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**Glossary**

- **biological rhythm** Any recurrent endogenous cycle (behavioral or physiological) that persists in constant conditions in the absence of geophysical or environmental temporal cues.
- **circadian rhythm** Endogenous rhythm that is approximately 1 day in length.
- **circannual rhythm** Endogenous rhythm that is approximately 1 year in length.
- **entrainment** Synchronization of an internal endogenous rhythm by a recurring external time cue such as the day–night cycle.
- **free running** Expression of a biological rhythm in the absence of any environmental temporal cues.
- **photoperiod** Amount of daylight in a given day; day length.
- **seasonal rhythm** Yearly rhythm that is exogenously regulated by geophysical cues.
- **suprachiasmatic nucleus** The primary “biological clock” located in the anterior hypothalamus of the brain that coordinates rhythmic and photoperiodic information via inputs and outputs of the nervous and endocrine systems.
Although many kinds of biological rhythms have been identified in both vertebrate and invertebrate species, and these rhythms are typically categorized by the length of a single cycle. For example, circadian rhythms are daily rhythms that are approximately 24 h and mimic the geophysical cycles of day and night. The alternating pattern of activity followed by periods of rest (sleep) that are observed in most vertebrate species is the most salient example of a circadian rhythm. However, biological rhythms need not be 24 h in length. Ultradian rhythms are rhythms that occur more frequently than 24 h. For example, many hormones (e.g., cortisol) and enzymatic reactions display rhythms only a few hours in length. In contrast, infradian rhythms are rhythms longer than 24 h but shorter than 1 year. Cycles of reproductive endocrine activity, such as menstrual cycles in humans and estrous cycles in nonhuman animals, are examples of this kind of rhythm. Finally, some species display circannual rhythms, with cycle lengths of approximately 1 year that persist in the absence of environmental influences. Circannual rhythms commonly involve yearly cycles in breeding activity and reproductive endocrinology. For example, some species of birds and rodents display yearly fluctuations in gonadal mass and changes in reproductive hormones (e.g., testosterone, estrogen), and these fluctuations persist when the animals are maintained within constant conditions of the laboratory. Closely related to circannual rhythms are seasonal rhythms, which also approximate 1 year. However, unlike true circannual rhythms, seasonal rhythms are generated in response to environmental cues and do not persist in the absence of these cues.

Although many kinds of biological rhythms have been identified, the majority of research within the field of circadian and circannual/seasonal rhythms. As will be seen later, the neuroendocrine mechanisms responsible for generating circadian rhythms are also intimately involved in generating seasonal rhythms. Because the circadian clock is necessary for seasonal rhythms, the discussion that follows outlines the means by which circadian rhythms are generated and maintained and then the mechanisms by which seasonal rhythms are generated. The article concludes with a discussion of various endocrine disorders that have been tied to abnormalities in circadian and circannual/seasonal rhythms.

**CIRCADIAN RHYTHMS**

“Circadian” comes from the Latin *circa* (meaning “around”) and *diem* (meaning “a day”). Virtually all measurable physiological and behavioral responses display circadian rhythms. For example, there are circadian rhythms in everything from heart rate and liver metabolism to attention and speed of decision making and reaction time. It is now known that all of these rhythms are controlled by a bilateral nucleus at the base of the brain. This brain region was identified in 1972 as an area of the hypothalamus called the suprachiasmatic nucleus (SCN). Lesions that destroy the SCN result in an abolition of all rhythmic processes from daily rhythms in hormone secretion to the sleep-wake cycle. As will be seen later, SCN lesions can also abolish seasonal rhythms.

Further evidence that the SCN is the circadian clock comes from studies showing that rhythmicity can be restored in SCN-lesioned animals by transplanting SCN tissue from a donor animal into the brains of animals with their own SCNs destroyed. This procedure restores circadian rhythms in these formerly arrhythmic animals, demonstrating that one can literally remove the circadian clock from one animal and provide it to another animal whose own clock is not functioning. Importantly, the rhythm is restored with the period of the donor, demonstrating that the restoration of circadian behavior is a property of the transplant rather than restoring function in the host animal's brain. Finally, the SCN can be removed from an animal and maintained in a culture dish, and it will continue to show circadian rhythms in neural firing rate. These studies are important because they show that circadian rhythms are contained within the SCN and are not simply being driven by temporal input to this brain region.

Knowledge of where the primary biological clock is located within the brain set the stage for investigations of the SCN at the cellular level to determine what makes the clock “tick.” To draw an analogy between the SCN and a watch, if one opened the back of a watch, a large number of gears could be seen. One might know that the gears are all working together to allow the watch to function properly. However, to fully understand the watch’s internal mechanism, one would have to carefully remove one gear at a time to see how it is connected to the next gear, and so on,
until all of the gears were taken out. In much the same way, one can study individual cells within the SCN to see how all of the cells (approximately 10,000) in a unilateral SCN work together to keep time. Unlike the gears of a watch, individual cells within the SCN are capable of showing their own independent circadian rhythms. When one begins to look at other cells, one can see that they too show rhythms, but each cell has its own intrinsic period. So, like the question of how all of the gears of a watch work together to keep accurate time, one question of interest to circadian biologists is how all the cells of the SCN work together to produce a rhythm of 24 h.

The knowledge that individual cells of the SCN can produce a rhythm on their own suggested that the complete machinery for producing a rhythm is contained within each cell of the SCN. This information allowed researchers to begin investigating the cellular mechanisms responsible for rhythm generation. Over the past 10 years or so, enormous progress has been made uncovering the cellular and molecular mechanisms responsible for the generation of circadian rhythms within a cell. It is now known that these rhythms are produced by a feedback loop within the cell that takes approximately 24 h. The process begins in the cell’s nucleus when two proteins called CLOCK and BMAL bind to one another and drive the transcription of messenger RNA (mRNA) of two genes called period (per) and cryptochrome (cry). The mRNA for these genes then migrates to the cytoplasm of the cell and is translated into PER and CRY proteins. Over the course of the day, these proteins build up within the cytoplasm, and when they reach high enough levels, they bind to one another (PER:CRY). These newly formed PER:CRY “dimers” then feed back to the nucleus, where they bind to the CLOCK:BMAL protein complex to turn off their own production. Although numerous other clock genes and their protein products have been identified, this regulatory loop provides the core molecular clock mechanism in mammals (Fig. 1).

Interestingly, over the past several years, the same clock genes (e.g., clock, bmal, per, cry) that are found in cells of the SCN have been identified in other brain areas as well as in many other peripheral tissues in the body. However, these “clocks” in other parts of the body are different from those found in the SCN. If these clocks are removed from the body, their endogenous rhythms will cycle for only a few days before dampening, whereas those present in the SCN will continue to cycle indefinitely. These findings suggest that the SCN is the master clock that is required to communicate with other subordinate
clocks so that they can continue to keep time. There are many reasons why these subordinate clocks might be needed in tissues other than the SCN. These clocks may be necessary for tissues to anticipate upstream signals stimulating production of specific factors. For example, the cellular machinery necessary to produce a hormone in response to stimulation could require hours of preparation within the cell. However, if the tissue has its own clock, it can turn on this machinery in advance of stimulation and be prepared to produce the hormone much faster.

The preceding findings summarize what is known about the physiological functioning of the SCN. However, for a clock to be adaptive for an organism, the clock needs to coordinate all of these rhythms with local time in the environment. In mammals, this synchronization is accomplished via a direct projection, the retinohypothalamic tract (RHT), from the eye to the SCN (Fig. 2). Unlike rod and cone photoreceptors in the retina that are responsible for black/white and color vision, respectively, the photoreceptors that communicate with the SCN are ganglion cells that are directly responsive to light because they contain a photopigment called melanopsin. Essentially, these melanopsin-containing ganglion cells project to the SCN to inform the SCN of the time in the environment. Because the SCN is synchronized (entrained) to local time, it can prepare the brain and body well in advance of the time that rhythmic processes need to occur. For example, the SCN can stimulate the pancreas to produce insulin before one eats lunch. In this way, one’s body can be prepared to digest the food before one even eats.

Now that the intrinsic rhythm within the SCN is synchronized to local time, this “time-stamped” rhythmic information needs to be communicated all over the brain and body to coordinate the timing of thousands of physiological and biochemical processes. For example, the SCN needs to communicate with brain areas involved in sleep to coordinate sleep with nighttime. The SCN accomplishes this communication using both neural and humoral signals. Researchers can determine neural communication from the SCN relatively easily by using chemicals to trace the “wiring” from the SCN to its targets. Through the use of tracing techniques, it is now known that the SCN communicates neurally to a vast array of brain targets as well as to targets in the periphery such as the liver and heart. It is also known that the SCN regulates some rhythmic functions through humoral signals. For example, if the fibers exiting the SCN in an animal are surgically cut, some circadian rhythms persist. However, because diffusible signals can essentially travel anywhere in the brain and body, the means by which these neurochemicals communicate is much more difficult to investigate experimentally. To date, two neurochemicals found in neurons of the SCN, transforming growth factor-α (TGF-α) and prokineticin-2, have been implicated as diffusible factors that may be used by the SCN to control locomotor behavior in...
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seasonally. However, the majority of scientific studies
suggest that animals rely mainly on day length as a
primary cue with which to estimate the time of year.
Most environmental cues other than day length vary
in relatively unpredictable ways throughout the year.
For example, although winter is usually associated
with lower ambient temperatures compared with
summer in the Northern Hemisphere, an unseason-
ablely warm “Indian summer” may occur during the
autumn/winter or a cold wave may roll through
during the summer. Furthermore, food and water
may be available to animals only sporadically through-
out the year. In contrast to these seasonal factors, day
length information is relatively “noise free” and can
be used to coordinate energetically expensive activities
(e.g., breeding) to coincide with adequate energy
availability. By relying on just two pieces of informa-
tion, the absolute period of daylight and the direction
of change across time, animals can determine the
precise time of year. For many species, breeding
occurs during the long days of summer, whereas
short “winter-like” days result in complete regression
of the reproductive system as well as in changes in body
weight and fur thickness. Interestingly, some species
(e.g., sheep) actually breed during the winter. As would
be predicted, the effects of day length on reproductive
physiology and behavior are generally reversed in these
species because their lengthy gestation time allows
for birth during summer. The ability of an animal to use
seasonal changes in day length to coordinate physio-
logical and behavioral adaptations is commonly
referred to as circannualism.

CIRCAANNUAL/SEASONAL RHYTHMS

Just as animals experience large fluctuations in physi-
ology and behavior throughout a single day, many
organisms experience pronounced changes across the
seasons of the year. Recall that circannual rhythms are
endogenously driven rhythms that approximate 1 year.
Such rhythms have been demonstrated in several birds
and a few mammalian species (e.g., ground squirrels,
sheep). In contrast to true circannual rhythms, the
majority of species display seasonal rhythms in behav-
ior and physiology in response to predictable changes
in the environment such as day length. Although
seasonal rhythms are not endogenously regulated,
they still produce pronounced changes in physiology
and behavior throughout the year. Much of the re-
search conducted in the area of seasonality has focused
on seasonal changes in breeding and reproductive
dermatology.

Many animals are faced with potentially large
seasonal fluctuations in environmental conditions, in-
cluding changes in day length, ambient temperature,
rainfall, humidity, food availability, and social
interactions. These potentially large fluctuations can
dramatically affect the world in which an animal lives.
For many animals, the energy required for thermo-
regulation is high during the winter, a time when
energy availability is typically low. Because of this
“energetic bottleneck,” many animals have evolved
specific physiological and behavioral adaptations to
cope with winter conditions. For example, some
animals may migrate or reduce activity (e.g., hiber-
nate, enter torpor) when food availability is low and
energetic demands are high. Other animals restrict
breeding to specific periods of the year (e.g., April–
August) (Fig. 3) because breeding at inappropriate
times can potentially compromise the survival of
both the parents and their offspring. But how does
an animal determine the optimal time of year?

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environmental factors can be used in the timing of
seasonal breeding, and all of these factors fluctuate
seasonally. However, the majority of scientific studies
suggest that animals rely mainly on day length as a
primary cue with which to estimate the time of year.
Most environmental cues other than day length vary
in relatively unpredictable ways throughout the year.
For example, although winter is usually associated
long days (i.e., winter vs summer), is responsible for inducing many seasonal changes, including gonadal regression and the cessation of breeding activities. Interestingly, surgical removal of the pineal gland (which removes the endogenous source of melatonin) prevents photoperiodic responses in nearly all mammalian species studied to date. Furthermore, it is the duration of the nocturnal melatonin secretion, and not the total amount of melatonin, that appears to provide important photoperiodic information, with longer durations (e.g., >12 h) associated with short days (i.e., winter) and shorter durations (e.g., <8 h) associated with long days (i.e., summer).

On secretion by the pineal during nighttime, melatonin travels to target tissues via the bloodstream, where it can bind to specific receptors located in either the brain or the periphery. Three types of melatonin receptors have been identified: Mel1a, Mel1b, and Mel1c. Mel1a and Mel1b receptors have been identified in a wide range of species, whereas the Mel1c receptor occurs exclusively in invertebrates. Furthermore, melatonin receptors have been identified in a wide variety of brain sites, including the SCN of the hypothalamus, the thalamus, and the pars tuberalis, a structure within the pituitary gland that is involved in regulating endocrine responses, suggesting that these brain sites may be important targets for the actions of melatonin. In addition, melatonin receptors have been isolated in several peripheral tissues, including the spleen, gonads, and adipose tissue.

The modulation of seasonal responses involves the effect of melatonin on brain mechanisms regulating peripheral responses as well as more direct actions of the hormone on organs and glands in the periphery. For example, in the context of seasonal breeding in rodents, melatonin can act on the hypothalamus to regulate the release of gonadotropin-releasing hormone (GnRH), a critical hormone in the endocrine axis regulating reproductive physiology and behavior. Thus, during short winter-like days, prolonged melatonin secretion can exert a negative influence on GnRH, resulting in reduced secretion of the reproductive hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. Decreases in LH and FSH, in turn, act at the level of the gonads (e.g., testes, ovaries) to decrease sex steroid hormones (e.g., testosterone, estrogen). Reductions in these hormones lead to regression of the reproductive system and cessation of reproductive behavior, typical of winter. As the days grow longer as spring approaches, the duration of melatonin release is reduced. This removes the inhibitory influence of this hormone on the reproductive endocrine axis, and reproductive physiology and behavior are restored.

**CLINICAL SIGNIFICANCE OF BIOLOGICAL RHYTHMS**

As mentioned previously, circadian and seasonal rhythms are critical for organisms to survive in a changing environment. To maintain homeostasis, hundreds of physiological and biochemical processes need to be coordinated temporally with both the environment and relative to one another within the body. As a result, normal behavioral, physiological, and psychological functioning is dependent on the body’s timing systems.

For example, one particular type of clinical depressive disorder, seasonal affective disorder (SAD), is of particular interest to chronobiologists. SAD is a cyclic illness characterized by recurrent episodes of winter depression alternating with periods of normal affect during the summer. Because of the seasonal component of SAD, it has been suggested that the shortened day lengths of winter may be part of the etiology of this disorder. In fact, exposure to bright lights during early morning or early evening results in marked improvements in clinical symptoms of SAD; therefore, bright light phototherapy has become the treatment of choice for SAD. Although the precise causes of SAD are still not known, abnormal phase shifts in one’s circadian rhythms and abnormal patterns of melatonin secretion both have been suggested. Phototherapy may act to shorten the duration of melatonin secretion by suppressing its production early in the morning. Alternatively, phototherapy may act to change the phase of circadian rhythms in numerous physiological factors that may contribute to this seasonal depression.

In addition to seasonal changes in mood, many organisms, including humans, display pronounced seasonal fluctuations in disease and death. Although some of these are due to seasonal changes in the pathogen (e.g., viruses, bacteria), there are also potentially large fluctuations in one’s immune system. These changes in immunity likely contribute to the seasonal fluctuations in disease, although researchers are just beginning to understand the physiological mechanisms underlying these changes. As with other seasonal adjustments, seasonal changes in immunity are regulated by changes in day length. As animals use the photoperiod to time changes in reproduction, this same signal can be used to organize the timing of
immune alterations throughout the seasons. Because most human societies use artificial lighting yet still experience seasonal changes in disease and death, the mechanisms regulating seasonal changes in human immune function are likely different and require further study.

See Also the Following Articles

Circadian Rhythms: Hormonal Facets(0293) • Circadian Rhythms, HPA Axis and*(0294) • Melatonin(0858) • Pineal Gland(1018) • Sleep, HPA Axis and*(1206) • Sleep, Neuroendocrine Regulation and*(1207) • Suprachiasmatic Nucleus (SCN)*(1242)

Further Reading


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