Heredity (2009) 103, 192–193

www.nature.com/hdy

NEWS AND COMMENTARY

Reproduction and senescence

Roaches, apoptosis and the ovarian clock: use it or lose it

DJ Holmes and LC Lavine

Heredity (2009) **103,** 192–193; doi:10.1038/hdy.2009.87; published online 15 July 2009

For many female animals, including humans, aging is accompanied by declines in reproductive success. Fecundity declines are often attributed to a loss of ovulatory capacity, either due to depletion of finite stores of ovarian follicles or loss of ability to generate viable eggs. In the view of evolutionary senescence and life-history theory, reproductive aging is an expected result of genetic and physiological trade-offs between investment in reproduction and long-term somatic maintenance, and of weakened natural selection on older organisms (Kirkwood and Austad, 2000).

Nutritional interventions, such as food restriction, have been shown to affect aging and reproductive lifespan in a wide variety of invertebrate and vertebrate species, and experimental manipulation of the timing and rate of reproduction often have a robust influence on aging and longevity (Partridge *et al*., 2005). But relatively little research has focused on how altered nutrition and reproduction early in the life span affect specific physiological or cellular changes correlated with ovarian senescence and female reproductive failure. In an intriguing new study, Edvardsson *et al*. (2009) estimated quantitative genetic variation in the regulation of aging-related rates of ovarian apoptosis (a measure of ovarian senescence) under both severe food restriction and ad lib feeding in the African cockroach, *Nauphoeta cinerea* (Figure 1). It is important to note that they found rates of ovarian apoptosis to be almost fourfold higher in food-deprived than ad lib-fed females. In addition, they report reductions in female reproductive lifespan and increased rates of ovarian apoptosis after food restriction (but not food excess) when combined with experimentally delayed first reproduction. Their results suggest that, at least under certain environmental circumstances, this cellular correlate of infertility is under additive genetic control, and hence is subject to natural selection.

Previous work by members of this group reported that loss of fertility in female cockroaches forced them to delay their first mating after sexual maturity, which is associated with higher rates of oocyte loss through apoptosis throughout the reproductive life span, effectively forcing females to adopt a 'use it or lose it' strategy (Moore and Sharma, 2005). In sexually reproducing animals, the balance between the rates of mitosis and apoptosis (programmed cell death) is continuously shifting during the healthy lifespan of an organism, including the developmental period (Hussein, 2005). During ovarian development and sexual maturation, coordinated waves of apoptosis set the stage for healthy oogenesis and staging of preovulatory follicles. As the ovary ages, higher rates of apoptosis are a benchmark of impending infertility.

But why study ovarian aging in cockroaches in the first place? Nauphoeta arguably is a much less popular laboratory animal than its distant insect relative, the fruit fly *Drosophila melanogaster*, the classical model for genetic studies and endocrinological basis of trade-offs between fecundity and longevity. Moreover, our molecular toolkit for understanding basic aging processes in invertebrates is far better developed in both Drosophila and the nematode, *Caenorhabditis elegans*. But cockroaches have established—if relatively unsung—utility for studies of basic neuroendocrinology and reproduction. Even more important from a comparative aging standpoint, insects exhibit immense diversity in their reproductive biology that may or may not be reflected in differences in the proximate mechanisms underlying reproductive trade-offs. While Drosophila is a marvelous genetic model for studies of reproductive trade-offs, unlike vertebrates and many other animals, fruit flies are oviparous, with ovaries that continuously generate new oogonia and viable new eggs over the course of the normal reproductive life span. Nauphoeta, in contrast, is ovoviviparous, and bears live offspring. 'Pregnant' female roaches carry embryos in a brood pouch until they reach the first-instar stage. Rather than reproducing continuously, they exhibit cycles of oocyte maturation followed by this specialized form of parental care.

In this and previous studies by Moore and Moore (2001), delays in first reproduction combined with severe food deprivation reduced female roaches' lifetime reproductive success and induced early infertility. In a general sense, these findings parallel the results of a plethora of food restriction studies from the aging literature. In the lexicon of biogerontology, however, 'food restriction' usually is not equated with complete food deprivation, as in the cockroach study. Instead, it usually entails a significant caloric restriction of 20–30% of normal ad lib food intake without actual starvation or malnourishment, and with adjustments in essential micronutrients to compensate for reduced food intake. In Drosophila and many other animal species, less

Figure 1 A female Nauphoeta with offspring. (Credit: Photograph by Allen Moore).

severe food restriction has been shown to extend lifespan, to retard aging and to protect against aging-associated disease (Partridge *et al*., 2005). Usually, this milder form of food restriction delays or reduces fertility; this has been suggested to be an adaptive mechanism for maximizing lifetime reproductive success during periods of resource scarcity. As in the Edvardsson *et al*. study, starvation in *Drosophila* has been shown to induce ovarian apoptosis and reduced egg production; however, the genetic basis for this has not been investigated (Terashima and Bownes, 2004).

There is an arguable need in the biology of aging for a more focused comparative approach, the development of additional, outbred invertebrate model systems, and a deeper understanding of the basic mechanisms responsible for the effects of caloric restriction and reproductive trade-offs. In flies and worms, a growing number of 'longevity genes' and several key metabolic and endocrine pathways underlying aging and lifespan have been identified, including the cell-signaling systems involving insulin and insulin-like growth factor (IGF-1) (Carter and Sonntag, 2006). The effects of food restriction are also much better studied in these species. But the genetic, physiological and evolutionary trade-offs influencing organismal senescence and the timing of infertility may not be obligate among diverse animal taxa, or under the same mechanisms of cellular control in all invertebrates. In *C. elegans*, for example, some mutations that alter IGF-1signaling, slow aging rates and extend lifespan do not result in a correlated decrease in fecundity.

In general, very little is known about natural genetic variability or genetic regulation of ovarian aging and apoptosis (Flurkey *et al*., 2007). On one hand Edvardsson *et al*. estimate that over 30% of the variation in ovarian apoptosis seen in food-restricted roaches can be attributed to additive genetic variation; on the other hand, litter additive genetic variance in apoptosis rates was detected in freely fed animals. Investigations of the genetic regulation of ovarian apoptosis and early influences on patterns of fertility loss in a diversity of animals, including these cockroaches, could ultimately lead to a better understanding of the evolution and physiological correlates of menopause in women and other female vertebrates.

DJ Holmes is at the School of Biological Sciences and Center for Reproductive Biology, Washington State University, Pullman, Washington, USA and LC Lavine is at the Department of Entomology and Center for Reproductive Biology, Washington State University, Pullman, WA, USA.

e-mail: djholmes@wsu.edu

Carter CS, Sonntag W (2006). Growth hormone, insulin-like growth factor-I, and the biology of aging. In: Masoro EJ, Austad SN (eds). *Handbook of the Biology of Aging*, 6th edn. Academic Press: New York, pp 534–569.

Edvardsson M, Hunt J, Moore AJ, Moore PJ (2009). Quantitative genetic variation in the control of ovarian apoptosis under different environments. *Heredity* (epub ahead of print 29 April 2009).

Flurkey K, Brandvain L, Klebanov S, Austad SN, Miller RA, Yuan R *et al*. (2007). PohnB6F1: a cross of wild and domestic mice that is a new model of extended female reproductive life span. *J Gerontol Biol Sci* **62A**: 1187–1198.

Hussein MR (2005). Apoptosis in the ovary: molecular mechanisms. *Hum Reprod Update* **22**: 162–178.

Kirkwood TBL, Austad SN (2000). Why do we age? *Nature* **408**: 233–238.

Moore PJ, Moore AJ (2001). Reproductive aging and mating: the ticking of the biological clock in female cockroaches. *Proc Natl Acad Sci USA* **98**: 9171–9176.

Moore PJ, Sharma S (2005). A delay in age at first mating results in the loss of future reproductive potential via apoptosis. *Evol Dev* **7**: 216–222.

Partridge L, Gems D, Withers DJ (2005). Sex and death: what is the connection? *Cell* **120**: 461–472.

Terashima J, Bownes M (2004). Translating available food into the number of eggs laid by *Drosophila melanogaster*. *Genetics* **167**: 1711–1719.

Editor's suggested reading

Fox CW, Stillwell RC (2009). Environmental effects on sex differences in the genetic load for adult lifespan in a seed-feeding beetle. *Heredity* **103**: 62–72.

Sinervo B, Clobert J, Miles DB, McAdam A, Lancaster LT (2008). The role of pleiotropy vs signaller–receiver gene epistasis in life history trade-offs: dissecting the genomic architecture of organismal design in social systems. *Heredity* **101**: 197–211.