



Research report

Removal of the olfactory bulbs delays photic reentrainment of circadian activity rhythms and modifies the reproductive axis in male *Octodon degus*Namni Goel^{a,*}, Theresa M. Lee^a, David R. Pieper^b^a Department of Psychology, 525 East University, University of Michigan, Ann Arbor, MI 48109, USA^b Department of Physiology, Providence Hospital, 16001 W. Nine Mile Road, Southfield, MI 48037, USA

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Abstract

The diurnal rodent, *Octodon degus*, exhibits robust sex differences in several circadian measures, including circadian period (τ) and reentrainment rates to photic and nonphotic (social) zeitgebers. The neural substrates underlying such physiological differences remain unknown. In female *degus*, olfactory bulbectomies (BX) inhibit socially-facilitated reentrainment, but do not alter photic reentrainment, entrained measures, or τ in constant darkness (DD). This experiment investigated the effects of BX in male *degus* on (i) photic reentrainment rates of circadian rhythms following a 6-h phase advance of the light–dark (LD) cycle; (ii) photic entrainment; (iii) τ of free-running activity rhythms in DD; and (iv) body weight, paired testis weight, and the reproductive hormones, testosterone, androstenedione and follicle stimulating hormone (FSH). BX significantly delayed photic reentrainment rates. They did not, however, modify τ , the phase of activity onset or offset, amplitude or duration (α) of the activity rhythm, mean daily locomotor activity levels, or body weight. FSH, testosterone and androstenedione were unaffected by BX, whereas paired testis weights were significantly greater in BX *degus* compared with shams. Thus, the olfactory bulbs influence photic reentrainment of circadian rhythms and modestly affect the reproductive axis in male *degus*. Our results suggest that the olfactory bulbs may be a neural source of observed sex differences in photic reentrainment in *degus*, and highlight interspecies variation in the olfactory bulbs' effects on entrained and free-running circadian rhythms and on reproduction. © 1998 Elsevier Science B.V.

Keywords: Testosterone; FSH; Testis; Body weight; Sex difference; Free-running; Diurnal; Rodent

1. Introduction

The diurnal rodent, *Octodon degus*, manifests sex differences in the formal properties of circadian rhythms. For example, the circadian period (τ) of free-running activity rhythms in constant darkness (DD) is shorter in males than in females [10,12]. Exposure to bright light (6000 lx) lengthens τ significantly more in males than in females housed in constant light (LL), and in males, but not females, yields faster reentrainment rates of activity rhythms to phase shifts of the light–dark (LD) cycle [[12], T.M. Lee, unpublished]. Similarly, under normal lighting

intensities, the circadian activity rhythms of males reentrain faster to 6-h phase advances of the LD cycle than do those of females [5]. By contrast, the entrained phase angle of activity onset and body temperature minimum, and the incidence of ‘morning’ and ‘evening’ chronotypes do not differ between adult male and female *degus* [11].

The neural substrates modulating such circadian sex differences are currently unknown. Because olfactory bulbectomies (BX) lengthen τ in DD and modify photic entrainment of circadian rhythms in other male rodents [1,13,20,26,27], the olfactory bulbs may modulate such variables in male *degus*, and thus may underlie some of the reported circadian sex differences in *degus*.

In female *degus*, BX impede socially-facilitated reentrainment rates, but do not alter reentrainment rates of circadian rhythms to photic cues alone or modify τ of free-running activity rhythms in DD [8]. In entrained conditions, BX decrease mean daily locomotor activity levels

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and the amplitude of the activity rhythm, but do not alter the phase of activity onset or offset, duration (α) of activity, or mean daily core body temperature. In the present experiment, we wanted to determine if the previously observed effects of olfactory bulb removal on entrainment, reentrainment and free-running circadian rhythms could be extended to male degus.

Our previous study in females also suggested possible interspecies differences in the role of the olfactory bulbs in circadian rhythm regulation. For example, olfactory bulbectomies lengthen τ of locomotor activity rhythms in male mice [26,27], hamsters [20] and rats housed in DD [13], but do not affect τ in female degus [8]. BX delay the phase of activity onset in male mice [26,27] and hamsters [1,20], and lengthen α of the activity rhythm in hamsters [20], neither of which is modified in female degus [8]. Furthermore, BX decrease daily mean activity levels in degus but increase activity levels in male mice housed in LD or DD [26]. BX also decrease the amplitude of the activity rhythm in degus, consistent with reports in rats [13]. Because other BX experiments in rodents exclusively have studied nocturnal males, the above interspecies variations resulting from olfactory bulb removal may be due to sex and/or diurnal–nocturnal differences. By studying males, we sought to examine whether sex was a factor underlying such variations.

In addition to their circadian effects, the olfactory bulbs influence the reproductive axis in mammals. For example, olfactory bulbectomies inhibit the negative feedback of testosterone on gonadotropins [25], and elevate gonadotropin levels in male and female Syrian hamsters [4,21,23,24]. In contrast to their changes in hamsters, follicle stimulating hormone (FSH) and luteinizing hormone (LH) are not altered in long-day, BX male rats [22] or in ovariectomized, estradiol-implanted, BX Suffolk ewes [9]. Thus, our third purpose was to examine the reproductive consequences of olfactory bulb removal in a male, diurnal rodent.

2. Materials and methods

2.1. Subjects and housing

Subjects were 18 mature male *Octodon degus* (1–2 years of age, with an average lifespan of 5–7 years) born in a laboratory colony at the University of Michigan. Prior to this experiment, animals were housed in LD 12:12, lights on at 0600 h (average light intensity was 250 lx) with room temperature at $21^\circ \pm 2^\circ\text{C}$ and humidity held at 50–60%. Degus were maintained on a diet of Purina Rodent Chow and Guinea Pig Chow supplemented weekly with apples and peanuts. Both food and water were available ad libitum.

During the entrained and photic reentrainment phases of the experiment, males were housed individually in $42.5 \times$

22×19 cm cages fitted with Nalgene running wheels (9 cm wide \times 34.5 cm in diameter) in LD 12:12 in the room conditions noted above. The same conditions applied in DD (0 lx).

2.2. Procedure

Degus were housed in LD 12:12, lights on at 0600 h for 3 weeks (Pre-SHAM/BX entrained phase; Fig. 1). Next, animals underwent either sham surgery ($n = 8$) or removal of the olfactory bulbs ($n = 10$; described below) and remained in LD 12:12, lights on at 0600 h for 3 additional weeks following surgical procedures (Post-SHAM/BX entrained phase; Fig. 1). The LD cycle was then advanced 6 h (a single shortening of the light phase; darkness began at 1200 h on the day of the advance), and experimental animals remained in the new LD cycle (LD 12:12, lights on at 2400 h) for 4 weeks to insure complete reentrainment of their circadian activity rhythms (Photic reentrainment phase; Fig. 1). Next, degus were released into DD, where they remained for 4 weeks (Free-running phase; Fig. 1). In the final stage of the experiment, degus were returned to LD 12:12 (lights on at 0600 h) for 2 weeks (Post-DD entrained phase; Fig. 1). At the end of this phase, degus were weighed, anesthetized with halothane, and rapidly decapitated in order to collect trunk blood. Brains were removed and examined under a dissection scope, and testes were removed, trimmed and weighed.

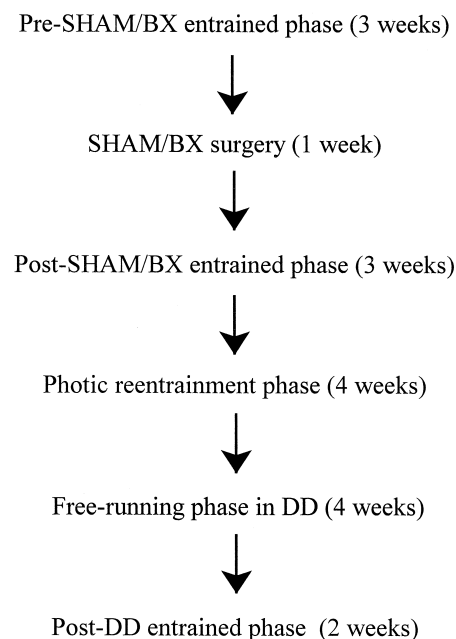


Fig. 1. Diagrammatic timeline of the different experimental phases. The number of weeks degus spent in each condition is indicated in parentheses. See text for details.

2.3. Blood collection and radioimmunoassays

Following decapitation, blood samples were collected and stored in unheparinized tubes, allowed to clot overnight, and then centrifuged at 3000 revolutions/min for 15 min. Plasma was stored at -20°C until assayed for testosterone, androstenedione and FSH.

Serum FSH was determined by using the National Institute of Diabetes and Digestive and Kidney Diseases' rat FSH radioimmunoassay (RIA) kit with RP-2 as the standard and anti-r-FSH S-11 as the primary antibody. The intra-assay coefficient of variation (CV) was 4.0%, and the sensitivity of the assay (defined as the concentration at 95% B/Bo) was 2.0 ng/ml. Serially diluted degu serum curves were parallel to the rat FSH standard inhibition curve.

Total serum testosterone was quantified using the 'Coat-A-Count' direct RIA kit (Diagnostic Products, Los Angeles, CA). Serum samples with or without diethyl ether extraction yielded similar results. The cross-reactivity was 3.3% with dihydrotestosterone and 0.5% with androstenedione. The intra- and inter-assay CVs were 2.8% and 5.1%, respectively, and the sensitivity of the testosterone assay was 0.04 ng/ml.

Serum androstenedione levels were determined using a double antibody RIA kit (Diagnostic Systems Laboratories, Webster, TX). The cross-reactivity was 0.33% with androsterone, 0.07% with dehydroepiandrosterone (DHEA), and 0.01% with DHEA-Sulfate. The sensitivity of the androstenedione assay was 0.02 ng/ml and the intra-assay CV was 3.1%.

2.4. Surgery

Following random assignment to either the SHAM or BX group, degus were anesthetized with 120 mg/kg Ketamine HCL (i.p.), 4 mg/kg Xylazine (i.p.) and 0.1 mg/kg Butorphanol (i.p.). Details of the surgery procedure have been described previously [8]. Briefly, sham animals were positioned in a Kopf stereotaxic, and a 2-cm hole was drilled through the skull bilaterally, lateral to the midline, and just dorsal to the anterior tip of the eye. An identical procedure was used for bulbectomies, except the olfactory bulbs were removed by aspiration using Suction Vac (Schuco, Toledo, OH).

2.5. Data collection and analysis

Running wheel activity data were collected, recorded and stored in 10-min bins by Dataquest III (Mini-mitter, SunRiver, OR). Using daily histograms, 5 measures were analyzed for data collected in entrained conditions (Pre- and Post-SHAM/BX entrained phases): mean daily activity level, activity onset, activity offset, α of activity, and amplitude of activity. For each measure, 10–12 days of entrained data were averaged to determine a mean value

per animal. The measures were defined as follows: mean daily activity level was the average number of revolutions per 10 min calculated across a 24-h interval beginning from midnight each day; activity onset was the point when 40 counts of activity per 10 min for at least a 20-min period occurred following a minimum 4-h hiatus of activity [5,6,8]; activity offset was the point when locomotor activity fell below the mean daily activity level for at least 4 h [8,11,12]; α of activity was the difference between activity onset and offset; and amplitude of the activity rhythm was the difference between the daily rhythm peak (maximum value in a 10-min data interval) and the mean daily activity level [5,8,10].

Following the 6-h phase advance, daily histograms and actograms of activity data were used to determine the number of days (reentrainment rate) it took for each animal's activity rhythm to reestablish its former phase relationship to the new lighting schedule [5–8]. Reentrainment of the activity rhythm was evaluated by monitoring activity onset (defined above).

2.6. Statistical analyses

The free-running τ of locomotor activity rhythms for the last 2 weeks of data collected in DD was determined by Cosine analysis and Fourier analysis (Dataquest) [8]. Multivariate repeated measures analysis of variance and post hoc comparisons using Bonferroni-adjusted probabilities were used to compare pre-SHAM/BX and post-SHAM/BX entrained circadian measures. One-way analysis of variance compared differences between groups in reentrainment rates, τ s, body weights, paired testis weights and hormone levels. Data are presented as mean \pm S.E.M. where applicable; $p < 0.05$ was considered significant.

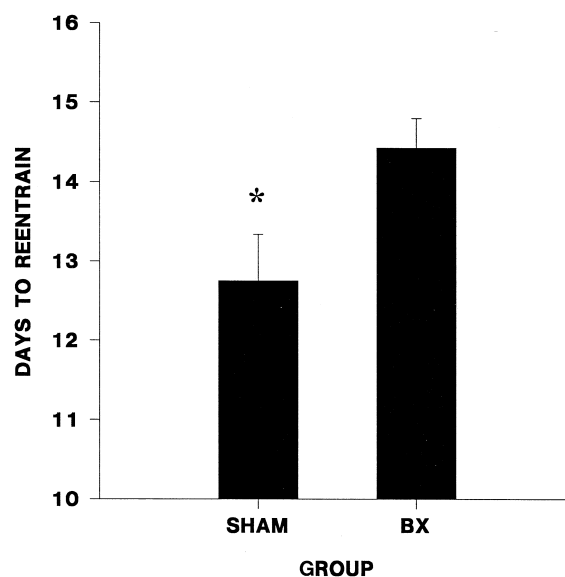
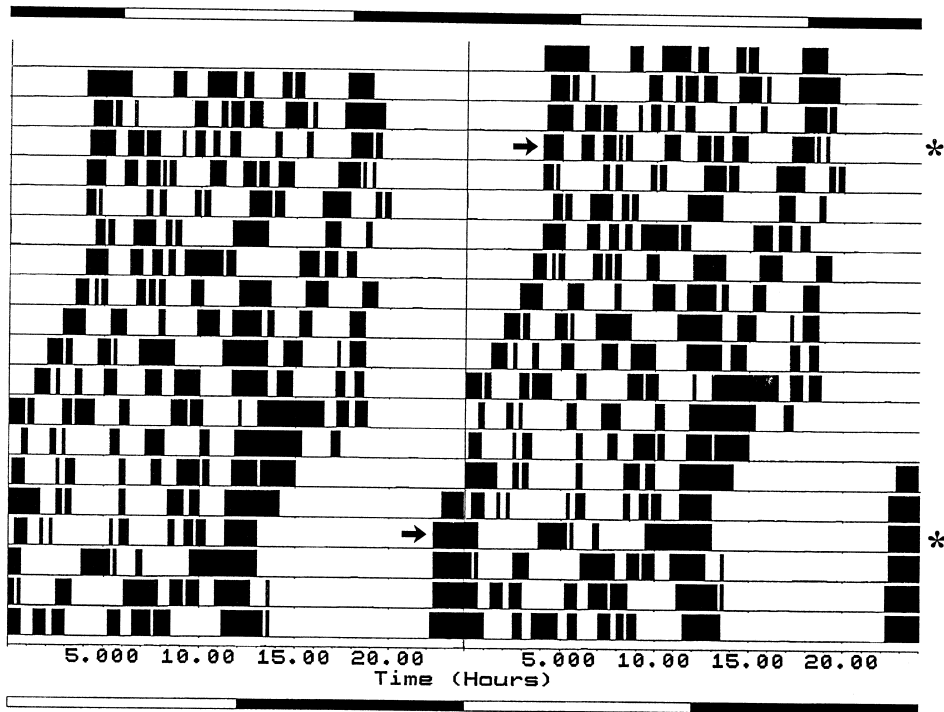


Fig. 2. Mean (\pm S.E.M.) number of days required for reentrainment of the locomotor activity rhythm to a 6-h advance of the light-dark (LD) cycle. Symbols: SHAM = sham surgery group ($n = 8$); BX = bulbectomized group ($n = 8$). * = significantly less than the BX group, $p < 0.05$.

A - SHAM



B - BULBECTOMY

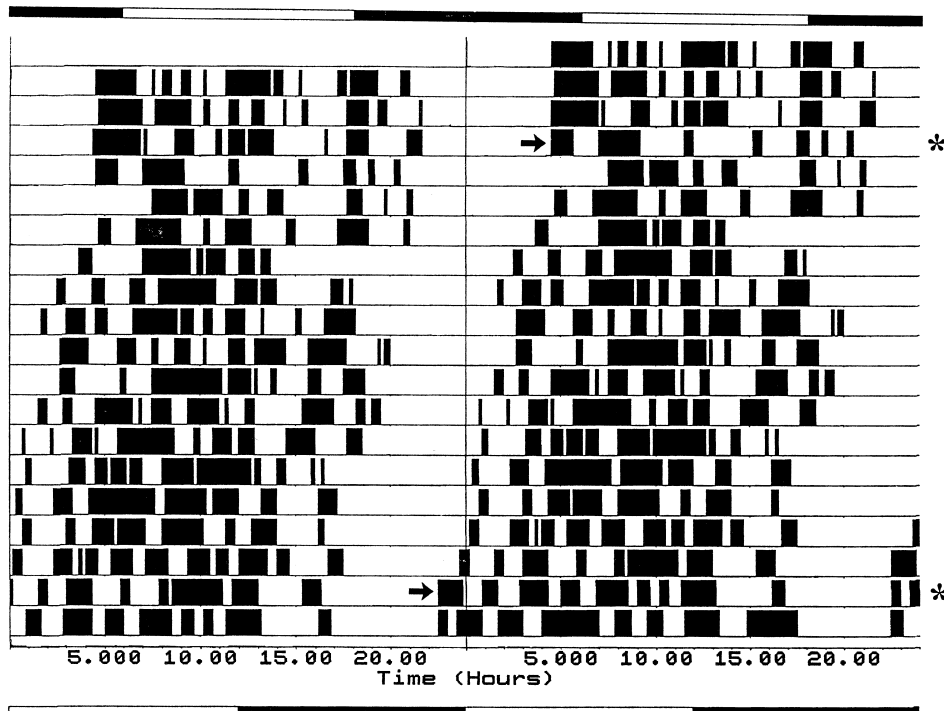


Fig. 3. Representative double-plotted actograms depicting reentrainment rates of the circadian locomotor rhythm to a 6-h phase advance of the LD cycle for a SHAM (A) and a BX (B) male degu. Each line represents one day of data, with the lowest 10% of activity values eliminated from the figure, for ease in viewing activity onset. Such elimination did not include activity bouts qualifying as part of activity onset. The top LD bar indicates the initial lighting schedule (LD 12:12, lights on at 0600 h). The first asterisk in the right margin marks the day of the phase shift (6-h advance) and the first arrow denotes the phase angle prior to the shift. The bottom LD bar indicates the new lighting schedule (LD 12:12, lights on at 2400 h). The second asterisk in the right margin denotes the day of reentrainment as determined by the reestablished phase angle (second arrow).

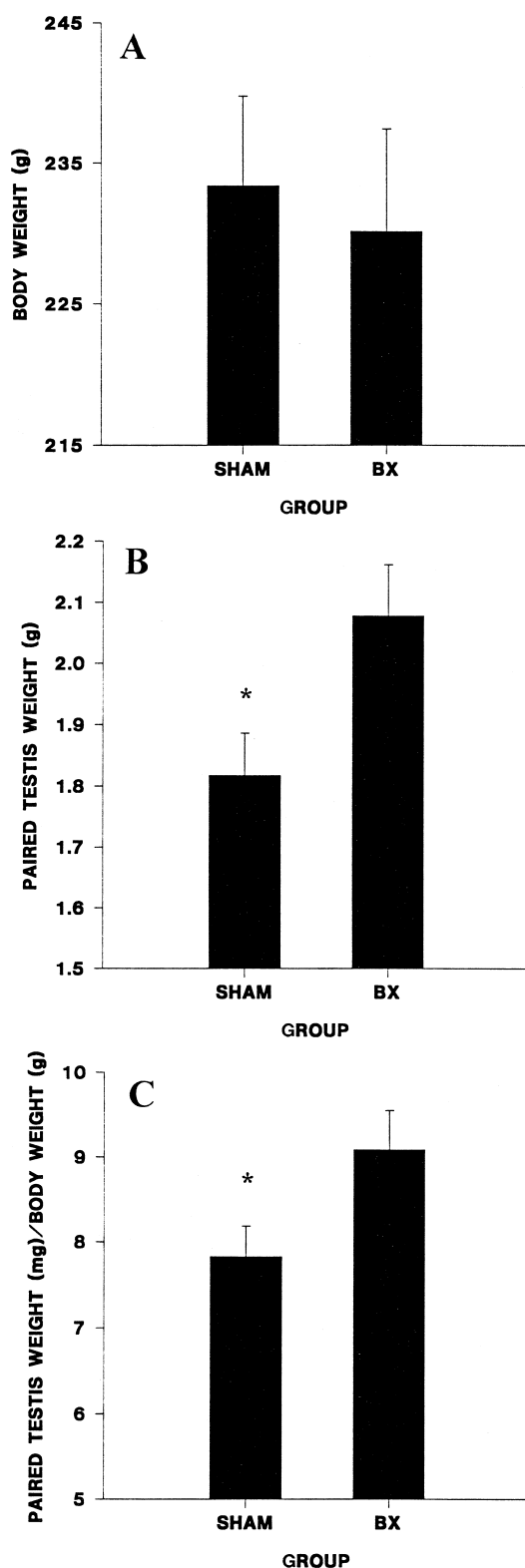


Fig. 4. Mean (\pm S.E.M.) body weight (A), paired testis weight (B) and paired testis weight/body weight (C) for the SHAM ($n = 8$) and bulbec-tomized (BX; $n = 8$) groups. Symbols as in Fig. 1. * = significantly less than the BX group, $p < 0.05$.

3. Results

3.1. Bulbectomy verification

The extent of neural damage was assessed via gross examination of the brains under a dissecting microscope. Of the 8 degus with complete extirpation of their olfactory bulbs, 3 also sustained slight bilateral frontal lobe damage. Data from the 2 males with incomplete damage to the olfactory bulbs were excluded from statistical analyses.

3.2. Photic reentrainment

The locomotor activity rhythms of the SHAM group reentrained faster after a 6-h phase advance of the LD cycle than those of the BX group (Figs. 2 and 3; $p < 0.05$).

3.3. Body weight, testis weight and hormonal assays

BX animals did not differ significantly in body weight from SHAM animals (Fig. 4A), although they had larger paired testis weights (Fig. 4B; $p < 0.05$) and paired testis weight/body weight ratios (Fig. 4C; $p < 0.05$). In contrast, the SHAM and BX groups did not differ significantly in hormone measures, including total testosterone [SHAM ($n = 5$): 0.80 ± 0.31 ng/ml; BX ($n = 6$): 0.36 ± 0.05 ng/ml; $p = 0.15$]; androstenedione [SHAM ($n = 8$): 0.60 ± 0.18 ng/ml; BX ($n = 8$): 0.74 ± 0.31 ng/ml; $p = 0.71$] or FSH [SHAM ($n = 8$): 5.07 ± 0.56 ng/ml; BX ($n = 6$): 4.52 ± 0.53 ng/ml; $p = 0.51$].

3.4. Entrained conditions

There were no significant differences between the BX and SHAM groups in the phase of activity onset or offset, α or amplitude of the activity rhythm, or daily mean locomotor activity for the last 10–12 days in entrained conditions prior to SHAM/BX surgery (Pre-SHAM/BX entrained phase). Similarly, post-SHAM/BX entrained measures were not significantly different between the two groups (see Table 1).

Table 1

Mean (\pm S.E.M.) values for 5 circadian activity measures collected in the post-SHAM/BX surgery phase

Measurement	Group	Mean value	p -Value
Phase of onset (h)	SHAM	$+0.60 \pm 0.15$	$p = 0.11$
	BX	$+1.01 \pm 0.18$	
Phase of offset (h)	SHAM	-16.36 ± 0.74	$p = 0.62$
	BX	-15.92 ± 0.49	
Duration (h)	SHAM	16.96 ± 0.83	$p = 0.97$
	BX	16.92 ± 0.46	
Amplitude	SHAM	597.20 ± 57.87	$p = 0.29$
	BX	514.82 ± 47.48	
Activity level (# revolutions/10 min)	SHAM	123.15 ± 17.31	$p = 0.46$
	BX	107.91 ± 10.70	

3.5. Free-running conditions

The groups did not differ significantly in τ of free-running activity rhythms in DD (SHAM: 23.42 ± 0.10 h; BX: 23.67 ± 0.14 h; $p = 0.20$).

4. Discussion

Removal of the olfactory bulbs in male degus significantly delayed photic reentrainment of circadian rhythms after a phase shift of the LD cycle, but did not modify τ of free-running activity rhythms in DD. Olfactory bulbectomies did not alter the phase of activity onset or offset, α or amplitude of the locomotor activity rhythm, or mean daily locomotor activity levels in entrained conditions. BX resulted in increased paired testis weights, but did not affect body weight, or testosterone, androstenedione or FSH levels. We conclude that the olfactory bulbs influence the effects of photic information on the circadian timing system during reentrainment and modestly affect the reproductive axis in male degus.

The olfactory bulbs may have a sexually differentiated role in the reentrainment of circadian rhythms to light in degus. Olfactory bulbectomies delayed photic reentrainment in males, but were without effect in female degus [8]. As such, our data may provide a neural explanation for the previously reported sex difference in photic reentrainment rates of circadian rhythms following phase advances [5]. Such a sex difference could be due to a facilitatory effect of the olfactory bulbs' on photic reentrainment in males, but not in females. Removal of the olfactory bulbs in males, therefore, may retard reentrainment by inhibiting responsiveness to environmental stimuli. In contrast to their apparent sexually-differentiated function in photic reentrainment, the olfactory bulbs do not appear to modulate sex differences in τ or in entrained circadian measures in degus. It should be noted that although males and females were not tested in the same experiment per se, they were investigated under very similar experimental conditions, permitting reasonable comparisons to be drawn between studies.

Because BX resulted in larger paired testes 4 months following surgery, the olfactory bulbs appear to tonically modulate gonad size and the neuroendocrine axis in males. There are several possibilities for why the testes weigh more in BX males than in shams. BX may decrease the sensitivity of the negative feedback effect of testosterone on gonadotropin secretion. However, because FSH remains unaltered in BX degus, decreased sensitivity selectively may target LH or prolactin. Alternatively, increases in testis weight may be independent of changes in pituitary hormone secretion. For example, BX degus may be hypersensitive to local testosterone as a result of increases in the number and/or affinity of androgen receptors within the testes. Finally, testosterone may have a faster clearance

and/or degradation rate in BX animals than in intact animals.

We did not detect changes in FSH or testosterone following BX. Similarly, FSH and LH are not altered in BX male rats housed in long days [22] or in ovariectomized, estradiol-implanted, BX Suffolk ewes [9]. By comparison, olfactory bulbectomies elevate gonadotropin levels in male and female Syrian hamsters [4,21,23,24] and inhibit the negative feedback of testosterone on gonadotropins [25].

Reported changes in hormone levels in BX animals often occur as a result of altered photoperiods. For example, BX disrupt gonadal regression normally induced by short photoperiods in male Syrian hamsters [1,4,21,24] and block short photoperiod-induced anestrus in females [23]. BX also delay, but do not prevent inhibitory responses to short days in male lesser mouse lemurs [18,30]. In some cases, BX make traditionally 'nonphotoperiodic' species overtly photoperiodic. For instance, following BX, prepubertal rats and mice are rendered sensitive to the inhibitory effects of short days [16,17,22] and female pigs undergo anestrus during the summer and fall [2], indicating that the olfactory bulbs mask responsiveness to photoperiodic regulation of gonadal functions in these species. Although systematic experiments must be conducted to determine whether degus are photoperiodic, preliminary data from our laboratory suggest that they are not overtly so (T.M. Lee, unpublished).

In contrast to their effects on paired testis weights, olfactory bulbectomies did not alter body weight in degus. Our findings are consistent with those in female rats, male Syrian hamsters, male house mice and male lesser mouse lemurs, in which BX do not significantly modify body weight [3,16,18,19,28]. Similarly, in male golden-mantled ground squirrels, although the period of the circannual rhythm of body mass is lengthened by BX, peak body weight values remain unchanged [29]. By contrast, removal of the olfactory bulbs decreases body weight in long-day male rats [22] and increases body weight by inducing hyperphagia in male European hamsters [14,15].

Olfactory bulbectomies failed to produce changes in entrained circadian measures in male degus. Our results differ from reports in male hamsters and mice [1,20,26,27], in which BX altered α and activity onset. In male degus, BX did not decrease the amplitude of the activity rhythm, as has been reported in male rats [13] nor did they increase activity levels as has been reported in male mice [26]. Olfactory bulbectomies also did not alter τ of activity rhythms in male degus, consistent with results reported in females [8], but different from those obtained in other rodent species, including male rats, hamsters and mice, in which τ was lengthened following BX [13,20,26,27]. Previously, we had proposed that the above species variations could be due to sex and/or nocturnal–diurnal differences [8]; data from this study in males eliminates the former as a possibility. However, differences in experimental proce-

dures, use of small sample sizes, and variations in definitions of circadian variables among studies also may underlie interspecies differences.

At present, a functional explanation for the olfactory bulbs' influence on circadian rhythms is lacking. Because olfactory bulbectomies delay reentrainment to photic cues in males, and impede reentrainment to combined photic and nonphotic (social) cues in females [8], the olfactory bulbs are implicated in the control and/or interpretation of photic (in males) and nonphotic (in females) signals reaching the circadian timing system. Adult males may be highly sensitive to photic cues, primarily relying on such cues for reentrainment, while females may respond to both photic and nonphotic information for reentrainment. Indeed, data from our laboratory support this notion. Males appear to be more sensitive to light than females: they reentrain faster to large phase shifts of the LD cycle during exposure to bright and normal lighting conditions, and their τ_s lengthen significantly more than those of females housed in constant bright light [[5,12], T.M. Lee, unpublished]. By contrast, females appear more sensitive to nonphotic (social) cues than males: females, but not males, reentrain faster to large phase shifts of the LD cycle in the presence of photic and social cues compared with photic cues alone [5–7].

BX delayed photic reentrainment of circadian rhythms to a 6-h phase advance in male degus. This result, coupled with that from a separate study in females in which BX did not delay photic reentrainment under similar conditions, provide evidence for a sex difference in the neural control of circadian rhythms, with a modulatory role for the olfactory bulbs. The olfactory bulbs also exert tonic effects upon the male reproductive axis, particularly gonad size. Finally, this study confirms and extends the notion of inter- and intra-species differences in the neural structures that influence circadian rhythms, underscoring the importance of investigating functional questions relating to circadian rhythms in a variety of species.

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