General Review

Circadian Rhythms in Anesthesia and Critical Care Medicine: Potential Importance of Circadian Disruptions

Seminars in Cardiothoracic and Vascular Anesthesia
2015, Vol. 19(1) 49–60

DOI: 10.1177/1089253214553066
scv.sagepub.com
SAGE

Jason Brainard, MD[1], Merit Gobel, BS[1], Karsten Bartels, MD[1], Benjamin Scott, MD[1], Michael Koeppen, MD[1,2], and Tobias Eckle, MD, PhD[1]

Abstract

The rotation of the earth and associated alternating cycles of light and dark—the basis of our circadian rhythms—are fundamental to human biology and culture. However, it was not until 1971 that researchers first began to describe the molecular mechanisms for the circadian system. During the past few years, groundbreaking research has revealed a multitude of circadian genes affecting a variety of clinical diseases, including diabetes, obesity, sepsis, cardiac ischemia, and sudden cardiac death. Anesthesiologists, in the operating room and intensive care units, manage these diseases on a daily basis as they significantly affect patient outcomes. Intriguingly, sedatives, anesthetics, and the intensive care unit environment have all been shown to disrupt the circadian system in patients. In the current review, we will discuss how newly acquired knowledge of circadian rhythms could lead to changes in clinical practice and new therapeutic concepts.

Keywords

anesthesia, circadian rhythm, cognitive dysfunction, critical care medicine, diabetes mellitus, genetic determinants, Per2, glucose oxidation, hypertension, inflammation

Circadian Rhythms: "External Cues" Versus "Internal Clock"

What would happen if there was no light? What would control the biological rhythm of a human being or a plant? Jean-Jacques d'Ortous de Mairan asked this question in 1729[1] when observing the movement of the leaves of a plant in synchrony with sunlight. He noted that a 24-hour pattern in the movement of the leaves of the *Mimosa pudica* plant continued even when the plant was kept in constant darkness. He concluded that there must be an "internal clock" that provided a circadian rhythm even without the presence of light. More than 200 years later, Jürgen Aschoff applied similar methods to investigations in humans by building an underground "bunker" to isolate human subjects from any external environmental cues.[2] Aschoff's research demonstrated that humans exhibited a persistent 25-hour biological cycle. A similar cycle has been identified in studies examining the circadian rhythms of blind persons.[3] However, it was not until researchers began experimenting with the circadian system in *Drosophila melanogaster* in the 1970s, that gene loci such as *Clock* or *Period* were identified as important regulators of these processes[4] (Figure 1). Results demonstrated that when *Clock* or *Period* genes were disrupted in animals, the circadian rhythm was severely compromised in conditions of constant darkness. To emphasize the endogenous self-sustained nature of biological rhythms, Franz Halberg coined the term *circadian* (Latin: circa = about; dies = day) time to refer to daily rhythms that are endogenously generated.[5] As such, any biological process in the body that repeats itself over a period of approximately 24 hours and maintains this rhythm in the absence of external stimuli is termed a *circadian rhythm*.

In contrast, the term *zeitgeber* (German for "time giver" or "synchronizer") was first used by Jürgen Aschoff to emphasize the existence of exogenous (external) cues that influence the timing of these internal clocks.[6] To maintain circadian synchrony, "zeitgebers" induce changes in the concentrations of the molecular components of the clock to levels consistent with the appropriate stage in the 24-hour cycle, a process termed entrainment (Figure 1). Thus, circadian entrainment describes a biological rhythm that is synchronized with the external physical environment. The

[1]University of Colorado Denver, Aurora, CO, USA
[2]Ludwig-Maximilians-University, Munich, Germany

Corresponding Author:
Tobias Eckle, Department of Anesthesiology, University of Colorado Denver, 12700 E 19th Avenue, Mailstop B112, RC 2, Room 7121, Aurora, CO 80045, USA.
Email: tobias.eckle@ucdenver.edu

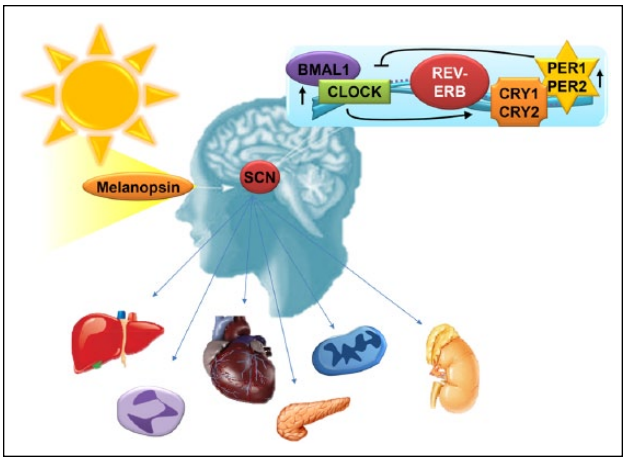

Figure 1. Regulatory mechanisms of the circadian system: The suprachiasmatic nucleus (SCN) in the brain is the central regulator of circadian rhythmicity. External stimuli such as light determine "zeitgeber" time. Light via melanopsin receptors in the retinal ganglion cells lead to the transcriptional induction of Clock and Bmal1, which leads in turn to the induction of Rev-Erb, Per1, Per2, Cry1, and Cry2. Via feedback inhibition of Clock and Bmal1, a cycle will be terminated and a new can begin. Hormonal and humoral factors are supposed to control circadian rhythms in peripheral organs.

most dominant zeitgeber appears to be sunlight, not surprising, as it is the strongest and most dependable representation of the time of day.[7,8]

As such, a hallmark of the mammalian circadian pacemaker—located in the suprachiasmatic nuclei (SCN) within our brain—is its ability to be synchronized by light, thus allowing organisms to adapt to temporal variations in natural light conditions.[9] Photic stimuli are transmitted from the retina to target neurons in the brain, where they are transduced to the molecular clockwork.[10,11] Light activation of melanopsin receptors[11] in the retinal ganglion cells leads to the transcriptional induction of circadian rhythm proteins (such as Clock, Bmal1, Rev-Erb, Period 1, Period 2, Cryptochrome 1, and Cryptochrome 2) and concomitant synchronization. Peripheral tissues display oscillations in circadian rhythm protein expression similar to those of the brain,[12,13] likely through secreted signaling molecules (Figure 1).[10,14,15]

Although it is now accepted that a component of our genome reflects the evolutionary influence of the earth's daily rotation about its axis,[16] little is known about how disturbances in this circadian system affect patient health and clinical outcomes. Further basic and clinical research addressing the importance of circadian rhythms in the context of critical care and anesthesia is highly warranted and necessary to develop a better understanding of complex pathophysiology and novel diagnostic and therapeutic approaches.

The Biology of Light

Earth's 24-hour rotational cycle with its light and dark periods has existed for more than 4 billion years and has led to the evolution of circadian rhythms in most organisms. Studies in numerous species have demonstrated that daylight is a powerful synchronizer that resets, in an intensity-dependent manner, endogenous circadian pacemakers.[17-21]

One of the most remarkable and measurable biological effects of light is suppression of melatonin production.[22] In 1980, a study demonstrated that bright light, both sunlight and intense artificial light, could suppress melatonin production in humans.[23] This research confirmed that humans have biological rhythms cued by sunlight and further, suggested that bright artificial light could be substituted for sunlight in order to experimentally, and perhaps therapeutically, manipulate biological rhythms in humans.

Sunlight has an intensity of greater than 10 000 lux, while ordinary room light is approximately 200 lux. It is compelling that light of different intensities appears to have different effects on the human body. With the exception of a few micro-environments, life on earth has adapted to a consistent pattern of alternating light-dark cycles. This was true for most of human evolution as well, until the widespread adoption of artificial lighting approximately 150 years ago. Beyond affecting circadian rhythms, recent evidence suggests that exposure to unnatural light cycles increases the risk for cancer,[24] sleep disturbances,[25] and mood disorders.[26] Furthermore, exposure to nighttime light has been linked to changes in metabolism. Shift workers who experience sustained nighttime illumination are at increased risk for cardiovascular disease and elevated body mass index[27-30] and nighttime light exposure at home is associated with increased body mass, waist circumference, elevated triglyceride levels, and poor cholesterol balance.[31]

Impact of Circadian Rhythms on Specific Clinical Disorders

While the analysis of circadian rhythm proteins and their misalignment in humans is difficult to assess, melatonin levels seem to be an excellent surrogate for a "normal" circadian rhythm.[32] As such sleep restriction has been shown to affect melatonin levels and circadian rhythms in humans.[32] On a molecular level, a mutation of the human circadian rhythm protein Per2 leads to a sleep disorder that is known as "familial advanced sleep-phase syndrome."[33] Interestingly, to identify somebody with this disease, early-morning serum melatonin levels are widely used and validated.[34]

Recent research has revealed that sleep duration has decreased in the United States.[35] Simultaneously, the prevalence of metabolic disease has increased over the same

time period.[35] Numerous cross-sectional and prospective clinical studies have demonstrated that shorter duration and poor-quality sleep predicts the development of obesity and type 2 diabetes, even after age, body mass index, and various other confounding variables are taken into account.[32,36-41] In one study, sleep restriction to 4 hours for 6 consecutive nights led to an impaired insulin sensitivity in a glucose challenge test.[42] These observations argue for the involvement of circadian rhythms in the pathogenesis of diseases, including diabetes and obesity. However, specific knowledge of circadian rhythm proteins and their molecular mechanisms will be required to prove causality.

Disruption of circadian rhythms may also play a role in a variety of central nervous system disorders. Examples include not only the aforementioned sleep disorders (delayed or advanced sleep phase disorder[33,43]) but also bipolar affective disorders.[44] Specific genetic variations in circadian clock genes have been identified for bipolar disease and schizophrenia,[45] and genetic polymorphisms in several clock genes have been linked to sleep disorders.[46]

In addition to central nervous system disorders, epidemiological studies have demonstrated that late-shift and overnight workers have a higher incidence of cardiovascular disease.[27,47-52] Evidence of an association between disrupted circadian rhythms and cardiovascular disease has been established in research on blood pressure,[53] heart rate,[54] endothelial function,[55] and the onset of myocardial infarction and stroke.[55,56] These clinical conditions all have distinct circadian patterns and disruption of biological rhythms may in particular contribute to the development of cardiovascular disease.[57] Other clinical diseases, including cancer, diabetes, and metabolic syndrome have also been associated with disrupted circadian rhythms.[36-40]

Unfortunately, genetic studies on circadian rhythm proteins in relation to those specific diseases are rare. A few polymorphisms of clock genes have been found in humans that are associated with metabolic diseases. For example, polymorphisms in *Clock* and *Bmal1*, have been linked to features of the metabolic syndrome. In small sample populations, polymorphisms in the *Clock* gene have been correlated with predisposition to obesity,[58,59] and 2 *Bmal1* haplotypes are associated with type 2 diabetes and hypertension.[60] Polymorphisms within other clock core genes (ie, *Per2*) have been associated with hypertension and high fasting blood glucose in studies of similar sample size.[61]

Recently, several genome-wide association studies led to the unexpected discovery that melatonin, a hormone implicated in seasonal and circadian rhythms, may be important in the regulation of mammalian glucose levels.[62,63] Indeed, genetic variants of the melatonin 1B receptor gene (MTNR1B) increase type 2 diabetes risk. In line with their role in type 2 diabetes, MTNR1B is expressed in pancreas cells, and melatonin modulates glucose-stimulated insulin secretion.[64] Interestingly, melatonin secretion is reported to be impaired in type 2 diabetic patients[65] and the melatonin profile relative to the feeding/fasting cycle is reversed when individuals are subjected to forced dyssynchrony.[66] These findings raise the possibility that disruption of circadian systems, either directly at the level of altered clock gene expression, or indirectly through effects on melatonin, may contribute to human metabolic syndrome and cardiovascular disease.

Novel Molecular Mechanisms

The organ-specific role of circadian rhythm proteins in the development of clinical disease has been an area of intense research over the past few years and significant advances in this field have recently been achieved. When specific circadian rhythm proteins are absent in mice, these animals develop similar medical conditions to those described in late-shift workers or patients with presumably disrupted circadian rhythms (Figure 2).

The Clock protein represents an important pacemaker of the circadian network acting in the SCN (Figure 1). When the *Clock* gene is deleted in mice, these animals develop "late-shift diseases," including diabetes[15] and cardiovascular disorders.[67] Clock even directly influences the endocrine function of the pancreas. When Clock is specifically deleted from the pancreas, mice are unable to secrete insulin and develop type 1 diabetes (Figure 2).[68]

Cryptochromes are another group of proteins known to play a role in circadian rhythms and have also been linked to the development of disease. Cryptochrome deficient mice exhibit enhanced aldosterone production leading to arterial hypertension[69] as well as disrupted regulation of hepatic gluconeogenesis and insulin resistance (Figure 2).[70]

Acute myocardial infarction is one of the most well-documented acute disease states with a diurnal or circadian incidence.[71-73] Investigations into the molecular mechanism of this clinical observation linked the circadian rhythm protein Per2 to myocardial ischemia.[13,15,71,74] In a mouse model of myocardial infarction, infarct sizes exhibited a circadian pattern. Furthermore, Per2 deficiency increased the size of myocardial infarcts. In contrast, when Per2 was overexpressed by intense daylight exposure, the size of the necrotic area after myocardial infarction was significantly reduced.[13] This study also reported elevated Per2 levels in human heart tissue of patients suffering from ischemic heart failure (Figure 2).[13]

Further studies have linked Per2 to noncardiac peripheral ischemia. Lack of the Per2 protein was injurious in a murine model for hind limb ischemia, leading to autoamputation of the affected legs.[75] In addition, Per2 seems to be involved in modulating the inflammatory response to tissue ischemia.[71] Together, these findings indicate an important role for the circadian system, and in particular the Per2 protein, in tissue ischemia.

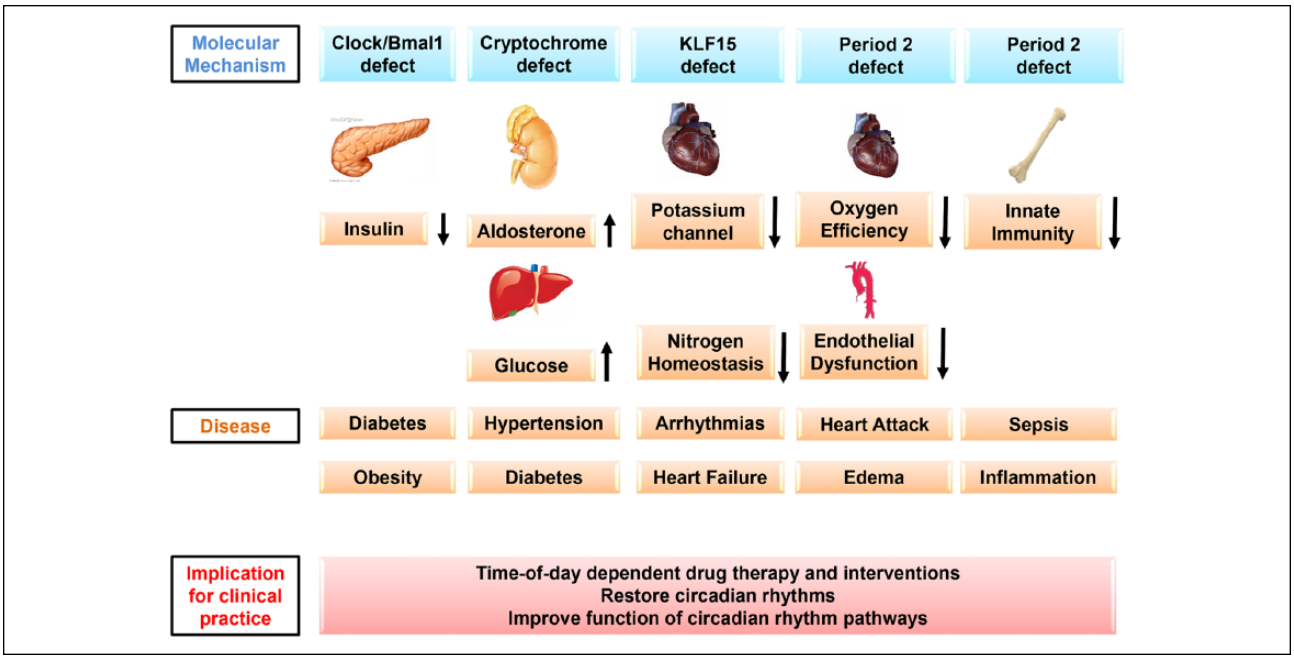

Figure 2. Disruption of the molecular "clock" and disease development. Numerous recent studies provide evidence that the circadian clock influences the development and progression of disease in an experimental setting. Nonfunctional circadian rhythm proteins in peripheral organs were linked to very specific disease (eg, Clock-diabetes, Cryptochrome-hypertension, Per2-heart attack, etc). These findings indicate that time-of-day–dependent drug therapy or interventions might be imperative. However, more important seems to be the restoration of circadian rhythms to improve the function of circadian rhythm pathways such as insulin secretion, inflammation, or metabolism.

Sudden cardiac arrest, often a consequence of cardiac arrhythmias, also exhibits a circadian pattern. A recent study identified a transcription factor, krueppel-like factor 15 (Klf15), as an important regulator of cardiac potassium channels.[76] Klf15 was shown to be transcriptionally under the control of the circadian rhythm proteins. Disruption of certain circadian rhythm proteins (Bmal1 or Per2) resulted in marked action potential prolongation due to near complete elimination of the fast component of the transient outward potassium current. As a result, deficiency or excess of Klf15 caused loss of rhythmic QT variation, abnormal repolarization, and enhanced susceptibility to ventricular arrhythmias. These findings point to circadian transcription of ion channels as a mechanism for cardiac arrhythmogenesis (Figure 2).

Finally, several recent studies found an association between circadian rhythms and the immune system. In particular, Toll-like receptors (TLRs) seemed to be substantially regulated in a circadian pattern. TLRs are a class of proteins that play a key role in innate and adaptive immunity and have been implicated in several diseases, including sepsis, various immunodeficiencies, atherosclerosis, asthma, and myocardial ischemia.[77] In this recent study, TLR9 exhibits circadian regulation in mice. This means that the inflammatory response to severe infection, as occurs in sepsis, is likely oscillating in a circadian fashion.[78] Other studies have demonstrated that the transcription factor Rev-Erb (Figure 1), an important regulator of the circadian network, also influences the synthesis and secretion of interleukin-17 (IL-17) from T helper cells.[79] IL-17 producing T helper cells are pro-inflammatory immune cells and circadian disruption has been associated with elevated intestinal T(H)17 cell frequencies and increased susceptibility to inflammatory disease (Figure 2).[79]

Taken together, this group of recently published studies indicates a very important role for the circadian rhythm network and its regulation in the development and progression of various diseases, including diabetes, hypertension, heart disease and sepsis. More specifically, this work has begun to describe the precise functions of the circadian proteins in peripheral organs and the mechanisms by which they may contribute to many important human diseases. Further clinical studies in humans are needed to apply this emerging knowledge to novel diagnostic and therapeutic strategies.

Implications for Clinical Practice

An improved understanding of the association between circadian rhythms and specific disease states could lead to significant changes in clinical practice and patient

outcomes (Figure 2). Timing of therapeutic interventions, ranging from medication delivery to major surgery,[80,81] may be altered based on comprehension of these biological systems. Research in chronotherapeutics[82] has already demonstrated promising results by improving the therapeutic index of several drugs. Chronotherapeutics involves synchronizing drug administration with a patient's daily, monthly, seasonal, or yearly biological clock, in order to maximize the health benefits and minimize adverse effects. For example, as a result of circadian variations in cholesterol synthesis (via the diurnal rhythmicity of the rate limiting enzyme HMG-CoA reductase) the efficacy of cholesterol-lowering statin medications is improved when these drugs are taken at bedtime. One of the first wide-scale applications of chronotherapeutics took place in the 1960s and involved synthetic corticosteroids.[83] However, the results did not necessarily translate into major changes in clinical practice and where changes did occur, they were not always recognized as chronotherapeutics.[84,85]

Recent studies on blood pressure medication made clear that bedtime administration is more effective than administration during morning hours. In addition, reduction in blood pressure during sleep has been identified as the most significant predictor of decreased cardiovascular risk in patients. As such, patients with chronic kidney disease have a high prevalence of increased blood pressure during sleep and a blunted sleep time–related blood pressure decline (a "nondipper" pattern), which is associated with disease severity. Administration of blood pressure lowering drugs at bedtime could therefore lead to significant improvement is this clinical setting.[80,86]

Inpatient insulin dosing may be optimized by incorporating recent evidence that supports a circadian pattern to insulin secretion and insulin sensitivity[87]. Further studies are required to determine the appropriate dosing and glucose level associated with best outcomes given the known dysfunction in the circadian system associated with critical illness.[88] Similarly, the improved clinical outcomes associated with intermittent versus continuous tube feeding may ultimately be explained by circadian patterns of hepatic metabolism.[89]

Circadian variation in immune system function may have broad impact in infectious disease states including sepsis and septic shock. The use of corticosteroids remains a common, albeit controversial, adjunct therapy for septic shock.[90] Sepsis has been shown to be associated with elevated serum concentrations of IL-17, which can in turn be dampened by treatment with hydrocortisone.[91] Given the nature of circadian rhythms and a recently described regulation of IL-17 by the circadian clock,[79] it is possible that the efficacy of corticosteroids in the management of sepsis could be greatly enhanced by synchronizing administration with these rhythms. Moreover, the clinical chronotherapy of corticosteroids might not only improve desired effects but, at the same time, avoid or minimize their side effects.

While some therapies, including anticoagulants, might already be administered at the correct time of day (we know, for example that in the early morning hours coagulation is enhanced) it remains unclear if these therapies are also effective when the normal circadian system has been disrupted. Successful pharmacotherapy may necessitate moving beyond identifying the optimal time of day for administration of a given drug (Figure 2). Indeed, restoration of a nonfunctional circadian system might be required before a treatment can be most effective. Daylight (and "real" night) simulation in intensive care units or novel drugs that could resynchronize the circadian system (Rev-Erb-agonists[92]) hold promise as emerging therapies to restore circadian function.

Circadian Rhythms in Anesthesia

Analgesics, including narcotics and various local anesthetics, are used on a daily basis by anesthesiologists. Early researchers discovered a time of day dependency for morphine-induced analgesia and duration of action for local anesthetics.[93-95]

Interestingly, recent reports support a strong association between surgery under general anesthesia and disturbances in circadian rhythms. It is proposed that these disturbances may lead to postoperative sleep and cognitive disorders.[96-98] Specific medications used during general anesthesia are thought to play a role in these circadian disruptions. Clinically, many patients experience profound sleep disruption and delirium following surgery and general anesthesia. Managing this effect has the potential to help expedite postoperative recovery and improve postoperative cognitive function. Restoration or resetting of the circadian rhythm following general anesthesia might help to blunt or alleviate symptoms of insomnia, confusion, and postoperative delirium. The prevention of postoperative delirium is crucially important given the strong association between postoperative delirium and increased morbidity and mortality.[99-104]

Circadian Rhythms in Critical Care Medicine

Effects on Sleep and Cognitive Function

Critically ill patients suffer from similar disruption in circadian rhythms and the clinical effects of altered sleep–wake cycles and cognitive dysfunction.[105-109] Medications used in the care of critically ill patients overlap and have similar pharmacology with those used in general anesthesia and thus the clinical effects of altered sleep–wake cycles and cognitive function are similar. Sedative medications used by

critical care practitioners in the treatment of agitation, delirium, and insomnia likely lead to worsening of these disorders.[110-112] Benzodiazepines appear to be one of the worst offenders and thus many experts advocate for discontinuing their use in critically ill patients.[112-115] Unfortunately, almost all sedative agents are associated with delirium and appear to worsen sleep quality.[110,111,116] Dexmedetomidine may be associated with the least risk of developing delirium.[117-120]

As discussed earlier, endogenous melatonin might play an important role in the development of circadian rhythms associated diseases.[62,63] Critically ill patients tend toward not only altered sleep patterns but also abnormal levels of melatonin. Results on melatonin expression have generated interest in the use of exogenous melatonin and melatonin agonists to improve sleep and cognitive function.[104,121] Earlier this year, a promising randomized controlled trial demonstrated effectiveness in the use of a melatonin agonist (Ramelteon) versus placebo in the prevention of delirium.[121] In the context of a possible melatonin–circadian rhythm–clinical disease axis, studies on endogenous and exogenous melatonin, pharmacological agonists, and associated genetics could provide important insight into the development and treatment of critical illness.

In general, the hypothalamic–pituitary–adrenal (HPA) axis is also under the control of the circadian rhythm and plays an important role in critical illness and sleep–wake patterns.[122,123] A prospective, observational study involving 24 critically ill sedated patients demonstrated the 24-hour profiles of blood melatonin or cortisol were greatly disturbed or even abolished compared with the well-known rhythmic 24-hour patterns in healthy control subjects.[124] Currently, there are gaps in our understanding of secretory patterns and control of cortisol during illness, and these gaps limit our ability to design optimal therapeutic regimens.[123]

Finally, environmental factors play a substantial role in the disruption of sleep–wake cycles. Critically ill patients in the intensive care unit suffer from more frequent sleep deprivation and sleep disturbances than patients on a general ward.[105,106,125] Several factors can contribute to the increase in altered sleep–wake cycles, including noise, patient care interactions, mechanical ventilation, pain, artificial light, fatigue, stress, delirium, and other cognitive dysfunction.[126,127] These same factors likely contribute to the increased risk of developing severe circadian rhythm disruptions (Figure 3). Clinical research on these circadian disruptions and the potential benefits of interventions to maintain normal sleep–wake cycles is needed.

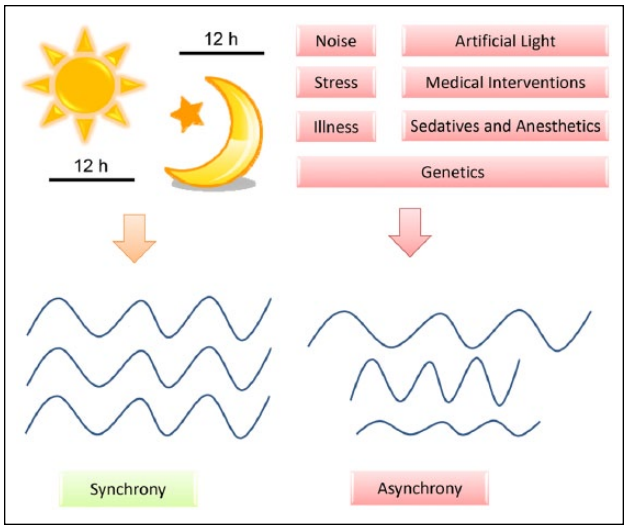

Figure 3. Factors influencing the circadian system. While regular day/night cycles with dark, quiet nights are supposed to be the basis of a well-synchronized circadian rhythm in humans, noise, interventions, artificial light, and drugs on intensive care units have proven to disrupt a functional circadian system and might lead to disease progression.

Effects on Sepsis and Disease Progression

Critically ill patients, and in particular patients diagnosed with sepsis, have been shown to exhibit a very distinct metabolic phenotype.[128] These patients experience dysfunction in mitochondria, endothelia, NO synthesis, and pyruvate dehydrogenase.[128] Previous studies have established that the above defects are all associated with a dysfunction of the circadian rhythm protein Per2 (Figure 4).[13,71,75] Two recent clinical trials demonstrate disrupted circadian system function in patients with severe sepsis as demonstrated by urinary 6-sulfatoxy-melatonin production.[129,130] This dysfunction was not observed in critically ill patients without sepsis.[129] In a rat model of sepsis, survival improved in animals maintained on a circadian light–dark cycle.[131] Thus, restoration of a circadian rhythm with normal Per2 levels could be beneficial in restoring the metabolic disruption associated with sepsis (Figure 4).

Therapy

General Considerations

Restoration of an intact circadian system is likely complex given the multifaceted etiology for these disruptions. Genetic factors (polymorphisms in core clock genes), medications (anesthetics, benzodiazepines), and environmental factors (noise, artificial lighting) can all result in disruption of the circadian system. Biologically, circadian rhythms are controlled by a cyclical expression of circadian genes. Mutations in these genes could result in a modification or disruption of the circadian oscillator and therefore it is important to analyze genetic factors that may contribute to circadian disruption.[132] The discovery of novel genes involved in circadian rhythm-related diseases

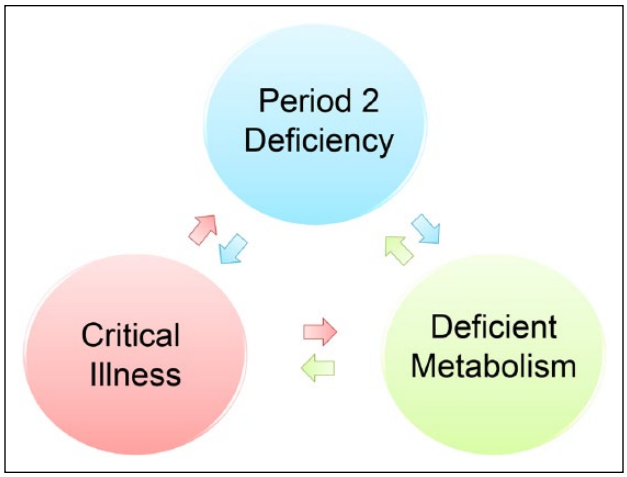

Figure 4. The link between critical illness and the circadian system. Sepsis can lead to disrupted mitochondrial function, nonfunctional NO synthesis and deficient glycolytic pathways. Period 2 (Per2) deficiency has been associated with such metabolic alterations in mice. Therefore, one could hypothesize that restoration of a circadian rhythm with a functional Per2 protein might help restore a nonfunctional metabolic phenotype in sepsis and thereby alleviating illness and disease progression.

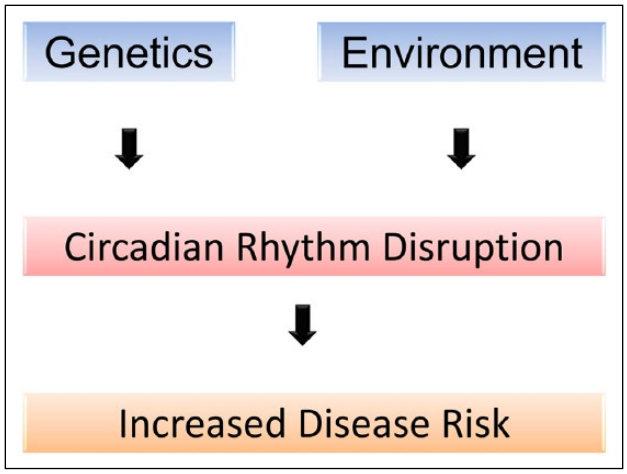

Figure 5. Model of disease development. Several environmental and genetic factors can cause disruption of the circadian rhythms. This disruption could contribute to multifactorial disease such as cardiovascular disease, a metabolic syndrome, or progression of critical illness.

will open up new opportunities for therapy and may identify biomarkers for detection and prognosis (Figure 5).

Avoidance of offending medications and improving environmental conditions may prevent circadian disruptions and increase the native ability of the body to maintain or restore an intact circadian system. Clinical outcome research is warranted to test this hypothesis. Studies in intensive care unit and non–intensive care unit patients have demonstrated a decreased incidence in delirium and improved sleep–wake cycles with nonpharmacological and environmental treatments.[133,134] Treatments may be very simple and cost-effective, including earplugs and eye masks[135-137] and early mobilization.[138,139] Future trials will help clinicians navigate the risks and benefits of interventions that may disrupt sleep and circadian function and develop guidelines for most effective patient care.

Beyond prevention of circadian disruption, it may be that enhancement of normal circadian rhythmicity has a role to play in disease states like sepsis. Recent efforts led to the discovery of specific enhancers of the circadian rhythm proteins. Compounds such as a "Rev-Erb" agonist[92] were shown to enhance the amplitude of circadian rhythmicity and—even more important—were able to improve metabolism in mice.[92,140] In addition to restoration of circadian cycles, these medications may become promising drugs in the treatment of diabetes, myocardial ischemia, sepsis, and other circadian associated illnesses (Figure 6).

Light Therapy

Given the primary importance of light in the control of circadian rhythms,[7,8] it can be postulated that exposure to light might be preventative or therapeutic in the treatment of circadian related illnesses. Regular room light is not as effective as sunlight in entraining the circadian oscillator because of its significantly lower intensity,[23,141] and even if timed appropriately, may result in chronic circadian misalignment.[141] Evidence demonstrates an association between artificial indoor lighting and a deregulation of hormonal rhythms.[142] Although studies from our group indicated daylight exposure in animals increased the expression of Per2 in the heart, ultimately resulting in cardioprotection, the exact timing and intensity of this exposure is unclear. Studies in animals have shown that either constant darkness or constant light were worse in an animal model for sepsis when compared with regular day–night cycles.[131] These results underline the potential importance of maintaining natural day–night cycles in humans. Many intensive care units in the United States and Europe have been rebuilt to increase exposure to natural light and some new intensive care units in Germany (Heart Center or ICU Charite, Berlin, Germany) have incorporated advanced noise reduction and daylight simulation. Further clinical trials on the use of natural or artificial light to prevent or treat circadian-related illness are needed (Figure 6). These studies will have to define the length (12 vs 16 hours) of daylight, the wavelength (blue light vs full spectrum light), and the light intensity (4000 vs 14 000 lux) that might be beneficial in treating illness. Finally, it remains to be seen whether such treatments will be able to prevent or restore a dysfunctional circadian rhythm network.

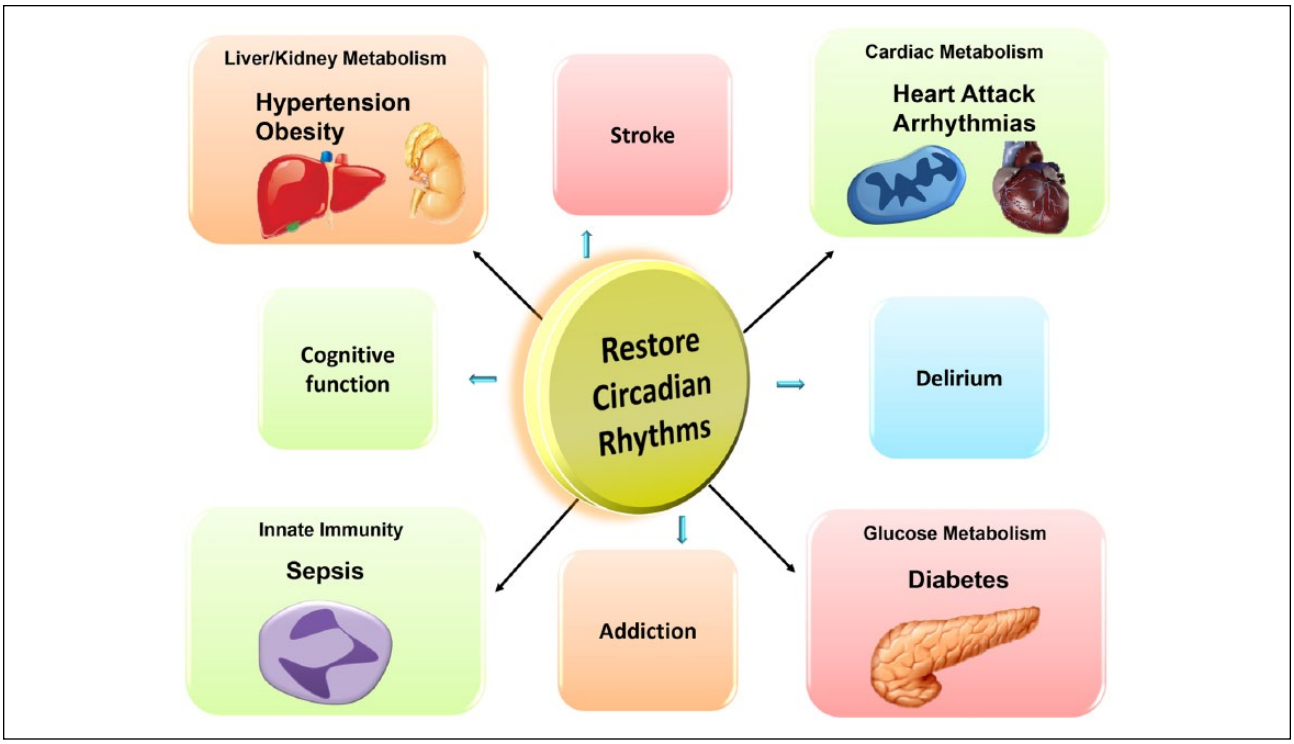

Figure 6. Restoration of circadian rhythms—potential for treatment. Recent improvements in our understanding of how circadian rhythms affect disease development, including diabetes, hypertension, heart ischemia, stroke, sepsis, or delirium, exhibits the potential to discover novel therapies for critically ill patients or those undergoing general anesthesia. Restoration of circadian rhythms might be key in treating associated disease.

Summary

The circadian system influences multiple human biochemical and physiological variables, including sleep–wake cycles, body temperature, hormone secretion, metabolism, and our immune system. Recent improvements in our understanding of how circadian rhythms impact important human disease states may enable the discovery of novel therapies for critically ill patients or those undergoing general anesthesia. Future research will need to include genetic data, as well as pharmacological and environmental factors in the maintenance and restoration of human circadian rhythms. Understanding the influence of disrupted circadian rhythms on outcomes in critical care and anesthesia and researching new therapeutic interventions might significantly improve the care we provide our patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The present research work is supported by National Heart, Lung, and Blood Institute (NIH-NHLBI) grant 1K08HL102267 to TE.

References

1. Edery I. Circadian rhythms in a nutshell. *Physiol Genomics*. 2000;3:59-74.
2. Aschoff J. Circadian rhythms in man. *Science*. 1965;148: 1427-1432.
3. Arendt J, Aldhous M, Wright J. Synchronisation of a disturbed sleep-wake cycle in a blind man by melatonin treatment. *Lancet*. 1988;1:772-773.
4. Tei H, Okamura H, Shigeyoshi Y, et al. Circadian oscillation of a mammalian homologue of the Drosophila period gene. *Nature*. 1997;389:512-516.
5. Cornelissen G, Halberg F, Halberg J, Schwartzkopff O, Cugini P. Remembering the father of chronobiology and chronomics: Franz Halberg, MD (5 July 1919–9 June 2013). *Clin Ter*. 2013;164:I-VI.
6. Aschoff J. Exogenous and endogenous components in circadian rhythms. *Cold Spring Harb Symp Quant Biol*. 1960;25:11-28.
7. Wright KP Jr, McHill AW, Birks BR, Griffin BR, Rusterholz T, Chinoy ED. Entrainment of the human circadian clock to the natural light-dark cycle. *Curr Biol*. 2013;23: 1554-1558.
8. Roenneberg T, Kumar CJ, Merrow M. The human circadian clock entrains to sun time. *Curr Biol*. 2007;17:R44-R45.

9. Jakubcakova V, Oster H, Tamanini F, et al. Light entrainment of the mammalian circadian clock by a PRKCA-dependent posttranslational mechanism. *Neuron*. 2007;54:831-843.
10. Takahashi JS, Hong HK, Ko CH, McDearmon EL. The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nat Rev Genet*. 2008;9:764-775.
11. Guler AD, Ecker JL, Lall GS, et al. Melanopsin cells are the principal conduits for rod-cone input to non-image-forming vision. *Nature*. 2008;453:102-105.
12. Bendova Z, Sumova S. Photoperiodic regulation of PER1 and PER2 protein expression in rat peripheral tissues. *Physiol Res*. 2006;55:623-632.
13. Eckle T, Hartmann K, Bonney S, et al. Adora2b-elicited Per2 stabilization promotes a HIF-dependent metabolic switch crucial for myocardial adaptation to ischemia. *Nat Med*. 2012;18:774-782.
14. Zhang J, Kaasik K, Blackburn MR, Lee CC. Constant darkness is a circadian metabolic signal in mammals. *Nature*. 2006;439:340-343.
15. Bonney S, Hughes K, Harter PN, Mittelbronn M, Walker L, Eckle T. Cardiac Period 2 in myocardial ischemia: clinical implications of a light dependent protein. *Int J Biochem Cell Biol*. 2013;45:667-671.
16. Carlson DE. Are you having a good day: a passing nicety or a fundamental question in the intensive care unit? *Crit Care Med*. 2012;40:344-345.
17. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol*. 2000;526(pt 3):695-702.
18. St Hilaire MA, Gooley JJ, Khalsa SB, Kronauer RE, Czeisler CA, Lockley SW. Human phase response curve to a 1 h pulse of bright white light. *J Physiol*. 2012;590:3035-3045.
19. Dewan K, Benloucif S, Reid K, Wolfe LF, Zee PC. Light-induced changes of the circadian clock of humans: increasing duration is more effective than increasing light intensity. *Sleep*. 2011;34:593-599.
20. Chang AM, Santhi N, St Hilaire M, et al. Human responses to bright light of different durations. *J Physiol*. 2012;590:3103-3112.
21. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science*. 2002;295:1070-1073.
22. Illnerova H, Vanecek J. Response of rat pineal serotonin N-acetyltransferase to one min light pulse at different night times. *Brain Res*. 1979;167:431-434.
23. Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in humans. *Science*. 1980;210:1267-1269.
24. Stevens RG. Light-at-night, circadian disruption and breast cancer: assessment of existing evidence. *Int J Epidemiol*. 2009;38:963-970.
25. Kohyama J. A newly proposed disease condition produced by light exposure during night: asynchronization. *Brain Dev*. 2009;31:255-273.
26. Driesen K, Jansen NW, Kant I, Mohren DC, van Amelsvoort LG. Depressed mood in the working population: associations with work schedules and working hours. *Chronobiol Int*. 2010;27:1062-1079.
27. van Amelsvoort LG, Schouten EG, Kok FJ. Impact of one year of shift work on cardiovascular disease risk factors. *J Occup Environ Med*. 2004;46:699-706.
28. Parkes KR. Shift work and age as interactive predictors of body mass index among offshore workers. *Scand J Work Environ Health*. 2002;28:64-71.
29. Knutsson A. Health disorders of shift workers. *Occup Med (Lond)*. 2003;53:103-108.
30. Ha M, Park J. Shiftwork and metabolic risk factors of cardiovascular disease. *J Occup Health*. 2005;47:89-95.
31. Obayashi K, Saeki K, Iwamoto J, et al. Exposure to light at night, nocturnal urinary melatonin excretion, and obesity/dyslipidemia in the elderly: a cross-sectional analysis of the HEIJO-KYO study. *J Clin Endocrinol Metab*. 2013;98:337-344.
32. Nguyen J, Wright KP Jr. Influence of weeks of circadian misalignment on leptin levels. *Nat Sci Sleep*. 2010;2:9-18.
33. Toh KL, Jones CR, He Y, et al. An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. *Science*. 2001;291:1040-1043.
34. Keijzer H, Smits MG, Duffy JF, Curfs LM. Why the dim light melatonin onset (DLMO) should be measured before treatment of patients with circadian rhythm sleep disorders. *Sleep Med Rev*. 2014;18:333-339.
35. Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev*. 2007;11:163-178.
36. Kawakami N, Takatsuka N, Shimizu H. Sleep disturbance and onset of type 2 diabetes. *Diabetes Care*. 2004;27:282-283.
37. Spiegel K, Tasali E, Leproult R, Van Cauter E. Effects of poor and short sleep on glucose metabolism and obesity risk. *Nat Rev Endocrinol*. 2009;5:253-261.
38. Suwazono Y, Dochi M, Sakata K, et al. A longitudinal study on the effect of shift work on weight gain in male Japanese workers. *Obesity (Silver Spring)*. 2008;16:1887-1893.
39. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet*. 1999;354:1435-1439.
40. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med*. 2004;1:e62.
41. Depner CM, Stothard ER, Wright KP Jr. Metabolic consequences of sleep and circadian disorders. *Curr Diab Rep*. 2014;14:507.
42. Spiegel K, Knutson K, Leproult R, Tasali E, Van Cauter E. Sleep loss: a novel risk factor for insulin resistance and type 2 diabetes. *J Appl Physiol (1985)*. 2005;99:2008-2019.
43. Ptacek LJ, Jones CR, Fu YH. Novel insights from genetic and molecular characterization of the human clock. *Cold Spring Harb Symp Quant Biol*. 2007;72:273-277.
44. Albrecht U. Circadian clocks and mood-related behaviors. *Handb Exp Pharmacol*. 2013;(217):227-239.
45. Cuninkova L, Brown SA. Peripheral circadian oscillators: interesting mechanisms and powerful tools. *Ann N Y Acad Sci*. 2008;1129:358-370.
46. He Y, Jones CR, Fujiki N, et al. The transcriptional repressor DEC2 regulates sleep length in mammals. *Science*. 2009;325:866-870.

47. Kivimaki M, Virtanen M, Elovainio M, Vaananen A, Keltikangas-Jarvinen L, Vahtera J. Prevalent cardiovascular disease, risk factors and selection out of shift work. *Scand J Work Environ Health*. 2006;32:204-208.
48. Harma M. Shift work and cardiovascular disease—from etiologic studies to prevention through scheduling. *Scand J Work Environ Health*. 2001;27:85-86.
49. Boggild H, Knutsson A. Shift work, risk factors and cardiovascular disease. *Scand J Work Environ Health*. 1999;25: 85-99.
50. Akerstedt T, Knutsson A, Alfredsson L, Theorell T. Shift work and cardiovascular disease. *Scand J Work Environ Health*. 1984;10:409-414.
51. Akerstedt T, Knutsson A. Cardiovascular disease and shift work. *Scand J Work Environ Health*. 1997;23:241-242.
52. Tuchsen F, Hannerz H, Burr H. A 12 year prospective study of circulatory disease among Danish shift workers. *Occup Environ Med*. 2006;63:451-455.
53. Curtis AM, Cheng Y, Kapoor S, Reilly D, Price TS, Fitzgerald GA. Circadian variation of blood pressure and the vascular response to asynchronous stress. *Proc Natl Acad Sci U S A*. 2007;104:3450-3455.
54. Malik M, Farrell T, Camm AJ. Circadian rhythm of heart rate variability after acute myocardial infarction and its influence on the prognostic value of heart rate variability. *Am J Cardiol*. 1990;66:1049-1054.
55. Tofler GH, Brezinski D, Schafer AI, et al. Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. *N Engl J Med*. 1987;316:1514-1518.
56. Panza JA, Epstein SE, Quyyumi AA. Circadian variation in vascular tone and its relation to alpha-sympathetic vasoconstrictor activity. *N Engl J Med*. 1991;325:986-990.
57. Staels B. When the Clock stops ticking, metabolic syndrome explodes. *Nat Med*. 2006;12:54-55.
58. Scott EM, Carter AM, Grant PJ: Association between polymorphisms in the Clock gene, obesity and the metabolic syndrome in man. *Int J Obes (Lond)*. 2008;32:658-662.
59. Sookoian S, Gemma C, Gianotti TF, Burgueno A, Castano G, Pirola CJ. Genetic variants of Clock transcription factor are associated with individual susceptibility to obesity. *Am J Clin Nutr*. 2008;87:1606-1615.
60. Woon PY, Kaisaki PJ, Braganca J, et al. Aryl hydrocarbon receptor nuclear translocator-like (BMAL1) is associated with susceptibility to hypertension and type 2 diabetes. *Proc Natl Acad Sci U S A*. 2007;104:14412-14417.
61. Englund A, Kovanen L, Saarikoski ST, et al. NPAS2 and PER2 are linked to risk factors of the metabolic syndrome. *J Circadian Rhythms*. 2009;7:5.
62. Bouatia-Naji N, Bonnefond A, Cavalcanti-Proenca C, et al. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. *Nat Genet*. 2009;41:89-94.
63. Prokopenko I, Langenberg C, Florez JC, et al. Variants in MTNR1B influence fasting glucose levels. *Nat Genet*. 2009;41:77-81.
64. Lyssenko V, Nagorny CL, Erdos MR, et al. Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. *Nat Genet*. 2009;41:82-88.
65. Radziuk J, Pye S. Diurnal rhythm in endogenous glucose production is a major contributor to fasting hyperglycaemia in type 2 diabetes. Suprachiasmatic deficit or limit cycle behaviour? *Diabetologia*. 2006;49:1619-1628.
66. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci U S A*. 2009;106: 4453-4458.
67. Pan X, Jiang XC, Hussain MM. Impaired cholesterol metabolism and enhanced atherosclerosis in clock mutant mice. *Circulation*. 2013;128:1758-1769.
68. Marcheva B, Ramsey KM, Buhr ED, et al. Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature*. 2010;466:627-631.
69. Doi M, Takahashi Y, Komatsu R, et al. Salt-sensitive hypertension in circadian clock-deficient Cry-null mice involves dysregulated adrenal Hsd3b6. *Nat Med*. 2010;16:67-74.
70. Zhang EE, Liu Y, Dentin R, et al. Cryptochrome mediates circadian regulation of cAMP signaling and hepatic gluconeogenesis. *Nat Med*. 2010;16:1152-1156.
71. Bonney S, Kominsky D, Brodsky K, Eltzschig H, Walker L, Eckle T. Cardiac Per2 functions as novel link between fatty acid metabolism and myocardial inflammation during ischemia and reperfusion injury of the heart. *PLoS One*. 2013;8:e71493.
72. Braunwald E. On circadian variation of myocardial reperfusion injury. *Circ Res*. 2012;110:6-7.
73. Frank A, Bonney M, Bonney S, Weitzel L, Koeppen M, Eckle T. Myocardial ischemia reperfusion injury: from basic science to clinical bedside. *Semin Cardiothorac Vasc Anesth*. 2012;16:123-132.
74. Eltzschig HK, Bonney SK, Eckle T. Attenuating myocardial ischemia by targeting A2B adenosine receptors. *Trends Mol Med*. 2013;19:345-354.
75. Wang CY, Wen MS, Wang HW, et al. Increased vascular senescence and impaired endothelial progenitor cell function mediated by mutation of circadian gene Per2. *Circulation*. 2008;118:2166-2173.
76. Jeyaraj D, Haldar SM, Wan X, et al. Circadian rhythms govern cardiac repolarization and arrhythmogenesis. *Nature*. 2012;483:96-99.
77. Eckle T, Eltzschig HK. Toll-like receptor signaling during myocardial ischemia. *Anesthesiology*. 2011;114:490-492.
78. Silver AC, Arjona A, Walker WE, Fikrig E. The circadian clock controls toll-like receptor 9-mediated innate and adaptive immunity. *Immunity*. 2012;36:251-261.
79. Yu X, Rollins D, Ruhn KA, et al. TH17 cell differentiation is regulated by the circadian clock. *Science*. 2013;342: 727-730.
80. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. *Chronobiol Int*. 2010;27:1629-1651.
81. Eckel-Mahan K, Sassone-Corsi P. Metabolism control by the circadian clock and vice versa. *Nat Struct Mol Biol*. 2009;16:462-467.

82. Chassard D, Duflo F, de Queiroz Siqueira M, Allaouchiche B, Boselli E. Chronobiology and anaesthesia. *Curr Opin Anaesthesiol*. 2007;20:186-190.
83. Smolensky MH, Reinberg A. The chronotherapy of corticosteroids: practical application of chronobiologic findings to nursing. *Nurs Clin North Am*. 1976;11:609-619.
84. Zhu LL, Zhou Q, Yan XF, Zeng S. Optimal time to take once-daily oral medications in clinical practice. *Int J Clin Pract*. 2008;62:1560-1571.
85. De Giorgi A, Mallozzi Menegatti A, Fabbian F, Portaluppi F, Manfredini R. Circadian rhythms and medical diseases: does it matter when drugs are taken? *Eur J Intern Med*. 2013;24:698-706.
86. Hermida RC, Ayala DE, Smolensky MH, et al. Chronotherapy improves blood pressure control and reduces vascular risk in CKD. *Nat Rev Nephrol*. 2013;9:358-368.
87. Egi M, Bellomo R, Stachowski E, French CJ, Hart G, Stow P. Circadian rhythm of blood glucose values in critically ill patients. *Crit Care Med*. 2007;35:416-421.
88. Leelarathna L, English SW, Thabit H, et al. Feasibility of fully automated closed-loop glucose control using continuous subcutaneous glucose measurements in critical illness: a randomized controlled trial. *Crit Care*. 2013;17:R159.
89. MacLeod JB, Lefton J, Houghton D, et al. Prospective randomized control trial of intermittent versus continuous gastric feeds for critically ill trauma patients. *J Trauma*. 2007;63:57-61.
90. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358:111-124.
91. Bosmann M, Meta F, Ruemmler R, et al. Regulation of IL-17 family members by adrenal hormones during experimental sepsis in mice. *Am J Pathol*. 2013;182:1124-1130.
92. Solt LA, Wang Y, Banerjee S, et al. Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists. *Nature*. 2012;485:62-68.
93. Lutsch EF, Morris RW. Light reversal of a morphine-induced analgesia susceptibility rhythm in mice. *Experientia*. 1971;27:420-421.
94. Morris RW, Lutsch EF. Susceptibility to morphine-induced analgesia in mice. *Nature*. 1967;216:494-495.
95. Reinberg A, Reinberg MA. Circadian changes of the duration of action of local anaesthetic agents. *Naunyn Schmiedebergs Arch Pharmacol*. 1977;297:149-152.
96. Guo X, Kuzumi E, Charman SC, Vuylsteke A. Perioperative melatonin secretion in patients undergoing coronary artery bypass grafting. *Anesth Analg*. 2002;94:1085-1091.
97. Dispersyn G, Pain L, Challet E, Touitou Y. General anesthetics effects on circadian temporal structure: an update. *Chronobiol Int*. 2008;25:835-850.
98. Karkela J, Vakkuri O, Kaukinen S, Huang WQ, Pasanen M. The influence of anaesthesia and surgery on the circadian rhythm of melatonin. *Acta Anaesthesiol Scand*. 2002;46:30-36.
99. Lin SM, Liu CY, Wang CH, et al. The impact of delirium on the survival of mechanically ventilated patients. *Crit Care Med*. 2004;32:2254-2259.
100. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291:1753-1762.
101. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med*. 2009;180:1092-1097.
102. van den Boogaard M, Schoonhoven L, Evers AW, van der Hoeven JG, van Achterberg T, Pickkers P. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. *Crit Care Med*. 2012;40:112-118.
103. Pandharipande PP, Girard TD, Jackson JC, et al; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369:1306-1316.
104. Bellapart J, Boots R. Potential use of melatonin in sleep and delirium in the critically ill. *Br J Anaesth*. 2012;108:572-580.
105. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med*. 2001;163:451-457.
106. Gabor JY, Cooper AB, Crombach SA, et al. Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *Am J Respir Crit Care Med*. 2003;167:708-715.
107. Bienert A, Bartkowska-Sniatkowska A, Wiczling P, et al. Assessing circadian rhythms during prolonged midazolam infusion in the pediatric intensive care unit (PICU) children. *Pharmacol Rep*. 2013;65:107-121.
108. Gehlbach BK, Chapotot F, Leproult R, et al. Temporal disorganization of circadian rhythmicity and sleep-wake regulation in mechanically ventilated patients receiving continuous intravenous sedation. *Sleep*. 2012;35:1105-1114.
109. Olofsson K, Alling C, Lundberg D, Malmros C. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. *Acta Anaesthesiol Scand*. 2004;48:679-684.
110. Pandharipande P, Ely EW. Sedative and analgesic medications: risk factors for delirium and sleep disturbances in the critically ill. *Crit Care Clin*. 2006;22:313-327.
111. Bourne RS, Mills GH. Sleep disruption in critically ill patients—pharmacological considerations. *Anaesthesia*. 2004;59:374-384.
112. Trompeo AC, Vidi Y, Locane MD, et al. Sleep disturbances in the critically ill patients: role of delirium and sedative agents. *Minerva Anestesiol*. 2011;77:604-612.
113. McPherson JA, Wagner CE, Boehm LM, et al. Delirium in the cardiovascular ICU: exploring modifiable risk factors. *Crit Care Med*. 2013;41:405-413.
114. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. 2006;104:21-26.
115. Barr J, Fraser GL, Puntillo K, et al; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41:263-306.
116. Kondili E, Alexopoulou C, Xirouchaki N, Georgopoulos D. Effects of propofol on sleep quality in mechanically ventilated critically ill patients: a physiological study. *Intensive Care Med*. 2012;38:1640-1646.

117. Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics*. 2009;50:206-217.
118. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009;301:489-499.
119. Pandharipande P, Cotton BA, Shintani A, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma*. 2008;65: 34-41.
120. Dasta JF, Kane-Gill SL, Pencina M, et al. A cost-minimization analysis of dexmedetomidine compared with midazolam for long-term sedation in the intensive care unit. *Crit Care Med*. 2010;38:497-503.
121. Hatta K, Kishi Y, Wada K, et al. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. *JAMA Psychiatry*. 2014;71:397-403.
122. Van Cauter E, Leproult R, Plat L. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *JAMA*. 2000;284:861-868.
123. Gibbison B, Angelini GD, Lightman SL. Dynamic output and control of the hypothalamic-pituitary-adrenal axis in critical illness and major surgery. *Br J Anaesth*. 2013;111:347-360.
124. Paul T, Lemmer B. Disturbance of circadian rhythms in analgosedated intensive care unit patients with and without craniocerebral injury. *Chronobiol Int*. 2007;24:45-61.
125. Cooper AB, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ. Sleep in critically ill patients requiring mechanical ventilation. *Chest*. 2000;117:809-818.
126. Toublanc B, Rose D, Glerant JC, et al. Assist-control ventilation vs. low levels of pressure support ventilation on sleep quality in intubated ICU patients. *Intensive Care Med*. 2007;33:1148-1154.
127. Chan MC, Spieth PM, Quinn K, Parotto M, Zhang H, Slutsky AS. Circadian rhythms: from basic mechanisms to the intensive care unit. *Crit Care Med*. 2012;40:246-253.
128. Ruggieri AJ, Levy RJ, Deutschman CS. Mitochondrial dysfunction and resuscitation in sepsis. *Crit Care Clin*. 2010;26:567-575.
129. Mundigler G, Delle-Karth G, Koreny M, et al. Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. *Crit Care Med*. 2002;30: 536-540.
130. Verceles AC, Silhan L, Terrin M, Netzer G, Shanholtz C, Scharf SM. Circadian rhythm disruption in severe sepsis: the effect of ambient light on urinary 6-sulfatoxymelatonin secretion. *Intensive Care Med*. 2012;38:804-810.
131. Carlson DE, Chiu WC. The absence of circadian cues during recovery from sepsis modifies pituitary-adrenocortical function and impairs survival. *Shock*. 2008;29:127-132.
132. Rosato E, Tauber E, Kyriacou CP. Molecular genetics of the fruit-fly circadian clock. *Eur J Hum Genet*. 2006;14:729-738.
133. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc*. 2001;49:516-522.
134. Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999;340:669-676.
135. Van Rompaey B, Elseviers MM, Van Drom W, Fromont V, Jorens PG. The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients. *Crit Care*. 2012;16:R73.
136. Le Guen M, Nicolas-Robin A, Lebard C, Arnulf I, Langeron O. Earplugs and eye masks vs routine care prevent sleep impairment in post-anaesthesia care unit: a randomized study. *Br J Anaesth*. 2014;112:89-95.
137. Hu RF, Jiang XY, Zeng YM, Chen XY, Zhang YH. Effects of earplugs and eye masks on nocturnal sleep, melatonin and cortisol in a simulated intensive care unit environment. *Crit Care*. 2010;14:R66.
138. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373:1874-1882.
139. Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil*. 2010;91:536-542.
140. Cho H, Zhao X, Hatori M, et al. Regulation of circadian behaviour and metabolism by REV-ERB-α and REV-ERB-β. *Nature*. 2012;485:123-127.
141. Boivin DB, Duffy JF, Kronauer RE, Czeisler CA. Dose-response relationships for resetting of human circadian clock by light. *Nature*. 1996;379:540-542.
142. Gooley JJ, Rajaratnam SM, Brainard GC, Kronauer RE, Czeisler CA, Lockley SW. Spectral responses of the human circadian system depend on the irradiance and duration of exposure to light. *Sci Transl Med*. 2010;2:31ra33.