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Health impact and management of a disrupted circadian rhythm and sleep in critical illnesses

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Two Billion Years ago all organisms had to adapt to two major changes: Sunlight and oxygen. Based on these significant changes, all organisms and finally the human body developed mechanisms to sense oxygen or light. Interestingly both systems share similarities: Proteins from those systems belong to similar gene families. As such the well know hypoxia inducible factor HIF1A belongs to the family of so-called 'PAS domain positive' proteins (1–3). HIF1A is a transcription factor that is stabilized under conditions of low oxygen conditions and leads to the up regulation of genes such as VEGF to promote vessel growth. More vessels eventually can help a tissue to maintain oxygen levels despite compromised oxygen availability. Interestingly Clock, Cryptochrome or Periods, key proteins of the circadian rhythm, also belong to the same family of PAS positive proteins (1). Even more compelling, the PAS domain can function as oxygen or light sensor (1). However, while scientists and physicians have recognized the importance of oxygen and the need to treat conditions of low oxygen availability in patients (e.g. during sepsis, heart ischemia or lung disease), the need to monitor light or to treat disrupted circadian rhythms has not been introduced into clinical practice yet. During the last 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 (2, 4, 5). Interestingly, the ICU environment in particular has been shown to disrupt the circadian system of patients (2). Newly acquired knowledge of circadian rhythms could now lead to changes in clinical practice and new therapeutic concepts for critical illness and associated diseases and complications. Critically ill patients suffer from disruption in circadian rhythms and the clinical effects of altered sleep-wake cycles and cognitive dysfunction. 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. 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. These same factors likely contribute to the increased risk of developing severe circadian rhythm disruptions. Clinical research concentrating on the circadian disruptions and whether interventions to maintain normal sleep-wake can improve patient outcomes are warranted.

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Therefore the thematic issue of the **Current Pharmaceutical Design** *'Health impact and management of a disrupted circadian rhythm and sleep in critical illnesses'* will review current literature in an attempt to initiate the implementation and discovery of new therapeutic concepts and to contribute to an emerging and important field of research. While critical illness is an example of a disrupted circadian system, current research realizes that life style changes over the last century might have contributed to circadian rhythm disruption in humans and the development of certain diseases such as metabolic disorders and many associated diseases.

The first article by Remi et al (8) gives an excellent introduction into the world of circadian rhythms. Details on the internal and external clocks are given to the reader which should help to become familiar with those concepts. Most importantly, Remi et al points out that 'sunlight is the most important 'zeitgeber' in humans (9). 'Zeitgber' is German and means 'time giver'. In fact, it means nothing else but that our organisms are synchronized to external stimuli and light seems most important. Interestingly, social cues, exercise, and food intake, even though very important in our lives seem not as critical as daylight. This thematic is a clear thread running through the current issue and points out that modern live styles with disruption of natural day night cycles might be a health threat. Remi et al also points out that the traditional disruption of a circadian system is the so-called 'jet lag'. As such the term 'social jetlag' was coined, meaning that our social lives are similar to a permanent 'jet lag'. Social jet lag means eventually that our internal clock is not aligned with the external clock. This could have significant consequences to our body, as we might be awake and eating, however our gut system is ready for a sleep. This misalignment seems most important for critical illness and future research will have to find ways to overcome those issues.

Wright et al (10) seamlessly connects to the review from Remi et al. In his review he points out that hospital lightening is crucial for the well-being of our patients. Interestingly newborns have still to develop a circadian rhythm entrained by daylight. If these early days in our lives are important to build a functional circadian system will need to be shown yet. However, there is enough evidence that controlled lightening on neonatal or adult intensive care units have the potential to improve sleep, alertness during the day, overall well-being and shorten the time until discharge. As such this review points out that our ability to control light gives us the opportunity to use light as treatment tool. In fact, a pain study found that more sunlight was associated with less pain medication. Anyhow, not only hospitals but also nursing homes or our own homes need to be taken care of. Future analysis of different light conditions in different settings seems mandatory to understand the impact on health and well-being. Future research will hopefully guide us how to use light a therapy (2, 4, 5).

Scott et al. (11) focuses on delirium, a disease of high interest as it is associated with high mortality rates (12, 13). In this review he finds plenty of evidence that disruption of a circadian rhythm could be the cause of delirium or at least - could make it worse. One line of evidence in support of circadian dysrhythmias as a cause of delirium has been the observation that circadian disruption and sleep fragmentation often precede the development of delirium. In fact, these prodromal symptoms, including inattention, irritability, restlessness, and dysphoria are all common symptoms of a broad range of circadian rhythm

disorders such as jet lag and shift-work sleep disorder. However, the pathophysiology and etiology of delirium are complex and multifactorial. It is at once a disorder of consciousness, of circadian disruption, and of inflammation and stress. Unfortunately, causal relationships remain unclear and most evidence to date provides only correlation. The same is true for treatment and prophylaxis strategies. Significant methodological challenges have impaired the study of both drugs and non-pharmacologic interventions. Anyhow, non-pharmacologic interventions aimed at restoring evolutionarily normative human environmental and behavioral factors, show great promise.

Rol et al (14) review how melatonin, an indicator of sleep, could be used as therapy – together with light – to enhance the day-night contrast in critical ill patients. Most importantly, Rol et al point out that circadian disruption or circadian misalignment is a new syndrome that needs to be recognized and probably has a significant impact on the outcome of critical ill patients. This might be due to the fact that a circadian rhythm disruption worsens delirium and sepsis. Melatonin, as a hallmark of the circadian rhythms (15), indicates sleep quality and a functional circadian rhythm. Melatonin has also been shown to have anti-inflammatory and antioxidant effects. Recent research on melatonin to treat delirium show first promising results. In fact, there is a strong connection, between sleep, dementia, depression and delirium – all probably linked to the circadian system. As such all these conditions improve with intense light therapy, a ‘circadian rhythm enhancer’. Rol at al provide an extremely comprehensive review on light or melatonin in the ICU environment. Not surprisingly they provide evidence for light or melatonin to be therapeutic in delirium, a major contributor to mortality in ICU patients. Future research will have to prove if enhancing the day-night contrast with intense light and melatonin could be a powerful strategy to reduce circadian disruption and treat delirium or sepsis in critical ill patients.

Koeppen at al. (16) discuss recent basic science findings on the interaction of the circadian rhythm and the innate immune system. This perfectly connects to the previous article from Rol et al reviewing the interaction of circadian disruption and sepsis. This review shows that many immunological factors are circadian. E.g. toll like receptors (17), IL-6, or tumor necrosis factor alpha have a circadian pattern and this might influence the outcome of infections in our patients. It seems compelling that restoring a disrupted circadian rhythm might be beneficial in critical ill patients that suffer from infections or even sepsis. If and how circadian rhythm dysfunction directly impacts bacterial infections will need future research. However, a recent study on the microbiome found that the circadian system is a major control point of our natural bacterial environment (18). If this bacterial system is out of balance we all know very well that certain infections take over and can be life threatening. In general, a better understanding of how the innate immune system fights infections and how the circadian rhythms influences this fight, could contribute to better therapeutic options in critical illness and beyond.

Tunez et al (19) provide a very detailed review on the relationship between melatonin, oxidative stress and central nervous system disorders. This review perfectly adds to the reviews on delirium and melatonin treatment in critical ill patients. Melatonin, a significant hormone needed for the regulation of the circadian rhythm and endogenous redox modulation, plays a major role for homeostasis in the CNS. Its depletion or lack

unequivocally leads to cell damaging processes linked to disruption of the circadian rhythm, oxidative stress and inflammatory processes that, altogether, could be the pathophysiological basis for several disorders of the CNS. Delirium can also be classified as central nervous system disorder and therefore the mechanisms provided by Tunez et al would explain why melatonin agonists have successfully been used in the treatment of delirium. Future studies will be necessary to identify and characterize the precise role of melatonin in health and disease states in humans.

Kolliputi et al. (20) bring a new aspect to the field of disrupted circadian rhythms. Here he reviews how hyperoxia is a factor that could contribute to circadian rhythm disruption in critical illness and enhance acute lung injury. Interestingly hyperoxia seems to have similar effects to the lung tissue as hypoxia (21). Kolliputi elegantly reviews how hyperoxia is a common treatment in critical ill patients with acute lung injury. In fact, hyperoxia was found to dysregulate the circadian rhythm gene expression. Future studies will be necessary to understand the impact of hyperoxia on the circadian system in this particular patient population. In addition to hyperoxia, which eventually induces oxidative stress, oxidative stress itself can change the expression of core circadian genes which finally could enhance inflammation. A better understanding of these concepts in critical ill patients will hopefully lead to better treatment options.

Schillaci et al (22) gives a broader review on obstructive sleep apnea and its impact on cardiovascular disease. This review serves as perfect connection between the reviews on how disrupted circadian rhythms affect lung disease and the following reviews on how – disrupted circadian rhythms affect cardiac disease. In obstructive sleep apnea it seems – at least in part- that CNS dysfunction leads to hypoxic events during the sleep that finally can result in disease such as heart attacks, stroke, or hypertension. So far no specific treatment for this disease is available and the benefit of CPAP (continuous positive airway pressure) has not been shown yet. Anesthesiologists are in particular afraid of patients with this disease as anesthetics worsen symptoms of obstructive sleep apnea and eventually lead to apneic events after surgery. This is probably associated with a higher mortality rate (23). As this disease occurs during the sleep phase and circadian rhythms control sleep, the involvement of circadian rhythms seems compelling. Future studies will be necessary to understand if circadian rhythms are involved in the pathogenesis and if circadian rhythm enhancers such as light treatment during the day or melatonin treatment for the night could help to improve this condition in patients.

Martino et al (24) follow with a review on how disrupted circadian rhythms could be a major player in the development of cardiovascular disease (3–5). The cardiovascular system exhibits significant daily rhythms in physiologic processes (heart rate, blood pressure, cardiac contractility and function), and molecular gene and protein expression. An increasing number of clinical and experimental studies demonstrate the circadian system is an important underlying mechanism that coordinates these rhythmic processes for the health of the cardiovascular system. However, what happens when rhythms are disturbed has been clinically unappreciated. Martino et al describe the profound adverse impact of disturbed circadian rhythms and sleep on the cardiovascular system, including recovery from myocardial infarction in acute care settings, shift work and heart disease, sleep disorders

including obstructive sleep apnea, and cardiovascular pathophysiology associated with disturbed nocturnal blood pressure profiles. Considering the importance of circadian rhythms and sleep provides novel approaches to improving the management and treatment of heart disease in clinical settings such as critical care patients and beyond.

Aizawa et al (25) continue with a review on the relation of circadian rhythms and cardiac arrhythmias. This has been found recently to be an important aspect affecting patient's outcome as it could be the cause of sudden cardiac death (26). In fact, it has been known that sudden cardiac death has a circadian pattern but just recently circadian rhythm genes have been identified as a potential cause (26). Interestingly sleep disorder breathing or obstructive sleep apnea is also associated with increased cardiac arrhythmias. It will be important for future studies to understand how genetic factors such as mutations in circadian rhythm genes could triggers those disease. On the other hand it will be important to understand if life style changes or critical illness could be the starting point of a circadian rhythm disruption that finally could lead to cardiac arrhythmias. Anyhow, better understanding of how circadian rhythm proteins can influence cardiac arrhythmias seems to be important to improve the way we deal with those diseases.

Yu-Xia Zhao et al. (27) finish this series with a review on how circadian rhythms might play a role in the aftermath of a heart attack. They report that circadian rhythms might directly regulate angiogenesis. Determining the mechanisms of angiogenesis and vessel maturation in the ischemic heart under the control of circadian rhythms could help in the development of novel and angiogenesis-targeted therapeutics for the treatment of myocadardial ischemia. In fact, circadian rhythm genes regulate almost all angiogenic pathways and vascular permeability. Circadian rhythms and circadian rhythm genes may be good therapeutic targets for angiogenesis after heart attacks. However, further investigations are needed and warranted.

In summary, this issue makes clear that many important biological functions such as sleep, alertness, breathing, hormone balance, heart rhythms, lung function, immune function, angiogenesis and many more are significantly influenced by the circadian system. However, more important is that disruption of a circadian rhythm function leads directly to disease development and might be an important factor for disease severity in critical ill patients (2, 5). Even though we have realized that our environment – in the hospital or at home - has a significant impact on the integrity of circadian rhythms and sleep we still have not established a monitoring system or a potent therapy to restore a dysfunctional circadian system.

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