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Short communication

Maternal pinealectomy increases depressive-like responses in Siberian hamster offspring

Joanna L. Workman [a,*], Zachary M. Weil [b], Christiana R. Tuthill [d], Randy J. Nelson [a,b,c]

[a] *Department of Psychology, The Ohio State University, 1835 Neil Avenue, Columbus, OH 43210, USA*
[b] *Department of Neuroscience, The Ohio State University, Columbus, OH 43210, USA*
[c] *Institute for Behavioral Medicine Research, The Ohio State University, Columbus, OH 43210, USA*
[d] *Department of Psychology, University of California, Berkeley, CA 94720, USA*

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Abstract

This study investigated the effect of maternal pinealectomy and postnatal pinealectomy on affective responses. Siberian hamsters were born to either pinealectomized or sham-operated dams and then underwent pinealectomy or a sham operation. Maternal pinealectomy increased depressive-like responses of offspring in the forced swim test. Maternal pinealectomy increased rearing behaviour and postnatal pinealectomy increased locomotor behaviour in the open field test. These results suggest that prenatal melatonin organizes adult affective responses.

Keywords: Pineal gland; Melatonin; Forced swim; Open field; Photoperiod; Seasonal affective disorder

1. Introduction

Siberian hamsters are seasonally breeding rodents that adjust physiology and behaviour throughout the year to take advantage of increased food availability during the spring and summer and to survive harsh conditions during the winter [7]. Hamsters use two pieces of information to synchronize internal processes with environmental conditions: (1) day length, and (2) the direction of change in day lengths [20]. Melatonin, a neurohormone that transduces night length information, is secreted primarily from the pineal gland at night and duration of secretion is inversely related to day length [7]. For Siberian hamsters, exposure to short days results in regression of the reproductive tract, altered metabolism [24,30], enhancement of some components of the immune system (for review, see [15]), elevated aggressive behaviour [3,34], and altered affective responses [21,23].

In addition, duration of maternal melatonin can organize physiology and behaviour of offspring in adulthood. Although Siberian hamsters regress their reproductive tracts and cease reproductive behaviour in the winter, social cues in the laboratory can override the effect of short day lengths on reproduction [10]. Heterosexual pairs will continue to breed when housed in short photoperiods [10]. Further, because maternal melatonin is communicated to the fetus [25,26], melatonin duration can be manipulated *in utero*. Importantly, maternal melatonin influences reproductive development prior to puberty [9,25] which presumably allows fetuses to anticipate environmental conditions before birth to develop traits that favor either winter survival or spring and summer breeding. In addition to the reproductive system, duration of maternal melatonin may organize components of the immune system [33] and affective responses [23] of offspring.

Specifically, Siberian hamsters increase depressive- and anxiety-like responses when housed in short day lengths [21]. These responses may be adaptive for surviving winter conditions. It may conserve considerable energy to disengage early from a task in which success is unlikely [16]. For example, adult hamsters housed in short day lengths float more in the forced swim test than their long-day counter parts [21,23]. Such a response might save energy that can be shunted towards biological processes, such as immune function, that promote winter survival. Affective responses in Siberian hamsters may

* Corresponding author. Tel.: +1 614 688 4674; fax: +1 614 688 4733.
E-mail address: workman.1113@osu.edu (J.L. Workman).

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approximate symptoms of seasonal affective disorder (SAD), which is characterized by symptoms of depression in the winter that are alleviated in the summer, by morning light, or by treatment with selective serotonin reuptake inhibitors.

One notable hypothesis regarding SAD, the Phase Shift Hypothesis (PSH), implicates melatonin in the etiology of the disorder [14]. The PSH stipulates that SAD may be a consequence of lengthened melatonin secretion in the winter when dim morning light is insufficient to inhibit melatonin secretion. Others have suggested that symptoms of SAD are vestigial adaptations that conferred energetic savings during winter conditions [6,12,16]. In addition, some psychological disorders are more common among individuals born at specific times across the year. For example, schizophrenia, bipolar disorder, and major depressive disorder are more prevalent among people born in winter and spring [27]. SAD is more prevalent among those born in spring and summer [1,18]. This information suggests that in humans, melatonin duration may contribute to the development of psychological disorders. In hamsters, perinatal photoperiods can organize adult affective responses [23] and this phenomenon may resemble season-of-birth variations in human psychological disorders. Taken together, this information suggests that Siberian hamsters may provide a means of studying the neuroendocrine substrates of SAD and other disorders that fluctuate seasonally in incidence or severity. Further, manipulation of perinatal photoperiod or perinatal melatonin may provide an approximation for studying mechanisms by which season of birth influences the incidence of disorders.

We hypothesized that hamster offspring would respond to the relative change in melatonin duration rather than the absolute length of duration. Therefore, hamsters that gestate in dams that lack pineal melatonin, but have an intact pineal gland throughout development would interpret this transition as a transfer to short day lengths and display more depressive- and anxious-like responses (i.e., more floating in the forced swim test and less central tendency and rearing in the open field). We hypothesized that all other hamster groups would behave similarly to long-day hamsters and not elevate depressive-like responses because they would undergo either a reduction of melatonin duration or no change in melatonin duration.

Twenty-two male Siberian hamsters (*Phodopus sungorus*) were used in this study. Hamsters were born to dams that underwent either pinealectomy (PNX; $n = 8$) or sham operation ($n = 8$) as previously described [29]. Dams and offspring were housed in 14L:10D with lights off at 1800 h Pacific Standard Time (PST). On postnatal day 3, offspring underwent either PNX or sham operation such that there were 4 groups: maternal PNX, postnatal PNX (PNX–PNX; $n = 6$), maternal PNX, postnatal sham (PNX–sham; $n = 6$), maternal sham, postnatal PNX (sham–PNX; $n = 5$), and maternal sham, postnatal sham (sham–sham; $n = 9$). Surgeries were performed in Dr. Irving Zucker's lab at the University of California at Berkeley and hamsters were transferred to animal facilities at The Ohio State University for testing when 60–90 days of age. Hamsters were housed with siblings in polypropylene cages (28 cm × 17 cm × 12 cm) in rooms with constant temperature and humidity (21 ± 4 °C and $50 \pm 10\%$, respectively). The light cycle was 14L:10D with lights-off at 1500 Eastern Standard Time (EST) and behavioural testing began at 1500 EST after 9 weeks of habituation. Hamsters were allowed to habituate to testing rooms for 15 min before behavioural testing. Food (Harlan Teklad 8640 Rodent Diet, Indianapolis, IN) and tap water were available *ad libitum*. All procedures were conducted in accordance with standards of the University of California at Berkeley and The Ohio State University Institutional Lab Animal Care and Use Committees.

To assess total locomotor behaviour and anxiety-like responses, hamsters were placed in a 40 cm × 40 cm clear acrylic chamber lined with corncob bedding, inside a ventilated cabinet. The center of the open field was defined as the central 30 cm × 30 cm. A frame at the base of the chamber consisting of 32 photobeams in a 16 × 16 arrangement, in addition to a row of beams above, detected the location of horizontal movements and rearing, respectively (Open Field Photobeam Activity System, San Diego Instruments Inc., San Diego, CA). Total movement was tracked for 60 min and analyzed for (1) the percentage of time spent in the center of the open field, (2) number of rears, and (3) total locomotor behaviour. An increase in central tendency and rearing are generally interpreted as a decreased anxiety-like response [22,23].

To assess depressive-like responses [19], hamsters were placed in room-temperature water ∼17 cm deep within an opaque, cylindrical tank (24 cm diameter, 53 cm height). Swimming behaviour was recorded on video for 7 min and scored by a blind observer with The Observer software (Version 5, Exeter Software, Setauket, NY) to quantify (1) latency to float, (2) total number of floating bouts, and (3) total time spent floating. More floating is interpreted as an increased depressive-like response.

Data were analyzed using 2 × 2 ANOVAs with maternal condition and neonatal condition as the independent variables and behavioural measures as the dependent variables. To determine simple main effects, *t*-tests were conducted based on *a priori* hypotheses and were limited to (1) within maternal condition, between postnatal conditions and (2) within postnatal condition, between maternal conditions. All data were analyzed using StatView software, version 5.0.1 (Cary, NC, USA). Mean differences were considered statistically significant when $p \leq 0.05$.

The main effect of maternal condition was significant for all three measures in the forced swim test. Maternal pinealectomy reduced the latency to float ($F_{1,22} = 19.208$; $p < 0.0005$; Fig. 1A), increased float bouts ($F_{1,22} = 14.602$; $p < 0.001$; Fig. 1B), and increased the time spent floating ($F_{1,22} = 4.481$; $p < 0.05$; Fig. 1C). The main effect of postnatal condition on number of float bouts was also significant; postnatal pinealectomy reduced the number of float bouts ($F_{1,22} = 4.351$; $p < 0.05$; Fig. 1B). Within the maternal pinealectomy group, postnatal pinealectomy significantly reduced the number of float bouts (Fig. 1B), but increased time spent floating (Fig. 1C).

There was a significant main effect of postnatal condition on total locomotor activity and percent central tendency. Postnatal pinealectomy increased basal locomotor activity ($F_{1,22} = 5.207$; $p < 0.05$; Fig. 2B) and the percent of beams broken in the center of the open field ($F_{1,22} = 13.311$; $p < 0.005$; Fig. 2C). Within the maternal sham condition, postnatal pinealectomy signifi-