Chapter 1
Introduction to Circadian Rhythms, Clocks, and Its Genes

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Abstract From conception to death, life encompasses innumerable processes in continuous change and in many instances repetition; after all, life on earth has to cope from its origin with a highly cyclic environment. Thus, it is not surprising that cyclic phenomena are found in all living organisms and at all levels of organization. When this processes repeat in a regular manner, we refer to them as rhythmic. Biological rhythms occur in a wide range of frequencies, from cycles per seconds to cycles per year. Of particular interest are those rhythmic functions which repeat daily. These are the circadian rhythms whose organization and relevance are the interest of the present book. In this brief introduction, a general perspective of circadian rhythmicity and its mechanisms will be presented; we will start by a brief summary of the basic concepts and its biological relevance; then we will provide an account of the main ideas which lead to the characterization of circadian clocks among different species and levels of organization; and finally, we will provide a brief account on the characterization of the molecular mechanism underlying circadian oscillators, the so-called clock genes, and its distribution in mammalian tissues.

1.1 Basic Concepts of Circadian Rhythms

Circadian rhythms are periodic variations shown by most organisms, which repeat every 24 h and present three main characteristics: (1) they are produced by processes endogenous to the organisms, generally referred to as biological clocks; (2) under natural conditions, they align to external cycles from the environment by means of processes known as entrainment or synchronization; and (3) the speed of the clock (period) is temperature compensated, so the time to complete each cycle is not significantly affected by changes in environmental temperature. In the following sections, we will refer to each of these characteristics.

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1.1.1 Free Running

The persistence of rhythmicity in the absence of external periodic time signals reveals the endogenous nature of these variations, and it is the main characteristic of circadian rhythmicity; otherwise the rhythm should be referred to as diurnal (Halberg 1960). The relevance of circadian rhythmicity in biology as an adaptive process to a perpetual cyclic environment has been recognized since the first half of the last century (Pittendrigh 1993; Bünning 1969). From this perspective, circadian rhythmicity reflects the ability of organisms to generate an estimate or measure of time—*biological time*—independently of geophysical cycles.

The endogenous nature of circadian rhythmicity can only be observed in laboratory constant conditions, in the absence of external periodic signal such as illumination, temperature, and humidity, and the rhythms thus observed are referred to as *free running* (Aschoff 1965). Free-running rhythmicity has a period (which is the time taken for each cycle to repeat) slightly different from 24 h (hence the term *circadian*); this is the endogenous period of the rhythm under observation (Fig. 1.1).

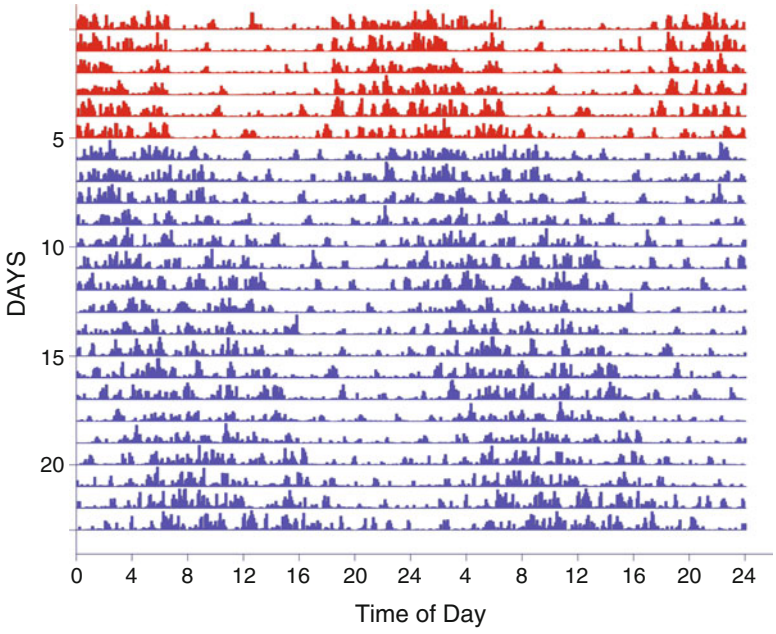

Fig. 1.1 Double plot actogram of locomotor activity in a rat kept under controlled environmental conditions. From day 1 to 5, white light (250 lux) was on at 07:00 h and off at 19:00 h. Dim red light (4 lux) was continuously on (LD). On day 6, white light was kept off until the end of the recording (DD). Each *line* is a histogram of 5 min bins of activity of two consecutive days; the 2nd day of each row is plotted again in the next row. During the first 5 days, the locomotion rhythm is entrained to the LD cycle (*red*); activity increases when white light goes off and decreases shortly before lights are on. On day 6, the rhythm starts to free run (*blue*) with a period of approximately 24:30 h. Room temperature was kept constant at 22 °C (±1°)

Free-running rhythms manifest the integration of processes able to measure time within the organism itself. Such internal processes have been called circadian clock, pacemaker, or oscillator, and although each term has very specific connotations on its meaning, they are often used as synonymous. Finally, it is important to realize that behavioral or other manifestations of circadian rhythms are considered as the overt expression (or handles) of a circadian clock.

1.1.2 Entrainment

In natural conditions, circadian rhythms are aligned with the light–dark cycle, other external cycle's secondary to the earth's rotation or periodic events such as food availability and biological or social cues. The adaptive nature of the circadian rhythms depends on entrainment, because it allows the organism to align the biological and geophysical times. Entrainment, also known as synchronization, refers to the processes to match the period of the circadian rhythm to the period of the external cycle (Fig. 1.1) and to establish a constant time relation on a particular event of the circadian rhythm (such as awakening) and a specific event of the environmental cycle (such as dawn or dusk). Thus, when entrained, a particular phase of the circadian rhythm is locked to a particular phase of the external cycle, and both rhythms have equal periods (Pittendrigh 1993). When entrainment is studied under light–dark cycles, light has shown to speed up the clock(s), thus shortening the period of rhythmicity; in turn, during darkness, the clock(s) slows down, thus lengthening the period, so the complete cycle has an average of 24 h (Daan and Pittendrigh 1976b).

1.1.2.1 The Phase Response Curve

Entrainment has also been studied by applying discrete light pulses (minutes to hours) at different times of the circadian cycle to animals in constant conditions and measuring the response of the free-running rhythm, which is known as a phase response curve (PRC). This approach has shown that the same stimulus applied at different times of a circadian cycle has different effects on the phase (see Box 1.1 for definitions) of the rhythm due to the dynamical response of the underlying clock(s) (Pittendrigh 1984; Daan and Pittendrigh 1976a). The PRC has three characteristic zones (Fig. 1.2) in different species: (1) the dead zone occurs during the subjective day and is characterized by the lack of response to light, therefore the phase of activity observed after the light pulse occurs at the time it was expected from projecting the phase before the light pulse; (2) the delay zone occurs early during the subjective night and is characterized by phase delays, that is, when activity after the light pulse occurs later than expected; and (3) the advance zone occurs late during the subjective night and is characterized by phase advances, when activity after the light pulse occurs earlier than expected from projecting the phase before the light pulse. Phase shifts reach a steady state after some transitory cycles and

Box 1.1 Parameters Related to Rhythmic Phenomena
The period of a cyclic phenomenon refers to time lapse for a complete cycle to occur; in natural conditions, the period of the circadian rhythmicity is 24 h (but see also Sect. 1.1.1). The amplitude refers to the change in the intensity of the oscillatory variable from its highest value (peak) to its lowest (trough); in the context of the cosinor analysis (which is used to fit cyclic phenomena to a cosine function), it also may refer to the change in the intensity of the variable from the mean value of the variable throughout the cycle (mesor) to the highest value of the best fitting cycle (acrophase). Finally, the phase of the rhythm refers to the time at which any particular value of the cyclic variable occurs, for example, the time of waking or sleep initiates correspond each to a particular phase of the sleep–wake cycle. Also the time at which the peak or acrophase occurs is also a clear-cut phase reference for cyclic or rhythmic phenomena. Finally, since each rhythmic variable has specific phase descriptors, the time relation between two variables is best referred to as phase relation; for example, the relation between waking and breakfast in a particular subject could be described as -1 h relation of breakfast with respect to awakening (a delay of 1 h after waking to have breakfast).

maintain the new phase until perturbed by another phase-shifting stimulus (Pittendrigh 1984). Phase shifts are measured (in minutes or hours) by subtracting the phase of the rhythm before the stimulus to the phase in steady state after the stimulus. It is worth noticing that although day and night are absent in constant free-running conditions, we can still discriminate a subjective day and a subjective night, which depends on the circadian organization of the species under study, either active during the day or during the night. Moreover, the length of a free-running rhythm differs from the period of the entrained rhythm (24 h in natural conditions); therefore, each hour of the free-running day will also differ from 60 min. To estimate the circadian time (CT), the free-running period is divided in 24 segments or circadian hours. The PRC depicts in the abscissa the CT at which the light pulse is applied, while the ordinate depicts the magnitude of the induced phase shift, usually delays as negative values and advances as positive ones. The analysis of the PRC provides information about the dynamics of the circadian clock(s) which generates overt rhythmicity in each of the species studied, and nowadays is a valuable tool to unravel the cellular and molecular mechanisms involved in the functioning of the clock(s).

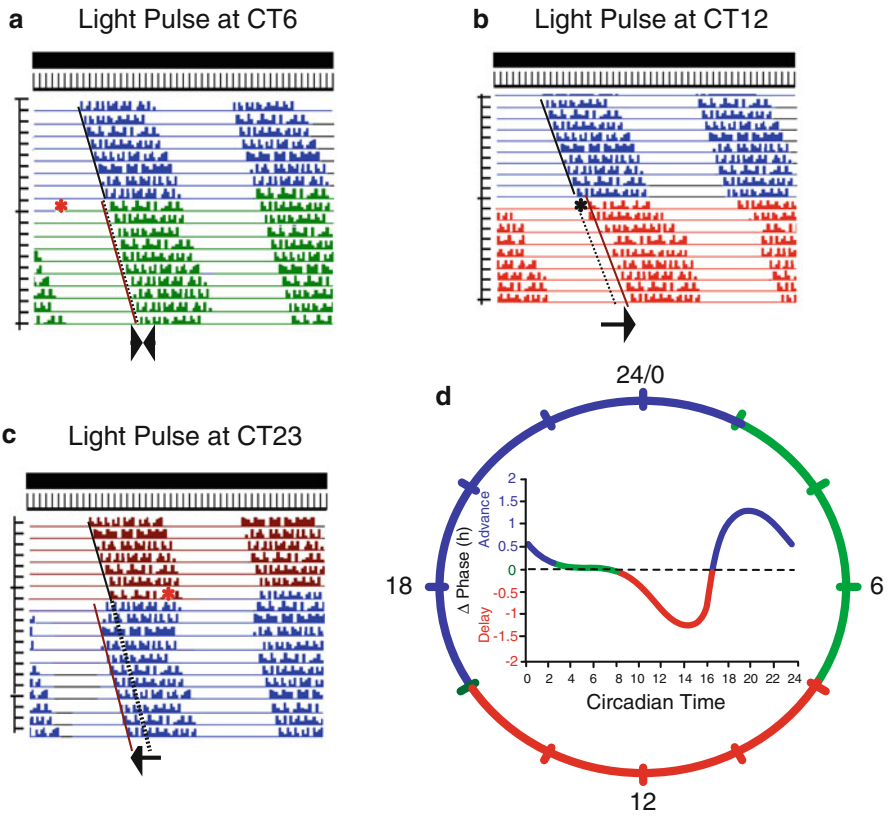

Fig. 1.2 Diagram of the phase response curve (PRC) to light pulses for a nocturnal rodent. The schematic actograms illustrate the phase responses to light pulses applied at different circadian times as indicated. The basal free-run recording is shown in *blue* (**a**, **b**) *dark red* (**c**); the effect on rhythmicity of a light pulse (*red asterisk*) at different circadian times (CT) is shown in *green* (at CT6), *red* (at CT12), or *blue* (at CT 23). The *arrows* below each actogram indicate the change on the activity onset after the light pulse (*dotted lines*) with respect to the recordings before the light pulse was applied (*continuous line*). The PRC is shown inside the 24 h dial; each color on the curve and the dial corresponds to the characteristic regions of the PRC: dead zone (*green*), the delay zone (*red*), and the advance zone (*blue*)

1.1.2.2 Masking

Complete cycles of light–dark or high–low temperature may also affect the behavioral expression of rhythmicity beyond the clock itself, therefore masking its phase and period; such effects of external factors on the expression of rhythmic behaviors are referred to as masking effects (Aschoff and von Goetz 1988; Rietveld et al. 1993).

1.1.3 Temperature Compensation

Temperature compensation was inferred by Pittendrigh as an essential property of circadian rhythms necessary to prevent the speed of the clock to be influenced by the temperature in the environment. For a detailed description on how this hypothesis was conceived and proved, we refer the reader to Pittendrigh (1993). The thermic coefficient or Q_{10} refers to the factor by which any metabolic process changes by an increase of 10 °C in the environment; thus, a Q_{10} of 1 indicates the process is not altered, while a Q_{10} of 2 means the speed of the process duplicates. The period of free-running rhythms has a Q_{10} close to 1 which indicates that it remains almost constant in a wide range of temperatures. This property was demonstrated in practically all species studied, and it is considered as a fundamental characteristic of circadian rhythmicity. The mechanisms involved in such property are still under investigation.

1.2 The Search for Circadian Clocks

During the 1970s circadian clocks became concrete biological entities in different species. In invertebrates the possible locus of circadian clocks was located in the brain of the silk moth (Truman 1972) and the eye of the *Aplysia* (Jacklet and Geronimo 1971) and *Bulla* (Block and Wallace 1982), while in vertebrates the clocks were identified in the pineal gland in birds (Gaston and Menaker 1968) and in the suprachiasmatic nuclei (SCN) in the rat hypothalamus (Moore and Eichler 1972; Stephan and Zucker 1972) (Fig. 1.3). All these studies stimulate the search for studying the mechanisms of circadian clocks at systemic, cellular, and molecular levels. When these and other studies were published, there was an intense debate whether they indicate or not the presence of a circadian oscillator or they were merely part of the clockwork or gear mechanism. It was thus necessary to outline the minimal criteria to be met in order to positively identify a circadian clock; such criteria included the following: circadian rhythmicity shall be completely disrupted when the putative cells are ablated; rhythmicity will be restored when the putative cells are transplanted from an intact donor to a lesion host; brief stimulation of the putative cells will induce phase shifts in overt rhythmicity; and when isolated from the organism, the putative cells shall continue to exhibit oscillations with a circadian period (Menaker et al. 1978). Although the criteria are enunciated here as referring to a cell or group of cells, the criteria are also valid to identify molecular components of the circadian oscillators such as genes, enzymes, and cell signaling processes.

Besides the characteristics summarized previously, a conceptual black-box model of circadian clocks was developed. The model involved an oscillator (the actual clock mechanism) which allowed the measurement of biological time; sensorial receptors which input to the oscillator and allows entrainment to environmental cycles; and output pathways which transmit the time signal from the

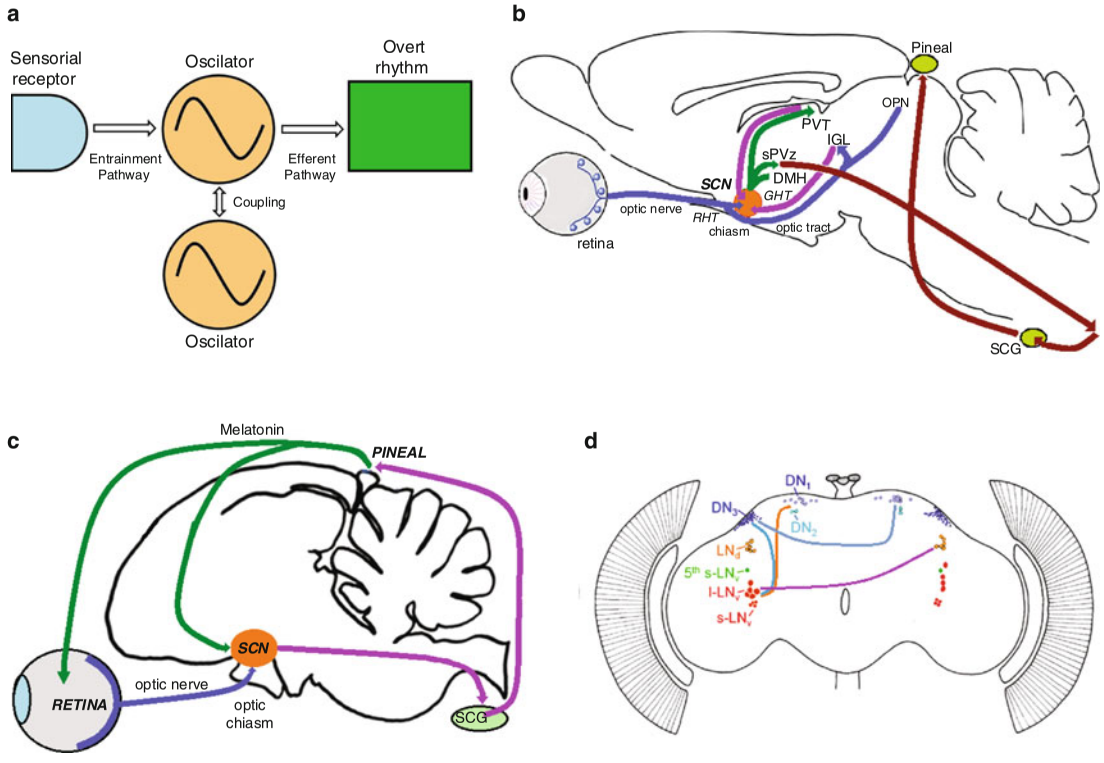

Fig. 1.3 Schematic of circadian systems in different species. (**a**) Conceptual model of the circadian system according to Eskin (Skinogram). (**b**) Rodent. (**c**) Avian. (**d**) *Drosophila*. Abbreviations in **b** and **c**: *SCN* suprachiasmatic nuclei (circadian clock), *sPVZ* subparaventricular zone, *DMH* dorsomedial hypothalamus, *PVT* thalamic paraventricular nucleus, *IGL* intergeniculate leaflet, *OPN* olivary pretectal nucleus, *SCG* superior cervical ganglion, *RHT* retino-hypothalamic tract, *GHT* geniculo-hypothalamic tract. Abbreviations in **d**: *DN* neuron clusters (1–3) in the dorsal brain, *LNd* dorsal–lateral brain, *I-LNv* large ventral lateral neurons, *s-LNv* small ventral–lateral neurons, *5th* fifth small ventral–lateral neuron

oscillator to the effector systems of the organism which will generate the overt rhythms (Eskin 1979). As circadian clocks were identified in different animals, the concept of the circadian clock was modified to that of circadian system, which differentiates among the time-measuring entity (the oscillator or clock itself) and the inputs and output elements of the clock. Furthermore, although the original circadian system referred to a single oscillator, evidence suggested that there might be several oscillators in an organism; in such case, in order to maintain its internal synchronization, it would be necessary to postulate signaling processes to couple the different oscillators among themselves and sustain the temporal organization of the individual (Fig. 1.3).

1.2.1 Unraveling the Molecular Circadian Clock

The general structure of a biological oscillator, circadian or otherwise, was proposed in the early 1980s from the analysis of a number of well-characterized biological and chemical oscillations. Thus, it was demonstrated that a system with a delayed negative feedback loop behaves as an oscillator. The delayed element of the system is necessary to set the system to oscillate, and its kinetics determines the periodicity of the oscillation (Friesen and Block 1984). It is worth noting that in the absence of a significant delay, the feedback loop will keep a constant output of the system (Wiener 1948). On the other hand, experiments involving pharmacological blockade of gene transcription or its translation into proteins in *Bulla gouldiana* were able to stop the circadian clock in a reversible manner (Khalsa et al. 1992); these evidences lead to propose that the circadian clock comprised a transcription–translation loop (Block et al. 1995). These two hypotheses had a great influence in our notion of how circadian oscillators were organized at the cellular and molecular level.

The first step in the search for the molecular substrate of circadian rhythms occurred in 1971 when Konopka and Banzer described an arrhythmic mutation in *Drosophila melanogaster*; they identified the affected locus and call it *per* from period (of rhythmicity). A decade later, the gene was cloned (Reddy et al. 1984), and about 1990, Hardin et al. demonstrated that the Per protein feeds back to the *per* gene to regulate its own mRNA level. In 1973 mutants of *Neurospora crassa* with altered circadian periods were identified and named frequency mutants, since the name period was already taken (Feldman and Hoyle 1973). Some years later, the gene *frq* was identified and cloned; a negative feedback loop was described, where the Frq protein regulates its own mRNA transcription (Aronson et al. 1994). Some years later, the *clock* mutation was identified in the mouse and the gene was cloned (King et al. 1997) and was named after the acronym of circadian locomotor output cycles kaput. Interestingly, mouse *clock* mRNA levels did not show circadian oscillations as in the *Drosophila* ortholog (Shearman et al. 1999). On the other hand, homology screens of mouse c-DNA libraries to *Drosophila per* gene led to the finding of a mouse ortholog which was named RIGI, while independently a second ortholog for *Drosophila per* was characterized in mice (Shearman et al. 1997; Sun

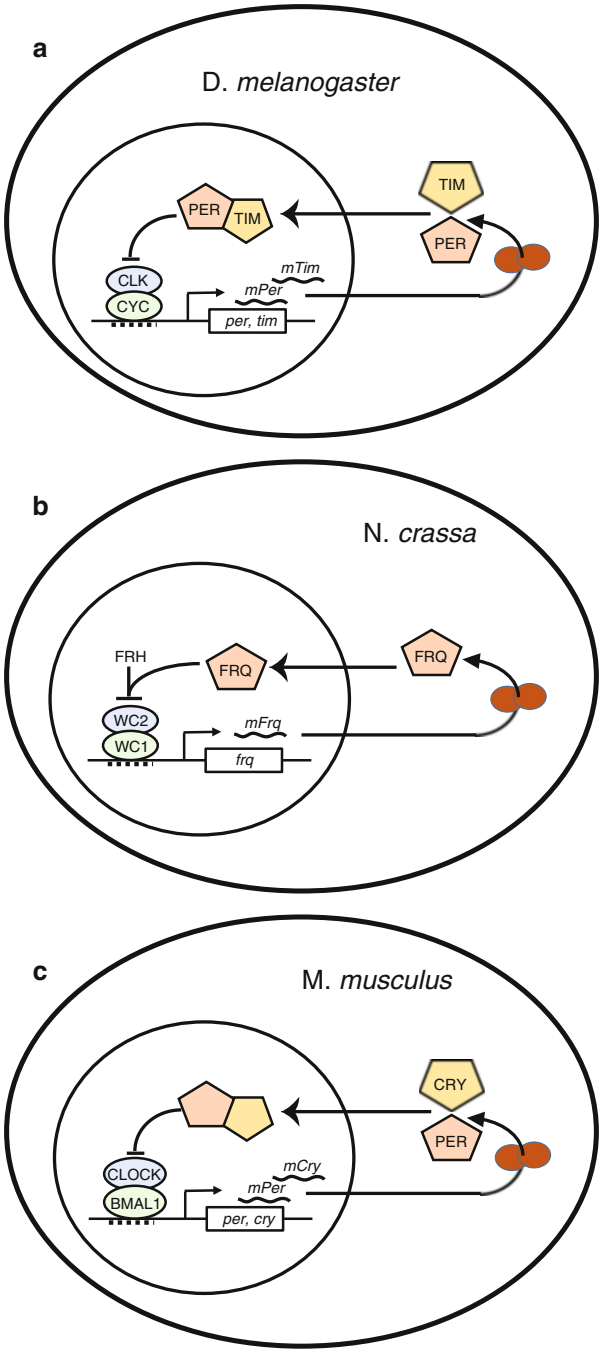

Fig. 1.4 The core molecular circadian clock in different species. Symbols: ↱, transcription; ~, messenger RNA; →, translation; ⟶, translocation to the nucleus; ⊥, repression. Abbreviations: *CLK* clock, *CYC* cycle, *PER* period, *TIM* timeless, *WC1* white collar 1, *WC2* white collar 2, *FRQ* frequency, *FRH* RNA helicase, *CRY* cryptochrome, *BMAL1* brain and muscle ARNT-like 1 protein. *Uppercase letters* indicate proteins, *lowercase* indicates DNA, and *upper- and lowercase* indicates RNA; *ellipses* indicate transcription factors; *pentagons* indicate proteins inhibiting its own transcription; *dotted line* indicates the promoter for the gene indicated in the box; *orange circles*, ribosomes

et al. 1997). These findings together with the contributions of other groups lay down the basis for the current knowledge on circadian clock genes (Fig. 1.4). Nowadays it has been shown that most circadian oscillators consist of delayed feedback transcription–translation loops of genes that regulate its own expression at least in eukaryotic cells (Lowrey and Takahashi 2004; Dunlap 1999; Hardin et al. 1990; Zheng and Sehgal 2012).

During the last 10 years, we have begun to understand the molecular basis of the circadian oscillators beyond the transcription–translation feedback loop. At the posttranslational level, the phosphorylation of "clock proteins" was the first process involved as a crucial step to set the speed of the clock in *Drosophila* (Chiu et al. 2011) and mammals (Lee et al. 2011), and recently, it has been suggested that the posttranslational feedback loop based on phosphorylation–dephosphorylation processes could also be a relevant part of the core molecular clock (Brown et al. 2012). Phosphorylation promotes dimerization of "clock proteins" necessary to translocate to the nuclei and inhibit its own transcription but also tag such proteins to ubiquitination and hydrolysis. Epigenetic regulation has also been found to participate in the transcription of "clock genes" and "clock-regulated genes" (Sassone-Corsi 2010; Feng and Lazar 2012; Sahar and Sassone-Corsi 2013). Epigenetic regulation involves histone phosphorylation and acetylation which allows transcription by remodeling chromatin and exposing DNA segments to transcription machinery, histone acetylation also induces chromatin remodeling and may stimulate or repress gene expression, and DNA methylation induces chromatin compaction and suppresses gene expression (Jenuwein and Allis 2001). These processes allow reversible responses to changes in the environment which can affect many physiological processes, including development, aging, and metabolism (Christensen and Marsit 2011). The activation of clock-controlled genes by CLOCK-BMAL1 has been shown to be coupled to histone modifications; thus, deacetylases SIRT1 and HDAC3 or methyltransferase MLL1 has been shown to be recruited in a circadian manner to these promoters (Etchegaray et al. 2003; Naruse et al. 2004). Clock also possesses histone acetyltransferase activity directed to histone H3 and also has acetylation activity on its partner BMAL1 (Hirayama et al. 2007) and the glucocorticoid receptor (Nader et al. 2009). Finally, H3 Ser-10 phosphorylation is involved in the transcriptional response to light in the SCN (Crosio et al. 2000).

1.3 Closing Remarks

In this book, we will provide a wide perspective on the organization and physiological relevance of circadian systems from invertebrates to mammals. It is organized in three sections: in the first section "Circadian Systems," the authors will outline the circadian system organization, including molecular, cellular, and systemic aspects in "Insects, Crustacean, Fish, Birds, and Primates"; the second section "Mechanism of Circadian Oscillation" will focus on mammalian models, and the role of the suprachiasmatic nuclei as a circadian clock will be reviewed from the cellular to the system level in rodents. The food-entrainable oscillator will also be reviewed in the lactating rabbit

model; finally, the last section "Clinical Relevance of Circadian Rhythmicity" will cover different aspects of circadian rhythms in relation with health and disease.

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