REVIEW

Boom and bust: a review of the physiology of the marsupial genus *Antechinus*

R. Naylor · S. J. Richardson · B. M. McAllan

Abstract The marsupial genus *Antechinus* is a group of small carnivorous marsupials from the order Dasyuromorphia (Family Dasyuridae) and is found in eastern Australia. The life history of all species in the genus is characterized by a complex, but highly synchronized life cycle in both sexes, culminating in a short mating period followed by total male mortality (semelparity). The breeding season is defined by a specific rate of increase in photoperiod, which is different for each species. In *Antechinus* spp., male mortality is due to the effects of high free testosterone and cortisol levels on many organ systems. Unusually, spermatogenesis is complete before testosterone levels begin to rise at the winter solstice. In males, low sperm counts have been compensated for by high proportions of sperm reaching the isthmus of the female reproductive tract and long-term storage in the crypts. The females survive to rear their young and may mate again in their second year. Gestation lasts from 26 to 34 days, depending on the species. However, developmental arrest can occur at several stages during embryogenesis, elongating the apparent gestation duration by several days. Several species have strong female sex biases in their litters. The high degree of life history synchrony and the cascade of endocrine-driven physiological events that result in male death are unusual physiological characteristics for mammals. Suggestions why semelparity may have evolved in *Antechinus* are discussed.

Keywords Marsupial · Renal function · Immunosuppression · Cortisol · Semelparity · Testosterone · *Antechinus stuartii* · *Antechinus agilis* · Reproduction · Seasonality

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Introduction

The marsupial genus *Antechinus* comprises small carnivorous marsupials from the order Dasyuromorphia (Dasyuridae). The life history of all of the species in the genus is characterized by a synchronized life cycle that culminates in a single short mating period followed by total male mortality. The best-studied species in this genus are two closely related species, *A. stuartii* and *A. agilis*, collectively referred to here as the *A. stuartii* complex. These species demonstrate many physiological features unusual amongst mammalian species. Male semelparity, the deaths of all male animals following a single, very brief breeding season, has been described only rarely among mammals and appears to be restricted to didelphid and dasyurid marsupials. The precise synchronization of all stages of the life cycle has not been identified in many other mammals. For

these reasons, the physiology, endocrinology, and the evolution of such a strategy in *Antechinus* deserve closer scrutiny.

This review will discuss the physiological ecology, life cycle, and changing hormone profiles of the species in the *A. stuartii* group. We will focus on why this physiology is unusual compared to other small mammals. Particular emphasis will be given to models explaining how this unusual life cycle may have evolved.

General biology

The life history of all species in the *Antechinus* genus is characterized by a complex, synchronized life cycle that culminates in a single short mating period followed by total male mortality. Male mortality is believed to be due to the effects of high circulating free plasma testosterone and cortisol on many organ systems. The most common pathologies are gastrointestinal hemorrhage, failure of the immune and inflammatory systems and hence parasite invasion, renal dysfunction, splenic involution, a negative nitrogen balance, weight loss, and a general deterioration in condition (Woollard 1971; Barnett 1973; Bradley et al. 1975, 1980; Barker et al. 1978; McDonald et al. 1981, 1986; Bradley 2003). It is known that males can survive the breeding season, but these males tend to be castrates or have nonfunctioning testes (Bradley and Monamy 1990). A minority of females survives to mate again in their second year. Semelparity, where individuals reproduce once and die afterwards, although common in plants, invertebrates and fishes (Braithwaite and Lee 1979), is believed to be an extremely rare life history trait among mammals, where it is restricted to male members of some species of Didelphidae and Dasyuridae (McAllan 2003; Woods and Hellgren 2003; Fisher and Cockburn 2006). Some authors hypothesize that this restricted pattern of male semelparity in a few genera, due to a combination of high mortality rates and predictable seasonal environments, may reflect an expansion of the general tendency for postreproductive senescence in these marsupial classes (Braithwaite and Lee 1979; Kraaijeveld et al. 2003).

The *Antechinus stuartii* complex is a group of closely related species of small insectivorous marsupials found in eastern Australia. These species, of which *A. agilis* and *A. stuartii* are the most well studied, are mostly crepuscular (active at twilight; Wood 1970) scansorial (specialized for climbing) insectivores (Wakefield and Warneke 1967; Lazenby-Cohen 1991). The *A. stuartii* complex displays unusual levels of sociality, with overlapping home ranges and nesting communally for part of the year (Wood 1970; Braithwaite 1974, 1979). Members of the genus usually exhibit pronounced sexual dimorphism, with males often

twice the size of females (Woolley 1966; Fisher and Cockburn 2006). They are generalistic, opportunistic predators of arthropods (Hall 1980; Fox and Archer 1984), consuming 60% of their body mass each day (Nagy et al. 1978; Hall 1980; Fox and Archer 1984).

The *A. stuartii* complex is found in moist environments from coastal plains to subalpine environments, inhabiting forests (particularly sclerophyll forests), heath, woodland and, in southern Queensland, rainforest (Hall 1980, Dickman 1986a). The range of *A. agilis* overlaps narrowly with *A. flavipes* in drier box and ironbark forest, while *A. stuartii* shows sympatry with both *A. agilis* in the south and *A. swainsonii* over much of its range (Righetti et al. 2000). Where sympatry occurs, the larger *A. swainsonii* excludes *A. stuartii* from its preferred microhabitats, with *A. swainsonii* reducing *A. stuartii*'s access to resources (Dickman 1986a; Righetti et al. 2000).

Members of the *A. stuartii* complex have a seasonally defined social structure. Outside of the breeding periods, members of both sexes are active in clearly defined home ranges, which can overlap extensively with other individuals (Braithwaite 1979; Lazenby-Cohen and Cockburn 1988). In winter, both sexes may leave their home ranges daily to spend the latter part of the night and most of the next day in communal nests. These nests may be used by up to 20 unrelated individuals simultaneously (Lazenby-Cohen 1991) and over 40 different individuals per winter (Lazenby-Cohen and Cockburn 1988). Individuals may nest communally because of the energy benefits that huddling brings in winter, although the use of torpor has also been described in *Antechinus* to conserve as much as 30% of daily energy expenditure (Geiser 1985; Geiser 1988; for review, see Geiser 2003). Males tend to have home ranges up to three times larger than females, and during the mating season they abandon their home ranges and aggregate in the communal nests (Lazenby-Cohen and Cockburn 1988). In contrast, females' foraging ranges are stable throughout the year, and they make excursions to male aggregations for mating, which has led to the suggestion that *Antechinus* engage in lekking behavior (male aggregations for display purposes for attracting mates; Lazenby-Cohen and Cockburn 1988, 1991).

The breeding season

Antechinus spp. have a single, brief (usually 1–2 weeks) annual breeding season that is highly synchronized among individuals within a population and occurs at the same time for different annual cohorts within that population (Dickman 1982; McAllan and Dickman 1986). In the *A. stuartii* complex, this brief breeding season occurs at some time between the winter solstice and spring equinox, the timing

of which depends on the locality, although it is at the same time every year for each locality (McAllan and Dickman 1986; McAllan 2006; Fig. 1). The precise timing of the period of associations for copulations, however, varies with both latitude and altitude, and is earlier and shorter as latitude and altitude increase (Dickman 1982; McAllan and Dickman 1986; McAllan et al. 2006a). The brief mating period can be as short as 3–4 days in the south and as long as 3 weeks in the north (McAllan and Dickman 1986; McAllan et al. 2006a). It has been suggested that the timing of the breeding season is such that lactation and weaning coincide with an abundance of insect food (Braithwaite 1979; Dickman 1986a, b; Fig. 1). The mechanisms for regulating the precise timing of the life cycle have been elucidated in part, and are related to changes in photoperiod and the hormone of photoperiodism, melatonin (McAllan and Dickman 1986; McAllan et al. 1991, 2002, 2006a), which is then perhaps modulated by pheromonal cues (Dickman 1985; Scott 1986; Toftegaards et al. 1999; Parrott et al. 2007).

Timing of the breeding season: photoperiodism and melatonin

The predictable, synchronous mating period and the involvement of altitude and latitude in the timing of mating would imply that photoperiodic cues control the reproductive cycle. In many species with distinct breeding seasons, photoperiod is the main proximate factor stimulating reproduction (e.g., Bronson 1985; Malpaux et al. 2001). Photoperiodism has been investigated for its involvement in the timing of reproduction in the *A. stuartii* complex. Early experiments on photoperiodism in *Antechinus* focused on exposing animals to unchanging photoperiodic regimes, which lead to inconsistent experimental results (Dickman 1985; Scott 1986, 1987). The conclusion was that environmental cues, such as photoperiod, did not allow for very precise timing of reproduction and that social cues, such as pheromones, must mediate the primary stimulus of photoperiod to ensure exact synchronicity (Dickman 1985; Scott 1986). Pheromonal cues appear to be important in enhancing reproductive synchrony, female mate choice, and aspects of male sociality, but do not drive the absolute synchrony of reproductive activities (Dickman 1985; Scott 1986; Toftegaards et al. 1999; Parrott et al. 2007).

Onset of the mating period correlates with the rate of change of photoperiod, not with the length of the photoperiodic exposure (McAllan and Dickman 1986). Absolute daylength differs at the time of mating for each species in most localities; however, the increasing rate of change of photoperiod does not vary at the time of mating for all populations of each species, and unlike photoperiodic length, a critical increasing rate of change only occurs once a year, not twice (see McAllan and Dickman 1986; McAllan et al. 2006a; Fig. 1). This provides a simple and reliable stimulus for ensuring a single brief mating season, instead of relying on other mediating factors. *A. agilis* was found to respond to between 127 and 137 s increase per day, while *A. stuartii* responded to an increase of 97–107 s increase per day. Analyzing the photoperiod and population data in this way not only demonstrated the reproductive isolation of the two species in the *A. stuartii* complex, but it also predicted the length of the mating period in each population at a given latitude and altitude (McAllan and Dickman 1986). The prediction of reproductive isolation and speciation has since been demonstrated to be true (Dickman et al. 1988, 1998). The use of rate of change of photoperiod is likely to be the reproductive cue for the whole genus (McAllan et al. 2006a).

Experimental data support theoretical predictions in both *A. stuartii* and *A. flavipes* (McAllan and Geiser 2006; McAllan et al. 1991). In *A. stuartii*, when the yearly photoperiodic cycle was artificially delayed by 2 months, animals receiving the cue in February or about 7 months before the mating period (at locality 33°52'S, 151°29'E) had reproductive synchrony delayed by 2 months. For animals receiving the cue in May (at locality 33°52'S, 151°29'E), their reproductive cycle was also delayed, but was unsynchronized (McAllan et al. 1991). In *A. flavipes*, exposure to an unchanging photoperiod from February until December
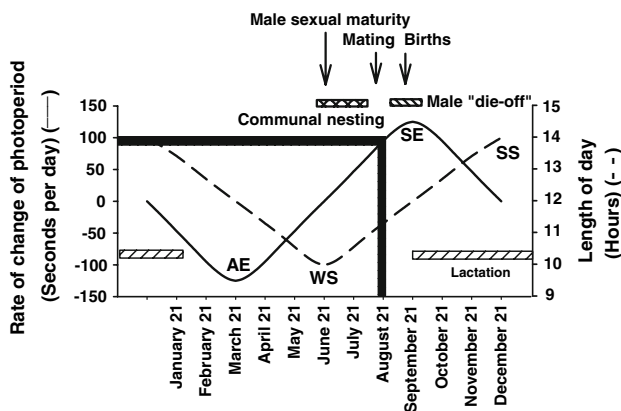

Fig. 1 Life history and calendar for *A. stuartii*. The life history calendar is for a population at the latitude of 33°30'S, and is typical of the calendar of life events for the genus. The photoperiodic cycle at different life cycle time-points is presented with daylength as a *dashed line*, and the daily rate of change of photoperiod is marked by a *solid line*. The rate of change of daylength alters fastest at the autumnal equinox (AE, −150 s/day) and the spring equinox (SE, +150 s/day). The *thick black line* of the rate of change of photoperiod of +97 to 107 s/day defines the breeding season in *A. stuartii*. The length of day at winter solstice (WS) is 10 h/day, and at summer solstice (SS) is 14 h/day, and the rate of change of photoperiod at both points is 0 s/day. The major life events are indicated by *arrows* or *horizontal bars*, depending on the length of time taken for each event

resulted in unsynchronous reproductive activity in males. Reproductive activity in almost all females did not occur unless they were exposed to the critical increasing rate of change of photoperiod. One female demonstrated spontaneous reproductive activity at approximately the time of mating in the wild and in laboratory females held under the natural photocycle (McAllan and Geiser 2006). Thus, it appears that reproductive synchrony is maintained by the changing photoperiod modulating an underlying endogenous rhythm. It is also moderated by the intense social interactions observed in *Antechinus* (Dickman 1985; Scott 1986; McAllan et al. 1991; Toftegaards et al. 1999; McAllan and Geiser 2006).

In *A. stuartii*, the photoperiodic cues inducing reproductive activity are mediated by melatonin, with the effects of melatonin administration varying depending on the time of year of administration (McAllan et al. 2002). Animals that were given melatonin at the autumnal equinox showed desynchronization of reproductive synchrony. Melatonin given at the winter solstice did not disrupt synchrony but did interrupt the precise determination of the breeding season, shifting oestrus forward and accelerating the postmating decline of males (McAllan et al. 2002). Thus, the temporal exposure of melatonin is important, in addition to the hormone's physiological presence and quantity.

The use of an increasing rate of change of photoperiod to determine timing for reproduction has not been described in eutherians, and amongst mammals, it is currently known to occur only in some dasyurid marsupials (McAllan 2003; Lee et al. 1982). However, we predict that the use of the rate of change of photoperiod by mammals to cue for the reproductive season is more common than that currently thought, particularly in species at temperate latitudes where rates of change of photoperiod alter in a defined, but less rapid manner than that at higher latitudes. For example, a mammal experiencing rates of change of photoperiod at 27°N would experience a maximum change of 2 min/day at the spring equinox, and at 50°N would experience a maximum change of nearly 4 min/day at the spring equinox. At temperate zone latitudes, the rate of change of photoperiod could very precisely induce reproductive timing to take advantage of a later period of abundant food for raising young. Many studies trying to determine the role of photoperiod in cuing for reproduction in temperate zone mammals have used unchanging photoperiods under artificial laboratory conditions, similar to Scott (1986) and Dickman (1985), perhaps leading to an incorrect conclusion that these mammals may be "nonphotoperiodic" reproducers (Demas and Nelson 1998; De Vleeschouwer et al. 2003; Heideman and Bronson 1992, 1993; Wayne and Rissman 1991). One consistent finding is that there can be differential responses to photoperiod by males and females, and frequently male spermatogenic and circulating androgen

cycles are found to be more resilient to photoperiodic change than the reproductive cycling of females (Demas and Nelson 1998; Heideman and Bronson 1992; Muteka et al. 2006). The differential reproductive response by males and females to photoperiod is especially pronounced in *Antechinus*, and is unusual for mammals in that the final reproductive outcome for all males is an abrupt death, usually prior to the birth of the young. The male *Antechinus* life cycle, therefore, deserves closer scrutiny.

Male endocrinology and life history

The life history of the male *Antechinus* spp. is dominated by the systemic circulation of two hormones: testosterone (an anabolic hormone, and involved in promoting male secondary sex characteristics) and cortisol (the "stress" hormone, initiating gluconeogenesis, glycogenolysis, lipolysis and immunosuppression). As well as affecting their social interactions, the integrated actions of these hormones on organ systems are believed to account for the unusual male mortality seen in this genus.

Testosterone

In male *A. stuartii*, circulating testosterone begins to increase in late June (approximately the winter solstice) until it reaches an eight-fold peak in August (Bradley et al. 1980; Kerr and Hedger 1983; Fig. 2). Prior to the winter solstice, the circulating testosterone concentrations are basal (Bradley et al. 1980; Kerr and Hedger 1983). The increase in circulating testosterone leads to increasingly aggressive, territorial behavior. Territorial vagrancy and interactions with other animals of both sexes increase significantly during the breeding season, which can modify the
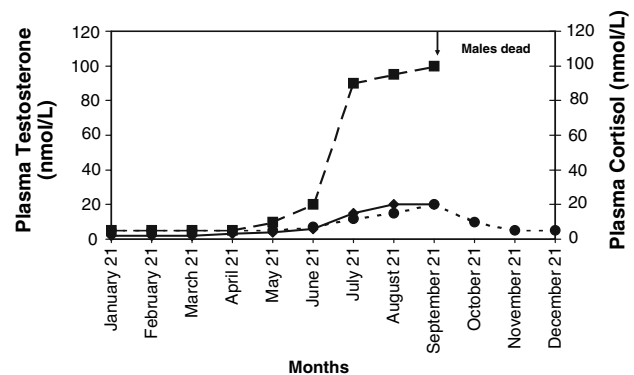

Fig. 2 Changes in plasma testosterone and free cortisol in *Antechinus* throughout the year. Circulating testosterone in males (*closed diamonds* and *solid line*) and free cortisol for males (*closed squares* and *dashed line*) and females (*closed circles* and *dotted line*) at monthly intervals are shown. Data are from Bradley et al. (1980), McDonald et al. (1980), and McDonald et al. (1986)

cortisol responses, with isolated males exhibiting lower circulating cortisol values than males involved in interactions with other males (Bradley et al. 1976; Braithwaite 1974; Wood 1970; Scott 1986). Testosterone has significant anabolic effects in *Antechinus*, promoting an increase in body mass and a concomitant increase in food consumption as circulating testosterone concentration increases (McAllan et al. 1997a; McAllan et al. 1998a; Fig. 2). Besides the musculoskeletal system, testosterone also affects other body systems, notably the renal system (McAllan et al. 1997a) and the accessory reproductive tract (McAllan 1998).

Renal structure and function exhibit seasonal changes in male, but not female, *A. stuartii*, and many of the changes are correlated with circulating concentrations of testosterone (McAllan et al. 1996, 1998b). In males, glomerular filtration rate (GFR) declines in July and August, coincident with the increase in circulating testosterone (McAllan et al. 1998b). Testosterone administration also significantly decreases GFR (McAllan et al. 1998a). Outside the breeding season, GFR of males is similar to that seen in female *A. stuartii* and to that found for other small mammals (Goldstein and Newland 2004; McAllan et al. 1998b). *A. stuartii* is the first animal in which it has been demonstrated that there is a seasonal alteration in GFR (McAllan et al. 1998b).

In other mammals, androgens cause hypertrophy but not hyperplasia in the kidney, and although gross renal morphology is largely unchanged in many mammals, morphological responses can be seen in the glomeruli, proximal and distal collecting tubules, cortical and medullary collecting ducts, and in gene expression (Selye 1939; Oudar et al. 1991; McAllan et al. 1997a; Levillain et al. 2005; Yabuki et al. 2006). In *A. stuartii*, McAllan et al. (1996) found seasonal changes in the renal morphology of males in July and August, with some minor changes in females. These seasonal changes in renal morphometry could be induced by testosterone administration in May to prebreeding males. These changes included hypertrophy of the proximal tubules, distal straight tubules, and cells of the cortical collecting ducts (McAllan et al. 1996, 1997a). While few studies have found the significant morphological and functional changes seen in *A. stuartii* associated with testosterone, testosterone is associated with increased apoptosis in renal tissue in male humans (Verzola et al. 2004), induces proteinuria in intact male rats (Remuzzi et al. 1988), affects renal size and enzyme production (Kochakian et al. 1948; Koibuchi et al. 1993; Takahashi et al. 2004), and increases the likelihood of ischemic renal damage (Park et al. 2004). The hypertrophy that is seen in *Antechinus* can only be induced in mice by pharmacological doses of testosterone (Selye 1939; Crabtree 1941).

Circulating testosterone may also increase hematocrit in *A. stuartii* (McAllan et al. 1998a). Other studies have found a decrease in hematocrit in male *A. agilis* during the breeding season (Barker et al. 1978; Cheal et al. 1976), mostly because of blood losses due to gastric ulceration. Gastric ulceration is an effect of relatively high circulating cortisol in males, but not females (McAllan et al. 1998a). Sex differences in hematocrit are uncommon, although are known in humans and in brush-tailed possums (Barnett et al. 1979). Another study found that the hemoglobin of male *A. stuartii* is more susceptible to oxidation compared to other mammals, and that the antioxidant defense enzymes glutathione peroxidase, reduced glutathione, superoxide dismutase and catalase are raised in *A. stuartii* erythrocytes compared to other mammals (Agar and McAllan 1995). Although trends in the results were detected between males and females, sample sizes in this study were too small to detect significant differences. High antioxidant defense enzymes have also been found in other marsupials (Agar and McAllan 1995).

Another effect of testosterone is on the morphology of the male *Antechinus* reproductive tract. In eutherians, androgens are believed to be essential for promoting spermatogenesis and for early germ cell development and later spermiogenesis (McLachlan et al. 1996). However, many marsupials, including *A. stuartii*, display a marked effect of testosterone on accessory reproductive tract growth (sternal glands, bulbourethral glands, and prostate, see Fig. 3) without any change in size or mass of the testes or effect on the spermatogenic cycle (Cook et al. 1978; Inns 1982; Kerr and Hedger 1983; Wilson and Bourne 1984; Gemmell et al. 1986; Jones et al. 1988; Curlewis 1991; McAllan 1998). Spermatogenesis in *A. stuartii* has ceased by the time plasma testosterone concentrations start to rise (McAllan 1998). Testicular testosterone concentrations may be ten times higher than peripheral levels, which are sufficient to maintain testicular activity in rats (Rommerts 1988; Walker and Cheung 2005). Thus, in marsupials that display no relationship between peak plasma testosterone levels and spermatogenesis, spermatogenic activity may be regulated locally by androgens released from mature Leydig cells (McAllan 1998). Although the actions of other hormones on spermatogenesis have been described in eutherians, these systems have not yet been described in *A. stuartii* (McFarlane et al. 1997).

In *A. agilis*, the testicular and epididymal development from birth until the time when plasma androgen concentrations become detectable occurs over about 5 months. The gonad appears undifferentiated at 3 days post-partum and well differentiated by 4–5 months of age (Taggart et al. 1993). The progression of spermatogenic stages in the seminiferous tubules is synchronized within each population from about 5 months of age onwards (Kerr and Hedger 1983). Similar observations have been made in other studies on *Antechinus* (Woolley 1966; Inns 1975; McAllan et al. 1997b).
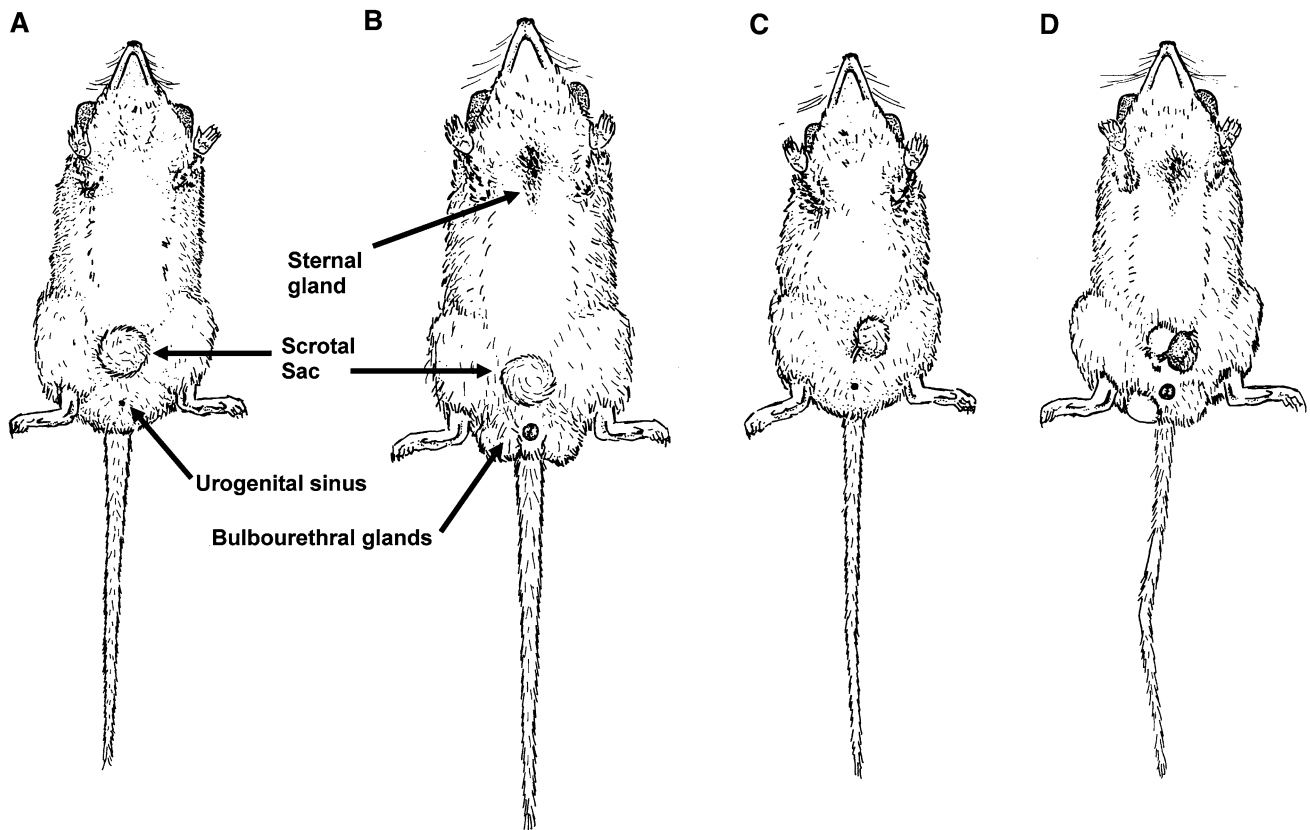
Fig. 3 Phenotypic changes in male *A. stuartii* treated with saline and physiological doses of testosterone-only, cortisol-only, or both (testosterone and cortisol). The saline-treated male (**a**) was indistinguishable from untreated males captured at the same time of year. Treatment with testosterone (**b**) promoted development of secondary sex characteristics (sternal glands, bulburethral glands, penis development, where the bifurcated penis is seen in the urogenital sinus) and also promoted anabolism independent of cortisol treatment. Cortisol treatment (**c**) promoted deterioration of connective tissue (including loss of control of the pendulous scrotal sac), and loss of muscle mass in some treated males. When treated with both testosterone and cortisol together (**d**), some of the anabolic effects of testosterone were negated, and this is reflected in body mass. Body masses of saline-treated males were 29.7 ± 1.2 g, of testosterone-only-treated males were 38.7 ± 1.7 g, of cortisol-only-treated males were 29.5 ± 2.2, and body masses of testosterone-and-cortisol-treated males were 31.9 ± 2.3. Data are from McAllan (1998) and McAllan et al. (1997a, 1998a). Illustrations of males whose body masses were closest to each mean body mass for each treatment group were drawn to scale by McAllan

Despite its lack of effect on spermatogenic activity in *A. stuartii*, an increase in plasma testosterone concentration is coincident with the observation of male secondary sexual characteristics, including sternal gland secretions, increase in size of bulbourethral glands and prostate, and pigmentation of the testes (Woolley 1966; McAllan et al. 1997b; Fig. 3). Testosterone administration to immature males has been shown to promote secondary sexual characteristics, causing hypertrophy in cells in the caudal end of the epididymis but not the caput epithelial cells, significant alterations in mass and morphology of the prostate and bulbourethral glands, and a mature penis is produced within 10 days of testosterone injections (McAllan 1998; Fig. 3).

The increase of plasma testosterone concentration in males, which continues from June until death in August/September (Bradley et al. 1980), is coincident with changes in the binding capacity of corticosteroid-binding globulins (CBGs) in the blood. The plasma concentration of circulating CBGs decline, and thus free or albumin-bound corticosteroids are available to exert their influences on the physiology of *Antechinus* (Bradley et al. 1976, 1980; Lee et al. 1977). These effects have also been observed in male rats, humans (Viau and Meaney 2004; Kajantie and Phillips 2006), *A. flavipes*, *A. swainsonii*, and *Phascogale calura* (Bradley 1987, 1990), but not in iteroparous (repeated reproductive bouts per lifetime) dasyurid marsupials such as *Sminthopsis crassicaudata* (McDonald et al. 1981). The influence of testosterone on the free circulating glucocorticoids (cortisol in marsupials) in male *Antechinus* has profound implications for their survival.

Cortisol

Glucocorticoids (cortisol and corticosterone) are corticosteroids, steroid-based hormones secreted from the adrenal cortex that modulate carbohydrate and protein metabolism.

Glucocorticoids are involved in the sustained response of the body to a stressor (Kudielka and Kirschbaum 2005), and control the expression of up to 1% of genes in the human genome (Janeway et al. 2001). In all mammals that have been studied, glucocorticoids decrease glucose transport and metabolism in peripheral tissues, reduce the permeability of the blood–brain barrier to glucose, initiate gluconeogenesis, increase protein catabolism and serum glucose levels, and are involved in immunosuppression and reduced inflammation (de Leon et al. 1997; McEwen 1999; Janeway et al. 2001). Cortisol also diminishes the general hypertrophic effects of testosterone in *A. stuartii* (McAllan 1998; Fig. 3), halves the plasma testosterone concentration in men without changing steroid-binding globulin capacity (Loriaux and Nieman 1990), and attenuates the testicular response to luteinizing hormone in baboons (*Papio anubis*, Sapolsky 1985).

In the *Antechinus* genus and in other semelparous dasyurids studied, circulating plasma cortisol levels increase dramatically just prior to and during the breeding season (Bradley 1987, 2003; Bradley et al. 1980; McDonald et al. 1981). These high plasma cortisol concentrations are causally related to male postbreeding mortality (Bradley 1987, 2003; Braithwaite 1974; Bradley et al. 1975, 1980; Barker et al. 1978). The continuing rise in circulating cortisol levels is believed to be the result of a combination of a testosterone-induced fall in CBG levels in the plasma and the failure of the glucocorticoid negative feedback mechanism mediated through the hypothalamic-pituitary-adrenal (HPA) axis (Bradley et al. 1976, 1980; McDonald et al. 1986; Bradley 1987, 2003). Cortisol administration to prebreeding males also causes a dose-dependent increase in mortality within 5–6 weeks of injection (Bradley et al. 1975, 1976; McAllan et al. 1997a; McAllan 1998).

Social stress in male *Antechinus*, which includes increasingly antagonistic male–male interactions, exacerbates the male "die-off," by promoting their cortisol production, and by interfering with usual male foraging patterns, reducing their nutrition intake (Woolley 1966; Woollard 1971; Scott 1987; McAllan et al. 1998a; Fig. 4a). In captivity, males isolated from the social pressures of mating and maintained with enough food and water to withstand the negative nitrogen balance associated with the mating period are able to survive the breeding season. Some individuals survive for more than a year, but never undergo spermatogenesis again (Woolley 1966; Woollard 1971; McAllan 1987). This is in contrast to dasyurids with partial or facultative male die-off, such as the dibbler (*Parantechinus apicalis*) and the northern quoll (*Dasyurus hallucatus*), where some males may survive to a second breeding season and successfully mate (Mills and Bencini 2000). Social stress appears to be important, as the completeness of the male die-off is related to population density with denser populations having fewer

males survive the breeding season (Dickman and Braithwaite 1992). In *P. apicalis*, the stresses of population density can be reduced by abundant resources in some populations (Wolfe et al. 2004).

In tree-shrews (*Tupaia belangeri*), persistent social stress is associated with cortisol-assisted death in males (Von Holst 1972; Fuchs and Flügge 2002; Flügge et al. 2001), but in contrast to *Antechinus*, not all males die (Fig. 4b). The stress response in shrews is not associated with failure of the HPA axis, and male shrews can recover to reproduce (Von Holst 1972; Fuchs and Flügge 2002; Flügge et al. 2001; Fig. 4b). Persistent social stress differs from the sympathetic arousal seen in the "flight or fight" first stage of stress. Social stress involves the HPA axis, and if it is sustained, it can kill other mammals besides treeshrews (lemmings, Andrews et al. 1975; wild Norway rats, Andrews et al. 1972).

In other mammals and in birds, an increase in circulating glucocorticoid concentration can be associated with the reproductive cycle. However, this increase serves to promote gluconeogenesis for the reproductive effort and is not associated with the cataclysmic physiological events seen in male *Antechinus*. That is, the allosteric load of producing and raising young in a short reproductive season are "resisted" in an effort to maintain the reproductive effort (Wingfield and Sapolsky 2003).

"Resistance" to stress during breeding can be seen in female *Antechinus*. During the breeding season, the total corticosteroid concentration in the plasma of females rises, but in some species there is a concomitant rise in plasma CBG. In other species, sex-steroid binding globulins rise in conjunction with the peak. As a consequence, the rise in free corticosteroids is blunted (Bradley et al. 1976; McDonald et al. 1981). In male *Antechinus*, the increase in plasma total cortisol concentrations, coupled with the decrease in circulating CBG levels, leads to a sharp rise in free (biologically active) cortisol concentrations just before male die off (Bradley et al. 1980; McDonald et al. 1981). Castration before July caused an increase in CBG concentrations and maximum corticosteroid binding capacity (Bradley et al. 1980; McDonald et al. 1981). The causes of the impaired negative feedback control of cortisol secretion are unknown (McDonald et al. 1986; Bradley 1990). In *A. swainsonii* and *Phascogale calura*, the adrenal cortex remains sensitive to ACTH (Bradley 1990), indicating that feedback is impaired at an earlier point in the HPA axis (Fig. 4a). The disturbance is associated with increased androgen levels, perhaps indicating that testosterone or melatonin is involved in hypothalamic regulation of the HPA axis, although direct damage to the hypothalamus by cortisol (via reduced availability of glucose to the brain) or temperature or nutrition cues are also possible (Lee and McDonald 1985; Bradley 2003). Brain pathology has been seen in male *A. stuartii*
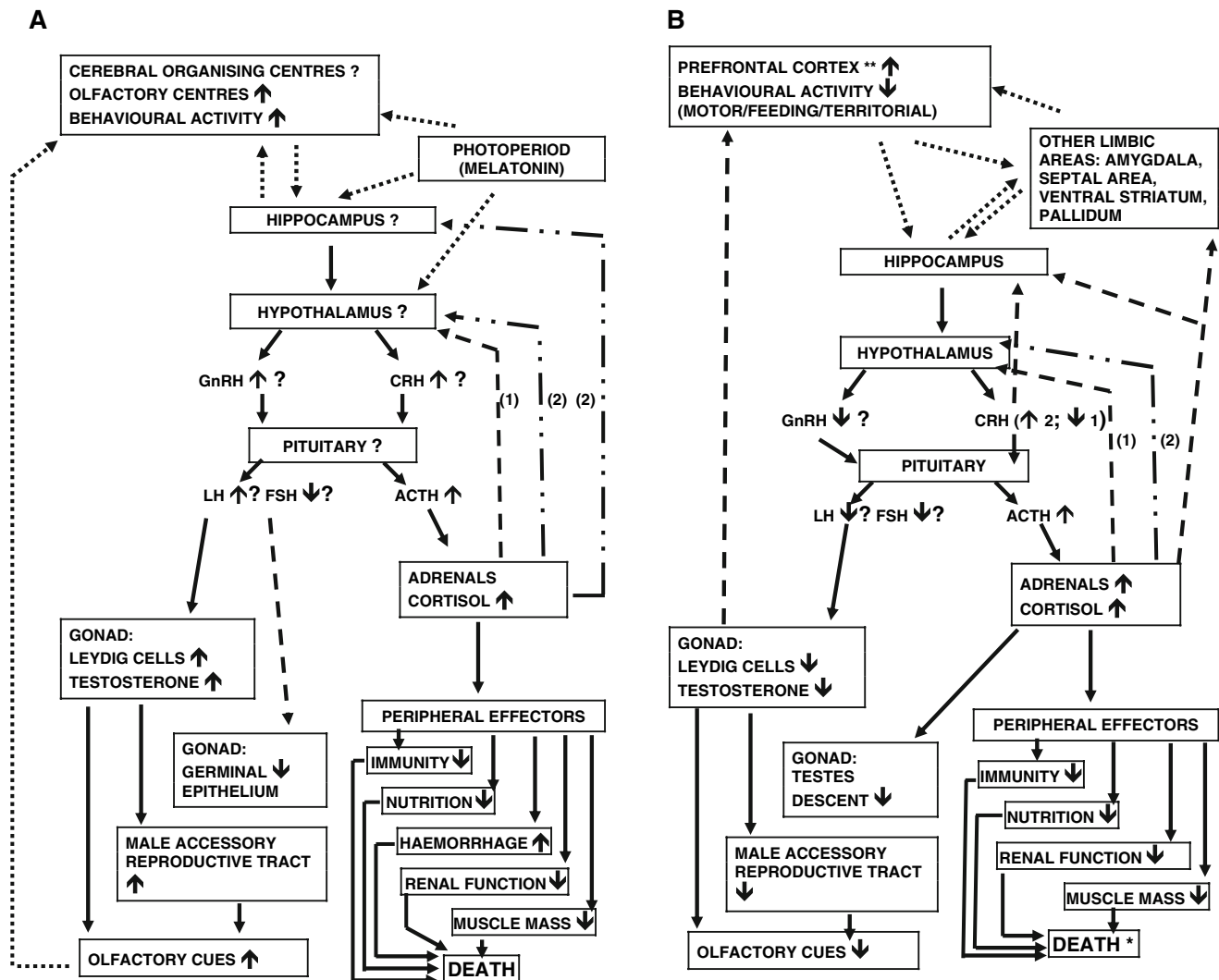
Fig. 4 a Life history flow diagram of male *Antechinus* showing the possible sequence of interactions between different body systems, which result in the death of males. The sequence starts with the regulation of the life history with the change in photoperiod and the hormone melatonin. *Dotted arrows* indicate the known influence of one system upon another, although the precise mechanism is not known or is unclear. *Solid arrows* indicate the upregulation of the next stage of the life history sequence. *Dashed arrows* indicate the negative feedback downregulating the next step in the life history pattern, and the *dashed line* and *dotted line* indicate the feedback on systems where the usual mechanism is no longer functional, but the exact mechanism is not known. The normal negative feedback mechanism that downregulates the HPA axis to reduce cortisol production, which is functional in males before the breeding season, is indicated by (1). The disrupted negative feedback mechanisms are indicated by (2), where it is hypothesized to affect hypothalamic and hippocampal areas during the breeding and "die-off" season. *Question marks* against parts of the body systems indicate where information is scant or not known. **b** Life history flow diagram of the tree shrew (*Tupaia belangeri*) showing the possible sequence of interactions between different body systems, which result in the death of many males. The sensory input to the limbic areas is believed to promote the endocrine changes. *Dotted arrows*

indicate the known influence of one system upon another, although the precise mechanism is not known or is unclear. *Solid arrows* indicate the upregulation of the next stage of the life history sequence. *Dashed arrows* indicate the negative feedback downregulating the next step in the life history pattern, and the *dashed line* and *dotted line* indicate the feedback on systems where the usual mechanism is no longer functional, but the exact mechanism is not known. The normal negative feedback mechanism that downregulates the HPA axis to reduce cortisol production via downregulation of corticotrophic-releasing hormone (CRH) then ACTH and finally cortisol, which is functional in socially dominant males, is indicated by (1). In these dominant males, the cascade of physiological events indicated on the diagram does not occur. The disrupted negative feedback mechanisms are indicated by (2), where it is hypothesized to affect hypothalamic and hippocampal areas in socially subordinate males, and the negative feedback mechanism fails so that the CRH-ACTH-cortisol cascade continues. *Question marks* against parts of the body systems indicate where information is scant or not known. The *asterisk* beside "death" indicates that this is escapable in some males, in so far as they can recover from the debilitating effects of excess cortisol. *Double asterisks* indicate the area where significant alterations to structure and function occur

during "die-off," especially in the hippocampus (McAllan et al. 2006b). Therefore, impairment to feedback mechanisms for both cortisol and perhaps testosterone (Bradley 1990, 2003) may be due to neuronal damage.

Mating and postmating male *A. agilis* exhibit negative nitrogen balance and are frequently found with empty stomachs (Woollard 1971; Bradley 2003). One hypothesis to explain why this occurs is that during the breeding season, males devote all their time to seeking out females and mating (or attempting to mate) and that foraging cannot occur as the communal nests are some distance from their usual foraging areas (Lazenby-Cohen and Cockburn 1988, 1991). The negative nitrogen balance is also associated with loss of body mass and with a cortisol-induced increase in total body water (Nagy et al. 1978). *Antechinus* males also exhibit hemoglobulinuria, ketonuria, proteinuria, and glycosuria during the last weeks of their lives (Bradley 2003), and these pathological outcomes are consistent with the metabolic disturbances seen as the result of raised plasma cortisol levels (Bradley 2003). When physiological doses (mimicking those seen in the breeding season) of cortisol or testosterone or cortsiol plus testosterone are administered to male *A. stuartii* 4 months prior to the breeding season, several aspects of male "die-off" physiology are mimicked (McAllan et al. 1997a, 1998b). Cortisol administration increases water consumption and plasma sodium levels, and decreases plasma chloride levels, urinary sodium, potassium, chloride, and urine osmolarity (McAllan et al. 1998a). However, when testosterone is administered at the same time as cortisol, the changes associated with the production of copious amounts of dilute urine were not seen, paralleling the seasonal changes seen in male *A. stuartii* (McAllan et al. 1998a, b).

Renal morphology is also affected by cortisol, and when physiological levels of cortisol administration are coupled with testosterone administration, many of the changes reflect the morphological and functional changes seen in males during "die-off" (McAllan et al. 1996, 1997a). Administration of physiological (mimicking those seen in the breeding season) concentrations of cortisol induces an increase in glomerular volume, with these changes occurring within the capillary bed rather than the Bowman's capsule; distension of outer medullary and cortical collecting ducts and distal convoluted tubules, precipitation in distal tubules and collecting ducts, and a disintegrated appearance of these tubules (McAllan et al. 1997a). Kidney mass is larger than that predicted for their body mass in males treated with cortisol, but smaller than that for males treated with testosterone. This is partly due to the distending effects of cortisol on the kidney, and the anabolic effects of testosterone on the musculoskeletal system, but not the kidney (McAllan et al. 1996, 1997a). Bradley (2003) proposes that the glomerular and tubular damage seen in male *A. stuartii* (McAllan et al.

1996, 1997a) would cause the proteinurias and hemoglobulinurias that are seen in "die-off" males. It may also be true that testosterone counteracts the destructive effects of cortisol on the kidney, allowing *Antechinus* to withstand the effects of persistent social stress, which are seen in other mammals, where the cortisol damage to renal tissue in subordinate animals causes their death (Von Holst 1972; Pasley and Christian 1971). Thus, this allows the male *Antechinus* to live long enough to mate, before succumbing to stress-related illnesses, which includes a renal component.

Finally, McAllan et al. (2006b) reported pathological changes similar to those reported by Maldonado et al. (2002) in the semelparous kokanee salmon (*Oncorhynchus nerka*), which also demonstrate cortisol-induced mortality. Neurofibrillary alterations, β-amyloid immunoreactivity, dendritic loss, and changes in patterns of tyrosine hydroxylase staining are evident in the brains of *A. stuartii* and kokanee salmon. These neuropathologies are also symptoms of Alzheimer's disease in humans. Although these changes are seen in *A. stuartii* of both sexes, the most widespread pathological changes are seen in postbreeding males. In the kokanee salmon, these changes are believed to be due to excess glucocorticoids. Corticosteroid dysregulation has been linked to Alzheimer's disease in humans (de Leon et al. 1997; McEwen 1999; Heininger 2000), especially as cortisol becomes neurotoxic to neurons by inhibiting glucose uptake and metabolism and causing selective dendritic damage (McEwen 1999). However, the β-amyloid cascade hypothesis, where the accumulation of β-amyloid peptide constitutes a critical event in the early disease pathogenesis, has become a more prevalent mechanistic explanation for Alzheimer's disease.

Other vertebrates that produce β-amyloid plaques and neurofibrillary tangles include *Caenorhabditis elegans*, *Drosophila melanogaster*, *Xenopus spp.*, sea lamprey (*Petromyzon marinus*), chick embryo, kokanee salmon, tree shrews, and several transgenic mouse models (Pawlik et al. 1999; Apelt et al. 2004; Götz et al. 2004; Schwab et al. 2004; Carrodeguas et al. 2005; Lee et al. 2005; Stoothoff and Johnson 2005). It is thought that β-amyloid formation is part of the aging process in many mammals, not just a predictor for Alzheimer's disease (Pawlik et al. 1999; Stoothoff and Johnson 2005). Further studies on *Antechinus* and other vertebrate models may help determine if this is true, or if glucocorticoid excess plays a role in β-amyloid formation. While β-amyloid plaques are present in many animals, a distinguishing feature of male senescence in *Antechinus* is the complete collapse of the germinal epithelium of the testes before the males go through "die-off" (Inns 1975; Kerr and Hedger 1983; McAllan et al. 1997b; Woolley 1966; Wilson and Bourne 1984). That sperm production occurs only once during the life of *Antechinus* is unusual for a mammal, and will be discussed in greater detail below.

Spermatogenesis, sperm competition, and male mating success

Unlike many other marsupial and eutherian mammals, the spermatogenic cycle in all *Antechinus* studied has only four stages dominating the seminiferous tubules, not six (Calaby and Taylor 1981; Inns 1975; Kerr and Hedger 1983; McAllan et al. 1997b; Taylor and Horner 1970; Woolley 1966; Wilson and Bourne 1984). Only one stage is present in the seminiferous tubules at any point in time, differing to all other mammals studied where at least four to six stages are present either in adjacent tubules or in wave-like progressions along the same tubule when males are mature and ready for breeding (Calaby and Taylor 1981; Inns 1975; Kerr and Hedger 1983; McAllan et al. 1997b; Taylor and Horner 1970; Woolley 1966; Wilson and Bourne 1984). Spermatogenesis is complete at the winter solstice, long before the breeding season begins, when plasma testosterone concentrations are barely detectable. When exogenous testosterone is administered in the nonbreeding period, the accessory reproductive tract develops, but the seminiferous epithelium remains unchanged (McAllan 1998). Thus, semelparity is independent of circulating testosterone concentrations (Kerr and Hedger 1983; McAllan et al. 1997, 2002). Germ cell maturation follows a similar progression to that in other mammals until May, after which depletion of the spermatogonia and early primary spermatocytes indicates spermatogenic failure (Kerr and Hedger 1983). Mature sperm, first appearing in the lumen of the seminiferous tubules in June are long (218–255 μm), streamlined, and move in a rapid sinusoidal fashion (Cummins and Woodall 1985; Taggart et al. 1990b). Sperm size in *Antechinus* spp. is large for mammals, with the known range being 28 μm (porcupine, *Hystrix africaeaustralis*) to 349 μm (honey possum, *Tarsipes rostralis*). Sperm size appears unrelated to changes in body mass (Gage 1998). In August, at the peak of circulating plasma testosterone levels, the seminiferous tubules have collapsed because of the depletion of the germ cells, and sperm have disappeared from the lumen of each seminiferous tubule in *A. agilis* (Kerr and Hedger 1983). Epididymal sperm number in *A. agilis* peaked in the distal caput and distal corpus/proximal cauda between late July and early August with recruitment of sperm into the epididymis from the testes ceasing by mid-August (Taggart and Temple-Smith 1990a).

Spermatorrhea (sperm release in urine) is a common phenomenon in rodents and marsupials (Bolliger and Carrodus 1938), and occurs in all dasyurid marsupials studied thus far (see McAllan 2003). This accounts for a constant loss of sperm in male *Antechinus*, spp. In *A. agilis*, sperm loss via spermatorrhea occured at a rate of 0.15×10^6 sperm per day beginning as soon as mature sperm are observed; so very few sperm remained in the epididymis by late August (Taggart

and Temple-Smith 1990a). *Antechinus* spp., do, however, display an unusual structure of the caudal epididymis that may partially compensate for this by restricting storage capacity and limiting the number of sperm available at each ejaculation (Taggart and Temple-Smith 1989, 1990a). In eutherians and most marsupials, the cauda is enlarged to form a bulbous segment for sperm storage, where tubule and luminal diameters and sperm numbers are greatest (Glover and Nicander 1971; Cummins 1976; Temple-Smith and Bedford 1976; Rodger and Bedford 1982; Jones et al. 1984; Cummins et al. 1986). In *A. agilis*, however, the epididymis narrows from the caput to the cauda (Taggart and Temple-Smith 1989). An increase in tubule diameter and epithelial height causes a decrease in the cross sectional surface area of the lumen, creating a transition from circular to a slit-shaped lumen at the caudal end (Taggart and Temple-Smith 1989). This results in very limited storage capacity of the caudal region and low epididymal sperm content (Taggart and Temple-Smith 1989). Similarly, limited caudal storage is also seen in other dasyurids, which are semelparous, and these marsupials deliver far fewer sperm per ejaculate than eutherians of equivalent size (Moore and Bedford 1978; Amann 1981; Bedford et al. 1984). Taggart and Temple-Smith (1990a) estimate that, depending on the number of sperm delivered per ejaculation, a male's sperm supplies could be exhausted after an average of 1.5–9 matings, and reduced sperm numbers may account for lower litter success rates of females mated late in the season (Selwood and McCallum 1987; Taggart and Temple-Smith 1990a).

Close synchronization between male and female reproductive cycles is essential to ensure fertilization, and mating strategies appear to compensate for low sperm numbers. Under laboratory conditions, mating in *Antechinus* has been recorded as taking as long as 8–12 h, with the male repeatedly gripping the neck of the female to prevent her from escaping, often injuring her in the process (Marlow 1961; Braithwaite 1979; Shimmin et al. 1999). Although such injuries are rarely seen in the wild, and mating would be expected to be briefer where other males are present and the female can escape, it has been observed to take 6–8 h on average (Shimmin et al. 1999). After the first hour of copulation, only 40% of males have ejaculated; three hours are required for all males tested to do so (Shimmin et al. 1999; Taggart et al 1999). However, it has been suggested that as little as 45 min are needed for a successful copulation (Lazenby-Cohen and Cockburn 1988).

Another strategy is the efficient transfer of sperm to the sites of fertilization in the female. In most marsupials and eutherians, the cervix and uterotubal junctions act as selective barriers to sperm. In *A. agilis*, 56% of sperm has reached the lower isthmus on average only 9 h after ejaculation, and large numbers of these sperm are viable (Shimmin et al. 1999). The ratio of ejaculated sperm to sperm that

reaches the isthmus is as much as 1 in 1 to 1 in 7, which compared to the ratios seen in rabbits of 1:5,000 to 1: 10,000 is very high (Overstreet and Cooper 1978, 1979; Taggart and Temple-Smith 1991). The high speed of sperm colonization and high ratios imply that few barriers are presented to sperm transport. These ratios, although high, are not unique to *A. stuartii*. American opossum (*Didelphis virginiana*) sperm colonize the upper female reproductive tract with a success ratio of 1 in 20 (Bedford et al. 1984), while *Sminthopsis crassicaudata* sperm has a fertilization ratio of 1 in 10 (Breed et al. 1989). In dasyurids and didelphids generally, sperm numbers produced and delivered are significantly less than those in similarly sized marsupials and eutherians (Breed et al. 1989; Taggart et al. 1997). Taggart and Temple-Smith (1991) and Shimmin et al. (1999) also reported longitudinal ridging in the uterine neck and a channel around the perimeter of the uterus to direct sperm, and suggest that the sinusoidal motility of *Antechinus* spp. sperm also contributes to individual sperm success in reaching the upper parts of the female reproductive tract.

The *A. stuartii* complex (Woolley 1966; Selwood 1983; Selwood and McCallum 1987), like some other dasyurid species (Hill and O'Donoghue 1913; Godfrey 1969) also have crypts in the lower isthmus to store sperm. By 7 days after mating, 91% of sperm are located in these crypts, while at later time points, all the sperm able to be isolated from the female reproductive tract are in the crypts (Taggart and Temple-Smith 1991; Taggart et al. 1999). Once in the crypts, sperm become immotile and often have their heads close to or entangled, but not embedded, in long microvilli of noncilliated crypt cells (Taggart and Temple-Smith 1991). However, it is unknown how sperm from different males are organized within the crypts, and sperm are continuously lost from the crypts by an unknown mechanism (Shimmin et al. 1999). Sperm storage is common in mammals, and has been reported in bats, llamas, hares, and mice (Hartmann 1933; Thibault 1973; Racey 1979). In many marsupials, oestrus is short and sperm are stored for a day or so (Godfrey 1969, 1975; Lyne and Hollis 1977), and thus the 2-week-long sperm storage recorded in females of the *A. stuartii* complex is long for marsupials (Selwood and McCallum 1987). Only the sperm storage for brush-tailed phascogales (*Phascogale tapoatafa*) is longer at up to 1-month duration (Rhind 2002).

The female reproductive cycle and embryonic development

The ovarian cycle

In all the *Antechinus* species that have been studied, the same general pattern of ovarian development has been observed, and the same pattern of spontaneous ovulation and mating strategies has been described. In the best-studied species, *A. stuartii*, females are monoestrus (single oestrus period, Marlow 1961; Woolley 1966), polyovular (more than one egg ovulated), and polytocous (many young born during the one parturition, Selwood 1980). Ovulation is spontaneous, with 6.4 ± 1.4 eggs per ovary ovulated, although ovulation rates decline in females breeding in a second year, with rates of 5.4 ± 1.1 per ovary (Selwood 1983). Ovulation rates appear to be similar in other species studied (Calaby and Taylor 1981; Taylor and Horner 1970; Wilson 1986). Ovulation is synchronized to fall within an 4- to 8-day period (Woolley 1966; Selwood 1980; Taggart et al. 1999). Like the males, female reproductive development is synchronized, although unlike males, gonadal development and maturation does not cease by the winter solstice.

The following describes the changes in *Antechinus* ovaries over the course of the seasons. When females are juvenile, the oocytes are small and have a single layer of granulose cells around the oocyte. As the year progresses toward the breeding season, secondary oocytes are seen with many layers of granulosa cells around the oocyte and small antra develop within the oocytes, eventually joining to become single large antra of the Graafian follicles. The sequence of events occurs at exactly the same time for a population of females, although this may differ slightly between populations of the same species. While the exact timing of these events differs between species, and also within species depending on the locality, the sequence of events is always the same, and like many strictly seasonal species, the ovary has limited oocyte cell types present at any one time. Unlike other seasonal species that have been studied, many of which are rodents, the sequence of events takes place over a 6-month period, rather than in only 6–8 weeks (Wilson 1986; Taylor and Horner 1970; Woolley 1966). During development of the follicles, the external morphological features are relatively unchanged, until after the winter solstice when secondary oocytes mature into Graafian follicles. At this point, the urogenital sinus enlarges, and the pouch begins to feature with thinning hair and guard hairs developing. The pouch continues to develop during the mating season, ovulation, and during pregnancy, such that by parturition the pouch ridges form with pronounced guard hairs, and the pouch itself is hairless, shiny and lactational tissue has developed. The external morphological changes parallel reproductive hormone cycles in *A. agilis*.

Hormonal cycles and embryonic development

The hormonal changes are also paralleled with the development of the corpus luteum. Moreover, the state of embryonic

development appears to parallel that of corpus luteum formation and positively correlates with plasma progesterone levels (Hinds and Selwood 1990). Gestation in *A. stuartii* is 27 days, and there are several periods when developmental arrest can occur (Selwood 1980, 1981). The first and second cleavage divisions are rapid, but are followed by a developmental arrest of up to 4 days (Selwood 1980). Tubal eggs and dividing fertilized eggs up to 32 cell stages are seen from 0 to 6 days gestation (Selwood 1983). Another period of arrest has been seen from days 11 to 13 or 14, when the embryo is at the unilaminar blastocyst stage. The unilaminar blastocysts are 0.42–0.60 mm in diameter, and the bilaminar blastocyts are 1.7–2.4 mm in diameter (Yousef and Selwood 1996). In the bilaminar blastocyst stage (from 16 days gestation), a small transparent pluriblast between 0.2 and 0.6 mm in diameter is usually observed at this stage (Selwood 1983; Yousef and Selwood 1996).

Until day 14, the formation of the corpus luteum is incomplete and the plasma progesterone concentration is low (Hinds and Selwood 1990). However, day 4 precedes a modest increase in progesterone level, while the completion of the corpus luteum is marked by a sustained increase in plasma progesterone concentration. Thus, an increase in plasma progesterone level is required at day 4 and day 14 to allow the embryo to continue developing. The uterus is required to mediate these changes in developmental rate, although it is likely that an embryonic signal is also required (Cruz and Selwood 1993). Cultured embryos in a stage of developmental arrest cannot resume development when progesterone is administered without uterine mediation (Hinds and Selwood 1990). Periods of slow or arrested development coincident with low progesterone levels have been observed in other marsupials with long gestation periods for their size (Hinds and Selwood 1990). One interrupter of gestational development is the use of torpor, which has been seen in other pregnant dasyurids (*Sminthopsis macroura*, Geiser et al. 2005; *Dasycercus cristicauda*, Geiser and Masters 1994).

Prenatal and neonatal mortality

The gestation period in *A. agilis* is relatively long for an animal of its size when the developmental state of the neonate is considered (Selwood 1980, 1981). The gestation period for other *Antechinus* species appears to be similar, with 26–34 days being the recorded ranges for *A. flavipes*, *A. bellus*, *A. minimus*, *A. stuartii*, and *A. swainsonii* (Marlow 1961; Calaby and Taylor 1981; Taylor and Horner 1970; Wilson 1986; Watt 1997). The number of young at parturition is the same or one less than the number of teats (6–10 depending on the area for *A. agilis*) (Selwood 1983) in all species studied (Wilson 1986; Watt 1997). The percentage of surviving embryos does not vary with year of

breeding, origin or age of the female, stage of development or number of times the females mated in laboratory settings (Selwood 1983). Prenatal losses may selectively target males rather than females. *A. agilis* litters are strongly female biased (32% male), with brood reduction insufficient to account for this (Davison and Ward 1998). It is speculated that female mate selection and subsequent modification of litters are important as strategies to maximize appropriate dispersal of juveniles (Fisher 2005; Fisher et al. 2006a, b). The evolution of such a mechanism, and indeed the complete physiology, will be discussed next.

Evolutionary biology

In mammals, the obligatory programmed die off of males is only found in dasyurid and didelphid marsupials (Bradley 2003; Woods and Hellgren 2003). It has been thought that the energy investiture required for the relatively large size and long generation times of mammals compared to insects makes semelparity, with its risks of reproductive failure, a potentially risky strategy for vertebrates (Braithwaite and Lee 1979). Many mammals, however, are of the same size or smaller than these dasyurids and hence, in terms of the simple energy investments required to reach adult size, have less to lose from becoming semelparous (it is less risky for them). This suggests that another reason exists for the evolution of semelparity in *Antechinus*. What then could account for the evolution of this unusual life history in some (but not all) genera of these marsupial families, and nowhere else in the mammalian class? Moreover, why would such a seemingly risky strategy be preferred enough to evolve several times in marsupials, as Krajewski et al. (2000) hypothesized?

Recent evidence from the edible dormouse (*Glis glis*) suggest that longevity can be traded for reproduction in a predictable way, with "good" reproductive years traded against high adult mortality, or relative semelparity, for that year (Ruf et al. 2006). It may be that a predictable environment promotes semelparous reproductive strategies in temperate zones. *Antechinus* are relatively long-lived for their size, with most females living for at least 1 year, depending on habitat quality (Fisher and Cockburn 2006). The similarly sized house mouse has most populations turning over within 4–6 months, although occasionally individuals can live for more than a year (Singleton and Redhead 1990; McAllan et al. 2003), underscoring the misconception that *Antechinus* "live fast and die young." One consequence of semelparity is that males and females must optimize reproductive output. Female reproductive fitness is determined by numbers of viable young weaned, and recent evidence suggests that females that mate multiple times maximize the numbers of viable young, and their selection of mates is

based on pheromonal cues (Fisher et al. 2006a, b; Parrott et al. 2007). Multiple matings by females with several males would promote sperm competition in males, and this has been suggested as a promoter of the male semelparity system (Taggart et al 1997). Male reproductive fitness is determined by fathering the maximum numbers of young, and the genus' sexual dimorphism, the intensity of the mating season in *Antechinus* spp., male postreproductive senescence, perhaps their single spermatogenic generation, the female sex bias of their litters, and even the evolution of cortisol resistance in breeding males. All the factors may be pushed by increased competitiveness between animals for mates. Females choose mates based on smell, and their choice reflects genetic distance (Fisher et al. 2006b; Parrott et al. 2007). Larger males can force matings, but when given a choice, females will prefer males with greater genetic dissimilarity (Fisher et al. 2006a; Parrott et al. 2007).

This suggests that the promotion of elevated levels of cortisol in breeding males is a secondary adaptation to maximize success in an intensely competitive breeding season, rather than a factor leading to semelparity directly. Raised cortisol as a secondary characteristic, rather than a driving characteristic of die-off, has been suggested for *Dasyurus hallucattus* (Oakwood et al. 2001). *Dasyurus hallucattus* is a larger dasyurid marsupial that lives in the Australian tropical savannah and frequently demonstrates male die off after breeding, although increased plasma total corticosteroid concentrations are not found (Oakwood et al. 2001). Thus, male *D. hallucattus* can sequester enough energy to compete for mates without requiring changes in free or total cortisol levels or CBG levels and do not exhibit spermatogenic failure. The reason why a partial die-off is seen in some other dasyurids remains unclear (Oakwood et al 2001).

An advantage of the deaths of the previous cohort of adult males also ensures that adult females and young are relatively free from competition for food and shelter, suggesting that kin selection could drive male semelparity. Synchronizing parturition and weaning could "swamp" predators (Scott 1986), which should further benefit the survival of offspring. "Swamping" predators is a tactic described in many species, from plants to coral to sea turtles (for review, see Ims 1990). This may suggest that semelparous dasyurids are able to raise larger litters than their iteroparous relatives (Braithwaite 1979). Data from closely related iteroparous dasyurids from New Guinea ("*Antechinus*" spp., *Murexia* spp., and *Phascolosorex dorsalis*) seem to support this suggestion (Woolley 2003).

Conclusions and future directions

The *Antechinus* genus of polyprotodont Australian marsupials has many unusual morphological, physiological, and metabolic traits. A specific increasing rate of photoperiod is the cue for the annual short period of breeding. *Antechinus* are unusual in that they have a highly synchronized life history of males resulting in complete die off following the short mating period, with the male mortality being due to a dramatic increase in testosterone and cortisol concentrations in blood. Highly derived reproductive strategies and morphologies of male and female reproductive tracts have evolved to adapt to semelparity.

There are still many gaps in our knowledge of the physiology of the *Antechinus* genus, and future research directions should focus on these conundrums. These include

(1) The mechanism of feedback control of the neuroendocrine axis, specifically, the feedback pathways for testosterone and cortisol in the brain. How is this regulated in a sex-specific manner?

(2) Why and how are litters strongly female biased? What mechanism controls the male/female ratio, and at what developmental stage(s) does this occur? Is this related to male semelparity?

(3) It has been established that specific and discrete increases in photoperiodicity are the cue for breeding in *Antechinus*. Now we need to build hypotheses to explain how and why such cues evolved as triggers for breeding. This is especially significant in light of male semelparity. What would be the selection pressure(s) determining species-specific differential increases in rates of photoperiod?

(4) *Antechinus* is a potentially good model for studying the effects of stress on reproduction and other physiological systems. For example, under laboratory conditions, males suffer from gastrointestinal damage but can cope with increased food consumption to compensate for the negative nitrogen balance. *Antechinus* could therefore be used to study the interaction of cortisol with the gut.

(5) *Antechinus* is a potentially exciting model for the study of amyloidosis. Amyloid occurs naturally in *Antechinus* brains, whereas mouse models rely on genetic modifications to produce amyloid deposits in their brain. As mammals, *Antechinus* are more similar to humans than kokanee salmon, which are at present a common nontransgenic model for amyloidosis. *Antechinus* have accelerated amyloid accumulation compared to mouse models. Although marsupials have not been used as animal models for amyloid research in the past, they should be exploited as a complementary model to murine models.

In summary, *Antechinus* are unusual mammals in a variety of aspects, and these features should be examined to improve our understanding of mammalian physiology, adaptation, and evolution.

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