REVIEW ARTICLE

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Neurobiology of Circadian Systems

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Abstract

Time is a dimension tightly associated with the biology of living species. There are cycles of varied lengths in biological activities, from very short (ultradian) rhythms to rhythms with a period of approximately one day (circadian) and rhythms with longer cycles, of a week, a month, a season, or even longer. These rhythms are generated by endogenous biological clocks, i.e. time-keeping structures, rather than being passive reactions to external fluctuations. In mammals, the suprachiasmatic nucleus (SCN) is the major pacemaker. The pineal gland, which secretes melatonin, is the major pacemaker in other phyla. There also exist biological clocks generating circadian rhythms in peripheral tissues, for example the liver. A series of clock genes generates the rhythm through positive and negative feedback effect of proteins on their own synthesis, and this system oscillates with a circadian period. External factors serve as indicators of the astronomical (solar) time and are called zeitgebers, literally time-givers. Light is the major zeitgeber, which resets daily the SCN circadian clock. In the absence of zeitgebers, the circadian rhythm is said to be free running; it has a period that differs from 24 hours. The SCN, together with peripheral clocks, enables a time-related homeostasis, which can become disorganized in its regulation by external factors (light, social activities, food intake), in the coordination and relative phase position of rhythms, or in other ways. Disturbances of rhythms are found in everyday life (jet lag, shift work), in sleep disorders, and in several psychiatric disorders including affective disorders.

As almost all physiological and behavioural functions in humans occur on a rhythmic basis, the possibility that advances, delays or desynchronization of circadian rhythms might participate in neurological and psychiatric disorders has been a theme of research. In affective disorders, a decreased circadian amplitude of several rhythms as well as a phase advance or delay have been described, leading to hypotheses about changes in biological clocks themselves or in their sensitivity to environmental factors, such as light or social cues. Molecular genetics studies have suggested the involvement of circadian clock genes, but no tight association has yet been found. Agomelatine is an antidepressant, agonist at melatonergic MT_1, MT_2 receptors and antagonist at $5\text{-}HT_{2C}$ receptors, and is able to phase advance circadian rhythms in humans. The fact that non-pharmacological (light therapy, sleep deprivation, rhythm therapy) and pharmacological (lithium, antidepressants, agomelatine) therapies of affective disorders influence circadian rhythms indicates that biological clocks play a role in the pathophysiology of these disorders.

Time-related changes exist at all levels of biology, from biochemical reactions to overt whole organism behaviours, and these changes are caused by a system of endogenous biological clocks as well as reactions to fluctuations in the environment. Over millions of years of evolution and selection, living species have developed strategies to accommodate to the cycle of night and day, as well as to other rhythmic fluctuations in their environments. Biological clocks offer the adaptive advantage of maintaining homeostasis by preparing the organism to respond to environmental changes. To give an example, physiological and metabolic activation should take place before the moment the individual wakes up, in order for the individual to be proactive rather than reactive to changes in the environment. In plants, endogenous clocks help to determine times of day when responses to light ought to be optimal, to enhance syntheses or to protect against the deleterious effect of ultraviolet rays.

Jean-Jacques D'Ortous de Mairan (1678–1771) was one of the first to observe experimentally that the rhythm of opening and closing of mimosa leaves persisted in the absence of light. Later, Augustin Pyrame De Candolle (1778–1841) showed that in constant light, the opening and closing of mimosa leaves had a period of 22 hours. Julien Joseph Virey (1775–1846), a pharmacist and medical doctor, proposed that the biological rhythms in humans were not solely explained by external changes in the environment. Still later, Erwin Bünning (1906–90) showed, by crossing experiments, that the different periods of circadian rhythms in strains of beans were transmitted genetically. Research in bacteria, insects and rodents was then instrumental in our present understanding of biological clocks. The paradigms discovered in these species were also studied in humans, expanding on the 1962 demonstration by Michel Siffre that circadian rhythms persist even in the absence of time clues; this speleologist lived alone in an underground cave for more than 6 months, and his rest/activity cycles showed a few long days and long nights, up to cycles of 50 hours. Jürgen Aschoff (1913–98) and Colin S. Pittendrich (1918–96) were among the founders of modern chronobiology and the promoters of chronobiological studies in animals and humans.[1]

The molecular basis of endogenous clocks has been discovered over the past decade, although several fascinating questions remain unanswered.[2] It also became obvious that the temporal dimension of homeostasis could be disrupted and that several of these disruptions in endogenous rhythm organization lead to clinically manifest disorders, for example in the fields of sleep medicine,[3,4] cardiovascular and metabolic medicine,[5] neurology and psychiatry.[6-8]

1. Phenomenology of Endogenous Circadian Rhythms

Most biological functions are expressed in an oscillating manner within a 24-hour period: rest/activity cycle and sleep phases, heart rate and blood pressure, body temperature, hormone concentrations in the blood (cortisol, melatonin, thyroid-stimulating hormone, insulin and other hormones), hepatic metabolism and detoxification (cytochrome P450 enzymes), renal elimination, gene transcription and translation. Figure 1 illustrates the 24-hour pattern of melatonin and cortisol concentrations in a normal human individual. These biochemical, physiological, biochemical or behavioural rhythms reflect the functioning of endogenous biological clocks, i.e. of an internal system capable of indicating the passage of time, as watches do. In the absence of time cues, these endogenous rhythms are self-sustained and have a period approximately that of the earth's rotation (hence the adjective circadian, meaning approximately one day).

1.1 Description of a Circadian Rhythm

The circadian rhythm of many biological variables can be described by approximating it to a sinusoidal curve, with its period (duration of one cycle), its mesor (mean value over one cycle), its amplitude (difference between highest and lowest values), and the time of occurrence of these highest and lowest values in relation to astronomical time (acrophase and bathyphase). The period can be described in various conditions, i.e. in the presence

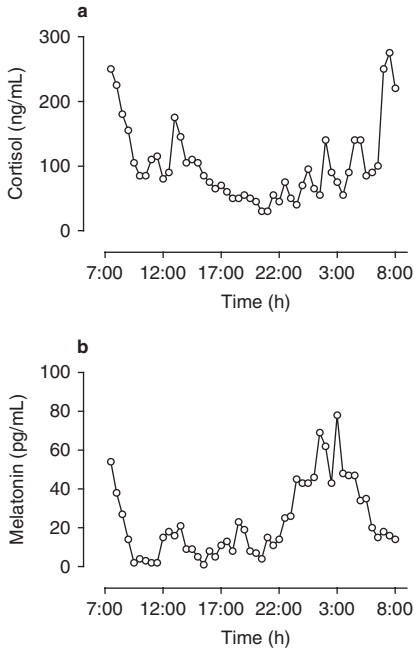

Fig. 1. Circadian changes in the concentration of melatonin and cortisol. Blood was taken every 30 minutes, over a 24-hour period in a normal healthy young man. The subject followed his usual daily professional activities. The circadian rhythm is seen, with an earlier nocturnal peak of melatonin in relation to cortisol. Secretory peaks are seen, indicating an ultradian rhythm of these hormones. The rise in cortisol in the early afternoon is secondary to lunch; food is considered a masking factor.

of zeitgebers (see below) or in free-running conditions, i.e. in relation to the absence (or constant presence) of zeitgebers. Situations of phase advance or phase delay mean that the cyclical variable measured shows an acrophase that occurs earlier or later than usual, in relation to astronomical time. Normal people are said to be either of the morning type (M-type or larks) or of the evening type (E-type or owls), depending on whether they prefer to wake up and go to bed early rather than late. Extreme M-type or E-type are situations of phase advance or phase delay in circadian rhythms.

Biological functions that are often used as clinical markers of the endogenous rhythms in mammals are the rest/activity cycle, the temperature curve, and the onset time of nocturnal melatonin secretion under dim light. When these parameters are within usual values, an individual can be qualified as having a normal chronobiological configuration, pattern or chronotype. The frontiers of normal circadian chronotypes are being evaluated precisely in large populations, to explore the clinical consequences of unusual rhythms in terms of actual clinical symptoms or of disease predisposition.[9]

1.2 Free-Running Rhythms and Zeitgebers

Under normal life conditions, the endogenous circadian rhythms are synchronized to days and nights; given behavioural and physiological events (temperature changes, sleep phases, hormone secretion, enzyme synthesis, etc.) occur regularly at the same time of the day. This synchronization occurs because biological clocks have a characteristic in common with ancient mechanical clocks, in that they have to be regularly reset in order to indicate time correctly. In usual environmental conditions, circadian biological clocks are reset daily to 24-hour astronomical time by the day/night cycle, i.e. through the influence of light, the main zeitgeber. In conditions with no external zeitgeber, the endogenous period of circadian rhythms of the individual (and that of his species) is expressed. This period generally differs from 24 hours, and is called the free-running period. Conditions without zeitgebers are, for example, constant darkness or constant light, respectively labelled DD or LL, in comparison with the usual light and darkness alternation or LD. In the first human free-running studies, the period of circadian rhythms was measured in so-called cave or bunker experiments; for days to months, subjects lived in special quarters where all possible zeitgebers could be manipulated experimentally. In such isolation from time cues, the mean human rest-/activity cycle was measured as 25 hours (±0.5 hour) in 150 subjects by Aschoff, who then considered that the subjects' possibility of turning the lights on and off at their discretion might have prolonged the period.[10] In a recent study using a protocol of forced desynchrony with constant routine imposed on subjects for 40 hours, a mean body temperature cycle period of 24.18 hours was found.[11] The expressed period of the circadian clock thus differs depending on the stringency of isolation from time cues.

Increasing or decreasing the duration of the imposed LD cycle in cave experiments enabled the study of the entrainment limits of the human biological clock; at an artificial LD cycle several hours above 24 hours, the rest/activity cycle of the subject is no longer entrained by the imposed periodicity.

Other environmental features that can serve as zeitgebers are the availability of food, social schedules and social exchanges, and even the earth's magnetic field.[12] Zeitgebers other than light are labelled non-photic. The non-visual pathway of their perception reaches brain regions other than the suprachiasmatic nucleus (SCN) that are involved in transmitting temporal information to the peripheral circadian system. For example, time-limited availability of food acts as a zeitgeber.[13] Physical exercise in the evening can lead to a delay in melatonin secretion, but the role of exercise as an important zeitgeber in humans is debated.[14]

Melatonin, the hormone secreted by the pineal gland, transmits information about the occurrence and duration of obscurity; during short winter days, the duration of nocturnal melatonin secretion increases, whereas it decreases during long summer days. Melatonin can thus be considered as a marker of the absence of the photic zeitgeber. It has itself a zeitgeber function; indeed, melatonin (secreted under the hierarchical dependence of the SCN) influences the SCN in return (the SCN is a structure rich in melatonin receptors). The seasonal changes in the duration of night are accompanied by changes in reproductive organs that depend on melatonin secretion.[15,16]

1.3 Phase/Response Curve

An acute and short application of a zeitgeber (in most studies, a pulse of light in free-running conditions under DD) influences the endogenous rhythm; it displaces the cycle, either advancing or delaying it. Acute exogenous administration of melatonin can entrain the next circadian period. This influence depends on the moment when the zeitgeber is applied in relation to the internal rhythm. In humans, applying light early in the morning advances the next cycles (rest/activity or body temperature cycles), whereas doing the same in the evening delays the next cycles. A phase/response curve is the graphical representation of this two-directional influence, from shifts towards advance to delay. In humans, in constant dim light laboratory conditions, a 3-hour pulse of 3000 lux induced a maximal shift of the melatonin secretion rhythm by 3 hours.[17] Even low levels of light can shift the cycle of melatonin secretion in humans.[18] Melatonin also shifts the circadian endogenous clock, with a maximal delaying effect at the time of awakening, whereas that of the maximal advancing effect is in the afternoon.[19] Information on the phase response curves of light and that of melatonin are relevant to situations such as shift work,[20] jet lag, social jet lag, seasonal affective disorder, and other disorders in which circadian rhythm parameters are out of the usual range. Social jet lag is a situation in which falling asleep only occurs late at night and when waking up in the early morning becomes very difficult. These persons do not have enough hours of sleep during the week and sleep more at weekends, although they then fall asleep even later in the night. Severe social jet lag might predispose to smoking, drinking alcohol and suffering from depression.[21]

Physical exercise during the second part of the day induces a delay in nocturnal melatonin secretion, but a phase/response curve has not been found in humans.[14]

1.4 External Desynchronization

A so-called external desynchronization occurs when endogenous rhythms have a period other than 24 hours, i.e. when they no longer follow astronomical time. This is observed in a proportion of totally blind persons; although they are subject to social zeitgebers and social constraints that have 24-hour periodicity, their endogenous rhythms are not entrained because of loss of ability to perceive light; the endogenous rhythms are out of phase with astronomical time. Cortisol and melatonin, which are normally secreted during the second part of the night, progressively shift from a night-time to a day-time secretion and back to a night-time secretion. When these

rhythms are out of phase with day-time secretion some of these blind persons experience fatigue, difficulty concentrating, or depression. Others do not feel clinical changes, although their rhythms are desynchronized in relation to astronomical time.[22] Still others have their rhythms entrained to the 24-hour day despite their blindness. Melatonin taken daily at doses as low as 0.5 mg can reset the circadian rhythm and help blind persons to remain entrained to the 24-hour day.[23] The prescription of melatonin should be adapted to each blind person's circadian rhythm phase position, by measurement of melatonin rhythm.[24] Another strategy consists in starting the melatonin administration at bedtime when the blind person's circadian rhythms are in a normal phase in relation to astronomical time, i.e. after a couple of days of normal sleep without the daytime complaints of fatigue and lack of concentration that characterize an abnormal phase position of the rhythms in blind persons.[24,25]

1.5 Internal Desynchronization

Another type of desynchronization is when the normal phase position between two or more endogenous rhythms is itself lost. For example, the temperature rhythm no longer follows the rest/activity cycle, with differences of a couple of hours or more between the periods of these rhythms, such as a temperature rhythm of 19 hours and a rest/activity rhythm of 25 hours. This dissociation is called internal desynchronization. In humans in free-running conditions it was found to be more frequent with age and also in individuals with higher neuroticism scores.[26]

1.6 Ultradian and Infradian Rhythms

Aside from the circadian endogenous rhythms discussed above, there are endogenous rhythms with shorter periods, of the order of seconds to hours, called ultradian rhythms, as well as longer rhythms, of the order of a week, a month, or a year. There are unsolved questions as to the role of the SCN in relation to these other rhythms. For example, SCN lesions suppress some but not all ultradian rhythms.[27] These lesions also modify the seasonal rhythm of reproduction of several mammals.[28] Finally, SCN lesions in rats suppress the scale-invariant patterns of motor activity within the 4–24-hour time range, which suggests a general role of the SCN in rhythm generation, i.e. not only for circadian rhythms.[29]

2. Functional Neuroanatomy

2.1 To and From the Suprachiasmatic Nucleus

In mammals, the SCN is the site of circadian rhythm generation, whereas in other phyla the pineal gland, the retina, or other structures have the function of the circadian clock. The SCN is a small bilateral nucleus located in the hypothalamus in the area above the optic chiasma, hence its name. When it is experimentally destroyed, the animal loses its circadian rest/activity cycle, as well as many rhythms, for example that of drinking behaviour.[30]

The SCN receives input from many other brain areas and also has efferents towards many areas, several of them in the hypothalamus.[31] A major afferent to the SCN is the retina (figure 2). In the retina, there are specific cells devoted to the perception of light intensity, rather than vision. These cells send their axons through the retinohypothalamic tract to the SCN, and this tract enables light to entrain the circadian rhythms. In given cases of blindness, when these specialized retinal neurons and efferents are preserved, the blind person can remain entrained to the photoperiod rather than have free-running rhythms.

In a second major pathway, axons from SCN neurons go the pineal gland, taking a rather complex path; these axons reach the sympathetic system (brain stem), go into the neck and then reenter the brain and reach the pineal gland by being associated with sympathetic innervation in the artery wall. The absence of a light message to the SCN is associated with an activation of this pathway to the pineal gland with the release of norepinephrine to stimulate the nocturnal secretion of melatonin. This anatomical and functional pathway from the SCN to the pineal gland, with its respective neurotransmitter and receptor, explains why patients taking beta-blocking drugs secrete minimal nocturnal amounts of melatonin,

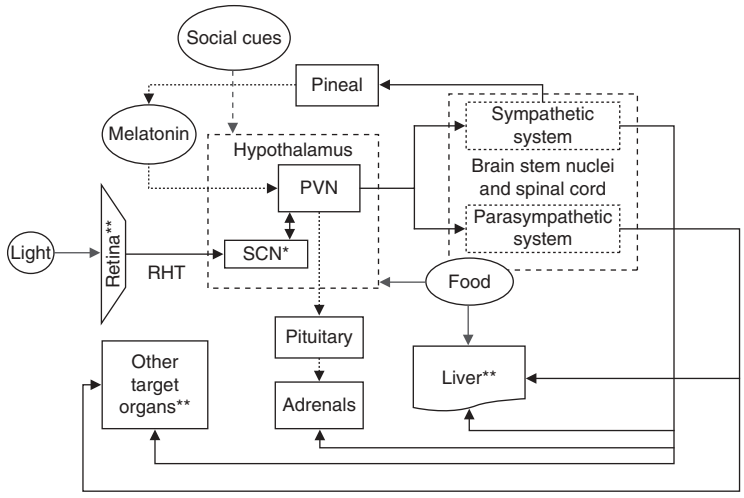

Fig. 2. Anatomy of biological clocks. The suprachiasmatic nucleus (SCN), a master clock, is labelled with an asterisk (*). Structures that express endogenous circadian rhythms, i.e. peripheral clocks, are labelled with two asterisks (**). Zeitgebers are indicated within ovals and their influence on target structures are indicated with open grey arrows. Thin black arrows summarize the neural paths for the synchronizing of peripheral clocks by the master clock (see text for explanation). PVN = paraventricular nucleus of the hypothalamus; RHT = retino-hypothalamic tract.

normally actively secreted during darkness.[32] Nightmares might be associated with this decreased secretion of melatonin.[33] Melatonergic receptors[34] are present at high density in the SCN, the anterior hypothalamus and the retina, which is in accordance with the role of melatonin as a temporal signal.

Several neurotransmitters are involved in the functioning of the SCN, its photic regulation and its influence on the pineal gland (glutamate, gamma-aminobutyric acid, norepinephrine), as well as many neuropeptides (vasopressin, vasoactive intestinal peptide, peptide histidine-isoleucine have the highest cellular concentrations).[31]

2.2 Peripheral Circadian Clocks

The presence of circadian rhythms outside the brain was demonstrated many years ago, for example in liver enzyme synthesis.[35] The existence of peripheral circadian clocks in many tissues has since been confirmed,[36] and genes responsible for the molecular machinery of circadian rhythm generation are expressed in several tissues, the liver, for example. As far as metabolism is concerned, liver circadian clocks are important, because deletion of a circadian clock gene leads to hypoglycaemia during the daily feeding cycle and to other changes in glucose metabolism.[36,37]

The electrical signals from SCN neurons spread to the central nuclei of the vagus nerve and to the central nuclei of the sympathetic system.[38] This leads to innervation of the gastrointestinal system, in particular the liver,[39] the respiratory system, but also fat tissue, the thyroid gland and the adrenal gland.[40] The message from the SCN neurons is also transmitted to peripheral circadian clocks through its action on adrenal secretion of glucocorticoids, hormones that activate the *Per1* gene in several peripheral tissues. The term of master clock has thus been applied to the SCN, whereas peripheral clocks are said to be slave clocks.[41] The influence of the master clock on these slave clocks is widespread. For example, the deposition of dentin on teeth follows a circadian rhythm in many mammals, as well as in humans. In rats, when the SCN is lesioned, this circadian rhythm in dentin increments disappears, while the ultradian rhythm persists.[42]

3. Molecular Biology of Circadian Clocks

The hereditary transmission of the period of circadian rhythms has been demonstrated in

plants,[43] in the insect *Drosophila*,[44] in mammals and in humans.[45] The molecular mechanism of this time measurement machinery was discovered during the past decade. Biological clocks were also discovered in several peripheral tissues, and the synchronizing role of the SCN has now been understood in great part.[46]

The molecular mechanism of the clocks consists of intracellular biochemical loops with positive and negative feedback that interacts at the levels of gene transcription (DNA into RNA) and of gene translation (RNA into proteins), as well as at post-translational levels. In other words, the loops consist of a few proteins either stimulating or inhibiting their own synthesis from clock genes. This time-constrained feedback generates the circadian cycle. A summarized description of the system is given in figure 3. Proteins such as CLOCK and BMAL (synthesized from the genes *Clock* and *Bmal*) associate as heterodimers and activate the synthesis of two families of proteins, PER and cryptochrome (CRY). The PER and CRY proteins are negative regulators that turn off their own synthesis from *Per* genes (*Per1*, *Per2*, *Per3*) and *Cry* genes (*Cry1*, *Cry2*). The synthesis of PER and CRY proteins can thus only re-start (under the influence of BMAL and CLOCK) when the level of intranuclear PER and CRY is low enough, i.e. after degradation of these proteins.[47]

These molecular events are themselves regulated by an array of other mechanisms. PER and CRY proteins are phosphorylated by several enzymes, for example, glycogen synthase kinase 3 beta, and this influences their stability and rate of entry into the nucleus. Histones, proteins

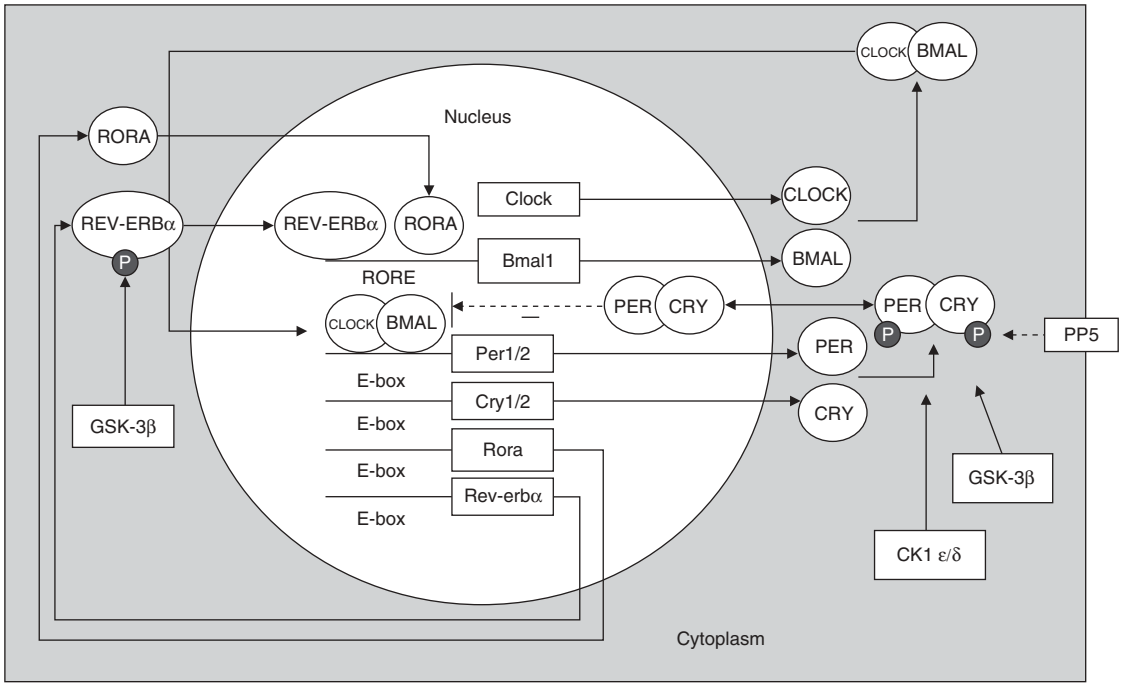

Fig. 3. Molecular mechanisms of endogenous clocks. This is a simplified scheme of the positive and negative regulations of protein synthesis that permit the generation of circadian rhythms. Clock genes are indicated in rectangles, and the proteins that they synthesize are indicated in ovals. In the cytoplasm, the proteins CLOCK and BMAL form CLOCK/BMAL dimers that bind to a specific chromosomal site (E-box) and activate the expression of several genes, notably *per1* and *per2* and *cry1* and *cry2*. The proteins PER and CRY form PER/CRY dimers. In the cytoplasm, these dimers are phosphorylated by kinases such as glycogen synthase kinase 3 beta (GSK3β), or dephosphorylated by phosphatases such as protein phosphatase 5 (PP5); these reactions modify their stability. The PER/CRY dimers have a negative feedback effect on their own synthesis. Several other genes and proteins are involved (RORA, Rev-erbα, etc.) (see text for explanation).

around which DNA is folded, can undergo modification by acetylation or methylation, under the direct or indirect influence of PER, CRY, CLOCK, or BMAL. There are regulations of the RNA stability of these proteins, for example, under the influence of CRY of microRNA molecules.[48] Also, the rate of formation and degradation of the BMAL/CLOCK heterodimers can be influenced by enzymes. These molecular regulators of the circadian system involve more than 20 genes, and mutations in these can influence the length or other parameters of the circadian period (for reviews, see Schibler[46] and Nolan and Parsons[49]). Even a synthetic mammalian biological clock has now been constructed.[50]

The many genes that show circadian rhythms in their expression both in the SCN and in other tissues seem to be regulated somewhat differently, which allows for tissue-specific responses to endogenous or exogenous fluctuations. Studies on the polymorphism of clock genes are of relevance to psychiatric disorders. In an animal model, a mutation in the *clock* gene was found to result in a behavioural configuration resembling mania, with hyperactivity, decreased sleep, less anxiety or despair in response to stress and increased proneness to cocaine consumption. Lithium treatment returned this behavioural configuration to normal.[51] In humans, polymorphism in some circadian clock genes might be related to a higher occurrence of affective disorders, but no tight association has yet been described.[52] It could be that given components of affective disorders are related to circadian clock gene mutations, for example, delayed sleep onset or duration of sleep.[53]

4. Affective Disorders and Chronobiology

Depressed or manic patients show changes in their biological rhythms. During depressive episodes, there is an overall tendency towards a phase advance of several rhythms, such as nocturnal cortisol secretion and body temperature. There is also a dampening in the amplitude of several rhythms, such as that of thyroid-stimulating hormone, of temperature and of nocturnal melatonin secretion.[54,55] Phase delays rather than phase advances were also found,[56] for example, with nocturnal melatonin.[57] When individuals enter remission, many of these changes disappear,[54] although several chronobiological characteristics might remain even in the non-depressed state, i.e. they could be trait markers, or endophenotypes, rather than state markers. Nevertheless, they are usually considered as predictors of depressive relapses. Sleep is abnormal during depression, with a shortened latency to the first rapid eye movement sleep episode (once individuals fall asleep), with a fragmentation of sleep, a difference in delta wave density and early morning awakening.[58] Sleep seems to be regulated by two processes, first a circadian process (process C), which depends on circadian clocks, and second a homeostatic process independent of endogenous clocks, characterized by the progressive accumulation during wakefulness of a metabolic propensity towards sleep (process S).[59] The balance between these two processes might differ in depression, with the hypothesis of a deficit in the accumulation of process S.[60]

Studies on the sensitivity to entrainment by zeitgebers have suggested that there are changes in light sensitivity in patients with seasonal affective disorder.[61,62] Social activities, which are zeitgebers, do not seem to entrain rhythms in depressed patients as well as in controls, at least for the cortisol rhythm.[63]

According to several hypotheses, chronobiological changes might account for changes in mood as in depression or mania (for a review, see Schulz[64]). Among the early hypotheses was the idea that biological functions that are usually successive might synchronize and that this would lead to symptoms.[65] This hypothesis might apply to some cyclical physical disorders such as intermittent hydarthrosis (recurrent acute accumulation of liquid in the knee articulation), but not to mood disorders. The abnormal phase position of circadian rhythms in relation to astronomical time (a phase delay or a phase advance) of several cyclical biological functions could be the factor leading to mood changes according to the hypothesis of the internal coincidence model. Still another hypothesis concerns a deficit in the influence of social events on rhythms, either because

depressed persons lead a disorganized life, or because the social zeitgebers have less power to entrain the circadian clock during depression. Agomelatine is the first melatonergic antidepressant with an innovative pharmacological profile: agonist at melatonergic MT_1 and MT_2 receptors and antagonist at 5-HT_{2C} receptors.[66] Both properties are needed for the antidepressant activity of agomelatine.[67] Agomelatine has been shown to resynchronize altered circadian rhythms both in an animal model of depression[68] and in humans.[69] As agomelatine influences biological clocks, it will be interesting to understand further how agomelatine might exert its antidepressant effects through regulation of the SCN circadian rhythms. Non-pharmacological regulation of abnormal endogenous rhythms also has an antidepressant effect; psychoeducation aimed at correcting irregularities in life habits improves the clinical condition of affective disorder patients.[70]

5. Conclusion

The physiological organization of plants, insects and vertebrates in the dimension of time reveals innumerable rhythms for series of variables, leading to the notion that the structure of living species in time is as complex as their structure in space. This temporal dimension is also inherent to the mechanisms of neurotransmission.[71] The SCN, the main biological clock in mammals, governs circadian rhythms, synchronizes the many peripheral biological clocks and might play a role in the generation of rhythms of periodicity longer or shorter than the main circadian rhythm.

For decades, antidepressants have served as tools to study the pathophysiology of affective disorders. The discovery of their pharmacological mode of action has led to the understanding of the involvement of monoamines in mood, as well as of the influence of these neurotransmitters on other systems, such as the sensitivity of the amygdala to negative emotional stimuli.[72] Many pharmacological and non-pharmacological therapies of depression influence circadian rhythms.[8] Agomelatine, a new antidepressant agonist at melatonergic MT_1 and MT_2 receptors and antagonist at 5-HT_{2C} receptors is able to phase advance circadian rhythms in humans[69] and in depressed patients.[73] Lithium and valproate are mood stabilizers that influence circadian clocks.[74,75] Sleep deprivation, light therapy, phase advance of sleep all have an antidepressant effect.[7] The ongoing evaluation of these treatments should lead to a better understanding of changes in endogenous biological clocks in affective disorders.

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