose-dependent (Table 1). The lower the food concentration, the greater the sex difference favoring females in longevity extension when begun at 9 months of age and continued throughout life. It should also be noted that this degree of sex-biased longevity enhancement is not apparently related to sex differences in the blood concentration of rapamycin between the sexes (Miller et al. 2014). A somewhat different paradigm was employed in Bitto et al. (Bitto et al. 2016). The authors began rapamycin treatment, either by daily injection or in food when mice were 20–21 months old and continued it for only 90 days. When calculated from the time of the initiation of treatment, Bitto and co-authors observed a 45% increase in median male longevity and a 39% increase in median female longevity when feeding the high dose of rapamycin (14% and 9%

Table 1 Dose dependence of sex specificity of rapamycin (Bitto et al. 2016; Miller et al. 2014)

Rapa dose	Male effect (%) [§]	Female effect (%) [§]
4.7 ppm*	3	16
14 ppm*	13	21
42 ppm*	23	26
126 ppm [¶]	14	9
8 mg/kg [¶]	14	0

*ppm = parts per million in food from 9 months of age throughout life

[§] Percent change in median longevity from birth

[¶] Concentration in food or in daily injections for 90 days beginning at age 20–21 months

when calculated from birth). With rapamycin injections, which the authors estimated was equivalent to 27 times the dose originally reported to extend life when administered in food, males lived a whopping 61% longer from the time of first injection compared with controls. Somewhat surprisingly, no change in median female longevity was seen with this treatment. Regardless of treatment dose and route of administration of timing, clear sex differences were apparent. Understanding the dynamics of these differences as affected by dose, route of administration, and timing will be critical to understanding the mechanism(s) of its impact on longevity.

The gonad–longevity connection

Consistently, important features of sex differences in longevity have to do with reproduction or reproductive capability. That is, animals that reproduce are typically shorter-lived than animals that do not. Evolutionary biologists term this the “cost of reproduction” (Harshman and Zera 2007). It is well known among animal breeders that too much reproduction by females will shorten life. What is less well known is that mating itself shortens male life span in numerous species. The cost of mating is particularly well described in *Drosophila* flies. Mating reduces longevity in both sexes of *D. melanogaster* (Chapman et al. 1995). In a different species, *D. subobscura*, unmated females live longer than males, but mating shortens female longevity more than male longevity, so mated males live longer than mated females (Maynard Smith 1958). Although there does not appear to be any straightforward link between

number of children and longevity among modern humans, there does appear a link in a population of healthy centenarians. This population of genetically and socially homogeneous Ashkenazi Jewish centenarians, selected for their health as well as their longevity, had fewer children, and had their children later, than a similar group of non-longevous Ashkenazi Jews. The lower number of children and delayed reproduction were observed for both male and female centenarians (Tabatabaie et al. 2011).

Perhaps more interesting than the impact of reproduction on longevity is the impact of reproductive *capability* on longevity. Gonadectomy increases longevity of both males and females in many species, including dogs, cats, and humans (Hamilton 1965; Hamilton and Mestler 1969; Hoffman et al. 2018; Min et al. 2012; O’Neill et al. 2013, 2015). In dogs and cats, the impact on longevity of gonadectomy in females is considerably larger than the sex difference (Hoffman et al. 2018; O’Neill et al. 2013, 2015).

The human studies deserve some explanation. As no human studies have been specifically designed to evaluate the longevity impact of gonadectomy, the only studies are retrospective, observational, and the special circumstances in which a number of people would be gonadectomized make it difficult to determine the appropriate control population. For instance, Hamilton and Mestler (1969) obtained records from a Kansas institution for the mentally deficient for patients born between roughly 1870 and 1930. Men in this institution were castrated generally for behavioral reasons. Women were ovariectomized in those pre-contraceptive days to prevent unwanted pregnancies. Controls were intact men and women from the same institution. These were not ideal controls as we have no information on whether they were treated differently than the surgically castrated group or why some were gonadectomized and others not, but these are the best available comparison groups. In the reasonably large sample of 297 castrated males compared with 735 intact males, median longevity of castrated males was an impressive 14 years longer (69.3 years vs 55.7 years). Moreover, the earlier in life that the men were castrated, the bigger the longevity difference compared with intact men. In the much smaller sample of women (23 ovariectomized vs 309 intact), there was no difference in survival. Median longevity for both groups was 65.2 years.

A similarly large longevity difference was found in a sample of Korean eunuchs compared with other

members of the Royal court (Min et al. 2012). Eunuchs, that is, castrated males, were used as guards and servants in the Royal harem. Excellent genealogical records, including birth and death dates, place of birth, and court rank, as well as names of wives and adopted sons, were kept on members of the Royal court such that Min et al. could extract longevity for a sample of 81 eunuchs and compare their longevity with intact men controlling for socio-economic and privilege status. Comparing eunuch longevity with that of intact men from three different Royal families, the eunuchs lived on average 14.4–19.1 years longer, data remarkably similar to that from the Kansas institution mentioned above. Thus, removing male gonadal hormones appears to have a significant impact on human health and longevity.

Occasional exceptions to this general trend have been reported. For instance, the Rottweiler dog breed, unlike dogs more generally, females are overrepresented by more than two-fold at extreme ages (in this case defined as living ≥ 13 years or roughly 30% beyond “normal” Rottweiler longevity). However, removal of ovaries within the first 4 years of life erases this female survival advantage (Waters et al. 2009). Removal of ovaries has also been reported to shorten life in female CBA mice if done prior to sexual maturation (Cargill et al. 2003). More interestingly, these authors found that transplanting the ovaries from young mice into 11-month-old post-reproductive mice and restored the estrus cyclicity for several months also led to 40% increase in post-surgical longevity. No difference in maximum longevity was observed, however.

Despite these rare exceptions, in general gonadal hormones appear to play an important role in longevity.

The brain–longevity connection

The first single-gene mutation known to lengthen life in a mammal was the Ames dwarf mouse mutation, which increased mean male and female longevity by a remarkable 49% and 68%, respectively (Brown-Borg et al. 1996). Ironically, the gene responsible for Ames dwarfism was identified in the same year (1996), named *prop-1*, a transcription factor involved in the development of the anterior pituitary (Sornson et al. 1996). The Ames dwarf mutation (*prop-1^{df}*) eliminates the anterior pituitary cells responsible for the production of circulating prolactin (PRL), thyroid-stimulating hormone (TSH), and growth hormone (GH) with all of the downstream

effects this implies (Bartke 2005). Several years later, it was discovered that the Snell dwarf mouse, which has a defective *pit-1* gene, was also long-lived (Flurkey et al. 2001). *Pit-1* is also a transcription factor involved in the anterior pituitary development. So Snell dwarf mice were deficient in the same hormones as the Ames dwarf and consequently displayed a very similar phenotype, including extending life in both sexes. The role of the *prop-1* gene appears to be confined to turning on *pit-1* in the pituitary. Ironically, the pituitary had long been suspected of being a master regulator responsible for many aspects of physiology, including longevity (Everitt 1973). It was then discovered that eliminating GH activity by inactivating its receptor also produced small mice with extended life in both sexes (Coschigano et al. 2000). Further implicating GH in life extension mice defective in growth-hormone-releasing hormone receptor, which leads to a circulating level of GH in only 1% of the controls, also exhibit extended life in both sexes (Flurkey et al. 2001). Thus, it has been assumed that it was the deficiency in GH rather than in TSH or PRL that was responsible for much if not all of the longevity effects observed in both Ames and Snell dwarfs.

One of the key effects of GH secretion is that it stimulates secretion of IGF-1 from the liver. It was soon reported that mice haploinsufficient in IGF-1 were also long-lived, but in this case the effect was significant only in females (Holzenberger et al. 2003). A second study found a similar result although the female longevity effect was much smaller (Bokov et al. 2011). Surprisingly, despite the fact that the impact of genetically reducing IGF-1 activity has a considerably smaller longevity effect than GH inactivation and the fact that IGF-1's effects are sex specific while inactivation of GH are not, it is still commonly assumed that the GH longevity effect is largely due to its impact on IGF-1. Clearly, some further investigation of the downstream effects of GH dynamics is warranted.

Another genetic manipulation that is reported to extend mouse life is reduced brain-specific signaling of the insulin receptor substrate 2 (IRS2) (Taguchi et al. 2007). IRS2 is found throughout the body, but a global reduction in IRS2 signaling has been reported to lead to about the same increase in longevity (~14%) as does brain-specific reduction in signaling. Unfortunately, survival results were not broken out by sex in this study. However, this result could not be replicated in a second study (Selman et al. 2008), a difference that may have to do

with small differences in the diets in the two studies. In that second study, reduced signaling of IRS1 did lengthen life, but in females only.

As with gonadal hormones, brain-derived hormones also clearly play a role in modulating aging and longevity.

The brain–gonad–longevity connection

Reproduction in vertebrates is well known to entail a complex hormonal dialog between the brain and gonads. Given the empirical relationship between gonadal hormones and longevity and neuroendocrine activity and longevity, it makes sense to hypothesize that longevity itself may be at least a partial consequence of this hormonal interplay between the gonads and brain—the hypothalamic–pituitary–gonadal (HPG) axis. An interesting feature of the HPG axis is that the same hormones occur in both sexes, but their tempo, amount, tissue specificity, and activity differ. That might help explain some of the clear and pervasive sex differences in aging and longevity. Another feature is that the hormones involved all have pleiotropic non-reproductive effects in multiple tissues as might be expected if they play major roles in aging.

This is not a new idea. Sex differences in the prevalence or rate of progression of specific age-related diseases have been hypothesized to be the result of gonadal hormones and their impact on neuroendocrine signaling for decades. For instance, more women than men die from Alzheimer’s disease even after adjusting for age (Austad 2017; Xu et al. 2016). One long-standing hypothesis for this difference is that it is due to changes with age in the amount of gonadal steroids, particularly estrogen but also testosterone (Pike 2017). However, empirical evidence for this hypothesis has been mixed at best. It is worth noting that the HPG axis comprises many more hormones than gonadal steroids. More recent hypotheses suggest that gonadotropins, particularly luteinizing hormone (LH), may play a role in Alzheimer’s pathogenesis (Webber et al. 2007).

But the HPG hormone hypothesis of longevity modulation suggests that it may be the total package of HPG hormones that matter. For that to be valid, one would expect HPG hormones to be found and active in multiple non-reproductive tissues. That has long been known to be true for gonadal steroids. Androgen and estrogen receptors are found in virtually every tissue. But it is also

true for the gonadotropins which, as gonadal steroid levels wane, become elevated in later life. LH receptors, for instance, in addition to their presence in ovaries and testes, are found in the skin, breast, adrenals, retina, and of course the brain (Ascoli et al. 2002). Similarly, the other gonadotropin, follicle-stimulating hormone (FSH), has receptors not only in ovaries and testes, but also in the endothelium, monocytes, bone, and fat (Lizneva et al. 2019).

Possibly the most interesting of lesser known hormones in this regard are activins and inhibins—both members of the TGF β protein superfamily—which along with follistatin are best known for helping regulate FSH synthesis and secretion from the pituitary and well as in modulating the effects of gonadotropins in the gonads (Baccarelli et al. 2001). Activin is produced in both gonads and pituitary where it has its canonical effect of increasing FSH production and activity. But it is also expressed in the heart, lung, kidney, gastrointestinal tract, muscle, and bone, where it plays roles in cell proliferation, differentiation, metabolism, and apoptosis as well as immune response and wound healing (Chen et al. 2006; Werner and Alzheimer 2006). In mammals, activin A (there are two major isoforms) appears to be neuroprotective (Bloise et al. 2019). In flies, activin has even been reported to interact with insulin signaling to improve muscle performance and extend life (Bai et al. 2013).

Inhibins (there are two major isoforms) generally antagonize the effects of activins (Makanji et al. 2014). Their primary site of production is the gonads, but it is also found at much smaller concentration in the adrenal glands, bone, eye, lung, kidney, pituitary, and spleen. In addition to its canonical reproductive role of inhibiting FSH it appears to play a role in bone turnover and hematopoiesis.

Finally like inhibins, follistatin also inhibits FSH. Its primary production site is in the gonads, particularly in the ovary, although it is also present in small amounts in virtually every tissue (Zhang et al. 2018). Follistatin is an inhibitor of multiple members of the TGF β superfamily, most potently activin, which is how it has its impact on FSH and on reproduction. However, beyond that, follistatin inhibits myostatin and bone morphogenetic protein (BMP). In tissues, it helps inhibit inappropriate cell proliferation and appears to function in the response to several kinds of stressors, including oxidative and energetic stresses (Zhang et al. 2018). To the extent

that these features of follistatin are valid, its potential impacts longevity and aging.

In conclusion, sex differences in aging and longevity are pervasive and little understood. One potentially productive approach to a better understanding of these differences may be to focus specifically on hormones involved in the HPG axis.

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