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SYMPOSIUM

Evolutionary Conflict Between Maternal and Paternal Interests: Integration with Evolutionary Endocrinology

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Synopsis Conflict between mates, as well as conflict between parents and offspring are due to divergent evolutionary interests of the interacting individuals. Hormone systems provide genetically based proximate mechanisms for mediating phenotypic adaptation and maladaptation characteristic of evolutionary conflict between individuals. Testosterone (T) is among the most commonly studied hormones in evolutionary biology, and as such, its role in shaping sexually dimorphic behaviors and physiology is relatively well understood, but its role in evolutionary conflict is not as clear. In this review, we outline the genomic conflicts arising within the family unit, and incorporate multiple lines of evidence from the bank vole (*Myodes glareolus*) system to outline how T impacts traits associated with reproduction and survival, resulting in a sexually antagonistic genetic trade-off in fitness. A major prediction arising from this work is that lower T is favored in females, whereas the optimal T level in males fluctuates in relation to social and ecological factors. We additionally discuss future directions to further integrate endocrinology into the study of sexual and parent–offspring conflicts.

Testosterone in evolution

As genetically based signalling systems that are capable of efficiently responding to environmental stimuli, hormones play crucial roles in adaptation by mediating life history trade-offs (McGlothlin and Ketterson 2008; Mills et al. 2008, 2009, 2012; John-Alder et al. 2009; Hau and Wingfield 2011; Mokkonen and Crespi 2015). One of the most studied hormones in evolutionary biology is the androgen testosterone (T)—a sexually dimorphic hormone that exhibits similar endocrinological functions across vertebrate taxa (Adkins-Regan 2005; Mills et al. 2008; Hau and Wingfield 2011; Cox et al. 2015). T is involved in the process of masculinizing the male brain, as well as the female phenotype for placental species that have mixed-sex offspring in one litter where T in utero is secreted maternally and fraternally (Hernández-Tristán et al. 1999; Kerin et al. 2003; Lummaa et al. 2007). These prenatal effects can have life-long consequences on the behavior and/or physiology of individuals (Ruuskanen and Laaksonen 2010). Recent work has argued that the programming effects of T on mammalian fetal brains is associated with psychiatric dysregulation (Lombardo et al. 2012; Baron-Cohen et al. 2015), and may also epigenetically influence sexual preference (Rice et al. 2012). Being an anabolic steroid, it is responsible for stimulating somatic tissue growth (including muscle mass, bone density, and strength) as well as secondary sex characteristics (e.g., Alatalo et al. 1996; but see Pizzari et al. 2004). It is also important in spermatogenesis, where it interacts with testicular Sertoli cells in the maturation of spermatagonia to spermatozoa (McLachlan et al. 1996; Zirkin 1998; Preston et al. 2012). The benefits of higher T for reproduction inherently trade off with other fitness-related traits such as parental effort (McGlothlin et al. 2007), as well as immunity and survival (Folstad and Karter 1992; John-Alder et al. 2009; Mills et al. 2009, 2010). Clearly, T impacts a

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range of traits that directly influence fitness across different ontogenetic stages. In this review, we consider the impact of T on competing evolutionary interests in mammals, concentrating on bank vole (*Myodes glareolus*) life histories to draw together behavioral, genetic, physiological, and ecological perspectives.

Evolutionary conflicts

Trade-offs between life history traits

Individuals are aggregates of interacting traits, some fixed, some exhibiting diverse variation in their expression. When this phenotypic variation is heritable and linked to variation in fitness, selection can act on a given trait to adapt a population of individuals towards an optimum value in a given environment (Falconer and MacKay 1996; Bell 2008; Mills et al. 2014). However, due to physiological constraints in morphology and energetics, fitness-related traits often represent a compromise value due to evolutionary trade-offs between them in an individual (Roff 1992; Stearns 1992). In such a classic life history trade-off, selecting for (or against) a value of a given trait will produce an effect on fitness, but will additionally produce an indirect effect on any correlated trait that may have an opposing effect on fitness (Oksanen et al. 2003). These trade-offs are apparent during reproduction, where females typically invest more resources in offspring, and must carefully balance the fitness benefits of current and future reproductive success with the associated fecundity costs that may also impact their own survival (Trivers 1972, 1974; Oksanen et al. 2002; Koivula et al. 2003; Mappes et al. 2008). In contrast, males maximize their reproductive success directly by balancing their investment in mating success with survival costs (Mills et al. 2009), and indirectly through genetic benefits that improve offspring survival via greater resource acquisition from mothers (Parker et al. 2002; Rutkowska et al. 2011; Collet et al. 2014; but see Oksanen et al. 1999). When these traits are genetically based and negatively correlated, the trade-off is the result of (intra)genomic conflict—an unresolved genetic conflict within an individual (Mappes and Koskela 2004; Schroderus et al. 2012; Haig 2014b).

Multiple lines of evidence (correlative observational data from the wild, as well as manipulation experiments involving phenotypic engineering with T-implants, or artificial selection) have demonstrated that T is one of the main determinants of reproductive success in male bank voles (Mills et al. 2007b, 2009). Males selected for higher T levels have higher behavioral dominance in male–male reproductive competition, leading to higher mating and reproductive success (Mills et al. 2009, 2012; Mokkonen et al. 2012). Despite directional (sexual) selection of this hormone in males, considerable phenotypic variation exists in populations. Manipulated field experiments and quantitative genetic analysis of a laboratory colony were conducted on individuals to reveal the costs of selecting for T. Individuals with higher T levels suffered lower specific (anti-BGG) immune responses making them more susceptible to pathogens, and had shorter lifespans due to decreased survival (Mills et al. 2009, 2010). Negative genetic correlations between T and immune function were observed in males (Schroderus et al. 2010).

Sexual selection and conflict

The reproductive differences between males and females have come under increasing scrutiny in evolutionary biology. Since females tend to bear the costs of gestation and parental care, the reproductive success of males is primarily limited by the number of mates and the reproductive success of females is mostly limited by the resources available (and physiological capacity) for producing the offspring (Bateman 1948; Parker and Birkhead 2013). Thus, to understand the evolution of sex roles, one must consider both pre-copulatory and post-copulatory processes in reproduction such as the adult and operational sex ratios, sexual selection, multiple mating, and the resource needs of the offspring (Mills and Reynolds 2003; Kokko and Jennions 2008).

More recent research has complemented existing knowledge of sexual selection by focusing on sexually antagonistic (SA) selection (Parker 1979; Rice 1992; Arnqvist and Rowe 2005; Bonduriansky and Chenoweth 2009; Cox and Calsbeek 2009; Mokkonen et al. 2011). When acting on a shared genetic locus, this type of selection often results in a ''compromise'' between males and females over a trait. The evolutionary interests between parent and offspring, as well as between mates, are dissimilar enough to result in genetic conflicts between the interacting individuals (i.e., intergenomic conflict; Rice 2013). Sexual and parent–offspring conflicts occur during reproduction and are essentially due to the differences in paternal versus maternal evolutionary interests (Trivers 1974; Rice 1998; Parker et al. 2002; Arnqvist and Rowe 2005; Wedell et al. 2006; Aloise King et al. 2013). It is possible to minimize these genetic conflicts by evolving processes such as sex-biased gene expression (Rice 1984; Stewart et al. 2010). However, genome-wide resolution of conflict

is unlikely to occur due to the changing (ontogenetic and sexual) environment of the alleles in conflict (Chippindale et al. 2001). Expression of SA alleles can result in genetic conflict in a variety of physiological, behavioral, and morphological characteristics important in reproduction (Fig. 1). Given that the expression of those genes often differs depending on the sex, it causes the trait to be sexually dimorphic (Rice 1984; Cox and Calsbeek 2009). If this dimorphism is due to sex-limited gene expression, so that only one sex expresses that gene product, then it may possibly solve the conflict between the sexes (though this has recently been questioned, e.g., Connallon et al. 2010).

The spread of genes that have sex-specific fitness effects is facilitated by sex-biased transmission (Pizzari and Birkhead 2002, and references therein), which has been further confirmed by studies on *Drosophila melanogaster* that show the X-chromosome is rife with SA genetic variation (Gibson et al. 2002; Innocenti and Morrow 2010). If sexual dimorphism is simply a difference in the value of the trait expressed by both sexes (with corresponding sex-specific fitness optima), then it can be said that there is a divergence in the evolutionary interests between the sexes for that trait (Parker 1979). Only when the fitness of one sex is negatively affected by the fitness gains of the other sex is the conflict realized. A ''gender load'' exists when the sex-specific values of a fitness-related trait are not at their optimal fitness values (Bedhomme and Chippindale 2007), thus constraining a population from attaining a maximum fitness value. Sexual conflicts arise over the genes at the same locus in males and females (intralocus conflict/sexual antagonism), or between different sets of genes located at different loci (interlocus conflict) (Parker and Partridge 1998; Arnqvist and Rowe 2005; Bonduriansky and Chenoweth 2009). Here, we focus primarily on conflicts over a shared locus, sexual antagonism. Under sexual antagonism, genetic benefits associated with good genes models of sexual selection can potentially be overwhelmed by the mounting fitness costs of SA alleles (Pischedda and Chippindale 2006). Sexually dimorphic phenotypes, such as those associated with hormones, indicate potential for sexual antagonism.

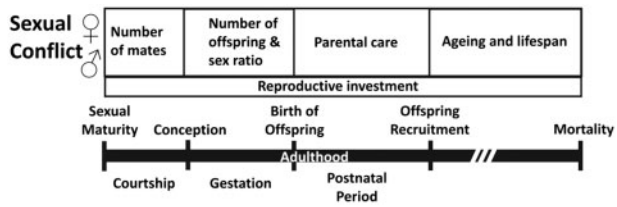

Fig. 1 Potential for sexual conflict over life history parameters.

In a variety of taxa, males with higher plasma T are more dominant in male–male competition for mates and as a result, sire more offspring (Alatalo et al. 1996; Ketterson and Nolan 1999; Hau 2007). Since greater T has been shown to be advantageous in male–male competition, the classic good genes and sexy sons models of sexual selection predict that females should mate with males with higher T, as their offspring (sons) will derive genetic benefits and fare better in future reproduction (Andersson 1994). However, these models have frequently failed to consider the fitness consequences of T selection in females, especially in the light of newer models of sexual conflict. As T and dihydrotestosterone mediate male primary and secondary sexual characteristics, respectively, males gain a fitness benefit when selection favors the aggregated phenotype characterized by higher T levels. However, mounting evidence has revealed that the sexes have different phenotypic optima for T levels (Ketterson et al. 2005; Cox et al. 2009a; John-Alder et al. 2009; Mills et al. 2012; Gerlach and Ketterson 2013). For example, among mammalian taxa, fitness in red deer, horn phenotype in Soay sheep, horn length in bighorn sheep, body mass in mountain goats, body size in primates, as well as 2D:4D digit ratios, height, cholesterol levels, facial attractiveness, schizophrenia risk, and homosexuality in humans all bear the hallmarks of sexual antagonism, and are likely mediated to varying degrees by the action of T (Manning et al. 2000; Lindenfors 2002; Robinson et al. 2006; Foerster et al. 2007; Ciani et al. 2008; Mainguy et al. 2009; Garver-Apgar et al. 2011; Stearns et al. 2012; Stulp et al. 2012; Mitchem et al. 2014; Power et al. 2013; Martin et al. 2014; Mokkonen and Crespi 2015). Selecting for a higher or lower T level will benefit one sex, while enacting sexually antagonistic fitness costs on the other.

In bank voles, negative genetic correlations between T and immune function were observed in males, and additionally, hinted that a difference in female and male phenotypic optima could potentially explain variation in T levels (Schroderus et al. 2010). Female bank voles would suffer deleterious fitness effects due to the genetic correlation between T and immune function (Schroderus et al. 2010), yet do not gain reproductive benefits from higher T levels as males do. In separate laboratory and field experiments, females were found to benefit from lower T: artificially selecting for higher T increased male reproductive success but decreased that of their sisters, while selecting for lower T increased female

reproductive success but decreased that of their brothers (Mills et al. 2012). These observations corresponded with sex differences in mating behavior, whereby males with higher T levels had greater mating success. In the laboratory, females from families selected for lower T had higher mating success compared to females from families selected for higher T levels (Mokkonen et al. 2012). This association between T and mating behavior was important for fitness because, like males, females can improve their reproductive success by increasing their number of mates, though, in accordance with Bateman's principles, female reproductive success is more constrained than male reproductive success (Mills et al. 2007b). Based on this set of studies, we conclude that a lower T level benefits female reproduction, while a higher T level benefits male reproduction. Despite the gender load imposed, sexually antagonistic alleles (and genetic variance) associated with T are maintained in the population due to processes such as balancing selection (Mappes et al. 2008; Mokkonen et al. 2011) or genotype–environment interactions (Mills et al. 2007a, 2014).

In general, the evolutionary interests are expected to be most similar between mates in monogamous systems: the only offspring produced by the male or female are jointly shared (Holland and Rice 1999; Hosken et al. 2001, 2009), though this is thought to be extremely rare among mammals (Kleiman 1977). Female bank voles employ a polyandrous mating strategy (Fig. 2a), which provides them with genetic benefits (Klemme et al. 2014). This strategy differs markedly from the reproductive outcome in paternity (Fig. 2b; Mokkonen et al. 2012) as most litters from polyandrous matings are sired by a single male. This difference in female behavioral and genetic mating strategies during polyandrous mating can constrain male reproductive success when mated males have unequal paternity probabilities (Mokkonen et al. 2012). Furthermore, this reduction in male mating success between copulation and conception can obscure paternity, which may be a female counter-tactic to combat sexual conflict through infanticide (Klemme and Ylönen 2010; Mokkonen and Lindstedt 2015), while it also introduces relatedness asymmetries within the family. Thus, the coevolution of parent and offspring can inform our understanding of evolutionary conflict between mates.

Grandparent–parent–offspring conflict and relatedness asymmetries

Parents—usually the mother—and offspring are often in conflict over the optimal level of parental investment (Fig. 3; Trivers 1972, 1974; Parker et al. 2002). From the mother's perspective, the investment placed in the current litter (or brood, etc.) should be balanced against her future reproductive interests (Trivers 1972; Royle et al. 2004). As the evolutionary success of an individual is largely determined by the number of offspring produced, individuals are predicted to maximize their lifetime reproductive success through the balance of current versus future reproductive effort (Williams 1966; Clutton-Brock 1991; Mappes et al. 1995). However, the interests of offspring can be quite different from those of the mother (Trivers 1974; Haig 2000). In a species where the probability of survival and reproduction is positively correlated with the amount of resource investment in offspring, it is generally in the interests of the offspring to obtain the maximum amount of resources possible (e.g., food, protection from predators, or heat loss), though recent work suggests that this type of conflict drives coadaptation between parent and offspring traits (Hinde et al. 2010). Nonetheless, a further consideration is that an offspring's investment needs are often dependent on sex, with males often proving to be more energetically costly to produce (Trivers and Willard 1973; Rutkowska et al. 2011). This feature reminds us that life history strategies and parental investment may be influenced by offspring sex ratios (Koskela et al. 2004).

Epigenetic processes, including genomic imprinting, alter the expression and not the sequence of DNA (Gregg et al. 2010a, 2010b), which can result in genomic conflict within an individual. Interestingly, the parental conflict hypothesis in mammals (also referred to as the kinship theory of genomic imprinting, Haig 2004, 2014a) pits the genes acquired from the mother against the genes acquired from the father within the offspring (i.e., maternally derived versus paternally derived genes within offspring): the father provides genes that are expressed to promote offspring growth (and hence, survival), whereas the mother confers genes that are expressed to limit growth. Mammals possess these imprinted genes (Barton et al. 1984), which are expressed in a parent-of-origin specific manner (e.g., IGF2R from mothers, Barlow et al. 1991; IGF2 from fathers, DeChiara et al. 1991). The silencing of alleles is primarily achieved through DNA methylation or histone protein changes. This hypothesis is supported in mammals through research into IGF2, KCNQ1OT1, and Air, growth enhancers that are paternally expressed, as well as IGF2R, CDKN1C, and Grb10, growth inhibitors that are maternally expressed (Haig 2004). Hence, the growth enhancers

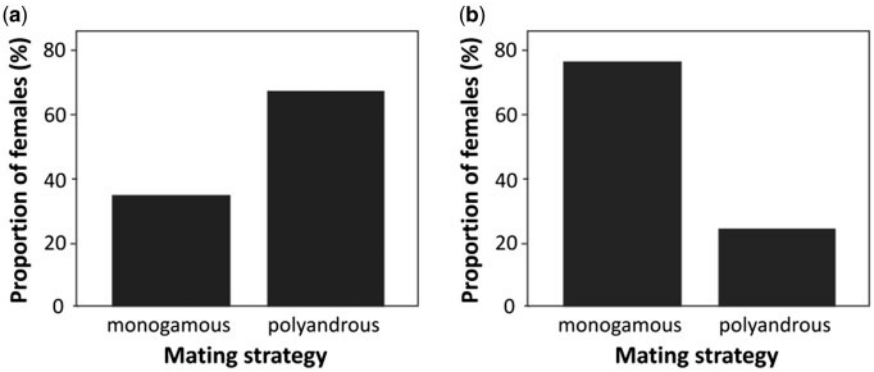

Fig. 2 A female's (**A**) behavioral mating strategy and (**B**) genetic outcome during reproduction. Data derived from, and methods found in Mokkonen et al. (2012).

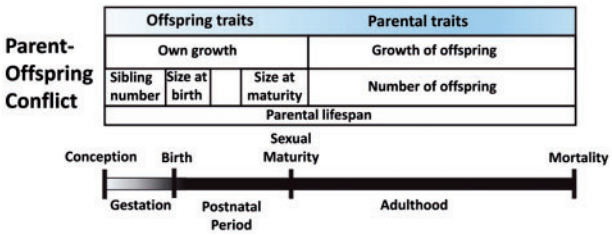

Fig. 3 Parent–offspring conflict over life history parameters.

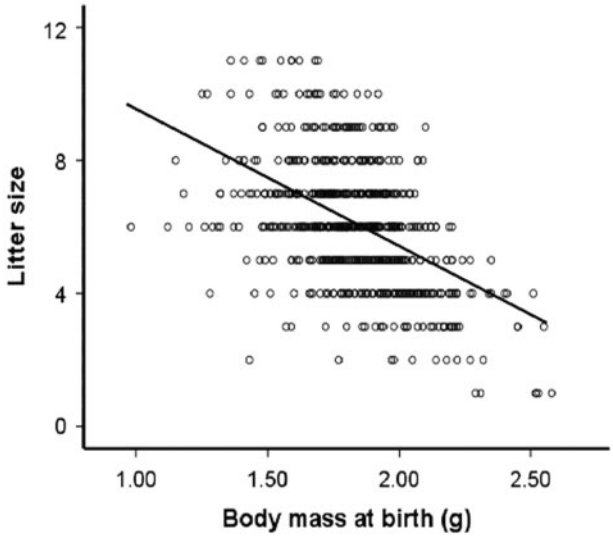

Fig. 4 Life history trade-off between body mass at birth (g) and litter size (number of offspring). Description of methods and data from Mokkonen et al. (2011).

provided by fathers may affect mother–offspring conflict. This type of conflict demonstrates that distinguishing between these intra-familial conflicts is often not clear-cut. However, an important distinction with kinship theory is that it should not be equated with sexual antagonism, as the conflict between paternally versus maternally derived genes is intragenomic, while the conflict between paternal versus maternal genes is intergenomic (Haig 2014a). Conversely, the dynamics of parent–offspring conflict (genes in mother versus genes in offspring) are more analogous to sexual antagonism, as this form of conflict is also intergenomic, arising from different maternal and paternal evolutionary interests. The main interest of the offspring is to ensure a maximum probability of survival, which can be achieved through either the interaction with the parent(s) providing care, or the interaction with siblings. Thus, the various intra-familial conflicts can render decisions about resource allocation particularly important.

In addition to sexual conflicts, there are further opportunities for evolutionary conflict in various bank vole life history features (Figs. 1 and 3). As with most species that invest much in their offspring, female reproduction is constrained by the trade-off between offspring size (quality) and number (Fig. 4; Smith and Fretwell 1974; Stearns 1992; Mappes and Koskela 2004; Schroderus et al. 2012). Sexual conflicts are most conspicuous when they manifest in the reproductive success component of fitness, and may thus indirectly affect life histories through this size-number trade-off (Koskela et al., unpublished data). In bank voles, the size at birth of females from families selected for lower T (but not higher T) exhibited a positive correlation with their future reproductive success (Fig. 5; Supplementary data 1). This finding indicates that T can mediate associations between life history measures, and may potentially provide an additional fitness cost for selecting lower T. In a population, average litter sizes are approximately 4–6 pups, ranging between 1 and 10 pups (Koivula et al. 2003; Mills et al. 2014), providing appreciable phenotypic and genetic variation

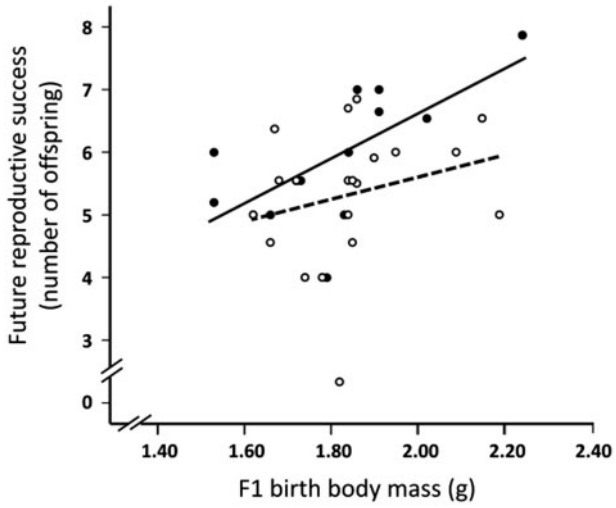

Fig. 5 Size at birth in relation to a female's future reproductive success. Open circles and dashed line indicate females derived from parents with high T-profiles, while closed circles and sold line indicate females derived from parents with low T-profiles. Linear regression for low-T individuals; $y = 3.59x - 0.56$, $R^2 = 0.384$, $\beta \pm \mathrm{SE} = 3.59 \pm 1.23$, $N = 13$, $t = 2.91$, $p = 0.014$.

(Mappes and Koskela 2004; Schroderus et al. 2012) for selection to act upon. However, females invest resources during the pre- and postnatal periods of offspring development, thus reducing the "time in" period available for courtship and mating compared to males, which ultimately results in a lower intensity of sexual selection acting upon them.

Physiologically, higher T levels tend to be associated with greater aggression and somatic tissue growth, which may cause offspring to both have a greater need for resources from the parent, and more intense competition with siblings. Under a resource-limited scenario, it is generally in an individual's interests to have fewer siblings due to the increase in sibling conflict that arises (Parker et al. 2002), while it may also be advantageous for parents to limit sibling competition among offspring due to the associated fitness costs (Godfray and Parker 1992). This type of conflict can generate interesting dynamics between siblings given the uncertain relatedness of individuals to each other (TABLE 1). In non-monogamous mating systems, "half-sibs" share only one parent and are predicted to compete more intensely for parental resources, and uncertain paternity can select for time-consuming mate guarding or sperm competition and constrain male success in reproduction (Simmons 2001; Arnqvist and Rowe 2005).

Relatedness asymmetries are an important consideration in understanding the conflicts between family members. While we understand now that an individual's mating decisions can impact the quality of its offspring for better or worse through various genetic and non-genetic effects (e.g., maternal effects, Mousseau and Fox 1998), we have less understanding of how more distant ancestors can also impact individuals. In a recent study, female bank voles with a higher T-profile had patrilineal grandsons with a greater birth body mass, suggesting that hormones such as T can exert transgenerational effects on life histories (Mokkonen et al., unpublished data). While the exact mechanism of this transgenerational effect of T is unknown and requires further study, an interesting feature of mammalian (and other XY species) chromosomes is their sex-biased inheritance to offspring. Y chromosomes are patrilineally inherited, while the X chromosome is derived from maternal grandparents or paternal grandmother. Hence, on average, females are slightly more related to their female ancestors than male ancestors, and the inheritance of sex chromosomes is more certain from the paternal—compared to maternal—grandparents (Fig. 6). The implications of this feature have only recently been gaining attention (Michalski and Shackelford 2005; Chrastil et al. 2006; Rice et al. 2010), but are still relatively under-explored. A recent hypothesis by Rice et al. (2010) called sexually antagonistic zygotic drive proposed an evolutionary explanation for the interests of grandparents in humans, a species with direct grandparental care (Friberg and Rice 2015). Taking into account the relatedness asymmetry of the sex chromosomes between male and female descendants, they proposed that grandmothers should evolve grandson-harming (or granddaughter-helping) phenotypes because of their closer expected relatedness to granddaughters. This human example demonstrates that there is potential for evolutionary conflicts to exist across the different life stages of an individual.

Ontogenetic conflict

Senescence, which is the biological deterioration of an organism associated with age, affects the evolution of fitness related traits. Interestingly, it has been suggested that the costs of ageing should begin to accumulate around sexual maturity as well, since the "usefulness" of the reproducing individual begins to decline in proportion to their reproductive success for species that experience age-related declines in fertility (Williams 1957). Williams (1957) proposed antagonistic pleiotropy to explain the evolution of senescence, whereby genes that confer a benefit earlier in life provide a fitness cost later in life. This hypothesis contrasts with other evolutionary explanations for aging such as the mutation accumulation

Table 1 Example of parent-offspring relatedness in a polygynandrous mating system with uniparental care

Family member	Relatedness (*r*)	Conflicting interests
Mother	0.5 to all offspring she produces	Father, offspring
Father	0 or 0.5 to mate's offspring uncertain paternity	Mother
Offspring	0.5 to mother 0 or 0.5 to mother's mate 0.5 to full siblings 0.25 to half siblings	Mother, siblings

Coefficient of relatedness (*r*) is expressed as a value between 0 and 1, which denotes the probability that the alleles between relatives are identical by descent.

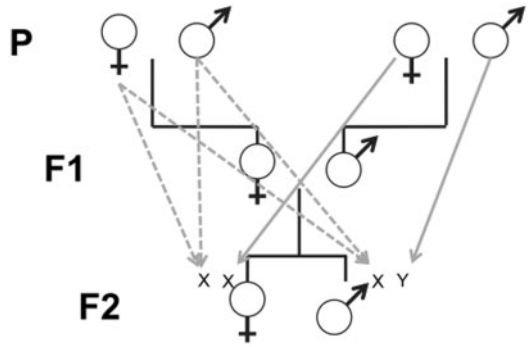

Fig. 6 Relatedness asymmetries of sex chromosomes in mammals. Solid lines indicate that sex chromosomal relatedness is assured, while broken lines indicate that the probability of sex chromosomal relatedness is only ~50%.

hypothesis (Medawar 1952) or disposable soma hypothesis that focuses on energetic constraints (Kirkwood 1977). However, despite currently being the favored hypothesis to explain the evolution of ageing, the antagonistic pleiotropy model has so far received weak support at best (Williams et al. 2006). If indeed reproductive benefits trade-off with ageing costs, then it is particularly important to consider evolutionary factors that influence reproduction to better understand ageing (Archer et al. 2015).

Evolutionary conflicts between life stages can arise due to changing selection pressures across these stages, and have implications particularly for sexually selected traits (Lancaster et al. 2014; Plesnar Bielak et al. 2014). Working with *Drosophila*, Chippindale et al. (2001) demonstrated that conflict arises between juvenile and adult life history stages by measuring the changing fitness correlation between the sexes. Similarly, Sinervo and McAdam (2008) found sex differences in survival to maturation in relation to breeding values, indicating a trade-off between life stages. These ontogenetic conflicts arise after sexual maturity due to the addition of the reproductive components of fitness and the resulting fitness shifts between females and males. Further integration of endocrinology into the study of ontogenetic conflicts would provide fruitful avenues to explore, given the dramatic divergence of androgen and estrogen levels between the sexes at the onset of sexual maturation.

Caveats and conclusions

One of the main aims of research in evolutionary biology is to understand the factors that contribute to the maintenance of phenotypic and genetic variation. Hormones, and T in particular, mediate important traits that directly determine the outcome of how well individuals survive and reproduce. It is likely that evolution by means of selection on hormone systems will inevitably harbour conflicts of interest between individuals. The very nature of selection translates to some individuals being more successful than others, which is rarely agreeable to all. As Darwin (1871) envisioned, reproduction is a "sexual struggle". By utilizing an integrative approach in evolutionary endocrinology, we can better understand the fitness costs of this struggle through proximate mechanisms. Sexual conflicts have implications for many areas of the biological sciences and related disciplines. For example, this perspective has recently been applied to understanding mental disorders in humans (Crespi and Badcock 2008; Badcock and Crespi 2008), density dependence in population ecology (Kokko and Rankin 2006), and speciation (Parker and Partridge 1998). Far from being a narrow topic, the study of genetic conflicts in reproduction encompasses different levels of organization, from genes to individuals to populations. Yet ultimately, it is grounded within the interactions that occur within a biological family.

Complicating the inheritance of biological information are maternal (and paternal) effects (Mousseau and Fox 1998; Schroderus et al. 2012). These effects can impose attributes of the maternal environment (e.g., availability of food resources) on the offspring without direct genetic control. In

Live fast vs. live long – how both strategies may allow males to prosper

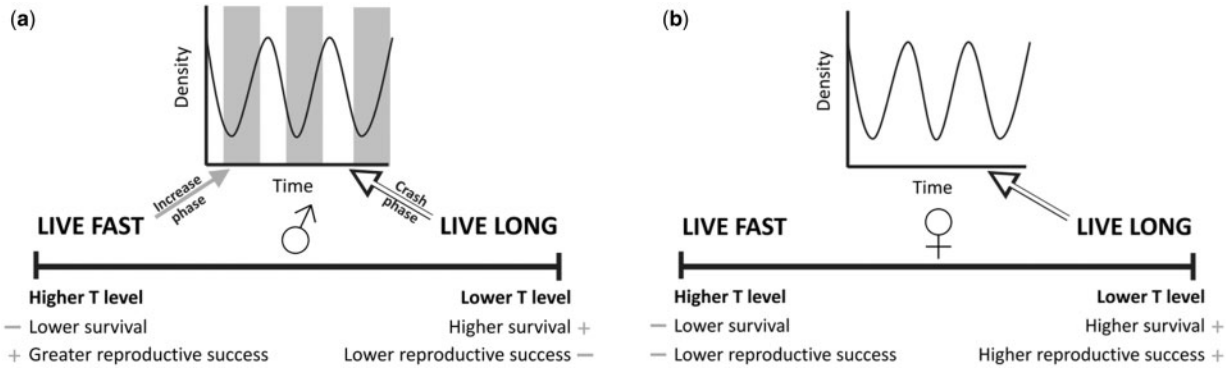

Fig. 7 The live fast/live long life history axis in (**A**) males and (**B**) females.

The contrasting strengths and directions of selection acting on the sexes during reproduction may be indicative of alternative life history strategies co-evolving. Bank voles, like many small mammals, experience multi-annual (3-4 year) population density fluctuations in the Northern hemisphere that peak in the summer/autumn and crash in the spring (Rikalainen et al. 2012; Krebs 2013; Korpela et al. 2014). These changes in density affect availability of food resources and territories (Krebs 2013), pathogen pressure (Soveri et al. 2000) and immunological parameters (Huitu et al. 2007). Combined with variation in predation pressure (Korpimäki et al. 2005; Korpela et al. 2014), these factors ensure that the environments of the peak and crash phases are distinct selective regimes that can impact the hypothalamus-pituitary-adrenal axis through chronic stress (Boonstra et al. 1998; Fletcher et al. 2015). Future work would benefit from also focusing on how population dynamics affect intrinsic factors in females relative to males during reproduction (Andreassen et al. 2013).

Given the divergent sex roles, the absence of paternal care may be selecting male life histories to evolve along a ''live fast—live long'' axis of strategies that is influenced by the social environment and corresponding ecological factors affected by conspecifics (Fig. 7a). Males selected for higher T level will benefit from greater reproductive success but have a fitness cost of lower survival, while males selected for a lower T level will have higher survival but reduced reproductive success. T can impact behavioral dominance and aggressive behavior in male bank voles, and will thus be sensitive to population density fluctuations (Mills et al. 2009; Mokkonen et al. 2011, 2012). Balancing selection associated with T levels during population density fluctuations may allow both strategies to be selected during different phases. As a result, we would predict males to experience balancing selection between the ''live fast'' (lower survival, greater RS) and ''live long'' (higher survival, lower RS) strategies associated with higher and lower T levels, respectively.

In contrast, given their relatively even mating success outside of peak densities, females are primarily concerned with optimizing the number and size of offspring (Mappes et al. 2008). Because they experience sexual antagonism over T that results in lower survival and reproductive success, they are not predicted to benefit from selection that results in higher T levels (Fig. 7b). This conflict renders directional selection for a life history strategy associated with lower T the more optimal female strategy throughout a changing social environment. Thus, we would predict females to experience directional selection that results in lower T levels throughout population density fluctuations (Mokkonen et al. 2011).

addition to promoting physiological growth, T exerts profound behavioral effects on offspring during the prenatal period. It plays an important role in organizing the fetal brain, and may over-masculinize female brains in dysregulated fetal development (Adkins-Regan 2005; Lummaa et al. 2007). Masculinization by T may cause females to provide lower quality care to offspring (Adkins-Regan 2005 and references therein). Yet, non-genetic effects are not the only potential caveat to elucidating evolutionary conflicts of interest mediated by hormones such as T.

Classifying sexual conflicts through purely phenotypic associations may misrepresent the genetic

underpinnings of the conflict. Pleiotropic genes can influence multiple traits in an organism, and the nature of these genes is still relatively unknown (Williams 1957; Fitzpatrick 2004; McGuigan et al. 2011). Caution is warranted when attempting to characterize relationships between traits. If these pleiotropic genes are found to act antagonistically across the sexes, then what may appear to be an interlocus sexual conflict involving different traits (e.g., immune function and T level) can actually be an intralocus conflict constraining individual optima (Schroderus et al. 2010). Focusing on gene expression data will help elucidate the link between phenotype and genotype (Mank et al. 2013), while the cascading effects of hormones, both upstream and downstream need to be further studied to better understand their role in pleiotropic interactions (Mills et al. 2008; Cox et al. 2009b).

The genetic mechanisms associated with how T mediates evolutionary conflicts are still relatively unknown, and require further study. For example, T may be acting through both shared and unique transcriptional pathways in the sexes (Peterson et al. 2014), or sexually dimorphic neural gene expression (Peterson et al. 2013). Coupling trait expression to sex differences in circulating T levels presents a plausible mechanism for how androgens can mediate sexual dimorphism (Cox et al. 2015). Work in the bank vole system has provided empirical support from manipulated laboratory and field experiments that shows that selecting on T levels produces a response in a variety of traits important for fitness, including circulating plasma levels. Yet, we acknowledge that the T system is a complex pathway, and selection could be acting on T precursors, aromatase, estradiol levels, T receptor densities, or additional elements important for the phenotypic expression of T.

While this article has focused primarily on the impact of T on evolutionarily salient traits important for reproduction and survival, individuals are awash in exogenous and endogenous endocrine signals (e.g., corticosteroids, Bonier et al. 2007). In the context of social interactions during reproduction, the oxytocin family of neuropeptides present particularly intriguing possibilities for future research to explore (Crespi 2016; Mokkonen and Crespi 2015). Oxytocin is important during parturition, copulation/intercourse, and promotes affiliative behaviors particularly between parents, offspring and mates (Adkins-Regan 2005; McCall and Singer 2012). These peptides, along with the closely related arginine vasopressin, are sexually dimorphic in plasma titers, behavioral effects, and physiological function. Given their central role in reproduction, much like T, these hormones (and their receptors) are predicted to mediate evolutionary conflicts between individuals through eco-evolutionary interplay in a fluctuating social environment (Lönn et al. unpublished data). An integrative approach can successfully bridge this gap in our understanding.

Supplementary data

Supplementary Data available at *ICB* online.

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