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Mammalian circadian systems: Organization and modern life challenges

Anna-Marie Finger[1,2] | **Achim Kramer**[1,2]

[1]Laboratory of Chronobiology, Institute for Medical immunology, Charité Universitätsmedizin Berlin, Berlin, Germany

[2]Berlin Institute of Health (BIH), Berlin, Germany

Correspondence
Anna-Marie Finger, Laboratory of Chronobiology, Institute for Medical immunology, Charité-Universitätsmedizin, Charitéplatz 1, 10117 Berlin, Germany.
Email: anna-marie.finger@charite.de

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Abstract

Humans and other mammalian species possess an endogenous circadian clock system that has evolved in adaptation to periodically reoccurring environmental changes and drives rhythmic biological functions, as well as behavioural outputs with an approximately 24-hour period. In mammals, body clocks are hierarchically organized, encompassing a so-called pacemaker clock in the hypothalamic suprachiasmatic nucleus (SCN), non-SCN brain and peripheral clocks, as well as cell-autonomous oscillators within virtually every cell type. A functional clock machinery on the molecular level, alignment among body clocks, as well as synchronization between endogenous circadian and exogenous environmental cycles has been shown to be crucial for our health and well-being. Yet, modern life constantly poses widespread challenges to our internal clocks, *for example* artificial lighting, shift work and trans-meridian travel, potentially leading to circadian disruption or misalignment and the emergence of associated diseases. For instance many of us experience a mismatch between sleep timing on work and free days (social jetlag) in our everyday lives without being aware of health consequences that may arise from such chronic circadian misalignment, Hence, this review provides an overview of the organization and molecular built-up of the mammalian circadian system, its interactions with the outside world, as well as pathologies arising from circadian disruption and misalignment.

KEYWORDS

circadian disruption, circadian misalignment, circadian morbidities, mammalian circadian clocks

1 | THE MAMMALIAN CIRCADIAN SYSTEM

The beginnings of biological rhythms research go back to the 18th century when Carl Linnaeus developed the 'flower clock' to predict time based on the flowering plants across the solar day. Nevertheless, chronobiology is a relatively young field with its molecular basics having been discovered only about 50 years ago. Today it is well accepted that endogenous circadian clocks serve to anticipate daily environmental changes, most importantly the light-dark cycle, to optimize the temporal coordination of physiology and behaviour. Thus, the increasing awareness about the crucial importance of circadian systems for human health, well-being and general physiology has cumulated in the 2017 Nobel Prize for circadian research, awarded to M. Rosbash, M. Young and

JC. Hall for their discovery of the molecular mechanisms controlling circadian rhythms.[1,2]

Circadian clocks are believed to have evolved in adaptation to periodically reoccurring environmental Zeitgebers (German for 'time giver'), for example light-dark, nutritional and temperature cycles.[3] Indeed, being 'circadian' provides a fitness advantage to organisms,[4] probably because it guarantees the temporal coordination of behaviour with ambient conditions, thereby optimizing survival-related activities such as foraging or encounters of predators and mating partners. In addition, endogenous clocks self-sustain rhythmic physiology even when environmental entrainment signals are absent, thereby temporally separating incompatible biological processes such as sleep and wakefulness or anabolism and catabolism. Experimental studies have accumulated evidence for the adaptive value of circadian systems. Most noteworthy, early chronobiological experiments using cyanobacteria strains with different circadian periods clearly demonstrated that resonance between environmental and intrinsic circadian rhythms provides a fitness advantage to bacteria with periods that match the external light-dark cycle.[5] Similarly, studies in mammalian species have demonstrated that functional circadian clocks are crucial for survival: behaviourally arrhythmic animals are exposed to increased predator attacks or mistime their hibernation.[6-8] Moreover, under laboratory conditions, housing of mice in abnormal light-dark cycles leads to increased mortality, emphasizing the importance of living in resonance with the outside world.[9]

2 | SYSTEM-LEVEL ORGANIZATION OF MAMMALIAN CLOCK NETWORKS

In mammals, including humans, the circadian system is hierarchically organized with the suprachiasmatic nucleus

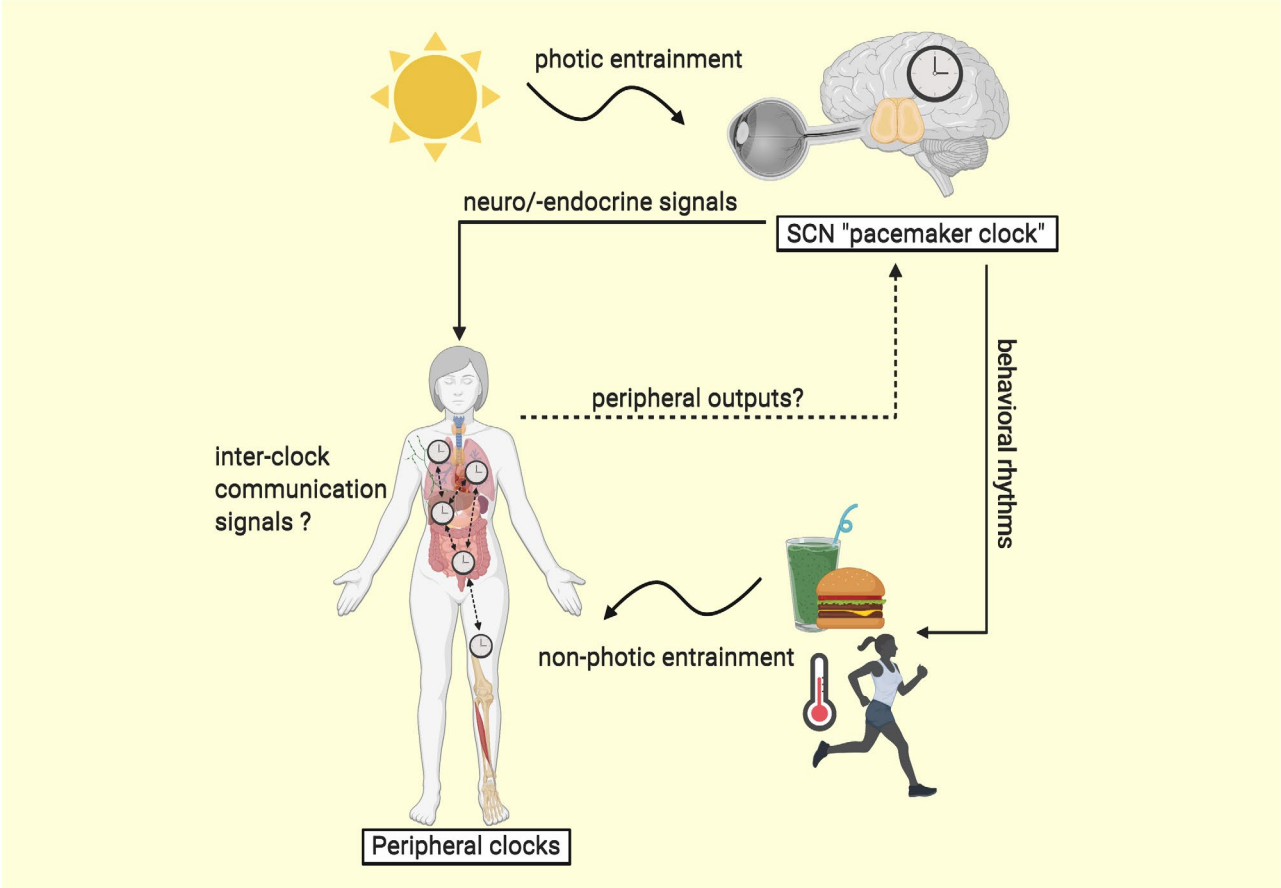

FIGURE 1 Organization of mammalian circadian systems. Mammalian circadian clocks are organized hierarchically. The suprachiasmatic nucleus (SCN) or pacemaker clock is superior to other body clocks as it is required for entrainment of the mammalian circadian system to the environmental light-dark cycle, as well as for driving rhythms in locomotor activity and hormones. Photic entrainment information, mainly sensed by intrinsically photosensitive retinal ganglion cells in the retina, is transmitted to the SCN *via* the retinohypothalamic tract (RHT). Subsequently the SCN aligns body clocks with each other and with the light-dark cycle by forming efferent connections that regulate endocrine and behavioural rhythms. In addition, peripheral clocks can entrain to rest-activity, feeding-fasting and (body) temperature cycles that may or may not be driven by the SCN. If and how body clocks exchange mutual time information or give feedback about their entrainment state to the pacemaker clock remains to be investigated in detail. Figure created with BioRender

(SCN) on top (Figure 1). In the 1970s, the SCN was discovered as endogenous mammalian clock that governs hormonal and behavioural rhythms.[10-12] As pacemaker clock, the SCN is very important for photic entrainment and transmission of light-dark signals to downstream tissue clocks. It consists of two bilaterally paired clusters made up by several thousand densely packed neurons located in the anterior hypothalamus superior to the optic chiasm. Organization and circuitry of the SCN are complex, comprising many different cell types, afferent and efferent connections, as well as heterogenous circadian gene expression and neuropeptide signalling.[13,14] Each SCN is divided into core and shell with region-specific functional roles that remain to be explored in detail.[13] Briefly, the SCN core contains vasoactive intestinal polypeptide (VIP) expressing neurons, which are important for light-perception *via* the retinohypothalamic tract (RHT) and tissue synchrony. The shell region, rich in arginine vasopressin (AVP) expressing neurons, is innervated by the hypothalamus, limbic areas and the SCN core and appears to be involved in setting the phase of non-SCN brain and peripheral body clocks.[15]

Diurnal changes in light intensity are transmitted to the SCN and intergeniculate leaflet (IGL) *via* intrinsically photosensitive retinal ganglion cells (ipRGC). These ipRGC are specialized neurons within the retina that, unlike other retinal ganglion cells, express the photopigment melanopsin (*OPN4*) and mediate light responses even when rod and cone photoreceptors are non-functional.[16-18] Interestingly, ectopic expression of melanopsin renders also peripheral cells photosensitive and enables phase shifts of circadian oscillations in response to light.[19,20] ipRGC are required for SCN driven photoentrainment of mammalian circadian systems to the environmental light-dark cycle[21,22] and even IGL-SCN circuit dependent non-photic entrainment to food in the early postnatal period.[23] At pre-synaptic connections from the RHT to the SCN electrical are transformed into biochemical signals resulting in the release of the neurotransmitters pituitary adenylate cyclase-activating polypeptide (PACAP) and glutamate, which activate receptor dependent kinase signalling and induce the elevation of intracellular calcium (Ca^{2+}) and cyclic AMP (cAMP) levels.[24] Ultimately, this results in the immediate early induction of the so-called clock genes *Period1* (*Per1*) and *Period2* (*Per2*),[25,26] as well as subsequent time-of-day dependent phase responses of the SCN clock, thereby enabling entrainment to the light-dark cycle.

Predominantly, the SCN forms efferent connections to intermediate neurons in other brain regions, mainly the hypothalamus, which then innervate endocrine neurons passing on SCN-derived information to non-SCN brain clocks and the periphery by rhythmic hormone release.[27] Alternatively, the SCN may project directly to endocrine or pre-autonomic neurons to regulate neuroendocrine responses. In addition to neuronal outputs, the SCN produces diffusible signals. Transplantation of encapsulated SCN, has been demonstrated as sufficient for the restoration of behavioural but not endocrine rhythms,[28,29] suggesting that SCN derived paracrine factors can signal to surrounding brain regions to regulate circadian locomotor activity rhythms. The origin and mechanism of diffusible SCN output signals are still mostly unknown, but prokineticin 2 (PK2), transforming growth factor alpha (TGF-α), cardiotrophin-like cytokine (CLC) and more recently neuronal-myocyte-specific enhancer factor 2D (MEF2D) have been proposed as candidate factors regulating behavioural rhythmicity.[30-33]

In addition to the SCN, virtually all peripheral and non-SCN central tissues possess cell-autonomous and self-sustained circadian oscillators, that can drive cell-type specific, rhythmic biological functions independently of the SCN.[34-37] Yet, the pacemaker clock is required to transmit environmental entrainment signals (from the light-dark cycle) to other, light-insensitive, body clocks to align their rhythms within the body and with the outside world. Without the SCN, phases of peripheral tissue rhythms drift apart.[36] As mentioned above, precise mechanisms and efferent connections underlying SCN-driven peripheral synchronization are still under investigation, but both, neuronal and humoral pathways are involved (Figure 1). In 2013, Gerber et al suggested that an unknown factor, rhythmically present in blood, may function as systemic synchronization signal through activating serum response factor, an important transcription factor inducing the immediate early expression of clock genes, *for example Per2*.[38] Whether or not abundance of this unknown serum factor is regulated by the SCN, remains to be investigated.

SCN-driven behavioural activity rhythms may lead to entrainment of peripheral clocks by regulating feeding-fasting, rest-activity and body temperature cycles. In vivo, restricted feeding, as well as voluntary (wheel running) and forced (treadmill exercise) activity cycles can serve as entrainment signals for peripheral clocks.[39-42] Mechanisms of food and activity driven entrainment remain to be explored in detail, however, rhythms in glucocorticoids (GC) appear to act as potent Zeitgebers for peripheral oscillators.[43,44] The SCN drives circadian glucocorticoid production directly *via* the hypothalamic-pituitary-adrenal (HPA) axis or indirectly *via* the autonomic nervous system.[45] However, rhythms in GC release may also be driven by local adrenal clocks, be induced during stress and physical exercise or following the ingestion of a meal *via* the activation of the HPA. Glucocorticoids act as resetting signal for circadian clocks by altering the molecular clock machinery.[46-48] Interestingly, glucocorticoid receptors have been found in peripheral tissues but not the SCN,[49] suggesting that GC act as entrainment signals specifically for peripheral clocks.[46] Indeed, presentation of feeding signals in anti-phase to rest-activity cycles (driven by the SCN) induces desynchrony among the SCN and peripheral body clocks.[39,50,51]

In addition to GC, feeding-related hormones and metabolites, as well as metabolic and redox states may transmit nutritional signals to circadian clocks.[52] Endogenous fluctuations in nicotinamide adenine dinucleotide (NAD^+) cofactors and H_2O_2,[53,54] as well as the activity of the NAD^+ sensing protein deacetylase SIRT1[55-57] can regulate circadian clocks. Insulin may alter circadian dynamics by inducing kinase depending signalling, including protein kinase B (AKT), mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways.[58,59] Moreover, gastrointestinal hormones, for example glucagon-like peptide 1 (GLP-1), vasoactive intestinal peptide (VIP), oxyntomodulin (OXM), gastrin, ghrelin and cholecystokinin (CCK) are rhythmically secreted and may regulate peripheral circadian clocks.[60-63] Recently, the mechanistic target of rapamycin (mTOR) pathway has been proposed as important link between feeding, metabolic state and peripheral circadian clock function.[64,65]

As mentioned beforehand, besides feeding-fasting and rest-activity cycles, the SCN governs rhythms in body temperature. Temperature cycles can entrain rhythms of peripheral tissues ex vivo and in vivo.[66,67] Transcriptional regulation of heat shock enhancer elements (HSE) by heat shock factor 1 (HSF1) or translational regulation of RNAs by cold-inducible RNA-binding protein (CRIP) are involved in temperature entrainment and responses of peripheral clocks to temperature pulses.[68-73]

The contribution of mutual interactions between non-SCN clocks, as well as of peripheral-to-central feedback mechanisms to the regulation of mammalian circadian systems on the organismal level are currently not well understood (Figure 1). Yet, progress in elucidating organizational levels of circadian networks has been made by targeted genetic (in) activation of selected tissue clocks. Koronowski et al (2019) showed that reconstituted liver clocks, in otherwise clock-less animals, are able to maintain circadian metabolism, whereas the majority of other rhythmic liver functions were lost. This suggested that full circadian tissue function requires input from other body clocks.[74] Interestingly, similar results were reported by Welz et al (2019) regarding the independence of skin circadian clock function.[75] Moreover, tissue-specific disruption of circadian clock function may result in alterations of the molecular clock machinery or circadian regulated transcriptomes in other tissues or even behavioural changes. An adipocyte-specific deletion of the core clock gene *Bmal1* (*Arntl*) has been reported to induce a shift in diurnal food intake and obesity in mice, likely by promoting altered neuropeptide expression in the hypothalamus.[76] However, when interpreting the effects of tissue-specific clock disruptions, one must recognize that gentic tools used to generate such models may not be completely specific and may induce off-target effects, for example due to overlapping tissue expression of promoters used to drive the expression of transgenes . For example, the aP2 (*Fabp4*) gene promoter, used to knock-out *Bmal1* specifically in adipocytes,displays limited expression in the brain[77,78], which may have impacted observed hypothalamic changes. Many cancerous tissues appear to emit signals that disrupt the molecular clock machinery at remote sites, inducing chrono-disruption of body clocks.[79-81] Moreover, the role of the microbiome as circadian regulator has gained interest in the last years. Intestinal microbiota compositions display circadian fluctuation. Mutual interaction between the gut microbiome and circadian clocks are known to alter host metabolism,[82,83] potentially *via* short chain fatty acids (SCFA) derived from bacterial fermentation.[84-86] Interestingly, SCFAs constitute a regulatory link to pancreatic islet cellular clocks by stimulating glucagon-like peptide-1 (GLP-1) secretion,[87] which can synchronize α- and β-cell oscillators.[88] In addition, gut microbiota-derived SCFAs act as Zeitgeber for mouse peripheral tissues.[85]

3 | THE MOLECULAR CLOCK MACHINERY

Circadian clocks can be found in virtually all cell types. Cellular oscillators are autonomous and self-sustained. This is because on the molecular level, circadian oscillations are generated and maintained by interlocked transcriptional-translational feedback loops (TTFL) between genes and their own protein products (Figure 2).[89] The so-called core loop consists of BMAL1 and CLOCK proteins that, as heterodimers, drive the expression of *Period* (*Per1-3*) and *Cryptochrome* (*Cry1-2*) genes by binding to E-box DNA sequences in the genes' promoters. After a defined time delay, necessary to generate about 24-hour oscillations, PERs and CRYs, as part of large macromolecular protein complexes,[90,91] translocate back into the nucleus and suppress the activity of their own activators BMAL1 and CLOCK. Interaction of PER and CRY proteins with casein kinase 1ε and 1δ (CK1ε/δ) is crucial for the generation of circadian rhythms as it regulates PER protein abundance, localization and half-life. Expression of casein kinase mutants is associated with altered circadian periods and sleep disorders.[92,93]

In addition to the core clock loop, accessory loops, consisting of RORs, REV-ERBs (NR1D1-2), DBP and NFIL3 (E4BP4) (Figure 2), fine-tune circadian oscillations generated by the core loop (periods and amplitudes). Besides *Pers* and *Crys*, BMAL1/CLOCK heterodimers drive the E-box dependent transcription of the retinoic acid-related orphan nuclear receptors *Rev-erb*-α/β, the RAR-related orphan receptor *Ror*-α/β, as well as of the D site albumin promoter binding protein *Dbp*. Expression of both, *Nfil3* and *Bmal1*, is regulated by the competitive action of REV-ERBs and RORs on their ROR/REV-ERB (RRE) enhancer elements. Depletion or loss-of-function of REV-ERBs and RORs leads to a shortened period of locomotor activity rhythms in mice under free-running

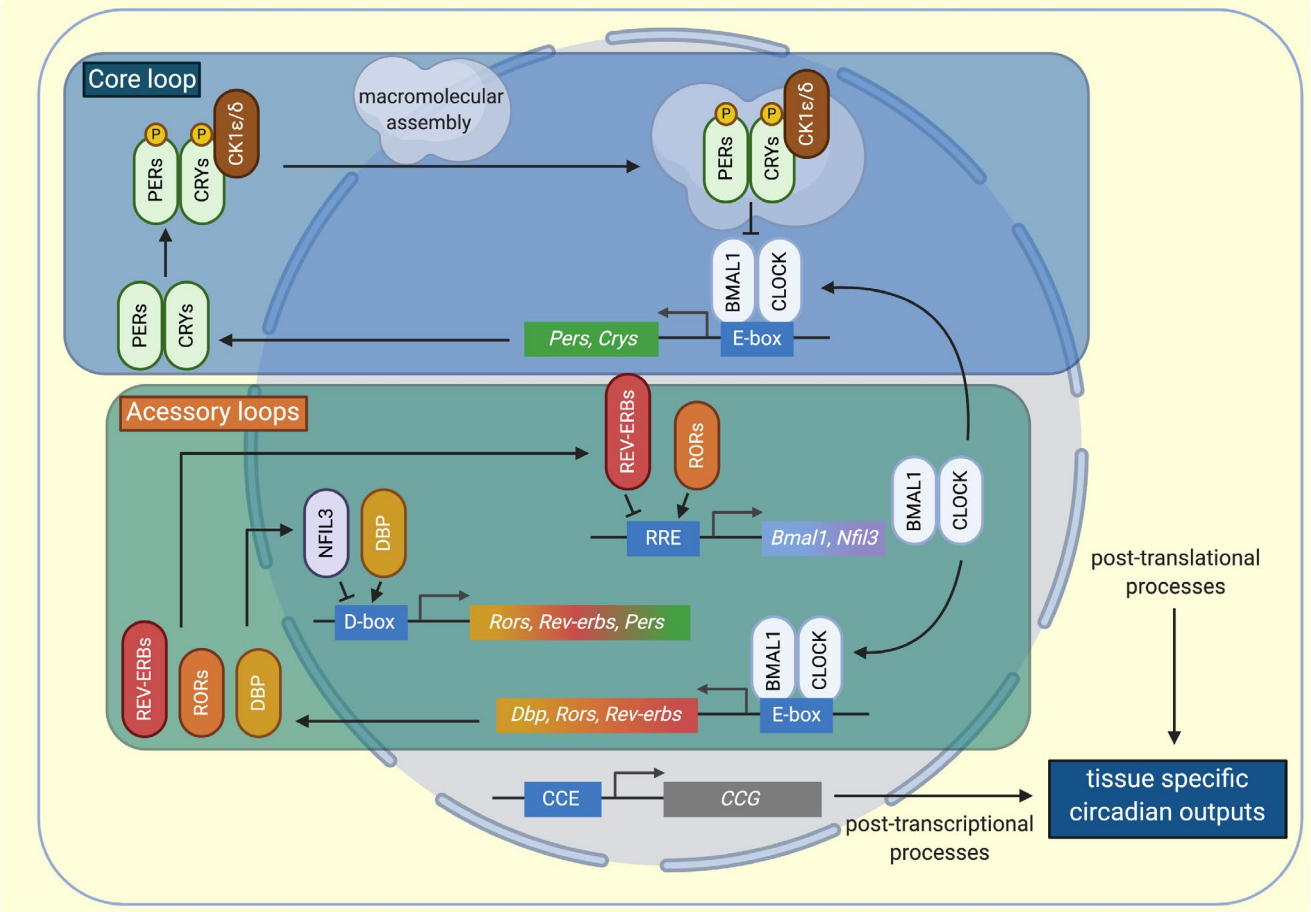

FIGURE 2 The molecular clock machinery in mammals. Circadian oscillations on the cellular level are generated by negative auto-regulatory feedback loops, so-called transcriptional-translational feedback loops (TTFL), between genes and their protein products. The rhythm generating core loop consists of BMAL1/CLOCK heterodimers that drive the E-box dependent and rhythmic expression of their target genes *Period* (*Per1-3*) and *Cryptochrome* (*Cry1-2*). After a biological delay, necessary for the generation of circadian rhythms, PER and CRY proteins, as part of large macromolecular protein assemblies, including casein kinase 1 (CK1), translocate back into the nucleus and suppress BMAL1/CLOCK activity. Two accessory loops, including the D-box regulators *Dbp* and *Nfil3*, as well as the RRE regulators *Rev-erb-α/β, Ror-α/β,* serve to fine-tune rhythms generated by the core loop *via* the transcriptional regulation of core clock genes. Tissue-specific circadian outputs are generated by the interplay of rhythmic transcriptional, post-transcriptional and post-translational processes (CCE = clock-controlled enhancer element, CCG = clock-controlled gene). This Figure was created with BioRender.

conditions.[94-96] In addition, DBP and NFIL3 proteins competitively regulate D-box dependent gene expression of *Rev-erb*, *Ror* and *Per* genes. Because of their anti-phasic expression and antagonistic transcriptional activity, DBP and NFIL3 have been proposed to regulate amplitudes of circadian oscillations.[97,98]

Besides the molecular TTFL, the rhythmic regulation of tissue-specific biological processes is controlled *via* the activation of clock-controlled enhancer elements (CCE), for example E-boxes, D-boxes and RREs, in the promoters of clock-controlled genes. Indeed, 5%-20% of transcripts, proteins and metabolites exhibit circadian rhythms in a tissue-specific fashion.[99-107] Interestingly however, rhythmic protein expression is not always correlated with rhythmic transcription, suggesting that post-transcriptional and post-translational processes are involved in driving circadian oscillations on the cellular level.[108-110]

4 | DEVELOPMENT OF CIRCADIAN CLOCKS

The mammalian circadian system develops gradually throughout development (for review see[111]). Whereas circadian rhythmicity, despite the expression of clock genes, has not been observed in germ line cells, zygotes, early embryos, as well as embryonic and induced pluripotent stem cells,[112-116] foetuses show circadian rhythms in behaviour (foetal breathing and limb movement), humoral factors and cardiovascular function (foetal heart rate). To what extent foetal circadian rhythms are self-sustained or driven by maternal circadian rhythms, as well as which communication factors promote synchronization between mother and foetus, is still under investigation. In vitro studies suggest that the cell-autonomous generation of circadian oscillations depends on the

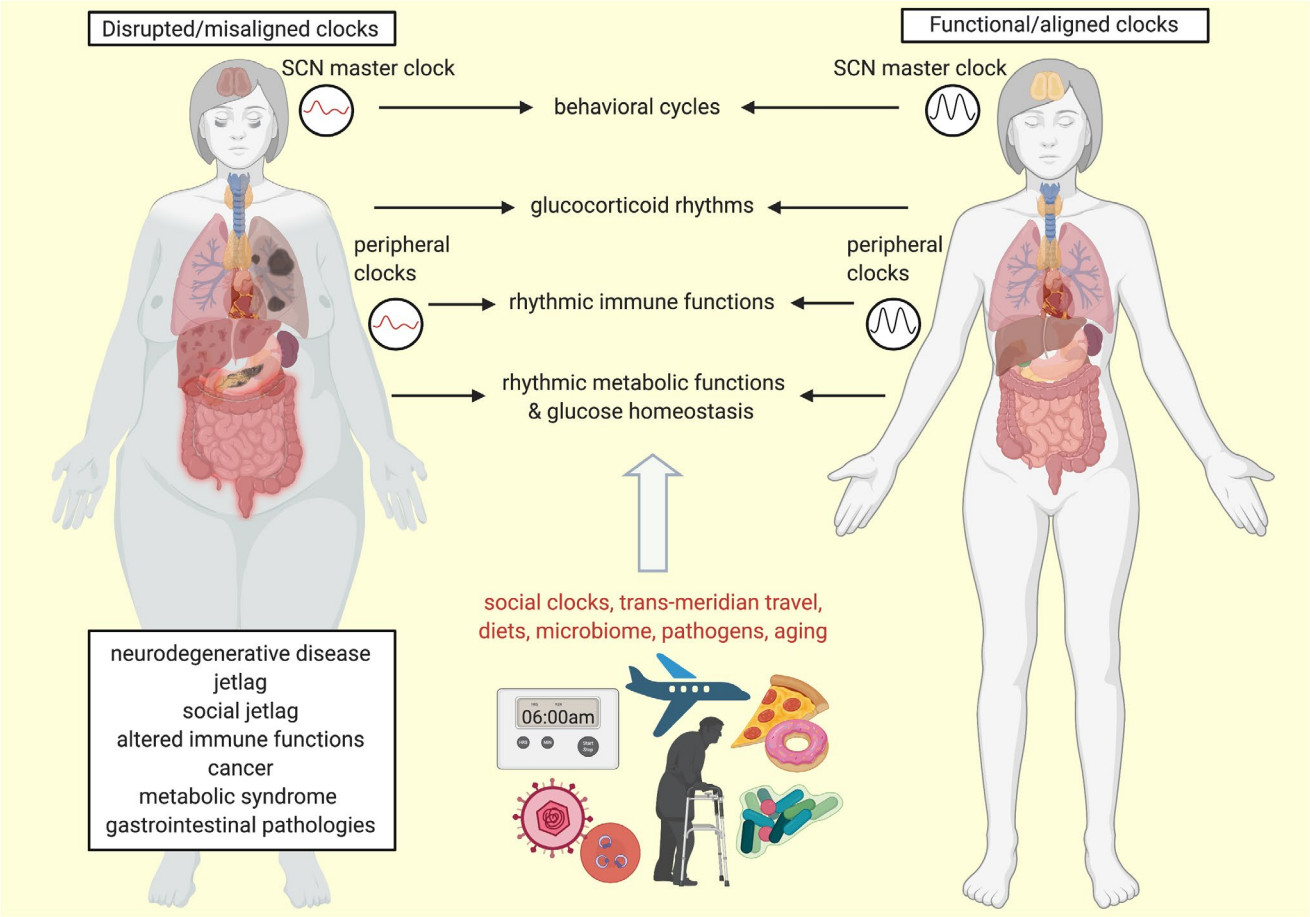

FIGURE 3 Modern life challenges to mammalian circadian clocks. Circadian clocks regulate rhythmic physiological and behavioural processes that are important for human health and well-being. Modern lifestyle encompasses many challenges to the endogenous circadian system that can induce circadian disruption and misalignment, as well as promote the development of associated diseases. For example a mismatch between endogenous circadian and social clocks (work/school schedules) promotes social jetlag, whereas trans-meridian travel causes travel-related jetlag, abnormal dietary habits and the gut microbiome impact rhythmic metabolic and gastrointestinal functions and may lead to metabolic syndrome or gastrointestinal pathologies, immune responses to pathogens are affected by the state of our circadian system, and neurodegenerative and tumorigenic diseases may arise from ageing-related clock changes. In addition, disruption/misalignment of body clocks feeds back to rhythmically regulated physiological and behavioural processes, thereby enhancing susceptibility to chrono-disruptive stimuli and aggravating associated pathologies. This Figure was created with BioRender.

cellular differentiation status with embryonic tissue and foetal SCN rhythms emerging around day 15 post-fertilization (in mice).[115,117-119] Precise mechanisms of circadian rhythm emergence, however, remain elusive. It has been suggested that (relative) clock genes expression levels are related to the robustness of circadian rhythms. In addition, post-transcriptional modulation of molecular clock components, for example suppression of CLOCK expression *via* the endonuclease-microprocessor complex DICER/DGRC8, may regulate circadian clock development.[120-122] Catheterized foetal models and fluid sampling have shown that human, monkey and sheep foetuses display 24-hour rhythms in hormones, behaviour and cardiovascular function.[123] Melatonin, glucocorticoids and dopamine have been proposed as candidate factors mediating maternal entrainment of foetal circadian clocks during pregnancy.[124] In addition, Sletten et al (2018) reported that circadian rhythms in human foetal heart rate are modified by gestational age, foetal gender, maternal physical activity and season.[125,126] If truly circadian and not imposed by the maternal circadian system, foetal rhythms should persist after birth and independently of environmental Zeitgebers. Studies report that circadian rhythms in body temperature and heart rate can be detected in about 50% of preterm infants in intensive care units (constant light and temperature conditions, 2-hour feeding intervals), as well as to a greater percentage in full-term neonates 2 days postnatally.[127,128] However, such rhythms displayed large variability with respect to acrophase, suggesting that synchronization with the environment is beginning at later postnatal ages.[128] Circadian rhythms of cortisol are established 2-4 months

after birth and rhythms in melatonin 48-52 weeks post-conception (for review see[129]).

5 | MODERN LIFE CHALLENGES TO THE HUMAN CIRCADIAN SYSTEM

Mammalian circadian systems regulate numerous physiological and behavioural functions. Perturbation of the molecular clock machinery, for example because of mutations or gene deletions, as well as misalignment between endogenous circadian and exogenous environmental cycles, for example because of travel across time zones, artificial lighting or shift work, can result in acute or chronic 'circadian disruption' (Figure 3; for review see[130]). To date, many severe health conditions, including metabolic syndrome, diabetes, psychiatric and autoimmune disorders, cardiovascular diseases and even cancer have been associated with disruption of the circadian system.[131,132]

6 | 'SOCIAL CLOCKS'

The period of human circadian clocks varies between individuals resulting in distinct 'phase-relationships' between internal and external rhythms. Such phase-relationships are referred to as chronotypes, simply put, the preference to behave as night owl (late types), morning lark (early types), or in-between. Most human populations display a slight tendency towards late chronotypes,[133] especially during teenage years, favouring the development of social jetlag, that is the discrepancy between sleep timing on work/school days versus work-free days arising from social obligations.[134,135] Trying to compensate for the mismatch between the endogenous circadian and exogenous rhythms has been reported to cause sleep deprivation[136,137] accompanied by sleep loss induced pathologies like immunodeficiency, cognitive and mood disorders, or obesity.[138-140] In mice, chronic jetlag protocols have been found to shift the temporal expression of clock genes in the SCN and peripheral clocks, to disrupt locomotor activity and feeding rhythms, to induce leptin resistance and dysregulation of the immune system, as well as to promote tumour growth, metastasis, weight/fat gain and metabolic disruption.[141-146] In particular, shift work, one of the major causes of chronic social jetlag, has been associated with increased mortality, as well as the development of metabolic disorders, for example reduced insulin sensitivity or even type 2 diabetes.[147-149] Exploring the role of inter-individual differences in chronotypes for the development of pathologies, as well as for individualized medical treatment plans and prevention has gained major attention in the field of chronobiology.[150,151] In recent years, researchers have been working on the establishment of practical, yet accurate, sensitive and reliable methods for the determination of endogenous circadian clock time. Such 'chrono-diagnostic' tools will help to develop recommendations not only for clinicians, for example for the optimization of drug treatment times and clinical study designs, but also for general political decisions, like consolidation of flextime (at the workplace and at schools) or chronotype-matched work schedules.

With respect to misalignment between endogenous and exogenous cycles, the impact of Daylight Saving Time (DST) on the human circadian system has become a highly debated topic.[152] While the European Commission decided on the abolishment of the biannual switch between DST and Standard Time (ST), it is currently debated whether DST or ST will be fixed as new annual time and whether all member states have to stick to the same standard. During the summer months (DST), social clocks are advanced by 1 hour, whereas sun clocks (daily progression of the sun) remain the same. As endogenous circadian clocks are predominantly set by the light-dark cycle, DST may promote misalignment between social and body clocks and further enhance social jetlag (for review see[153,154]). Moreover, acute DST-ST switching can promote sleepiness. Thus, not surprisingly it has been correlated with an increased risk of accidents, hospitalization and cardiovascular incidents.[155-157] Constitutive DST on the other hand may result in chronic health effects, comparable to chronic social jetlag.[156] From a chronobiological perspective referring to natural clock time (sunset and sunrise) as new annual standard and in a region-specific manner may be most advisable for EU member states.

In contrast to social jetlag, travel induced jetlag is transient and caused by misalignment of our endogenous circadian system with the new light-dark cycle of the travel destination. Trans-meridian travel has been associated with sleep-wake disorders, daytime sleepiness, general malaise, impaired alertness and motivation, as well as gastrointestinal upset with severity of symptoms depending on the number and direction of time zones crossed.[159-161] In addition, body clocks may adjust to the new light-dark cycle with different rates, thereby aggravating symptoms resulting from circadian misalignment rather than from poor sleep. Commonly, jetlag is perceived to be worse when travelling eastward rather than westward. This was supported by a study looking at performance of professional Baseball players, who displayed impaired parameters of home-team offensive, as well as home and away defensive performance following mainly eastward travel.[162] Using computational models, Diekman and Bose (2018) report that this east-west asymmetry stems from a combination of endogenous clock period (commonly >24 hours in humans) and external day length and predict that changes in day length may even induce jetlag when travelling from north to south.[163] On the other hand, Zhang et al (2020) reported that west-to-east jetlag induced

brain and neuroendocrine changes that were related to jet-lag symptoms.[164] Noteworthy, repeated long distance travel, as experienced by aircrews, may induce more severe health consequences than less extensive trans-meridian travel. For example, flight attendants display more variable melatonin rates (potentially correlated with menstrual irregularities), higher salivary cortisol levels, as well as exacerbation of cognitive and psychiatric disorders.[165-168]

7 | CLOCKS AND METABOLISM

In addition to the light-dark cycle, other environmental cues have been discovered to act as important entrainment signals for mammalian circadian systems (see above). Meal timing acts as Zeitgeber for circadian clocks and time-restricted feeding can uncouple peripheral clocks from the SCN.[50,51,169] Many studies focus on the impact of time-restricted and mistimed feeding on health and well-being. Hypercaloric diet in mice has been shown to alter molecular and locomotor activity rhythms, as well as entrainment to the light-dark cycle.[170-172] Sundaram et al (2020) reported that high-fat diet alters circadian rhythms in mammary glands of pubertal mice,[173] potentially contributing to early childhood puberty in girls. Moreover, Sato et al (2018) showed that nutritional timing alters tissue-specific metabolomic profiles in a time-of-day-dependent fashion,[174] indicating that feeding-related cues play an important role for rhythmic metabolic organ functions.

On the other hand, circadian clocks temporally regulate metabolic processes and energy expenditure,[175,176] thus it does not only matter what and how much we eat but also when we eat. Indeed, genetic disruption of endogenous clocks by mutation of the *Clock* gene results in hyperphagia and development of metabolic syndrome in mice.[177] In addition, misalignment of endogenous and exogenous cycles, for example during shift work, promotes the development of metabolic morbidities.[176] Recently, it has been demonstrated that, besides lunch and dinner, an additional meal in the late evening, rather than in the morning, attenuates overnight lipid catabolism,[178] potentially counteracting weight loss. In mice, pathological consequences of high-fat diet, that ismetabolic disruption and obesity, depend on the time of food intake rather than calories consumed.[179-181]

Shift work promotes unhealthy snacking behaviour, as well as abnormal glucose tolerance,[182-186] thereby increasing the risk for obesity and type 2 diabetes. In addition, circadian disruption because of genetic perturbation or misalignment of endogenous and exogenous rhythms has been found to cause dysbiosis of the gut microbiome.[187-190] Vice versa, changes to the microbiome, for example by antibiotics, altered diet, age or stress, may disrupt endogenous clock functions of the gastrointestinal tract and promote metabolic disease.[191] Gut microbiota and host circadian rhythms are intertwined by their concomitant regulation of the host's metabolism and their response to feeding-related signals. Drivers of a so-called 'microbiome-circadian clock-axis' are still under investigation. However, as mentioned earlier, microbiota-derived short chain fatty acids (SCFA), as well as microbiota modified host bile acids (BA) have been reported to regulate host metabolism and energy balance, as well as to be altered upon changes in feeding regimens.[83] Kuang et al (2020) recently demonstrated that intestinal microbiota regulate diurnal metabolic rhythms of the host by inducing the epithelial expression of histone deacetylate 3 (HDAC3).[192] Ku et al (2020) showed 3-(4-hydroxyphenyl)propionic acid (4-OH-PPA) and 3-phenylpropionic acid (PPA), two metabolites derived from *Clostridium sporogenes*, induce changes in the molecular clock machinery in a fibroblast model of peripheral clocks.[193] Thus, maintenance of cyclic variations in gut microbiota may play an important role for the prevention of metabolic and gastrointestinal pathologies.[194]

Lastly, diets may reprogram glucocorticoid (GC) rhythms, another important entrainment signal for peripheral circadian clocks. In mice, glucocorticoid receptors (GR) regulate rhythmic metabolism through time-dependent target gene induction and rhythms in GR target genes are altered by high-fat diet.[195] This may be a consequence of arrhythmic corticosterone levels following high-fat diet as shown by Appiakannan et al (2019).[196] In humans, shift work at young adult age has been found to be associated with elevated cortisol levels, which were further correlated with increased body mass index.[197] Interestingly, in patients with Cushing's disease, caused by hypercortisolism and commonly accompanied by weight gain and metabolic syndrome, rhythmic clock gene expression is impaired.[198] These findings highlight the interplay between the circadian, glucocorticoid and metabolic system. Thus, not surprisingly prolonged administration of synthetic glucocorticoids, for example in systemic and topic anti-inflammatory therapy, is often accompanied by severe side effects, such as hyperglycaemia, hepatosteatosis or increased body fat accumulation.[199] Moreover, abnormal GC levels may cause the disruption of intrinsic circadian clocks and promote associated pathologies.[200]

8 | CLOCKS AND INFECTION

In the light of the 2020 SARS-CoV-2 pandemic, the interplay between the circadian and immune system has become more relevant than ever. As other bodily cell types, cells of the immune system possess circadian oscillators that drive rhythms in synthesis and release of cytokines, chemokines and cytolytic factors, thereby gating rhythmic innate and adaptive immune responses.[201-203] On the molecular level circadian clock components acts as transcription factors driving cyclic expression of important immune genes, but also

clock regulated post-translational modifications (*eg* histone acetylation and methylation) or direct interaction with inflammatory pathways (*eg* the NFκB pathways) play a role in controlling inflammatory processes and immune cell trafficking.[204,205] Through gating immune functions, the circadian system governs time-of-day susceptibility to pathogens. Generally, circadian variability in severity of infections appears to be related to differences in pathogen burden resulting from daytime dependent inflammatory responses.[206-208] Sengupta et al (2019) showed that endogenous rhythms affect survival in influenza infection by altering the host tolerance, leading to worse outcomes when mice where infected just prior to their active phase.[209] Thus, the time of infection with SARS-CoV-2 may predict disease outcomes and better knowledge about such dynamics may help to optimize treatment strategies. On the other hand, inflammatory processes may induce complex re-organization of cellular and molecular circadian rhythms.[210] Circadian disruption, often accompanied by sleep deprivation, alters the immune response to pathogen challenge,[211-213] potentially leading to an excess risk for SARS-CoV-2 infection among shift workers, including health care professionals.[214,215] In addition, prolonged social distancing and home stay to counteract the spread of the pandemic may affect circadian health by reducing daylight exposure from outdoor activities or altering meal timing, diets and physical activity.[216]

Besides virus infections, parasitic infections are the cause of a tremendous burden of disease, with malaria causing the most deaths globally. Even today, about 660.000 people per year, mostly young children, die from malaria infections (according to CDC, Centers of Disease Control and Prevention). Many parasitic infections display rhythmic daily patterns, potentially to predict circadian environments and coordinate the parasite's metabolism, life cycle and transmission with the host's circadian rhythm.[217,218] Malaria parasites (*Plasmodium*) exhibit circadian rhythms during replication and transmission. Recently, Rijo-Ferreira et al (2020) demonstrated that *Plasmodium chabaudi* possesses flexible and intrinsic circadian clocks that can be adjusted to the host's circadian rhythm and persist despite the absence of rhythmic feeding signals or functional circadian clocks in the host.[219] Similarly, two other studies published in recent years reported that *Plasmodium* cell cycle occurs in synchrony with the host's circadian cycle. However, while Hirako et al (2018) show that rhythms of systemic TNFα production and host food intake govern synchronization of *Plasmodium* stages with the host,[220] Subudhi et al (2020) report that malaria parasites are at least partly responsible for generating about 24-hour rhythms in their intra-erythrocytic developmental cycle and coordinating their developmental cycle with their host.[221]

9 | CLOCKS AND AGEING

Today, one of the most prevalent population trends is ageing. This is mainly because of an increased life expectancy (better nutrition, health care, sanitation, education) and reduced birth rates. The United Nations Population Fund predicts that by 2050, almost 22% of the global population will be older than 60 years. Ageing not only alters sleep timing, duration and quality, it also affects the circadian system leading to differences in entrainment, reduced amplitudes and altered phases of endogenous rhythms.[222,223] Such changes may stem from altered transmission of clock resetting blue light, for example because of yellowing of the lens with age,[224,225] from changes to electrical activity, neuropeptide expression and intercellular coupling within the SCN,[226-231] or from altered clock gene expression[232-234] (for review see 235,236). Interestingly, *Bmal1* knock-out mice display phenotypes resembling premature ageing, including sarcopenia, cataracts, reduced subcutaneous fat and organ shrinkage.[235] However, except for irradiation induced premature ageing in *Clock* mutant mice,[238] no other clock gene mutant models display ageing-related phenotypes comparable to *Bmal1* knock-out mice, suggesting that phenotypic changes may be a consequence of pleiotropic functions of *Bmal1* rather than circadian disruption. Other prevalent pathologies related to old age, and possibly resulting circadian disruption, are neurodegenerative diseases and cancer.[111,239,240] In older people, decreased activity rhythms (with respect to robustness, amplitude and mesor) have been associated with higher likelihoods of developing dementia, mild cognitive impairment, or Parkinson disease.[240,241] Alzheimer's and Parkinson disease, commonly occurring during later stages in life, have been linked to single nucleotide polymorphisms in the clock genes *BMAL1*, *PER1* and *CLOCK*[242-245] and are usually accompanied by disruptions of sleep-wake cycles.[246] Moreover, it has been reported that the absolute expression levels and day-night differences of AVP mRNA, as well as the density of AVP/VIP- and MT1 (melatonin receptor)-expressing neurons in the human SCN are diminished in Alzheimer's patients.[247,248] Sirtuin 1 (SIRT1), an NAD-dependent deacetylase known to regulate circadian clock components, appears to be involved in both, ageing and circadian-clock regulation. While in aged mice, SIRT1 levels in the SCN are decreased, in young mice lack of SIRT1 promotes premature ageing and ageing-related circadian phenotypes.[249,250] In addition, age-related neoplasms have been associated with aberrant levels of SIRT1, potentially promoting circadian and cell cycle disruption, as well as tumorigenesis.[251-254]

10 | CLOCKS IN SPACE (A BRIEF PERSPECTIVE)

Space Extrapolation Technologies Corp. (SpaceX), an American aerospace manufacturer and space transportation service, is the first private company to have launched astronauts into orbit. Considering that space transportation may someday be available to the broader public, dissecting interactions between weightlessness in space and human circadian systems may be worthwhile.[255] During space flight, astronauts are exposed to changes in basically all environmental Zeitgebers experienced on earth. Sunrise and sunset occur approximately every 45 minutes, instead of every 24-hours, diets and potentially feeding-fasting cycles are altered, and microgravity entails prolonged muscle unloading and induces a fluid shift in the human body, impacting the metabolic, mechano-skeletal and cardiovascular systems.[256,257] Interestingly, however, circadian rhythms in blood pressure have been shown persist in space with lower pressure during sleep.[258-260] A study conducted in a *Drosophila* model of space travel showed that rhythms of clock genes, as well as fly locomotor activity and sleep are maintained during space flight.[261] Additionally, a study in 21 astronauts collected over almost 9 years demonstrated that alignment of the sleep schedule to the endogenous circadian cycle (estimated using the Circadian Performance Simulation software) enhances sleep time and quality, as well as reduces the use of medication.[262] Together these findings suggest that maintaining 'circadian health' during space travel is beneficial for astronaut's physiology and performance and may be able to improve health deterioration during prolonged weightlessness.

11 | CONCLUSIONS

In summary, modern life poses widespread challenges to our circadian systems. Social jetlag, abnormal diets, ageing-related processes and infections can disturb circadian clock systems and prevent a correct entrainment to periodically changing environmental conditions, most importantly the light-dark cycle. Disruption of and misalignment between internal and external rhythms has been associated with numerous health consequences, including metabolic and cardiovascular diseases, psychiatric disorders, cancer or even increased mortality.[130,132,152,263,264] For most of these 'circadian pathologies', molecular mechanisms are not well understood. Thus, elucidation of molecular links between circadian clocks and human pathologies should enable the development of personalized preventative and therapeutic strategies. Along that way, continuous progress in biomarker testing to determine people's chronotypes,[265,266] in human study designs to assess the impact of feeding-fasting and shift work cycles on our well-being,[149,267-269] as well as in studying molecular oscillator properties in vitro and in vivo[270] will help to achieve harmony between our body clocks and the outside world.

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CONFLICT OF INTEREST

There is no conflict of interest to declare.

ORCID

Anna-Marie Finger https://orcid.org/0000-0001-9148-4490

Achim Kramer https://orcid.org/0000-0001-9671-6078

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