REGULATION OF CIRCADIAN RHYTHMS THROUGH SENSORY SYSTEMS

Nathaniel Brown
Nicci Fickenscher

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Chapter 1

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1.1 INTRODUCTION

All biological processes operate in a 24 hour cycle. This cycle is referred to as the circadian rhythm, "circa" for around and "dian" for day or "around a day." The endogenous rhythm is entrained by external environmental stimuli, the dominating stimuli being light. This allows for living entities to anticipate, prepare for, and engage in reproduction, consumption, periods of latency, migration, and hibernation. The biological clock persists in constant conditions with a period of approximately 24 hours, maintains the same period over a range of temperatures, and can be reset by exposure to external cues. This rhythm is maintained by periodic release of hormones that control the timing of sleep/wake, body temperature, thirst, and appetite.

The primary circadian "clock," or pacemaker, in mammals is located in the suprachiasmatic nucleus (SCN), a pair of distinct groups of cells located in the hypothalamus. It is this tiny region on the brain’s midline in a shallow impression of the optic chiasm that is responsible for controlling endogenous circadian rhythms. The SCN interacts with many other regions of the brain and contains several different peptides and neurotransmitters. Other "clocks" outside the SCN are found in many organs and cells such as in the esophagus, lung, liver, pancreas, spleen, thymus, and the skin. These
independent circadian rhythms are referred to as peripheral oscillators. For example, liver cells appear to respond to feeding rather than light.

Of the various environmental cues that influence the synchronization of biological processes, light exposure to the eyes is the strongest factor. For example, in mammals, illumination intensity that excites the circadian system has to reach up to 1000 lux and strike the retina. In addition to light intensity, the wavelengths of light are a factor in the entrainment, or synchronization, of the body’s pacemaker. The wavelength that causes the most efficiency is between 420 - 440 nm, which is seen as the color blue. The direction of the light is also a factor. The light coming from above verses below has a greater effect on entraining.

Although light is the principle sensory stimuli responsible for entrainment to a diurnal cycle, other sensory modalities are capable of generating rhythmicity in nature. Little is known about the specific selective pressures that encouraged the generation of different modes of entrainment. It is likely that single cell oscillatory behaviors are ubiquitous, yet the adaptive forces that led to it may have arisen independently for many species and taxa. The absence of specific theories for the evolution of sensory modalities in entrainment does not mask the central point of periodic states: the balance between maximization and conservation of energy resources. Light is able to mediate this balance for many organisms, and as such serves as the primary Zeitgeber. Other Zeitgeber exist in nature and have both complementary and overlapping functions. These so-called "weak Zeitgeber" will be covered based on the sensory system used as the mechanism of entrainment.

How do external environmental cues signal to an organism to inhibit or begin a biological process? What is the mechanism of a sensory input transforming to a chemical signal? What is it about light that can control biological patterns? In the next sections, discussion of these questions will be answered. Though all living organisms exhibit circadian rhythms, from plants, fungi, and bacteria, we will focus on the mammalian circadian rhythm.

1.2 SENSORY SYSTEM: EYE

The circadian rhythm of mammals, and many invertebrates, is dominantly affected by signals received from specialized cells in the eye. These cells, photosensitive retinal ganglion cells (pRGC), sense light and send a signal to
the SCN along the retinohypothalamic tract. (Fig. 1.1)

Unlike other retinal ganglion cells, pRGC are intrinsically photosensitive which means that they are a third class of retinal photoreceptors, the classical photoreceptors being the rods and cones. (Fig. 1.2) The intrinsic light responses of the pRGC differ radically from those of the rods and cones. Light depolarizes pRGC but hyperpolarizes rods and cones. The pRGC are less sensitive than the classical photoreceptors and are far more sluggish, with response latencies as long as one minute. Bright continuous illumination evokes a remarkably sustained depolarization in pRGC that faithfully encodes stimulus energy. This sets these cells apart from essentially all other mammalian retinal ganglion cells.

Photosensitive ganglion cells contain a photopigment, melanopsin, that recent studies show has a direct involvement in circadian photoreception.
When light activates the melanopsin signaling system, the melanopsin-containing ganglion cells discharge nerve impulses, which are conducted through their axons along the retinohypothalamic tract to the SCN. These melanopsin-containing ganglion cells are unique in neurochemistry in that they contain pituitary adenylate cyclase-activiting peptide (PACAP). It is thought that these cells influence their targets by releasing from their axons the neurotransmitter PACAP along with glutamate. SCN neurons downstream of retinal ganglion cell terminals receive and process photic input via these neurotransmitters. The principal neurotransmitters of the retinohypothalamic tract are glutamate and PACAP. (Fig. 1.3) Almost nothing is known about the signaling cascade that couples photopigment activation to the voltage response, and this will be a major research focus in the future.

![Figure 1.3: Principle Neurotransmitters](image)

The signal of light reaching the 20,000 neurons of the SCN entrains the organism to the solar cycle. The SCN, being the master pacemaker, synchronizes the organism’s biological processes by releasing various hormones and neuropeptides to other pacemakers elsewhere in the brain. This in turn
sends signals via hormones to the rest of the body, thus coordinating the organism’s biological processes. The signal of light reaching the 20,000 neurons of the SCN entrains the organism to the solar cycle. The SCN, being the master pacemaker, synchronizes the organism’s biological processes by releasing various hormones and neuropeptides to other pacemakers elsewhere in the brain. This in turn sends signals via hormones to the rest of the body, thus coordinating the organism’s biological processes. There are a number of proteins involved in the cellular regulation of biochemical processes. The clock period in a cell is set by a balance of activating and deactivating factors. Factors that activate gene expression are the CLOCK (Circadian Locomotor Output Cycles Kaput) and BMAL (brain and muscle aryl hydrocarbon receptor nuclear translocator (ARNT)-like) proteins as well as the light signal. When the light signal reaches the SCN neuronal cell, it induces the transcription and translation of the period family genes, or the Per genes, and other clock controlled genes. These genes inhibit transcription and translation of CLOCK and BMAL. There are three genes of the period family, Per1, Per2, and Per3. The protein products of these genes form a complex. CLOCK and BMAL proteins dimerize and transactivate gene expression of the period genes. Therefore, when CLOCK and BMAL protein’s transcription are inhibited, this stops the transcription of the Per genes. Thus, the products of the Per genes inhibit their own production in a negative feedback loop. It is this loop that causes the molecular oscillations. (Fig. 1.4)
1.3 SENSORY SYSTEM: OLFACITION

The bulk of data on entrainment via olfactory cues are with rodents and insects. In mice and rats, olfactory cues have been found to regulate the expression of c-fos, a metabolic marker of neuronal activity, in the olfactory bulb, modulating sensitivity even in the absence of light. Antennal neurons in the housefly, Drosophila, can be entrained to olfactory neurons without the aid of a central pacemaker. Isolations of the antennal neurons demonstrate oscillatory rhythms in vitro. These effects are controlled by transcriptional feedback loops in the antennal neurons themselves. Insects show changes in the ability to discriminate between two odors based on the time of day in which the learning paradigm is carried out. Circadian rhythmicity appears to control the ability to acquire memory of conditioned stimuli.

1.4 SENSORY SYSTEM: GUSTATION

A central feature of circadian rhythms is the oscillation in feeding patterns, metabolism, and locomotor activity. There is strong evidence to suggest that
metabolic homeostasis is controlled by the central pacemaker in the brain, the suprachiasmatic nucleus (SCN). However, accumulating evidence indicates that food intake and metabolism may in turn alter the core circadian oscillator (CCO) and even mitigate the ability of the CCO to entrain to photic stimuli. (Fig. 1.5) Although the precise mechanism of how metabolic changes entrain biological rhythms remains unknown, it is thought that the cellular redox state might be a candidate. In cyanobacteria, iron-based oxidants are able to entrain the organism by affecting genes that are normally activated in response to photic stimuli. In flies, circadian rhythms have been linked to fluctuations in levels of antioxidant enzymes by either suppressing or activating the transcriptional feedback loop. (Fig. 1.6) Correlation studies done in rats demonstrate a link between the peak of the phase response curve (PRC) in circadian rhythms (DNA binding of CLOCK:BMAL1 and NPAS2:BMAL1) and reduced NADH/NADPH co-factor levels, while the oxidized forms of these co-factors are correlated with inhibition of transcriptional activity of the CCO.

Peripheral organs such as the liver also appear to be entrained by metabolism. Altered feeding patterns have a significant effect on the rhythmic output of metabolites and enzymes in the liver. Locomotor activity and energy expenditure also seem to have bidirectional influences on the CCO. (Fig. 1.7) In rodents, physical activities such as wheel-running are able to entrain the biological clock. Studies in humans have demonstrated that physical exercise can act as an effective Zeitgeber, particularly in the blind and the elderly.
1.5 SENSORY SYSTEM: THERMOSENSE

As stated before, animals that are able to regulate their own internal body temperature are able to compensate for fluctuations in the temperature of the...
environment, and thus are resistant to circadian entrainment by differences in heat and cold. Ectothermic (poikilothermic) organisms on the other hand are much more susceptible to these environmental fluctuations and are regularly entrained to them. The precise mechanism whereby thermoreception is able to interact with the CCO is unknown, but evidence suggests that this is a pervasive feature and can have effects that rival photic entrainment in their robustness.

1.6 SUMMARY

For most organisms, the entraining stimuli of circadian rhythms are most often light. In mammals, the primary circadian pacemaker is located in the SCN. These daily rhythms are mediated via complex transcriptional feedback loops where genes such as per, cry, and others are activated by large protein complexes (i.e., CLOCK/BMAL1). It has become increasingly obvious; however, that biological rhythmicity can have multiple modes of action. Oscillatory behavior can be induced by changes in temperature, olfactory cues, feeding habits, physical activity, social activity, redox states, and even weak electric fields (Wever, Rutger, 1974). For most of these cues, the cellular and molecular modes of interaction are largely unknown. It is clear, also, that these cues can show great variability in effectiveness between species and even within them. Future research will no doubt demonstrate a multitude of ways in which organisms have evolved to adapt to periodic fluctuations in the environment.
1.7 REFERENCES

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