



Review article

Stress, sleep, and sex: A review of endocrinological research in *Octodon degus*Carolyn M. Bauer^{a,*}, Loreto A. Correa^{b,c}, Luis A. Ebensperger^c, L. Michael Romero^d^a Biology Department, Adelphi University, Garden City, NY, USA^b Escuela de Medicina Veterinaria, Facultad de Ciencias, Universidad Mayor, Santiago, Chile^c Departamento de Ecología, Facultad de Ciencias Biológicas, P. Universidad Católica de Chile, Santiago, Chile^d Department of Biology, Tufts University, Medford, MA, USA

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ABSTRACT

The Common Degu (*Octodon degus*) is a small rodent endemic to central Chile. It has become an important model for comparative vertebrate endocrinology because of several uncommon life-history features – it is diurnal, shows a high degree of sociality, practices plural breeding with multiple females sharing natal burrows, practices communal parental care, and can easily be studied in the laboratory and the field. Many studies have exploited these features to make contributions to comparative endocrinology. This review summarizes contributions in four major areas. First are studies on degu stress responses, focusing on seasonal changes in glucocorticoid (GC) release, impacts of parental care on offspring GC responses, and fitness consequences of individual variations of GC responses. These studies have helped confirm the ecological relevance of stress responses. Second are studies exploring diurnal circadian rhythms of melatonin and sex steroids. These studies have formed important work translating circadian biology from nocturnal laboratory rodents to diurnal humans. Third are studies that exploit the open nature of degu natural habitat, combined with laboratory studies, to explore the impact of testosterone on agonistic behavior. Studies have focused primarily on male:male, female:female, male:female, and parental behaviors. Fourth, are contributions to the study of female masculinization from male siblings in the uterus. These studies have focused on both the behavioral consequences of masculinization and the impact of those behaviors on fitness. Taken together, the studies reviewed here have formed a strong foundation for further studies in the degu so that future studies can address how endocrinological components underlie new mechanistic connections to the ecological effects on behavior and fitness.

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1. Introduction

The Common Degu (*Octodon degus*) is a caviomorph semi-fossorial rodent. Degus are endemic to central Chile, where they experience a Mediterranean climate of cool, wet winters and hot, dry summers. The matorral is the preferred habitat for degus, which is typified by large, open grassy areas with scattered acacia trees (*Acacia cavens*) and shrubs.

Degus mate at the beginning of the austral winter when winter precipitation boosts vegetative growth. After a 3 month gestation period, female degus give birth to a mean of six precocial young during peak food availability in early spring (Ebensperger and Hurtado, 2005). Females lactate for about 1 month after parturi-

tion, after which offspring become independent (Ebensperger et al., 2007). Occasionally, females can get pregnant immediately after parturition, and may have a second litter during early summer (Ebensperger et al., 2013). Precipitation generally decreases throughout the austral spring, thus causing low food availability during the subsequent austral summer and autumn, which is when 60–70% of mortality occurs. Generally, degus do not surpass 2 years of age in the wild (Ebensperger et al., 2013).

Degus are plural breeders, meaning that several females share one or more underground burrow systems where they raise their offspring together (Ebensperger, 1998; Ebensperger et al., 2014, 2002). Communal parental care is also practiced by degus, where females will provide care such as thermoregulatory huddling, licking, grooming, and even nursing for group member's offspring (Ebensperger et al., 2010, 2006). Degus remain highly social year-round, and social groups may range from 1 to 12 members,

* Corresponding author at: Biology Department, Adelphi University, 1 South Ave, Garden City, NY 11530, USA.

E-mail address: cbauer@adelphi.edu (C.M. Bauer).

including multiple female and male members, and female-male pairs (Ebensperger et al., 2009; Hayes et al., 2009).

In this review, we summarize the contributions of research in degus towards the field of comparative endocrinology. Specifically, we focus on degu endocrinological studies in four different areas including 1) stress, 2) circadian rhythms, 3) reproductive behavior, and 4) female masculinization (Fig. 1). We include studies from both the field and the laboratory, as degus have been well-studied under both conditions.

2. Stress endocrinology

Degus have proven to be a popular model organism for studies in stress endocrinology. Because degus live in a highly seasonal environment, they have been a suitable system for examining seasonal rhythms in stress hormone levels. By measuring different components of the endocrine stress response, several studies have used degus to correlate seasonal rhythms of glucocorticoids (GCs) with different life history challenges (Bauer et al., 2014; Kenagy and Place, 2000; Quispe et al., 2014; Soto-Gamboa et al., 2005). Degus have also been a popular model organism for studies examining how early life conditions affect development of the endocrine stress response. This is partly because parental care behaviors, which have strong effects on post-natal development of the endocrine stress response (Francis et al., 1999; Liu et al., 1997), are very frequent in degus during the first few weeks following parturition (Bauer et al., 2016; Ebensperger et al., 2010, 2006). Additionally, degus are also excellent models for post-natal development of the stress response because they are plural breeders that practice communal care, which provides a unique opportunity to examine the relative importance of care from fathers (Braun et al., 2013; Gos et al., 2014; Seidel et al., 2011) and other group members (Bauer et al., 2016, 2015; Ebensperger et al., 2017). Finally, degus are also an excellent model system for examining relationships between the endocrine stress response and fitness because researchers can obtain relatively good fitness estimates from wild populations (Ebensperger et al., 2016, 2013).

Degus are an amenable study system for stress studies in that they are relatively easy to trap (Burger et al., 2009; Lapointe et al., 2015), do not disperse far from their birth site (Quirici et al., 2011), and typically do not live more than 2 years (Ebensperger et al., 2013). Additionally, degus experience highly variable environmental conditions (Ebensperger et al., 2014), which allows the chance to investigate how relationships between fitness and the endocrine stress response may vary between years and under different environments.

The vertebrate stress response is essential for helping animals appropriately respond to environmental stimuli. Glucocorticoids (GCs), are one of the primary classes of hormones of the endocrine stress response. They affect numerous physiological processes

including metabolism, reproduction, immune function, and cardiovascular performance (Romero and Wingfield, 2016). At baseline levels, GCs primarily bind to high-affinity receptors (mineralocorticoid receptors) where they mostly have permissive actions (e.g. priming the flight-or-fight response) (Sapolsky et al., 2000). After stress exposure, GCs rapidly increase and begin binding to low-affinity receptors (glucocorticoid receptors) where they may exert stimulatory, suppressive, or preparative actions depending on the physiological system and environmental context (Sapolsky et al., 2000). GC release is stimulated by adrenocorticotrophic hormone (ACTH), which is secreted by the pituitary, and in turn is stimulated by corticotropin-releasing factor (CRF) and arginine vasopressin (AVP), which are primarily secreted by the hypothalamus (Sapolsky et al., 2000).

In degus, the predominant GC is cortisol (CORT) (Kenagy et al., 1999), although there is evidence that the adrenal glands also produce very low concentrations of corticosterone (Galli and Marusic, 1976; Gruss et al., 2006; Kenagy et al., 1999). In this review, we examine how research on degu stress endocrinology has contributed to our understanding of 1) the seasonality of the endocrine stress response, 2) effects of early life stress, and 3) relationships between the stress response and fitness.

2.1. Seasonality of the endocrine stress response

Under wild free-living conditions, most vertebrate species seasonally modulate baseline and stress-induced GC release (Romero, 2002; Romero et al., 2008). Documenting these seasonal rhythms allows inferences to be made about which predictable environmental conditions may cause animals to be more sensitive or reactive to stressors. Additionally, from a conservation standpoint, knowledge of seasonal rhythms may help determine times of year when at-risk populations are most sensitive to stress. While seasonal GC rhythms have been well-described in many bird and reptile species, less is known about mammals (Romero, 2002). One of the aims of this review is to synthesize different studies in wild, free-living degus (see Table 1) to obtain a consensus for the degu seasonal CORT profile.

For baseline CORT levels, we only considered studies where blood samples were obtained within 3 min of trapping the animal, as CORT levels rapidly increase 3 min after stress exposure (Romero and Reed, 2005). Combining results from these studies (Bauer et al., 2014; Quispe et al., 2014), we found little variation in baseline CORT across the whole year (Fig. 2). However, Quispe et al. (2014) observed that baseline CORT levels tended to be lower during the end of the non-breeding season compared to the mating season. Baseline CORT concentrations were similar between males

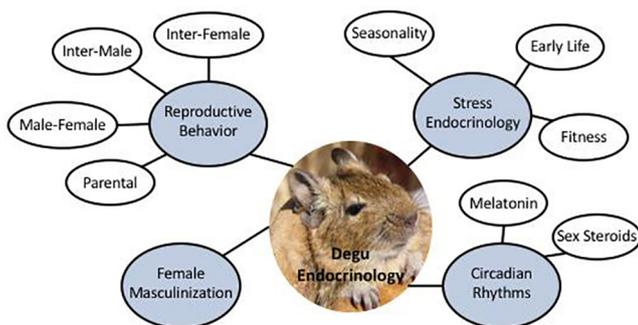


Fig. 1. Summary of major endocrine themes studied in degus.

Table 1

Four different studies have measured seasonality of the degu stress response using a combination of baseline (BL) and stress-induced (SI) cortisol samples and negative feedback measures on both males and females. Relative life history stages (LHS) include non-breeding (November–April), mating (late May–early July), late pregnancy (late August–early September), the first bout of lactation (late September–early October), and the second bout of lactation (late December–early January).

Study	Sample	Male LHS	Female LHS
Kenagy, Place, and Veloso (1999)	SI	Mating, lactation	Non-breeding, mating, lactation
Soto-Gamboa et al. (2005)	SI	Non-breeding, mating	
Quispe et al. (2014)	BL, SI	Non-breeding, mating	Non-breeding, mating
Bauer et al. (2014)	BL, SI, Negative Feedback	Non-breeding, mating, late pregnancy	Non-breeding, mating, late pregnancy, 1st lactation, 2nd lactation

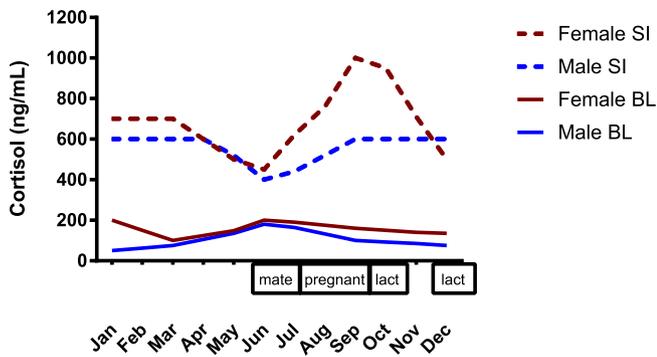


Fig. 2. Consensus seasonal patterns of baseline (BL) and stress-induced (SI) cortisol levels in male and female degus. Life history stages (in boxes) are as follows: mating (late May–early July), pregnancy (early July–mid September), first bout of lactation (mid September–late October), second bout of lactation (late November–early January), and non-breeding (November–early May).

and females over the entire year except during the early non-breeding period, where females have higher levels.

For stress-induced CORT levels, we used studies that took blood samples within 2 h of capture (i.e. animals had either been in traps for an undisclosed amount of time, or were sampled 30 min after baseline sample). Studies examining more than two life history stages found significant sex differences in stress-induced CORT; compared to males, females had higher stress-induced CORT levels during pregnancy and the first bout of lactation (Bauer et al., 2014; Kenagy et al., 1999). Both sexes showed significant seasonal variation in stress-induced CORT. For females, stress-induced CORT was highest during late pregnancy and lactation, and then steadily declined over the non-breeding season to a nadir during the mating season (Fig. 2). Low stress-induced CORT levels were also observed in females that underwent a second bout of lactation (Bauer et al., 2014). Males tended to have lower stress-induced CORT levels during the mating season compared to the rest of the year (pregnancy, lactation, and non-breeding).

Negative feedback efficacy is another important component of the endocrine stress response, as weak negative feedback causes individuals to be exposed to higher, integrated amounts of CORT, thus increasing the risk of pathology. However, Bauer et al. (2014) found no significant seasonal variation or sex differences in degu negative feedback efficacy.

Two prevailing hypotheses are used to explain seasonal variation in GC release (Romero, 2002). The Energy Mobilization Hypothesis proposes that, because baseline levels of GCs facilitate energy mobilization, baseline GC levels should be highest during times of year that are most energetically expensive. The Preparative Hypothesis posits that, because GCs mediate the stress response, GC levels should be highest during times of year when there is a greater chance of encountering stressors. It should be noted that these two hypotheses are not mutually exclusive.

Under the Energy Mobilization Hypothesis, it's predicted that baseline CORT should be highest during lactation for females and during mating for males (Bauer et al., 2014), as these are generally the most energetically expensive life history stages for each sex (females, Speakman, 2008; Veloso and Bozinovic, 2000; males, Boswell et al., 1994; Ebensperger and Hurtado, 2005; Soto-Gamboa et al., 2005). However, as neither male nor female baseline CORT levels significantly vary with season, findings from degus do not support the Energy Mobilization Hypothesis.

According to the Preparative Hypothesis, both baseline and stress-induced CORT levels should be highest during times of year when animals have a greater chance of encountering stressors. For both males and females, it is predicted that one of these seasons

would be the austral spring (corresponding to pregnancy and first bout of lactation, Fig. 2), as degus are most susceptible to predation during this time of year (Bauer et al., 2014). It is also predicted that males would have high baseline and stress-induced CORT levels during the mating season, due to increased agonistic interactions (Ebensperger and Hurtado, 2005; Soto-Gamboa et al., 2005). Our consensus degu CORT profile only partially fits the predictions of the Preparative Hypothesis—female stress-induced CORT levels were highest during the austral spring, although male stress-induced CORT levels were not highest during the austral spring and mating season, and baseline CORT levels did not seasonally vary for either sex. Bauer et al. (2014) proposed that seasonal stress-induced CORT patterns may be better explained by “energy balance,” as female and male stress-induced CORT levels are highest during times of year with plentiful food.

2.2. Early life stress

The degu has also been a popular model organism for examining potential long-term effects of early life stress, particularly the consequences of reduced parental care on the development of the offspring stress response. The quality and quantity of parental care may have especially strong effects on degu pup development, as offspring receive care over an extended period (4 + wks) from several different adults (social groups range from 1 to 12 adults). These forms of care can include thermoregulatory huddling, licking, grooming, retrieving, and nursing (Ebensperger et al., 2010, 2006). While parental care influences the development of many different physiological and behavioral functions in offspring, the endocrine stress response is especially known for being sensitive to parental care quality (Liu et al., 1997). Work in laboratory rodents has shown that certain amounts of parental licking and grooming are necessary for proper development of the offspring stress response (Francis et al., 1999; Liu et al., 1997). Pups receiving insufficient amounts of licking and grooming increase GC secretion, which can then alter development of the stress response by modifying epigenetic processes in the brain (Francis et al., 1999). Typically, these pups develop hyper-reactive stress responses, which are characterized by heightened CORT secretion in response to stressors and weak negative feedback. Ultimately, these hyper-reactive stress responses cause pups to be exposed to higher, integrated amounts of CORT, which has been linked to fitness consequences (Cottrell and Seckl, 2009; Matthews and Phillips, 2010; Monaghan et al., 2012). Here, we review 1) how parental care quality affects development of the degu pup stress response, and 2) how stress affects parental care quality in adult degus.

Several studies have examined how parental separation influences the density of CRF-expressing neurons in different brain regions in male degu pups (Becker et al., 2007; Gos et al., 2014; Seidel et al., 2011). Parental separation included either daily 1 h isolation from all parents and littermates from 1 to 21 days after birth (Becker et al., 2007), or complete removal of the father from the day after birth (i.e. pups were only housed with their own mother and littermates, Gos et al., 2014; Seidel et al., 2011). Both forms of parental separation caused significant changes in the density of CRF-expressing neurons in several regions of the limbic system at 21 days of age. Specifically, the two studies examining paternal separation found decreased CRF-containing neuron density in the dentate gyrus and medial bed nucleus of the stria terminalis (BNST), and increased density in the lateral orbitofrontal cortex, ventromedial orbitofrontal cortex, and basolateral amygdala complex at 21 days of age (Gos et al., 2014; Seidel et al., 2011). However, out of these five brain regions, differences caused by paternal separation were only maintained in the BNST at 90 days of age. This suggests that paternal deprivation may only cause transient changes in CRF-expressing neuron density, and/or that

processes later in life may ameliorate paternal deprivation. However, as degus typically live in social groups with multiple adult members, future studies are needed to assess whether these developmental effects can also be caused by removal of other adults within the group.

Repeated parental separation was also used in a study examining the development of offspring CORT profiles (Gruss et al., 2006). This study found no differences in baseline CORT levels at 21 days of age between un-manipulated pups and those that were separated for 1 h per day since birth. However, CORT levels measured after the final 1 h separation (i.e. stress-induced CORT) at 21 days of age were lower in female pups that experienced repeated separation (no difference was found in male pups). While the repeated stress of separation may have affected development of female pups' CORT response to all stressors, it is difficult to rule out that pups may have simply habituated to daily separation (Cyr and Romero, 2009).

Bauer et al. (2015, 2016) also examined how parental care affects development of the offspring stress response in degus, but used parental implantation with CORT pellets (after parturition) and captivity stress to manipulate parental care quality. In the wild, Bauer et al. (2015) found that pups from social groups where all adult females were implanted with CORT pellets had lower baseline CORT than pups from social groups where only some or none of adult females had CORT implants. Additionally, among male pups, weaker negative feedback was detected in those from groups where all adult females received CORT implants. These findings suggest that post-parturition implantation of CORT may impact maternal care, but that effects on the offspring stress response can be ameliorated if un-implanted adult females are within the social group. This relationship is further supported from a companion lab study (Bauer et al., 2016) that found maternal stress in the lab also caused weaker negative feedback in both male and female offspring and that this effect was likely regulated by the amount of maternal licking, grooming, and other forms of contact.

Bauer et al. (2016) also examined how maternal stress affected rates of different maternal care behaviors. Maternal stress was manipulated by transference to captivity; “stressed” females were caught in the wild and transported to captivity during the last trimester of gestation, while “unstressed” females had either been born in captivity or housed in captivity for at least 9 mo. Compared to unstressed mothers, stressed mothers had significantly lower rates of pup contact behaviors, which included licking, grooming, and other affiliative behaviors initiated by the mother. Stressed mothers also had much lower rates of pup retrievals compared to unstressed mothers, although the amount of time on the nest did not differ between groups. In a different laboratory study, however, Ebensperger et al. (2010) did not find a correlation with circulating, baseline CORT levels and rates of maternal care in un-manipulated laboratory females. This may suggest that maternal care rates are only affected when mothers face significant biological or ecological stressors.

Most recently, Ebensperger et al. (2017) addressed whether nonbreeding female group members can buffer offspring from socially stressful postnatal conditions. During this experiment, mothers either experienced prenatal social instability (by means of rotation of group members), or complete stability. Offspring were exposed to periodic removal of all adults, nonbreeding females, or their mother exclusively. Nonbreeding females of socially unstable groups exhibited less alloparental care, and thus, offspring received less parental care overall. This study implies that prenatal social instability may compromise the ability of other female group members to support offspring during postnatally stressful conditions (Ebensperger et al., 2017). Intriguingly, neither social instability nor postnatal social challenges influenced stress reactivity of offspring.

Together, these findings indicate that maternal stress may decrease rates of maternal care, which may directly affect development of the offspring stress response. In addition to maternal stress, prenatal social instability may also negatively affect alloparental care. More studies are needed, however, to determine whether these altered stress responses result in decreased fitness, and how group members other than the mother may ameliorate these effects. Alternatively, maternal stress may act as a mechanism to adaptively program offspring stress responses for challenging environments (Dantzer et al., 2013; Love et al., 2013). And finally, while individual degu stress profiles have been shown to be repeatable in the short-term (Lapointe et al., 2015), future studies also need to examine if this is also true over the degu's entire lifespan so we can better predict the consequences of certain stress profiles on lifetime fitness.

2.3. Stress and fitness

The endocrine stress response, also referred to as the hypothalamic-pituitary-adrenal (HPA) axis, plays a central role in mediating animal responses to ecological and social stressors (Romero and Wingfield, 2016). Since these responses may involve multiple measures of performance, including behavior, metabolism, immunocompetence, growth, and reproduction (Breuner, 2008; Jessop et al., 2013), these generalizations have led to predicted associations between components of the endocrine stress response and measures of fitness (Beehner and Bergman, 2017; Bonier et al., 2009b; Breuner, 2008). Accordingly, studies reporting associations between stress hormones and fitness have slowly accumulated over recent years. A dominant view emerging from these studies is that connections between components of the stress response and fitness may be indirect and modulated by environmental and individual factors (Dantzer et al., 2016). In particular, studies conducted mostly on birds and reptiles highlight how stress hormone-fitness associations vary with ecological context (e.g., food availability), and individual condition (e.g., body weight, reproductive stage) and attributes (e.g., sex, coping style, reproductive strategy) (Bokony et al., 2009; Bonier et al., 2009a; Breuner, 2008; Dantzer et al., 2016; Hau et al., 2010).

Examination of these connections in degus come from field studies where CORT levels have been estimated from glucocorticoid metabolites in the feces (fGCM), and fitness estimated from measures of reproductive success and adult survival. These studies show that females with higher fGCM during early lactation produce more per capita offspring that survive to weaning and to breeding age (Ebensperger et al., 2011). These associations do not seem to be influenced by mean yearly ecological conditions in the population. Occasionally, female degus may breed twice within the same year as a consequence of postpartum estrus, and findings indicate that the probability of females to produce a second litter decreases with increasing fGCM during early lactation of their main breeding event (Ebensperger et al., 2013). In contrast to estimates of reproductive success, fGCM during early breeding does not predict female or male survival to breeding time during the next year (Ebensperger et al., 2013). Instead, fGCM levels in females predict variation in immunocompetence. Females with higher fGCM during their main lactation event increase lymphocytes and monocytes in circulation relative to other measures of immunocompetence, and females with lower fGCM show an increase in neutrophil to lymphocyte ratios, neutrophils, and total G immunoglobulins (Ebensperger et al., 2015). Together, these results support a stronger connection between CORT levels and breeding effort (in the females) than with adult survival. We have hypothesized how these findings represent physiological adjustments needed to sustain maximum breeding within the constraints imposed by the mostly semelparous life-history of these

animals, as 90% of adult individuals only survive long enough to breed once (Ebensperger et al., 2015). Females need to keep high levels of CORT and some components of immunocompetence to sustain a greater number of offspring during lactation and offspring rearing, but at the cost of failing to produce a second litter (Ebensperger et al., 2015). Intriguingly, available studies do not support modulatory roles of overall ecological conditions or individual attributes (e.g., sex) on hormone-fitness associations. However, studies still need to determine how degu density, social instability, food availability, and predation risk may be playing such roles. Some of these factors are already known to modulate social effects on degu reproductive success (Ebensperger et al., 2016, 2014).

Social context (e.g., extent of sociality), including the array of social interactions involved, remains an important environmental condition that may further modulate hormone-fitness associations. In social or group-living species the presence of multiple adult conspecifics may ameliorate (i.e., “buffer”) the behavioral, hormonal, or immunological responses of other group members and offspring exposed to physical or socially challenging conditions (Branchi et al., 2013; Cohen and McKay, 1984). However, individuals in groups also may experience enhanced challenging conditions due to competition over critical resources (food, mates) and experience agonistic interactions (Pride, 2005). Thus, the number of adult group members (i.e., group size) is expected to modulate the connection between components of stress response and fitness (Pride, 2005). Contrary to this expectation, neither group size nor the number of females (two proxies of sociality) influence female degu CORT levels (Ebensperger et al., 2011). A recent study further examined how growth and the endocrine stress response were affected in weaned offspring whose mothers were members of stable or unstable groups (Ebensperger et al. 2016). Results revealed that offspring of socially stable groups grow at faster rates compared with offspring of unstable groups. Intriguingly, this social effect on offspring quality was associated with reduced care by females other than the mother, but not with variation in the endocrine stress response of the offspring (Ebensperger et al. 2016). Collectively, these findings contrast with the relatively abundant evidence from neuroendocrinological studies, which conclude that altered social conditions during early development shapes the reactivity of the HPA axis and subsequent social interactions (Colonnello et al., 2016, 2011). Thus, endocrine signals of these social effects on fitness are not always evident, suggesting that other factors play roles. In particular, some current studies are aimed to examine how variation in the endocrine stress response tracks fitness is contingent upon the matching between juvenile and adult environments (Bateson et al., 2014; Breuner, 2008).

On the other hand, the probability of offspring dispersal in degus rises with increasing number of offspring per burrow system (a measure of competition within communal litters), and offspring raised in relatively large communal litters tend to exhibit higher levels of fGCM (Quirici et al., 2011). Thus, degus provide additional, multiple social contexts and opportunities to examine links between CORT levels, competition within communal litters during postnatal development, decision to disperse, and subsequent fitness effects.

3. Circadian rhythms

Degus have been an attractive model organism for circadian rhythm research for several reasons. One is that they are diurnal, which makes them a more relevant study system for human-related disorders such as jet-lag (Mohawk et al., 2005). Degus are also relatively easy to maintain and breed in the lab (Long and

Ebensperger, 2010), and their activity can be monitored via standard methods. Similar to humans, degus also show changes in their activity patterns around the time of puberty (Hagenauer et al., 2011). This has inspired studies examining the organizational and activational effects of sex steroid hormones on circadian rhythms in a diurnal rodent system (Hagenauer et al., 2011; Hummer et al., 2007; Jechura et al., 2006a,b, 2003, 2000; Jechura and Lee, 2004; Labyak and Lee, 1995). As degus are highly social, they have also been used as a model to examine the relative importance of social cues on activity patterns (Jechura et al., 2006a,b, 2003; Jechura and Lee, 2004). Researchers have focused on a number of circadian rhythm parameters including melatonin synthesis patterns, general activity levels, chronotype, and response to phase shifts. Briefly, we summarize circadian rhythm research in degus that have focused on 1) melatonin and 2) relationships between sex steroid hormones and re-entrainment rates.

3.1. Melatonin

Melatonin is an indoleamine secreted from the pineal gland. Primarily secreted during the dark (scotophase), melatonin plays a key role in regulating endogenous rhythms in many vertebrates including degus (Morris and Tate, 2007). While most circadian rhythm studies have used nocturnal rodents, such as mice and rats (Dunlap et al., 2004), degus provide a model system more relevant to humans as they display diurnal activity patterns under natural conditions. Lee et al. (2009) confirmed that daily rhythms of degu melatonin synthesis are more similar to humans than to any other rodent. When brought into the laboratory, some degus will display nocturnal activity patterns, which has also given researchers the opportunity to compare degus with different chronotypes. However, studies have not found any differences in daytime or nighttime melatonin levels between diurnal and nocturnal degus (Otalora et al., 2010; Vivanco et al., 2009). While Morris and Tate (2007) found that melatonin administration significantly affected wheel running activity in degus held under constant dark conditions, studies using exogenous melatonin administration have found little or no effects on activity patterns or body temperature in degus under light-dark conditions (Vivanco et al., 2009). Bilu and Kronfeld-Schor (2013), however, did find that melatonin administration increased anxiety-like behaviors in captive degus during the daytime.

3.2. Sex steroid hormone effects on circadian rhythms

Compared to males, adult female degus have a free-running circadian rhythm that is ~30 min longer (Labyak and Lee, 1995). This sex difference is likely due to organizational effects of sex steroid hormones during the pre-pubertal stage, as degus gonadectomized before puberty show no sex difference in free-running circadian rhythm (Hummer et al., 2007). Specifically, Hummer et al. (2012) found that exposure to estradiol between 7 and 12 months of age caused males to shorten their circadian rhythms.

To simulate jet-lag, many circadian rhythms studies subject animals to drastic changes in light cycle (phase shifts) and then observe the amount of time needed before behavior rhythms appropriately match (re-entrainment). Jechura et al. (2003) found that adult female degus re-entrain much faster when they're exposed to the odor of a neighboring, intact (un-ovariectomized) female adult degu. This process is likely regulated by circulating sex steroid hormones in the focal degus, however, as re-entrainment rate is enhanced with endogenous progesterone but delayed after ovariectomy (Jechura and Lee, 2004). While sex steroid hormones enhance re-entrainment rates in adult female degus, they delay rates in adult male degus, as castration also increases the rate of re-entrainment (Jechura et al., 2003). Furthermore,

while juvenile male degus only require the odor from one, unrelated intact adult female degus to increase re-entrainment rates, adult male degus require two (Jechura et al., 2006b).

4. Agonistic behavior and hormonal correlates

Studies in both wild and captive degus have examined reproductive behavioral endocrinology in both males and females, at both the adult and juvenile stages, and in different social and reproductive contexts (Correa et al., 2013; Ebensperger et al., 2010; Kenagy et al., 1999; Soto-Gamboa, 2005; Soto-Gamboa et al., 2005). Studies have specifically focused on agonistic (including aggression) interactions and female masculinization. For aggression, degus have been a good model system because they have a defined mating season (Soto-Gamboa et al., 2005). Additionally, it is feasible to observe aggressive behaviors in the wild, as degus are diurnal and live in relatively open environments.

4.1. Inter-male interactions

Across the year, wild male degus have very low testosterone levels, although levels increase and become detectable during the mating season (Kenagy et al., 1999), which is when male-male agonistic interactions are most frequent (Soto-Gamboa et al., 2005). Soto-Gamboa et al. (2005) also found that male degu testosterone levels increased from the pre-breeding to mating stage. While both free and total testosterone were highest during the mating period, free testosterone was more closely associated with aggressive behaviors between males. Additionally, resident males (those that permanently shared a burrow with several females) had both higher testosterone and CORT than transient males (those that moved frequently among burrows). High testosterone levels in resident vs. transient males are likely due to endogenous differences, rather than female presence, as male degus in the laboratory have similar testosterone levels whether they are housed alone or with multiple females. These endogenous differences could be influenced by the organizational effects of testosterone during puberty (Kenagy et al., 1999).

4.2. Male-female and parent-offspring interactions

In the wild, Soto-Gamboa et al. (2005) found very low levels of agonistic interactions between males and females during both the pre-breeding and mating periods. However, (Ebensperger et al., 2010) found that in the lab, mothers housed alone or with sires had higher levels of CORT and lower body mass than females housed with non-breeding females. Whether these differences are caused by male aggression or other social factors is unknown. Towards pups, however, males never performed agonistic behaviors, and actually provided significant rates of parental behavior including huddling, licking, and grooming. While levels of circulating testosterone did not predict rates of parental care from males, it was negatively associated with rates of care in females.

4.3. Inter-female interactions

Agonistic behavior has also been studied in female degus. Correa et al. (2013) examined the nature and frequency of inter-female interactions and the formation of dominance hierarchies between females with different levels of phenotypical masculinization. This lab study examined the hypothesis that differences in social behaviors are related to a female masculinization gradient. The authors compared three types of social groups, including: (i) groups composed of six masculinized females, (ii) groups composed of six feminized females, and (iii) groups composed of two

feminized, two masculinized, and two intermediate females (see Section 5 for definitions of masculinization morphotypes). Affiliative, submissive, and dominance behaviors were recorded. Results indicated that the frequency of aggressive interactions was higher in masculinized females. Frequency of affiliative interactions was higher in feminized female social groups. Submissive interactions were most frequent in social groups composed of all female phenotypes, and these social groups were the only ones that formed dominance hierarchies. In these mixed-phenotype groups, females were linearly hierarchized with masculinized females occupying the dominant positions, feminized females occupying the subordinate positions, and intermediate females occupying the intermediate positions. Females were hierarchized in relation to water bottle access, likely because water was a scarce and valuable resource in their lab environment. Curiously, feminized females were the ones that built the hierarchy. Feminized females avoided contact and “gave” resources to dominant females, while masculinized females did not show hyper-aggressive behavior towards other females. Plasma concentrations of total testosterone did not differ between females of different levels of masculinization and social rank (Correa et al., 2013).

5. Female masculinization

Degus have been a good system for female masculinization studies as a female's anogenital distance matches the number of neighboring males in her intrauterine environment (Correa et al., 2013). An interesting set of studies has furthered explored this phenomenon, and how female masculinization ultimately affects female fitness (Correa et al., 2016).

Through analysis of anogenital distance, a gradient of female phenotypical masculinization has been detected in degus from both wild and laboratory populations (Correa, 2012; Correa et al., 2016). In this continuous gradient, masculinized and feminized females represent the extreme morphotypes. Previously, these alternative morphotypes were described in several rodent species and domestic rabbits. Evidence from these studies shows that masculinized and feminized females differ in several traits such as anogenital distance (AGD), hormone profiles during prenatal development, aggressiveness, home range size, age at the first estrus, reproductive lifespan, attractiveness to males, litter sex ratio, and litter size (Clark and Galef, 1998; Hackländer and Arnold, 2012; Ryan and Vandenberg, 2002; vom Saal et al., 1999; vom Saal, 1989; Zehr et al., 2001). Evidence from European rabbits (*Oryctolagus cuniculus*) (Bánszegi et al., 2012) and Mongolian gerbils (*Meriones unguiculatus*) (Clark and Galef, 1998) indicates that feminized females deliver larger litters, while this tendency was not recorded in house mice (*Mus musculus*) (Szenczi et al., 2013), mound-building mice (*Mus spicilegus*) (Szenczi et al., 2013), or yellow bellied marmots (*Marmota flaviventris*) (Monclús and Blumstein, 2012), where masculinized and feminized females deliver litters of equal size.

During prenatal development, the uterine environment plays a decisive role in modeling the phenotype of undifferentiated female embryos (Clark and Galef, 1998; Ryan and Vandenberg, 2002; vom Saal et al., 1999). Three proximal mechanisms could be responsible for generating variation in female phenotype, including (i) the intrauterine position (IUP) phenomenon (Clark and Galef, 1998; Ryan and Vandenberg, 2002; vom Saal, 1989; vom Saal et al., 1999), (ii) the “horn effect” (Hotchkiss and Vandenberg, 2005), and (iii) the relative activity of the maternal stress response during pregnancy (Kaiser et al., 2003; Kaiser and Sachser, 2005). During the IUP phenomenon, males neighboring female siblings transfer testosterone to undifferentiated female embryos through the amniotic fluid and/or blood (Clark et al.,

1993; Clemens, 1978; Gandelman et al., 1977; vom Saal, 1989). The 'horn effect' depends on the total number of males in the same uterine horn, as non-neighboring males can also increase female embryo exposure to testosterone (Hotchkiss and Vandenberg, 2005). Additionally, maternal adrenal glands release androgens during a stress response, which can cross the placenta and reach developing female pups, thus masculinizing their phenotypes (Kaiser et al., 2003; Kaiser and Sachser, 2005). Given that prenatal exposure to androgens affects the development of perineal tissue, the distance between the genitals and anus (anogenital distance) is longer in females that are exposed to high concentrations of androgens, and shorter in females that are exposed to lower concentrations of androgens (Bánszegi et al., 2009; Clark and Galef, 1998; Clemens, 1978; Hotchkiss and Vandenberg, 2005; Vandenberg and Huggett, 1994; vom Saal, 1989). Thus, anogenital distance (AGD) allows a non-invasive assessment of female masculinization level (Fouqueray et al., 2014).

To analyze how IUP relates with female degu pup AGD, Correa (2012) performed cesarean surgeries on pregnant females. Thus, the exact position of each female pup relative to male pups was known. Females located between two male siblings (2M) had the longest AGDs, while females located between two female siblings (0M) had the shortest AGDs, and females located between one male and one female sibling (1M) had intermediate AGDs (Correa, 2012). Additionally, amniotic fluid from 2 M female sacs had higher concentrations of testosterone than fluid from 0 M female sacs. Correa (2012) also found a positive relationship between a female's AGD and the number of male siblings in the same uterine horn. Therefore, these results suggest that both intrauterine position and the number of males within a uterine horn may significantly affect female offspring AGD. By following these female pups into adulthood, Correa (2012) also found that these birth differences in AGD were conserved through adulthood. Finally, Correa et al. (2013) measured circulating plasma concentrations of testosterone and found that adult females of different AGD morphotypes did not differ in testosterone profiles; this suggests that female AGD is determined via organizational rather than activational effects.

To determine whether the maternal stress response could influence female pup AGD in degus, Correa (2012) subjected pregnant females to stressful conditions and used metyrapone to block CORT release in one group of mothers. Once again, the effect of IUP was controlled via AGD analyses. After birth, female pups from metyrapone-injected mothers had shorter AGDs compared to female pups from control (CORT-released) mothers. Curiously, this effect only was detected in the daughters of mothers with short (feminized) or intermediate AGDs. Stress treatment did not affect the AGDs of daughters from masculinized (long AGD) mothers. Thus, daughters from masculinized females could be relatively more insensitive to maternal stress effects in terms of phenotypical masculinization. While these results suggest that maternal CORT release during the prenatal period may masculinize female pups, it should be noted that we cannot specify the mechanism that lengthens female pup AGD, because we did not isolate the effects of other female stress mediators, such as testosterone. Therefore, we do not know if CORT, testosterone, adrenaline, dehydroepiandrosterone (DHEA), or their metabolites were the responsible for female pup masculinization in control (CORT-released) mothers (Correa, 2012).

To determine whether female masculinization has any functional consequences, a wild, free-living population of degus was studied for seven years. Correa et al. (2016) found that feminized females deliver female-biased litters while masculinized females deliver male-biased litters, although the number of weaned offspring does not differ between masculinized and feminized females. Offspring from masculinized females weighed more at

weaning compared to offspring from feminized females, which generally has a positive effect on post-weaning survival (Rieger, 1996), adult body weight (Clutton-Brock, 1991), and subsequent female adult fertility (Campbell and Slade, 1995). Heavier weight at weaning may be due to a longer gestation, as masculinized females give birth later in the reproductive season (Correa et al., 2016). Increased body mass at weaning could also be due to augmented milk production during lactation, as a lab study found that masculinized females lost more body weight during lactation compared to feminized females (Correa, 2012). These results, in addition to the observation that masculinized females are more tenacious and aggressive when defending their offspring (Correa, pers. obs), suggest that masculinized females make a higher maternal investment and perform better parental care relative to feminized females.

6. Conclusion

Although a substantial amount of endocrine research has been done on degus (Fig. 1), further work remains. Studies to date have exploited two major advantages of using degus as a model system – they are diurnal and they can easily be studied in both the laboratory and the field. These advantages have allowed research to make several major contributions to comparative endocrinology. First, studies have been able to determine whether endocrine phenomena discovered in common laboratory rodents (e.g. mice and rats) have both broader taxonomic relevance and occur under natural conditions. Studies on female masculinization and maternal impacts on pup stress responses are good examples of these types of contributions. Second, diurnal rodent models are uncommon, making degu studies important for translating laboratory rodent studies to humans. Studies on degu circadian rhythms are good examples. Finally, field studies on small mammals are often difficult since most species are nocturnal. Degus provide a diurnal mammal model for comparative field endocrine studies that can be used for taxonomic comparisons with other vertebrates. Studies on degu stress responses and behavioral endocrinology exploit this advantage. In conclusion, the degu studies reviewed here will form the foundation for continued contributions with this important model species.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.ygcen.2018.03.014>.

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