CHRONIC SLEEP DEPRIVATION AND ITS RELATIONSHIP TO METABOLIC AND ENDOCRINE REGULATION

By Karen L. Copeland *

Introduction

Sleep research has repeatedly demonstrated a positive correlation between sleep disorders and hormonal regulation. Chronic sleep restriction is known to reduce the capacity of even young healthy adults to perform basic metabolic functions like processing and storing carbohydrates, as well as, regulating hormone secretion.[1]

Over the last several years, Americans have to face the fact that they currently work longer hours than any industrialized nation in the world. However, they also had to admit that there is a high price to pay for supposedly been more productive. The (2003) annual Sleep in America poll sponsored by the National Sleep Foundation emphasized that sleep deprivation is a problem for more than one half of the nation's workforce. Sleep related complaints reflect not only the middle aged Americans-but also a growing number of young adults and children. The survey revealed startling statistics about the state of what has been euphemistically coined "*Sleepless in America*":

- Greater than 50% of the American workforce finds that sleepiness on the job interferes with the amount of work they get done and that they have difficulty concentrating, solving problems, and handling stress.
- Over half of adults 18 to 29 years of age admit to staying up too late, and an equal percentage would sleep last in order to get more done.
- More than half of adults and 60% of 18-29 year olds report driving while drowsy during the past year; almost a quarter of younger drivers confessed to having dozed off at the wheel at some point during the previous year.

"By any measuring stick, the deaths, illnesses, and damage due to sleep deprivation and sleep disorders represent a substantial problem for American society."

> - from Wake Up America: A National Sleep Alert Report of the National Commission on Sleep Disorders Research [2]

Over 70 million and Americans suffer from a sleep problem; among them nearly 60% have a chronic disorder. Sleep problems have the same clinical relevance in women as men and some sleep problems are more common in women.

*** President, Satori Scientific and Biomedical Communications, LC, 1636 Roosevelt Ave. Ste.100, Salt Lake City, Utah 84105. E-mail: klcopeland@satoriscientific.com**

Each year, sleep disorders, sleep deprivation, and sleepiness accounts for greater than $15.9 billion added to the national health care bill. Additional costs for society such as lost worker productivity and accidents have never been calculated. Inarguably, sleep problems and associated disorders have had a major impact on society, but have not yet received sufficient attention in clinical practice outcomes, such as in the education of healthcare providers, medical researchers, and public intervention programs.[3]

As costly as it is, the $5.2 trillion national debt never killed anyone. But the national sleep debt is another story, according to Cornell University psychologist and sleep expert James Maas. One hundred thousand traffic accidents caused by drivers falling asleep claim more than 1,500 lives each year in the United States. "We've become a nation of zombies. More than half the adult population of the United States is carrying a substantial sleep debt," Maas said. The professor defines sleep as the difference between the hours of restorative rest people need-- for optimal physical and mental well-being--and the number of hours they actually get.[4]

"At any given time, the American sleep debt totals nearly half a billion hours or close to two hours every night for the average American. And just because you're lucky or smart enough not to incur sleep debt, that doesn't mean you're not affected," Maas added. "Any one of those sleep-debt zombies can kill or hurt you in other ways."

Maas believes that if people can get eight hours of sleep a night, it would be wonderful, although still not optimal. "Between the seventh and eighth hour is when we get most of our REM (rapid eye movement) sleep, the time when the mind repairs itself, grows new connections and puts it all together. REM sleep occurs about every 90 minutes, and the periods of REM sleep get longer as the night progresses. If you're a six-hour a night sleeper, you're probably missing that last, important opportunity to repair and to prepare for the coming day."

Moreover, the contribution of sleep disorders to such serious problems as heart disease, diabetes, and stroke, which kill and debilitate thousands each year, has not been quantified.

Sleep Debt is the Modern American Diet?

Americans are sleeping less than ever before. In the past 100 years, Americans have decreased their nightly sleep by two hours. The ever increasing demand of work and home are to blame. Research shows that sleep needs vary from infancy to adulthood, as well as from individual to individual, but still most Americans are simply not getting enough sleep.

The sleep state is an active, well-organized sequence of events made up of two separate and distinctly different states: 'non-rapid eye movement' sleep (NREM) and 'rapid eye

movement' sleep (REM) or dreaming sleep. NREM and REM sleep states differ completely in their functional consequences and mechanisms.

NREM sleep can further be divided into stages 1-4 depending on the brain waves generated by the sleeper. Stages 3 and 4 of NREM sleep have the biggest and slowest brain waves. These larger, slow waves are called delta waves, and stages 3 and 4 sleep combined, are called "delta sleep." During stages 1 and 2 the lighter sleeping occurs, which takes place during the majority of the night. Stages 3 and 4 of the deep sleeping phase, or REM phase, is often referred to as the dream sate which not only involves rapid eye movement but also rest and relaxation.

Developmentally, our sleep patterns change from many short sleep periods to a consistent block of well defined sleep (**Fig.1**). Science tells us that a newborn requires about 16 to 18 hours of sleep a day for proper development, however, the sleep needs decrease over time from childhood to adolescence. An average 10-year old demands 10 hours of sleep, whereas, the typical adult needs 8 hours to function at their best. When sleep needs are not met on a consistent basis, a state of "sleep deprivation" develops and can actually feel normal over time. A person can really forget what it is like to feel rested and fully awake!

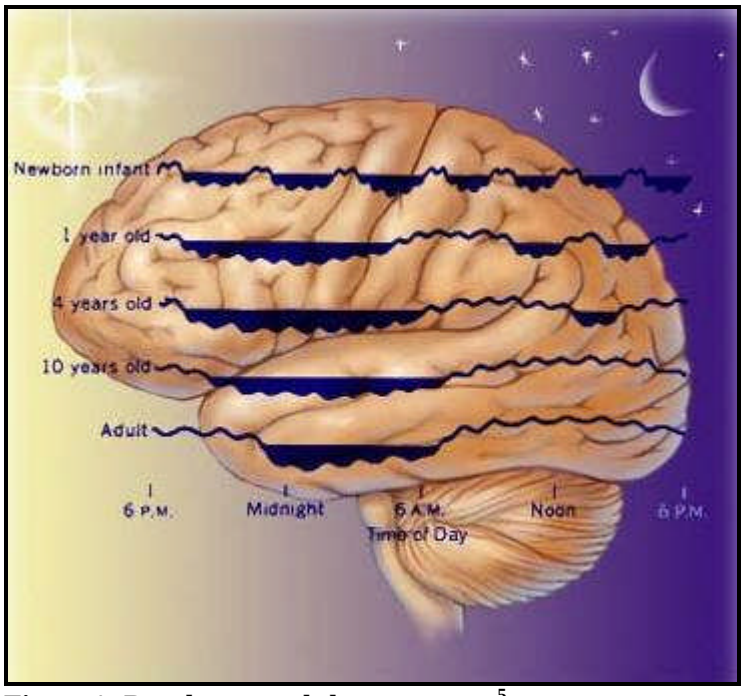


Figure 1. Developmental sleep patterns [5]

Connection to Sleep Disorders

Sleep disorders can create a state of "virtual" sleep deprivation. Just because an individual is resting in bed for 8 hours a night, it doesn't necessarily follow that the

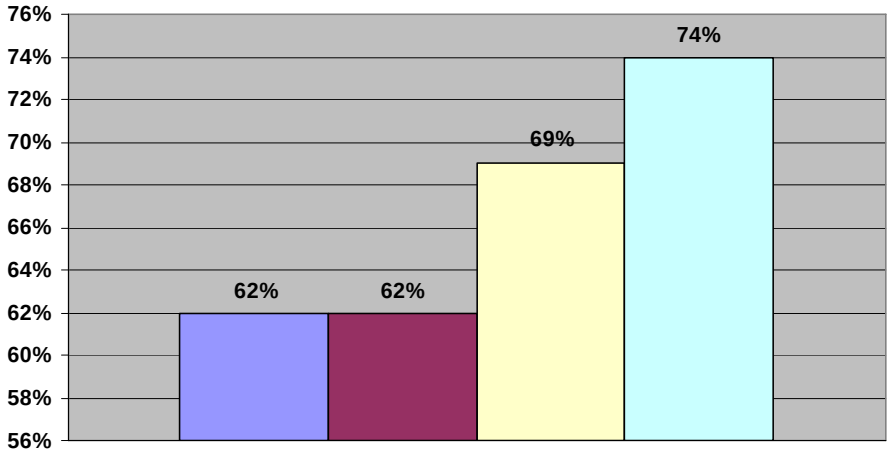
crucial stages of sleep are being achieved. Certain sleep disorders are known to cause an interference with the natural progression of sleep stages throughout the night, such as the deeper stages or the Rapid Eye Movement (REM) phase needed for a variety of critical physiological functions. When sleep is normal, one should awake and feel refreshed throughout the day with little or no need for napping. If poor sleep quality and excessive daytime sleepiness become chronic, an individual should seek medical intervention.[6] Other startling statistics about sleep disorders include the following: about 25% of American children aged 1 to 5 have a sleep disturbance; an estimated 250,000 people suffer from narcolepsy; more than 50% of Americans aged 65 and older have a sleep problem; and disrupted sleep is one of the primary reasons for complaints cited by caretakers of the elderly in institutionalized settings.[2]

The National Sleep Foundation conducts a survey yearly to assess the state of sleep in America. In their 2002 poll [7] they found that 74% of all respondents experienced at least one symptom of a sleep disorder a few nights a week or more, presenting a small but significant increase from those who experienced at least one symptom of a sleep disorder in 2001 (69%) or in previous years (62%), (**Fig.2**).

Those who are most likely to experience a symptom of a sleep disorder a few nights a week or more in include:

- Adults between the ages of 18 and 29 (77%) or 30 to 64 (76%) compared to those 65 years of age or older (60%);
- Those who experienced daytime sleepiness at least a few days a month (88% versus 65% rarely or never); and
- Those who report been in fair or poor health (93% versus 66% excellent or very good health or 78% good health).

Figure 2. Percent Reporting One or More Symptoms of a Sleep Disorder (a few nights a week or more) by Year



The prevalence of sleep related disorders is known to increase with advancing age. Due to the rapid rise of older individuals in the US population, studies suggest that we will encounter and ever increasing public health burden in the years to come. It has been estimated that 18 million Americans will have a sleep problem by the year 2010, and 100 million will have one by the year 2050. [2]

RECENT RESEARCH LINKS GROWING EPIDEMICS OF WEIGHT GAIN, METABOLIC, AND ENDOCRINE CHANGES TO CHRONIC SLEEP DEBT

It is a well-known fact that the American population is gaining weight at an unprecedented rate, and as a recent research suggests, sleep may play a significant factor in the alarming rise of obesity. Lack of sleep has been known for some time to impair metabolism, including the processing and storing of carbohydrates. The ability to regulate blood sugar and produce important weight-regulating hormones such as thyroid, and growth hormone is compromised by sleep loss. Chronic sleep loss even without overeating and inactivity may be a significant factor in the obesity epidemic seen in modern America.

Recent studies have shown that fragmented sleep, results not only in reduced growth hormone secretions, but also in profound changes in the body's ability to fight infection. Even a single night of partial sleep loss, is known to result in abnormally high levels of the stress hormone, cortisol, the following afternoon and evening. [8] Continuing research suggests that the effects of semi-chronic sleep loss may be as significant as those of physical inactivity. Sleep researchers are learning though what it is about sleep that promotes health and cures sickness, and they are finding answers on a molecular level- in studies of *cytokines.*

Cytokines are hormone-like proteins secreted by many different cell types, which regulate the intensity and duration of immune responses. The human body produces about 30 different cytokines, which at any given time may amplify some parts of the immune system and suppress other parts.

Interleukin-1, an immune response modifier, was the first sleep inducing brain cytokine to be discovered.[9] In later experiments using laboratory animals, James Krueger, PhD., and his colleagues at Washington State University, were able to show that sleep induced deprivation stimulated interleukin-1 levels to increase in the brain. This was the first time that cytokines had been intricately connected to sleep.[10]

To understand why sleep is so crucial to health, we need to envision two very critical internal mechanisms regulating sleep and wakefulness. The first, our circadian clock, is a small structure found in the hypothalamus of the brain. This clock operates on a 24-hour rhythm, telling the body which hormones to release and which not to release throughout each day; essentially controlling when sleep begins, as well as, how long we sleep.

In older adults, nocturnal sleep is very often shallow resulting in decreased daytime alertness. The timing of sleep is also altered, resulting in earlier bedtimes and earlier morning awakenings. This earlier timing accompanied with a decrease in amplitude has also been implicated with other 24-hour rhythms, including hormonal secretions. These observations are thought to be indicative of age-related changes in brain physiology that controls circadian rhythms and/or the sleep-wake state.

Another key mechanism, sleep-wake homeostasis, regulates the time period for staying awake and the quantity of sleep we actually need. Both mechanisms however, are vitally important to the daily variations in physiological parameters such as body temperature, hormone release, carbohydrate metabolism, and cardiovascular function.[11, 12, 13]

Researchers at the University of Chicago Medical Center conducted a landmark study to assess the harmful effects that sleep debt may have on carbohydrate metabolism and endocrine function.[14] Although previous studies have examined the short-term effects of acute, total sleep deprivation on the brain, this study was the first of its kind to investigate the impact that chronic sleep loss has on the body, by measuring metabolic and hormone secretion levels of test subjects after stringent sleep restriction and sleep recovery schedules.

Eve Van Cauter, Ph.D., professor of medicine at the University of Chicago and director of the study, was surprised at the results." We found that the metabolic and endocrine changes resulting from a significant sleep debt mimic many of the hallmarks of aging," said Van Cauter. “We suspect that chronic sleep loss may not only hasten the onset, but can also increase the severity of age-related ailments such as diabetes, hypertension, obesity, and memory loss."

In this pioneering study, eleven healthy young men, aged 18-27 years, were followed for 16 consecutive nights. For the first three nights the subjects were allowed to sleep eight hours, from 11 p.m. to 7 a.m. The following six nights the subjects were only allowed four hours of sleep, from 1 a.m. to 5 a.m. The last seven nights they spent 12 hours in bed, from 9 p.m. to 9 a.m. In all conditions, the diets were the same and the time in bed was centered around 3 a.m.

The researchers continued to monitor the test subjects for their state of wakefulness following the end of both sleep-debt and sleep-recovery. They also performed sleep studies on the final eight-hour nights, as well as, the last two 12-hour nights. Intravenous glucose tests were performed on the fifth day of both sleep deprivation and sleep recovery. Hormone levels along with glucose were monitored every 30 minutes during the sixth day of deprivation and recovery.

RESULTS

Glucose and insulin levels were found to be in the normal range at the end of sleep recovery, however, during the sleep debt condition, results were consistent with a clear

impairment of carbohydrate tolerance. These profound alterations of glucose metabolism were parallel with those observed in patients with type-two diabetes, during sleep deprivation. Subjects took 40% longer than average to regulate their blood sugar levels following a high carbohydrate meal. Similarly, the rate of glucose clearance after intravenous glucose injection was nearly 40% slower in the sleep-debt condition than in the sleep-recovery condition (1.45 vs. 2.40% per minute, P<0.02), Fig.3.

It should be noted that glucose tolerance values around 1.60% are typical of older adults with impaired glucose tolerance,[15] whereas values of 2.2%-2 .9% per minute are typical of fit young adults.[16] In addition, the test subjects ability to secrete insulin and to respond to insulin both decreased by about 30% in the sleep-debt condition compared to the sleep-recovery condition. Differences in the acute insulin response to glucose of a magnitude similar to that seen between the sleep-debt and the fully rested conditions have been described in aging [17] and gestational diabetes.[18]

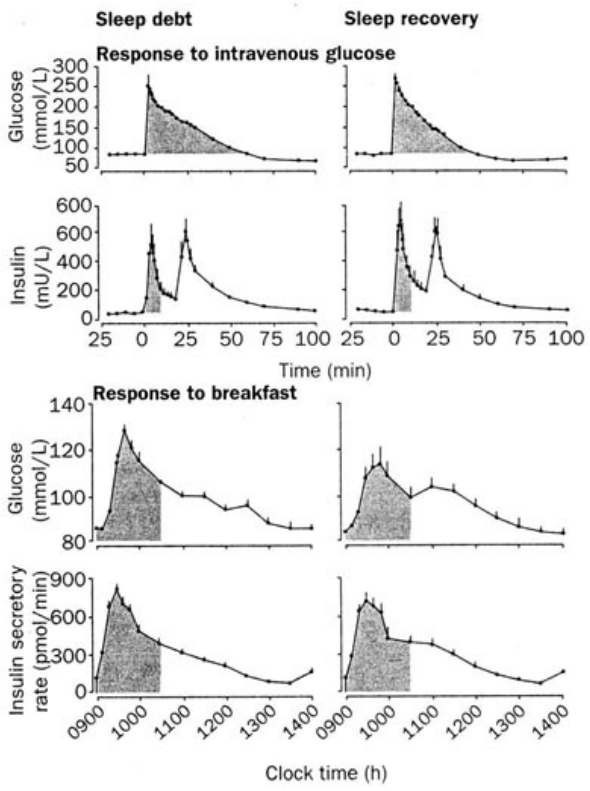


Figure 3. Mean (SE) profiles of blood glucose and serum insulin during intravenous glucose tolerance test, and glucose and insulin responses to breakfast.[8]

Figure (3) shows the increase in glucose response following breakfast to be higher after sleep-debt versus sleep-recovery (p=0.05), even though similar insulin secretion levels were observed. Peak levels of glucose following breakfast between sleep-debt and sleep-

recovery conditions (0.8 mmol/L) can be correlated to that observed in young versus old adults (age 20-36 vs. 60-72 years).[19] This comparison suggests that, when a sleep-debt condition is met, the response to a standard morning oral glucose tolerance test would be abnormal. Profiles of blood in glucose and insulin secretion in response to lunch and dinner however, were not significant in their findings between the two groups.

Other tests performed showed an alteration in the production and action of other hormones during the sleep-debt condition. A decrease in thyroid stimulating hormone and an increase in blood cortisol levels, particularly during the afternoon and evening were noteworthy. Elevated evening cortisol levels are typical in older subjects and are thought to be associated with age-related health problems such as insulin resistance and memory impairment.[20, 21]

Even more striking than the numerous aberrations observed during the sleep-debt study, was the discovery that during a 12 hour recovery, all of the abnormal readings observed quickly returned to normal. Furthermore, when sleep recovery periods extended beyond the normal eight hours per night, laboratory values were better than "normal" baseline standards established for young healthy adults.

Conclusions

"While the primary function of sleep may very well be cerebral restoration," noted the authors, "our findings indicate that sleep loss also has consequences for peripheral function that, if maintained chronically, could have long-term adverse health effects."

Recent studies of sleep deprivation and its adverse affects on the cardiovascular and endocrine system, and metabolism, have been unequivocal. Sleep loss over time is associated not only with decreased vigilance and depressed mood, but also with altered hormone production. Fragmented sleep, results in reduced growth hormone secretion, and even partial sleep loss one night results in higher stress hormone levels the following evening.

Due to the pervasive problems inherent in modern day societies, sleep research is expanding and attracting more and more attention from scientists. We are now able to show from sleep studies performed over the last decade, that sleep is an active and dynamic state that can greatly impact our waking hours. In fact, it is imperative that we fully understand the mechanisms of sleep to fully understand the brain. Innovative techniques such as brain mapping and imaging are emerging as useful tools to help researchers unravel the mysteries of sleep functions, and how sleep disorders affect sleep patterns. Understanding these factors in health and disease may also lead to potential therapies for treating sleep disorders, as well as, ways to treat jet lag and the problems associated with shift work. The future holds many promises from this research, and hopefully in the near term, an understanding of sleep's impact on our daily lives.

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