Clocks in the clinic: circadian rhythms in health and disease

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ABSTRACT

Circadian rhythms are endogenously generated recurring patterns of around 24 hours with well-established roles in physiology and behaviour. These circadian clocks are important in both the aetiology and treatment of various psychiatric and metabolic diseases. To maintain physiological homeostasis and optimal functioning, living life synchronised to these clocks is desirable; modern society, however, promotes a '24/7' lifestyle where activity often occurs during the body's 'biological night', resulting in mistimed sleep and circadian misalignment. This circadian desynchrony can increase the risk of disease and can also influence treatment response. Clinicians should be aware of the influence that circadian desynchrony can have on health and disease, in order to potentially develop new therapeutic strategies and to incorporate chronotherapeutics into current treatment strategies to enhance their utility.

INTRODUCTION

Sleep and wake cycles in a rhythmic world

The award of the Nobel Prize for Physiology or Medicine in 2017 to the scientists who uncovered the mechanisms of circadian timing has highlighted an important, yet often overlooked, truth: we live in a rhythmic world. The daily rotation of the earth on its axis creates profound 24 hour variations in environmental factors, such as temperature and light. Life on earth has evolved mechanisms to optimally exploit these changes, with the most obvious manifestation of this being the daily sleep/wake cycle. All mammals appear to have a biological need for sleep, with humans on average spending one-third of their lives asleep or trying to sleep.[1 2] Sleep timing is regulated by two overlapping processes: the sleep dependent homeostatic drive for sleep, which accumulates with increasing time spent in the awake state and the circadian process that imposes an underpinning rhythm of about 24 hours on sleep/wake behaviour.[3 4] The appropriate timing of sleep is emerging, along with other sleep parameters such as sleep quality and sleep duration, to be a key determinant of health and well-being. Poor sleep quality, short sleep duration and mistimed sleep are associated with an increased risk of disorders, pathologies and dysfunctions such as insulin resistance, type 2 diabetes (T2DM), obesity, metabolic syndrome (MetS), cardiovascular disease and even all-cause mortality.[5–8] As such, the processes that govern sleep are increasingly recognised as potential substrates for the improvement of health and the development of new therapeutic strategies (and better leveraging of existing approaches through chronotherapy).[9]

Circadian rhythms are recurring patterns of near 24 hours that occur in all eukaryotic organisms independent of external factors and are driven by an organism's endogenous clock.[10] The molecular basis of the circadian clock is a transcriptional-translational autoregulatory feedback loop of the products of a panel of clock genes (including *CLOCK*, *BMAL1*, *PER1/2*, *CRY1/2* and *REV-ERB-a*) which encode transcription factors. These clock gene products interlock in a series of feedback and feed-forward loops to regulate their own expression, with post-translational modifications tuning protein stability and turnover to produce a cycle with a period of near 24 hours.[11 12] This clock gene cycle also imposes a pervasive temporal regulation on the transcriptome; in mouse, 40% of genes show rhythmic expression in at least one tissue.[13] It is now recognised that there are molecular clocks present in the vast majority of tissues and cell types, and that the circadian system is a network of oscillators distributed throughout the brain and periphery.[14] Within this system, there is a master circadian pacemaker located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus; experimental lesion of the SCN results in profound circadian arrhythmicity and desynchronisation of peripheral oscillators.[15]

Setting, and mis-setting, clock time

As the period of the circadian clock is *approximately* 24 hours, a mechanism is required whereby this internal rhythm becomes synchronised ('entrained') to the external solar cycle. This entrainment occurs via the circadian phase being set by environmental time cues ('zeitgebers'), with light being the most prominent entraining agent.[16] Light input from the 24 hour solar cycle is received by the master circadian clock and conveyed to the peripheral clocks throughout the organism in order to achieve more precise, entrained 24 hour biological rhythms.[17] The master clock orchestrates and synchronises other brain and peripheral clocks to result in a coherent organism-wide regulation and integration of homeostasis and behaviour.[18] An individual's phase of entrainment reflects the relationship between external and internal time; interindividual differences in the circadian processes described above result in different chronotypes, and these are shaped by genotype, ontogeny, environment and gender.[10 19 20] In humans, chronotype manifests itself as preferred sleep and wake times and ranges

Figure 1 The entrainment of the circadian clock. The 24 hour solar cycle entrains the endogenous circadian rhythm to a period of exactly 24 hours. Interindividual differences in this phase of entrainment shaped by genotype, environment, gender and age lead to different chronotypes whereby an individual is more morning or evening orientated, falling somewhere on the scale from an extreme morning person 'lark' to an extreme evening person 'owl'.

from extreme early types to extreme late types (see figure 1), with chronotype following a normal distribution in the general population and most of us falling somewhere in the middle.[21 22]

For most of human history, environmental light was provided predominantly by natural sunlight, with dawn and dusk time varying little between successive days. In current times, however, modern technology promotes a 24/7 society where individuals can work, socialise, travel and sleep during the body's biological night, the phase of the circadian cycle during which the endogenous clock is promoting sleep. Humans experience daily social pressures and imperatives, and these may vary greatly from day to day (eg, between work and free days). Social obligations can affect the alignment of an individual's behavioural cycle to the endogenous biological rhythm, through altered sleep and wake times on work and free days, resulting in circadian misalignment.[23 24] This disruption may be temporary, as occurs with travel between time zones 'jetlag' or with society-wide changes to wake times via daylight savings time, or more permanent as with ongoing shift work. Night shift work, in particular, may result in profound circadian misalignment and many studies on shift workers have demonstrated the negative influence this can have on health.[25] A milder, yet chronic, form of circadian misalignment is social jetlag (SJL). SJL is the daily and ongoing discrepancy between social time (when an individual's sleep and wake time is dictated by social or work obligations) and internal biological time.[26] A large proportion of the population have social schedules that interfere with preferred sleep/wake schedules, and individuals with an endogenous chronotype at greatest divergence from the societally determined sleep and wake times are at greater risk of developing SJL; in other words, late types ('owls') display sleep/wake preferences that do not conform to usual, earlier daily work schedules (see figure 2).

Given that the daily rhythmic expression of many vital homeostatic functions (feeding, activity and rest, body temperature, hormone secretion, cardiac function, innate immunity, neurophysiology) are driven by the endogenous biological clock,[27] it is perhaps not surprising that disruption of these rhythms is associated with negative health and behavioural outcomes.[23] There is an emerging understanding of the role of circadian clocks in many disease processes, and below we highlight evidence for the

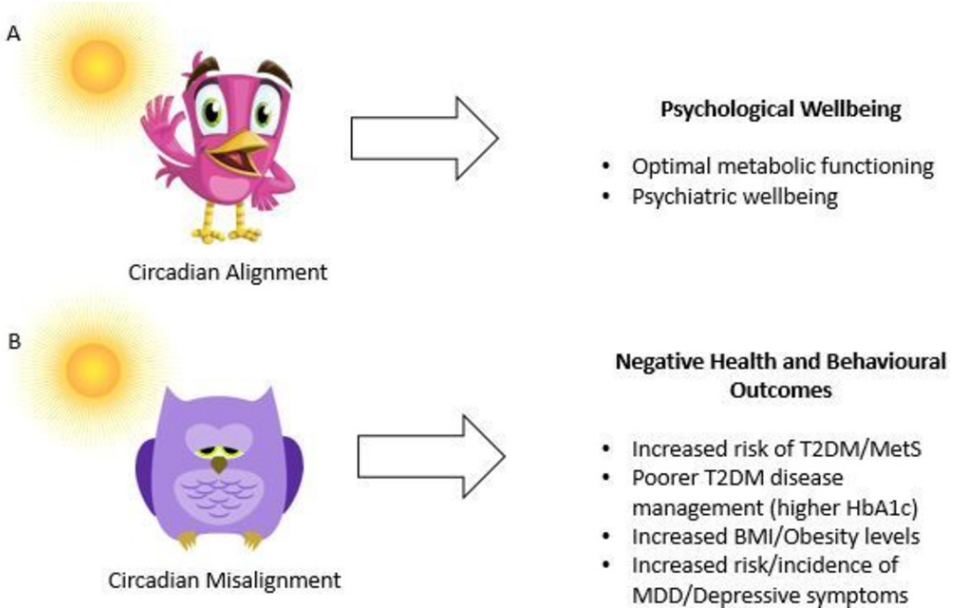

Figure 2 Consequences of chronotype and circadian misalignment. (A) The typical day favours a morning orientated individual. A morning 'lark' displays psychological wellbeing as daily behavioural rhythms are aligned to the social work schedule. (B) Evening orientated individuals are likely to experience more sleep debt and circadian misalignment due to social/work schedules. The resultant misalignment may have various negative health and behavioural outcomes. BMI, body mass index; MDD, major depressive disorder; T2DM, type 2 diabetes; MetS, metabolic syndrome.

role of clocks in the aetiology, symptomatology and treatment of psychiatric conditions and metabolic disorders.

CIRCADIAN RHYTHMS AND HEALTH

Circadian rhythms and psychiatric disorders

Reports of circadian rhythm disturbance in depression date back over 50 years.[28] Patients with major depressive disorder (MDD) display altered daily patterns of affect, with the rhythms of low mood showing a later trough in the early morning and a blunted amplitude of the mood rhythm compared with controls (although mood is always lower in patients with depression irrespective of time-of-day).[29 30] Patients with non-seasonal major depression show markedly later chronotypes and delayed sleep onsets than control populations.[31–33] A recent review has supported this finding by reporting that the relationship between later chronotype and depression was well established in cross-sectional studies and that longitudinal studies are preliminarily reporting the same.[34] This does not clarify the direction of this relationship as late chronotype may be a marker and/or a risk factor for depression. A recent cross-sectional study from the UK BioBank revealed that MDD was also linked with a lower amplitude of the daily rest/activity rhythm.[35] These findings indicate that a phase-delay of the circadian clock is associated with non-seasonal depression, and this forms the basis for the use of bright-light morning therapy as a treatment. The applicability of this as a treatment is based on our knowledge of the phase response curve; a light stimulus before the critical phase of the core body temperature minimum causes a phase delay while a light stimulus after this critical phase causes a phase advance.[36 37] With this phase delay observed in depression the clock's phase is essentially delayed to a later time zone, and early-morning light exposure phase-advances the clock, and counteracts the pre-existing phase-delay. A recent randomised controlled trial demonstrated that morning light therapy or a combination or light therapy and fluoxetine were more effective than either fluoxetine alone or placebo in lessening depression symptoms.[38]

From a further chronotherapeutic perspective, underlying circadian phase may also modulate the efficacy of antidepressant pharmacotherapy: recent research has demonstrated that evening types report lower SSRI (selective serotonin reuptake inhibitor) efficacy and more depressive symptoms during SSRI treatment,[39] while a phase-delay after initiation of fluoxetine treatment predicted poorer treatment response in females.[40] There are currently no evidence-based guidelines for the time of dosing for various SSRI antidepressants, although animal studies indicate that fluoxetine can alter timing in the master clock of the SCN.[41] The antidepressant agomelatine is a mixed melatonin receptor agonist and 5HT-2C receptor antagonist with a putative primary mode of action through the circadian system and similar efficacy to SSRIs,[42] a finding that further points to the potential clinical utility of targeting the circadian system for treatment of mood disorders.

Circadian factors are also associated with subclinical depressive symptoms. A recent meta-analysis identified that evening-orientation is associated with more severe mood symptoms.[43] A similar finding was demonstrated between evening orientated individuals and depressive symptoms in more recent research and poor sleep quality may mediate this relationship.[44] In an adolescent population, evening types demonstrated more depressive symptoms and a higher prevalence of depressogenic cognitions.[45] The impact of chronotype on symptoms of depression may be mediated through SJL, as adolescents and younger adults with later chronotypes experience greater levels of SJL, which in turn is associated with depressive symptoms.[46] However, analysis of a patient sample with MDD and healthy controls found no association between SJL and depressive symptoms in either sample when the analysis was stratified.[47] As SJL is a function of both intrinsic chronobiology and social factors such as employment status, and such factors are culturally-determined and also heavily influenced by age, further study in diverse populations is required.

Seasonal depression has long been associated with changes in the circadian system in response to changes in the photoperiod across the year.[48] Winter depression, the most common manifestation of seasonal affective disorder (SAD), may coprecipitate with changes in sleep parameters including lower sleep efficiency, shorter sleep time, more sleep inertia, longer sleep latencies and later sleep and waking time.[49] Two-thirds of patients with winter depression display phase delays of the dim-light melatonin onset (a key marker of circadian phase), while one-third display phase advances.[50] Further, treatment with light therapy and melatonin timed appropriately to counteract the underlying phase shift alleviated the symptoms of SAD. Intrinsic circadian characteristics may be a risk factor for SAD; there is a relationship between SAD and diurnal preference,[51] adolescents with later chronotype display higher mood seasonality[52] and SJL may also elevate SAD risk in females.[49] However, chronotherapy approaches have so far not been proved to be effective in preventing SAD.[53]

Circadian disruptions and alterations in circadian parameters have been reported in patients with bipolar disorder (BD). A recent systematic review reports phase delays in daily cortisol and melatonin rhythms, and depression (more so than during euthymia) was associated with circadian disruption.[54] Interestingly, some studies showed more sleep/social rhythm dysregulation in BD than MDD.[55] It has long been recognised that alterations in circadian timing, for example as a result of jetlag, can precipitate mood cycling in BD,[56] and a recent study has demonstrated that in rapidly cycling BD, sleep/wake cycles appear to synchronise to the lunar cycle through an unknown mechanism.[57] From a chronotherapy perspective, mood stabilisers such as lithium are known to impact directly on the core molecular clockworks;[58] further, chronotherapy involving bright light therapy in combination with sleep deprivation has been shown to elicit a rapid and long-lasting amelioration of bipolar depression.[59–61] From a mechanistic perspective, a number of cellular and molecular processes have been identified to interact with the clock and modulate mood, including hypothalamic-pituitary-adrenal axis function, immune and neuroimmune processes, neurogenesis and direct control of neurotransmitter and neuromodulator systems.[62] Circadian changes have also been described in a number of other psychiatric conditions, including schizophrenia,[63] attention deficit hyperactivity disorder,[64] obsessive compulsive disorder[65] and borderline personality disorder.[66] As such, circadian processes appear to be important transdiagnostic factors to consider in psychiatry and clinical psychology.

Circadian rhythms and metabolic health

Given the pervasive influence of the circadian clock in regulating homeostasis and physiology, it is not surprising that circadian rhythms are associated with multiple facets of physical health.[67] Furthermore, since a central function of the circadian system is to provide a temporal organisation of metabolism that synchronises with behavioural rhythms and likely environmental availability of food, circadian processes have been strongly implicated in metabolic health. An important finding in this regard was the discovery that mice deficient in the circadian *CLOCK* gene demonstrated higher levels of obesity and more weight gain on

both a regular and high fat diet when compared with wild-type controls and also displayed features of the metabolic syndrome including hyperglycaemia and hypoinsulinaemia.[68] The development of many metabolic disorders including obesity, T2DM and MetS has also been linked to genetic variations in the *CLOCK* gene in human populations.[69–71] These *CLOCK* polymorphisms have been associated with greater total energy intake,[71] and the resulting haplotypes have been suggested to influence obesity susceptibility.[70] Metabolic homeostasis is affected, therefore, by circadian genotype.[12] Fundamental research has shown that the circadian clocks serve to regulate metabolism and energy homeostasis in a tissue-specific manner through molecular pathways that include NAD^+-dependent Sirtuin signalling, haem biosynthesis, fatty acid biosynthesis, glucose metabolism and insulin release.[72] Environmentally induced circadian disruption is also associated with metabolic derangement; forced desynchronisation of the circadian and sleep/wake and feeding cycle in human participants results in hyperglycaemia and insulin resistance indicative of a prediabetic state.[73] Circadian desynchronisation is likely experienced by shift workers who undertake night work, and shift work is associated with elevated risk of T2DM of approximately 40% for those with an established history of night work, an effect that is independent of genetic risk for T2DM.[74] A recent study has also demonstrated that in simulated shift work, the metabolic rhythms follow the behavioural, but not the circadian, cycle.[75]

As mentioned above, SJL may represent a more common, milder, but chronic form of circadian misalignment occurring with high prevalence in the general population. Notably, research on the independent association between SJL and metabolic health is growing. In three large cohort studies, SJL has been associated with increased body mass index (BMI) (independently of other health parameters and short sleep), and particularly associated with risk of moving to obesity from overweight.[76–78] A recent cross-sectional study identified a twofold increased risk of both pre-diabetes/diabetes and MetS in individuals below 61 years with high SJL.[79] This study demonstrated a prevalence ratio for MetS of 2.13 and diabetes/prediabetes of 1.75 for participants with more than 2 hours of SJL and a prevalence ratio of 1.29 and 1.39, respectively for those with 1–2 hours SJL compared to those with SJL of less than 1 hour. These findings have recently been replicated in a Japanese population with greater likelihood of having MetS and SJL being associated.[80] Furthermore, this research demonstrated that the relationship between SJL and MetS persisted after adjusting for various confounding variables such as alcohol consumption, sleep quality, caloric intake, breakfast skipping and leisure time exercise. SJL has also been associated with higher BMI, triglycerides, fasting plasma insulin, insulin resistance and greater fat mass.[77 78] For patients with non-communicable chronic disorders, SJL and fasting glucose were associated, most so in metabolically unhealthy obese (MUO) participants; SJL was also associated with higher risk of being obese and fitting the MUO category and thus risked metabolic complications.[81] Chronotype is also associated with diabetes and obesity risk, with individuals with a later chronotype having an increased likelihood of T2DM compared with morning types with a 2.5 fold OR.[82] In addition to this, a recent study from the UK BioBank comparing definite evening and definite morning types identified an increased likelihood of diabetes in evening orientated individuals with an OR of 1.30.[8] Later chronotype is associated with higher HbA1c levels, independent of confounding sleep and clinical variables, in T2DM[83] and prediabetes.[84] There are conflicting reports of the association of chronotype with glycaemic control in type 1 diabetes: one study reports that more SJL is associated with poorer glycaemic control in adults,[85] while in an adolescent cohort chronotype or SJL was not associated with HbA1c levels.[86]

CONCLUSION

It is clear that the endogenous circadian clock plays a crucial role in various aspects of health, with increasing evidence demonstrating the important roles of the clock in both disease risk and management. Further work is needed to incorporate the circadian concept into the core of medicine in order to maximise its potential for disease prevention and treatment.

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Main messages

- Circadian rhythms, and the rhythmic nature of the world, have emerged as key factors in health and well-being, with circadian misalignment and mistimed sleep being associated with various pathologies and risk of disorders.
- Major depressive disorder has been associated with a later chronotype which may act as a risk factor for developing depressive symptoms or also occur as a result of depressive symptoms. The use of bright light therapy to advance this phase may decrease depression severity and also improve existing treatment. The circadian system needs to be used further to reduce the burden of mood disorders.
- Research is accumulating for the independent role that social jetlag (SJL) and chronotype may play in metabolic health. SJL has been associated with higher body mass index, increased risk of type 2 diabetes and metabolic syndrome even when confounding variables are controlled for, while later chronotype has been associated with diabetes risk and management. Novel behavioural interventions to reduce SJL that promote having more regular schedules across the week may be simple yet important in both preventing and treating these metabolic diseases.

Current research questions

1. What is the nature of the relationship between the circadian system and mood disorders? Is the relationship between depressive symptoms and chronotype due to evening orientation or does social jetlag (SJL) mediate this relationship? As such, what chronotherapeutic approach could be used or would a simple behavioural intervention be of use to reduce symptoms?
2. How beneficial will simple novel behavioural interventions to reduce SJL be for decreasing the risk of developing various metabolic disorders as well as treating them?
3. What is the causal relationship between chronotype and both mood disorders and metabolic dysfunction?

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Self assessment questions

1. The light-dark cycle is the strongest signal that entrains the circadian system?
2. Morning orientation has been associated with more depressive symptoms?
3. More circadian rhythm disruption has been observed in major depression than bipolar disorder?
4. Severe circadian misalignment due to shift work has been associated with an increased risk of metabolic disease, however social jetlag has not?
5. Later chronotype has been associated with higher HbA1c levels in type 2 diabetes?

Author note All contributors met the criteria for authorship.

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Answers

1. True
2. False
3. False
4. False
5. True