

PHOTOPERIOD AND STRESS REGULATION OF CORTICOSTEROID RECEPTOR, BRAIN-DERIVED NEUROTROPHIC FACTOR, AND GLUCOSE TRANSPORTER GLUT3 MRNA IN THE HIPPOCAMPUS OF MALE SIBERIAN HAMSTERS (*Phodopus sungorus*)

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Abstract—In response to changing day lengths, small photoperiodic rodents have evolved a suite of adaptations to survive the energetic bottlenecks of winter. Among these adaptations are changes in metabolism, adiposity, and energy balance. Whereas hypothalamic and neuroendocrine regulation of these adaptations has been extensively studied, the impact of day length, and interaction of day length and stress, on the energy balance of neurons within the central nervous system remains unspecified. Thus, we exposed male Siberian hamsters (*Phodopus sungorus*) to either short or long day lengths for 14 weeks to induce the full suite of adaptive responses, exposed them to 4 h of restraint, and then measured relative mRNA expression in the hippocampus for low- and high-affinity glucocorticoid receptors (glucocorticoid receptor (GR), mineralocorticoid receptor (MR)), brain-derived neurotrophic factor (BDNF), and the neuron-specific glucose transporter GLUT3. Independent of photoperiod, restraint elevated plasma cortisol (CORT) concentrations and reduced expression of GR, MR, and BDNF. Neither restraint nor photoperiod significantly altered GLUT3 expression. Among all groups, plasma cortisol concentrations were negatively correlated with GR and MR expression. MR, BDNF, and GLUT3 levels were positively correlated with one another, even when controlling for photoperiod and CORT. Taken together, these results suggest that, as peripheral energy balance changes across day length in this photoperiodic species, the neurons of the hippocampus do not alter relative gene expression levels of three proteins involved in monitoring neuronal glucose regulation and morphology. © 2012 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: day length, restraint, gene expression, GR, MR, BDNF.

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Abbreviations: BDNF, brain-derived neurotrophic factor; CORT, cortisol; EST, Eastern Standard Time; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal axis; LD, long day; MR, mineralocorticoid receptor; OSU, Ohio State University; qPCR, quantitative PCR; SD, short day.

INTRODUCTION

Photoperiodism is the ability of organisms to determine the time of year by measuring day length. Photoperiodic mammals use day length information to engage in seasonally appropriate adaptive responses to reallocate energy resources to survive seasonal energetic bottlenecks to maximize fitness (reviewed in Walton et al., 2011b). Among photoperiodic rodents, Siberian hamsters (*Phodopus sungorus*) have been extensively studied for their seasonal regulation of endocrine function and energy balance (Morgan et al., 2006; Scherbarth and Steinlechner, 2010). Seasonal regulation of energy balance and body mass in photoperiodic rodents involves a complex interplay among multiple types of peptide- and hormone-sensitive neurons in the hypothalamus. Among these neuronal populations are those monitoring adiposity by leptin-sensitive neurons, which drive feeding behaviors and satiety via multiple populations of orexigenic and anorexigenic neurons in the hypothalamus (reviewed in Walton et al., 2011b). Downstream of the hypothalamus, the autonomic nervous system, which is dynamically regulated by photoperiod (Weil et al., 2009), is also critical for controlling lipid regulation and metabolism via direct innervation of both white and brown adipose tissue (Bartness et al., 2002; Demas et al., 2002). Most importantly, global glucose mobilization is driven by the hypothalamic–pituitary–adrenal (HPA) axis, which closely monitors energy demands and can respond rapidly to mobilize energy stores needed during times of high metabolic output. Photoperiod-induced changes of hypothalamic neurons and their influences on peripheral mechanisms of energy balance and glucose metabolism have been the focus of many studies, however few studies have investigated the role of photoperiod on changes in energy balance within the neurons of the central nervous system with higher energy demands, such as cortical and hippocampal pyramidal neurons.

The brain is one of the most energetically demanding organs in the body. In humans it accounts for over 20% of the basal metabolic rate (Attwell and Laughlin, 2001) and consumes approximately half of the daily glucose while only comprising a small portion of the total body mass (Owen et al., 1967), whereas in rodents CNS energy consumption estimates range from 2% to 10% of basal metabolic rate (Mink et al., 1981). Because of its pivotal role and that it only uses glucose for energy, and operates within a fixed energy budget determined by total neuron

number independent of brain size (Herculano-Houzel, 2011), the brain is a glucose-privileged organ that overrides other systems in controlling glucose metabolism and energy balance in the body (Fehm et al., 2006). Among brain regions, the hippocampus is the most sensitive to fluctuations in energy (*viz.* glucose) availability (Smith et al., 1984). The hippocampus is also rich with both high-affinity (mineralocorticoid, MR) and low-affinity (glucocorticoid, GR) glucocorticoid receptors, presumably to regulate the HPA axis control of energy utilization during both circadian and dynamic stress fluctuations in energy demands (Jacobson and Sapolsky, 1991).

The structure and function of hippocampal pyramidal neurons are also altered by stress and photoperiod (Walton et al., 2011a; Workman et al., 2011). Furthermore, photoperiod modulates HPA axis reactivity (Weil et al., 2006), and glucose utilization (Stamper et al., 1999). In neurons, glucose uptake is primarily modulated by the neuron-specific glucose transporter GLUT3 (solute carrier family 2 facilitated glucose transporter member 3, SLC2A3) (Simpson et al., 2008). Taken together, we hypothesized that photoperiod and activation of the HPA axis (via restraint) would interact to alter the expression of a suite of genes, expressed in hippocampal neurons, implicated in controlling glucose metabolism.

EXPERIMENTAL PROCEDURES

Animals

Forty adult male Siberian hamsters (*P. sungorus*) from our breeding colony maintained at The Ohio State University (OSU), derived from wild-caught stock courtesy of Dr. Katherine Wynne-Edwards (Calgary, Alberta, Canada), were born in long-day (LD; 16L:8D; lights on 23:00 Eastern Standard Time [EST], off 15:00 EST) conditions and group-housed with same-sex littermates until reaching maturity (> 60 days). Upon reaching maturity, hamsters were singly housed and randomly assigned to either LD ($n = 20$), or short-day ($n = 20$; SD: 8L:16D; lights on 7:00 EST, lights off 15:00 EST) conditions. Hamsters remained in their assigned photoperiods for 14 weeks. Although hamsters generally show maximal reproductive responses to SD after 8–12 weeks, they do not become refractory to photoperiodic inhibition of reproductive responses until after 18 weeks in SD, in the periphery (Prendergast et al., 2000) as well as in multiple brain sites (Freeman and Zucker, 2001). For the duration of the study hamsters were housed in polycarbonate cages (32 × 18 × 14 cm), provided *ad libitum* filtered tap water and food (Harlan Teklad 8640, Indianapolis, IN, USA), maintained at constant temperature and relative humidity (21 ± 4 °C; 50 ± 5% RH), and received care from the University Laboratory Animal Resource staff. All procedures were approved by the OSU IACUC and comply with guidelines established by the National Institutes of Health (Institute of Laboratory Animal Resources (US) Committee on Rodents, 1996).

Restraint and sample collection

After 14 weeks in LD and SD, half of the hamsters ($n = 10$) in each lighting condition were restrained for 4 h during the light phase nadir of the circadian cortisol rhythm (9:00–13:00 EST), ending before endogenous increase in cortisol concentrations. This restraint presumably served as an acute stressor (Pare and Glavin, 1986; Glavin et al., 1994), and restraint durations > 2 h in rodents elevate glucocorticoid concentrations above

those values observed after shorter durations of restraint (Luine et al., 1996). Immediately following restraint, hamsters were deeply anesthetized with isoflurane vapors, blood was collected from the retro orbital sinus, and then hamsters were rapidly decapitated. Brains were rapidly removed, immediately placed in RNAlater (Ambion, TX, USA), and held at 4 °C to maintain mRNA integrity for gene expression analysis. Plasma was collected by centrifugation and held at –80 °C for cortisol analysis. To verify photoperiodic responsiveness, reproductive tissues (testes, seminal vesicles, epididymides) were collected and weighed.

Gene expression

To assess the contribution of stress and photoperiodic differences in gene expression of GR (*nr3c1*), MR (*nr3c2*), brain-derived neurotrophic factor (*bdnf*), and the brain-specific glucose transporter 3 (*slc2a3*) in the hippocampus, we sequenced, designed probes, and performed quantitative PCR (qPCR) for the aforementioned genes as previously described (Pyter et al., 2007). Although the official IUPHAR nomenclature is provided above, for ease of understanding, we will refer to each gene by its common name (GR, MR, brain-derived neurotrophic factor (BDNF), and GLUT3 respectively). Briefly, degenerate primers based on *Mus* and *Rattus* sequences (GenBank) were designed using PrimerExpress V3.0 software (Applied Biosystems, CA, USA). Amplicons using these primers were generated from pooled *P. sungorus* hippocampal cDNA, sequenced, and sequences that had >90% homology to the *Mus* gene were accepted as the correct *P. sungorus* gene of interest. The hippocampus was dissected from each brain hemisphere under a dissecting microscope by gently separating it from the overlying cortex and underlying thalamus, and then RNA was extracted using RNeasy mini kit (Qiagen, CA, USA) following the manufacturer's instructions. cDNA was generated using the M-MLV RT system (Promega, WI, USA), quantified using the NanoDrop 1000 (ThermoScientific, IL, USA), and held at –20 °C for qPCR. Amplification was performed on an ABI 7500 Fast Real-Time PCR System using Taqman Universal PCR Master Mix and universal two-step RT-PCR cycling conditions: 50 °C for 2 min, 95 °C for 10 min followed by 40 cycles of 95 °C for 15 s, and 60 °C for 1 min. 18S rRNA primer and probe set (labeled with VIC dye; Applied Biosystems) was used as a control gene for relative quantification along with the following primers and 5' FAM labeled probes for each gene of interest: GR forward 5'-AATCATGTGGGAGCTGTAAAGTATTCTT-3'; GR reverse 5'-ACAGTCATTTCTCCAGCACAAAG-3'; GR probe 5'-AAAAGAGCA GTGGAAGGA-3'; MR forward 5'-CATAATGAAGGTTTTGCTGCTACTG-3'; MR reverse 5'-AATGCAGCTTGGGCTTTGA-3'; MR probe 5'-GTTCCAAAAGATG-3'; BDNF forward 5'-AAGGCACTGGAAGCTCGCAAT-3'; BDNF reverse 5'-CCATAGTAA GCGCCCGAACA-3'; BDNF probe 5'-CCGAAGTACCCAG TCGT-3'; SLC3 forward 5'-GTGGCATGATGGGCTCTTTT-3'; SLC3 reverse 5'-GAGTTGCGTCTGCCAAAGC-3'; SLC3 probe 5'-CTGTTGGACTCTTTG-3'.

Cortisol RIA

Plasma samples were processed in one assay in duplicate using an ¹²⁵I radioimmunoassay kit (DSL-2000; DSL Inc., TX, USA) following the manufacturer's instructions. Intra-assay coefficient of variation was < 10%.

Data analyses

All data were analyzed using SPSS software (v18.0.2; IBM, NY, USA). Gene expression and cortisol data were analyzed using 2 × 2 ANOVAs, with photoperiod and stress as fixed factors, and relative gene expression and cortisol as dependent variables. Significant interactions were followed up with a one-way

ANOVA using Tukey HSD post-hoc test. Because we predicted that restraint and photoperiod would interact to alter expression of the genes of interest, Pearson's correlation analyses were performed among gene expression and cortisol levels. Reproductive tissue data were analyzed using independent samples Student's *t* tests. Body mass data across photoperiod exposure were analyzed using a repeated measures ANOVA. All mean differences were considered significant at $P \leq 0.05$. Two hamsters that failed to express reproductive responses to SD exposure (paired testes mass > 2.5 standard deviations over the SD mean) were excluded from gene expression and cortisol analyses.

RESULTS

Tissue mass

Across 14 weeks of SD exposure, body mass ($F_{(1,24)} = 8.948$, $P < 0.05$; Fig. 1A) and food intake ($F_{(1,38)} =$

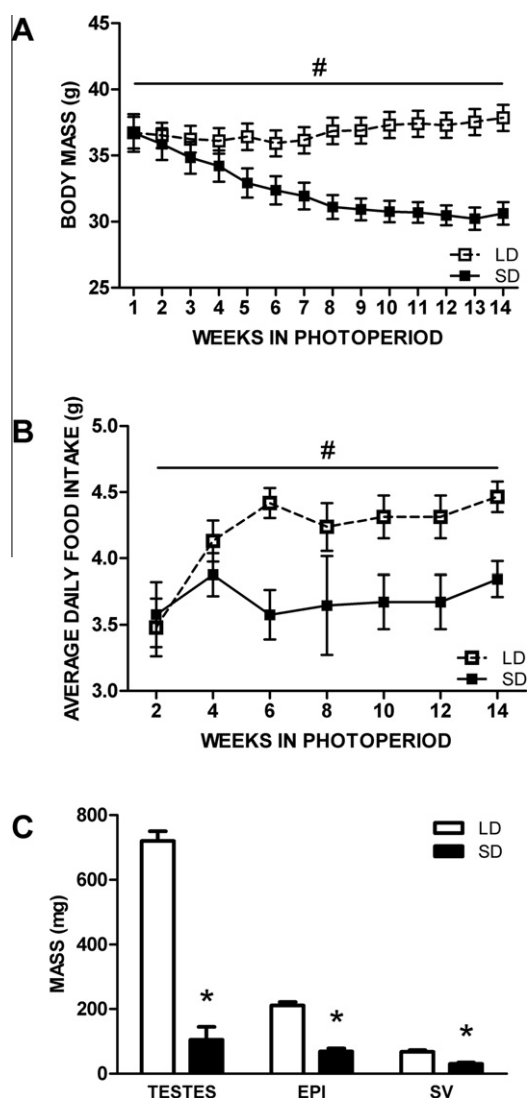


Fig. 1. Body and food intake responses to short day lengths. Exposure to short days for 14 weeks reduced body mass (A; $F_{(1,13)} = 8.948$, $P < 0.05$), food intake (B; $F_{(1,38)} = 8.373$, $P < 0.05$), and masses of paired testes, ($t_{(38)} = 12.480$, $P < 0.05$), epididymides ($t_{(38)} = 9.963$, $P < 0.05$), and seminal vesicles (C) ($t_{(38)} = 6.129$, $P < 0.05$) in male Siberian hamsters. # $P < 0.05$ repeated measures ANOVA; * $P < 0.05$ Student's *t* test.

8.373 , $P < 0.05$; Fig. 1B) were reduced compared to LD hamsters. Fourteen weeks of exposure to SD also reduced paired testes ($t_{(38)} = 12.480$, $P < 0.05$), epididymides ($t_{(38)} = 9.963$, $P < 0.05$), and seminal vesicles ($t_{(38)} = 6.129$, $P < 0.05$) masses (Fig. 1C).

Cortisol

Four hours of restraint after 14 weeks of photoperiod exposure increased plasma cortisol concentrations ($F_{(1,33)} = 19.757$, $P < 0.05$), photoperiod alone did not have an effect ($F_{(1,33)} = 0.624$, $P > 0.05$), and there was no interaction of photoperiod and stress on plasma cortisol levels ($F_{(1,33)} = 0.100$, $P > 0.05$; Fig. 2).

Gene expression

After 14 weeks in photoperiod, there was a main effect of restraint ($F_{(1,32)} = 4.164$, $P < 0.05$), an effect of photoperiod ($F_{(1,32)} = 4.595$, $P < 0.05$), and an interaction of restraint and photoperiod ($F_{(1,32)} = 4.569$, $P < 0.05$) on GR expression (Fig. 3A). A follow-up one-way ANOVA with a Tukey HSD test revealed SD unrestrained hamsters had elevated GR expression compared to all other groups ($F_{(1,3)} = 4.119$, $P < 0.05$; Fig. 3A). For MR mRNA expression there was a main effect of restraint ($F_{(1,33)} = 5.354$, $P < 0.05$), no effect of photoperiod ($F_{(1,33)} = 1.661$, $P > 0.05$), nor an interaction of restraint and photoperiod ($F_{(1,33)} = 0.129$, $P > 0.05$; Fig. 3B). After 14 weeks in photoperiod, there was a main effect of restraint ($F_{(1,34)} = 4.578$, $P < 0.05$), but no effect of photoperiod ($F_{(1,34)} = 0.205$, $P > 0.05$) or interaction of restraint and photoperiod ($F_{(1,34)} = 0.594$, $P > 0.05$) on BDNF gene expression (Fig. 3C). For GLUT3 expression, there were no effects of photoperiod or restraint, and no interaction at 14 weeks in photoperiod ($F_{(1,33)} = 0.779$, $P > 0.05$; $F_{(1,33)} = 0.051$, $P > 0.05$; $F_{(1,33)} = 0.222$, $P > 0.05$ respectively; Fig. 3D).

Correlations

Correlations among variables of interest are shown in Table 1. Among all groups, MR, BDNF, and GLUT3 relative mRNA expression levels were positively correlated

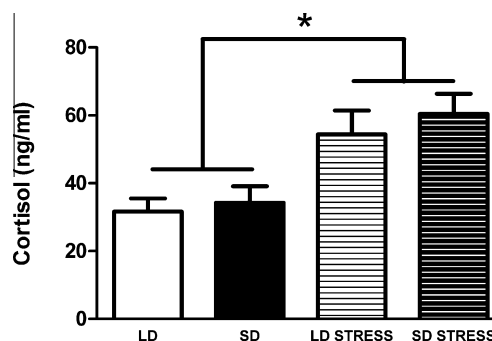


Fig. 2. Photoperiod and restraint effects on plasma cortisol concentrations. Four hours of restraint elevated plasma cortisol concentrations in male Siberian hamsters ($F_{(1,33)} = 19.757$, $P < 0.05$). There was no effect of photoperiod ($F_{(1,33)} = 0.624$, $P > 0.05$), or interaction of restraint and photoperiod ($F_{(1,33)} = 0.100$, $P > 0.05$). * $P < 0.05$.

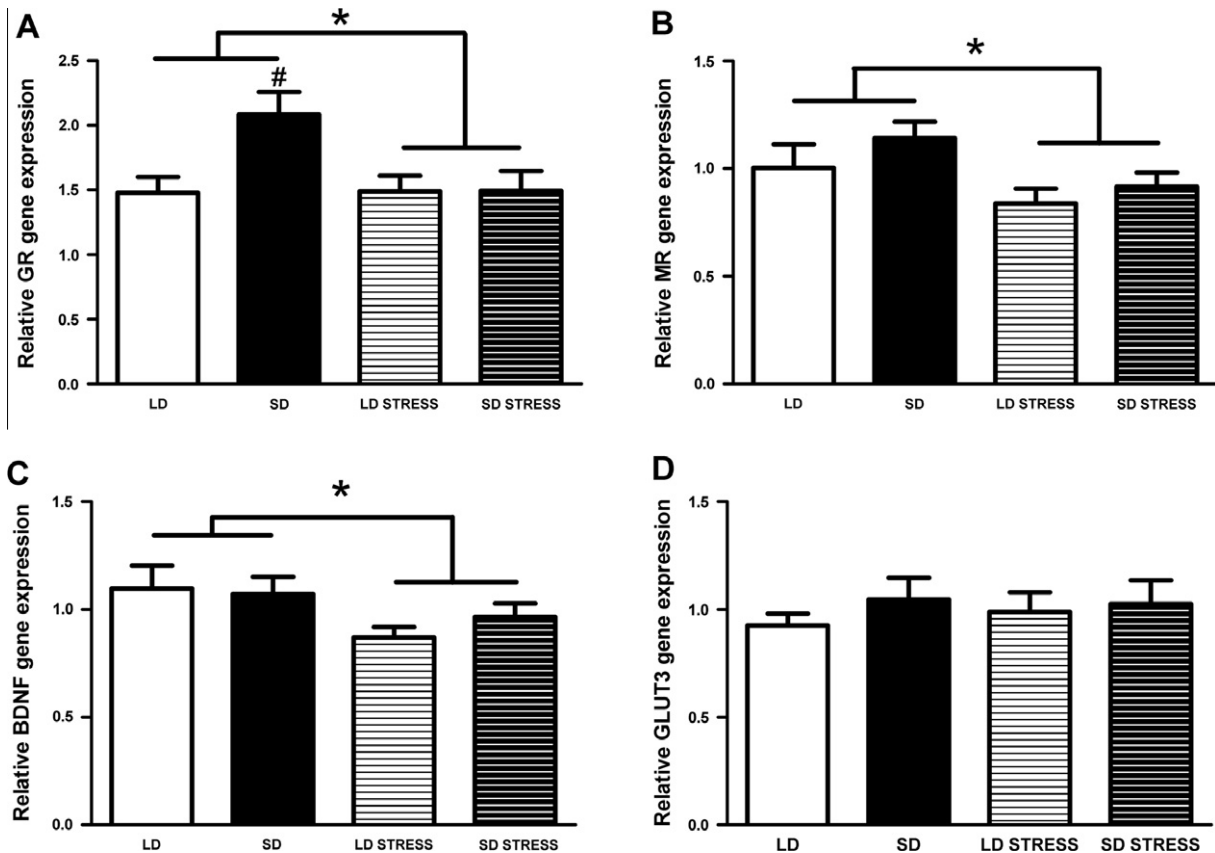


Fig. 3. Photoperiod and restraint effects on hippocampal gene expression of (A) glucocorticoid receptor (GR), (B) mineralocorticoid receptor (MR), (C) brain-derived neurotrophic factor (BDNF), and (D) the neuron-specific glucose transporter GLUT3. (A) For GR there was a main effect of restraint ($F_{(1,32)} = 4.164, P < 0.05$), an effect of photoperiod ($F_{(1,32)} = 4.595, P < 0.05$), and an interaction of restraint and photoperiod ($F_{(1,32)} = 4.569, P < 0.05$). Tukey's post hoc analysis revealed SD hamsters had increased GR expression compared to all other groups, which accounts for the significance measures revealed by MANOVA. (B) For MR there was a main effect of restraint ($F_{(1,33)} = 5.354, P < 0.05$), and no effect of photoperiod ($F_{(1,33)} = 1.661, P > 0.05$) or interaction of restraint and photoperiod ($F_{(1,33)} = 0.129, P > 0.05$). (C) For BDNF there was a main effect of restraint ($F_{(1,34)} = 4.578, P < 0.05$), but no effect of photoperiod ($F_{(1,34)} = 0.205, P > 0.05$) or interaction of restraint and photoperiod ($F_{(1,34)} = 0.594, P > 0.05$). For GLUT3 expression, there were no effects of photoperiod or restraint, and no interaction ($F_{(1,33)} = 0.779, P > 0.05$; $F_{(1,33)} = 0.051, P > 0.05$; $F_{(1,33)} = 0.222, P > 0.05$ respectively). * $P < 0.05$ MANOVA, # $P < 0.05$ Tukey's HSD.

Table 1. Correlations among gene expression, photoperiod, and plasma cortisol

	GR	MR	GLUT3	BDNF	CORT	Photoperiod ^a					Photoperiod ^a , CORT ^a					
						GR	MR	GLUT3	BDNF	CORT	GR	MR	GLUT3	BDNF		
GR	1	0.487**	0.156	0.212	-0.412*	GR	1	0.439**	0.137	0.193	-0.452**	GR	1	0.297	0.083	0.104
MR		1	0.512**	0.689**	-0.456**	MR		1	0.506**	0.699***	-0.486**	MR		1	0.505**	0.672***
GLUT3			1	0.421**	-0.104	GLUT3			1	0.418*	-0.133	GLUT3			1	0.391*
BDNF				1	-0.285	BDNF				1	-0.300	BDNF				1

^a Pearson's partial correlation control variables.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

with one another. GR and MR were positively correlated with each other and negatively correlated with plasma CORT levels. Controlling for photoperiod alone had no effects on these correlations. When controlling both photoperiod and CORT together, the positive correlations among MR, GLUT3, and BDNF were retained, potentially indicating that the coupling of the expression of these three genes across photoperiod and HPA axis activation

states may be critical for neuronal function, especially in the hippocampus.

DISCUSSION

Activation of the HPA axis by 4 h restraint altered GR, MR, and BDNF gene expression in the hippocampus of both LD and SD Siberian hamsters. Independent of

photoperiod, CORT concentrations were negatively correlated with GR and MR gene expression in the hippocampus. Controlling for photoperiod and plasma cortisol concentrations, there was a strong positive correlation among MR, GLUT3, and BDNF mRNA expression in the hippocampus. These data indicate that the expression of genes implicated in the critical roles of energetic and trophic maintenance of hippocampal neurons (MR, GLUT3, BDNF) (Crochemore et al., 2005; de Kloet et al., 2005; Ferreira et al., 2011; Noble et al., 2011) may be coupled together, independent of photoperiod and fluctuating CORT concentrations.

Glucose is the primary fuel of neurons and maintaining glucose concentrations within a strict narrow range in the brain under varying conditions is of primary importance (Attwell and Laughlin, 2001; Fehm et al., 2006). Allocation of energy resources among competing physiological processes is regulated in a top-down manner by the hypothalamus, which drives both behavioral and endocrine modulation of energy intake, storage, and retrieval (Bartness et al., 2002; Fehm et al., 2006; Morgan et al., 2006; Walton et al., 2011b). Indeed, the differential allocation of energy among competing physiological processes across the year is the most parsimonious theory to explain the evolution of photoperiodism (Walton et al., 2011b). The dynamic and well-described photoperiod-dependent regulation of metabolism and energy allocation in Siberian hamsters makes this species an excellent model to ask the question: Do day length-induced changes in hormonal milieu, metabolism, body mass, and adiposity alter glucose transport at the neuronal level?

Energy-independent facilitated transport of glucose across membranes is mediated by members of the GLUT family of proteins in mammals (Manolescu et al., 2007). Glucose is carried through circulation in the blood and GLUT1 transports glucose across the blood–brain barrier and through astrocytes to reach neurons, which can then take up the available glucose, mainly through GLUT3 (Manolescu et al., 2007; Simpson et al., 2008) and potentially through sodium-coupled glucose transporters (Yu et al., 2010). Although the structure and function of neurons in this and other photoperiodic rodent species are altered by photoperiod and stress (Pyter et al., 2005; Walton et al., 2011a; Workman et al., 2011), and neuronal activity can drive GLUT3 expression (Burkhalter et al., 2003; Ferreira et al., 2011), neither photoperiod nor stress altered GLUT3 expression in the current study. This does not necessarily preclude glucose transport in the brain from being altered by photoperiod. A previous study has shown that neither GLUT3 mRNA nor protein were affected by stress in rats (Reagan et al., 1999); however, glucose uptake could be regulated at the functional level by glucocorticoids interacting with GLUTs (Horner et al., 1990) or other members of the GLUT family of transporters, such as the insulin-dependent transporter GLUT4 (Srivastava and Krishna, 2010). The effects of stress and photoperiod on GLUT protein–glucocorticoid interactions and the expression of GLUT4 remain unstudied in photoperiodic rodents.

The release of corticosteroids is regulated by the HPA axis, and they are critical for regulating systemic energy

balance through positive modulation of blood glucose concentrations and negative modulation of the effects of insulin (Fehm et al., 2006). The HPA axis is regulated by feedback at the level of the pituitary and the hypothalamus, and the hippocampus plays a critical role in HPA axis modulation (Jacobson and Sapolsky, 1991). In the hippocampus, glucocorticoid concentrations at basal levels (ultradian fluctuations) are monitored by MR occupancy, whereas during bouts of HPA axis activation (circadian peak, stress), GR occupancy and the ratio of MR:GR occupancy are critical parameters (de Kloet et al., 2005; Joels et al., 2008). Occupancy of the high-affinity glucocorticoid receptors (MRs) is critical for basal functioning, survival, and maintenance of neurons in the hippocampus (Crochemore et al., 2005; Joels et al., 2008). MRs have also been implicated in the survival of newborn adult neurons in the hippocampus (Gass et al., 2000; Crochemore et al., 2005), and in the regulation of neurotrophins in the hippocampus, such as BDNF (Chao et al., 1998; Hansson et al., 2000). BDNF can also drive expression for GLUT3 (Burkhalter et al., 2003). Taken together, the current findings suggesting that MR, GLUT3, and BDNF expression in the hippocampus may be coupled across varying hormonal and environmental conditions is not unexpected: co-expression of this trio of genes is critical for neuronal development, function, and survival. However, it is possible that the mechanisms controlling expression of these three genes are unrelated. These data support the hypothesis that although short days and stress can interact to alter connectivity, morphology, and function of hippocampal neurons, the neurons operate within a narrowly defined range of energetic constraints.

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