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Neonatal monosodium glutamate treatment counteracts circadian arrhythmicity induced by phase shifts of the light-dark cycle in female and male Siberian hamsters

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Abstract

Studies of rats and voles suggest that distinct pathways emanating from the anterior hypothalamic-retrochiasmatic area and the mediobasal hypothalamic arcuate nucleus independently generate ultradian rhythms (URs) in hormone secretion and behavior. We evaluated the hypothesis that destruction of arcuate nucleus (ARC) neurons, in concert with dampening of suprachiasmatic nucleus (SCN) circadian rhythmicity, would compromise the generation of ultradian rhythms (URs) of locomotor activity. Siberian hamsters of both sexes treated neonatally with monosodium glutamate (MSG) that destroys ARC neurons were subjected in adulthood to a circadian disrupting phase-shift protocol (DPS) that produces SCN arrhythmia. MSG treatments induced hypogonadism and obesity, and markedly reduced the size of the optic chiasm and primary optic tracts. MSG-treated hamsters exhibited normal entrainment to the light-dark cycle, but MSG treatment counteracted the circadian arrhythmicity induced by the DPS protocol: only 6% of MSG-treated hamsters exhibited circadian arrhythmia, whereas 50% of control hamsters were circadian disrupted. In MSG-treated hamsters that retained circadian rhythmicity after DPS treatment, quantitative parameters of URs appeared normal, but in the 2 MSG-treated hamsters that became circadian arrhythmic after DPS, both dark-phase and light-phase URs were abolished. Although preliminary, these data are consistent with reports in voles suggesting that the combined disruption of SCN and ARC function impairs the expression of behavioral URs. The data also suggest that light thresholds for entrainment of circadian rhythms may be lower than those required to disrupt circadian organization.

Keywords

photoperiod; ultradian rhythms; locomotor activity; retinal photoreceptors; sex differences

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Introduction

Ultradian rhythms (URs), with periods that range from ~0.5 to 8 hours, figure prominently in temporal organization of mammalian behavioral and physiological processes, including hormone secretion, sleep-wakefulness cycles, and locomotor activity (see Prendergast et al., 2012a, 2012b; Prendergast and Zucker, 2012; Prendergast et al., 2013a, 2013b). The mechanisms that generate URs remain poorly understood and little studied. Specification of the molecular basis of URs is hampered by the absence of localized ultradian pacemakers in the CNS. It is unknown whether single or multiple oscillators generate the several URs.

The hypothalamic arcuate nucleus (ARC) is a critical generator of the primate GnRH ultradian rhythm that controls LH pulsatility (Knobil, 1999). Ablation of the anterior ARC, when combined with anterior hypothalamic deafferentation, blocks URs of rat LH secretion (Soper and Weick, 1980); the ARC is implicated in the generation of URs of rat growth hormone secretion (Zeitler et al., 1991) and ARC cells sustain URs in somatostatin binding (Tannenbaum et al., 1993).

Only one study has assessed ARC involvement in the generation of behavioral URs. Feeding and wheel-running URs were eliminated in 5 field voles (*Microtus agrestis*) with combined ablation of the ARC-retrochiasmatic area and the suprachiasmatic nucleus (SCN), and in three individuals with damage to the ARC and retrochiasmatic area that spared the SCN (Gerkema et al., 1990). Interpretation of these results is complicated by the pronounced suppression of locomotor activity in brain-damaged voles. The studies of Soper and Weick (1980) and Gerkema et al. (1990) raise the possibility that two pathways, one emanating from the anterior hypothalamus (e.g., SCN) and a second from the posterior mediobasal hypothalamus (ARC), may independently generate URs.

Siberian hamsters exhibit URs in locomotor activity and body temperature during both the light (L) and dark (D) phases of the illumination cycle (Bräulke & Heldmaier, 2010; Prendergast & Zucker, 2012); the relation of URs to circadian rhythms and the relative insensitivity of URs to broad classes of hormones in this species, render hamsters suitable for probing neural control of behavioral URs (Prendergast et al., 2012b; Prendergast et al., 2013a, 2013b).

The present experiment assessed the relative contributions of the ARC and SCN in ultradian organization of Siberian hamsters. Hamsters were treated neonatally with monosodium glutamate (MSG) according to a regimen that permanently destroys ~ 80% of ARC neurons (ARCx; Ebling et al., 1998). ARCx and control hamsters were then subjected to a circadian phase-shifting protocol that abolishes circadian rhythms of locomotor activity, body temperature and SCN clock gene expression (Grone et al., 2011; Ruby et al., 1996; 2004) to determine the impact of combined disruption of ARC and SCN function on behavioral URs.

Results

Influence of MSG on morphology

Body mass—Perinatal MSG treatments resulted in significantly higher body masses at necropsy ($F_{1,62}=44.4$, $P<0.001$), and the effects of MSG differed between the sexes (drug $\times$ sex: $F_{1,62}=14.4$, $P<0.001$). Females treated with MSG weighed significantly more than controls treated with the PBS vehicle ($P<0.001$); MSG treatment also increased body mass of males ($P<0.05$), although to lesser extent than in females, reflecting the larger body mass among male than female PBS controls ($P<0.001$; Fig. 1A); the sex difference in body mass was absent in the MSG cohort ($P>0.80$).

Gonadal mass—MSG treatment did not affect ovarian mass ($F_{1,28}=0.29$, $P>0.50$), but testes of MSG-treated males were substantially lighter than those of PBS controls ($F_{1,34}=71.5$, $P<0.001$; Fig. 1B).

Spleen mass—MSG exerted different effects on males and females (drug $\times$ sex: $F_{1,62}=6.57$, $P<0.05$). Spleens of MSG-treated females were hypertrophied relative to those of PBS-treated females ($P<0.01$) and were also heavier than those of MSG males ($P<0.05$; Fig. 1C). There were no sex differences in splenic masses of the PBS cohort ($P>0.20$), and MSG did not affect spleen mass of males ($P>0.80$; Fig. 2C).

Neuroanatomical dimensions—MSG treatment resulted in marked structural changes in visual projections and in diencephalic morphology (Fig. 2A–2C). Neither drug ($F_{1,55}=0.93$, $P>0.30$) nor sex ($F_{1,55}=1.92$, $P>0.15$; Fig. 2D) significantly affected mid-hypothalamic width but values for MSG females were lower than those of PBS females, $p<0.01$; the dimensions of the optic nerve ($F_{1,53}=158.3$, $P<0.001$; Fig. 2E) and optic chiasm ($F_{1,54}=127.3$, $P<0.001$; Fig. 2F) were markedly reduced in MSG-treated hamsters, with no evident sex differences (Fig. 2E, 2F).

Influence of MSG on behavioral rhythms

Sex differences in CRs and URs—The period of the UR (τ') tended to be longer in females than males in the dark-phase, but this effect did not reach statistical significance. Aside from this trend, sex did not affect any quantitative aspect of the dark-phase or light-phase UR waveform (see Supplemental Table 1). Consequently, subsequent analyses of CR and UR waveform parameters were collapsed across sex to increase statistical power.

Circadian rhythms—The phase shift protocol disrupted circadian rhythms (CRs) in 50% of PBS-treated hamsters: 13 of 28 individuals became arrhythmic and one displayed a free-running rhythm; the remaining 14 hamsters entrained to the photocycle (Fig. 3A). In sharp contrast, only 2 of 34 MSG hamsters (6%; 1 male, 1 female) became circadian arrhythmic ($\chi^2=14.5$, $P<0.001$ compared to the PBS cohort), the remainder manifesting normal entrainment. Fig. 3 illustrates representative actograms of two PBS-treated hamsters, one with a normal (Fig 3B) and the other with a disrupted CR (Fig 3C), and one MSG-treated hamster with a normal CR (Fig 3D).

Among hamsters that remained entrained to the photocycle, MSG treatments were without effect on any quantitative parameter of the CR waveform (robustness: $F_{1,44}=1.22$, $P>0.25$; mesor: $F_{1,44}<0.01$, $P>0.90$; absolute amplitude: $F_{1,44}=0.04$, $P>0.80$; relative amplitude: $F_{1,44}=0.43$, $P>0.50$; data not illustrated).

Ultradian rhythms—Only 2 MSG-treated hamsters exhibited circadian arrhythmia in response to the DPS treatment, therefore the effect of MSG treatments on URs was assessed separately for hamsters with and without CRs.

In hamsters with entrained CRs, MSG treatments did not affect the incidence of URs: dark-phase URs were detected in the Lomb-Scargle periodogram in 7 of 14 (50%) PBS-treated hamsters, and in 9 of 32 (28%) MSG-treated hamsters ($\chi^2=2.05$, $P>0.15$); light-phase URs were evident in 6 of 14 (43%) PBS-treated hamsters, and 10 of 32 (31%) of MSG-treated hamsters ($\chi^2=0.58$, $P>0.50$). Likewise, MSG treatments were without effect on any quantitative aspect of the dark-phase or light-phase UR waveform in entrained hamsters (i.e., UR complexity, period, robustness, mesor and relative amplitude; dark phase, all trait-specific ANOVAs: $F_{1,14}<1.03$, $P>0.30$, all comparisons; light phase, all trait-specific ANOVAs: $F_{1,15}<1.19$, $P>0.20$, all comparisons; not illustrated)

Among circadian arrhythmic hamsters, light-phase and dark-phase URs were present in 3 of 13 (23%) PBS-treated hamsters. In contrast, neither dark-phase nor light-phase URs were detectable in the 2 MSG-treated hamsters that became circadian arrhythmic ($\chi^2=0.58$, $P>0.40$, both comparisons). Because URs were not evident in circadian arrhythmic MSG-treated hamsters, further quantitative assessments of the effect of MSG on UR waveform parameters in arrhythmic hamsters were not possible.

Lastly, collapsing data across drug treatments, dark-phase URs were higher in amplitude among hamsters with entrained CRs than those that were circadian arrhythmic ($F_{1,17}=5.34$, $P<0.05$; Fig. 4).

Discussion

Our assessment of the effects of combined interdiction of SCN and ARC neural activity was unsuccessful because neonatal MSG treatment unexpectedly counteracted the effects of phase shifts of the light-dark cycle on SCN function in the vast majority (94%) of hamsters (cf. Ruby et al., 1996, 2004; Prendergast et al., 2012b). As a result of this protective effect of MSG on DPS-induced circadian arrhythmia, the final sample sizes in this study were inadequate to permit strong conclusions about interactions between SCN and ARC function in the generation of behavioral URs. It is noteworthy however, that URs were present in >40% of ENTR hamsters treated with PBS, and in 23% of ARR hamsters treated with PBS, but neither dark-phase nor light-phase URs were detectable in the 2 MSG-treated hamsters that became circadian arrhythmic following DPS. These data are consistent with reports in voles, in which combined ablation of the SCN and ARC resulted in the loss of behavioral URs (Gerkema et al., 1990). Neonatal MSG treatment combined with surgical ablation of the SCN in adulthood will be required to fully evaluate the hypothesis that normal ARC and SCN neural activity are necessary to sustain ultradian rhythms.

It is presently unknown which of the several changes in the visual system account for the protective effect of MSG on circadian disruption by DPS. MSG treatment markedly reduces the size of both the optic chiasm and primary optic tract in Siberian hamsters (current study) and in Syrian hamsters (Pickard et al., 1982), and severely depletes the retinal ganglion cell layer in several rodents (Pickard et al., 1982; Schmidt et al., 2008). The protective effect of MSG treatment may be mediated, either individually or in concert by: (1) an omnibus reduction in visual input to the CNS, (2) selective elimination of fibers projecting to visual areas that transduce disruptive effects of phase-shifts, or (3) neurotoxic lesions of brain nuclei (e.g., ARC, subcortical visual nuclei) that mediate DPS-induced disruption of CRs.

MSG treatment did not interfere with entrainment of circadian locomotor rhythms to the light-dark cycle in Siberian hamsters of both sexes (present study), rats (Edelstein et al., 1995), or Syrian hamsters (Pickard et al., 1982). Despite extensive damage to the retina, including degeneration of amacrine, bipolar and ganglion cells, and damage to the superior colliculus, the retinohypothalamic tract-SCN projection retains sufficient integrity to mediate non-image forming visual function in rats (Edelstein et al., 1995) and Syrian hamsters (Chambille and Servier, 1993). The survival of a subset of retinal ganglion cells with axons projecting to the retinohypothalamic tract provides sufficient visual afference to entrain circadian rhythms in MSG-treated rodents. MSG treatments similar to those employed in the present study destroyed 89% of ganglion cells in Syrian hamsters (Chambille, 1998) but those spared may mediate entrainment.

The protective effect of MSG treatment on circadian rhythms was first reported in a study of rats maintained in constant light (LL; Edelstein et al., 1995). CRs of body temperature were disrupted by LL in control subjects, but not in their MSG counterparts (Edelstein et al.,

1995). The attenuation of feeding-related activity during the light portion of a 4 h LD cycle in control but not MSG rats also is compatible with a loss of direct inhibitory effects of light on behavior (Mistlberger and Antle, 1999). Edelman et al. (1995) suggested that the IGL/vLGN projection mediates the effects of constant light on rat circadian rhythms, but subsequently electrolytic lesions of the IGL did not prevent the disruptive effects of LL on CRs (Edelman and Amir, 1999). The authors speculated that retinal or superior collicular damage induced by MSG eliminates the disruptive effects of LL. Whether or not abrogation of the IGL projection to the SCN, or retinal and collicular damage, mediates the protective effect of MSG on circadian rhythms of Siberian hamsters remains to be determined. The substantial decreases in ARC-NPY Y1 receptors and alpha-MSH cells of Siberian hamsters treated neonatally with MSG (Dailey and Bartness, 2010) may contribute to the protective effects on CRs. Differences in the pattern of release of NPY into the SCN rendered MSG-treated rats unresponsive to the disruptive effects of LL (Edelman and Amir, 1999).

In male Siberian hamsters subjected to a protocol similar to that in the present study, MSG treatment destroyed neurons in the ventrolateral portion of the ARC but spared a small portion of the dorsomedial region of the nucleus (Ebling et al., 1998); 24% of tyrosine hydroxylase-ir cells and some NPY mRNA expressing cells of the dorsomedial region also survived after MSG treatment. A re-analysis of data from Ebling et al. (1998) reported by Barrett et al. (2005) indicated that a dorsal region of the medial posterior area of the ARC (dmpARC) is histologically unaffected by neonatal MSG treatment. Residual ARC cells may contribute to the protective effect of MSG on circadian rhythms, and may also participate in the generation of URs in the presence of a functional SCN.

The reduced testis weight of MSG-treated males confirms earlier observations (Ebling et al., 1998); terminal body mass of males was not affected by neonatal MSG treatment, although females in the present study treated with MSG weighed substantially more than controls. Changes in ovarian hormone secretion in MSG-treated females (Rodriguez-Sierra et al., 1980) may contribute to increased weight gain.

In addition to its profound effects on the ARC and visual structures, MSG also damages neurons in the area postrema (Jászai et al., 1998), and subfornical organ (Pesini et al., 2004) among other sites with a semipermeable blood brain barrier during early postnatal life (Olney, 1969). The extent to which these structures contribute to the phenomena detailed in the current report is unknown and merits study.

Experimental Procedure

Animals

Siberian hamsters (*Phodopus sungorus*) derived from a breeding colony housed in a long-day photoperiod (15L:9D; lights off at 18:00 h CST; light intensity of ~400 lux at the level of the cage lid) were housed in polypropylene cages, with food (Harlan, Teklad) and filtered tap water provided *ad libitum*; cotton nesting material was also available in the cage. Ambient temperature and relative humidity were held at $19 \pm 2^\circ\text{C}$ and $53 \pm 10\%$, respectively. All procedures conformed to the USDA Guidelines for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the University of Chicago (protocol numbers 71383 and 71443).

Perinatal neurotoxic MSG treatments

Breeding pairs were inspected daily for the presence of litters, with the day of birth designated *day 0*. On postnatal *days 4–8*, pups ($n=74$) were weighed (± 0.1 g) and injected s.c. with 4 mg/g L-glutamic acid monosodium salt hydrate (Sigma, G5889; dissolved in

sterile phosphate buffered saline (PBS) at a concentration of 200 mg/ml; “MSG”; n=34) or sterile PBS (“PBS”; n=28). Injection volumes ranging from 0.04 to 0.15 ml were delivered 1–2 h prior to the onset of the dark phase.

Post-treatment housing

Pups were weaned on *day 21* and group housed (1–4/cage), segregated by sex (females: n=27; males, n=35). At 2.5 months of age, hamsters were weighed (± 0.1 g).

Disruptive phase shift (DPS) procedure

At 5 months of age, hamsters were single housed and subjected to a disruptive phase shift (DPS) procedure. The DPS destabilizes the hamster circadian pacemaker via treatment with phase-resetting light stimuli, rendering a majority of hamsters permanently circadian arrhythmic (“ARR”; Ruby et al., 1996; 2004). After 4 weeks in a 16L:8D photoperiod, a 2 h light pulse was administered during the 5th through 7th h of the dark phase. On the next day, the 16L:8D photocycle was phase-delayed by 3 h, via extension of the light phase (new lights off: 21:00 h). The DPS protocol typically renders 50% of hamsters permanently circadian arrhythmic (“ARR”; Ruby et al., 2004). Control hamsters (n= 7 males, n=5 females) were subjected to the 3 h phase-delay but did not receive the 2 h light pulse on the preceding night (sham-DPS); 11 of 12 sham-DPS hamsters re-entrained to the new photocycle (Ruby et al., 2004; Prendergast et al., 2012b). Circadian-entrained hamsters receiving the sham-DPS treatment did not differ from those in which entrainment persisted after the DPS procedure (dark-phase URs: $F < 2.74$, $P > 0.10$, all measures; light-phase URs: $F < 0.21$, $P > 0.60$, all measures) and were combined into a single ‘circadian entrained’ (ENTR) treatment group. Additionally, because one objective of this experiment was to assess the effects of circadian arrhythmia on URs, the single sham-DPS hamster that exhibited circadian arrhythmia in response to the 3 h phase-delay was included as a member of the ‘circadian arrhythmic’ (ARR) phenotype group in subsequent analyses (see *Circadian and ultradian waveform analyses*, below).

Circadian and ultradian waveform analyses

The presence/absence of CRs was determined using criteria identical to those described in prior reports of DPS-induced arrhythmia in this species (Ruby et al., 2004; Ruby et al., 1998). χ^2 periodogram analyses (ClockLab; Actimetrics) were performed on 10-day blocks of activity data, 2–3 months after the phase-shift was administered (cf. Ruby et al., 1998). Peaks in the χ^2 periodogram were considered statistically significant if they exceeded the 99.9% confidence interval limit ($P < 0.001$). Hamsters were considered arrhythmic (ARR) if there were no significant peaks in the periodogram in the circadian range, activity was distributed throughout the light-dark cycle, and daily activity onsets and offsets could not be identified via visual inspection of the periodogram (Ruby et al., 1998). Hamsters with significant circadian activity in the χ^2 periodogram were considered entrained (ENTR). Supplemental analyses after completion of χ^2 periodogram analyses were adopted as recommended by Refinetti et al. (2007); to this end, the cosinor periodogram (Bingham et al., 1982), a reliable curve-fitting tool to quantify rhythm parameters, was used (Refinetti et al., 2007) to calculate the mesor and amplitude of the best-fit cosinor waveform in the circadian range (22–26 h). Relative amplitude of the CR was calculated as the quotient of CR amplitude divided by CR mesor (Prendergast et al., 2012a). Quantitative aspects of the ultradian waveform were assessed via Lomb Scargle periodogram analyses, followed by cosinor analyses (see *Locomotor activity data analysis*).

Locomotor activity monitoring

Passive infrared motion detectors (Coral Plus, Visonic, Bloomfield, CT) were positioned outside the cage, 22 cm above the cage floor. Motion detectors registered activity when 3 of 27 zones were crossed. Activity triggered closure of an electronic relay recorded by a computer running ClockLab software (Actimetrics, Evanston, IL). Cumulative activity counts were collected at 6 min intervals.

Locomotor activity data analysis

For the analysis of ultradian behavioral rhythms (URs), activity data (binned in 6 min intervals) were parsed into light-phase only (160 data points/24 h) and dark-phase only (80 data points/24 h) files. Successive days of photophase activity data were concatenated into a single file, as were successive nights of scotophase activity, and separately subjected to Lomb-Scargle periodogram (LSP) and cosinor periodogram analyses, as described in detail elsewhere (Prendergast et al., 2012a, 2012b).

Lomb-Scargle periodogram analyses (Lomb et al., 1976) identified the statistical presence/absence of URs and CRs, and UR *complexity*—the number of significant peaks (distinct periods) in the UR spectrum (range: 0.1 – 7.9 h; Prendergast et al., 2012b). The level of statistical significance (α) was set to 0.01. In records that exhibited significant URs in the LSP analysis, cosinor analyses determined several quantitative measures of behavioral URs (range: 0.1 – 7.9 h) and CRs (range: 22 – 26 h): *robustness* (or ‘prominence’, the percent of variance accounted for by the best-fit cosine model, which corresponds to the coefficient of determination R^2 in regression analyses; Refinetti et al., 2007); *mesor* (rhythm-adjusted mean value around which the waveform oscillates); *amplitude* (the difference between the peak or trough value and the mesor), expressed as absolute values (activity counts) and relative values referenced to the photophase-specific mesor values); the latter measure incorporates baseline activity levels during each photophase in determining rhythm amplitude. For cosinor analyses, α was set to 0.05 with a Bonferroni correction for multiple comparisons.

The LSP detects ultradian periodicities from incomplete evenly-sampled time series, is well-suited for measurement of data binned into separate scotophase/photophase files and optimizes detection of URs by not displaying peaks at multiples of all rhythms detected (Ruf, 1999; van Dongen et al., 1999). Supplemental analyses after completion of LSP analysis (van Dongen et al., 2001) were adopted as recommended by Refinetti et al. (2007). The cosinor periodogram (Bingham et al., 1982) is a reliable, preferred curve-fitting tool to quantify rhythm parameters (Refinetti et al., 2007).

Neuroanatomical, reproductive and somatic measurement

At the conclusion of locomotor activity testing, hamsters were deeply anesthetized with 4% isoflurane mixed with medical oxygen, weighed and rapidly decapitated. The skull was removed in a manner that preserved the integrity of the pre- and postchiasmatic optic tracts, and the ventral surface of the brain was photographed in the presence of a scale bar. In the resulting images, the absolute width of (1) the hypothalamus, at the midpoint in the rostro-caudal axis, (2) the optic chiasm at the point of decussation and (3) the left and right prechiasmatic optic tracts, were determined by an observer uninformed about the hamster’s sex and treatment condition. Paired ovaries and paired testis were weighed (± 0.1 mg) and the spleen was dissected and weighed.

Statistical analyses

Analyses of variance (ANOVAs) and post-hoc pairwise comparisons were performed with Statview 5.0 (SAS Institute, Cary, NC, USA) and LSP and cosinor analyses with software written by R. Refinetti (available at <http://www.circadian.org/softwar.html>; Refinetti et al., 2007). Effects of sex, drug treatment and circadian phenotype on physiological, morphological and behavioral dependent variables were assessed using ANOVA followed by two-tailed paired t-tests, where warranted by a significant omnibus F statistic. Chi-square tests were used to evaluate the effect of drug treatment on circadian response to DPS, and the effect of circadian phenotype on the presence/absence of URs. Differences were considered significant if $P \leq 0.05$.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Mean $\pm$ SEM (A) body mass, (B) ovarian (females) and testis (males) mass, and (C) spleen mass of adult hamsters treated neonatally with monosodium glutamate (MSG; dark bars) or phosphate-buffered saline (PBS; light bars). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. PBS value, within sex. # $P < 0.05$, ### $P < 0.001$ vs. male value, within drug treatment group.

Figure 2.

Representative photographs of the ventral hypothalami of hamsters treated neonatally with (A) PBS or (B, C) MSG. Note atrophy of the optic nerves (diagonal arrows) and diminution of the optic chiasm (OC) in MSG-treated hamsters (Vertical arrows = lateral extent of the hypothalamus; i = infundibulum. Scale bar = 1 mm). Mean $\pm$ SEM (D) width of the hypothalamus at the rostro-caudal midpoint, (E) width of the primary optic tract distal to the optic chiasm, (F) maximum width of the optic chiasm. ** P < 0.01, *** P < 0.001 vs. PBS value, within sex.

Figure 3.

(A) Percentage of hamsters exhibiting disrupted (arrhythmic or persistent free-running) circadian locomotor activity rhythms after DPS treatment. (B–D) Representative double-plotted activity records of a hamster treated with PBS that re-entrained to the light-dark cycle after DPS treatment (panel B); a hamster treated with PBS that became circadian arrhythmic after DPS treatment (panel C); a hamster treated with MSG that re-entrained to the light-dark cycle post DPS treatment (panel D). Clock time is indicated on the horizontal axis at the top of each actogram, along with light (white bar) and dark (black bar) phases of the 16L:8D photocycle. Chi-square periodogram analyses are depicted to the right of each actogram. *** $P < 0.001$ vs. PBS value.

Figure 4.

Mean $\pm$ SEM dark-phase (left panel) and light-phase (right panel) ultradian rhythm (UR) amplitude of hamsters treated neonatally with PBS or MSG that remained entrained to the light-dark cycle (ENTR) or became circadian arrhythmic (ARR) in response to DPS treatment in adulthood. * $P < 0.05$ vs. ARR value.