Slow-wave sleep, diabetes, and the sympathetic nervous system

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Sleep oscillates between two different states: non-rapid eye movement (NREM) sleep and rapid-eye movement (REM) sleep. Slow-wave sleep (SWS) is a substate of NREM sleep, and its identification is based primarily on the presence of slow waves, i.e., low-frequency, high-amplitude oscillations in the EEG. Quantification of SWS is accomplished by visual inspection of EEG records or computerized methods such as spectral analysis based on the fast Fourier transform (FFT). Slow-wave activity (SWA; also referred to as delta power) is a quantitative measure of the contribution of both the amplitude and prevalence of slow waves in the EEG. The EEG oscillations reflect the field potentials associated with synchronized burst-pause firing patterns in cortical neurons (1). In view of these brain-based defining characteristics of SWS, it is not surprising that most theories on the functional significance of SWS have focused on the brain. In a recent issue of PNAS, Tasali *et al.* (2) draw attention to another aspect of SWS: the effects of SWS disruption on glucose tolerance and insulin resistance. What do these new data tells us about SWS and its functional significance? Is it for the body as well as the brain?

Regulation of SWS

The notion that SWS is an important substate of sleep has its foundations in the early observations that it is regulated accurately in response to variation in the duration of wakefulness. SWS increases in response to wake extension and is reduced after daytime naps, and these changes are observed in all EEG derivations, although they are most pronounced in frontal derivations (3). Variations in the nature of the waking experience, which may be associated with activation of specific neuronal populations, exhibit a significant, but minor and localized, influence on SWS (4). SWS and SWA are predominant at the beginning of sleep and decline in the course of sleep. This decline of SWS during sleep is not determined by circadian phase; it is observed at all circadian phases. It is also not simply determined by the time elapsed since sleep onset, but rather by the amount of SWS that has accumulated. The latter conclusion was derived from SWS deprivation experiments in which stimuli, usually acoustic stimuli [although early on in the history of SWS deprivation, mild electric shocks were used (5)], are delivered in response to the ongoing EEG. The drive to enter SWS is strong and is particularly so in young individuals. Frequent and loud stimuli (up to 110 dB) are required to prevent SWS from occurring. When these procedures are applied diligently, as in the experiment by Tasali *et al.* (2), SWS can be suppressed without reducing total sleep time, even though brief awakenings and microarousals will be induced. Upon cessation of this suppression, a rebound of SWS is observed, either within the sleep episode or during subsequent, undisturbed sleep episodes (6). Thus, SWS deprivation leads to an increase in the "pressure" for SWS. These data provide strong evidence for the accurate homeostatic regulation of SWS. In accordance with the notion that SWS is for the brain, negative effects of SWS deprivation on waking function have emerged (7). However, many authors have attributed these effects of SWS deprivation on the associated effects on sleep continuity rather than to the absence of slow-wave oscillations or SWS *per se*.

Short habitual sleep has been associated with increased risk for diabetes.

Correlates of SWS

A second line of evidence for the importance for SWS stems from non-EEG correlates of SWS, including endocrine and autonomic variables. This view of SWS emphasizes its characteristics as a behavioral and physiological state, i.e., a constellation of multiple variables in the brain and body. The major phase of daily growth-hormone secretion is associated with SWS (8). Even though it is now recognized that this association is not as tight as once thought, it nevertheless provides supportive evidence for the notion that SWS is restorative also for the body and that negative effects associated with disruption of this state may extend to the body.

Many other physiological variables are affected by the behavioral-state sleep, the NREM–REM cycle, and SWS. Upon the transition from wakefulness to sleep, heart rate slows down. During sleep, the balance of sympathetic and parasympathetic tone oscillates in synchrony with the NREM–REM cycle. Analysis of autonomic control of the variability of heart rate demonstrates that, within each NREM episode, as SWA gradually increases, sympathetic tone gradually diminishes and vagal tone gradually increases (9). At the transition to REM sleep, this state of low sympathetic activity gives way to sympathetic activation. The sleep-stage-dependent modulation of the autonomic nervous system can be observed not only indirectly on the basis of heart rate variability, but also directly by microneurography (10).

The autonomic nervous system affects not only the heart but also other visceral systems, including the insulin-producing B cells of the pancreas, the leptin-producing adipocytes, the vascular system, etc. The autonomic nervous system is thus a powerful pathway through which sleep can affect the entire organism and its physiology.

Sleep Disorders, Sleep Deprivation, and the Autonomic Nervous System

Alterations of the autonomic nervous system can also mediate the negative effects of sleep disruption on physiological systems. Sleep apnea constitutes one of the prime examples. In this condition, repeated cessation of airflow leads to oxygen desaturation and frequent arousals from both REM sleep and NREM sleep. These arousals are associated not

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only with a reduction in SWS and sleep continuity but also with sympathetic activation (11). The sympathetic activation is not only present during sleep but also carries over in wakefulness when breathing is normal. This activation of the sympathetic nervous system is thought to be responsible, at least in part, for the increased prevalence of diabetes in people with sleep apnea.

The data by Tasali *et al.* (2) provide a new approach to investigate the systemic consequences of SWS disruption on physiology and its consequences for glucose control in particular. Surprisingly, the data show that, after as few as three nights of disruption of SWS, the clearance of glucose after a glucose infusion was markedly reduced and that this reduction was not compensated for by an increase in insulin secretion by the beta cells of the pancreas. Assessment of sympathetic activation through analyses of heart-rate variability during wakefulness implicated a shift toward sympathetic dominance as the mechanism underlying this change in glucose tolerance. This all fits well with both our understanding of the role of sympathetic activation in insulin sensitivity as well as the association between SWS and reductions in sympathetic tone. However, on the basis of sleep apnea studies (11) and previous SWS deprivation studies (12), it may have been anticipated that the frequent arousals induced by the acoustic stimulation provided the link between SWS suppression and changes in insulin sensitivity. Surprisingly, the authors report that no significant correlations between measures of sleep continuity and changes in insulin sensitivity were observed. Instead, the authors observed correlations between the time spent in SWS and changes therein and changes in insulin sensitivity. If we accept that changes in sympathetic tone mediate the alteration in insulin sensitivity, then these correlations imply that the extent to which large parts of the cortex oscillate in synchrony, leading to the state of SWS as we observe it in the EEG, must have an impact on sympathetic tone. Variations in SWS are thought to be related to changes in local cortical connectivity and variation in neuromodulatory systems such as the noradrenergic, serotonergic, histaminergic, and cholinergic systems (13). Current understanding of the functional neuroanatomy of sleep and SWS allows for a two-way interaction between sleep and activity of these neuromodulatory systems, and these systems may in turn have an impact on the autonomic nervous system. Thus in this scenario, the full development of SWS leads to a reduction in the activity of activating systems and the sympathetic branch of the autonomous nervous system.

Research Implications

Most of us will not be exposed to hundreds of loud tones while we sleep. However, many of us will experience circumstances in which SWS will be reduced. For example, apprehension about the next day's activities is correlated with a suppression of SWS and an increase in the number of arousals (14). Repeated partial sleep deprivation leads to an increase in the pressure for SWS (15), similar to SWS deprivation, as well as changes in glucose tolerance (16). Furthermore, short habitual sleep has been associated with increased risk for diabetes in a number of epidemiological studies (e.g., ref. 17), and short sleepers carry a sleep debt (18). The age-related reduction in SWS is the most marked change in sleep physiology that can be observed, and aging is associated with increased incidence of diabetes. Men have less SWS than women at all ages (19). Genes and the polymorphisms therein that are predictive of interindividual variation in SWS in humans have now been identified (20, 21). The study by Tasali *et al.* (2) provides a rationale for the investigation of the role of SWS as well as the sympathetic nervous system as a final common pathway in the risk for diabetes and other ailments of the body in all of these populations. Restful and deep sleep serves the body as well as the brain.

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