Hormones and Behavior 65 (2014) 301–307

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Increased photic sensitivity for phase resetting but not melatonin suppression in Siberian hamsters under short photoperiods

G.L. Glickman *, E.M. Harrison, J.A. Elliott, M.R. Gorman

University of California, San Diego, Department of Psychology, Center for Chronobiology, 9500 Gilman Drive, La Jolla, CA 92093, USA

ARTICLE INFO

Article history:
Received 7 October 2013
Revised 8 January 2014
Accepted 10 January 2014
Available online 17 January 2014

Keywords:
Light
Photoperiod
Melatonin
Circadian
Sensitivity
Phase shift
Hamster

ABSTRACT

Light regulates a variety of behavioral and physiological processes, including activity rhythms and hormone secretory patterns. Seasonal changes in the proportion of light in a day (photoperiod) further modulate those functions. Recently, short (SP) versus long days (LP) were found to markedly increase light sensitivity for phase shifting in Syrian hamsters. To our knowledge, photoperiod effects on light sensitivity have not been studied in other rodents, nor is it known if they generalize to other circadian responses. We tested whether photic phase shifting and melatonin suppression vary in Siberian hamsters maintained under LP or SP. Select irradiances of light were administered, and shifts in activity were determined. Photic sensitivity for melatonin suppression was examined in a separate group of animals via pulses of light across a 4 log-unit photon density range, with post-pulse plasma melatonin levels determined via RIA. Phase shifting and melatonin suppression were greater at higher irradiances for both LP and SP. The lower irradiance condition was below threshold for phase shifts in LP but not SP. Melatonin suppression did not vary by photoperiod, and the half saturation constant for fitted sigmoid curves was similar under LP and SP. Thus, the photoperiodic modulation of light sensitivity for phase shifting is conserved across two hamster genera. The dissociation of photoperiod effects on photic phase shifting and melatonin suppression suggests that the modulation of sensitivity occurs downstream of the common retinal input pathway. Understanding the mechanistic basis for this plasticity may yield therapeutic targets for optimizing light therapy practices.

Introduction

Circadian rhythms include a host of physiological and behavioral processes that maintain an endogenous period of approximately 24 h in the absence of any environmental cues. Common examples of circadian rhythms in mammals include sleep–wake cycles, hormone fluctuations, and core body temperature patterns. Under natural conditions, light resets the phase of the pacemaker in the suprachiasmatic nuclei (SCN) of the hypothalamus in order to maintain a stable relationship between circadian functions and the daily photocycle via a process called entrainment (Elliott and Tamarkin, 1994; Pittendrigh, 1981; Pittendrigh and Daan, 1976). Such shifts reflect the differential effects of light on the SCN at different circadian phases, which are described experimentally in phase response curves (PRCs) (Johnson et al., 2003).

Acute exposure to light during the night resets the phase of circadian rhythms and suppresses nocturnal elevations of the pineal hormone melatonin. Both responses require ocular photoreception in mammals (Czeisler et al., 1995; Lockley et al., 1997, 1998; Wright and Czeisler, 2001), and similar spectral sensitivity further suggests a shared photoreceptor system (Brainard et al., 2001; Hattar et al., 2003; Provencio and Foster, 1995; Thapan et al., 2001; Yoshimura and Ebihara, 1996). Anatomical studies also support the existence of a common neural circuit (Klein et al., 1991; Moore, 1995; Panda et al., 2002). A well-established neural pathway conveys photic input for phase resetting and melatonin suppression, including phototransduction by melanopsin-containing ganglion cells (ipRGCs) that project directly to the SCN via the retinohypothalamic tract (RHT) (Klein et al., 1991; Panda et al., 2002). From the SCN, light information follows a multisynaptic pathway to the pineal gland for melatonin regulation, with intermediate connections in the paraventricular hypothalamus, the upper thoracic intermediolateral cell column, the superior cervical ganglion, and the post-ganglionic sympathetic fibers (reviewed in Moore, 1995). The precise point of divergence between the pathways for phase resetting and the acute suppressive effects of light on plasma melatonin remains unknown.

Because melatonin suppression by light shares similar properties to phase resetting, it has been a useful method for characterizing the physiology underlying the circadian system (Arendt, 1998; Brainard et al., 2001; Klein et al., 1991). Both demonstrate a characteristic dose-dependent function wherein a threshold amount of light is required to elicit a response; a steep rise in response occurs with increasing light intensities; and finally, a maximal saturating response is achieved, which cannot be surpassed with brighter light (Brainard et al., 1982, 2001; Nelson and Takahashi, 1991a,b; Zeitzer et al., 2000). Sensitivity is commonly indexed as the ED_{50}, defined as the

* Corresponding author.
E-mail address: glickman@ucsd.edu (G.L. Glickman).

0018-506X/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.yhbeh.2014.01.002

quanta of light required to produce half of the maximum response. Melatonin suppression has been shown to be relatively more sensitive to light than phase resetting, as indicated by the leftward displacement of the melatonin fluence response curve to lower irradiances relative to that for phase shifts (Nelson and Takahashi, 1991b; Zeitzer et al., 2000).

Not only is light the primary environmental cue for entraining rhythms to a 24-h day, but the duration of light within a given 24-h cycle (i.e. photoperiod) regulates the seasonality of myriad functions including reproduction, body weight, pelage, immunocompetence and behavior, to name a few (Goldman, 2001). Photoperiod also alters the 24-h waveform, or shape, of circadian rhythms. In both nocturnal and diurnal animals, the high nighttime levels of pineal melatonin are sustained for longer intervals in winter than in summer (Bartness et al., 1993; Binkley et al., 1977; Goldman and Elliott, 1988; Lerchl and Schlatt, 1993; Rollag et al., 1980; Wehr et al., 1993). Parallel lengthening of nocturnal activity under short days (Elliott and Tamarkin, 1994) along with alterations in waveform of SCN neuronal activity (vanderLeest et al., 2007) indicate that these photoperiod influences reflect changes in pacemaker network organization. With regard to phase resetting, under winter photoperiods, light-induced phase shifts occur across a broader fraction of the circadian cycle and the magnitude of the shifts is markedly greater (Goldman and Elliott, 1988; Millette and Turek, 1986; Pittendrigh et al., 1984; Puchalski and Lynch, 1986). These seasonal differences in circadian organization reflect entrainment effects and not sequela of immediate light history since they persist for many days after release into constant conditions (Pittendrigh and Daan, 1976).

In the Syrian hamster, the known effects of photoperiod on circadian function have recently been extended to include the modulation of photic sensitivity. The ED_{50} is approximately 40-fold lower in hamsters entrained to a short photoperiod than in a long photoperiod (Glickman et al., 2012). Furthermore, those behavioral differences are preceded by differential expression of SCN activation, with a much greater amount of light being required to induce similar levels of expression of pERK, PER1, and cFOS in animals previously maintained under long versus short days (Glickman et al., 2012). Importantly, the increased sensitivity of the short day pacemaker appears to be specific to light inputs since enhanced responsiveness is not found with non-photic resetting cues (Evans et al., 2004). Thus, the enhanced short day sensitivity may be specific to the light input pathway.

In view of the potential utility of enhancing sensitivity to light for treatment of circadian and affective disorders, it is important to identify whether photoperiod effects generalize to melatonin suppression, a response that is often used as a proxy for studies of circadian regulation by light in humans. Limited previous works suggests that photic sensitivity for melatonin suppression by light may indeed be altered by seasonal changes in photoperiod (Owen and Arendt, 1992; Thompson et al., 1990). However, the influence of photoperiod on light sensitivity for melatonin suppression has not previously been studied in an animal model wherein light history can be rigorously controlled and monitored. Siberian hamsters are a particularly good model for studies of circadian function as they demonstrate rhythms in locomotor activity and melatonin secretion, both of which also show robust and predictable changes in waveform as a function of photoperiod (Goldman and Elliott, 1988; Millette and Turek, 1986; Puchalski and Lynch, 1986). In order to determine whether photoperiod history alters sensitivity to light for melatonin suppression, we constructed complete fluence–response curves for light-induced melatonin suppression in Siberian hamsters previously maintained under short versus long days. We also tested the generality of photoperiod influences on photic sensitivity to phase shifts in this species. Increased sensitivity to light for both responses under shorter days would suggest a common mechanism of action is serving to alter light sensitivity as a function of photoperiod. Alternatively, a photoperiod difference in light-induced phase shifts, but not melatonin suppression, would indicate the seasonal modulation of photic response is targeting mechanisms unique to phase resetting.

Methods

Male Siberian hamsters (*Phodopus sungorus*), 4–6 weeks old, were selected from a breeding colony established in 1994. In both studies, animals for each photoperiod condition were maintained in separate large ventilated, light-tight, matte white interior chambers. On test nights, cages were temporarily transferred to a separate matte white interior pulsing cabinet (43 cm × 36 cm × 46 cm) for the 15-min light exposure regime. For the phase shift experiment, animals were individually housed in polypropylene cages (27 cm × 20 cm × 15 cm) equipped with 12 cm diameter wheels from when they first entered their randomly assigned photoperiod entrainment condition until the completion of the study. Animals in the melatonin experiment were group housed in polypropylene cages (48 cm × 27 cm × 20 cm) until the test night, when each animal was transferred to the smaller polypropylene cage (27 cm × 20 cm × 15 cm) immediately before placement in the pulsing cabinet. Food and water were available ad libitum. All procedures were approved by UCSD Institutional Animal Care and Use Committee.

Phase shifting experiment

General protocol

An Aschoff type II randomized within-subjects design was employed in a group of Siberian hamsters that were entrained to LD14:10 (LP, 14 h light, 10 h dark; $n = 10$) or LD10:14 (SP, $n = 10$) for 6 weeks. To examine photosensitivity associated with phase delay shifts, light pulses were administered 2 h into the dark (ZT14; with ZT12 representing the time of lights out) for both LP and SP. Each animal received three 15-min short wavelength light pulses at 0 (dark control), 0.11 and 3.14 μW/cm^2, with each test night separated by 21 days and each photoperiod group counterbalanced for the order of irradiance condition. Animals were exposed to constant darkness beginning at the normal time of lights-off on the night of each test pulse, remained under constant conditions for 10 days following the pulse, and were then re-entrained to their original photoperiod for 11 days. Cages were changed on day 1 of re-entrainment near the expected time of activity onset, under dim red illumination.

Assessment of wheel-running activity

Each one-half wheel revolution generated a switch closure signal that was recorded via VitalView software (Mini-Mitter, Bend, OR). Actograms were analyzed via Clocklab software (Actimetrics, Evanston, IL). Activity onsets and offsets were determined in Clocklab, with adjustments to automated selections being made via eye-fit by raters who were blind to pulsing condition. As a check of proper entrainment to photoperiod condition, activity duration (α) was determined as the mean difference between regression lines fitted to the onsets and offsets for the 2 weeks preceding the first test pulse. Due to significantly greater variance in offsets versus onsets in baseline entrainment data, the more reliable activity onset was the phase marker used for calculation of phase shifts. Phase shifts were calculated as the difference between the time of activity onset on the day of the light pulse (as determined by a regression line fitted to the onsets of the 7 days prior to the pulse) and the time of the activity onset on the day after the pulse (as predicted by the post-pulse regression line, calculated through activity onsets for days 4–10 following the light pulse). Two animals were eliminated from our analysis due to recording issues on days of constant conditions, making an accurate assessment of phase shift difficult. Phase-shift scores were expressed relative to each animal's phase shift in response to the sham control condition. All group values are expressed as means ± SEM and analyzed with analysis of variance (ANOVA).