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Phyllis C. Zee

Neurobiology of Circadian Rhythm Regulation 403

Alan M. Rosenwasser and Fred W. Turek

Over the past few decades, multilevel research has elucidated the basic neuroanatomy, neurochemistry, and molecular neurobiology of the master circadian pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN). The circadian timing system is composed of a large number of cellular oscillators located in the SCN, in non-SCN brain structures, and throughout the body. Cellular-level oscillations are generated by a molecular feedback loop in which circadian clock genes rhythmically regulate their own transcription, as well as that of hundreds of clock-controlled genes. The maintenance of proper coordination within this network of cellular- and tissue-level clocks is essential for health and well-being.

Genetics of Circadian Rhythms 413

Tomas S. Andreani, Taichi Q. Itoh, Evrim Yildirim, Dae-Sung Hwangbo, and Ravi Allada

Nearly all organisms exhibit time-dependent behavior and physiology across a 24-hour day known as circadian rhythms. These outputs are manifestations of endogenous cyclic gene expression patterns driven by the activity of a core transcription/translation feedback loop. Cyclic gene expression determines highly tissue-specific functional activity regulating such processes as metabolic state, endocrine activity, and neural excitability. Entrainment of these cellular clocks is achieved through exogenous daily inputs, such as light and food. Dysregulation of the transcription/translation feedback loop has been shown to result in a wide range of disorders and diseases driving increased interest in circadian therapies.

Aging and Circadian Rhythms 423

Jeanne F. Duffy, Kirsi-Marja Zitting, and Evan D. Chinoy

Aging is associated with numerous changes, including changes in sleep timing, duration, and quality. The circadian timing system interacts with a sleep-wake homeostatic system to regulate human sleep, including sleep timing and structure. This article reviews key features of the human circadian timing system, age-related changes in the circadian timing system, and how those changes may contribute to the observed alterations in sleep.

Effect of Light and Melatonin and Other Melatonin Receptor Agonists on Human Circadian Physiology 435

Jonathan S. Emens and Helen J. Burgess

Circadian (body clock) timing has a profound influence on mental health, physical health, and health behaviors. This review focuses on how light, melatonin, and other melatonin receptor agonist drugs can be used to shift circadian timing in patients with misaligned circadian rhythms. A brief overview of the human circadian system is provided, followed by a discussion of patient characteristics and safety

considerations that can influence the treatment of choice. The important features of light treatment, light avoidance, exogenous melatonin, and other melatonin receptor agonists are reviewed, along with some of the practical aspects of light and melatonin treatment.

Consequences of Circadian Disruption on Cardiometabolic Health **455**

Sirimon Reutrakul and Kristen L. Knutson

Cardiovascular disease, diabetes and obesity are highly prevalent diseases associated with reduced quality of life and life expectancy. We discuss a novel risk factor for these cardiometabolic diseases: circadian disruption. Circadian disruption occurs when the internal circadian (~24-hour) rhythms are not in synchrony with the environment or each other. This paper reviews (1) cardiometabolic health of shift work, which often leads to circadian disruption, (2) effects of experimentally disrupted circadian rhythms on cardiometabolic function, (3) observational studies of sleep timing and behavioral chronotype, and (4) potential mediators linking chronotype and shift work to circadian disruption and cardiometabolic health.

Consequences of Circadian Disruption on Neurologic Health **469**

Aleksandar Videnovic and Phyllis C. Zee

Circadian rhythms have a major role in physiology and behavior. Circadian disruption has negative consequences for physiologic homeostasis at molecular, cellular, organ-system, and whole-organism levels. The onset of many cerebrovascular insults shows circadian temporal trends. Impaired sleep-wake cycle, the most robust output rhythms of the circadian system, is significantly affected by neurodegenerative disorders, may precede them by decades, and may also affect their progression. Emerging evidence suggests that circadian disruption may be a risk factor for these neurologic disorders. This article discusses the implications of circadian rhythms in brain disorders, with an emphasis on cerebrovascular and neurodegenerative disorders.

Circadian Disruption in Psychiatric Disorders **481**

Stephanie G. Jones and Ruth M. Benca

Evidence suggests that abnormalities in circadian rhythms might prove causally or pathophysiologically significant in psychiatric illness. The circadian regulation of hormonal and behavioral timekeeping processes is often altered in patients with major depression, bipolar disorder, and schizophrenia, and a susceptibility to rhythm instability may contribute to the functional impairment. For some patients, interventions that stabilize or resynchronize circadian rhythms prove therapeutically effective. Circadian disruption in the clinical profiles of most psychiatric illnesses and the treatment efficacy of chronobiological interventions suggest that attention to circadian phenotypes in a range of psychiatric disorders may help to uncover shared pathophysiologic mechanisms.

Non–24-Hour Sleep–Wake Rhythm Disorder in Sighted and Blind Patients **495**

Makoto Uchiyama and Steven W. Lockley

Non–24-hour sleep–wake rhythm disorder (N24SWD) is a cyclic debilitating circadian rhythm sleep disorder characterized by an inability to sleep on a 24-hour schedule. Individuals isolated from a 24-hour light–dark cycle exhibit sleep–wake

cycles different from 24 hours. Relatively rare in sighted patients, it may be associated with delayed sleep–wake rhythm disorder or psychiatric disorders. It is more common in totally blind individuals owing to the lack of light information reaching the circadian pacemaker in the hypothalamus. We review the clinical characteristics of patients with N24SWD, discuss the biological mechanisms that may underlie its development, and describe treatment strategies.

Irregular Sleep-Wake Rhythm Disorder **517**

Sabra M. Abbott and Phyllis C. Zee

Irregular sleep-wake rhythm disorder is a circadian rhythm disorder characterized by multiple bouts of sleep within a 24-hour period. Patients present with symptoms of insomnia, including difficulty either falling or staying asleep, and daytime excessive sleepiness. The disorder is seen in a variety of individuals, ranging from children with neurodevelopmental disorders, to patients with psychiatric disorders, and most commonly in older adults with neurodegenerative disorders. Treatment of irregular sleep-wake rhythm disorder requires a multimodal approach aimed at strengthening circadian synchronizing agents, such as daytime exposure to bright light, and structured social and physical activities. In addition, melatonin may be useful in some patients.

Jet Lag and Shift Work Disorder **523**

Kathryn J. Reid and Sabra M. Abbott

Jet lag and shift work disorder are circadian rhythm sleep-wake disorders resulting from behaviorally altering the sleep-wake schedule in relation to the external environment. Not everyone who experiences trans-meridian travel or performs shift work has a disorder. The prevalence of jet lag disorder is unclear, approximately 5%–10% of shift workers have shift work disorder. Treatment aims to realign the internal circadian clock with the external environment. Behavioral therapies include sleep hygiene and management of the light-dark and sleep schedule. Pharmacologic agents are used to treat insomnia and excessive sleepiness, and melatonin is used to facilitate sleep and circadian realignment.