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Research Report

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 compromize 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 optic nerves. 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 two 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.

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1. Introduction

Ultradian rhythms (URs), with periods that range from ~0.5 to 8 h, 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, 2013a, 2013b; Prendergast and Zucker, 2012). 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 five 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 (Braulke and Heldmaier, 2010; Prendergast and Zucker, 2012); the relation of URs to circadian rhythms (CRs) 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, 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.

2. Results

2.1. *Influence of MSG on morphology*

2.1.1. *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 × 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 ($P>0.80$).

2.1.2. *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).

2.1.3. *Spleen mass*

MSG exerted different effects on males and females (drug × 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

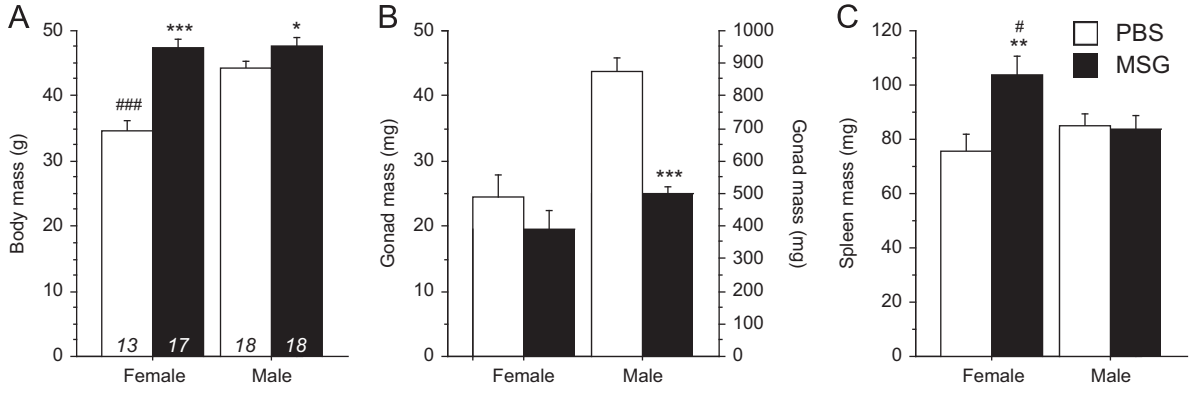

Fig. 1 – Mean ± SEM (A) body mass, (B) ovarian (females) and testis (males) mass, and (C) spleen mass of adult hamsters treated neonatally with monosodium glutamate (MSG; dark bars) or phosphate-buffered saline (PBS; light bars). *$P<0.05$, **$P<0.01$, ***$P<0.001$ vs. PBS value, within sex. #$P<0.05$, ###$P<0.001$ vs. male value, within drug treatment group.