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Review

The clock shop: Coupled circadian oscillators

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ABSTRACT

Daily rhythms in neural activity underlie circadian rhythms in sleep–wake and other daily behaviors. The cells within the mammalian suprachiasmatic nucleus (SCN) are intrinsically capable of 24-h timekeeping. These cells synchronize with each other and with local environmental cycles to drive coherent rhythms in daily behaviors. Recent studies have identified a small number of neuropeptides critical for this ability to synchronize and sustain coordinated daily rhythms. This review highlights the roles of specific intracellular and intercellular signals within the SCN that underlie circadian synchrony.

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Introduction

What woke you up today? If you ask this question of people in developed countries today, over 80% will credit their alarm clock (Roenneberg et al., 2012). But when they permit themselves a morning without an external timer, they will wake naturally to the call of an internal, daily clock. This chapter is about the cellular organization of this daily clock. We review evidence that this daily clock is comprised of thousands of intrinsically oscillatory cells that must synchronize with environmental cues and with each other. We summarize what is known about the signaling pathways involved in their communication with each other to generate a coherent daily rhythm in behavior.

Life on Earth has evolved in the presence of a daily light–dark, warm–cool cycle. Nearly all organisms alive today anticipate and synchronize (entrain) with these potent cues (Dunlap, 1999). These daily rhythms persist in the absence of these cues, for example in a deep cave or during the dark winter months near the Poles (Cavallari et al., 2011). Under these constant conditions, most organisms will wake and sleep with a period close to 24 h. These circadian (from the Latin, *circa* meaning approximately and *diem*, a day) rhythms

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include cycles of sleep–wakefulness, feeding–fasting, metabolism and hormone release (Honma et al., 2003; Sack et al., 2007). This same circadian clock regulates seasonal changes in many mammals including breeding, fat storage and hibernation (Geiser, 2004).

A simple circadian system: input–pacemaker–output

It has been useful to evaluate the circadian system conceptually as a pacemaker that regulates a variety of rhythmic outputs and entrains to a variety of environmental timing cues through input pathways. Anatomically, the master circadian pacemaker of mammals has been localized to the suprachiasmatic nucleus (SCN), a group of cells in the base of the anterior hypothalamus situated directly above the optic chiasm (Fig. 1). The bilateral rodent suprachiasmatic nuclei are composed of about 20,000 neurons packed into an area approximately 1 mm in diameter (Klein et al., 1991).

Pacemaker

Evidence that the SCN acts as a master circadian pacemaker comes primarily from lesion and transplantation studies. Destruction of the SCN results in a loss of daily rhythms in a wide variety of functions including sleep–wake, locomotor activity, feeding, drinking, body temperature and secretion of adrenal, pineal and pituitary hormones (Meyer-Bernstein et al., 1999; Moore and Eichler, 1972; Stephan and Zucker, 1972; Tahara et al., 2012). Rhythms in locomotion, feeding, drinking and body temperature can be restored by a SCN transplant, remarkably, with the period of the donor (Cho et al., 2005; Meyer-Bernstein et al., 1999; Ralph et al., 1990; Silver et al., 1996). In addition, the isolated SCN displays circadian rhythms in glucose metabolism, electrical firing, neuropeptide secretion, and gene expression (Earnest and Sladek, 1986; Green and Gillette, 1982; Meijer et al., 1997; Shibata and Moore, 1993; Yamazaki et al., 2000). Taken together, these results indicate that the coordinated daily rhythms of SCN cells drive circadian rhythms in the brain and, ultimately, the body.

Input

In mammals, the eyes are required to entrain the SCN to light cycles (Berson et al., 2002; Hattar et al., 2002; Morin et al., 2003; Wee et al., 2002; Yamazaki et al., 1999). This was not a foregone conclusion since all other vertebrates need the presence of extraocular photoreceptors for entrainment (Meijer et al., 1999; Nelson and Zucker, 1981). Intriguingly, some "blind" patients with rod/cone degeneration, while unable to form images, can respond to light by entraining their circadian rhythms, suppressing their nighttime melatonin production, constricting their pupils and, in a few cases, reporting awareness of the light (Czeisler et al., 1995; Klerman et al., 2002; Zaidi et al., 2007). These residual light responses arise from a subset of intrinsically photosensitive retinal ganglion cells (ipRGCs) that express the photopigment, melanopsin (Berson et al., 2002; Hattar et al., 2002). ipRGCs form the retino-hypothalamic tract and convey light information transduced by rods and cones in addition to their intrinsic light responses (Foster et al., 2007; Freedman et al., 1999; Guler et al., 2008). Thus, ipRGCs are the sole conduit for light information of all intensities to the SCN and for photic entrainment (Guler et al., 2008; Hatori et al., 2008). Light is not the only input signal important for entrainment of the clock, as other non-photic input signals have been also implicated to participate. For example, exercise, social signals, temperature cycles or sleep deprivation can reset the clock (Hastings et al., 1997; Herzog and Huckfeldt, 2003; Mistlberger and Skene, 2005; Mrosovsky, 1996).

Output

The SCN can convey time-of-day information to the rest of the brain and body via neuronal and humoral pathways (Hatcher et al., 2008; Kalsbeek and Buijs, 2002; LeSauter and Silver, 1998). Efferents from the SCN project primarily to nuclei within the hypothalamus (see Chapter by Larry Morin).

Many intrinsically circadian cells of the SCN collectively encode the precision, amplitude, waveform and robustness of daily rhythms

In 1995, David Welsh and colleagues demonstrated that individual SCN neurons fire action potentials each day and fall silent each night for many days in vitro (Welsh et al., 1995). Remarkably, they found that when dispersed into a culture dish at relatively low density (~3000 cells/mm^2), SCN neurons expressed different circadian periods from each other so that, for example, some neurons started their daily firing every 23 h while others initiated firing every 28 h.

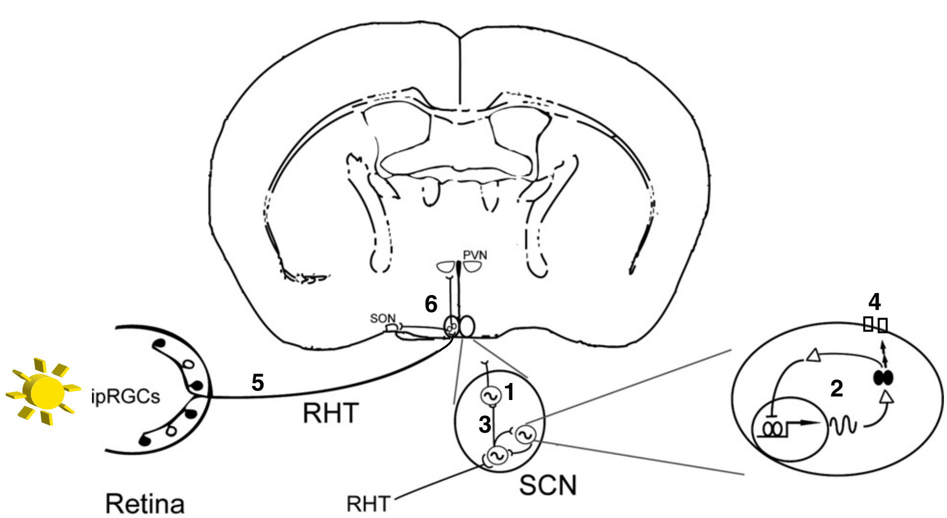

Fig. 1. The cellular and molecular organization of the mammalian circadian system. Neurons within the suprachiasmatic nucleus (SCN) are competent circadian pacemakers (1). They depend on intracellular, transcription-translation negative-feedback (2) mechanisms to generate near 24-h oscillations. When they synchronize with each other through neuropeptide signaling (3), they drive daily rhythms including metabolism, gene expression, cAMP levels, membrane excitability, firing rate and neuropeptide secretion (4). The coordinated daily rhythms of the SCN are entrained to light cycles by direct input from intrinsically photosensitive retinal ganglion cells (ipRGCs) (5). Projections from the SCN to other hypothalamic structures (6) convey time-of-day information to regulate daily rhythms in the brain, body and behavior. SON, supraoptic nucleus; PVN, paraventricular hypothalamic nucleus.