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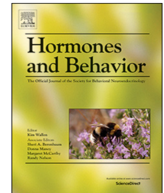

Circadian disruption of food availability significantly reduces reproductive success in mice

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ABSTRACT

Circadian disruptions impair reproductive health in human populations and in animal models. We tested the hypothesis that mistimed food, a common disruptive feature of shift work, impairs reproductive success in mice. Male and female *mPer2^{Luc}* mice on a C57BL/6 background were fed during the light or dark phase in two experiments. Food-induced internal misalignment of the liver clock was verified by in vivo bioluminescence in anesthetized mice in both experiments. In Experiment 1, food-restricted pairs were monitored for litters for 18 weeks. In the light-fed group, birth of the first litter was significantly delayed, and total reproductive output was significantly reduced by 38%. In Experiment 2, estrous cycling was monitored for 3 weeks, and then after pairing, copulatory plugs, pregnancy, litter sizes, and uterine implantation sites were measured. Fewer light-fed females birthed litters (25% versus 73%). This was attributable to a difference in behavior as mating success was significantly reduced in light-fed mice: 42% were observed with a copulatory plug compared to 82% for dark-fed mice. The proportion of mice displaying uterine implantation sites was the same as the proportion observed with copulatory plugs, suggesting no deficit in initiating pregnancy after mating. Estrous cycling and pregnancy maintenance did not differ between the groups. We conclude that mistimed feeding inhibits reproduction in mice by reducing successful mating behavior.

1. Introduction

The transition to parenthood is an important life history event that can be challenging: the infertility rate among women in the United States is 16%, jumping to 24% in nulliparous women (Stanford, 2013; Thoma et al., 2013). Among potential exposures contributing to adverse reproductive health, shift work is highly prevalent, with up to 9 million Americans working on night, evening, or rotating shifts [18% of the work force and 16% of working women (McMenamin, 2007; United States Department of Labor, 2005)]. Shift work is associated with a number of poor reproductive outcomes (Mahoney, 2010), including irregular menstrual cycles (Lawson et al., 2011), endometriosis (Marino et al., 2008), infertility and miscarriage (Fernandez et al., 2016), and preterm birth and low birth weight (Bodin et al., 1999; Xu et al., 1994; Zhu et al., 2004). Some of these risks are moderate; their analysis is clouded by difficulty in collecting accurate shift information in the field (Fernandez et al., 2016; Gamble et al., 2013).

Shift work may impair health by disrupting circadian rhythms—the daily 24 h cycles in physiology and behavior that are governed by cell autonomous clocks in the brain and peripheral tissues (Mohawk et al., 2012). Under normal conditions, light synchronizes the brain's clock in the suprachiasmatic nucleus (SCN) which in turn synchronizes molecular clocks throughout the brain and body (Kalsbeek et al., 2006a; Kalsbeek et al., 2006b). Both environmental and genetic disruptions of the circadian clock markedly affect reproduction. Shifting light-dark cycles (simulated jetlag), or mismatches between the external light-dark cycle and the internal clock, impair reproductive function and pregnancy success (Endo and Watanabe, 1989; Summa et al., 2012; Takasu et al., 2015; Yoshinaka et al., 2017). Mutations of the core clock genes have similar effects: global mutation of *Period* or *Clock* or knockout of *Bmal1* causes irregular estrous cycles and pregnancy failure (Alvarez et al., 2008; Miller et al., 2004; Pilorz and Steinlechner, 2008;

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Ratajczak et al., 2009). Ovary-specific knockout of *Bmal1* disrupts ovulation and embryo implantation, pointing to a role for the local circadian clockwork outside of the brain (Liu et al., 2014; Mereness et al., 2016).

Part of the stress of shift work may result from mis-timed meals. Meals eaten during the biological active phase (night-time in nocturnal organisms) can promote health, whereas meals consumed during the rest phase can be deleterious in both human and rodent studies (Arble et al., 2009; Chaix et al., 2014; Salgado-Delgado et al., 2010; Scheer et al., 2009). Therefore, we tested whether meal timing would affect reproductive success and where, in the timeline of pregnancy, meal timing might be consequential.

2. Methods

2.1. General methods

2.1.1. Animals and housing

*mPer2^Luc^* mice on a C57BL/6 background, containing a knockin fusion gene of the Period2 protein and a firefly luciferase reporter (PER2::LUC, Yoo et al., 2004), were purchased from Jackson Laboratories (B6.129S6-Per2^{tm1Jt}/J, Strain Code: 006852). Mice were bred and maintained in a Thoren ventilated caging system in a pathogen-free barrier facility and housed 3–4/cage on BioFresh Performance Bedding (1/4″ pelleted cellulose, Absorption Corp, Ferndale, WA), with food (LabDiet 5L0D) and water available ad libitum. Mice remained on a 12 h light : 12 h dark cycle. Body mass was measured at least once per week, and during restricted feeding, at the time of food provision and removal. The Institutional Animal Care and Use Committee of Oregon Health & Science University approved all procedures. Timelines for experimental procedures are shown in Fig. 1.

2.1.2. Restricted feeding schedule

Food was restricted to either the light or dark phase. Food restriction was accomplished by manually exchanging lids with chow for lids without. Water was always available.

2.1.3. PER2::LUC in vivo imaging protocol

Circadian rhythms of PER2::LUC bioluminescence were measured by in vivo imaging of the liver and submandibular gland every 4 h (Tahara et al., 2012). The submandibular gland is predicted to be entrained by the light-dark cycle and the other peripheral organs by the food schedule (Vujovic et al., 2008). Prior to taking the first image, the neck and abdominal fur was shaved. Mice were then injected s.c. (15 mg/kg) with D-luciferin potassium salt (Promega, Madison, WI) dissolved to a concentration of 3 mg/mL in sterile phosphate buffered saline and filtered (0.2 µm; injected at 0.05 mL/10 g bw). Bioluminescence was measured 10 min after injection using an Electron Magnified (EM) CCD camera (ImageEM, Hamamatsu, Japan, controlled by Piper software version 2.6.89.18, Stanford Photonics, Stanford, CA) connected to an ONYX dark box (Stanford Photonics) in which mice were maintained under light isoflurane anesthesia on a temperature controlled stage (mTCII micro-Temperature Controller, Cell MicroControls, Norfolk, VA). Bioluminescence was captured by the camera in EM mode (sum of eight 125 msec exposures, gain 500). A brightfield reference image of the anesthetized mouse was taken each time under dim red light (633 nm, half band width 15 nm, 1 lux). After imaging, the animals were immediately returned to their cages.

Bioluminescence was scored offline (ImageJ, NIH). Each image was opened in ImageJ, and the intensity of the 24 bit greyscale image quantified using circular regions of interest centered on the brightest areas of the tissue (liver, 6 mm diameter; submandibular gland, 11 mm diameter). Different sized regions of interest did not alter the conclusions (data not shown; see also Tahara et al., 2012).

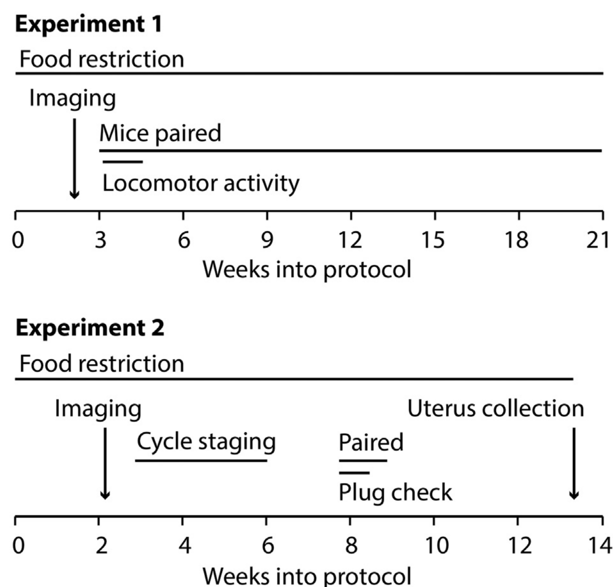

Fig. 1. Timeline of procedures.

2.2. Experiment 1. Effects of long term feeding restricted to the dark or light phase.

2.2.1. Protocol

Adult male and female mice were transferred to light-tight animal enclosures (Phenome Technologies) in a conventional housing room and placed on restricted feeding schedules (n = 32 mice to eat during the light and n = 20 mice to eat during the dark); these mice were offspring of 10 different parent pairs. Light was provided by green LEDs (130 lux, 525 nm, 25 nm half band width); dim red light (0.2 lux, 625 nm, 25 nm half band width) was on continuously to aid in animal husbandry and dark-phase procedures. The use of monochromatic light allows estimates of the photon flux and impact on specific retinal cell types, but does not alter the patterns of entrainment (Butler and Silver, 2011). After 15 days of restricted feeding, PER2::LUC bioluminescence rhythms in the submandibular gland and liver were measured (n = 4 females and 2 males per condition). Mice were then paired at day 20 (with no sibling pairing) and males and females remained together on their original restricted-feeding schedule for 18 weeks (Fig. 1). No special attempt was made to match parents for age or body mass for this experiment. The number of pups born and the number weaned were counted for each breeding pair.

2.2.2. Locomotor activity

General locomotor activity of dyads was measured for 10 days after pairing in 10 min bins by passive infrared motion detectors mounted above the cage lids (Telos Discovery Systems). The locomotor activity profile was constructed in ClockLab (Actimetrics).

2.3. Experiment 2. Estrous cycle stability, mating behavior, and pregnancy maintenance.

2.3.1. Protocol

A second set of 24 females and 24 males from 10 litters was transferred to an animal enclosure with a light cycle as in Experiment 1 (Fig. 1). Siblings were distributed evenly to both groups *a priori* to control for developmental effects, and to ensure that groups were balanced in age and initial body mass. Food restriction (dark- or light-phase) commenced, and after 17 days of acclimation, PER2::LUC bioluminescence rhythms were measured (n = 6 females and 3 males per condition). Estrous cycle stage was then measured for 3 weeks in all females (see below; days 20–42 of restricted feeding). Seven weeks after food restriction began, mice were paired

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