Octodon degus: A Diurnal, Social, and Long-lived Rodent

Theresa M. Lee

Abstract

Octodon degus is a moderate-sized, precocious, but slowly maturing, hystricomorph rodent from central Chile. We have used this species to study a variety of questions about circadian rhythms in a diurnal mammal that readily adapts to most laboratory settings. In collaboration with others, we have found that a number of fundamental features of circadian function differ in this diurnal rodent compared with nocturnal rodents, specifically rats or hamsters. We have also discovered that many aspects of the circadian system are sexually dimorphic in this species. However, the sexual dimorphisms develop in the presence of pubertal hormones, and the sex differences do not appear until after gonadal puberty is complete. The developmental timing of the sex differences is much later than in the previously studied altricial, rapidly developing rat, mouse, or hamster. This developmental timing of circadian function is reminiscent of that reported for adolescent humans. In addition, we have developed a model that demonstrates how nonphotic stimuli, specifically conspecific odors, can interact with the circadian system to hasten recovery from a phase-shift of the light:dark cycle (jet lag). Interestingly, the production of the odor-based social signal and sensitivity to it are modulated by adult gonadal hormones. Data from degu circadian studies have led us to conclude that treatment of some circadian disorders in humans will likely need to be both age and gender specific. Degus will continue to be valuable research animals for resolving other questions regarding reproduction, diabetes, and cataract development.

Key Words: circadian; hystricomorph; maturation; sex difference; steroid hormones

Introduction

Circadian Research Problems in Need of Diurnal, Laboratory-friendly Species for Study

Most animals exhibit daily fluctuations in behavior and physiology that are dependent on complex neural mechanisms. These fluctuations have evolved as an adaptation to cyclic events in the environment, primarily daily photocycle changes (Aschoff 1981; Aschoff et al. 1982; Daan 1982; Enright 1970; Pittendrigh and Daan 1976a,b,c). In most animals the underlying neural mechanism, a circadian pacemaker, produces daily rhythmic changes independent of environmental changes and is kept in precise synchrony with the environment by slight corrections in the endogenous mechanism by specific environmental events (Johnson and Hastings 1986; Pittendrigh 1981a,b; Turek 1985). The advantage of a system that allows an internal timing mechanism to be altered by daily environmental fluctuations is the ability of the animal to anticipate changes in the local environment and to prepare behaviorally or physiologically in advance of those changes. The daily light:dark cycle provides the most salient timing information, but specific nonphotic daily events are also effective.

The formal properties of the circadian pacemaker are well described for nocturnal mammals. In constant darkness, nocturnal species free-run (i.e., produce endogenous daily oscillations in the absence of environmental change) with a period (ϑ) close to, but on average less than, 24 hr (Aschoff 1979). The shape of their phase response curve (PRC[1])—phase shifts in response to short pulses of light, or other timing cues, across the subjective circadian cycle of day and night—reflects the difference of the free-run from 24 hr (DeCoursey 1972, 1973). Entrainment for a nocturnal mammal occurs when it is exposed to a brief light pulse (as little as a few seconds every few days) at the beginning of its active phase, thereby causing a delay in activity onset and delaying the endogenous rhythm sufficiently to maintain a 24-hr cycle (e.g., DeCoursey 1986a,b; Moore-Ede et al. 1982). Thus nocturnal species are highly sensitive to the entraining effects of even brief, dim light pulses.

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[1]Abbreviations used in this article: PRC, phase response curve; PVT, paraventricular nucleus of the thalamus; SCN, suprachiasmatic nuclei.

When we[2] began research with *Octodon degus* (common name: degu), significant differences in the circadian properties of nocturnal and diurnal mammals had been described. For example, day-active mammals responded poorly to brief, low-intensity light pulses (Decoursey 1972, 1973) and therefore only partial PRCs were available for a small number of species (Kramm 1973, 1974, 1975, 1976; Strogatz 1990). Much brighter or longer light pulses were effective for generating PRCs, but often at intensities that completely depleted photopigments in the eyes of nocturnal species. In addition, the PRCs of nocturnal mammals typically had a period during mid-subjective day that was insensitive to light exposure, but in at least two diurnal species, there was no evidence of such a period of insensitivity. Some diurnal mammals also failed to entrain to short daylengths (DeCoursey 1972, 1973), suggesting a different mechanism of entrainment than that hypothesized by Aschoff's proportional theory of entrainment (Aschoff 1979).

Because the suprachiasmatic nuclei (SCN[1]; site of the mammalian dominant circadian pacemaker) demonstrated a similar diurnal rhythm of 2-deoxy-glucose uptake in both nocturnal and diurnal species, many researchers assumed that the primary difference between the circadian function of these species would be in the interpretation of the SCN signal and not within the SCN itself. However, by the early 1990s, Abe and colleagues (1995) reported that Fos activation in the SCN after light pulses (i.e., increased presence of the immediate early gene product, Fos, after neural stimulation) differed between diurnal chipmunks and nocturnal rats; and Meijer and colleagues (1989) demonstrated that photically responsive neurons in and around the SCN behaved quite differently in 13-lined ground squirrels and rats.

The primary problem, at the time, in further testing theories of entrainment in diurnal species was finding an appropriate small to medium-sized animal for the laboratory that produced readily analyzable circadian data. The majority of previously tested diurnal squirrel species did not breed readily in captivity; and virtually all well-studied Sciuridae (*Eutamias, Tamias, Spermophilus, Marmota*) are seasonal hibernators, limiting study to a few months each year, even in the laboratory. Other Sciuridae, particularly the tree squirrels (*Sciurus, Tamiasciurus*), are intractable in the laboratory, with the exception of palm squirrels (*Funambulus pennanti,* Rajaratnam and Redding 2001). A second problem was that many diurnal species had a high level of variability in the onset of activity under entrained or free-running conditions, which made many standard descriptive studies (such as development of a PRC) very difficult. Thus the description of circadian rhythms in diurnal species (e.g., tree squirrels [Pohl 1982], many North American ground squirrels [Carmichael and Zucker 1986; DeCoursey 1972; Kenagy 1978; Kramm 1973, 1974, 1975, 1976; Lee et al. 1986], prosimian tree shrews [Meijer et al. 1990], and squirrel monkeys [Albers et al. 1984a,b; Gander and Moore-Ede 1983; Gander et al. 1985b; Hoban and Sulzman 1985; Moore-Ede et al. 1979]) had not resulted in development of a uniform theory that integrated the workings of the free-running endogenous pacemaker with photoentrainment mechanisms.

At the time, several other circadian behavioral research questions were receiving increased attention, but only in nocturnal species. For example, Mrosovsky's laboratory and a few others were exploring the mechanism by which nonphotic interactions could alter patterns of entrainment (Kavaliers 1980; Mrosovsky 1991, 1995). Hamsters, a relatively asocial species, were most often used to explore the effects of induced exercise and various conspecific interactions (Mrosovsky 1988, 1996a). The conspecific interactions were described as social, but in fact among adult hamsters, only estrous females and males have positive social interactions. Eventually, Mrosovsky suggested that all effective nonphotic cues in hamsters functioned by causing arousal and increased motor activity (Mrosovsky 1995). Thus I wanted to find a species that was not only diurnal but was also highly social (i.e., lives in extended family or other conspecific groupings).

Finally, a number of papers had reported that circadian function, and perhaps the neural mechanisms, were sexually dimorphic and changed across development. Again, nearly all of the species that had been studied in this regard were altricial, myomorph nocturnal rodents. However, similar data exist for humans (e.g., Carskadon and Acebo 2002; Wever 1979, 1984), suggesting that such age and sex differences might be common to many species, including those that are not nocturnal or altricial and have a longer maturation period. Finding a laboratory-friendly species with a slower maturation rate than most laboratory rodents could allow us to examine the development of circadian rhythms, particularly at the peripubertal stage, when humans demonstrate alterations in circadian function (Carskadon and Acebo 2002).

Octodon degus

We have found that degus, a common hystricomorph rodent from central Chile (Figure 1), is a particularly useful species for studying the questions posed above. We were able to obtain a few animals from several zoos in the eastern United States, a laboratory colony that was being closed, from some local pet stores and, eventually, wild-caught animals (from Dr. Peter Meserve) to begin and expand our breeding colony.

In the field, degus live in social groupings of five to 10 animals (Fulk 1976), believed to include close female family members and one to three adult males (relatedness among animals has not been verified by genetic markers). Field animals typically breed only once per year, during early winter when the rainy season begins, but will produce

[2]In this article, subsequent discussions of the author's studies refer to work with colleagues in her laboratory in the Department of Psychology, University of Michigan, Ann Arbor, Michigan.

Figure 1 Adult female (left) and male (right) laboratory-bred degus. Photograph by Tammy J. Jechura.

a second litter if vegetation does not dry out too quickly (Meserve et al. 1995). There is some evidence from field and laboratory data that the male reproductive organs may be at least mildly sensitive to photoperiod changes (Carballada et al. 1995; Rojas et al. 1995), although no data exist on females. Gestation lasts 90 to 95 days, and lactation lasts 4 to 5 wk (Kleiman et al. 1979). There is evidence from laboratory colonies (including those at the University of Michigan) of postpartum estrus, but not all animals become pregnant at that time. First reproduction in the field occurs at the next breeding season, when animals are approximately 9 mo old (Weir 1970, 1974; Woods and Boraker 1975).

We have developed, with the help of the University of Michigan Unit on Laboratory Animal Medicine, a set of husbandry and breeding practices that maximizes the health, breeding capacity, and longevity of the species (A. T. Young, T.M.L., H. G. Rush, in preparation). The reproductive maturation of degus can be readily monitored by observing the timing of vaginal opening in females and penile development in males (Labyak and Lee 1995; T. J. Jechura and T.M.L., University of Michigan, unpublished data). Typically, females begin cycling between 12 and 16 wk of age, and males are reproductively competent by 16 wk. However, they do not reach full adult body size (180-250 g, adult males are about 10% larger than females; A. T. Young, T.M.L., H. G. Rush, in preparation) until 6 to 8 mo of age (Reynolds and Wright 1979). Thus we do not form breeding pairs until animals are at least 6 mo old. The colony is maintained on a 12:12 light:dark cycle.

We found that pine shavings sometimes cause irritation to the skin of the animals, so we use only inert bedding such as ground corn cobs. Degus do not readily build nests, although some will keep new litters in shelters. After 6 mo of age, unless females are pregnant or lactating, adult animals are maintained on Laboratory Rodent Diet 5001 (LabDiet®, PMI Nutrition International, Richmond, IN). However, we found that offspring development and survival were poor on this diet, and after systematic experimentation with several diets, we found that Prolab RMH 2000 5P06 diet (LabDiet®) provided much better weight gain and health in lactating females and pups (A. T. Young, T.M.L., H. G. Rush, in preparation). At 3 mo of age, animals are switched to the maintenance diet (to avoid obesity). Degus should never be fed fresh root vegetables or fruits (high in sugars and carbohydrates) because they readily become hyperinsulinemic, which leads to cataracts and kidney damage (Datiles and Fukui 1989; Spear et al. 1984; Tripathi et al. 1991). Alfalfa or other hays are appropriate additions to the diet, although the LabDiet chows are sufficient. Additionally, because degus are susceptible to *Pseudomonas* infections, we acidify the water provided to pups through 3 mo of age. After that age, we have found that acidification is not necessary. For the entire colony, fresh sanitized bottles are provided twice weekly to inhibit any growth in standing water. With these husbandry practices, 90% of pups reach 6 mo of age, and we have no diarrheal diseases apparent in our adult population.

In our laboratory colony, females typically have four to six pups in their first litter and six to 10 pups in subsequent litters. Single male-female pairs are housed in 20 in × 20 in × 8 in cages with and without their litters. Females produce three to four litters per year, depending on whether they become pregnant during the postpartum estrus; if not, they will not become pregnant until after the pups are weaned. We have found that laboratory degus housed in 12:12 light: dark with ad libitum access to food and water have 18- to 21-day estrous cycles (Labyak and Lee 1995; B. V. Rossi and T.M.L., in preparation). Note that common nocturnal rodent models do not have a spontaneous luteal phase that occurs in the longer ovarian cycles typical of degus. The role of the circadian system in such a species has been examined only in sheep and rhesus monkeys. In those species, there is no evidence of a circadian control of luteinizing hormone release that is found in rodents without spontaneous luteal phases (e.g., rats, mice, hamsters; see review in Mahoney 2003). It is unclear at this time whether the lack of a circadian timed release of luteinizing hormone in sheep and rhesus monkey is because they have a spontaneous luteal phase or because they are not rodents. Degus can be used to address this question.

Pups are precocious. At birth they are fully furred, their eyes are open on the first day, their teeth erupt, and they are readily mobile (Fentress 1981). They remain in the nesting site, where the dam closely attends them until they are about 2 wk of age (males may also huddle with the pups, and we have never had a case of male infanticide). By 2 wk, pups begin gnawing on pieces of food and moving around the entire cage. In the field, they begin to emerge at the burrow opening at about 3 wk of age (Fulk 1976). We find that weaning at 4 to 5 wk and 60 to 80 g ensures continued good health. Pups live in same-sex social groups until they reach

maturity. Poeggel and colleagues (2003) reported severe behavioral and neural deficits in animals raised in isolation after weaning. We also found that young isolated animals exhibited excessive fear of conspecifics at a later age and became very difficult to handle. After 6 mo of age, isolated housing appears not to cause behavioral anomalies.

We have found that nearly all degus in our laboratory live at least 5 yr, and a sizable number will live as long as 7 to 8 yr. However, female reproduction drops off after 4 to 4.5 yr. As a result, we consider animals aged after 4 yr and no longer use them in our circadian research.

Overall, we have found that degus adapt well to the laboratory environment and are useful for circadian research as long as we are mindful of a few quirks. First, we maintain the animal rooms at 17 to 18°C for animals housed with running wheels. When housed at higher temperatures and placed in wheels, many animals demonstrate masking (i.e., altered circadian pattern without a change in SCN function); their activity is crepuscular, and some are even nocturnal (Kas and Edgar 2001; Kenagy et al. 2002a,b). Second, degus develop liver damage with halothane and metofane gas anesthetics, and they are not easily maintained on a constant plane of anesthesia with injectable drugs such as phenobarbital or a ketamine/rompun cocktail. However, 2 to 4% isoflurane gas anesthesia provides long, stable anesthesia and results in excellent recovery after a variety of short and long surgical manipulations.

Study Results

Fundamental Circadian Function

Since we first brought degus to the laboratory, several other diurnal species also have been successfully introduced to laboratories, each with special properties that make them of interest. *Arvicanthus niloticus* (common name: grass rat), a myomorph rodent from Africa, for example, has exceptionally precise daily onset of activity for measurement of circadian rhythms, and they breed and mature in the laboratory much as do laboratory rats. Smale and colleagues (Mahoney et al. 2000, 2001; Novak and Nunez 2000a; Novak et al. 2000b; Rose et al. 1999; Smale et al. 2001) have successfully used this species to explore the function of the SCN and its control over the circadian activity of the lower subparaventricular area and the ventrolateral preoptic nuclei (structures important for controlling the timing of sleep).

Comparison of the data from diurnal degus and grass rats suggests that rodents from different lineages appear to have evolved different mechanisms for producing a diurnal circadian activity pattern from a nocturnal progenitor. For example, the PRC of grass rats and their Fos response to light pulses do not differ from the nocturnal muroid rodents to which they are related (Mahoney et al. 2001). In contrast, degus have a PRC that lacks a period of insensitivity to light (as is true in ground squirrels and humans). They respond to light pulses during early subjective day by reducing Fos in the dorsal SCN (whereas muroid animals have undetectable Fos during subjective day and reduction cannot be measured) (Krajnak et al. 1997). In addition, electrophysiological recording of photically sensitive cells in degus differs from nocturnal rats but is the same as diurnal ground squirrels (Jiao and Rusak 2003; Jiao et al. 1999). Thus examination of three different types of diurnal rodents leads to the conclusion that there are multiple ways for diurnality to evolve (see Smale et al. 2003 for a review).

Degus do not have the extremely precise daily onset of activity found in hamsters or grass rats (onset varies only a few minutes each day in hamsters and grass rats rather than up to 15 min in degus). Typically they have peaks of activity during the morning and late afternoon, with varying amounts of activity throughout the day, largely depending on ambient temperature (Labyak and Lee 1997). The inter- and intraindividual variability is similar to that reported for humans. Kas and Edgar (1998) suggested that degus are crepuscular rather than diurnal; however, they later demonstrated that housing the animals with running wheels was inducing a masked activity pattern (Kas and Edgar 1999). In the field degus are never active during the night, but when ambient temperature increases above 25°C, degus retire to their burrows. The result is changing activity patterns across the year, such that degus appear diurnal/crepuscular (activity during early morning and late afternoon) during the summer (Kenagy et al. 2002b). We consider the animals diurnal in the laboratory because, on average, more than 75% of their activity occurs between 1 hr before lights on and 1.5 hr after lights off as long as the animals have no running wheels or are maintained at 17 to 20°C.

By using the Aschoff II method to develop phase response profiles, we have been able to produce PRCs for both photic and nonphotic cues (Lee and Labyak 1997, T. M. Buckley, T. J. Jechura, and T.M.L., University of Michigan, unpublished data). Briefly, this procedure releases an animal from an entrained state, which is very stable, into constant conditions (constant darkness or constant light) 24 to 48 hr before a brief light or nonphotic signal pulse. The alternative method (Aschoff I) allows the animal to establish a stable free-run in constant condition before pulsing with a timing signal. Either method provides reliable data, but for the degu the response after a short release provides more within- and between-animal consistency of responses (also true in other species, Mrosovsky 1996b). The degu is one of five diurnal mammals for which at least partial PRCs in response to light and/or nonphotic cues have been reported (DeCoursey 1973; Hut et al. 1999; Kas and Edgar 2000 2001; Kramm 1974; Lee and Labyak 1997; Mahoney et al. 2001). Interestingly, the nonphotic PRC is very similar to that of nocturnal species, which is surprising to many researchers. Nonlight cues cause large phase advances during early subjective day and small phase delays during late subjective day and in the night (Hut et al. 1999; Lee and Labyak 1997; Mrosovsky 1988). In addition, Hut and colleagues (1999), working with ground squirrels, found that activity level does not correlate with the effec-

tiveness of the nonphotic cue as it does with hamsters (Mrosovsky 1996a). Many researchers expected diurnal species to have sensitivity to nonphotic cues while they slept (as is true for nocturnal species; Eastman et al. 1995), rather than when they are awake and active. Nonphotic cues are effective in both nocturnal and diurnal animals at a time of day when light has its smallest effects.

Additional studies of the interactive effect of photic and nonphotic signals on the function of the circadian system at the behavioral, anatomical, and cellular levels of analysis are urgently needed as we attempt to discern how to control circadian disorders in humans. Currently, the degu is the only diurnal species that is well adapted to the laboratory environment in which the effects of both photic and nonphotic cues are well established.

Sex Differences in Circadian Function

Sex differences in entrained and free-running circadian rhythms have been described in several species. For example, the phase angle of activity onset differs between male and female hamsters, as does the range of entrainment to non-24-hr periods (e.g., Daan et al. 1975; Davis et al. 1983, 1987; Zucker 1979; Zucker et al. 1980a,b). The difference in hamster entrained rhythms may result from the sex difference in the PRC and/or free-running period (Davis et al. 1983, 1987; Morin and Cummings 1981; Zucker 1979; Zucker et al. 1980a,b). Similar differences in entrained and free-running rhythms have been described in rats and mice (Albers et al. 1981; Daan et al. 1975). Such sex differences are not confined to rodents; humans also demonstrate sex differences in some entrained circadian rhythms such as core body temperature, duration of sleep, and ability to cope with shift work (Czeisler et al. 1992; Dinges 1995; Dinges et al. 1997; Wever 1979, 1984).

Many of the sex differences in circadian function described in rats, mice, and hamsters are still present in the absence of adult hormones (Albers et al 1981; Davis et al 1983; Zucker et al. 1980a,b). Pre- and perinatal testosterone exposure masculinizes circadian function in these species, much as testosterone alters the hypothalamic-pituitary axis (see review, Gorman and Lee 2002). Interestingly, no one had ever determined whether or when sex differences in circadian function occur in a diurnal rodent, or in a precocial or more slowly maturing mammal. The degu provides an ideal opportunity to explore these questions, and they have provided some surprising and exciting answers.

Sex differences in adult circadian function appear common; not surprisingly, male and female degus also demonstrate robust differences. The ϑ of adult male degus is approximately 30 min shorter than that of females (Labyak and Lee 1995; Lee and Labyak 1997). Females are more responsive to the effects of olfactory nonphotic signals (Goel and Lee 1995a,b), and males are more responsive to changes in light intensity (Lee and Labyak 1997). This latter difference appears to be reflected in the fact that males recover from phase-shifts of the light cycle (jet lag) faster than females (Goel and Lee 1995a,b; C. D. Stimpson, G. H. Jacobs, and T.M.L, in preparation). As in other species, female degus have large phase advances in activity onset on the day of estrus (approximately 2.5 hr) (Labyak and Lee 1995), and male phase is similarly altered by testosterone (when comparing intact and castrated males) (Jechura et al. 2000). Thus adult hormones can alter entrainment phase in both sexes. However, castration of adults does not alter ϑ, the fundamental speed of the circadian mechanism (Jechura et al. 2000; Labyak and Lee 1995). These latter data suggested that steroid hormones during development might organize the sex difference in ϑ for degus as it does for rats, mice, and hamsters.

We were quite surprised to find that peripubertal (2- to 4-mo-old) degus do not yet demonstrate a sex difference in ϑ, phase angle of entrainment, responsiveness to nonphotic odor signals, or rate of recovery from a phase-shift in the light cycle (Jechura 2002; Figure 2). The latter effects (all but ϑ) were predicted because we had found that adult castration altered these measures in males. In contrast, ϑ was determined by pre- and perinatal testosterone exposure in the altricial nocturnal rodents; the sex difference was already evident when they were first able to run in wheels (Albers et al 1981; Daan et al. 1975; Davis et al. 1983, 1987). Clearly, some developmental mechanisms are delayed in the sexual differentiation of the fundamental clock speed (ϑ) in degus.

There are two interesting aspects of this system. First, as in humans, circadian rhythms of degus undergo a change during and after puberty that has not been noted in more rapidly developing rodents (Jechura 2002). Carskadon's group (Carskadon and Acebo 2002; Carskadon et al. 1998) has demonstrated that human entrainment is altered during puberty, producing disruption in the sleep patterns of many teenagers. Whether these entrainment changes in humans are consistent with a change in ϑ is unclear (Carskadon et al. 1999). However, entrained morning arousal phase is also altered by steroid hormones in degus (Jechura 2002) and is changing during puberty in humans. Second, the timing of the ϑ change in degus is at least 3 to 4 mo after the onset of puberty. The developmental change might, therefore, be independent of the rising pubertal gonadal hormones, except that gonadectomy prevents the sexual differentiation of ϑ. Many developmental neural changes take place in humans during and well after the increase in pubertal hormones, such as the development of the prefrontal cortex. We do not know which of these changes eventually lead to sex differences in cognitive function or which are dependent on pubertal exposure to steroid hormones.

The degu provides an excellent opportunity to explore the mechanisms underlying late developmental changes in the nervous system, particularly those that are triggered by steroid hormone exposure. This exploration is possible because we have a defined system in which much of the biochemical machinery for the generation of circadian period is well understood. In general, such late development studies

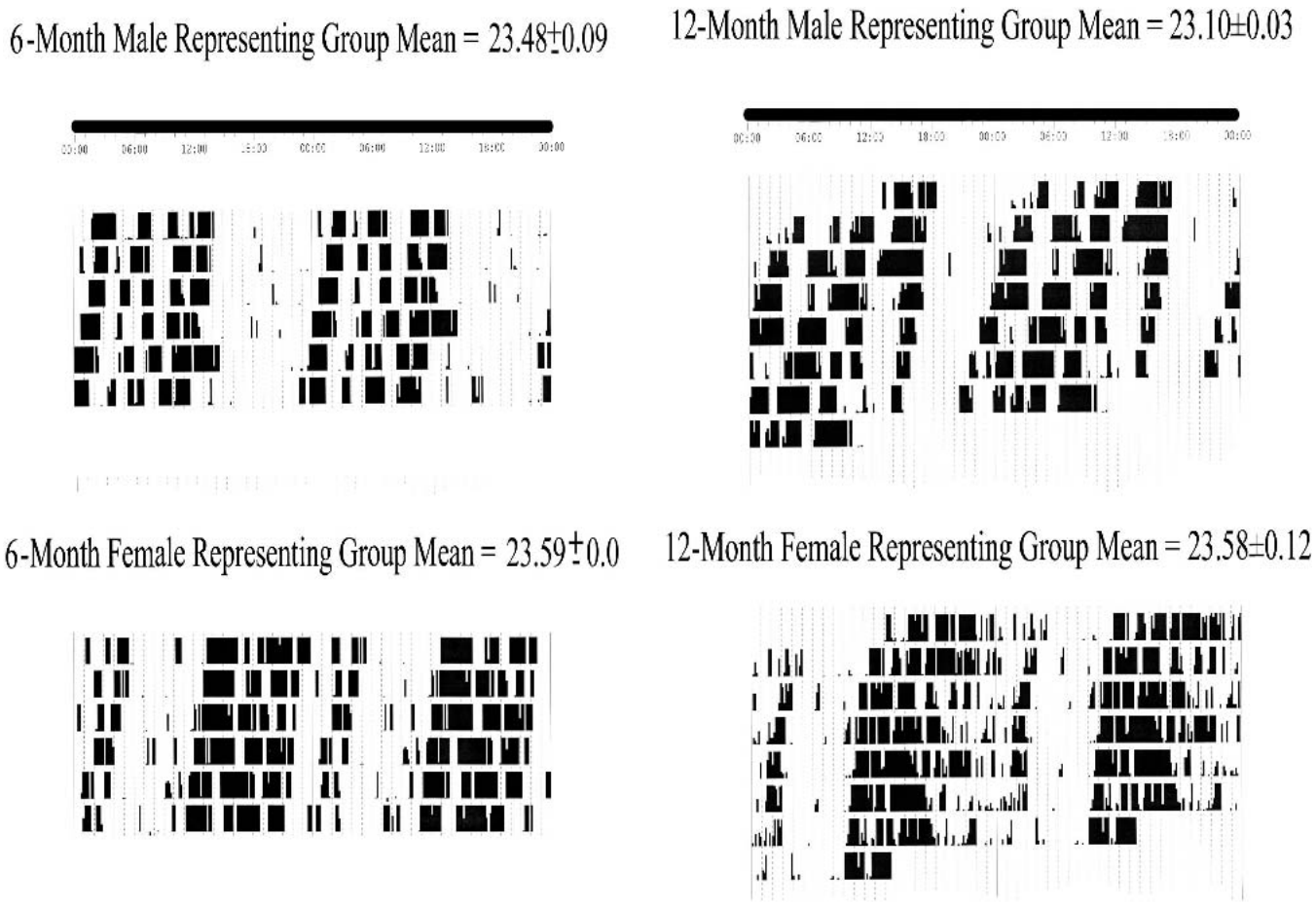

Figure 2 Examples of double-plotted free-running activity rhythms for male and female degus housed with running wheels at 6 and 12 mo of age in constant conditions for 2 wk before the determining period (ϑ). In a longitudinal study, males significantly decreased ϑ between 6 and 12 mo, and females did not. Through 6 mo of age, males and females did not differ. Data from Jechura TJ. 2002. Sex differences in circadian rhythms: Effects of gonadal hormones in *Octodon degus*. PhD Dissertation, University of Michigan, Ann Arbor, MI.

are difficult in other rodents because of the very short time between weaning and puberty. Such work is possible in larger, long-lived species, but it will be comparatively more expensive than working with small degus.

A Model for Recovery from Jet Lag

One of the more interesting circadian problems we have been able to model with degus is the interaction of photic and nonphotic entraining cues for hastening recovery (re-entrainment) from a phase-shift of the light cycle. The re-entrainment process is particularly relevant for humans because modern technology permits us to move across several time zones within a few hours, thereby developing desynchronosis, more commonly called jet lag (Gander et al. 1985a,b; Gundel and Wegman 1989). Desynchronosis leads to reduced sleep and alertness resulting in cognitive deficits and increased accident rates (Cho 2001; Cho et al. 2000; Dinges 1995; Dinges et al. 1997), as well as metabolic and endocrine disruptions (e.g., Spiegel et al. 1999), which lead to a variety of symptoms including gastrointestinal distress, ulcers, and depression (Wegman et al. 1986; Winget et al. 1984), particularly when there is chronic circadian disruption. Similar symptoms develop for individuals chronically changing work times and likely in response to other health concerns such as aging, long illness, hospitalization, and some pharmacological agents that cause desynchronosis (e.g., Closs 1988; Miles and Dement 1980). The most severe of these symptoms are likely the result of elevated cortisol (Cho 2001; Cho et al. 2000). Recent data demonstrate a close link between the hypothamamic-pituitary-adrenal axis function and duration of the re-entrainment period after a phase-shift in degus and rats (K. Cashen, J. M. Mohawk, T.M.L., in preparation; Weibel et al. 2002). Longer periods of elevated cortisol may well lead to the more severe symptoms associated with repeated or long-term desynchronosis. Thus it is imperative to find ways to maintain internal circadian synchrony and to resynchronize individuals with the new environment's light cycle rapidly.

Numerous nonphotic timing cues have been used to entrain or re-entrain circadian rhythms in humans and other species, including timed meals, exercise, sleep, exposure to darkness, and social interactions (e.g., Eastman et al. 1995; Klein and Wegmann 1974; Mrosovsky 1995). Klerman et al. (1998) have the most convincing data for humans that nonphotic interactions can supply an entraining signal to some retinally blind individuals (for whom no light information reaches the brain). They concluded that social interactions might be a particularly important timing cue for these individuals. A few other studies have examined the possible interaction of social cues with photic cues during recovery from a phase-shift in the light cycle after transmeridian travel (Honma et al. 1995; Klein and Wegmann 1974). The evidence was promising, but not completely convincing, that social interactions hastened recovery from jet lag.

One reason we chose to use degus as an animal model was to address the question of whether social interactions could act as a timing cue in a highly social species. In the field, social behavior is extensive; male and female degus engage in collaborative grooming, alternate sentinel duties during group feeding episodes, produce alarm calls in response to potential predators, and jointly maintain territorial boundaries; and females share nests during lactation with burrow mates (Fulk 1976; Vasquez 1997, 1998). Kleiman (1975) demonstrated that female degus are readily able to distinguish individuals by odor, whereas the males' abilities to distinguish others by odors were somewhat less impressive (Fischer and Meunier 1985; Fischer et al. 1986). These data led us to hypothesize that social interactions that influence circadian function, if they acted through an olfactory mechanism, would likely be sexually dimorphic in their effectiveness in degus.

Indeed, Goel and Lee (1995a,b) demonstrated that female degus recover from a phase-shift of 6 hr (phase-shifter) 25 to 40% faster when they are housed with another entrained female degu (donor) than either when they are housed with another female that is also recovering from the phase-shift or when they are housed alone (Figure 3). When female phase-shifters were paired with male donors, there was a positive effect on recovery from phase delays, but not phase advances (Goel and Lee 1995b). In the paradigm in which animals are paired with a single donor, there was no significant improvement in recovery from the phase-shift for males whether they were housed with male or female donors (Goel and Lee 1995a,b). Jechura and colleagues (2003) subsequently demonstrated that adult males provided with at least two female donors, or who were castrated, were able to re-entrain as quickly as adult females with a single female donor. Thus, adult testosterone levels diminish the ability of the males to respond to the social interaction. The role of adult steroid hormones was later shown to be important for females as well; ovariectomized females do not improve recovery times when housed with an intact female donor (T. J. Jechura and T.M.L., in preparation). This sexual dichotomy is interesting: Intact males are less sensitive than females to the effects of donors on re-entrainment when testosterone is present, and females are sensitive only when ovarian hormones are present. Additionally, Jechura (2002) found that only ovarian-intact females produce the signal.

In several experiments, we have gone on to show that odors from entrained conspecifics (without any other visual, auditory, or tactile contact), particularly from females, are sufficient to improve the re-entrainment rate (Goel and Lee 1997b; Governale and Lee 2001). Governale and Lee (2001) also demonstrated that the ϑ of free-running animals could

Figure 3 Double-plotted general activity (no running wheel) rhythms for a phase-shifting female housed with (A) and without (B) an entrained female donor on the other side of a screen barrier. Each horizontal line represents 2 days of activity, and the darkened areas indicate the time when the animal was active. The second day of each line is repeated as the first day on the line below it, allowing one to see the changing pattern vertically down the page. The top light:dark bar indicates 12:12 light:dark, lights on at 1200 hr; the bottom light:dark bar indicates the new 6-hr phase-light cycle that occurred on day 4 (first arrow on left of actograms). The second arrow on the actograms indicates when re-entrainment was completed. Re-entrainment is defined as complete when the phase angle of activity onset returns to the phase established before the phase-shift in the light cycle. Data from Goel N, Lee TM. 1995b. Social cues accelerate reentrainment of circadian rhythms in diurnal female *Octodon degus* (Rodentia-Octodontidae). Chronobiol Int 12:311-323.

be altered by brief daily exposure to the odors of donors, and in some cases rhythms were entrained for many days. In addition, if females are bulbectomized before a phase-shift, then exposure to a donor has no effect on the rate of re-entrainment (Goel and Lee 1997a). These data demonstrate that degu conspecific odors can act as a nonphotic zeitgeber, even in the absence of light.

These data have provided us with several unique opportunities to study the mechanism by which nonphotic and photic interactions can influence the circadian mechanism. Because the neural pathway by which odors reach various areas of the brain is well described in rats and hamsters (and likely to be similar in other mammals), we can test hypotheses about how odors might alter SCN function. For example, odors alter neural activity in areas of the amygdala projecting to the paraventricular nucleus of the thalamus (PVT[1]). The PVT has reciprocal connections with the SCN. Data from Moga and colleagues (Moga and Moore 2000; Moga et al. 1995) suggest that PVT-SCN projections may modulate the circadian signal from the SCN. This modulation could occur by altering light signals into the SCN (as with raphe serotonergic afferents), by directly influencing the biochemical process (circadian oscillations in the amount of Per protein within the SCN cells; Per cycles) that generates the circadian signal, or by modulating the efferent neural signal from the Per-containing cells.

At a different level of analysis, we would like to know whether the circadian systems of other highly social mammals are sensitive to social interactions, and specifically to odors. Data from Amir et al. (1999a,b) suggest that odors can alter the function of the SCN in rats. It is not yet clear whether such signals interact with light or can act as independent timing cues during re-entrainment. Mammals, in general, are highly sensitive to olfactory cues. And although humans are considered to be poor at such responses, compared with rodents or canines (for example), recent work from Jacob et al. (2001) suggests that we may be unaware of the extent of olfactory influence on neural function. Finally, these data, in conjunction with other results demonstrating the great variety of nonphotic timing cues in many species, suggest that such cues may be quite species-specific and may have developed effects on the circadian system due to their great importance to the species in specific contexts. For example, birds (Gwinner 1966; Menaker and Eskin 1966) can be entrained by the sound of other bird calls. In degus, we found that vocalizations occurred so rarely that they could not provide such a signal (Goel and Lee 1996); and we would not expect conspecific odors to have the same impact on birds as on burrow-dwelling social rodents.

Conclusion

Although we originally chose to develop the degu as a model to study fundamental circadian properties in a diurnal species, in the effort to determine how they might differ from nocturnal species, we have discovered a much richer array of research questions that can be answered because of their specific species characteristics. Their precocious state at birth combined with their slow rate of development (for a rodent) and multiple sexual dimorphisms in circadian function provide numerous opportunities to address research questions that are relevant to human circadian rhythms and particularly to appreciate the differences in circadian function of different sexes and different ages. Ultimately, they may lead us to consider the importance of age and gender in the context of human public health as it relates to circadian-related disorders.

Comparative work with other diurnal and nocturnal rodents has demonstrated that the original nocturnal circadian system of mammals has the evolutionary flexibility to enter a diurnal time niche through several different modifications of the underlying mechanism. Studies with degus have uniquely combined an examination of the role of photic and nonphotic signals on the fundamentals of circadian entrainment. Furthermore, I believe that degus will prove very useful in understanding the interactions between the reproductive and stress axes and the circadian system, that is, not only how the circadian system influences those neuroendocrine functions, but also how those axes can affect the function of the circadian system. Because degus have long ovarian cycles with a luteal phase and they have not been bred for laboratory docility, they may be uniquely appropriate for these studies among the rodents currently used in laboratory studies.

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