Chapter 4
Processes Underlying Chronodisruption and Their Proposed Association with Illness

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Abstract Regularly alternating periods of light and darkness, such as normally occur with the rising and the setting of the sun, are essential for the maintenance of undisturbed circadian rhythms in all organisms including humans. The light–dark environment, as detected by specialized photoreceptors in the retinas, impacts the endogenous circadian clock in the anterior hypothalamus, the suprachiasmatic nuclei. These nuclei, via both neural and humoral signals, communicate with cells throughout the organism to establish regular circadian rhythms. The introduction of artificial sources of light roughly 150 years ago has significantly undermined the naturally occurring light–dark environment and, likewise, has disturbed circadian rhythms since light is now available at unusual times, i.e., at night. Light at night is known to cause circadian disruption and melatonin suppression. Of many potentially pathophysiological consequences of these artificial light-mediated changes, female breast cancer has become of major interest. Additionally, however, there is currently data suggesting that not only breast cancer, but cancer in general, cardiovascular diseases, insomnia, metabolic syndrome, and affective and cognitive disorders may be aggravated by the increased exposure to light at night, which is inevitable in well-developed societies that have undergone extensive electrification.

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Abbreviations

SCN	Suprachiasmatic nucleus
CD	Chronodisruption
LD	Light–dark
LAN	Light at night
ACTH	Adrenocorticotropic hormone
BMAL1 or ARNTL or MOP3	Aryl hydrocarbon receptor nuclear translocator-like
PER2	Period homolog 2 (Drosophila)
CLOCK	Circadian locomotor output cycles kaput
MetS	Metabolic syndrome
WT	Wrist temperature
BP	Blood pressure

Introduction

Clearly, circadian rhythms are so commonplace in animal and human physiology that, a priori, we must assume they are relevant to optimal function. Indeed, this fact is becoming progressively more apparent as scientists examine 24-h variations in the physiology of organisms, organs, cells and cellular organelles [1–3]. With an estimated 10–20 % of the genes in each cell under control of the central oscillator, the suprachiasmatic nuclei (SCN) in the anterior diencephalon, it is easy to envisage that disturbances of these clock mechanisms, particularly when repeated or chronic, may well lead to pathologies.

While the SCN exhibits an intrinsic rhythm of approximately 24 h, corresponding roughly to the normal environment light–dark cycle, it is not precisely of 24-h duration. Thus, light information detected by specialized ganglion cells (the intrinsic photoreceptive ganglion cells, i.e., *ip*RGC) [4–6] in the retinas and the transfer of this information via the retinohypothalamic tract to the SCN, serves as an important and critical Zeitgeber for the central oscillator. This, in turn, influences the circadian physiology of all peripheral oscillators. Thus, whereas cells in organs throughout the body are incapable of direct photoreception, they do receive information as to whether it is day or night from the central clock and they adjust their functions accordingly.

The means by which the SCN conveys circadian information to the peripheral cellular oscillators includes both neural and humoral messages. One important humoral message is the melatonin signal from the pineal gland [7]. Due to information detected by the *ip*RGC of the retina and relayed through the SCN, the pinealocytes are apprised of the prevailing light–dark environment. During the day messages from the *ip*RGC render the SCN dormant relative to its ability to activate the pineal gland. During darkness, the SCN, via a circuitous neural route that involves portions of the central and peripheral sympathetic nervous system, stimulates the pinealocytes

to synthesize and quickly release the chemical mediator, melatonin [7, 8]. This agent then circulates throughout the body and informs, perhaps every cell, of the prevailing photoperiodic environment so that functional adjustments can be made [9, 10].

Considering that the circadian system is composed by multiple body clocks, it is important to note that, aside from light–dark influences to the SCN, other peripheral oscillators are very sensitive to non-photic synchronizers such as feeding time, scheduled exercise, sleep time and social contacts. This complexity, together with the weakness of exposure to synchronizers in developed countries, makes the circadian system prone to suffer from chronodisruption (CD).

What Causes Chronodisruption?

Circadian disruption or CD is defined as a relevant disturbance of the internal temporal order of physiological and behavioral circadian rhythms. It is also a breakdown of the normal phase relationship between the internal circadian rhythms and 24-h environmental cycles. In our modern society, CD may be common in several conditions such as jet lag, shift work, light at night, or social jet lag [11]. In addition clock gene polymorphisms and aging may have also chronodisruptive effects. Thus, CD can be induced by any impairment of the inputs, oscillators and outputs (Fig. 4.1).

Inadequate Inputs

Importance of a Regular Light–Dark Cycle

Since the light–dark (LD) cycle regulates the 24-h melatonin synthesis/secretion rhythm, it is obvious that perturbations of this regularly recurring cycle would likewise alter the melatonin message leading to misinformation being sent to the peripheral cellular clocks. Throughout eons of evolution, disturbances of the LD environment did not occur since the SCN was regulated and the melatonin rhythm was determined exclusively by the rising and the setting of the sun. Only after the invention of the artificial light source by Thomas Alva Edison in 1879 were humans capable of imposing the LD cycle they desired. This was a major turning point for circadian biology since it allowed humans to inadvertently alter an important basic system, the circadian system, and to also perturb the melatonin rhythm. These perturbations in the melatonin rhythm could not be ignored by the peripheral cellular oscillators and they then were required to make unexpected adjustments to their physiology at unusual times. Not surprisingly, these atypical changes of a very basic

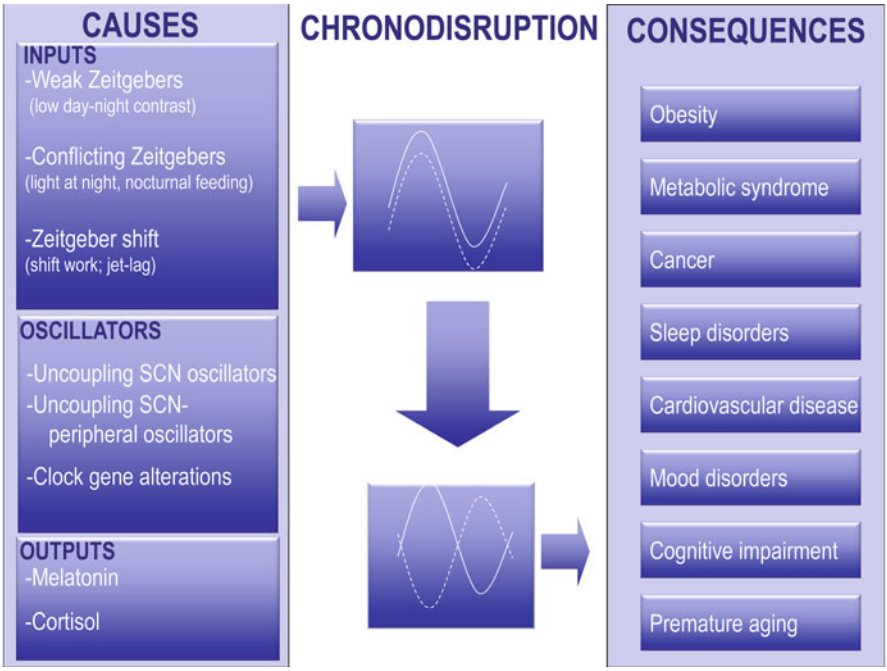

Fig. 4.1 Causes and consequences of chronodisruption. Circadian disruption is the result of an abnormal phase relationship between the rhythms regulated by endogenous oscillators (*solid line*) and activity-controlled physiological processes (*dotted line*). Chronodisruption can be induced by factors related to the following: (1) Impairment of the inputs to the circadian pacemaker: low contrast between day and night synchronizing agents (continuous light, frequent snacking, low levels of physical exercise, etc.); exposure to zeitgebers of different periods or unusual phasing (i.e., light at night, nocturnal feeding, nocturnal physical exercise) or by frequent shifts in the time provided by zeitgebers (i.e., jet lag, shift work). (2) Circadian oscillators: the uncoupling between different subpopulations of oscillators inside the SCN caused by aging or clock gene alterations and the uncoupling between central pacemaker and peripheral oscillators also result in chronodisruption. (3) Outputs: the suppression of nocturnal melatonin and the loss of cortisol rhythm are also chronodisrupters. CD is related to the increasing risk of developing certain diseases and with the impairment of preexisting pathologies

rhythm, which had been unvarying throughout evolution, would be expected to cause abnormal physiology and perhaps pathologies [2, 12, 13].

Already several decades ago it was shown that the exposure of animals or humans to light at night (LAN) depresses elevated nighttime melatonin levels, i.e., it changes the melatonin message [14–18]. Since these early discoveries in this field, numerous subsequent investigations have more precisely defined the mechanisms by which LAN inhibits the synthesis and discharge of melatonin, thereby destroying its regular circulating rhythm [6, 7].

LAN has a number of unnatural effects on the circadian system and on pineal melatonin production. In the well-developed countries of the world where electricity is readily available, it is usual to turn on manufactured lights at the time the

sunsets. Likewise, when humans awaken in the morning and it is still dark, their first activity is to turn on a light. What this obviously means is that humans are no longer allowing the natural LD cycle to regulate their SCN and the production of melatonin; rather they unwittingly manipulate these processes with the misuse of artificial light.

In the situation summarized above, where light is extended into the normal period of darkness and light exposure also occurs in the morning before sunrise, the SCN must adjust its signaling processes accordingly; one result of this imposed artificial light is a shortening of the nightly duration of melatonin production by the pineal gland [19]. Thus, in highly industrialized societies, humans have become relatively melatonin deficient since they truncate the normal period of darkness and, thereby, the duration of elevated melatonin.

In general, the only time humans are in darkness is when they sleep. Thus, depending on their nightly sleep duration, which is also becoming progressively shorter in developed societies [20, 21], the total amount of melatonin produced may be reduced by 50 % or more relative to what would have been generated had they been exposed to the natural LD cycle. Given the multiple beneficial actions of melatonin [22–25], a 50 % loss of the total amount of melatonin nightly would be expected to have consequences, including negative effects, i.e., pathologies, [26–28].

A second danger of the availability of manufactured light is the ability of humans to acutely expose themselves to light during the normal dark period. During the night, the *ip*RGC detect the light that is actively imposed and they signal the SCN that it is "day," when in fact it is night. The SCN, in turn, communicates with organs throughout the organism, including the pineal gland, and provides them with misinformation. Even though the information received is inappropriate for the time, molecular and physiological adjustments are made by peripheral organs consistent with the normal daytime period. Thus, the physiology of these cells is no longer in synchrony with the normal LD cycle. This incoordination results in chronodisruption [10], a situation which could certainly lead to pathophysiologies [2, 13, 15, 29].

One conspicuous result of acute bright light exposure at night is a rapid plummeting of circulating melatonin levels [14, 17]. This abnormal drop in blood melatonin is also "read" by numerous cells throughout the body and, since melatonin values are normally low only during the day, again the peripheral organs are misled as to time. Such severe perturbations and dyssynchrony between organ physiology and the prevailing LD environment would not surprisingly be expected to cause functional casualties.

There is one other hazard associated with the massive electrification that has occurred in many places in the world. In cities especially, LAN has become unavoidable because of light pollution. Photographs of America, Europe, Japan, etc., taken from outer space at night reveals the degree of light pollution that has taken place in recent decades and predictably will become progressively worse in the years ahead. What this means is that it is becoming more difficult for humans to avoid LAN and, as a result, we may be becoming progressively more chronodisrupted. Moreover, in the sleeping environment it is sometimes difficult to evade transpass light, i.e., light that is out of the control of the person being exposed. The degree to which light pollution, transpass light, etc., impacts circadian physiology and pineal melatonin

production has not been well defined, but deserves close scrutiny. Finally, parents should be discouraged from permitting their children to sleep in a lit room because they are intimidated by darkness. In the case of children, LAN may be particularly harmful since this is the age at which their circadian system is maturing. Presumably, any pathologies that may develop as a result of chronic chronodisruption may appear years or even decades after the disturbances have occurred.

Consequences of disturbing the light–dark cycle, as already mentioned, the extension of the light phase into the normal period of darkness and likewise truncating the night by artificial light exposure in the morning, limits the total amount of melatonin that would normally be produced in a seasonally appropriate LD cycle. While these maneuvers reduce the total quantity of melatonin produced, they do not eradicate its basic circadian rhythm [19]. The reduction in the total amount of melatonin produced during a 24-h period by itself may, however, be consequential in terms of at least one pathophysiological state, i.e., cancer [23, 30–32].

Sleep Deprivation

In addition to limiting the quantity of melatonin generated nightly, the excessive use of light in the evening and in the morning is usually associated with abbreviated nightly sleep periods. Adequate sleep is also essential for optimal health [33]. The daily sleep interval is becoming shorter in a number of countries. For example, in the USA the nightly sleep period has been dropping over the last half century. In the 1960s, the duration of sleep by US citizens was on the order of 8 h; the current best measures indicate that this is currently about 6.5 h [34]. Since sleep duration is usually associated with dark exposure, there has been a corresponding drop in melatonin production in the last 50 years as well. In addition to the obvious reduction in work efficiency that accompanies sleepiness, the health consequences of insufficient rest combined with reduced melatonin are likely also substantial [15, 29].

Virtually all studies that have examined a possible association between nightly sleep duration and cancer, most often female breast cancer, have found a relationship, i.e., short sleep correlated with elevated cancer incidence [35–37]. Each of these workers also noted that reduced sleep likely also meant limited elevated melatonin levels every night. Considering the multiple means by which this indole inhibits tumors, its reduction would likely be a contributing factor to the higher breast cancer incidence [30, 38, 39].

Feeding Time

Rhythmic feeding appears to be the major synchronizer for peripheral oscillators. Thus, unusual feeding time can produce CD by inducing internal desynchronization through decoupling of peripheral oscillators from the SCN. For example, it has been

described that clock gene expression in the liver can synchronize to scheduled feeding in 2 days while SCN remains locked to LD cycle [40]. This differential synchronization induced by abnormal feeding habits could produce unhealthy consequences also in humans. Thus, when nocturnal (characterized by late awakening, omitting breakfast and late dinner) and diurnal (early awakening and early dinner) lifestyles were compared among healthy young people, glucose tolerance and insulin response were found to be well regulated in the diurnal group, while sustained hyperglycemia and hypoglycemia in the morning were observed in the case of nocturnal lifestyle [41] In addition, plasma levels of melatonin and leptin were reduced during the night in the nocturnal lifestyle group.

Different laboratory experiments are inducing internal desynchrony in human by forced desynchronization protocols placing subjects with sleep–wake and feeding rhythms on a 28-h daily routine for several days [42]. Interestingly, under such artificial conditions, body temperature, which is under the SCN control, remains near 24 h cycle, whereas rhythmicity in different metabolic hormones such as leptin and insulin, adhered to the imposed 28-h behavioral cycle of sleep and food intake. This misalignment induces a suppression of plasma leptin, increase in glycemia, and hypertension. Therefore, unusual feeding times are likely an overlooked risk factor to the health in modern societies.

Impaired Pacemakers

Jet lag and rotating shift-work are two well documented factors inducing CD. These two factors share a common mechanism in the CD generation involving the differential rates of synchronization of biological variables. This may be the result of the different contribution of SCN and peripheral oscillators to the generation of biological rhythms in different variables. For example, following a 6-h phase delay, the acrophase of ACTH and cortisol rhythms need up to 7 days to resynchronize, while it takes only 3 days in the case of sleep–wake cycle. Thus, during these days each function shifts at a different rate and the organism is suboptimally organized to efficiently accomplish its functions [11]. This condition is even more serious in the case of shift-workers because its chronic character.

CD can also be produced by the impairment of the molecular machinery of the circadian clock; however, discerning the relative influence of disrupted circadian rhythms induced by clock gene alteration from the potential pleiotropic effects of core clock gene inducing pathological process will therefore be a challenge [43]. Alterations in some clock genes have been associated with specific diseases such as premature aging, cancer, and obesity among others.

Mice without Bmal1 gene are arrhythmic and are subjected to premature aging and the mean lifespan of these animals is of 37 weeks as compared with 120 weeks for wild-type animals. In addition, Bmal1-knockout mice exhibit sarcopenia, vision problems, and altered lymphocytopenia [44].

Mutations in Per2 gene, another core clock gene, increases the susceptibility of mice to develop spontaneous and irradiation-induced tumors, through the stimulation of the protooncogene c-myc and repression of the oncostatic p53 gene [45]. Another well known example of clock gene induced pathology is obesity and metabolic syndrome associated with impaired Clock gene expression. CLOCK protein is a key factor involved in the synchronization of metabolic processes with the environment and in the control of mammalian energy balance. As expected, Clock-mutant mice show reduced or abolished rhythms in food intake and metabolic rate, but, in addition these animals are obese, exhibit adipocyte hypertrophy, hepatic steatosis, and alteration in leptin blood levels [29].

Outputs

The third element which can cause CD are the alteration of the outputs of the central pacemaker which act as internal coupling synchronizing signal to maintain the internal temporal order among different rhythmic functions. Impairment of the melatonin rhythm is the best known output factor mediating CD, as has been mentioned at the beginning of this chapter.

Pathological Consequences of CD

In the last decade, the effect of CD on human health has become an important issue. Indeed nowadays we certainly know that several chronic diseases, which widely affect our society, are influenced by chronobiological components (Fig. 4.1).

Chronodisruption and Cancer

Experimentally, it is well documented that unusual changes in the LD cycle that cause chronodisruption lead to accelerated growth of cancers. Using mice bearing transplanted Glasgow osteosarcomas, Filipski et al. [46] noted that these tumors grew more rapidly when the mice were exposed to a simulated eastward flight that caused an 8-h phase advance every 2 days. This recurring unusual 8-h photoperiodic change, which would duplicate a flight from the mid-USA to central Europe caused chronic circadian disruption relative to mice maintained in a stable photoperiodic cycle.

In the study by Filipski and colleagues [46], in addition to the mice suffering circadian misalignment, they very possibly exhibited an abnormal or more likely, no nighttime rise in melatonin production and secretion. Since the actual levels of melatonin were not measured in these animals, it remains undetermined if melatonin suppression was a factor in the more rapid tumor growth. It seems likely, however,

that several changes, i.e., circadian disruption, melatonin suppression, sleep deprivation, etc., conspired to promote the accelerated growth of the transplanted osteosarcoma cells.

That electrolytic destruction of the biological clock, i.e., the SCN, and the resultant circadian disruption, stimulates cancer progression was confirmed in a study performed by the same group. In this case, Filipski and Li [47] electrolytically lesioned the SCN of mice bearing implanted tumors. This destructive procedure caused the cancers to grow more rapidly. While loss of the SCN would certainly destroy and/or severely compromise the circadian rhythms of all organs, the lesions also surely demolished the cyclic production and release of pineal melatonin; therefore, the mice were deficient in this cancer-inhibiting indoleamine. Because of the multiple negative actions resulting from lesions of the SCN, the basis of the accelerated progression of the cancer in the mice lacking their central clock remains undetermined.

Other studies also point to a role of the circadian network and chronodisruption in the acceleration of cancer growth [48]. The expression of the *Per2* gene is a critical factor in circadian organization. In mice genetically devoid of the *Per2* gene, the typical circadian cycle of 24–25 h becomes shortened to less than 24 h. A high percentage of the mice with this circadian malady spontaneously develop lymphomas by the time they are 16 months of age. Normally, these tumors in intact mice do not appear until the animals are beyond 20 months of age. The findings of Fu and coworkers [45] also support a role for the involvement of circadian genes in cancer cell proliferation.

Similar to that described in experimental animals, several evidences link CD and cancer also in human. Thus, for at least two decades, epidemiologists have been interested in the association between LAN, along with the associated changes in the underlying physiology, and the elevated incidence of breast cancer risk. The initial reports claimed that a higher frequency of breast cancer was apparent in attendants who routinely worked as airline hostesses on long flights over multiple time zones [49, 50] and in women who commonly performed night shift work over long periods of time [51, 52]. The workers most commonly invoked chronodisruption as a major contributory factor to the reported rise in breast cancer rather than a disturbance or a reduction in the melatonin rhythm [26, 53, 54]. More recently, however, interest in the possible or likely involvement of depressed melatonin levels is attracting greater interest [55, 56]. This surely stems from the experimental studies that document melatonin as a significant endogenous anticancer agent, not only for breast cancer [46, 57, 58] but cancer in general [59–61].

Following the initial observations on breast cancer in females as a consequence of LAN, prostate cancer also began to attract attention. While the studies are not as numerous as those for breast cancer nor is the evidence as provocative, an elevated frequency of prostate cancer may likewise be more frequent in males who experience what would be divergent LD environments [62, 63]. Moreover, it has been speculated that in fact routine perturbations of the LD cycle may be a factor that significantly influences cancer development of many types, not only breast and prostate [59]. Chronodisruption and melatonin suppression as being potentially carcinogenic has even been noted by the World Health Organization, inasmuch as they have classified circadian disturbance as a Group 2A carcinogen; this classification

suggests that there is likely (although not definitively proven) a relationship between the elevated frequency of certain cancer types and chronic alterations in the naturally occurring LD cycles [64]. While a considerable amount of data, most of which is observational, suggests that some aspect of circadian disruption contributes to a higher prevalence of certain cancer types, the idea is not enthusiastically supported by some [65]. On the other hand, to assume that routine chronodisruption due to what must be considered abnormal or unusual LD cycles is totally inconsequential in reference to potential pathophysiologies would seem imprudent. Other cancer types that have been tentatively linked to LAN/chronodisruption include endometrial [66], colorectal [67] and lung [68].

If a definitive link between chronic perturbations of the LD cycle and pathologies, i.e., cancer, is established, it will be important to identify the mechanisms involved. With the exposure to light at night, at least three things can happen, i.e., the individual may experience chronodisruption, there may be a reduction in sleep duration or efficiency, and nocturnal melatonin levels may be suppressed (Fig. 4.2). At this point, it is not known which of these contribute to the presumed physiological rearrangements and the alleged pathologies that may occur. Certainly each of these, i.e., chronodisruption, sleep deprivation, and melatonin suppression, may individually be capable of contributing to any pathology that occurs. It would seem what is most likely, however, is that these unusual disturbances conspire to precipitate molecular physiological perturbations at the level of individual cells that then eventually cause overt pathologies.

Interestingly, the changes caused by light exposure at abnormal times, i.e., during darkness, cause functional changes that are reminiscent of those seen in older humans, when pathologies of various types are more likely to be manifested. Thus, aging is associated with changes typical of chronodisruption [1], sleep is often impaired in the elderly [15, 21, 38, 39], and melatonin levels diminish with advanced age [69, 70].

Finally, if cancer, particularly breast cancer, is one manifestation of excessive and chronic exposure to light at night, it would seem likely that this would not be the only pathology that would occur. Indeed, within the last decade many diseases have been at least theoretically related to disturbances of biological rhythmicity, sleep deprivation and less than adequate amounts of sleep [29, 38, 71–73]. Thus, it would seem likely that many pathologies which are common in the aged, may in fact also be aggravated by chronic exposure to excessive light at night (Fig. 4.2).

Fig. 4.2 (continued) period (night shift work or light pollution/trespass light). Light of adequate intensity and wavelength is detected by the intrinsic photoreceptive retinal ganglion cells (*ip*RGCs), melanopsin containing neurons, with the resulting signal being sent via the axons (the retinohypothalamic tract) of these cells to the biological clock, i.e., the suprachiasmatic nuclei (SCN). Clock disturbances can then be transferred, via neural or humoral signals, to all cells in the body, all of which possess genes that are under circadian regulation. The resulting disturbances in cell physiology may culminate in functional disturbances that lead to a variety of pathologies. One challenge for scientists/clinicians is to definitively establish whether there exist serious pathologies that relate to light at night and, if so, to clarify the mechanisms involved so corrective actions can be instituted

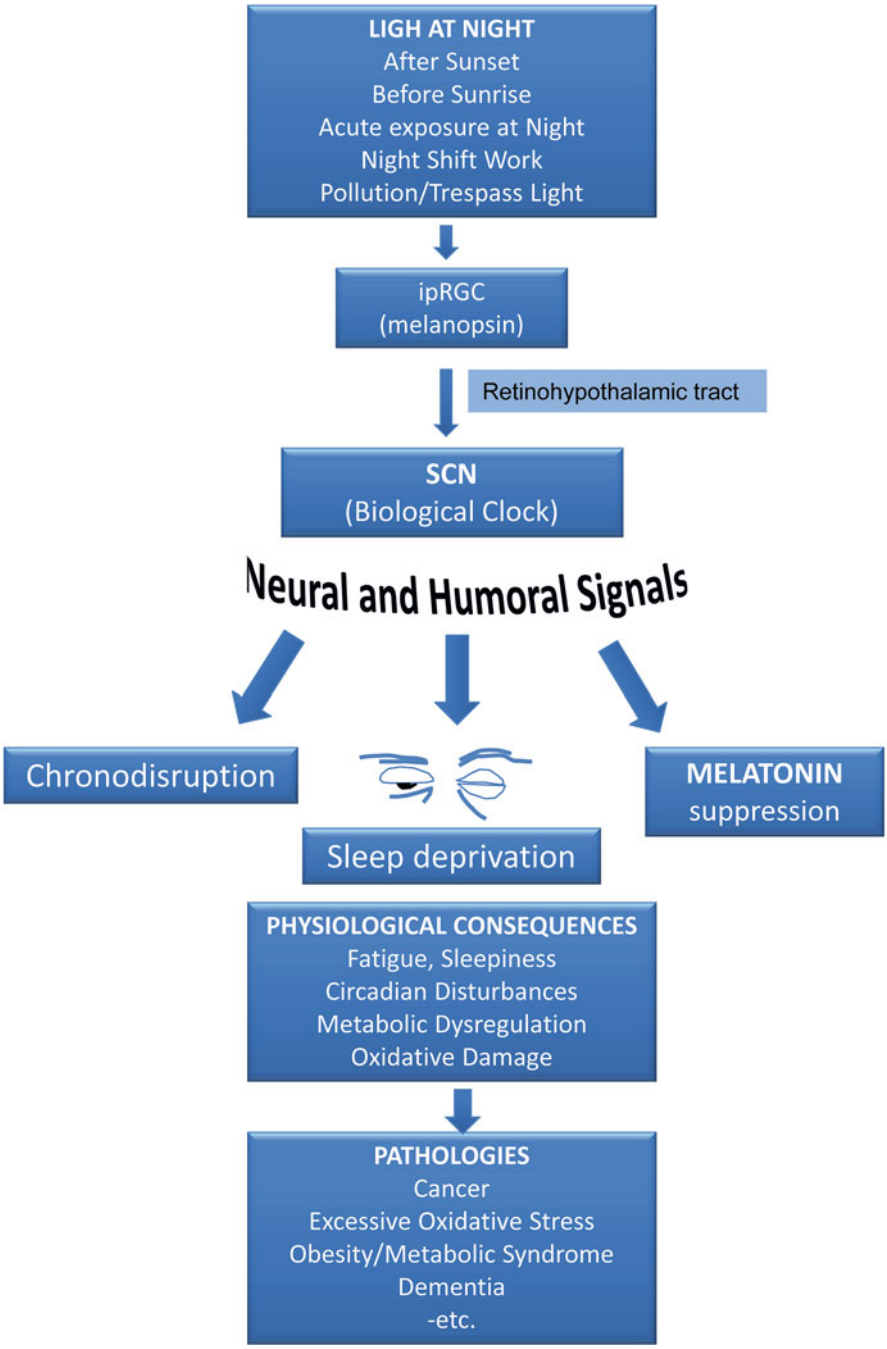

Fig. 4.2 A flow diagram illustrating the sequence of events that may lead to pathologies reportedly associated with light at night. Light at night may take many forms such as reducing the duration of the dark period (light after sunset and before sunrise), transitory interruption of the period of darkness (acute light exposure at night), and total or near total elimination of the daily dark

Chronodisruption, Metabolic Syndrome (MetS), and Obesity

Since the discovery of the CLOCK mutant mice, to the present moment many outstanding and consistent studies have demonstrated the important connection between CD and obesity (Fig. 4.3).

Although the connection between obesity and CD will be treated in several chapters along the present book, it is important to highlight that our experiments in humans are showing that MetS metabolic disturbances such as increased blood pressure, increased glucose and plasma lipids regulation, and changes in adipocyte-secreted hormones such as leptin and adiponectin, associates with diminished daily amplitude in melatonin and cortisol circadian patterns, demonstrated the existence of chronodisruption with metabolic syndrome [74]. In this line, in another experiment also performed by our group, analyses of skin temperature indicated that obese women displayed significantly lower mean wrist temperature (WT) with a more flattened 24-h pattern, a lower-quality rhythm, and a higher intradaily variability. Particularly interesting were the marked differences between obese and normal-weight women in the secondary WT peak in the postprandial period, considered as a marker of chronodisruption and of metabolic alterations. These 24-h changes were associated with higher MetS risk [75].

Other Pathologies Related to CD

While this chapter considered mainly the potential association of chronodisruption with cancer and with obesity, there may well be other health-related problems that occur as a consequence of imposed chronic changes in the LD environment that severely disturb circadian rhythmicity [76].

Multiple records link CD with the increased risk of developing premature aging, cardiovascular diseases, cognitive impairment and mood disorders, among others.

Similar to that observed in many physiological processes, the functioning of the circadian system changes with *age.* Phase advance, reduced amplitude, circadian fragmentation, impaired ability to resynchronize after a time shift and internal desynchronization among different rhythms are the major characteristics of aged rhythms [77]. However, less well known is the fact that CD has a direct role in inducing accelerated aging [78, 79]. Although it is generally believed that disruptions in circadian rhythms lead to reduced life expectancy, whereas their appropriate resetting leads to well-being and increased longevity [77].

Cardiovascular diseases are also related to chronodisruption. In people with normal blood pressure (BP) and uncomplicated essential hypertension, BP declines to its lowest levels during night-time sleep, rises abruptly with morning awakening and attains a maximum during diurnal activity. It has been shown that night-time BP is the best predictor of stroke and myocardial infarction risk [80, 81]. Thus, hypertensive patients with a normal reduction in nocturnal BP (dipper) had a relative

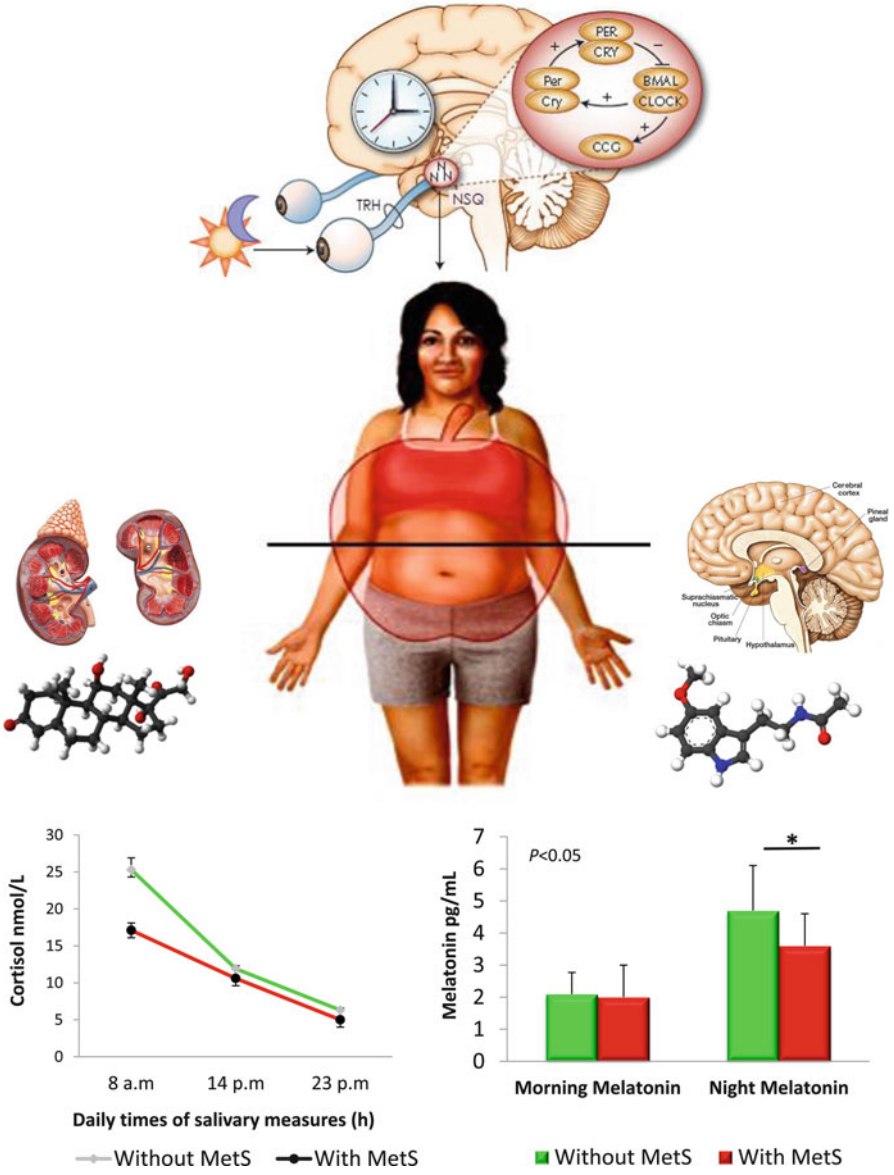

Fig. 4.3 Relationship between circadian disruption and obesity. The photic inputs that reach the SCN are processed and forwarded to a small number of other hypothalamic nuclei and to the adrenal and pineal gland to regulate cortisol and melatonin rhythms. Melatonin is the end product of a biosynthetic pathway that begins with the nutrient amino acid tryptophan. The relationship between light and melatonin is inverse. When the SCN is stimulated by daylight signals from the retina, it instructs the pineal gland to suppress melatonin production. Then, when daylight fades in the evening, melatonin secretion is increased many times over, creating a physiological condition of "biological darkness" in the person. The circadian rhythm of cortisol and melatonin secretion together with sleep–wake rhythm are impaired in obese people. Morning cortisol levels and evening melatonin levels are reduced in obese compared with control women (Data from Corbalán-Tutau et al. 2011. Chronobiol. Int. 28:425–433)

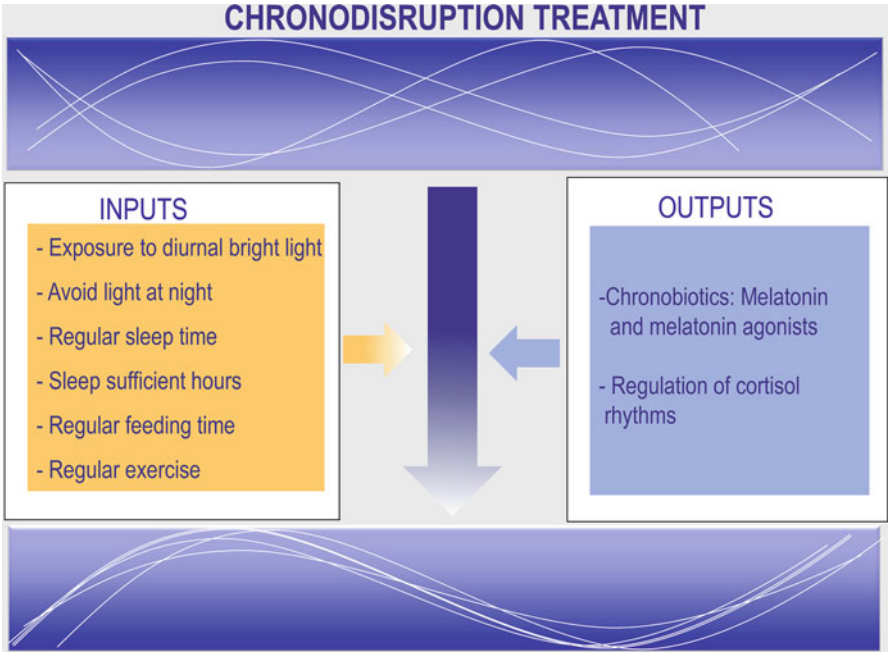

Fig. 4.4 Strategies for circadian enhancement. The adequate functioning of the circadian system is dependent on regularly timed exposure to synchronizers. Regarding the outputs, regularly timed melatonin treatment enhances circadian robustness as occurred with a stable cortisol rhythm

hazard of cardiovascular mortality similar to that in non-dipper normotensives. It is noteworthy that the non-dipper circadian pattern is more frequent among shift workers and elderly people [80, 81].

The circadian system modulates cognition and affective function by projections from SCN to arousal and sleep systems and through eliciting changes in clock genes in extra-SCN brain regions. Chronodisruption in the sleep–wake circadian rhythm has important implications for learning, memory and emotion [82]. When wakefulness occurs at appropriate internal biological times, circadian system benefits human cognitive and emotion function. However, when wakefulness occurs at inappropriate biological times because of social pressures, such as early school start times, work at night, shift work, and jet lag, or because of circadian sleep disorders, the resulting misalignment between circadian and wakefulness–sleep physiology leads to impaired cognitive performance, learning, emotion, and safety [82].

Experimental studies specifically addressing the treatment of chronodisruption are lacking. However, the development of technical improvement in healthy lighting systems and all behavioral and pharmacological treatments that improve the circadian system status (chronoenhancement) may help to reduce the risk of pathologies associated to chronodisruption (Fig. 4.4).

Concluding Remarks

As discussed in this brief review, the misuse of artificial light, i.e., light after darkness onset, causes disintegration of biological clock processes such that the temporal architecture of cells, which is the basis of optimal physiology, breaks down, thereby contributing to pathophysiologies. Additionally, LAN reduces an important chemical messenger from the pineal gland, melatonin, the loss of which likely also contributes to increased pathologies, e.g., cancer, and reduced quality of life. While this brief review considered the potential association of chronodisruption and cancer, there may well be other health-related problems that occur as a consequence of imposed chronic changes in the LD cycle and other non photic synchronizers that severely disturb circadian rhythmicity [76].

Summary Points

- The suprachiasmatic nucleus conveys circadian information to the peripheral cellular oscillators through both neural and humoral messages. One important humoral message is the melatonin signal from the pineal gland.
- Melatonin, also known as "chemical darkness," shows a circadian rhythm which is regulated by a double mechanism: an endogenous pattern driven by the suprachiasmatic nucleus of hypothalamus and an acute inhibitory effect of nocturnal light.
- The introduction of artificial sources of light roughly 150 years ago has significantly undermined the naturally occurring light–dark cycle and, likewise, has disturbed circadian rhythms since light is now available at unusual times. Light at night is known to cause circadian disruption and melatonin suppression.
- In our modern society, circadian disruption may be common in several conditions such as jet lag, shift work, light at night, or social jet lag. In addition clock gene polymorphisms and aging may also predispose to chronodisruption.
- In the recent years chronodisruption is being associated with an impairment of several pathologies such as cancer, cardiovascular diseases, sleep disorders, premature aging, obesity, metabolic syndrome, and cognitive and affective disorders.

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