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Research Report

Pregnancy affects FOS rhythms in brain regions regulating sleep/wake state and body temperature in rats

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ABSTRACT

Circadian rhythms in behavior and physiology change substantially as female mammals undergo the transition from a non-pregnant to a pregnant state. Here, we examined the possibility that site-specific changes in brain regions known to regulate the sleep/wake cycle and body temperature might reflect altered rhythms in these overt functions. Specifically, we compared daily patterns of immunoreactive FOS in early pregnant and diestrous rats in the medial septum (MS), vertical and horizontal diagonal bands of Broca (VDB and HDB), perifornical lateral hypothalamus (LH), and ventrolateral, medial, and median preoptic areas (VLPO, MPA, and MnPO, respectively). In the pregnant animals, FOS expression was reduced and the daily rhythms of expression were lost or attenuated in the MS, VDB, and LH, areas known to support wakefulness, and in the MPA, a brain region that may coordinate sleep/wake patterns with temperature changes. However, despite the well-documented differences in sleep patterns between diestrous and pregnant rats, reproductive state did not affect FOS expression in the VLPO or MnPO, two brain regions in which FOS expression usually correlates with sleep. These data indicate that plasticity in sleep/wake patterns during early pregnancy may be driven by a reduction in wakefulness-promotion by the brain, rather than by an increase in sleep drive.

1. Introduction

Circadian rhythms have a period of roughly 24 h and are generated endogenously. When synchronized to the external environment, these rhythms allow individuals to appropriately time behavioral and physiological events in relation to predictable changes in the environment (Moore-Ede et al., 1982). These rhythms are essential to the regulation of

Abbreviations: 3v, third ventricle; AC, anterior commissure; ANOVA, analysis of variance; ARC, arcuate nucleus; f, fornix; HDB, horizontal diagonal band of Broca; ir, immunoreactivity; LD, light/dark; LH, lateral hypothalamus; LSD, least significant difference; LV, lateral ventricle; MnPO, median preoptic nucleus; MPA, medial preoptic area; MS, medial septum; mt, mammillothalamic tract; NREM, non-rapid eye movement; ocx, optic chiasm; Pe, periventricular hypothalamus; PER2, Period2; PH, posterior hypothalamus; PRL, prolactin; REM, rapid eye movement; SCN, suprachiasmatic nucleus; VDB, vertical diagonal band of Broca; VLPO, ventrolateral preoptic area; VMPO, ventromedial preoptic area; ZT, Zeitgeber time

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mammalian reproduction and may be subject to change as individuals progress through various reproductive states. For example, during early pregnancy in laboratory rats, locomotor activity is reduced and becomes arrhythmic (Rosenwasser et al., 1987), whereas the body temperature rhythm shows an advance in its rising phase and a reduction in amplitude attributable to increases in the daily temperature minimum (Kittrell and Satinoff, 1988). Sleep patterns are also altered, with the total amount of both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep increased, as is the number of REM sleep bouts, during the dark phase of the day (Kimura et al., 1996), a time when non-pregnant rats are most active. While these changes in sleep/wake and body temperature rhythms during early pregnancy have been well-established, the neural mechanisms underlying them have yet to be identified.

We have documented altered rhythms in protein expression in specific components of the circadian system of the brain in early pregnant rats, as compared to diestrous females (Schrader et al., 2010, 2011). This circadian system includes a primary circadian pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Moore and Eichler, 1972; Ralph et al., 1990; Rusak, 1977; Stephan and Zucker, 1972), as well as various extra-SCN oscillators (Guilding and Piggins, 2007; Hastings et al., 2003; Reppert and Weaver, 2002; Weinert, 2005). The SCN and extra-SCN oscillators contain rhythmic cells that have a molecular transcription/translation loop that takes approximately 24 h to complete (Bell-Pedersen et al., 2005; Dunlap, 1999; Reppert and Weaver, 2002). The phase of the rhythm in expression of the protein Period2 (PER2), a key component of the molecular oscillator, is altered in both the SCN and some extra-SCN oscillators during early pregnancy in the rat (Schrader et al., 2010, 2011). Additionally, expression of FOS, the protein product of the immediate early gene *cfos* that often rises after neuronal activation (Kovacs, 2008), is elevated during the mid-light phase in the SCN and at other times in some extra-SCN oscillators in early pregnant rats (Schrader et al., 2010, 2011). These data indicate that circadian outputs to systems regulating overt functions, such as the sleep/wake and temperature cycles, may be changing with the transition from the non-pregnant state to pregnancy.

It is unlikely that changes in patterns of sleep, wakefulness, and body temperature rhythms that occur during early pregnancy are brought about by circadian influences alone. Non-circadian systems that more directly regulate these phenomena may also be affected by transitions in reproductive state, perhaps in ways that are not the same as those affecting the circadian system. The fact that the changes in rhythms in sleep/wakefulness and body temperature are dissociated in early pregnancy in the rat is consistent with the view that a single adjustment of a central circadian timekeeping system is unlikely to account entirely for the patterns typical of that reproductive stage. In this study, we begin to explore this issue by comparing early pregnant and diestrous rats with respect to their rhythms in expression of FOS in brain regions known to regulate these functions in a relatively direct fashion. The first group was examined on day 6 of pregnancy, as the changes in overt rhythms described above are all established by that time. Gonadal hormones, such as estrogens and progesterone, are known to influence locomotor activity, sleep, and components of the circadian system of the brain (reviewed in Mong et al. (2011)). Therefore, we selected females on day 1 of diestrus, when circulating gonadal hormones are lowest, for our non-pregnant controls.

We characterized patterns of FOS expression in portions of the basal forebrain, preoptic area, and lateral hypothalamus

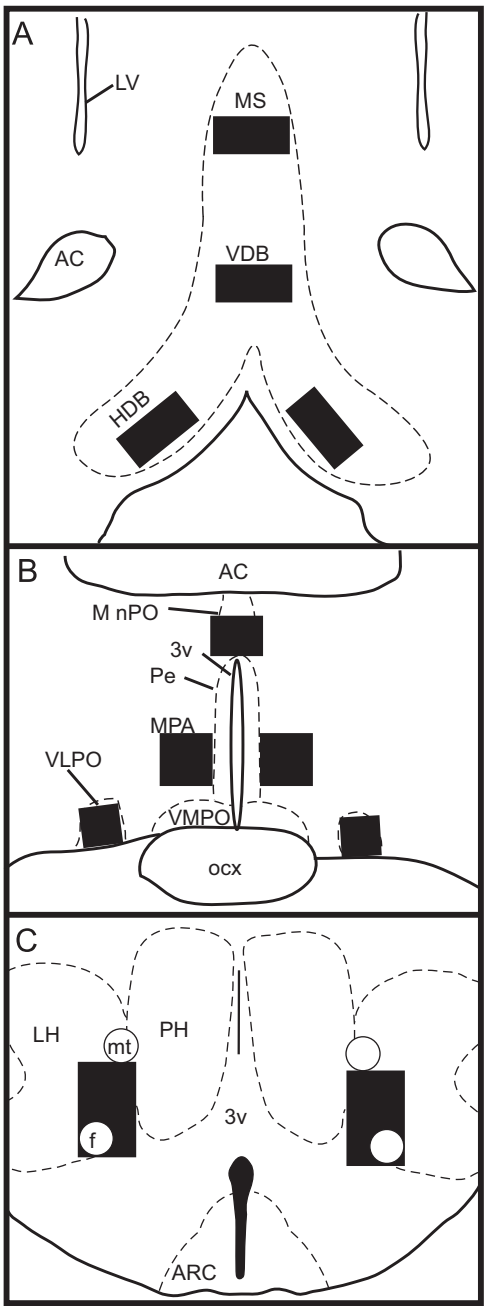

Fig. 1 – Line drawings depicting location of the MS, VDB, and HDB (A), MnPO, MPA, and VLPO (B), and LH (C). Sampling boxes (black squares) were used for cell counts in all regions as described in Section 4. Anatomical boundaries are based on Paxinos and Watson (1997). 3v: third ventricle; AC: anterior commissure; ARC: arcuate nucleus; f: fornix; LV: lateral ventricle; mt: mammillothalamic tract; Pe: periventricular hypothalamus; PH: posterior hypothalamus; ocx: optic chiasm; VMPO: ventromedial preoptic area.