REVIEW

Circadian Disruption as a Risk Factor for Development of Cardiovascular and Metabolic Disorders – From Animal Models to Human Population

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Summary

The lifestyle of human society is drifting apart from the natural environmental cycles that have influenced it since its inception. These cycles were fundamental in structuring the daily lives of people in the pre-industrial era, whether they were seasonal or daily. Factors that disrupt the regularity of human behaviour and its alignment with solar cycles, such as late night activities accompanied with food intake, greatly disturb the internal temporal organization in the body. This is believed to contribute to the rise of the so-called diseases of civilization. In this review, we discuss the connection between misalignment in daily (circadian) regulation and its impact on health, with a focus on cardiovascular and metabolic disorders. Our aim is to review selected relevant research findings from laboratory and human studies to assess the extent of evidence for causality between circadian clock disruption and pathology.

Keywords

Circadian clock • Chronodisruption • Metabolism • Cardiovascular disorders • Spontaneously hypertensive rat • Human • Social jetlag • Chronotype

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Introduction

Physiological processes are controlled to maintain homeostasis, the basic principle that sustains a stable balance in the body under changing environmental conditions. Since some of these environmental changes are regularly repeated in cycles, organisms have evolved a mechanism that allows them to respond appropriately in anticipation of the changes in order to achieve homeostasis more effectively. Such a mechanism requires an internal timer, a "clock" that tracks time endogenously [1]. The best understood mechanism, called the circadian clock (from the Latin circa-diem; about a day), generates approximately 24-hour cycles that organize biological processes even in the absence of regular environmental cycles [2]. The circadian clock uses external signals that regularly oscillate with the period of the solar day to adjust its endogenous period to exactly 24 hours and achieve the correct phase relative to a particular time of day through a process known as entrainment [3]. The most important signal is the alternation of light and darkness, but other signals such as food availability, temperature, humidity, social interaction, the presence of predators, etc. are also relevant factors depending on the species. In everyday life, the human circadian clock is primarily controlled by exposure to light and food intake [2], i.e. by factors that are strongly dependent on the daily regime and lifestyle.

It is important to note that the presence of a circadian clock is not conditional for survival [4,5], especially for organisms that live in a constant environment where anticipation of environmental change is meaningless [6]. Such organisms are able to respond to a light/dark (LD) cycle and entrain to it in terms of behaviour and molecular rhythms, but become arrhythmic

immediately after transfer to constant darkness, as has been shown in the cavefish species Astyanax mexicanus [7]. However, organisms lacking the clock but living in a cyclic environment have been found to have shorter lifespans, whether in the laboratory [8] or in natural habitats [9]. The situation is even more detrimental when the clock is present but its resonance with the environmental and behavioral cycles is disturbed [10, 11]. This leads to the loss of internal synchrony between the clocks in our body, and eventually the circadian system cannot fulfill its role in predictive homeostasis. This situation applies to people living in contemporary societies where artificial light at night and unlimited access to food are predominant factors causing the internal desynchrony.

In this review, we contextualize data supporting the evidence that disruption of circadian regulation increases the risk of cardiometabolic disorders. The evidence comes mainly from experimental work in animal models, but also from studies in humans. Despite the exponential increase in our knowledge of these processes and the flood of reviews on this topic in the scientific literature, we argue that still more studies are needed to prove a causal relationship. Understanding the impact of our everyday lifestyle preferences on our health could pave the way to mitigate the detrimental effects of technological development on human health.

Complexity of the circadian system

There is a hierarchy between cellular circadian clocks in our body that determines their sensitivity to external signals and their role within the circadian system. Light is the dominant signal for the mammalian central clock in the suprachiasmatic nuclei of the hypothalamus (SCN), which is the only clock capable of perceiving it directly via a connection to the retina [12, 13]. The central clock entrains to a LD cycle and consequently drives 24-hour rhythms in multiple signals involving neural, hormonal and behavioral pathways to relay information about the time of day to peripheral clocks in other parts of the body (brain, liver, intestine, pancreas, heart, adipose tissue, etc.) (reviewed in [14-17]). The SCN has the most robust clock, whose sensitivity to non-photic rhythmic signals is much lower compared to light and depends on the signal, the species and the specific context (reviewed in [18]).

On the other hand, peripheral clocks depend on the non-photic signals derived from the SCN to maintain synchrony with the solar day (reviewed in [19]), although data suggest that individual clocks in the periphery may differ in their dependence on SCN signals [20]. For example, exposure of rats to constant light abolishes the rhythmic output of the SCN, as documented by behavioral arrythmicity, but affects clocks in the liver, duodenum and colon to a different extent [21]. One of the strongest entraining signals for most peripheral clocks are hormones such as glucocorticoids (reviewed in [22]), whose rhythmic production in the adrenal gland is under the control of the SCN [23, 24]. These hormones and their synthetic analog dexamethasone represent robust synchronizing cues for clocks not only in peripheral tissues [25], but also in extra-SCN brain regions [26, 27] and cell lines [28]. Nevertheless, even clocks in functionally related tissues of the gastrointestinal tract (jejunal mucosa, liver, renal cortex and epididymal adipose tissue) responded very differently to absence of circulating glucocorticoids due to adrenalectomy [29], demonstrating that signaling from the SCN to these clocks is tissue-specific and more complex. Changes in energy balance resulting from the feeding/fasting cycle controlled by the SCN clock are another example of a significant cue to which peripheral clocks in some tissues are highly sensitive [25, 30, 31]. However, similar to glucocorticoids, clocks in functionally related tissues of the gastrointestinal tract (liver, duodenum and colon) differ in their sensitivity to feeding [21]. Peripheral clocks also respond to other SCN-controlled signals such as body temperature cycles [32, 33] and autonomic nervous system activity (reviewed in [34]), but these are beyond the scope of our review.

All of these findings demonstrate that the synchrony between the clocks of the circadian system is fine-tuned to provide tissues with specific local temporal organizations in alignment with expected changes in the environment over the solar day. Understanding the complexity and specificity of the pathways that synchronize clocks in individual cells is one of the major challenges of chronobiology.

How do circadian clocks control cellular processes?

The interaction between the molecular clock machinery and a specific physiological process begins at the cellular level. The circadian signal results from a mechanism based on mutually interlocked transcriptional-translational feedback loops (TTFLs) that

autonomously activate and inhibit the expression of a set of clock genes in cycles with a circadian period. The protein products of these clock genes serve as transcription factors that rhythmically activate (positive elements) or inhibit (negative elements) the expression of genes inside and outside the feedback loop. In this way, the TTFL drives the rhythm of a large number of clock-controlled genes that encode either transcription factors or "functional" proteins directly involved in cell functions. The mechanism of mammalian TTFL has already been reviewed many times in detail [35-38], so we only provide a brief overview of the process here. At the core of the clock mechanism, a feedback loop is formed by *Clock, Npas2* and *Bmal1* (also known as *Arntl*) as positive elements and *Per1,2,3* and *Cry1,2* as negative elements. *Bmal1* is the only clock gene whose absence cannot be substituted, as its functional paralog's (*Bmal2*) expression is tissue-specific and dependent on *Bmal1*. Its rhythmic expression is controlled by a secondary feedback loop in which *Rorα,β,γ* and *Nr1d1,2* (also known as *Rev-Erbα,β*) participate as positive and negative elements, respectively. In additional feedback loops, the rhythmic expression of *Nr1d1,2* is directly controlled by *Clock, Npas2* and *Bmal1*, and the expression of *Rorα,β,γ* is controlled by *Dbp* (regulated by *Clock* and *Bmal1*) and *Nfil3* (also known as *E4bp4*, regulated by *Rorα,β,γ* and *Dbp*). All loops are interdependent, which enables their mutual coordination. The approximately 24-hour period of TTFL is maintained by complex posttranscriptional (e.g. RNA methylation) and posttranslational mechanisms mediated by several kinases (CK1ε, CK1δ, GSK3β, etc.), ubiquitin ligases (β-TrCP, FBXL3,21), enyzymes involved in protein glycosylation, acetylation or SUMOylation that modulate the activity, stability or dynamics of the bidirectional nuclear-cytoplasmic transport of clock proteins (reviewed in [39]). It is important to note that although the genes referred to as "clock genes" are necessary for the clock machinery, they also fulfil functions outside the circadian system. Therefore, genetic deletion of any of the clock genes can affect the function of the clock, but also disrupt other cellular functions *via* clock-independent mechanisms [40-42]. Conversely, since TTFL-indepen-dent [43] circadian regulation has been documented as a likely evolutionarily conserved mechanism even in human cells [44], deletion of the clock genes may theoretically not abolish rhythmicity at all levels of biological regulation.

While the vast majority of cells are capable of generating cellular circadian rhythms, there is great variability in the self-sustainability and robustness of the rhythms, which is largely determined by the level of the intercellular communication network that facilitates rhythmicity at both the cellular and tissue level. The SCN is a unique example of a clock built of cellular oscillators that are more or less self-sustaining when separated from each other [45], but generate much more robust rhythmicity when their intercellular communication is preserved (reviewed in [13]). The intercellular communication depends on sodium channel action potentials [46], interneuronal neuropeptide signaling [47-49] and neuron/glia interactions [50-52]. In addition, a recent study pointed to the involvement of cilia in a subpopulation of SCN neurons as an important subcellular component for their synchronization [53]. For synchronization of the peripheral clocks, inter-cellular communication was not expected to be important [54], as they were thought to be driven by SCN-related signals. However, recent research has shown that such communication, which is likely paracrine, can contribute to the rhythmicity of cellular oscillators in hepatocytes [55]. These results indicate that the circadian system must be synchronized at multiple levels – *level 1*: with the external environment, *level 2*: between central and peripheral clocks, and *level 3*: between cellular oscillators in the same tissue. This organization highlights the potential multiple targets where the coherence of the circadian system can be compromised.

What do we mean by chronodisruption?

The term chronodisruption was introduced as an equivalent to "circadian disruption" to refer to disrupted circadian regulation in consequence of misalignment of entraining signals with environmental cycles, causing internal desynchrony between oscillators in the organism. Many comprehensive reviews have been published on this topic [56-59].

In pre-industrial communities that were dependent on sunlight, chronodisruption was unlikely due to behavioral activities associated with daylight and the onset of sleep linked to sunset. The spectrum and intensity of light from fire or the moon, the only available light sources, were not efficient enough to disrupt synchrony with the solar cycle as people spent much time outdoors and were maximally exposed to natural daylight. Moreover, the journey across time zones, if happened, took much longer than necessary to resynchronize the clock to solar time at the destination. In

the real life of modern societies where electric light sources are available, chronodisruption may result from the decision to postpone our activities to the time interval that our clock determines as "subjective night". It happens due to personal choices related to work requirements or leisure activities. Additionally, the use of artificial light to extend our active time into the night appears to be facilitated by our personal preference for timing of activity/sleep, known as chronotype [60-62]. The combination of these factors leads to chrono-disruption.

Ambient electric light at night per se ("light pollution") is often blamed for chronodisruption and its health consequences. However, it is important to clarify that this light would not exist if there was no demand for people to be active at night and for most people in the population, unlike for animals and plants in the wild, exposure to light at night is actually controllable. Humans can adapt behavior to the conditions of life in urban society by exposing to outdoor light as much as possible during the day, shielding ambient light with blinds at night, and avoiding nighttime activities associated with light exposure whenever possible. Using the findings from chronobiology research provides us with a guide on how to properly synchronize our internal clock and points to the importance of such adaptation to the conditions of modern societal lifestyles. While light at night is massively medialized as a cause of chronodisruption, we hear much less about the lack of light during the day. City dwellers in particular spend most of the day indoors and are shielded from natural daylight [63]. Houses, schools and factory halls are often built with inadequate indoor lighting, and the intensity and spectral properties of light from electric bulbs cannot fully replace natural daylight. As a result, urban population is not exposed to sufficient natural daylight, which is crucial for proper entrainment of circadian clocks with solar cycle. Chronotype *per se* is also not the cause of chronodisruption, as people with late chronotype, who prefer to shift their activities to the late night hours, are able to entrain to the solar cycle by exposing themselves fully to natural daylight and avoiding light at night [64].

Furthermore, in real life, many people voluntarily place themselves in situations that lead to internal desynchronization when they are on trans-meridian flights that span more than six time zones. Under such conditions, most people experience jetlag symptoms because their internal time is dictated by the endogenous clock, that is out of sync with the social time at their destination [65, 66]. These symptoms persist until their clocks attain resonance with the new environmental cycles and begin to fulfill their role in the temporal organization of physiological processes. For the majority of the population, such a situation is not frequent and long-term impact on health is not documented. Nevertheless, this is probably the best evidence of the benefits of having our clocks well-synchronized that each person can experience individually.

Of course, modern society requires human-powered services around the clock, forcing part of the population to work during the night, expose themselves to intensive artificial light, and eat and sleep at inconvenient times of the day. Around 20 % of the world's population work night shifts, forcing them to be physically, mentally and metabolically active during their subjective night [67]. Despite progressive technological development, including robotization and artificial intelligence, many professions, such as healthcare, will continue to require human labour around the clock. Therefore, we need to understand the biological underpinnings of this altered human behavior and ascertain its link to pathology in order to reduce the detrimental impact on society's health.

How to study chronodisruption?

Using animal models, chronodisruption can be experimentally induced genetically (by disruption or alteration of molecular clocks in various organs), surgically (by removal of the suprachiasmatic nuclei as the site of the central clock) or by environmental conditions (by exposure to conditions that jeopardise synchrony between internal and social time). For the latter, several methods have been developed in chronobiological research that effectively induce internal desynchrony via various mechanisms, such as long-term exposure to constant light (LL), repeated shifts in the LD cycle, irregular LD regimen, a non-24-hour LD cycle, and decoupling access to food and sleep time. The research is mainly conducted with laboratory rodents, that are nocturnal species and differ in their sensitivity to the choronodisruption protocols [57, 68]. Therefore, the results can be translated to the human situation with limitations [69].

In experimental research on humans, it is a question of ethical standards whether and to what extent subjects can be exposed to unfavorable conditions that could affect their health. The gold standard for

experimentally inducing chronodisruption is the forced desynchrony protocol [70, 71], in which subjects are exposed to a 20- or 28-hour daily regimen of the scheduled sleep/wake cycle and mealtime in dim LD cycle. The period of this cycle is too extreme for the SCN clock to entrain, so that after a few days it becomes uncoupled from the imposed sleep/wake cycle and begins to run freely with the endogenous period. As a result, such subjects sleep when their clocks are preparing their bodies for activity and vice versa, as is the case with night shiftwork. These studies provided important insights into the impact of chronodisruption on circadian organization at the level of circadian regulation of the transcriptome [72] and the development of pathology [73]. Strikingly, hyperglycemia, insulin resistance, poor glucose tolerance, increased arterial pressure, and reversed cortisol rhythms developped in human participants exposed to a forced desynchrony protocol when they were approximately 12 hours out of phase with the environmental LD cycle [73]. The advantage of these studies is their well-controlled design and the ability to accurately capture the actual state of the circadian clock, but they are limited by high costs and a small sample size that cannot achieve population representativeness. Therefore, large-scale, population-representative studies are being conducted to analyze correlations between circadian misalignment and health parameters (see below).

Multilevel effect of chronodisruption on circadian regulation in our body

Chronodisruption disrupts synchrony in the circadian system at all levels defined above. This is because the clocks in cell populations that span anatomical boundaries are sensitive to the same entraining signals, and the clocks in cells of the same anatomical structure can be sensitive to different entraining signals (Fig. 1).

Food intake restricted to rest/sleep time only (mistimed feeding) impairs synchrony between the SCN clock and clocks in metabolically relevant tissues [25]. However, the desynchrony has more levels. An example from our recent study showed that desynchrony can occur even between functionally distinct cellular subpopulations of the same organ [74]. We found that restricting food intake to the light phase in nocturnal animals (sleep time) robustly shifted the circadian clock in the pancreatic islets to feeding time, just like the clock

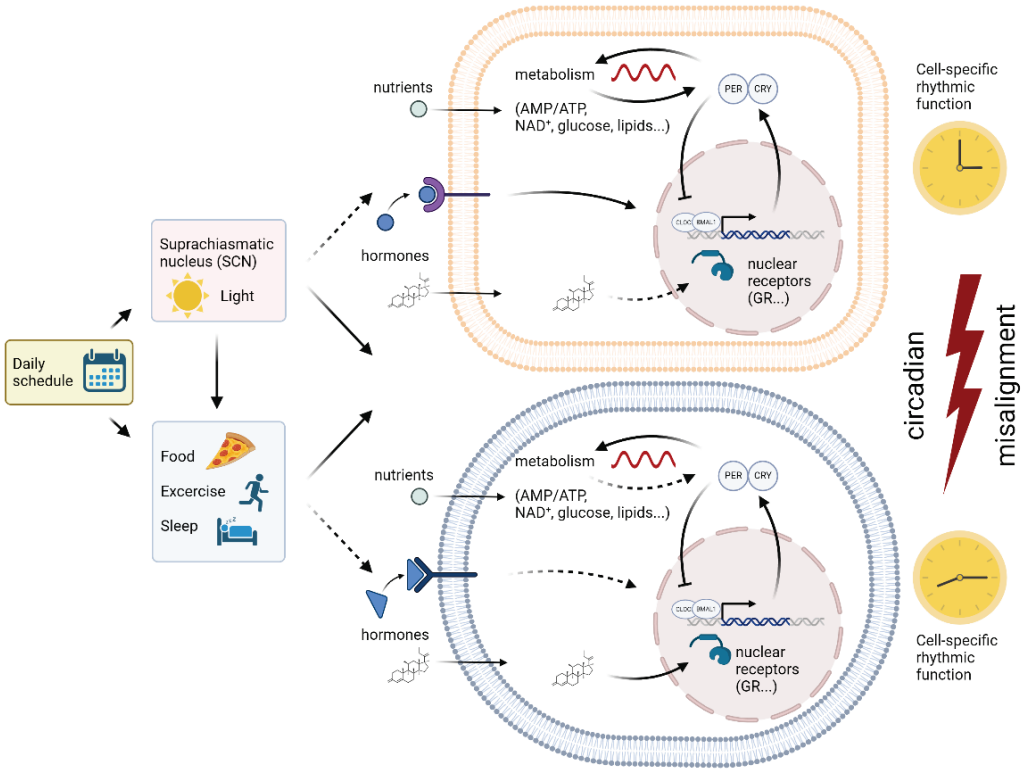

Fig. 1. Circadian misalignment results from desynchrony among cellular oscillators. Circadian clock in different cell types (depicted by different shapes and colour) may differ in their sensitivity to rhythmic cues, such as light-dark cycle entrained SCN cues, activity or food, resulting in circadian misalignment between their rhythmic functions when the cues are out of sync with each other (for example due to social jetlag). Full vs. dashed arrows indicate differences in relative strength of entrainment. Created with BioRender.com

in the liver, but severely dampened the clocks in the cells of the exocrine pancreatic tissue [74]. The mechanism behind this effect was attributed to a different sensitivity of the clocks in these two functionally distinct cellular subpopulations to two different hormones, insulin and corticosterone. These hormones are released rhythmically, with their peaks synchronized under *ad libitum* conditions, but uncoupled under the reversed feeding protocol [74]. The effect of mistimed feeding on the suppression of the rhythmicity of the exocrine pancreas is rather unexpected and may underlie its dysfunction. It gives rise to speculation about its initially potential adaptive value. If food is not provided at the opportune and predictable time for a short period, it might be more advantageous to turn off the clock, which is not needed to anticipate it, but to operate on an "as-needed" basis to supply the organism with energy as needed for survival. An analogous situation arises for organisms living in an environment where there are no daily cycles (high latitudes, deep water/caves), where anticipating daily cycles is not meaningful [7, 75]. However, in the case of presence of daily cycles, such a situation leads to pathology.

Experimental chronodisruption impairs cardiometabolic health – lessons from "old-fashioned" animal models

Research on the relationship between chronodisruption and cardiometabolic disorders has focused on revealing their causality. One of the “classic studies” demonstrating the impact of chronodisruption on cardiovascular health used tau mutant hamsters, an animal model with a spontaneously mutated clock. The hamsters carried a single autosomal mutation in the gene encoding the enzyme *casein kinase 1 epsilon* (CKIe), which resulted in a significant shortening of the period of free-running activity rhythms (to approximately 22 hours in heterozygotes and 20 hours in homozygotes) [76]. Keeping the tau mutant hamsters in LD12:12 shortened their survival time and led to the development of renal dysfunction and cardiomyopathy with fibrosis and impaired contractility. This effect occurred only in the heterozygotes but not in the homozygotes, which remained free-running because the LD cycle was out of entrainment range for their SCN clock [77, 78]. Survival and pathology was improved if the heterozygotes were either SCN lesioned and thus became arrhythmic, or if they were maintained on their endogenous day length of 22 hours (LD11:11). These studies paved the way for the current understanding that long-term maladaptation to environmental cycles, which is highly relevant to the human situation, has adverse health impact. Moreover, these studies showed that such a situation is more harmful than that resulting from the absence of the clock or its inability to predict environmental cycles [79]. In this case, when investigating the impact of a non-resonant clock on health, the tau mutant hamster was discovered not only as a model with a mutated clock, but also as an experimental model for the cardiovascular disease.

The opposite approach was based on the study of the circadian phenotype of an animal model already known for the spontaneous development of cardiometabolic disorders, namely the *spontaneously hypertensive rat* (SHR), that identified the rat strain as a model for a maladapted circadian system [80, 81]. The SHR strain has been used as a popular model to study the mechanism of hypertension since its introduction in the early sixties of the last century [82], and later it was also used as a model for *attention deficit hyperactivity disorder* (ADHD) [83] or metabolic syndrome [84]. From this perspective, and in comparison to mouse models with targeted deletion of a single gene, the model is considered outdated for studies on the mechanisms of disrupted circadian regulation. However, the pathophysiology of most disorders, including hypertension or ADHD, involves multiple genes and signaling pathways, so this model remains a valuable complementary tool for studying the complex mechanisms involved in the development of these disorders. Several earlier studies pointed to the possibility that circadian regulation in SHR differs from that of normotensive controls. In particular, the early discovery that the day/night ratio of blood pressure is reduced [85] and sleep patterns are modulated [86] prompted investigation of the circadian system in SHR. One study reported increased expression of the *vasoactive intestinal polypeptide* (VIP) gene in the SCN of SHR [87], which may influence SCN clock function by enhancing intercellular communication [49]. The finding fits with a recent report that SCN-driven behavioral rhythms are more stable and less fragmented in SHR [88]. However, the amplitude of clock gene expression profiles in the SCN of SHR was not reduced [80]. The period of the peripheral clock of SHR fibroblasts measured in vitro with real-time recordings of the *Bmal1-dLuc* reporter also did not differ from that of controls [32]. Furthermore, although SHR did not differ in level of locomotor activity in LD12:12 or constant

darkness compared to normotensive controls, the amplitudes of SHR activity rhythms were reduced in both conditions [80]. For the clock gene and clock-controlled gene expression profiles in the peripheral tissues of SHR, higher amplitudes were reported in the heart but not in the aorta [89] and liver [80], while a reduced amplitude was found in the colon [80]. In addition, the onset of behavioral activity and phases of clocks were significantly advanced in the SCN and colon in SHR compared to controls [80]. This reflects the positive phase angle of entrainment of their clocks relative to the LD cycle, which resembles an earlier chronotype in humans (see below).

Even more striking evidence of the abnormal circadian phenotype of SHR came from the finding that SHR were more sensitive to mistimed feeding compared to controls. SHR developed earlier and more pronounced anticipatory activity prior to the presence of food, and their activity profile shifted entirely to mealtime, in contrast to control rats, which only redistributed their activity into two bouts, one nocturnal and one associated with the anticipation and presence of food [81]. As a potential mechanism, the expression rhythm of clock gene *Bmal2* (a paralog of *Bmal1*) increased in the liver of SHR in contrast to controls and was advanced to a similar phase as *Bmal1* due to the altered feeding regime. It is tempting to speculate that the higher response of the *Bmal2* gene to mistimed feeding was likely the reason why the expression profiles of other clock genes were not attenuated as in controls and were more shifted to mealtime in SHR, because the facilitated BMAL2::CLOCK-mediated transactivation could assist the canonical BMAL1::CLOCK mechanism and enhance clock oscillations [81]. Since *Bmal2* expression in the liver is dependent on its paralog *Bmal1*, the data are consistent with other studies showing a possible direct link between the pathological phenotype of SHR and the circadian system through an association between *Bmal1* promoter polymorphisms and metabolic syndrome in SHR [90]. A better understanding of the mechanisms would be necessary as the *Bmal1* promoter acts as one of the major "hubs" linking the circadian system to metabolism (reviewed in [91]).

Surprisingly, despite the well-defined cardiometabolic pathology and circadian abnormality of SHR, evidence for their causal relationship is sparse, and the important question of whether circadian system dysfunction is involved in the development of the disease remains to be answered. Nevertheless, several studies suggest that strengthening circadian regulation may improve the pathologic phenotype of SHR. The introduction of a regular feeding regime at an appropriate time of day led to a restoration of the diurnal rhythm of blood pressure as well as clock- and metabolism-related gene expression in cardiovascular tissues [92]. In addition, caloric restriction prevented hypertension in SHR [93]. In our opinion, the most compelling evidence comes from a study in which both circadian disruption and pathology were reversed by aligning the developing clocks of SHR pups with LD cycle since birth [94]. Maternal care provided by a foster mother of a normotensive control strain (Wistar rat) promoted the development of rhythmic *Bmal1* expression in the SCN clock as well as the clock-driven activity/rest rhythm in SHR pups. Importantly, the activity/rest rhythm of the pups was aligned with the external LD cycle, thereby protecting the SHR pups from developing the typical phase-advanced phenotype. Surprisingly, proper entrainment of the circadian system by maternal care was able to improve the dampened rhythm of the colonic clock as well as certain cardiovascular functions. Specifically, the increase in heart rate that SHR spontaneously develops with age was not present in offspring raised with aligned circadian clocks [94]. The results provide evidence that modulation of circadian regulation can attenuate pathological symptoms in SHR, even when the development of heart rate is genetically programmed.

What can we learn from human population studies?

It is estimated that up to half of the population in industrialized societies have a circadian clock that is out of sync with their daily schedule [95], with cardiovascular [96, 97] and metabolic [98, 99] diseases being the most common consequences. As mentioned above, population-based studies are an alternative way of gaining insight into the relationship between chronodisruption and human health. Their advantage is that they reflect the real situation in a larger population sample, but their disadvantage is low level of their control and the fact that they cannot prove causality, but only correlation with a study-specific degree of statistical power, which makes the conclusions less straightforward. Here the postulate "*the larger the sample, the higher the statistical power*" appears to be even more relevant. It is also important to keep in mind that this type of study

requires multifactorial statistics. Let us give an example of a pitfall when the multifactorial complexity is underestimated. In the literature and in the media, we are confronted with statements such as "*light pollution causes cancer because it is more common in people who live in larger cities and thus are exposed to more light at night*". This statement is based on making a causal link between the light-induced suppression of nocturnal production of the hormone melatonin in the pineal gland and the results indicating a possible protective role of the hormone in the development of certain types of cancer. It may be true that there is more light pollution in larger cities, and it may also be true that cancer is more common in larger cities, but can we really approximate causality so simply? Although these two factors could hypothetically be related, their direct link is rather vague and supported by weak evidence. Urban populations are certainly more exposed to many other potent cancer risk factors than rural populations. Furthermore, there is insufficient evidence that the light-senstitive melatonin produced in the pineal gland is responsible for the anticancer effects, considering that its main physiological role is to transmit information to the organism about the changing ambient light. Instead, it is more likely that the presumably not photosensitive melatonin produced in various tissues plays a role in these processes [100]. As mentioned above, nocturnal light is undoubtedly a dominant factor that disrupts the synchrony of the circadian clock with the LD cycle, but the same is true for ambient lighting in the city and for indoor light emitted by overhead lamps or electronic devices such as televisions or computer monitors. It is well documented that constant light, when chronic, disrupts circadian regulation in nocturnal species that are highly light-sensitive, however, it does not affect their sleep but their activity during nocturnal wakefulness [101]. In humans, the opposite is true: light at night impairs sleep. In addition, recent evidence suggests that the mechanism by which the SCN clock perceives light from the retina differs between nocturnal rodents and humans [102]. These facts point to the limitations of simply transferring the data on the effects of light from nocturnal animals to humans.

Most population-based studies on the prevalence of chronodisruption are based on online internet surveys, which, although aimed at a large cross-national sample, are not fully representative (limited internet access, language barrier, level of interest, etc.). Filling out specialized questionnaires can also involve a bias resulting from knowledge of the purpose for which they are created. This can be overcome by a more difficult and more labor- and cost-intensive population-representative study, which may, however, be limited by political geography (country). Therefore, the results of both approaches are valuable for population-wide explorations.

Numerous studies that provided evidence of an association between chronodisruption and impaired health focused on pre-specified subpopulations, e.g., shift workers, specific employment types or extreme chronotypes. Rotational shift work is the most devastating factor associated with increased cardiovascular risk, obesity, high triglyceride and low HDL cholesterol levels as markers of the development of metabolic syndrome [103]. Interestingly, in the population of non-shift workers similar cardiovascular and metabolic health markers correlated with (1) an extreme chronotype, defined as a preference for sleep time on free days significantly deviating from the population mean [63, 104-106], and (2) social jetlag, defined as the extent of misalignment between sleep time on work days and free days [107-110]. Chronotype and social jetlag are closely inter-related and positively correlated, and both concepts have been described in more detail elsewhere [62, 111]. Therefore, population studies indicate that chronodisruption, resulting from the maladaptation of the internal clock to solar time, whether induced by shiftwork or other lifestyle factors, exerts a comparable impact on cardiometabolic health.

Conclusion

Technological development is accelerating rapidly and outpacing human evolutionary adaptation. There is strong evidence that chronodisruption results from this conflict and is associated with adverse health outcomes, of which cardiometabolic disorders are the most prevalent. To avoid the impact on our health, human society cannot return to preindustrial lifestyle. Instead, further research is needed to uncover the underlying mechanisms to propose strategies for knowledge-based adaptation of our everyday life and protection of human health in the face of rapidly evolving environmental changes.

Abbreviations

ADHD, Attention Deficit Hyperactivity Disorder; BMAL1,2, Brain and Muscle Arnt-Like protein 1, 2;

β-TrCP, Beta-Transducin Repeat Containing Protein; CK1ε, δ, Casein Kinase 1 epsilon, delta; CLOCK, Circadian Locomotor Output Cycle Kaput; *dLuc*, destabilized Luciferase; FBXL3, 21, F-Box And Leucine Rich Repeat Protein 3, 21; GSK3β, Glycogen Synthase Kinase 3 Beta; LD, Light-Dark cycle; LL, constant light; SHR, Spontaneously Hypertensive Rat; SCN, Suprachiasmatic Nucleus; TTFL, Transcriptional-Translational Feedabck Loop; VIP, Vasoactive Intestinal Polypeptide.

Conflict of Interest

There is no conflict of interest.

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