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SHORT COMMUNICATION

Does the degree of endocrine dyscrasia post-reproduction dictate post-reproductive lifespan? Lessons from semelparous and iteroparous species

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Abstract Post-reproductive lifespan varies greatly among species; human post-reproductive lifespan comprises ~30–50% of their total longevity, while semelparous salmon and dasyurid marsupials post-reproductive lifespan comprises <4% of their total longevity. To examine if the magnitude of hypothalamic-pituitary-gonadal (HPG) axis dyscrasia at the time of reproductive senescence determines post-reproductive lifespan, we examined the difference between pre- and post-reproductive (1) circulating sex hormones and (2) the ratio of sex steroids to gonadotropins (e.g., 17β-estradiol/follicle-stimulating hormone (FSH)), an index of the dysregulation of the HPG axis and the level of dyotic (death) signaling post-reproduction. Animals with a shorter post-reproductive lifespan (<4% total longevity) had a more marked decline in circulating sex steroids and corresponding elevation in gonadotropins compared to animals with a longer post-reproductive lifespan (30–60% total longevity). In semelparous female salmon of short post-reproductive lifespan (1%), these divergent changes in circulating hormone concentration post-reproduction equated to a 711-fold decrease in the ratio of 17β-estradiol/FSH between the reproductive and post-reproductive periods. In contrast, the decrease in the ratio of 17β-estradiol/FSH in iteroparous female mammals with long post-reproductive lifespan was significantly less (1.7–34-fold) post-reproduction. Likewise, in male semelparous salmon, the decrease in the ratio of testosterone/FSH (82-fold) was considerably larger than for iteroparous species (1.3–11-fold). These results suggest that (1) organisms with greater reproductive endocrine dyscrasia more rapidly undergo senescence and die, and (2) the contribution post-reproduction by non-gonadal (and perhaps gonadal) tissues to circulating sex hormones dictates post-reproductive tissue health and longevity. In this way, reproduction and longevity are coupled, with the degree of non-gonadal tissue hormone production dictating the rate of somatic tissue demise post-reproduction and the differences in post-reproductive lifespans between species.

Keywords Post-reproductive lifespan · Sex hormones · Semelparous · Iteroparous · Menopause · Salmon

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Introduction

Post-reproductive lifespan varies greatly among species. Certain animals, like humans and most mammals, have a comparatively long post-reproductive lifespan that comprises ~30–50% of their total longevity. Conversely, other animals such as semelparous salmon and dasyurid marsupials have short post-reproductive lifespans comprising <1–4% of their total longevity (Table 1). Indeed, both female and male semelparous salmon die rapidly after their reproductive episode is complete (Truscott et al. 1986), as do certain semelparous male dasyurid marsupials (Braithwaite and Lee 1979; Diamond 1982; Dickman 1993; Fisher et al. 2006; Humphries and Stevens 2001; Oakwood et al. 2001; Woolley 1966), polychaetes (Lawrence and Soame2009), and insecta (Fritz et al. 1982). These differences in post-reproductive lifespan and total longevity are related to the survival strategies of different species (i.e., requirement or not, for post-reproductive care of offspring, transfer of survival knowledge, optimal mate selection or mating strategy, optimal sperm selection/competition). However, a mechanistic explanation of what regulates this range of post-reproductive lifespans between and within species has been elusive.

The Reproductive Cell-Cycle Theory of Aging posits that the hormones that regulate reproduction act in an antagonistic pleiotropic manner to control aging via cell cycle signaling; promoting growth and development early in life in order to achieve reproduction, but later in life, in a futile attempt to maintain reproduction, become dysregulated and drive senescence (Atwood and Bowen 2011; Bowen and Atwood 2004). In essence, the theory postulates that longevity is dictated by the dysregulation of sex hormones (endocrine dyscrasia) of the hypothalamic-pituitary-gonadal (HPG) axis that occur when the gonads can no longer produce sufficient sex steroids, inhibins, anti-Müllerian hormone (AMH), and other gonadal hormones. Since reproductive hormones regulate cell cycle dynamics (*division*: *gonadotropins/gonadotropin-releasing hormone (GnRH); differentiation*: *sex steroids*, *activins*), this reproductive endocrine dyscrasia is thought to promote aberrant cell cycle signaling ("dyotic signaling") leading to cell dysfunction and death, and the eventual dysfunction of tissues leading ultimately to tissue failure and the death of the organism (Bowen and Atwood 2004; Sun et al. 2006). Importantly, these sex hormones when in balance drive organismal growth and development early in life, and also are required for the normal

Table 1 Post-reproductive lifespan of representative iteroparous and semelparous species

Species	Lifespan (mean, years)	Post-reproductive lifespan (mean or range; years)	Proportion of post-reproductive lifespan (mean or range in %)
Human (*Homo sapiens*)	79 (Wang et al. 2013)	24–34 (Cohen 2004)	37
Chimpanzee (*Pan troglodytes*)	60 (Videan et al. 2008)	15–20 (Videan et al. 2008)	29 (25–33)
Rhesus monkey (*Macaca mulatta)*	25 (Uno 1997)	5–10 (Hodgen et al. 1977; Uno 1997)	30 (20–40)
Rat (*Rattus norvegicus*)	2.5 (Segall 1977)	0.7–1.3 (McShane and Wise 1996)	60 (27–53)
Mouse (*Mus musculus*)	2.2 (Rowlatt et al. 1976)	0.7–1.3 (Rowlatt et al. 1976)	60 (30–52)
Japanese quail (*Coturnix coturnix japonica*)	4.5 (http://eol.org/pages/1049255/overview)	1.5–2.5 (Ottinger et al. 1983)	44 (33–56)
Bush rat (*Rattus fuscipes*)	1 (McDonald et al. 1988a; Taylor and Calaby 1988)	0.04 (McDonald et al. 1988a; Taylor and Calaby 1988)[a]	4[a]
Salmon (*Oncorhynchus nerka*)	5 (Truscott et al., 1986)	0.06 (Truscott et al. 1986)	1

[a] Post-reproductive lifespan has not been accurately determined

maintenance of structure and function of the tissues of the body (Atwood and Bowen 2011; Berndt et al. 2009; Berndt et al. 2006; Bowen and Atwood 2004; Cole 2009; Prior 1990; Rogers et al. 2009; Vadakkadath Meethal and Atwood 2005; Wang et al. 2005; Zygmunt et al. 2002). Recent parabiosis experiments of young and old mice support this concept that the (reproductive) hormones that regulate cell growth and differentiation also regulate tissue maintenance and health in adult animals (Eggel and Wyss-Coray 2014; Katsimpardi et al. 2014; Sinha et al. 2014a; Sinha et al. 2014b). Based on this, a simple explanation for differences in post-reproductive lifespan might be that the rate and magnitude of post-reproductive HPG axis dysregulation determines the rapidity of cellular, tissue, and organismal dysfunction and death. If this scenario is true, then we might expect that for animals with a long post-reproductive lifespan, there is a significant non-gonadal tissue production of sex steroids, inhibins, AMH, etc., i.e., endocrine dyscrasia is less in these animals and the rate of demise is slower. Conversely, animals that have a short post-reproductive life, such as semelparous animals, would have less non-gonadal tissue production of sex hormones, i.e., endocrine dyscrasia is greater in these animals since their non-gonadal (and/or gonadal) tissues post-reproduction cannot compensate for the loss of gonadal sex steroids and inhibins, and their rate of demise is faster.

In this paper, we address this hypothesis by comparing changes in HPG axis hormones during reproduction and post-reproduction in semelparous and iteroparous species. We find that endocrine dyscrasia following reproduction in semelparous species is significantly greater than in iteroparous species and discuss the role of non-gonadal sex hormone production as a mechanism to regulate post-reproductive lifespan.

Methods

A PubMed search was performed for animals with short and long post-reproductive periods where circulating concentrations of both sex steroids and gonadotropins had been measured during- and post-reproduction in order to assess endocrine dyscrasia of the HPG axis. Data on the concentrations of circulating sex steroids (testosterone (T) and 17β-estradiol (E_2)) and gonadotropins FSH and luteinizing hormone (LH)) were obtained from published reports (see Tables 2 and 3) for animals with short (*Oncorhynchus nerka*—sockeye salmon—free-living; *Rattus fuscipes*—bush rat—free-living) and long (*Homo sapiens*—human; *Pan troglodytes*—chimpanzee; *Macaca mulatta*—rhesus monkey; *Rattus norvegicus*—rat; *Mus musculus*—mouse (C57BL/6); *Coturnix coturnix japonica*—Japanese quail) post-reproductive lifespans. Animals were only included in the study if reproductive and post-reproductive hormone concentrations had been reported. Fold changes in the concentration of each hormone between the reproductive and post-reproductive periods were determined. The ratios of sex steroids/gonadotropins were calculated from this data. Information on the average lifespan, average post-reproductive lifespan, and average proportion (%) of post-reproductive lifespan for these animals was obtained from published data (see references in Table 1).

Results and discussion

Post-reproductive sex steroid concentrations regulate post-reproductive lifespan

Between species analysis

To examine the relationship between sex hormones and post-reproductive lifespan, we analyzed the post-reproductive concentrations of sex hormones in animals with different post-reproductive lifespans (Table 1). Animals whose sex steroids and gonadotropins had been measured during the reproductive and post-reproductive stages of life were included (Tables 2 and 3; data from published papers). Since post-reproductive circulating hormones are derived from sex steroids released primarily from non-gonadal tissues (adipose tissue, adrenals, brain, etc.), we used circulating concentrations of sex hormones as a proxy for the whole body post-reproductive non-gonadal sex hormone production. The contribution of gonadal sources of steroids may not be significant since low levels of enzymes necessary for steroid biosynthesis are expressed in the post-reproductive ovary (Havelock et al. 2006). It is known that the post-menopausal ovary contributes few if any estrogens to the circulating pool by way of direct production, although it appears to retain some capacity to produce androgens (Adashi 1994; Ushiroyama and Sugimoto 1995; Vermeulen 1976).

Table 2 Female reproductive and post-reproductive circulating sex hormone concentrations

	17β-estradiol			FSH			LH		
	ng/mL		Ratio	ng/mL		Ratio	ng/mL		Ratio
	Reproductive[a]	Post-reproductive[b]	Fold change	Reproductive[a]	Post-reproductive[b]	Fold change	Reproductive[a]	Post-reproductive[b]	Fold change
Human (*Homo sapiens*)	0.15 (Mayo Clinic; Quest Diagnostics)	0.02 (Mayo Clinic; Quest Diagnostics)	−7.5	10 (Mayo Clinic; Quest Diagnostics)	50 (Mayo Clinic; Quest Diagnostics)	5.0	5 (Mayo Clinic; Quest Diagnostics)	20 (Mayo Clinic; Quest Diagnostics)	4.0
Chimpanzee (*Pan troglodytes*)	0.048 (Videan et al. 2008)	0.030 (Videan et al. 2008)	−1.6	4 (Videan et al. 2008)	17 (Videan et al. 2008)	4.2	1.0 (Videan et al. 2008)	0.3 (Videan et al. 2008)	3.3
Rhesus Monkey (*Macaca mulatta)*	0.070 (Downs and Urbanski 2006; Gore et al. 2004)	0.038 (Downs and Urbanski 2006; Gore et al. 2004)	−1.8	1.4 (Downs and Urbanski 2006; Gore et al. 2004)	5.0 (Downs and Urbanski 2006; Gore et al. 2004)	3.6	24 (Downs and Urbanski 2006; Gore et al. 2004)	59 (Downs and Urbanski 2006; Gore et al. 2004)	2.5
Rat (*Rattus norvegicus*)	0.033 (Goya et al. 1990)	0.032 (Goya et al. 1990)	−1.0	1.9 (Kurosumi et al. 1991)	3.2 (Kurosumi et al. 1991)	1.7	0.29 (Kurosumi et al. 1991)	0.60 (Kurosumi et al. 1991)	2.1
Mouse (*Mus musculus*)	0.097 (Cousins et al. 2003)	0.036 (Cousins et al. 2003)	−2.7	5 (Belisle et al. 1990)	39 (Belisle et al. 1990)	7.8	2 (Belisle et al. 1990)	13 (Belisle et al. 1990)	6.5
Salmon (*Oncorhynchus nerka*)	18.5 (Truscott et al. 1986)	1.2 (Truscott et al. 1986)	−15.4	2 (Truscott et al. 1986)[c]	90 (Truscott et al. 1986)[c]	45	–	–	–

[a] Representative mean hormone concentration across the estrus/menstrual cycle

[b] Representative mean hormone concentrations for post-reproductive animals

[c] Values for salmon represent total gonadotropins using antiserum raised against chum salmon gonadotropin preparation G7511 (Idler et al. 1975; Truscott et al. 1986). Summing the gonadotropin (LH and FSH) concentrations for iteroparous species (to allow comparison with the salmon gonadotropin concentrations) does not greatly alter the fold changes in concentrations between the reproductive and post-reproductive periods.

Where possible hormone concentrations from the same rodent strains have been compared

Table 3 Male reproductive and post-reproductive circulating sex hormone concentrations

	Testosterone			FSH			LH		
	ng/mL		Ratio	ng/mL		Ratio	ng/mL		Ratio
	Reproductive	Post-reproductive[a]	Fold change	Reproductive	Post-reproductive[a]	Fold change	Reproductive	Post-reproductive[a]	Fold change
Human (*Homo sapiens*)	6.45 (Mayo Clinic; Quest Diagnostics)	2.30 (Mayo Clinic; Quest Diagnostics)	−2.8	0.6 (Mayo Clinic; Quest Diagnostics)	2.3 (Mayo Clinic; Quest Diagnostics)	3.8	0.6 (Mayo Clinic; Quest Diagnostics)	2.0 (Mayo Clinic; Quest Diagnostics)	3.3
Chimpanzee (*Pan troglodytes*)	4.8 (Young et al. 1993)	2.9 (Young et al. 1993)	−1.7	–	–	–	–	–	–
Rhesus monkey (*Macaca mulatta*)	1.4 (Schwartz and Kemnitz 1992)	0.5 (Schwartz and Kemnitz 1992)	−2.8	–	–	–	–	–	–
Rat (*Rattus norvegicus*)	1.1 (Zirkin and Chen 2000)	0.8 (Zirkin and Chen 2000)	−1.4	5.3 (Zirkin and Chen 2000)	7.6 (Zirkin and Chen 2000)	1.4	9.1 (Parkening et al. 1983)	1.1 (Parkening et al. 1983)	0.1
Mouse (*Mus musculus*)	1.4 (Nelson et al. 1975)	1.2 (Nelson et al. 1975)	−1.2	83 (Lacombe et al. 2007)	93 (Lacombe et al. 2007)	1.1	0.9 (Lacombe et al. 2007)	0.5 (Lacombe et al. 2007)	0.6
Japanese quail (*Coturnix coturnix japonica*)	2.4 (Balthazart et al. 1984; Ottinger et al. 1983)	0.6 (Balthazart et al. 1984; Ottinger et al. 1983)	−3.8	400 (Balthazart et al. 1984)	1069 (Balthazart et al. 1984)	2.7	27.0 (Balthazart et al. 1984)	24.3 (Balthazart et al. 1984)	0.9
Bush rat (*Rattus fuscipes*)	5 (McDonald et al. 1988a)	0.7 (McDonald et al. 1988a)	−7.0	–	–	–	–	–	–
Salmon (*Oncorhynchus nerka*)	56 (Truscott et al. 1986)	22 (Truscott et al. 1986)	−2.5	1.5 (Truscott et al. 1986)[b]	48.3 (Truscott et al. 1986)[b]	32	–	–	–

[a] Only data where the male animal was definitely aged (last 10–20% of lifespan) and reproduction was significantly declined were included

[b] Values for salmon represent total gonadotropins using antiserum raised against chum salmon gonadotropin preparation G7511 (Idler et al. 1975; Truscott et al. 1986). Summing the gonadotropin (LH and FSH) concentrations for iteroparous species (to allow comparison with the salmon gonadotropin concentrations) does not greatly alter the fold changes in concentrations between the reproductive and post-reproductive periods.

Where possible hormone concentrations from the same rodent strains have been compared

In female mammals, there is an approximately 1- to 8-fold decrease in circulating 17β-estradiol concentrations post-reproduction and a corresponding approximately 2- to 7-fold and an approximately 2- to 8-fold increase in LH and FSH, respectively (Table 2). These increases are the result of the loss of negative feedback by the sex steroids on the hypothalamus and pituitary.

Like *Mammalia*, *Osteichthyes* (fish) have an HPG axis complete with negative feedback regulation by gonadal-produced sex steroids and inhibins on the hypothalamus and pituitary (Poon et al. 2009). In salmon, this axis regulates gonadal development and maturation for spawning (reproduction). Circulating sex steroids such as testosterone and 17β-estradiol increase during reproductive maturation and peak well before spawning (sometimes several hundred kilometers before reaching natal spawning grounds and several weeks before final maturation (Hinch et al. 2006)). Remarkably, in maturing female *O. nerka* (sockeye salmon), circulating 17β-estradiol concentrations are 123- to 264-fold higher than reproductive females of common mammalian species (Table 2), illustrating a crucial function for 17β-estradiol in normal tissue maintenance and function in *O. nerka*. Intriguingly, around the time of spawning, there is a precipitous 15-fold decrease in circulating 17β-estradiol concentrations and a corresponding 45-fold increase in total gonadotropins in female *O. nerka* (Table 2, Truscott et al. 1986). Accompanying these changes, there is a large increase in 17-hydroxyprogesterone, the precursor of 17β-estradiol and testosterone, from undetectable levels to 85 ng/mL post-spawning. Also, the fish oocyte meiotic maturation-inducing hormone 17α, 20β-dihydroxy-4-pregnen-3-one (both free and conjugated) increases from undetectable levels to 34 and 16 ng/mL, respectively, post-spawning (Truscott et al. 1986), indicating that the rate of conversion of these precursors into estradiol (and testosterone) is dramatically decreased. Indeed, the circulating concentration of testosterone also decreases from 587 to 178 ng/mL, while that of conjugated testosterone increases from undetectable levels to 200 ng/mL post-spawning (Truscott et al. 1986).

In male *O. nerka*, free testosterone levels, like 17β-estradiol in females, are higher (9 to 51-fold) than males of iteroparous mammalian and fish species (Table 3), suggesting testosterone also is crucial for normal tissue maintenance and function in *O. nerka*. Around the time of spawning, similar hormonal changes are observed in male *O. nerka* (with the exception of 17β-estradiol which is low throughout, Table 3; (Truscott et al. 1986); circulating testosterone decreases 2.5-fold while total gonadotropins increase 32-fold (Table 3; Truscott et al. 1986). Sex steroids also have been found to diminish and continue to decline prior to death in other species, including in pink salmon *Oncorhynchus gorbuscha* (Dye et al. 1986; Williams et al. 1986), coho salmon *Oncorhynchus kisutch* (Fitzpatrick et al. 1986), and chum salmon *Oncorhynchus keta* (Onuma et al. 2009). Thus, these results indicate that at around the time of spawning, sufficient bioactive 17β-estradiol and testosterone can no longer be synthesized while there is an increase in bound sex steroids that would together dramatically decrease bioavailable and bioactive sex steroid signaling. Although unreported for salmon, there is a decline in inhibin A expression in the follicles of zebrafish whose oocytes undergo spontaneous maturation or germinal vesicle breakdown (see Poon et al. 2009). These authors demonstrated that human inhibin A induced a slight but significant inhibitory effect on 17α, 20β-dihydroxyprogesterone-induced oocyte maturation, suggesting that inhibin production maintains HPG axis homeostasis and that its loss upon follicle maturation contributes to the endocrine dyscrasia associated with spawning and the demise of body tissues. Unlike some salmon, zebrafish possess ovarian follicle reserves for subsequent reproductive episodes.

Since both male and female *O. nerka* die rapidly around the time of spawning, and 17β-estradiol levels are not altered in male *O. nerka*, the elevations in gonadotropins and loss of testosterone (and likely inhibin) signaling in both males and females appear to be the primary dyotic signals in salmon (Table 2). The loss of 17β-estradiol (and inhibin) signaling also may be important for the demise of female *O. nerka* (Table 2; Jeffries et al. 2011), as supported by the high 17β-estradiol concentrations in *O. nerka* prior to spawning (Table 2), and the lack of a decrease in testosterone signaling in post-menopausal women with aging (Rohr 2002). Although post-spawning female *O. nerka* circulating 17β-estradiol (and male *O. nerka* testosterone) is considerably higher than in mammals, their relative concentration declines by a far greater extent (Tables 2, 3, 4, and 5), thereby triggering robust dyotic signaling.

Within species analysis

Differences in sex hormone production as a regulator of post-reproductive lifespan within a species also have

been identified (Atwood and Bowen 2011). Post-reproductive lifespan in humans varies from ~24–34 years or more (Thomas et al. 2001; Table 1). Those individuals with greater dyotic signaling post-menopause and during andropause are more likely to develop Alzheimer's disease (AD) (Bowen et al. 2000; Hogervorst et al. 2004; Hyde et al. 2010; Manly et al. 2000; Rodrigues et al. 2008; Short et al. 2001; Verdile et al. 2008); coronary artery disease (see Yeap 2010); and osteoporosis (Bagur et al. 2004; Randolph et al. 2004; Sowers et al. 2006). With respect to the brain, it has been demonstrated that the concentration of 17β-estradiol and testosterone is decreased in women and men, respectively, with AD compared to age-matched controls (Rosario et al. 2009; Yue et al. 2005). Similarly, circulating testosterone concentration is significantly inversely correlated with stroke severity, infarct size, and 6-month mortality in men (Elwan et al. 1990). These results suggest that those post-reproductive individuals with a lower capacity to synthesize sex steroids are more likely to develop age-related diseases sooner.

Ratio of sex steroid/gonadotropin as a measure of dyotic signaling

Examination of the changes in individual circulating hormones in reproductive and post-reproductive animals indicates clear differences between salmon and humans. For example, there is a 2- to 6-fold increase in circulating gonadotropins in humans, but a 45-fold increase in circulating gonadotropins between salmon pre- and post-reproduction. We have suggested that this altered endocrine milieu post-reproduction leads to dyotic/death signaling that drives altered cell cycle dynamics (overwhelming mitotic signaling), dysfunction and death (Bowen and Atwood 2004). In this example, it is clear that salmon have far greater mitotic signaling than human post-reproduction. Since cell cycle dynamics is determined by the relative concentrations of mitogenic to differentiation hormones of the HPG axis, the extent of dyotic signaling can be determined by the ratio of these hormones. We have chosen to use the ratio of sex steroids/gonadotropins/GnRH since the loss of sex steroids (i.e., differentiation) and elevation of gonadotropins/GnRH (mitogenic) gives an index of differentiation/mitogenic (dyotic) signaling. In particular, we have chosen to examine the ratios of 17β-estradiol/FSH (and testosterone/FSH) because (1) the decline in sex steroids necessarily promotes dyotic signaling and results in the loss of feedback on the hypothalamus-pituitary, (2) FSH is a good marker of the loss of negative feedback inhibition on the hypothalamus-pituitary, (3) FSH acts as a proxy for the loss of inhibin signaling and feedback on the hypothalamus-pituitary (Downs and Urbanski 2006) and inhibin concentrations are generally not measured, (4) FSH has a longer half-life in mammals thereby obfuscating the need for multiple hormone measurements (such would be the case with LH or GnRH), and (5) data on 17β-estradiol, testosterone, and FSH is readily available. The more dysregulated the axis, the larger will be the change in the ratio. Finally, the use of ratios helps to mitigate incorrect interpretations from absolute circulating hormone concentrations due to any differences between

Table 4 Female reproductive and post-reproductive circulating sex hormone ratios

	E_2/FSH ratio ($\times 10^{-3}$)		E_2/FSH ratio	E_2/LH ratio ($\times 10^{-3}$)		E_2/LH ratio
	Reproductive	Post-reproductive	Reproductive to Post-reproductive ratio	Reproductive	Post-reproductive	Reproductive to Post-reproductive ratio
Human (*Homo sapiens*)	15	0.4	34	30	1.1	27
Chimpanzee (*Pan troglodytes*)	12	1.8	6.7	48	100	0.5
Rhesus monkey (*Macaca mulatta)*	50	7.6	6.6	3	0.6	5
Rat (*Rattus norvegicus*)	17	10	1.7	113	53	2
Mouse (*Mus musculus*)	19	0.9	21	48	2.8	17
Salmon (*Oncorhynchus nerka*)	9250	13	711	–	–	–

Table 5 Male reproductive and post-reproductive circulating sex hormone ratios

	T/FSH ratio			T/LH ratio		
	Reproductive	Post-reproductive	Reproductive to Post-reproductive ratio	Reproductive	Post-reproductive	Reproductive to Post-reproductive ratio
Human (*Homo sapiens*)	11	1	11	11	1.2	9
Rat (*Rattus norvegicus*)	0.2	0.1	2	0.1	0.7	0.1
Mouse (*Mus musculus*)	0.017	0.013	1.3	0.16	2.4	0.07
Japanese quail (*Coturnix coturnix japonica*)	0.006	0.00056	11	0.1	0.025	4
Salmon (*Oncorhynchus nerka*)	37	0.45	82	–	–	–

assays utilized and differences in tissue receptor densities.

During the time iteroparous female mammals are fertile, the ratio of 17β-estradiol/FSH varies between 12 and 50 and is indicative of non-dyotic signaling (Table 4). However, once they enter their post-reproductive phase, the ratio declines to between 0.4 and 10, indicative of dyotic signaling. Thus, the cut-off for female dyotic signaling (for mammalian species) is around 10–12. Similarly, the ratios for 17β-estradiol/LH vary between 3 and 113 (non-dyotic) and 0.6–100 (dyotic) in reproductive and post-reproductive species, respectively (Table 4). The large overlap in ratios of 17β-estradiol/LH between mammalian species makes this ratio less predictive of dyotic signaling compared to the 17β-estradiol/FSH ratio. In salmon, the reproductive 17β-estradiol/gonadotropin ratio was 9250 and fell dramatically to 13 post-reproduction.

In iteroparous males, the ratio of testosterone/FSH in fertile and post-reproductive animals was between 6×10^{-3}–11 and between 6×10^{-4}–1, respectively (Table 5). The ratios for testosterone/LH in fertile and post-reproductive male animals were between 0.1 and 11 and between 0.025 and 2.4, respectively. In salmon, the reproductive testosterone/gonadotropin ratio was 37 and fell dramatically to 0.45 post-reproductive.

The larger the change in mitogenic:differentiation (dyotic) signaling (i.e., the more dysregulated the HPG axis), the faster an organism's tissues are predicted to degenerate leading to death. Examination of the reproductive to post-reproductive 17β-estradiol/gonadotropin ratio in semelparous salmon as compared to mammals/birds indicates salmon have a far greater dyotic signaling index (711) than mammals/birds (1.7 to 34) post-reproduction (Table 4). Likewise in males, there is a larger reproductive to post-reproductive testosterone/gonadotropin ratio in semelparous salmon (82) as compared to mammals/birds (1.3–11; Table 5). Although post-reproduction gonadotropin data for other semelparous species is not available, the decline in circulating testosterone by 7-fold post-reproduction in *Rattus fuscipes* is suggestive of dyotic signaling promoting rapid senescence in this semelparous-like species.

In male rodents, it is interesting to note that circulating LH levels are not increased post-reproduction, but rather decreased (0.1 and 0.6-fold decreases in rat and mouse, respectively) while circulating FSH is modestly elevated (1.4 and 1.1, respectively; Table 3). Thus, in the case of the mouse, dyotic signaling is driven by the decreases in testosterone relative to the gonadotropins resulting in a reproductive to post-reproductive ratio of 1.3–2 for FSH and 21-1.7 for LH (Table 5), and explaining why they have a relatively long post-reproductive lifespan (Table 1).

These differences in the concentration of LH, FSH, GnRH, various sex steroids, activins, and inhibins post-reproduction will provide a unique dyotic signaling pattern that may dictate tissue-specific degeneration and the development of specific, different, age-related diseases between (and within) species. For example, elevations in post-reproductive LH may drive neurological and vascular diseases while

elevations in FSH drive immunological (cancer) and bone diseases.

Dyotic signaling, tissue degeneration, and functional decline

The large dyotic signaling in salmon (and other semelparous species) post-reproduction leads to dramatic and rapid (within 1–3 weeks) changes in tissue structure and function (phenoptosis) that are similar to the degenerative changes found in other aging vertebrates, including humans: the brain (amyloidosis), liver, stomach (peptic ulcers), spleen, thymus, thyroid, pituitary, kidney, and cardiovascular system exhibit degenerative changes, the adrenocortical tissue and pancreas display hyperplasia, and immune system collapse results in skin infections (Dickhoff et al. 1989; Maldonado et al. 2000, 2002a, b; Robertson and Wexler 1960, 1962). At this time, the suppression by 17β-estradiol on the utilization of pregnenolone as a substrate for cortisol synthesis by the interrenals (adrenals) is lost (McQuillan et al. 2003). Together with the marked elevation in circulating gonadotropins (Tables 2 and 3; Hruska et al. 2010; Jeffries et al. 2011), which are known to upregulate tumor necrosis factor (Clark and Atwood 2011) and subsequently glucocorticoid synthesis (Villar et al. 2013), there is a large growth of the adrenal glands that produce very high concentrations of glucocorticoids which has been postulated to drive tissue degeneration/dysfunction and death of salmon (Carruth et al. 2000; Finch 1990; Hruska et al. 2010). A similar adrenocortical mechanism impacting immune function has been proposed for the post-mating deaths of males from dasyurid marsupials (*Antechinus stuartii* and *A. favipes*) of eastern Australia (Bradley et al. 1980; McDonald et al. 1981), although in the larger dasyurid *Dasyurus hallucatus*, there is no evidence of elevated corticosteroid levels during male die-off (Oakwood et al. 2001). These results do not however support the *primacy* of cortisol as the trigger of death suggested by others. Rather, the loss of male gonadal cells (germ and somatic cells) with mating might be predicted to drive endocrine dyscrasia of HPG hormones (as a consequence of the loss of gonadal sex hormones) that subsequently signal elevations in circulating glucocorticoids as described in iteroparous species (Alevizaki et al. 2006). Indeed, Carruth and colleagues (Carruth et al. 2000) concluded that "the presence of elevated plasma cortisol in upstream migrating, landlocked Pacific salmon suggests that stressors previously considered to cause cortisol increases, such as long-distance migration and changes in salinity, may not be primary causes of the hypothalamic-pituitary-interrenal axis activation." Cortisol in individual *O. nerka* has been demonstrated to already be high in seawater prior to their upstream migration, and has been suggested to play a role in ionoregulation in the gill as they adapt to freshwater (Flores et al. 2012). Cortisol is a well-known osmoregulator (Bradford et al. 2010; Milla et al. 2009; Mommsen et al. 1999; Shrimpton et al. 2005); regulation of osmolarity is crucial for the survival of migrating salmon, there being a close correlation between the loss of osmoregulation and death (Jeffries et al. 2012). This study by Jeffries and colleagues further examined temporal biochemical/endocrine changes in *O. nerka* over the final 6 weeks of maturation and senescence (in 2008) and demonstrated that dyotic signaling (low 17β-estradiol in females, low testosterone in males) was present in all fish that died, irrespective of the timing of death (at first sampling, second sampling, third sampling, and final sampling (~week 6)). Cortisol levels were only excessively elevated in those fish near death; control fish did not demonstrate altered sex hormones, cortisol, or death. Thus, alterations in the HPG axis upon spawning (or at least maturation of eggs/sperm to the point of limited steroid or inhibin production) appear to upregulate cortisol, and together this dyotic signaling leads to *O. nerka* death. In iteroparous species, chronic stresses such as starvation (caloric restriction) that moderately elevate circulating cortisol (Qiu et al. 2012) extend, not shorten, lifespan. The upregulation of glucocorticoids during the estrous cycle, pregnancy, and lactation also supports a critical role for these steroids in reproductive success (Fanson et al. 2014).

This post-reproductive corticosteroid response also is seen in humans later in post-menopause (Rozenberg et al. 1988), and has been postulated as the cause of death in other semelparous species such as the dasyurid and didelphid marsupials (Fisher et al. 2013; Fisher et al. 2006; Oakwood et al. 2001; Schmidt et al. 2006). However, in contrast to smaller dasyurid and didelphid marsupial species, the larger dasyurid *D. hallucatus* species, which shows complete male die-off after mating, do not display elevated corticosteroid levels. Elevated cortisol levels also were not detected in the male Virginia opossum (*Didelphis virginiana)* which exhibits a life history

akin to semelparity. Together, these results suggest that the dysregulation of hormones of the HPG axis, those hormones that normally maintain tissue structure and function, is more likely driving semelparous species from the gene pool (Oakwood et al. 2001; Woods and Hellgren 2003). However, which changes in sex hormones drive death remains to be elucidated; elevations in testosterone have been reported for dasyurid and didelphid marsupial species (Bradley et al. 1980; McDonald et al. 1981; Oakwood et al. 2001), while there is a precipitous decline in testosterone concentrations and survivability of male *R. fuscipes*, which do not live long beyond the breeding season (Table 3; McDonald et al. 1988b). Further research in other iteroparous species is required to validate the elevated post-reproductive dyotic signals observed in male and female sockeye salmon. Moreover, the exact endocrine dyscrasia and dyotic signaling that follows mating in semelparous species warrants closer investigation.

Reproductive strategies that regulate the survival of the species are mediated via HPG hormones

When adult sockeye salmon *O. nerka* migrate upriver to their natal spawning area they have already ceased feeding and have begun rapid gonadal maturation in preparation for a single spawning (Jeffries et al. 2011). The above discussed hormonal changes occur rapidly in *O. nerka* over a 2–3 week period around the time of spawning. Interestingly, the reproductive development of the salmon varies from year to year, with sea temperature being one variable that determines the speed with which salmon mature (Onuma et al. 2009). This can result in the development and maturation of the gonadal germ and somatic cells that leads to the gonadal cells no longer being able to synthesize sex steroids and inhibins, initiating dyotic signaling, and leading to the death of salmon before reaching the spawning grounds (Gilhousen 1990). This "inflexible schedule" could have dire consequences for species survival given spawning success of only 3–24% in certain years (Gilhousen 1990), and might be why salmon have a 2–5 year growth phase in the ocean prior to spawning, mitigating the negative effects of any one year where the timing of maturation is not matched timewise to reaching their spawning grounds.

The dyotic signaling around the time of spawning appears to be responsible for the rapid demise of salmon. This rapid demise has been demonstrated to be important for the survival of the individuals in this species since mineral nutrients from the adult salmon are released back into ponds which help support the developing salmon fry/parr ecosystem (Field and Reynolds 2011). Or, put another way, since semelparous salmon and marsupials do not need to maintain their tissues post-reproduction, they have not evolved sufficient non-gonadal (peripheral) tissue sex hormone and/or gonadal sex hormone (steroid and inhibin) synthesis (as indicated by the low circulating levels post-reproduction; see Tables 2 and 3). Conversely, mammals/birds have evolved post-reproductive non-gonadal/gonadal tissue steroidogenesis to maintain tissue health and function (brain, adipocytes, immune system, fibroblasts, adrenals; Bain et al. 1991; Deshpande et al. 1967; Lubik et al. 2013; MacKenzie et al. 2008; Martini and Melcangi 1991; Slominski et al. 2004) since this is advantageous to the individuals of the species. In summary, we propose that post-reproduction in iteroparous species, tissue production of sex steroids and inhibins is greater and results in less dyotic signaling compared with semelparous species, where peripheral tissue steroid and inhibin production is lower (based on circulating hormone concentrations post-reproduction), relative to reproductive levels. The loss of the gonadal contribution to total circulating sex steroids/inhibins results in dyotic signaling; the greater the loss of gonadal sex steroids/inhibins relative to peripheral sex steroid/inhibin sources, the greater the dyotic signaling and speed of senescent decline. In this way, reproduction and longevity are coupled in all species (Bowen and Atwood 2004), with the degree of peripheral tissue hormone production dictating the rate of somatic tissue demise and thereby allowing for different reproductive strategies (i.e., length of post-reproductive period) and lifespans for different species. The longer post-reproductive period in humans for example has been evolutionarily advantageous to those members of the species, while the short post-reproductive period in salmon has been evolutionarily advantageous to the individuals in that species. Animal species that have longer parental care have a reproductive hormone axis that dysregulates later and/or a higher capacity for post-reproductive hormone production by non-gonadal tissues to maintain somatic tissue function. Conversely, semelparous species that provide no parental care have a reproductive hormone axis that dysregulates after reproduction and insufficient post-reproductive hormone production by non-gonadal tissues to maintain somatic tissue function.

Conclusion

The data and arguments presented in this paper suggest that longevity is regulated not only by the timing of HPG axis initiation (puberty) and dysregulation (i.e., menopause and andropause; Yonker et al. 2013), but also by the contribution post-reproduction of non-gonadal/gonadal tissues to sex hormone production to compensate for the loss of sex steroid/inhibin production and the maintenance of structure and function of non-gonadal tissues. Those organisms that have limited post-reproductive tissue sex hormone production relative to reproductive gonadal sex hormone production will die sooner than those with greater post-reproductive tissue sex hormone production, explaining why salmon die quickly around the time of spawning and why humans can live 30–60 years post-reproduction. In humans and rodents, all non-gonadal tissues studied to date produce sex steroids (Bain et al. 1991; Deshpande et al. 1967; Lubik et al. 2013; MacKenzie et al. 2008; Martini and Melcangi 1991; Slominski et al. 2004), albeit at levels insufficient to allow for the rebalancing of the axis. These observations also provide a biological rationale for the increase in circulating cortisol post-reproduction, one that is secondary to the HPG axis changes that lead to dyotic signaling. These data and insights will hopefully promote further research into strategies to maintain the HPG axis in balance longer to further extend human post-reproductive lifespan.

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