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EQUIPPED FOR LIFE: THE ADAPTIVE ROLE OF THE STRESS AXIS IN MALE MAMMALS

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Habitat constrains and shapes successful ecological and physiological strategies and thus provides the context for the evolution of life-history traits. The stress axis plays a vital role in the endocrine system and is a critical component adapting mammals to particular habitat pressures. It is subject to both individual activational and organizational plasticity as well as to evolutionary modification. To illustrate, I examine the suite of traits of the stress axis associated with breeding frequency in male mammals, which varies in a continuum from semelparity to iteroparity. During the breeding season, males in species at the semelparous end of the continuum exhibit high concentrations of free corticosteroids, low concentrations of glucocorticoid-binding protein, a failure of the negative feedback system, a gonadal axis that is not inhibited by high corticosteroid concentrations, and immunosuppression. Iteroparous species exhibit the opposite traits. The evolutionary constraints selecting for the former may partially be related to phylogeny (in marsupials) as well as to an interaction of the restrictions imposed by the environment on female reproduction, the mating system, the high costs of reproduction, and the low adult survival during the nonbreeding season.

Key words: cost of reproduction, habitat, iteroparity, life history, mating systems, seasonality, semelparity, stress axis, winter survival

The goal of individuals is to maximize lifetime reproductive fitness, and the functioning of the stress axis is key to making this happen. There is a tendency to think of this axis only in relation to the response of the body to short-term stressors, yet it plays a key role all the time—winter and summer, in and out of breeding condition—to both carry out the daily functions of living and to cope with environmental challenges (McEwen 2001). The functional basis for life-history theory is still rudimentary, and understanding how this stress axis functions under different life-history scenarios will aid in our understanding of that theory.

The stress axis is multitasking throughout the life of an organism, but is subject to modification and permanent change if environmental conditions dictate. The stress axis is composed of the limbic system of the brain (dentate gyrus and hippocampus) and the hypothalamic–pituitary–adrenocortical axis and is pivotal for successful adaptation for 3 reasons. First, the stress axis is involved in normal day-to-day activities associated with the diurnal cycle of waking such as increased locomotion, exploratory behavior, increased appetite, and food-seeking behavior (reviewed by McEwen et al. [1988], Reeder and Kramer [2005], and Wingfield and Romero [2001]). Second, the stress axis permits short-term adaptation to maintain survival in the face of acute, environmental stressors (Sapolsky 2002). This is the classic "flight or fight" reaction to a wide variety of stressors such as bouts of severe weather, physical stressors such as attacks by a conspecific or a predator, or psychological stressors such as the fear of an imminent attack. Although I focus on the limbic system and the hypothalamic–pituitary–adrenocortical axis here, it is only one part of the stress response, and other hormones, neurotransmitters, opioid peptides, cytokines, and brain functions are also rapidly called into play (Sapolsky et al. 2000). Third (the subject of this paper), the axis is central to certain long-term evolutionary adaptations to particular ecological and habitat pressures.

Time and space are 2 key dimensions that organisms must successfully integrate to maximize their breeding success (Southwood 1977). The choices that they must make with respect to time and breeding are whether they do it "now" or "later," and with respect to space and breeding, whether they do it "here" or "elsewhere." The dichotomy in life-history characteristics between those mammals that are semelparous and those that are iteroparous is a reflection of integrating these 2 dimensions. A semelparous life history is characterized by a single reproductive episode followed by death, whereas an iteroparous life history is characterized by multiple reproductive episodes over the lifespan of the organism. Semelparity tends to be found in those animals in which adults face low or variable

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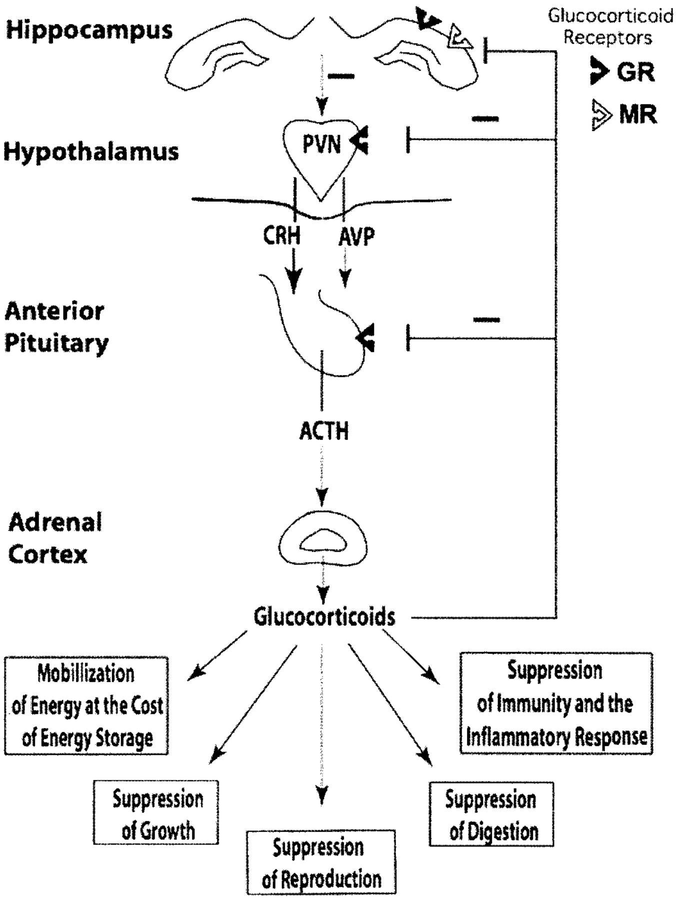

FIG. 1.—The hypothalamic–pituitary–adrenal axis, the major impacts on body processes, and the glucocorticoid (GC) feedback in the mammalian brain. A stressor causes the hypothalamic paraventricular nucleus to release corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP), which causes the anterior pituitary to release adrenocorticotrophin (ACTH). ACTH initiates the synthesis and release of GCs (corticosterone in some rodents; and cortisol in lagomorphs, primates, and squirrels) from the adrenal cortex. GCs act at multiple sites within the body to maintain homeostasis, but because of the damaging effects of extended exposure to GCs, the hypothalamic–pituitary–adrenocortical axis is tightly regulated through feedback (inhibition is indicated by –) on GC receptors to inhibit further hypothalamic–pituitary–adrenocortical activity. Glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) occur in the limbic system (hippocampus and dentate gyrus) and glucocorticoid receptors occur in the paraventricular nucleus (PVN) and anterior pituitary. In the brain, mineralocorticoid receptors have a higher affinity than do glucocorticoid receptors for GCs, and at basal concentrations of cortisol, mineralocorticoid receptors are occupied, whereas glucocorticoid receptors remain largely unoccupied. During periods of stress, elevated plasma GCs result in the increased occupation of glucocorticoid receptors. Hippocampal mineralocorticoid receptors may be primarily involved in feedback regulation during basal secretion, whereas glucocorticoid receptors become important during periods of increased GC secretion. Short-term effects result in suppressive impacts on body processes; long-term chronic effects result in inhibitory impacts on body processes (from de Kloet et al. 1999; Matthews 2002; Sapolsky 2002).

probabilities of survival (Roff 1992; Stearns 1992) or in which juveniles face higher survival in one season than another (Braithwaite and Lee 1979). The broadscale patterns explained by allometric relationships with adult body size (e.g., Charnov 1993) do not map easily on to the stress-axis spectrum we see in mammals.

Boonstra and Boag (1992) proposed a model to account for differences in the hormonal and physiological responses between species with semelparous males and those with iteroparous males. The former strategy was termed the "adaptive stress response," in which animals traded off survival for reproduction by maximizing the energy available for a brief period of intense reproduction. The normal feedback mechanisms fail to function and, along with other associated changes, cause the males to die from immunosuppression, gastric ulceration, renal pathology, and anti-inflammatory responses (Bradley 2003). The iteroparous strategy was termed the "homeostasis stress response," in which reproductive effort was spread out over a longer breeding season. The normal feedback mechanisms of the stress axis remain intact throughout the breeding season. Recent evidence indicates a continuum in the suite of physiological and hormonal adaptations occurring between the extremes of semelparity and iteroparity (Boonstra et al. 2001; Woods and Hellgren 2003), reflecting the continuum of life histories that mammals experience.

Can we predict which of these 2 stress axis strategies will evolve given our knowledge of the environment of a species? In this paper, I concentrate on the functioning of the stress axis during a critical phase of a male mammal's life—the mating period—when all the resources at the disposal of a male must be brought to bear to maximize the chances for reproductive success. I then relate this to the range of habitat pressures that may select for this type of stress response. I focus on males because they illustrate the range of possibilities that can evolve and because the progress of reproduction in females causes rapid changes in the hormones of the stress axis that make it more difficult to "standardize" subjects and thus to study.

THE STRESS RESPONSE

An external stressor sets off a rapid cascade of responses in vertebrates to deal with the threat and then to reestablish homeostasis (Fig. 1). Within seconds of the stressor, the sympathetic nervous system causes the adrenal medulla to release catecholamines (epinephrine and norepinephrine) into the general circulation and the paraventricular nucleus of the hypothalamus releases primarily corticotrophin-releasing hormone, but also arginine vasopressin, into the portal system. These cause the anterior pituitary to release adrenocorticotropic hormone (ACTH) into the general circulation. Within minutes, the adrenal cortex releases glucocorticoids (GCs) into the general circulation. In some small mammals (voles and mice), the GC is corticosterone and in other mammals it is cortisol or a mixture of cortisol and corticosterone (e.g., marsupials, hares, squirrels, ungulates, and primates). Immediate catabolic effects result in the mobilization of glucose for the muscles, the stimulation of hepatic gluconeogenesis (the breakdown of other body tissues such as protein), and the shunting of energy resources away from peripheral tissues not needed for short-term survival. Cardiovascular tone is increased, immune function is stimulated, reproductive physiology and behavior are inhibited, feeding and appetite are decreased, and cognition is sharpened. Under conditions where the stressor is acute, GCs exert feedback at 3 levels in the brain (Fig. 1) to return the body back to preactivation state. Key to this feedback are the intracellular GC receptors (mineralocorticoid receptors and GC receptors) in the critical brain areas (Fig. 1; de Kloet et al. 1999).

Changes in the concentrations of a plasma carrier protein, corticosteroid-binding globulin (CBG) play a major role in the life histories of male mammals, especially the semelparous and partially semelparous species. The mammalian body is typically buffered from the immediate impact of GCs in the blood because they are tightly bound to CBG. Only about 5–10% of GCs are unbound and free and only the free GCs are biologically active (Rosner 1990). Free GCs are normally rapidly excreted by the kidneys. CBG is thought to act as a reservoir of GCs so that GCs can be rapidly released in response to an environmental stressor (Rosner 1990). Blood CBG concentrations are affected both by the stress axis and by the gonadal axis. Chronic stress results in high concentrations of GCs, resulting in a marked reduction in CBG (Boonstra et al. 1998, 2001; Frairia et al. 1988; Schlechte and Hamilton 1987) and an increase in free GCs. High levels of testosterone also inhibit CBG production because castration (e.g., in rats—Mataradze et al. 1992) or reduction of testosterone to low levels in the nonbreeding season (e.g., in the dasyurids—McDonald et al. 1981) result in an increase in CBG concentrations.

The stress response and the homeostatic set point are not fixed, life-long species-dependent characteristics, but are modified by experience, by development, and by the annual pattern of life-history changes. First, experience may alter the stress-axis response. The stress axis functions well when the stressor is acute (minutes to hours); thereafter the negative, inhibitory effects of chronic stress become evident and intensify. Under conditions where the stressor becomes chronic (days to months), the normal suppressive effects of GCs grade into inhibition (Fig. 1), affecting long-term survival and fitness through infertility, impaired resistance to disease, and inhibition of growth. Second, pre- and postnatal periods of development are particularly sensitive to permanent modification by stressors affecting the mother (Matthews 2002; Welberg and Seckl 2001). The stress axis and its response to stressors will be programmed differently than if the mother had not been stressed. An interplay also occurs between changes in the stress axis and the reproductive axis, which ultimately translates into changes in adult fitness. Finally, in mammals living in seasonal environments, the annual cycle of reproduction, migration, and coping with winter may require the stress axis to be modulated in different ways at different times to optimize reproduction, survival, or both in the face of environmental challenges. This modulation has been referred to as allostasis (i.e., achieving stability through change—McEwen and Wingfield 2003; Wingfield 2005). Challenges that are recurrent and predictable, such as the direct male–male aggression often associated with the rut, would, if the animal did not evolve a modifying solution, inhibit reproduction. Neither basal GC concentrations nor response to stressors remain constant over the annual cycle and changes in the 2 are not necessarily closely correlated (e.g., baseline concentrations may be high at some times, but response to a stressor dampened—for an overview, see Romero [2002]).

METHODS FOR ASSESSING THE STRESS AXIS

Before and after measurements.—Glucocorticoid concentrations can be determined before and after the application of a stressor (e.g., before and after hunting—Bateson and Bradshaw 1997) and their concentrations compared. The results can be compared among categories but only give insight into the overall impact of the stressor.

Measurements in urine and feces.—The urine or feces of animals can be collected in the field and concentrations of GC metabolites measured (e.g., Teskey-Gerstl et al. 2000; Wasser et al. 2000). This simple, noninvasive method gives an integrated index of what the animals were experiencing sometime over the 24 h before defecation or urination. If the sex and rank of the individual and what the individual was experiencing during the period the urine and feces were produced (i.e., whether it was stressed and for how long) are not known, the results may only allow one to make general statements about the stress status of entire populations. Because GC concentrations show a pronounced circadian rhythm (Dallman et al. 1990), being highest at the onset of daily activity and the lowest at the end of it, lack of knowledge about when the feces or urine were produced may complicate interpretation of these results as well. However, detailed knowledge of the individuals producing the feces or urine (i.e., through knowledge of social status, behavior, sex, and so on) and standardization of collection techniques can mitigate these limitations (Creel 2005; Creel et al. 2002).

Challenge protocol.—A challenge protocol uses a standardized, artificial stressor as an index of an animal's ability to respond to natural stressors. Two basic approaches have been used—a capture-challenge protocol and a hormonal-challenge protocol. The capture-challenge protocol uses the capture of the animal as the stressor. Typically within 3 min of capture, a baseline blood sample is taken. Timing is critical because the stress response is so rapid that GC concentrations start increasing within 3–5 min of capture (e.g., Hellgren et al. 1985; Reeder et al. 2004; Waas et al. 1999). Thereafter, serial bleedings are taken at regular intervals (e.g., 5, 10, 30, and 60 min—Kenagy and Place 2000). A modification of this protocol is to dart animals with an anesthetic and use the response to the anesthetic as the standardized stressor (e.g., Sapolsky 1983).

The hormonal-challenge protocol uses injections of hormones or analogs of them that are part of the normal stress response and measures the animal's response over a series of blood samples. This protocol is particularly useful when the techniques of capture (e.g., overnight livetrapping) exceed the 3-min window. This protocol results in an integrated picture of the animal's recent physiological past (days to weeks) while overriding the immediate stress response the animal experienced because of capture. Typically, a dexamethasone suppression test is followed by an ACTH stimulation test. Dexamethasone, a synthetic glucocorticoid agonist, should inhibit GC secretion through negative feedback mechanisms at the level of the brain by causing a reduction in ACTH release. Dexamethasone resistance (i.e., GC concentrations do not decline as much as expected), may indicate that the animal has been chronically stressed (e.g., Brooke et al. 1994; Hik et al. 2001; Sapolsky 1983). However, certain mammal species are naturally dexamethasone resistant (prairie voles—Taymans et al. 1997; red squirrels—Boonstra and McColl 2000; guinea pigs—Keightley and Fuller 1996; and some New World primates—Chrousos et al. 1982; Yamamoto et al. 1977) and this resistance is associated with elevated levels of GCs (Chrousos et al. 1993). The ACTH stimulation test probes the responsiveness of adrenal glands directly. Exposure to chronic stressors can cause adrenal hypertrophy and a greater response than normal in some species (e.g., snowshoe hares—Boonstra et al. 1998) and a lower response than normal in others (e.g., cougars—Harlow et al. 1992). Thus, for comparative purposes, it is critical to establish a benchmark as to what constitutes the ''normal'' unstressed condition in all these tests.

BREEDING FREQUENCY AND THE STRESS AXIS

Semelparity.—True semelparity, where males die after 1 breeding season, is restricted to the males of several small dasyurid and didelphid species (Bradley 2003). Females can survive for a 2nd year (Bradley 2003; Cockburn 1997). Semelparity is found in 15 species (12 in Australia—7 *Antechinus* species, 2 *Phascogale* species, *Dasykaluta rosamondae*, *Parantechinus apicalis*, and *Dasyurus hallucatus*; 2 in South America—*Monodelphis dimidiata* and *Marmosa incana* and 1 in North America—*Didelphis virginiana*; for summaries, see Bradley [2003], Cockburn [1997], and Woods and Hellgren [2003]). The physiological events that culminate in total male die-off after breeding have been examined in detail in the Australian species (Bradley 1987, 1990; Bradley et al. 1980; McDonald et al. 1981, 1986). To illustrate these changes, I will use evidence from the red-tailed phascogale (*P. calura*).

The red-tailed phascogale is a small (30- to 45-g), nocturnal, arboreal squirrel-like insectivorous marsupial now found only in small woodland isolates in the southwestern wheat belt of western Australia (Bradley 1987, 1997). The breeding season lasts only 3 weeks in July, followed by the complete disappearance of males from the population. The increase in testosterone before the rut (Fig. 2) precipitates the initial decline in CBG (measured as the maximum corticosterone binding capacity; Fig. 2), with testosterone concentrations reaching their maximum and CBG concentrations their minimum just before the disappearance of males. The decline in CBG concentrations is androgen-dependent, because castration increases CBG concentrations whereas testosterone injections cause CBG concentrations to fall again (Bradley 1987). This CBG decline results in increasing competition of the 2 GCs (cortisol and corticosterone) for CBG-binding sites and a 25-fold increase in free cortisol, the most potent GC. No change occurs in female CBG concentrations at this time, and consequently the free GC levels in females remain low (Bradley 1987). Normally, an increase in GC in the blood results in a negative feedback at the level of the hypothalamus and pituitary, causing ACTH levels to fall. Negative feedback (through assessments with dexamethasone) continues to work well in males up until early July, but then fails in late July (Fig. 2; Bradley 1990). Thus, just before disappearance from the population, the GC feedback control of ACTH is almost abolished, GC concentrations reach their highest levels, and feeding stops. The failure of the feedback regulation is at the level of the brain rather than the adrenal glands, because ACTH injections continue to elicit marked increases in GC levels in late July (Bradley 1990). This failure also occurs at the level of the gonadal axis. Normally, high levels of GCs inhibit testosterone production. Dexamethasone inhibits testosterone before and early in the rut but fails to do so when the rut is at its peak (Bradley 1990). The highly aggressive interactions among male dasyurids cause the increase in ACTH that results in the failure of the feedback system and ultimately death, because isolated male *Antechinus* in the laboratory can live much longer than those in the field (Bradley 2003; Lee and McDonald 1985). The proximate cause of death in these dasyurids is gastrointestinal hemorrhage, immunosuppression and disease, a negative nitrogen balance, anemia, and unspecified degeneration of major organs (reviewed by Bradley [2003] and Lee and McDonald [1985]). Bradley (1997) proposed that these rapid changes are equivalent to accelerated ageing.

In 2 larger marsupials, males are also semelparous but their hormonal changes apparently differ from those found in the antechinuses and in *Phascogale*. The northern quoll (*Dasyurus hallucatus*) weighs about 1 kg, lives in topical savannah in Australia, and exhibits male die-off after the rut. Males of this species show physiological similarities to the other Australian semelparous marsupials such as weight loss, fur loss, parasite infection, increased testosterone levels, and anemia, although they continue to eat during the rut (Oakwood et al. 2001). However, they apparently show no evidence of elevated levels of GCs before disappearance. One study reported no evidence of gastrointestinal ulceration (Oakwood et al. 2001), although another found it to be common (Bradley 2003).

The Virginia opossum is common throughout the eastern United States in many habitats, weighs 2–3 kg, continues to eat during the rut, and also shows complete male mortality (Woods and Hellgren 2003). However, unlike all the other semelparous species, the males show an extended breeding season, living through 2 breeding bouts within 1 year (the 1st in January–February and the 2nd in April–May) before all die. They show similarities to the small Australian marsupials such as the sequence of changes in testosterone levels, decreased hematocrit, increased parasite levels, and hypertrophy of the adrenals (Woods and Hellgren 2003). As with the quoll, male opossums apparently also show a lack of change in cortisol concentrations. However, both studies failed to measure the CBG concentrations and thus the concentrations of free glucocorticoids could not be calculated. It is thus possible that the final disappearance is a consequence of high levels of free glucocorticoids.

Partial semelparity.—Partial semelparity occurs in species in which many, but not all, of the males die after 1 mating

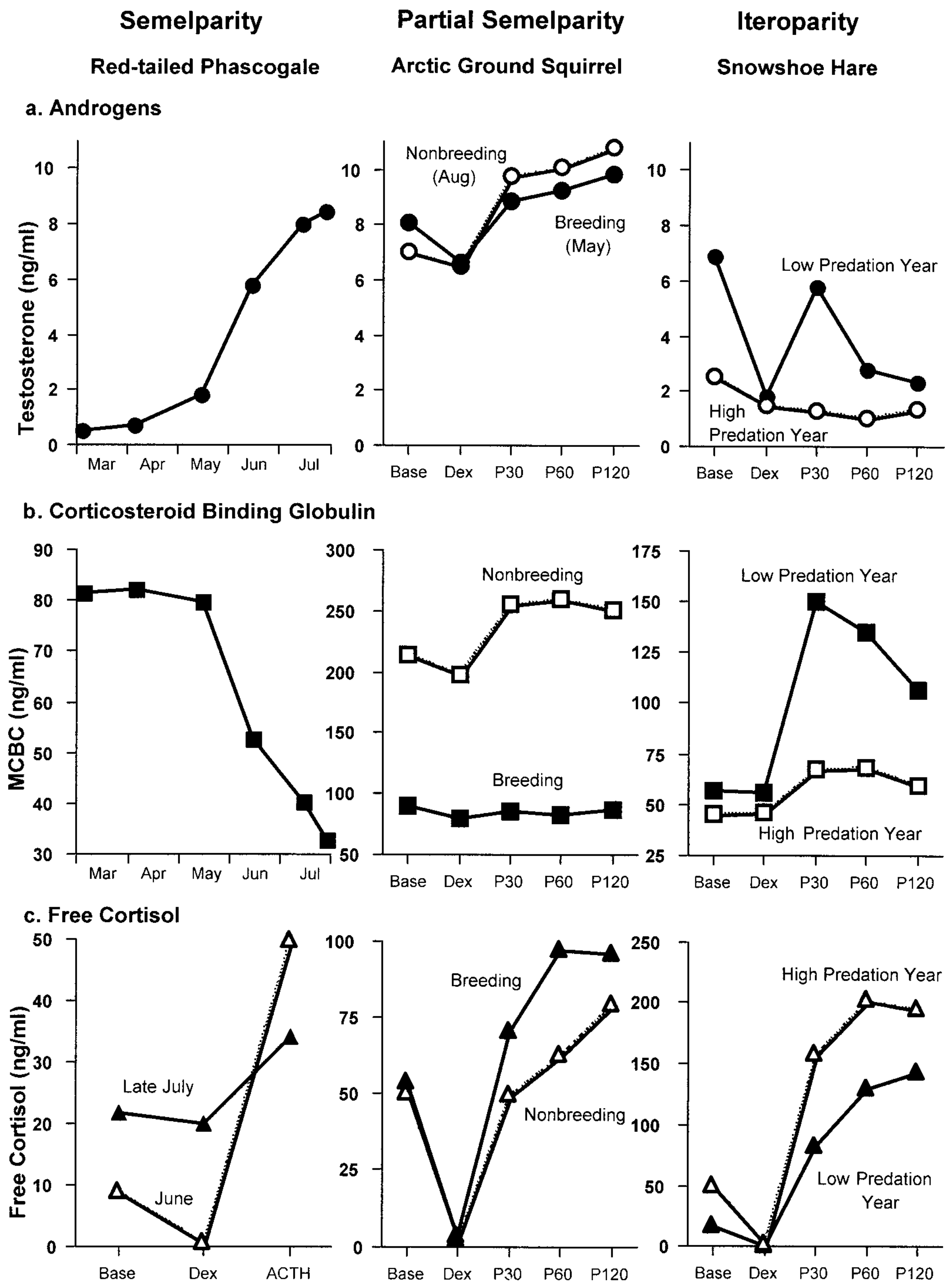

FIG. 2.—Life history variation in breeding frequency in male mammals and the associated endocrine plasma changes. In the red-tailed Phascogale (*Phascogale calura*), the top 2 panels (a and b) show sequential values obtained from field-captured males; the bottom panel (c) is data for males brought to the laboratory and subjected to the treatments indicated. Measurements from June occurred before the breeding season and those from late July occurred at the end of the breeding season. In arctic ground squirrels (*Spermophilus parryii*) and snowshoe hares (*Lepus americanus*), the hormonal-challenge protocol was used. Base levels indicate initial values; Dex indicates values 2 h after dexamethasone injection; and P30, P60, and P120 indicate values 30, 60, and 120 min after injection of adrenocorticotropic hormone (ACTH). In ground squirrels, breeding males (scrotal testes) were trapped in May and nonbreeding males (abdominal testes) were adults trapped in August. In hares, males were captured either during a year with high predation risk (1991) and hence were under chronic stress conditions or during a year with low predation risk (1994) and hence were experiencing low stress conditions. Means (but not standard errors—see original publications) are presented. Data for the red-tailed phascogale come from Bradley (1987, 1990), for arctic ground squirrels from Boonstra et al. (2001), and for snowshoe hares from Boonstra et al. (1998). Corticosteroid-binding globulin was measured as maximum corticosteroid-binding capacity (MCBC—see Boonstra and Boag [1992] for the method).

FIG. 3.—An arctic ground squirrel male photographed in spring 2002 before (26 April) and near the end of the breeding season (16 May). Its condition was monitored by livetrapping and radiotelemetry. Over this period, it lost 26% of its body mass (27 April, 680 g; 3 May, 625 g; 10 May, 540 g; 18 May, 500 g). On 10 May, it had numerous puncture wounds on the back of the neck and top of the head and the right side of the face was badly wounded. On 18 May it was limping. On 23 May it was located by radiotelemetry but disappeared that day and was presumed dead. Photographs by T. J. Karels.

period. Examples include some ground squirrels (Boonstra et al. 2001; Michener and Locklear 1990) and ungulates that breed just before winter followed by high mortality rates (e.g., Clutton-Brock et al. 1982; Festa-Bianchet 1989). The critical variable may not be the maximum lifespan, but rather the reproductive lifespan. I examine the male arctic ground squirrel (*Spermophilus parryii*), in which the stress response has been worked out in detail (Boonstra et al. 2001).

This ground squirrel is found throughout the alpine and mainland arctic areas of northern North America. These ground squirrels are medium-sized (ca. 500- to 1,000-g), diurnal, burrowing herbivores. They are obligate hibernators, emerging above ground from a 7- to 8-month hibernation in early to mid-April (Buck and Barnes 1999). During the brief northern summer, females have only sufficient time for 1 litter. Virtually all yearlings are reproductively mature and thus almost the entire population breeds each year. During the synchronized 2- to 3-week mating period, males compete intensely for access to females, roam widely, sustain severe injuries, eat less, and lose more weight than females. To avoid inbreeding, all adult males and all juveniles that will mature the next year disperse in summer to new sites (Byrom and Krebs 1999; Byrom et al. 2000). Females are long lived (up to 7 years in the Yukon—T. J. Karels, pers. comm.) and males short lived (most living no more than approximately 2 years—Gillis 2003).

Breeding males in May are chronically stressed during the mating period (Fig. 2). They have the highest concentrations of free cortisol and the lowest CBG concentrations (measured as the maximum corticosterone binding capacity) relative to adult males with abdominal testes from August (Boonstra et al. 2001). Dexamethasone resistance is modest and thus negative feedback regulation remains largely intact (Fig. 2, bottom panel). The ACTH challenge results in a rapid rise in free cortisol that exceeds those of nonbreeding males after 1 h. Unlike the responses of males in other species to dexamethasone and ACTH, testosterone concentrations remain high. ACTH injections actually cause testosterone levels to increase, not decrease, reaching higher concentrations than those at the baseline bleeding (Fig. 2, top panel) and this pattern is unique in mammals. Immunosuppression is pronounced, being reflected in the poorest ability to develop antibodies to the foreign antigen challenge (sheep red blood cells) and the lowest number of white blood cells.

The detrimental impact of breeding on male survival is dramatic, being immediate in some males and delayed in others. In the boreal forest, 48% of the male ground squirrels disappear during the mating season (Boonstra et al. 2001), whereas in an adjacent alpine area, 28% die (Gillis 2003). Older males (i.e., those who had gone through at least 2 breeding seasons) showed a higher rate of mortality (Gillis 2003), and also expend more effort on reproduction (more severe wounding and greater loss of body weight; Fig. 3) than yearling males (Gillis 2003). For those that survive the mating period, summer survival is high (Gillis 2003). However, despite apparent recovery in summer, more than one-half die while hibernating the next winter (Gillis 2003; Hubbs and Boonstra 1997), suggesting long-term consequences of the severe conflict during the previous spring. Again, older males tend to survive more poorly than yearling males at this time. The net result is that 80% of adult males die annually (Gillis 2003). Thus, the intensity of male–male competition during the mating season chronically stresses them and increases their mortality rate dramatically. However, unlike the total and immediate death of males found in the semelparous marsupials, the mortality is partial, age-dependent, and graded over time.

Iteroparity.—Iteroparity occurs in most mammals, with males having multiple mating opportunities over the length of their adult lives, either during 1 breeding season for species that live ≤1 year (e.g., voles and mice) or over multiple breeding seasons for long-lived species. I will examine the stress axis in 2 small mammals (a marsupial and a rodent) and 2 medium-sized mammals (a rodent and a lagomorph). The hormonal challenge protocol was carried out in the latter 2.

The fat-tailed dunnart (*Sminthopsis crassicaudata*) is a small (10- to 20-g), iteroparous dasyurid found throughout southern Australia from open woodlands to tussock grasslands. Some males survive through the 6- to 8-month breeding season and have 2 windows of opportunity to inseminate females, who breed twice. Free GC concentrations in males are always low during the breeding season because CBG levels (measured as maximum corticosteroid binding capacity) always exceed total plasma GC concentrations and show little change (McDonald et al. 1981). Although androgen concentrations are higher than in the antechinuses, no correlation occurs between androgen and CBG concentrations.

The meadow vole (*Microtus pennsylvanicus*) is an iteroparous small rodent (ca. 30–50 g) found throughout grasslands of central and northern North America. It has a promiscuous mating system, is short-lived (<1 year), and breeds continuously (ca. 3–5 litters per summer) throughout the summer and often into winter; young born early in the breeding season can mature in that season, and males are not territorial (see references in Hansen and Boonstra [2000]). Free GC concentrations in breeding males are usually low (ca. 5%), with CBG concentrations always exceeding total plasma corticosterone concentrations by about 3–4 times (Boonstra and Boag 1992). In breeding males, androgen concentrations are not correlated to CBG concentrations.

The red squirrel (*Tamiasciurus hudsonicus*) is an arboreal tree squirrel (ca. 250 g) whose distributional range covers the entire boreal forest of North America. It is highly territorial, asocial except during mating, has 1 or 2 litters per summer, has a sex ratio skewed toward males in the older age classes, and is long-lived (4–7 years; Obbard 1987). During the breeding season, males have very high concentrations of cortisol and CBG (5 and 7 times, respectively, those of Arctic ground squirrels—Boonstra and McColl 2000). They are dexamethasone resistant, with cortisol concentrations declining only to 33% of those at baseline (in nonresistant species, GC concentrations decline to ca. 5% or less). However, they do respond to ACTH with an increase in cortisol concentrations. The gonadal axis is very sensitive to the inhibitory effects of glucocorticoids. At the baseline bleeding, testosterone concentrations are negatively correlated to free cortisol concentrations and then decline markedly with the dexamethasone injection and remain low with the ACTH injection (which mobilizes cortisol). There is no correlation between testosterone and CBG concentrations. Immunologically, breeding male red squirrels have 4 times the numbers of white blood cells that arctic ground squirrels have. The proportion of lymphocytes was significantly lower (the lymphocyte to neutrophil ratio was lower in ground squirrels, indicative of immunosuppression acting through a lymphocytic effect of cortisol) and of eosinophils significantly higher (indicative of possible nematode infections) in ground squirrels than in red squirrels.

Snowshoe hares (*Lepus americanus*) are medium-sized mammals (ca. 1,500–1,800 g) that live throughout the boreal forests of North America, are nonterritorial, have up to 4 litters per year, 1st breed in the year after their birth, have even sex ratios throughout life, and live up to 5 years (Hodges 1999; Hodges et al. 2001). Their populations are characterized by 10-year cycles and, during the decline, hares suffer chronically high predation risk because predators kill most of them (Krebs et al. 2001) and their stress axis reflects this chronic stress in high-predator years (Fig. 2; Boonstra et al. 1998). However, in low-predator years (Fig. 2), breeding males exhibit the typical mammalian response to the hormonal challenge protocol; and they respond dramatically both to the dexamethasone injection (free cortisol concentrations declining to 5% of those at the base bleed) and to the ACTH injection (free cortisol concentrations increasing to 3 times those at the base bleed). Testosterone concentrations are inhibited by high GC concentrations (Fig. 2), resulting both from the dexamethasone injection and from the ACTH injection (which stimulates cortisol release). However, note that in the low-predator year, the ACTH injection resulted in a temporary pulse of testosterone, before it dropped again, characteristic of good-condition animals (see references in Boonstra et al. [1998]). At the base bleeding, testosterone concentrations are not correlated to CBG concentrations in breeding animals (R. Boonstra, pers. comm.). Finally, the immune system remains functional under low stress conditions (Boonstra et al. 1998).

Summary.—The general pattern for breeding males in iteroparous species (in contrast to most of the semelparous ones) is that the gonadal axis is inhibited by high GC concentrations, resulting in declines in testosterone; that high testosterone concentrations do not drive down CBG levels; that dexamethasone resistance, although it may occur under chronic stress conditions, is not the rule under normal conditions; and that immunosuppression does not occur as a normal condition. Thus, the negative feedback system continues to function well. The negative feedback system also continues to function in the partially semelparous arctic ground squirrels, but as in the semelparous marsupials, the gonadal axis becomes insensitive to the inhibitory effects of high GCs and testosterone levels remain high. The consequences for both of these groups is that free GCs increase, but especially so in the semelparous species. Immunosuppression also occurs in both groups but especially in the semelparous species.

CONSTRAINTS ON THE STRESS RESPONSE

Phylogeny.—Schaffer (1979) argued that the dichotomy between the iteroparous Pacific salmon (*Oncorhynchus*) and the semelparous Atlantic salmon (*Salmo salar*) was not related to severity of the costs of migration in their respective habitats, but rather to phylogenetic and physiological constraints. In mammals, semelparity is indeed phylogenetically constrained, occurring only in 2 large families of carnivorous marsupials, the

Dasyuridae and Didelphidae (Armstrong et al. 1998; Cockburn 1997). Oakwood et al. (2001) proposed that members of these families exhibit an unexplained phylogenetic predisposition toward semelparity and that the stress-axis machinery needed to make it happen are secondary modifications of this tendency.

Seasonality and habitat.—Semelparity and partial semelparity occur in highly seasonal habitats and 3 potential factors related to seasonality could select for the associated suite of adaptations of the stress axis. First, high predictability of seasonality has been proposed for the evolution of semelparity in the marsupial groups (Lee and Cockburn 1985), with many species confined to the coastal fringe of Australia. However, this argument is difficult to apply to other marsupial species (Cockburn 1997) such as the quoll, which has a much wider distributional range. In the arctic ground squirrels, strong seasonality is obvious but predictability may be low. Snow cover can vary in winter, affecting survival in the hibernacula (Gillis 2003), and weather conditions can vary in the active season, affecting reproduction (e.g., snowmelt is delayed in spring because of a late snow storm or cold conditions—Hubbs and Boonstra 1997). Second, Braithwaite and Lee (1979) argued that semelparity in the marsupials was directly related to the prolonged period required for females to wean the 1st litter and that there was simply insufficient time to try for a 2nd. This is echoed in ground squirrels, where 60–75% of the active season is required to raise the 1st litter to independence. In contrast, many small and medium-sized mammal species living in seasonal environments, but not having the added constraint of hibernation, can have multiple litters (e.g., voles can have ≥ 3 litters per summer and snowshoe hares can have 4 litters). However, hibernation is not the key factor selecting for an adaptive stress response. In a related, slightly smaller, hibernating ground squirrel species (the Columbian ground squirrel [*Spermophilus columbianus*]) from the Rocky Mountains of Alberta, Canada, males live at least 6 years (Neuhaus and Pelletier 2001). Body mass also is irrelevant, because both smaller hibernators (e.g., jumping mice [*Zapus* species], which have an active-season mass of 16–22 g and male lifespan of up to 3 years—Cranford 1983; Hoyle and Boonstra 1986; and little brown bats [*Myotis lucifugus*], which have an active-season mass of 7–9 g and lifespan of up to 30 years—Keen and Hitchcock 1980), and larger ones (e.g., the yellow-bellied marmot [*Marmota flaviventris*], which has an active-season mass of 3–4 kg and male lifespan of up to 9 years—Frase and Hoffmann 1980; Schwartz et al. 1998) are iteroparous. Third, mating may occur at a time that is optimal for females, but not for males, with the result that less food is available to males either to sustain or to replenish energy required for reproduction. High GC concentrations permit the replacement of external food resources with internal body reserves through the mobilization of energy by gluconeogenesis. Breeding in *Antechinus* and *Phascogale* occurs in late winter when it is comparatively more difficult to obtain food and in places away from normal foraging areas (Cockburn 1997). Thus, to maximize mating opportunities, these animals rely heavily on body reserves to sustain themselves and thus they lose mass (Lee and Cockburn 1985). In arctic ground squirrels, mating in the alpine region occurs when snow still covers all or most of the ground and thus males must rely either on body stores or underground caches. However, in both the quoll and the opossum, the males continue to forage, although the quoll (Oakwood et al. 2001), but not the opossum (Woods and Hellgren 2003), does lose mass. Hence, the energetic arguments may be sufficient but not necessary for semelparity to evolve.

Mating systems.—In all cases where semelparity or partial semelparity occurs, the mating system is one in which intense, direct aggression occurs among males for access to females and male territoriality either is not present or breaks down. Male mammals exhibit a wide range of mating systems from monogamy to various types of polygyny (Clutton-Brock 1989). An adaptive stress response would be expected in situations of nondefense polygyny (Dobson 1984), where the females are defended directly either individually or in dominance hierarchies, but not in mating systems where the territory holder has exclusive mating access to females (monogamy and various types of resource-defense polygyny). In *Antechinus stuartii*, breeding takes place in communal congregations (Lazenby-Cohen and Cockburn 1988). It is the conflict between breeding males that drives up ACTH and with it, the free cortisol concentrations, leading to death (Scott 1987). In the laboratory, isolated males of this genus can live 18–24 months (Lee and McDonald 1985) and up to 4 years in *A. subtropicus* (Bradley 2003). In the arctic ground squirrel, male territoriality occurs, helping to assure the territorial holder 1st mating of females on the territory most of the time (71%—Lacey and Wieczorek 2001). However, conflict between males is intense for the 1st copulation (90% of the offspring are sired from the 1st copulation—Lacey et al. 1997), sometimes resulting in wounds severe enough to cause death (Gillis 2003; Watton and Keenleyside 1974). Although territoriality is common among the ground squirrels, multiple paternity and the associated conflict among breeding males also occurs frequently in most species (see references in Lacey and Wieczorek [2001] and Murie [1995]). In spite of this, males in other species of ground squirrels live much longer than male arctic ground squirrels. Male Columbian ground squirrels are territorial, but females mate with an average of 4 males (a minimum of 16% of litters are multiply sired—Murie 1995; Murie and Harris 1978), yet adult males live up to 6 years (Neuhaus and Pelletier 2001). Thus, although a mating system resulting in direct male–male aggression may be necessary for semelparity or partial semelparity to evolve, it is not sufficient.

Reproduction versus survival.—The circularity between whether reproduction or survival drives a species toward semelparity has not been resolved by a simple appeal to theory (Roff 1992). Is a semelparous or partially semelparous life history and a stress response dedicated to that end a consequence of low expectation of adult survival or of extreme costs of reproduction? Theory indicates that high adult mortality and low juvenile mortality will favor semelparity (Stearns 1992). The relevant period for this mortality to act would be that that occurs during the nonreproductive season. On the other hand, the costs of reproduction may be so great that the evolution of semelparity is inevitable because no energy remains afterward, as is the case in Pacific salmon. The reason for the evolutionary decision to commit all resources to 1 reproductive event rather than spread them out over multiple events is not obvious. We cannot resolve this ''which came 1st, the chicken or the egg'' problem by examining purely semelparous populations. Rather we need to look at the stress response in populations within species or among closely related species where a range of mortality patterns is found.

Poor survival independent of reproduction may select for a strategy to commit maximal resources to the 1st mating season as the expectation of future ones is low. For example, in the long-lived Columbian ground squirrel from mid-latitude mountain areas, annual winter survival of adult males is more than 90% (Neuhaus and Pelletier 2001) versus only 17–50% in the short-lived arctic ground squirrels from high-latitude mountain areas (Gillis 2003; Hubbs and Boonstra 1997). Mammals on islands typically have higher survival rates than those on the adjacent mainland and this has been tied to lower rates of predation on islands (Adler and Levins 1994; Palkovacs 2003). If males have a higher probability of survival from one year to the next, this may select for a more iteroparous life history and thus more of a homeostasis stress response. Although the males of the dasyurid *Parantechinus apicalis* are semelparous on the Australian mainland, those on islands sometimes survive to breed a 2nd or 3rd year (see references in Bradley [2003]).

If high costs of reproduction are the culprit, removing these costs by preventing males from breeding in the 1st place by castrating them should enhance survival and thus lifespan. Castrated male *Antechinus* in the field can live beyond the normal time of death of intact males, but we do not know their lifespan (Bradley 2003). In the Soay sheep (*Ovis aries*), a promiscuous species with a consort mating system involving sequential pairing with individual females, the mean life span for males that have attained 6 months of age is 2 years (Stevenson and Bancroft 1995), which is similar to that of arctic ground squirrels. Castration of Soay sheep as lambs can extend male lifespan to almost 17 years (Jewell 1997). Young males will attempt to breed in their 1st year (at 7 months); temporary hormonal castration of these juveniles just before the rut significantly improves their survival during the following winter (Stevenson and Bancroft 1995). Thus, overwinter survival is contingent on reproductive status during the breeding season (i.e., there is a cost of reproduction). We do not know how the stress axis responds during the rut in these sheep, but predict it to be similar to ground squirrels.

FUTURE DIRECTIONS

We understand the functioning of the stress axis relative to differences in life-history strategies in very few mammal species. I suggest 4 areas that will advance the field. First, examine more species, particularly those in which reproductive lifespans may be short, such as in some ungulates. Second, to give fundamental insight into forces selecting a suite of stress-axis traits, it would be most informative to target a group such as ground squirrels that inhabit a wide range of environmental conditions in terms of severity and predictability, exhibit variation in mating systems, and experience variation in longevities. Third, study populations within a species known to differ in degree of semelparity (e.g., on islands versus mainlands or among populations on the mainland). Finally, my discussion of the variation in the stress response in mammals has ignored females, largely because few studies have been carried out on them in the wild and it may be difficult to do without compromising reproduction. However, a complete understanding of the adaptive responses of the stress axis that can evolve in females as a function of life history is critically needed.

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