Biological Timekeeping

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KEYWORDS

• Biological rhythms • Sleep • Circadian
• Suprachiasmatic nucleus • Acetylcholine
• Advanced Sleep Phase Syndrome • Glutamate • Melatonin

The daily transition from light to darkness has shaped the evolution of most living species, from unicellular organisms to mammals. Adaptation to this environmental constraint occurred through the emergence of a circadian system capable of adjusting behavioral and physiological processes to this light-dark cycle. Superimposed upon the daily light–dark cycle is a seasonal influence that modifies the relative durations of day and night over the course of a year. Be they day-active or night-active, all organisms need a means of keeping time in a 24-hour world in order to adapt to the availability of food, and to avoid predators. In addition, they require a means of adjusting to changes in day length or transition times that may occur.

Interestingly, rather than simply reflecting the external day–night cycle, these rhythms in behaviors persist in the absence of exogenous timing cues such as light, food availability, or social cues. Every organism expresses an endogenous rhythm that varies slightly from 24 hours, making it circadian, or about a day. Uninterrupted, this circadian rhythm persists.

These circadian rhythms can be observed in outputs such as the patterning of the sleep–wake cycle, and in people, core body temperature often is used as a marker of circadian phase. In addition, numerous endogenous hormones can be used as markers.[1] Although hormonal rhythms exhibit complex waveforms because of combined effects of the circadian pacemaker; organismic state, such as activity level, sleep and feeding; and the pulsatile nature of secretion, clear diurnal patterns of secretion have been reported.[2] Plasma melatonin,[3,4] growth hormone,[5] prolactin,[6] thyrotropin-releasing hormone,[7] luteinizing hormone,[8] and leptin[9,10,11] are elevated during the night, in antiphase to adrenocorticotropic hormone and cortisol.[12,13] These oscillations in hormone secretion continue in a constant environment, and therefore, are clock-regulated. Circadian rhythmicity appears to be present at virtually every level of functioning studied. In fact, maintenance of a constant milieu interior may be a consequence of a balance among rhythmic, mutually opposed control mechanisms.[2]

This article explains the neurobiology of circadian timekeeping, describing what is known about the master pacemaker for circadian rhythmicity, how various biological systems can provide input to the endogenous biological timing, and how the pacemaker can in influence the physiology and behavior of the individual. It discusses how the circadian system can adapt to a changing environment by resetting the circadian clock in the face of various inputs, including changes in light, activity, and the sleep–wake cycle. Finally, the article

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discusses the genetics of circadian time keeping, highlighting what is known about heritable disorders in circadian timing.

THE CIRCADIAN CLOCK

In mammals, circadian rhythms are regulated by a paired set of nuclei located at the base of the hypothalamus, directly above the optic chiasm, hence their name, the suprachiasmatic nuclei (SCN) (**Fig. 1**). Multiple experiments have demonstrated the role of the SCN as a central pacemaker for circadian rhythms. Lesioning studies found that damage to the SCN disrupts rhythmicity in corticosterone levels, drinking, and wheel-running behavior.[14,15] This provided the initial evidence that the central pacemaker for the mammalian clock lay within the SCN.

In later work, it was found that transplanting fetal SCN tissue into the third ventricle of animals in which the SCN had been lesioned could restore rhythmicity.[16] Furthermore, if fetal SCN tissue from a wild-type hamster was implanted into a hamster with a genetic alteration that shortened the free-running period, the new free-running period resembled that of the SCN donor rather than the host animal. This evidence suggested that not only was the SCN necessary for generating rhythms, but also that this rhythmicity was an intrinsic property of the SCN cells, which could drive the rhythms for the entire animal.[17]

In the mouse, each SCN measures approximately 300 μm medial to lateral, 350 μm dorsal to ventral, and spans approximately 600 μm from rostral to caudal end. One SCN contains approximately 10,500 cells.[18] Based on peptide localization, it is common to divide the rodent SCN into a ventrolateral or core region, and a dorsomedial or shell region (see **Fig. 1**). The core neurons are small and contain vasoactive intestinal peptide (VIP), calretinin (CALR), and gastrin-releasing peptide (GRP) colocalized with γ-amino butyric acid (GABA), while the shell neurons are larger and contain arginine vasopressin (AVP), met-enkephalin (mENK), and angiotensin II (AII).[18] There are topographic connections between the contralateral shells and the contralateral cores, and a unidirectional connection between the core and shell within each nucleus.[19]

The human SCN is not as compact as the rodent but contains many of the same subdivisions. The dorsal and medial regions contain neurophysin/vasopressin neurons. The core region contains calbindin, synaptophysin, and VIP neurons, while the ventral and rostral regions contains synaptophysin, calbindin, and substance P.[20]

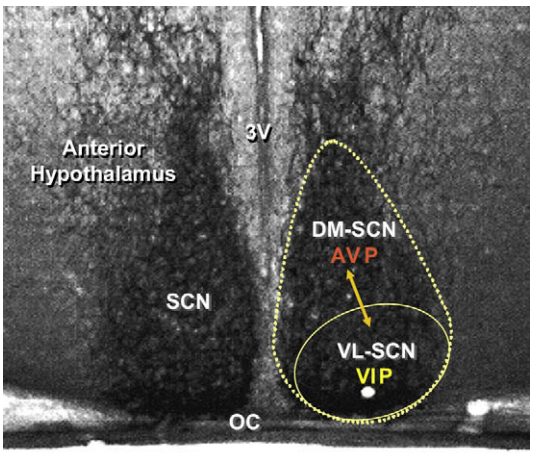

Fig. 1. Anatomy of the mammalian suprachiasmatic nucleus (SCN). This medial, transverse section of the rat anterior hypothalamus shows the bilateral SCN stained darkly with an antibody to an endogenous peptide. The paired SCNs are at the base of the brain, flanking the third ventricle (V3) and positioned directly above the optic chaism (OC). The two major subdivisions of the SCN are delineated. The dorsomedial SCN (DM-SCN) is marked by neurons expressing arginine vasopressin (AVP), whereas neurons of the ventrolateral SCN (VL-SCN) express vasoactive intestinal peptide (VIP).

Inputs

In conjunction with its ability to regulate circadian timing, the SCN also is positioned to receive information about the behavioral and environmental state of the animal in order to ensure proper setting of the circadian clock. This information is conveyed to the SCN by projections from various different brain regions.

One of the most extensively studied inputs to the SCN comes from a subpopulation of retinal ganglion cells whose central projections form the retinohypothalamic tract (RHT). Lesions of the SCN disrupt the development of these neurons,[21] and disruption of the RHT results in an inability to respond to resetting light signals.[22,23] Recent work has found that many of the retinal ganglion cells that comprise the RHT contain a photopigment, melanopsin.[24] These melanopsin-containing cells are photosensitive at the same wavelengths that are most effective for circadian resetting.[25] Additionally, the terminals of the melanopsin-positive retinal ganglion cells collocalize glutamate (GLU) and pituitary adenylate cyclase-activating polypeptide (PACAP),[26] the putative neurotransmitters of the RHT.

The RHT also sends projections to the thalamic intergeniculate leaflet (IGL), which in turn sends

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