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Review article

The volcano mouse *Neotomodon alstoni* of central Mexico, a biological model in the study of breeding, obesity and circadian rhythms

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ABSTRACT

The “Mexican volcano mouse” *Neotomodon alstoni*, is endemic of the Transverse Neovolcanic Ridge in central Mexico. It is considered as least concern species and has been studied as a potential laboratory model from different perspectives. Two lines of research in neuroendocrinology have been addressed: reproduction and parental care, particularly focused on paternal attention and the influence of testosterone, and studies on physiology and behavior of circadian rhythms, focused on the circadian biology of the species, its circadian locomotor activity and daily neuroendocrine regulation of metabolic parameters related to energy balance. Some mice, when captive, spontaneously develop obesity, which allows for comparisons between lean and obese mice of daily changes in neuronal and metabolic parameters associated with changes in food intake and locomotor activity. This review includes studies that consider this species an attractive animal model where the alteration of circadian rhythms influences the pathogenesis of obesity, specifically with the basic regulation of food intake and metabolism and differences related to sex. This study can be considered as a reference to the comparative animal physiology among rodents.

1. Introduction

The mouse *Neotomodon alstoni* Merriam, 1898, is an endemic nocturnal murid rodent of the Neotominae subfamily restricted to the Transverse Neovolcanic Ridge of the central zone of Mexico, hence its name of “Mexican volcano mouse.” *N. alstoni* inhabits pine forests, especially in areas covered with grass. Its altitudinal distribution is between 2600 and 4600 m and can be located in the States of Morelos, Michoacán, Veracruz and Estado de México (García-Becerra et al., 2012). Nowadays, *Neotomodon alstoni* is listed as Least Concern given its wide distribution, according to the red list of the International Union for Conservation of Nature (IUCN) (Álvarez-Castañeda and Castro-Arellano, 2016). *N. alstoni* cohabits with other rodents such as *Peromyscus maniculatus, Reithrodontomys megalotis* and *Microtus mexicanus* (Castillo-Guevara et al., 2012; Sánchez-Cordero and Canela-Rojo, 1991; Sánchez-Cordero and Méndez, 2014). *N. alstoni* lives in burrows and has an omnivorous diet based on grains and insects, which does not seem to vary according to the time of year (Alvarez and Mayo, 1993). In adults, the nasoanal length is 100–130 mm, and the tail ranges from 80 to 105 mm. Ears are almost bare; hair of the dorsal region is dense and gray while the ventral fur is whitish. Adults usually weigh from 40 to 50 g (Nowak, 1999). A cytogenetic analysis shows that its chromosome number is $2n = 48$ with a fundamental number $NF = 66$, like *Peromyscus* (Uribe et al., 1974). Diverse studies on its reproductive biology show that *N. alstoni* may adapt favorably to captive conditions (Granados and Hoth, 1989; Luis and Granados, 1990) and, in captivity, it can live up to five years (Ayala-Guerrero et al., 1998).

2. Reproduction and paternal care

N. alstoni is reproductive throughout the year but mainly during the dry season of spring, with a higher birth rate from April to May, decaying during the summer rainy season (Sánchez-Cordero and Canela-Rojo, 1991). *N. alstoni* can reach sexual maturity in both sexes at three months of age. The estrous cycle lasts between 4 and 5 days, and it is characterized by typical variations of vaginal histology in mice, accompanied by fluctuations in estradiol, that in females may influence the amplitude of activity, also referred to as “scalloping” (Juárez-Tapia and Miranda-Anaya, 2017). Ultrastructural studies of follicular development indicate that the first preovulatory follicles, as well as Corpus luteum, are observed after 40 days of age, and the ovulation is spontaneous (Luis et al., 2008). In males, spermatozoa show an asymmetric head and a recurved hook. They also present long flagella composed of a medium piece and a thin end region, and asymmetric development of microfiber 1,5 and 6 of the axoneme, possibly related to its mobility, which increases in bicarbonate solutions (Villalpando et al., 2000).

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When in captivity, the litter size is three mice on average, with nearly 70% of survival (Granados and Hoth, 1989; Luis and Granados, 1990). The males exposed to long-days photoperiod (16 h light: 8 h darkness) have a discrete increase in testicular volume, not related to changes in circulating levels of testosterone, as occurring in hamsters, which suggests that this species has not a photoperiodic induction of reproduction (Fuentes-Granados et al., 2010). Under captivity, *Neotomodon* also shows the behavior of monogamous species, such as parental care in transportation and care of offspring, as well as nest defense, maintenance, and grooming. Males show parental care similar to mothers, such as snuggling, sniffing, fixing and recovering the young, as well as care and surveillance in the nest (Granados and Hoth, 1989). In captivity, male and female build a nest together and remain close without aggression (Luis et al., 2000, 2008, 2009). When the couple is together, the female presents less attention to the offspring than the male. With paternal care, offspring grow better and the litter survival increases (Luis et al., 2000, 2004). Paternal care in this rodent is integrated by huddling, grooming, and retrieving pups (Luis et al., 2000). The onset of paternal behavior seems to be related to high levels of testosterone (Luis et al., 2012, 2017), and it does not seem to change as pups age. After mating and during breeding, parents can be notably aggressive with other males (Granados et al., 1996), which implies possible hierarchical relationships if several organisms are found in the same place.

3. Circadian rhythms in behavior and physiology of *Neotomodon alstoni*

The diversity of functions in an organism are related to a biological oscillator coupled to the day-night cycle. The daily rhythms observed in nature, which persist in constant conditions with a period close to 24 h, are known as circadian rhythms. They are genetically regulated and influence a wide variety of physiological and behavioral functions. In mammals, the suprachiasmatic nucleus (SCN) in the hypothalamus is a circadian pacemaker that receives information from cycles of ambient illumination; it synchronizes and aligns diverse systems with neuroendocrine influences. The genetic basis of circadian rhythms consists of a circadian molecular clock, which is a set of transcriptional modulators and their protein products. The CLOCK and BMAL1 proteins are the positive transcriptional factors that bind to an E-box in the promoter region of clock genes *Per* and *Cry* to activate their transcription. PER and CRY proteins form a dimer that translocates into the nucleus inhibiting the activity of CLOCK/BMAL1 (Partch et al., 2014). Molecular clocks synchronize signals of the extracellular environment including neuroendocrine regulators. The temporal interactions between tissues with circadian oscillators, inputs and outputs of the circadian pacemaker are known as a “circadian system” (Aguilar-Roblero, 2015). Tissues different to SCN in which circadian clock genes oscillate in vitro conditions are known as “peripheral oscillators” (Mohawk et al., 2012).

A critical behavioral output of the circadian regulation in a mouse is the locomotor activity rhythm. The mouse *N. alstoni* has a steady circadian structure of locomotor activity, both in conditions of activity wheel or freely moving in a cage (Fuentes-Granados et al., 2010). In constant darkness, it presents a circadian rhythm of locomotor activity with periods between 23.5 h and 23.9 h. Its activity profile shows two main components, one at the beginning and the other at the end of the subjective night. The onset of activity presents a precision with minute variation, which allows projecting the start of the next activity cycle when the value of the circadian period is known (Miranda-Anaya et al., 2016, 2017). During the resting phase, *N. alstoni* presents discrete sprouts of activity, especially in recordings without an activity wheel. The circadian rhythm of locomotor activity synchronizes to pulses of light that emulate the sunrise and sunset of the photoperiod. During the full 12-hour light and 12-hour darkness, the mouse is mainly nocturnal with a sudden onset of activity when the light goes out. In records without activity wheel, exposure to prolonged photoperiod (16 h of light and 8 of darkness) can show remarkable changes in the activity profile, and some organisms become diurnal (Fuentes-Granados et al., 2010). An interesting feature in this species is that the records of locomotor activity obtained through crosses of infrared switches, preserve the structure of the phase, the amplitude, and robustness (Miranda-Anaya et al., 2017) that allows avoiding the motivational influence of the wheel of activity (Novak et al., 2012). In constant light (300 lx) circadian locomotor activity lengths its period to ~24.5 h, as other nocturnal vertebrates (Aschoff, 1981). Furthermore, studies on the electrophysiological constitution of sleep have been published. *Neotomodon alstoni* shows a robust structure like other nocturnal mammals, with phases of wakefulness, quiet wakefulness, slow wave sleep and REM sleep (Ayala-Guerrero et al., 1998; Fuentes Granados et al., 2012).

The photic synchronization of the circadian rhythm of activity is achieved daily through an effect of advances or delays of the circadian pacemaker. The construction of the circadian pacemaker’s light sensitivity is plotted by a phase response curve (Pittendrigh, 1981), where a pulse of light is presented at a specific time of the circadian cycle, and the difference between the previous phase is evaluated compared to the last one (photic phase-shifting). The obtained curve for *N. alstoni* shows larger photosensitivity to achieve phase delays in the early subjective night than the advances in the late subjective night. Synchronization to new photoperiods indicates that the onset and the end of activity entrain at a different speed (Miranda-Anaya et al., 2016, 2017). In females, ovariectomy has significant effects on circadian locomotor activity rhythm; it shortens the circadian period and reduces the amplitude and duration of activity in constant darkness. Ovariectomy has a greater effect on the photic phase shifting, and in photoperiod conditions: it induces an increase in the average activity as well as an advance in the acrophase (Juárez-Tapia and Miranda-Anaya, 2017).

Food Restriction (FR) protocols induce Food Anticipatory Activity (FAA) associated with a circadian oscillator named Food Entrained Oscillator (FEO), which in mammals is independent of the SCN (Stephan, 2001). In *N. alstoni*, locomotor activity of lean mice with restriction of 5 h access to food show a robust FAA and the body weight of mice is not compromised (Luna-Illades et al., 2014, 2017). FAA persists for a couple of days in constant darkness and fasting, indicating that a FEO may drive such component.

Day-Night variation in prooxidant variations in diverse tissues such as hypothalamus, liver, and pancreas have also been explored. Hypothalamus and liver do not show significant differences between day and night in lipid peroxidation or conjugated dienes, but pancreas does vary in conjugated dienes, with a more considerable amount at night (Vázquez-Martínez et al., 2016).

4. Obesity and circadian rhythms in *N. alstoni*

Obesity condition involves changes in the endocrine and metabolic functions. It is a risk factor for many cardiovascular and metabolic diseases, including diabetes. Diverse models of obesity exploring this condition have been studied. However, most of them require nutritional or genetic manipulations (Berthoud, 2002). The pathogenesis of obesity is also associated with circadian biology, particularly with a circadian disruption (Green et al., 2008), where basic regulation of food intake and lipid metabolism may be affected.

In captivity conditions, when fed standard ad libitum rodent diet, some *N. alstoni* mice develop obesity while others remain lean 4–7 months after capture (Carmona-Alcocer et al., 2012) or born in a vivarium (Pérez-Mendoza et al., 2017), suggesting a genetic basis of obesity not yet defined. Fig. 1 shows representative examples of lean and obese mice, body weight increasing and the differences in activity profile.

The condition of obesity in *Neotomodon* is characterized by a gradual increase in visceral and subcutaneous fat. This condition is accompanied by metabolic syndrome characterized by hyperglycemia, hyperinsulinemia, high triglycerides (Carmona-Alcocer et al., 2012)

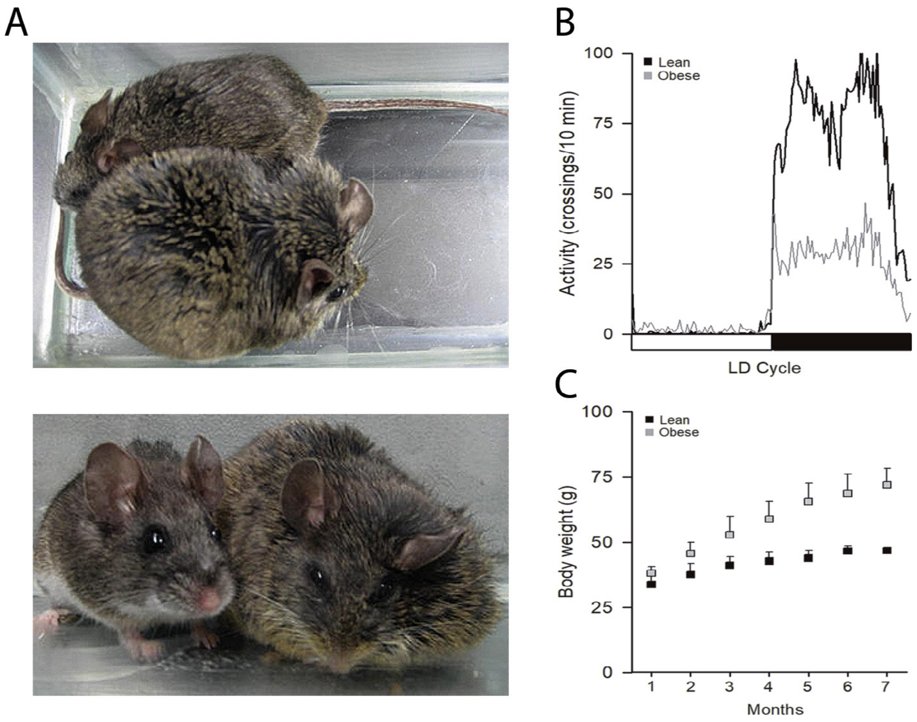

Fig. 1. In A, lean and obese mice Neotomodon alstoni (up and frontal view). In B, average of daily locomotor activity profile (5 consecutive days) show low amplitude in 7 months old obese compared to a lean mouse. In C, (± SE, n = 10 each) body weight along followed along 7 months in two groups of male lean (black squares) or obese mice (white squares).

and free fatty acids. The increase in visceral fat is clearly evaluated in males through the weight of the epidydimal fat without affecting the size of vital organs (Miranda-Anaya et al., 2017). Obesity in these mice is often accompanied by the development of lipomas and fatty liver.

Obesity in *N. alstoni* is behaviorally related to a low amplitude activity profile and, even though obese eat more than lean mice, their food intake/g of body weight is less than lean mice (Pérez-Mendoza et al., 2017) suggesting that low energy expenditure develops part of this condition.

Circadian rhythms alterations in obese *Neotomodon* include differences in amplitude and phase in the explored metabolic parameters as circulating glucose, insulin, leptin, ghrelin, and triacylglycerides (Carmona-Alcocer et al., 2012), as well as in hypothalamic neural integration of leptin and ghrelin (Pérez-Mendoza et al., 2017; Luna-Moreno et al., 2017), indicating dysregulation of the circadian rhythms of metabolic parameters and its neural integration. Oxidative stress in obese *Neotomodon* is increased. There is a larger day–night change in pro-oxidant status in the hypothalamus and pancreas, suggesting a differential equilibrium between oxidative reactions and antioxidant defenses in the different tissues during the day-night cycle (Vázquez-Martínez et al., 2016). When obese *Neotomodon* are exposed to a restricted feeding protocol, the behavioral FAA is reduced or absent with 5 h of food access; mice do not eat as much as when they are fed ad libitum and, consequently, lose weight. Their hypothalamic presence of protein CFOS in neural centers involved in food intake behavior is also reduced (Luna-Illades et al., 2017).

Preliminary studies on the expression of estradiol (E2) and estrogen receptors (ER) indicate that obese female mice present an increase in circulating estradiol and luteinizing hormone, and a rise in hypothalamic and ovary ERβ and ERα. But, the day-night differences are opposite to the observed in lean mice; also, obese females lose regularity of the estrous cycle suggesting dysregulation of signaling in reproductive hormones in obese females (unpublished results).

Entraining the circadian rhythm of locomotor activity to environmental light cycles is also affected in obese *Neotomodon*. Photic phase shifting in the early subjective night is reduced as well as entraining to a jet lag photic protocol. The circadian pacemaker drives the onset and offset of activity at a different speed, and the main differences in obese mice are noted in the offset of activity (Miranda-Anaya et al., 2016). Photic phase shifting in obese is reduced at circadian time (CT) 14 and increased in CT22. This response correlates with a decreased and increased photoinduction of the vasointestinal peptide (VIP) as well as CFOS expression in the SCN (Miranda-Anaya et al., 2017), indicating that hypothalamic photic integration of the entrainment of circadian rhythms is affected in the obesity condition in *Neotomodon alstoni* mice.

5. Obesity affects the daily hypothalamic integration of orexigenic and anorexigenic signaling in *Neotomodon*

Feeding is mainly controlled in the arcuate nucleus of the hypothalamus (ARC) in part by the leptin and the ghrelin sensitive neurons (Andrews, 2011). The leptin hormone is released by the adipose tissue, and it constitutes an endocrine signal related to the satiety condition. Leptin activates the long form of its receptor (LepRb). The transcription factor signal transducer and activator of transcription 3 (STAT3) is a downstream target of the leptin signaling pathway and regulates two distinct populations of cells in hypothalamus, *i.e.,* it stimulates proopiomelanocortin (POMC)-producing neurons and inhibits agouti-related protein (AgRP)/neuropeptide Y (NPY)-producing neurons (Bjørbaek, 2009).

Ghrelin is a hormone predominantly synthesized in the stomach. It is a ligand of a secretagogue receptor GHSR1a and acts as a regulator of hunger and feeding. Ghrelin requires of a posttranslational acylation to be active which activates the GSR1a. There is more de-acylated ghrelin than active acylated ghrelin in plasma. In the ARC, orexigenic neurons expressing NPY receiving active ghrelin starts a signaling process mediated by AMPK-PGC1-UCPs that release NPY to Periventricular Neurons, inducing feeding behavior (Andrews, 2011).

Obesity alters signaling of leptin and ghrelin in ARC in such way that the hypothalamic circuitry controlling the behavior of food intake becomes resistant. The ARC also receives circadian influence from the suprachiasmatic nucleus (SCN) as part of the circadian regulation of feeding-fasting behavior (Buijs et al., 2017). Therefore, an alternating influence of leptin-ghrelin signaling has a correspondence with the active-rest cycle of the animal. In obese *Neotomodon alstoni*, a hyperleptinemia is correlated with an attenuated leptin signaling in the hypothalamus, with a lower relative abundance of POMC and reduced pSTAT3/STAT3 ratio and leptin receptors. This condition is also associated with a low display of locomotor activity during the night and an increasing during the day. Obese mice also fed more during the day. Behavioral and biochemical differences were more evident in obese females than in obese males indicating that obesity affects hypothalamic leptin signaling according to sex (Carmona-Alcocer et al., 2012; Báez-Ruiz et al., 2014; Pérez-Mendoza et al., 2017).

Ghrelin is secreted primarily by the endocrine cells of the oxyntic glands and, in smaller amounts by other organs such as the intestine, pancreas, placenta, kidney, and testicles (Kanamoto et al., 2004). Total ghrelin is secreted in response to fasting. It also causes a positive energy balance, controls gastric mobility, secretes HCl, modulates endocrine pancreatic function and glucose metabolism, and also exerts cardiovascular effects. Ghrelin is received into the hypothalamus by the GHSR receptor, coupled to a typical G protein (Davis et al., 2011). Therefore, the function of ghrelin -as well as its signaling in the hypothalamus- is of great interest to study the animal model of obesity (Atalayer et al., 2014). In a recent study in obese *Neotomodon*, total circulating ghrelin was always higher in lean than in obese mice. Acylated (active) ghrelin was detected along the 24 h cycle in lean animals, but not in obese mice. The highest presence of total and acylated ghrelin in lean animals occurs at lights off when the mice initiate their phase of locomotive activity and feeding. However, obese mice show an attenuated rhythm in total ghrelin and its peak was delayed with an acrophase at midnight with low or no presence of active ghrelin (Luna-Moreno et al., 2017).

6. Obesity, hepatic lipid metabolism, and circadian clock

Obesity is associated with abnormal production of some cytokines like leptin, adiponectin, and resistin, which are secretory products of white adipose tissue. Overexpression of leptin can be leading to insulin resistance by a mechanism of expression of SOCS3 blocking IRS1/2. While Leptin regulates hepatic insulin sensitivity and glucose homeostasis, as well as food intake and energy expenditures by activating the leptin receptor, STAT3 and PGC-1α independently regulate hepatic gluconeogenesis and carbohydrate metabolism (Inoue et al., 2004). PGC-1α also regulates mitochondrial morphology by activating the estrogen-related receptor (ERR) to elevate the mitochondrial fusion protein expression, Mfn (Martínez-Abundis et al., 2012), and it is leptin that increases PGC-1α levels in mice (Rodriguez et al., 2015). PGC-1α regulates as well carbohydrates (Inoue et al., 2004; Chen et al. 2014); lipid metabolism (Hsu et al., 2014); and mitochondrial function (Zhao et al., 2014). Leptin may perform an important role in PGC-1α reducing blood glucose levels and mitochondrial function by regulating PGC-1α, PPARα, ERα and STAT3 (Hsu et al., 2015).

The liver regulates lipoprotein synthesis, lipid uptake, and conversion, de novo synthesis, and oxidation of fatty acids. The lipids are potential regulators of circadian rhythmicity, and the circadian clock regulates most aspects of hepatic lipid metabolism (Adamovich et al., 2014, 2015). Circadian lipid metabolism is not surprisingly controlled, to a large extent, by the clock dependent regulation of key enzymes and transcription factors. Likewise, lipid regulatory factors such as peroxisome proliferator-activated receptor (PPAR), PGC1, SREBP1, NR1D2, and ROR are expressed in rhythmic patterns in liver cells (Adamovich et al., 2015; Le Martelot et al., 2009). The disruption of Clock genes alters the expression of several lipid metabolism genes, which results in dysregulated lipid metabolism in the liver (Eckel-Mahan et al., 2012; Grimaldi et al., 2010).

Recent studies demonstrated that insulin signals promoted the circadian rhythm and associated functional gene expression in peripheral tissues (Yamajuku et al., 2012; Tahara et al., 2011; Sato et al., 2014). These studies indicate that the development of insulin resistance may disrupt the circadian rhythm, reducing the circadian variation of the gene expression of liver *Bmal1* (Kohsaka et al., 2007). Obese mice *Neotomodon alstoni* show hyperleptinemia, hyperinsulinemia, and hypoghrelinemia. In this mouse, the obesity affects liver daily changes in the presence of BMAL1 and proteins of lipid metabolism, more notably in females than in males. Hepatic lipid homeostasis is regulated by the circadian clock protein BMAL1 that in turn, interacts with other lipid metabolism regulators (PGC-1α, PPARα-γ, SREBP-1c, and CPT-1α), as well as in free fatty acid (FFA) and hepatic triacylglyceride (TAG) metabolites. This suggests that the circadian regulation of lipid metabolism is deeply affected in obese *N. alstoni* mice (Perez-Mendoza et al., 2018).

7. Concluding remarks

Diverse animal models have been used to study obesity etiology and its consequences. Such models consider genetic, physiological, epigenetic and obesogenic environmental factors (Speakman et al., 2007). *Neotomodon alstoni* is an interesting biological model that presents spontaneous obesity. Emergent questions that can be explored by this species include the basis of spontaneous obesity itself. Animal models presenting spontaneous single-gene loss-of-function mutations include leptin-deficient ob/ob mice and the leptin receptor-deficient db/db mice, Zucker fatty rats, Zucker diabetic fatty rats, SHR/N-cp rats, and JCR:LA-cp rats (Wang et al., 2014). The genes that appear important in single-gene mutation events seem to be involved in a common pathway that includes leptin and insulin as signaling molecules. In *Neotomodon alstoni,* it is more likely that this condition is the result of a genetic deficiency since only some animals develop obesity in an environment with standard rodent chow. In *Neotomodon,* there are intermediate phenotypes of pre-obese mice that suggest a heterozygous phenotype.

Obesity in *Neotomodon* is also linked to a gradual change in the food intake and low locomotor activity that can be noted near week 15th after weaning (unpublished observations). It is, therefore, an aim to understand if food intake patterns are preceding the other changes in behavior, associated to the obese mice such as the changes in the circadian rhythm of locomotor activity, its entrainment, and the relations between the circadian clock and the lipid metabolism in the liver.

Nowadays, functional characterization studies can lead us to compare *Neotomodon* with other murines used as obesity models and recognize its advantages as an animal model. The new opportunities that the volcano mouse offer is to understand whether the origin of obesity is similar to other animal models presenting spontaneous single-gene loss-of-function mutations.

So far, we have shown that a potential candidate may be the difference in the mechanisms of the leptin signaling (Pérez-Mendoza et al., 2017); and possible Ghrelin resistance (Luna-Moreno et al., 2017). Obesity in *Neotomodon* is not linked to a seasonal photoperiodic response as it is in hamsters and voles (Fuentes-Granados et al., 2010; Speakman et al., 2007), hence, would not be considered as a seasonal model of obesity. Obese *Neotomodon* may also be induced with high fat or high sucrose diets, and the mice become obese faster than the obesity spontaneously developed (unpublished). Studies comparing induced vs. spontaneous obesity may be desirable in order to understand the possible advantages of each model.

Neotomodon alstoni has proved to be an interesting biological model for studying the neuroendocrinology of obesity and its relationship with circadian rhythms and reproduction; it also offers interesting insights on monogamy and paternal behavior. Other studies on endocrine systems in *Neotomodon* include: the morphological and biochemical approach of the harderian gland (Villalpando et al., 2005), the molecular cloning and functional analysis of the FSH receptor gene promoter (Pérez-Solís et al., 2010), and the ryanodine receptor binding constants in diverse organs (Martínez-Merlos et al., 1997).

Much work is still required to gain a better understanding of the particularities that this biological model offers to the knowledge of rodent physiology and, mainly, the sex differences associated with the obesity condition.

Studying nontraditional models may provide us a with a scope of the variability of physiological processes among species, and give us the opportunity to better understand the pathology of both the metabolic and endocrine functions and its relationship with animal behavior, that may also help us in gaining in-depth knowledge of the metabolic, physiological, and behavioral disorders in humans.

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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.2018.04.024.

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