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Effects of light, food, and methamphetamine on the circadian activity rhythm in mice

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HIGHLIGHTS

- Food anticipatory activity phase shifts coordinately with the light–dark cycle.
- The phase of food anticipatory activity is delayed by methamphetamine consumption.
- Coupling of the SCN and MASCO is affected by exposure to restricted feeding.
- The outputs of the SCN, FEO and MASCO collectively drive behavior.

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ABSTRACT

The circadian rhythm of locomotor activity in mice is synchronized to environmental factors such as light and food availability. It is well-known that entrainment of the activity rhythm to the light–dark cycle is attained by the circadian pacemaker in the suprachiasmatic nucleus (SCN). Locomotor activity is also controlled by two extra-SCN oscillators; periodic food availability entrains the food-entrainable oscillator (FEO) and constant consumption of low-dose methamphetamine reveals the output of the methamphetamine-sensitive circadian oscillator (MASCO). In this study, we sought to investigate the relationship between the SCN, FEO, and MASCO by examining the combinatorial effects of light, food restriction, and/or methamphetamine on locomotor activity. To investigate coupling between the SCN and FEO, we tested whether food anticipatory activity, which is the output of the FEO, shifted coordinately with phase shifts of the light–dark cycle. We found that the phase of food anticipatory activity was phase-delayed or phase-advanced symmetrically with the respective shift of the light–dark cycle, suggesting that the FEO is strongly coupled to the SCN and the phase angle between the SCN and FEO is maintained during *ad libitum* feeding. To examine the effect of methamphetamine on the output of the FEO, we administered methamphetamine to mice undergoing restricted feeding and found that food-entrained activity was delayed by methamphetamine treatment. In addition, restricted feeding induced dissociation of the MASCO and SCN activity rhythms during short-term methamphetamine treatment, when these rhythms are typically integrated. In conclusion, our data suggest that the outputs of the SCN, FEO and MASCO collectively drive locomotor activity.

1. Introduction

Light and food availability are periodic environmental factors that entrain circadian oscillators in mammals. Entrainment is believed to improve fitness and survival by allowing anticipation of predictable daily changes in environmental conditions and coordinating precise phasing of rhythms in behavior and physiology.

It is well-known that light entrains the circadian pacemaker in the suprachiasmatic nucleus (SCN) through monosynaptic projections from the retina [1]. Numerous studies have also examined the effect of periodic food availability on circadian locomotor activity. When a single daily meal is provided at a fixed time of day (i.e. restricted feeding), locomotor activity increases 2 to 4 h before the scheduled feeding time [2,3]. Even though this food anticipatory activity disappears during *ad libitum* feeding, it reappears at the previous time of restricted feeding when rodents are subsequently food deprived, demonstrating that it is controlled by a self-sustained oscillator [2]. In addition, food anticipatory activity persists when the SCN is lesioned and displays properties of a circadian oscillator, namely a limited range of entrainment and transients following phase shifts of mealtime [4–10]. Thus, the food-

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entrainable oscillator (FEO) that controls food anticipatory activity is distinct from the SCN, although its anatomical locus is unknown [11].

Compared to the SCN and FEO, relatively few studies have examined the methamphetamine-sensitive circadian oscillator (MASCO). The MASCO-controlled wheel-running activity rhythm is observed when rats and mice are continuously administered low-dose methamphetamine [12,13]. During chronic (>30 days) methamphetamine treatment, the MASCO-controlled activity rhythm dissociates from the SCN-controlled activity rhythm and the MASCO rhythm also persists when the SCN is lesioned, demonstrating that the MASCO is distinct from the SCN [13–17]. Like the FEO, the anatomical locus of MASCO is unknown. This has, in part, led to speculation that the FEO and MASCO are the same oscillator (but see [18]; for discussion see [17]).

The SCN is regarded as the master pacemaker because it coordinates the phases of peripheral clocks and controls rhythmic locomotor activity [19,20]. Like the SCN, the FEO and MASCO can coordinate the phases of

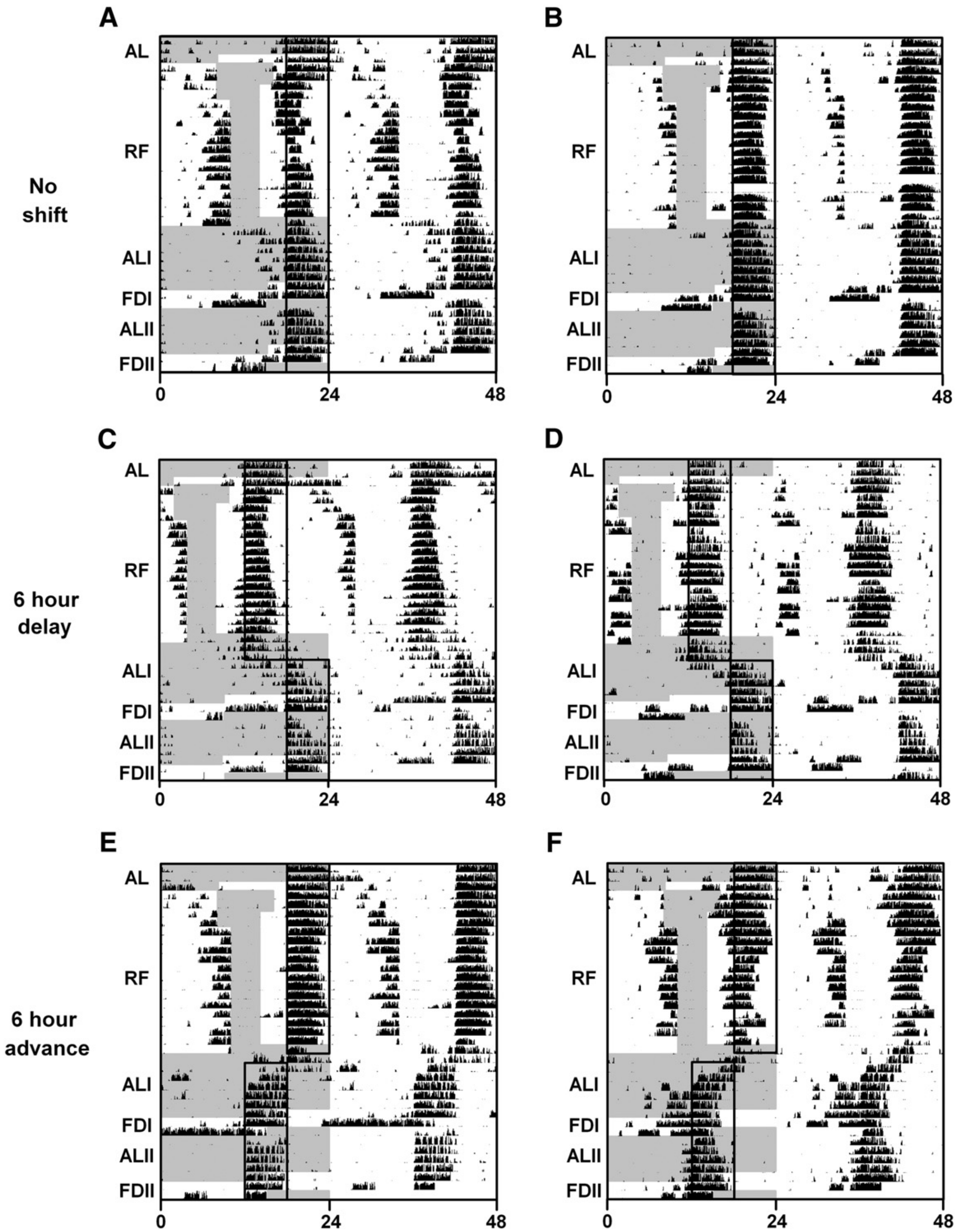

Fig. 1. Effect of shifting the light–dark cycle on the phase of food anticipatory activity. Double-plotted actograms of wheel-running activity (5-min bins) of wild-type mice (A, C, E: males; B, D, F: females) maintained in 18L:6D (*x*-axis: time in hours; *y*-axis: days). Darkness is outlined with black boxes and the time when food was available is indicated by gray shading (shown only on the left halves of the actograms). The mice were fed *ad libitum* (AL) for 2 days, and then deprived of food for 25 h. Food availability was then gradually reduced from 8 h (2 days) to 6 h (2 days) and then to 4 h (15 days) per day (RF). Mice were then fed *ad libitum* (ALI) for 7 days. On the third day of *ad libitum* feeding, the light–dark cycle was either not shifted (A, B), delayed 6 h (C, D), or advanced 6 h (E, F). Four days later, mice were food deprived (FDI) for 50 h. Then, mice were fed *ad libitum* (ALII) for 5 days and then food deprived (FDII) again for 48 h.