

Stahl's Illustrated

Chapter 1

Neurobiology and Genetics of Sleep/Wake Disorders

In Chapter 1, we address the sleep/wake cycle and how this circadian behavior is affected by a myriad of neurotransmitter systems. We also discuss the molecular clock, a series of interacting transcription factors that influence sleep and many other physiological processes, and how genetic variation in molecular clock components may influence the sleep/wake cycle as well as cardiometabolic health, mental illness propensity, and risk of cancer. We hope that this chapter will convey the importance of sleep to whole body wellness so that readers will more enthusiastically appreciate the need for accurate diagnosis (Chapter 2) and appropriate treatment (Chapter 3) when the sleep/wake cycle is disrupted.

Epidemiology and Costs of Sleep/Wake Disorders

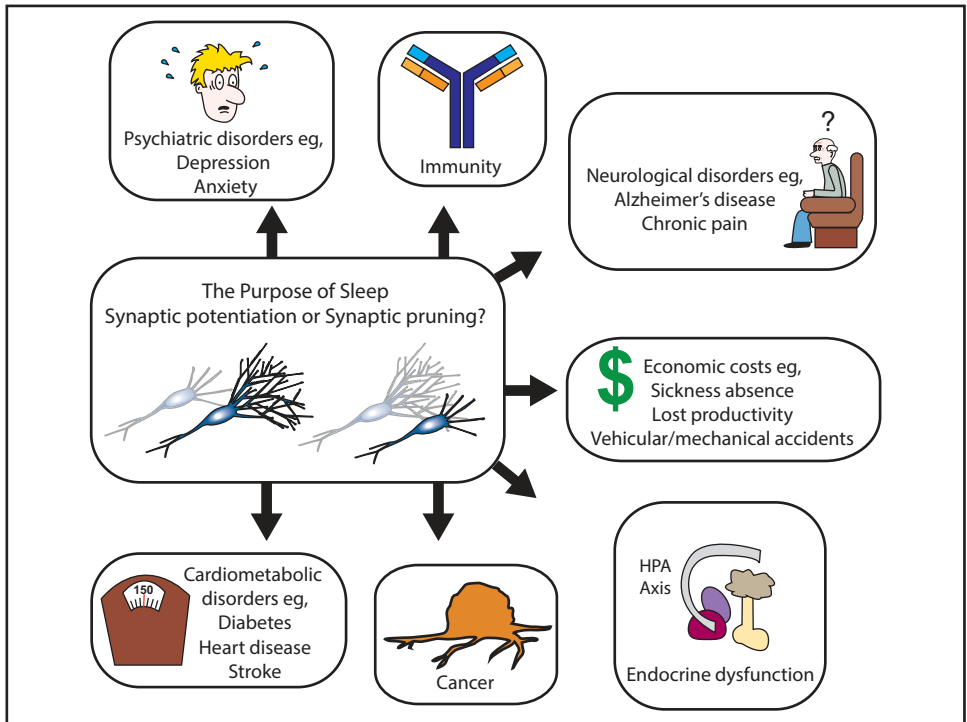


FIGURE 1.1. There is still much debate over the purpose of sleep. Some propose that sleep is essential for synaptic growth, while others argue that sleep is necessary for synaptic pruning (Mignot, 2012; Dresler et al., 2014). Regardless of which hypothesis—or some combination of both—is more accurate, it has become increasingly evident that disturbances of the sleep/wake cycle have a detrimental effect on a myriad of physiological and psychiatric functions. Aside from the economic costs of sleep/wake disorders, the risk of cardiometabolic disease, cancer, mental illness, and overall poorer quality of life are all increased when the sleep/wake cycle is disturbed (Cappuccio et al., 2010; Guo et al., 2013; Lallukka et al., 2014; Liu et al., 2013; Ohayon, 2012; Palma et al., 2013; Pigeon et al., 2012).

Sleep: How Much Is Too Much? Too Little?

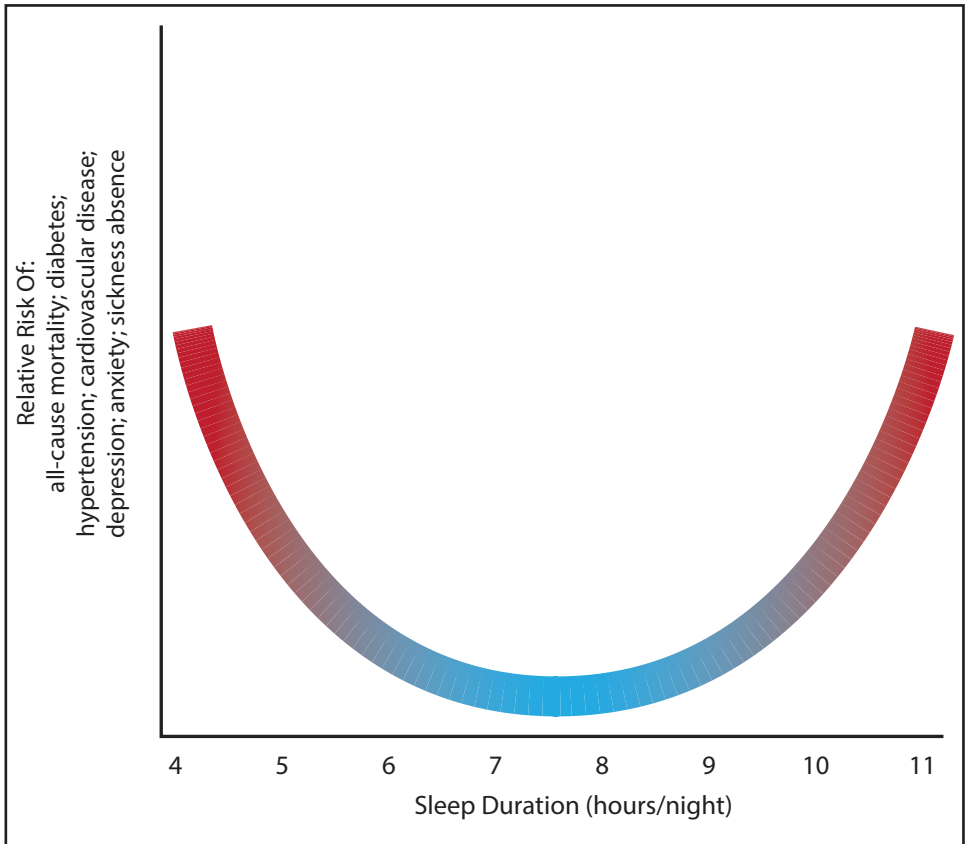


FIGURE 1.2. Both a short duration (<7 hours/night) and a long duration (>9 hours/night) of sleep have been associated with a variety of physiological and psychiatric illnesses, such as diabetes and depression, as well as an increased risk of death (Cappuccio et al., 2010; Guo et al., 2013; Lallukka et al., 2014; Liu et al., 2013). These data, represented here as a U-shaped curve, depict the sleep/wake cycle as a homeostatic process that requires a careful balance in order to maintain optimal health.

Arousal Spectrum

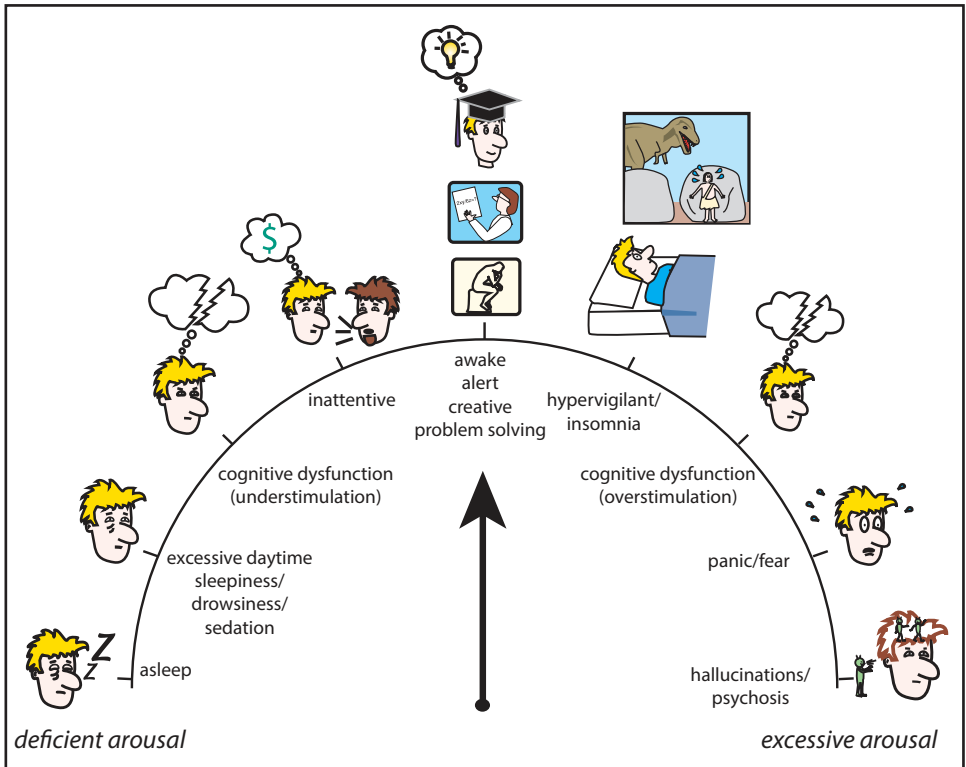


FIGURE 1.3. One's state of arousal is more complicated than simply being awake or asleep. Arousal exists as if on a dimmer switch, with many phases along the spectrum. Where on the spectrum one lies is largely influenced by 5 key neurotransmitters: histamine, dopamine, norepinephrine, serotonin, and acetylcholine. When there is balance between too much and too little arousal, one is awake, alert, and able to function well. As the dial shifts to the right, there is too much arousal, which may cause hypervigilance and consequently insomnia at night. Further increases in arousal can cause cognitive dysfunction, panic, and in extreme cases hallucinations. On the other hand, as arousal diminishes, individuals may experience inattentiveness, cognitive dysfunction, sleepiness, and ultimately sleep (Stahl, 2013).

The Sleep/Wake Cycle

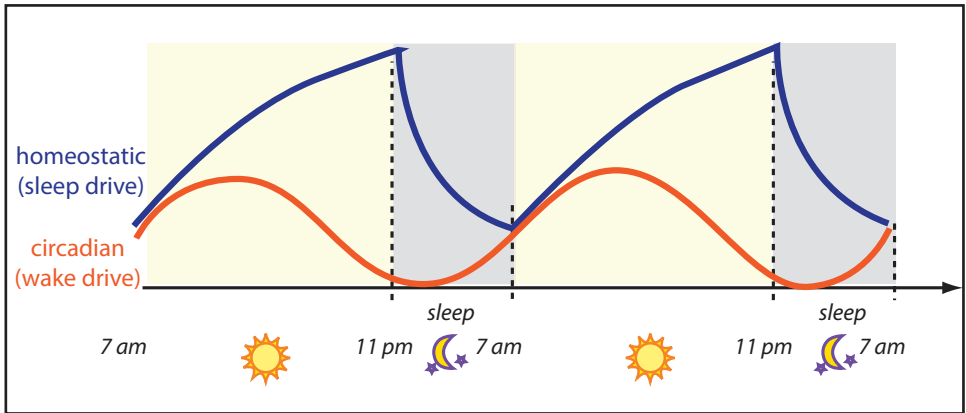


FIGURE 1.4. The sleep/wake cycle is mediated by 2 opposing drives: the homeostatic sleep drive and the circadian wake drive. The homeostatic drive accumulates throughout periods of wakefulness and is opposed by the circadian drive. The longer an individual is awake, the greater the homeostatic drive (Krystal et al., 2010). The homeostatic drive is dependent upon the accumulation of adenosine, which leads to the disinhibition of the ventrolateral preoptic (VLPO) nucleus and the release of GABA/galanin as part of the sleep circuit. The circadian drive, mediated by light acting upon the suprachiasmatic nucleus (SCN), stimulates the release of hypocretin/orexin as part of the wake circuit (Wulff et al., 2010).

The Sleep Cycle

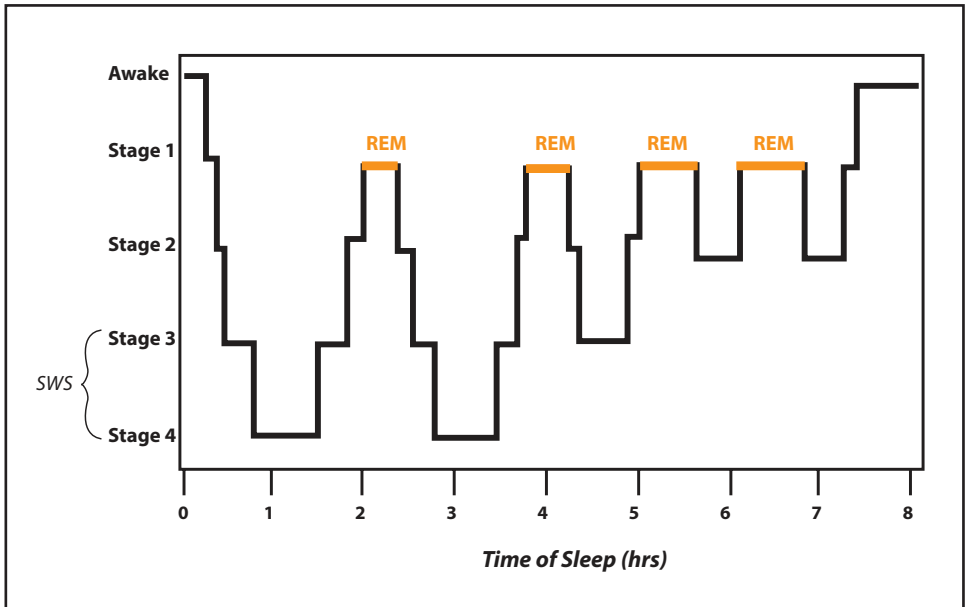


FIGURE 1.5. The complete sleep cycle (non-REM and REM) lasts approximately 90 minutes and occurs 4 to 5 times a night (Reeve and Bailes, 2010). Stages 1 and 2 comprise non-REM sleep, whereas stages 3 and 4 are part of deeper, slow-wave sleep (SWS) (Tafti, 2009). During the normal sleep period, the duration of non-REM sleep is gradually reduced while the duration of REM sleep is increased. REM sleep is characterized by faster activity on an electroencephalogram (EEG)—similar to that seen during periods of wakefulness—as well as distinct eye movements and peripheral muscle atonia. It is during REM sleep that dreaming occurs, and PET studies have shown activation of the thalamus, the visual cortex, and limbic regions accompanied by reduced metabolism in other regions, such as the dorsolateral prefrontal cortex (DLPFC) and the parietal cortex, during REM sleep. In contrast, there is overall reduced brain activity during non-REM sleep (Larson-Prior et al., 2014).

Circadian Rhythms

Zeitgebers: External Cues to Synchronize Circadian Rhythms





- Light 
- Melatonin 
- Eating and Drinking Patterns 
- Social Interactions 

FIGURE 1.6. Virtually all living creatures have an internal molecular clock that synchronizes biological processes such as the sleep/wake cycle and metabolism to a 24-hour circadian rhythm. Although the molecular clock is self-sustaining, it needs to be reset daily. If the molecular clock is not reset, it will drift and become out of sync with environmental cues. These synchronizing cues, termed zeitgebers, include light/dark cycles generated by the movement of the Earth, endogenous or exogenous melatonin, social interactions, and food availability (Van Someren et al., 2007).

Light: The Most Powerful Zeitgeber

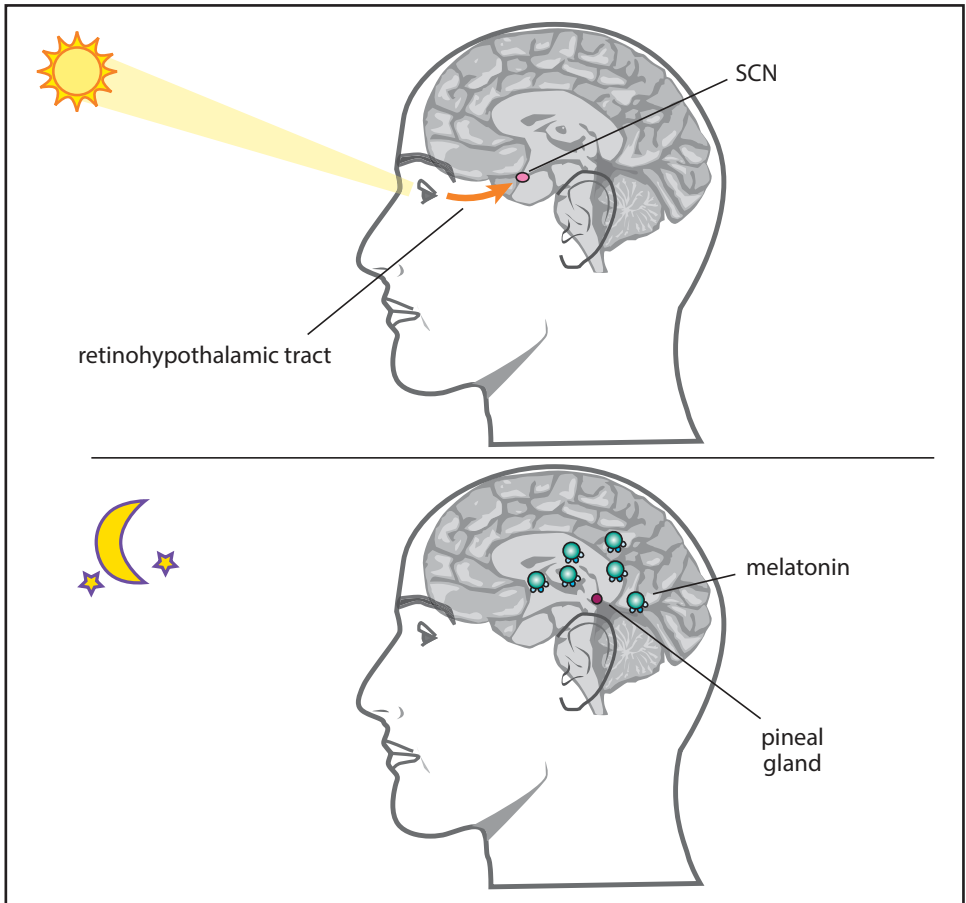


FIGURE 1.7. Although various factors can reset the clock, light is the most powerful synchronizer. When light enters through the eye, it is transferred via the retinohypothalamic tract to the suprachiasmatic nucleus (SCN) within the hypothalamus. During periods of darkness, the SCN induces the release of melatonin from the pineal gland, whereas light suppresses the release of melatonin (Zawilska, 2009).

Control of Sleep by the Suprachiasmatic Nucleus

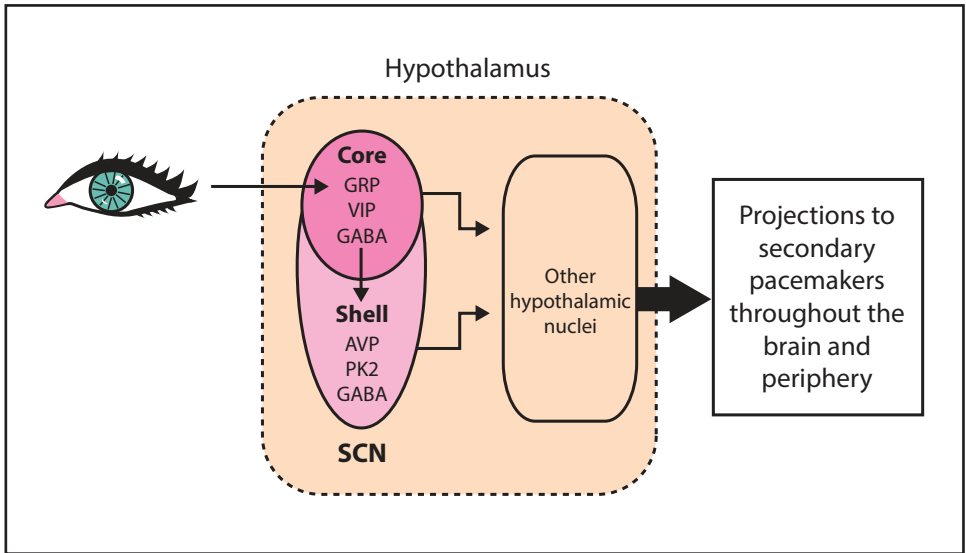


FIGURE 1.8. The main circadian pacemaker is the suprachiasmatic nucleus (SCN), which is located in the hypothalamus. The hypothalamus coordinates the secondary oscillators that are located throughout the periphery and that control many physiological functions, including metabolism, hormone secretion, and cell division. The SCN consists of 2 primary subregions: a ventrolateral core and a dorsomedial shell. The core contains neurons that release the neuropeptides vasoactive intestinal peptide (VIP) and gastrin-releasing peptide (GRP) as well as the neurotransmitter GABA. The core receives the majority of the light coming through the retinohypothalamic tract (as well as input from other brain regions) and utilizes this information to synchronize the SCN with light/dark cycles. The shell of the SCN contains neurons that release arginine vasopressin (AVP), prokineticin 2 (PK2), and GABA. These neurons receive input from the SCN core and use this information to synchronize the SCN with peripheral oscillators (Brancaccio et al., 2014; Colwell, 2011).

Brain Regions Involved in the Sleep/Wake Cycle

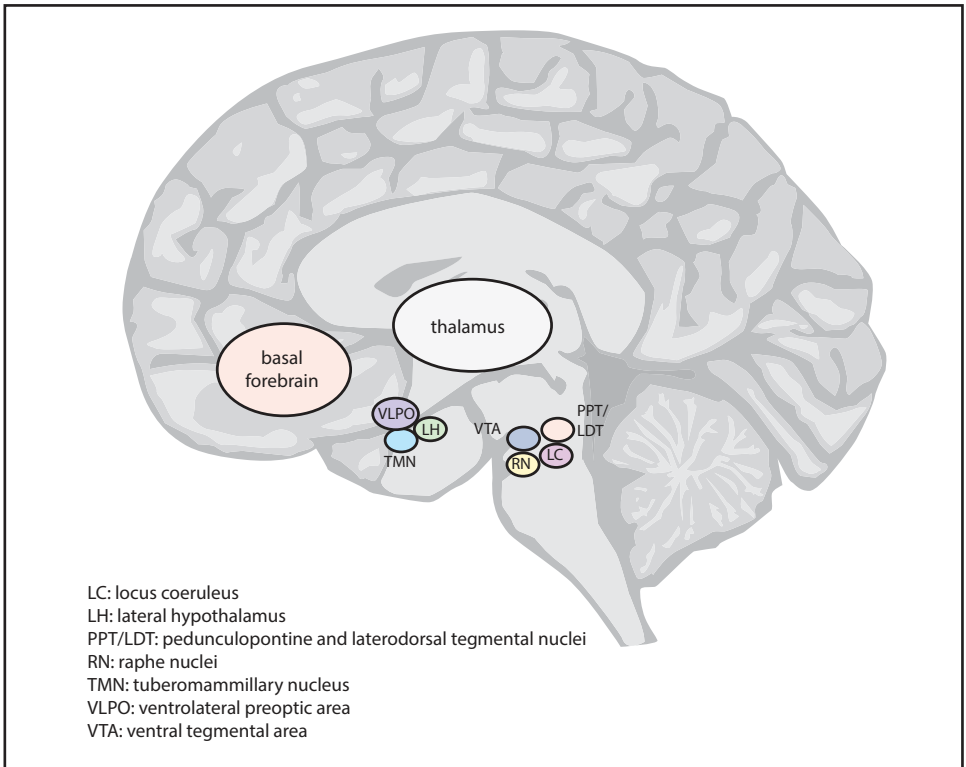


FIGURE 1.9. The sleep/wake cycle is maintained by a series of sleep-promoting and wake-promoting circuits located throughout the brain. Utilizing a variety of neurotransmitter and neuropeptide molecules, these circuits modulate one another via an intricate series of interacting loops (Roth and Roehrs, 2000).