



Perspective on sleep and aging

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There is a strong body of data directly interrelating sleep problems with mood disorders. There is a growing data base directly associating sleep disorders with attention and memory problems. Motor disorders, especially involving the dopaminergic system, may produce sleep problems, including a possible association between disordered sleep and nocturnal falls. Sleep disorders may be causal conditions for metabolic diseases and increased risk for morbidity and mortality. Sleep and health are directly interrelated. To further probe these issues, especially as related to the aging process, investigators need to utilize tools and concepts from genomics and epigenetics, proteomics, metabolomics, any future ...omics, molecular neuroimaging, and cognitive neuroscience.

Keywords: aging, circadian rhythms, health, sleep, sleep disorders

This Perspective article is not meant to be an inclusive review of research on sleep and aging. It is meant to provide the reader with my idiosyncratic view of the field, highlighting some research areas that I found interesting and concluding with a summary of where I think the field might go in the future.

Why study sleep in the aging organism? There are a number of problematical issues. One has to wait while the individual ages. During this period there are many physiological and environmental changes that may act as confounds to any system that one focuses upon. Identification of controls may be problematical. Given all of these problems, and more, why study aging and sleep? First, the aging process is a natural perturbation of the organism that we all go through. It involves a complex interaction of bodily systems, neuronal, hormonal, circulatory, and psychosocial to name a few. This makes the research protocols and problems intellectually challenging as well as of great public health significance. Insomnia, in fact, is the most prevalent sleep problem reported not only among the older, but across all population age groups within the industrialized countries of the world.

More than half of all people aged 65 and older experience sleep problems. Insomnia affects approximately one-third of older Americans and can result in excessive daytime sleepiness, attention and memory problems, depressed mood, falls, physical function, and a lower quality of life (Brassington et al., 2000; Jean-Louis et al., 2000a,b; Stepnowsky et al., 2000; Cricco et al., 2001; Foley et al., 2001; Moore et al., 2001; Bixler et al., 2002; Dam et al., 2008). Other factors associated with aging may also contribute to sleep problems. These include disease, changes in environment, or concurrent age-related processes. Analysis of the Studies of Women Across the Nation (SWAN) data found an association between psychological distress and natural menopause in a community sample of African American, White, Chinese, Hispanic, and Japanese women aged 40–55. Psychological distress was defined as feeling tense, depressed, and irritable in the previous 2 weeks, and was highest in early perimenopause (28.9%) and lowest in premenopause (20.9%) and post menopause (22%). In comparison with premenopausal women, early perimenopausal women were at a greater risk of distress, with and without adjustment for vasomotor and sleep symptoms and

covariates. Complaints of difficulty sleeping were more frequent among the White women than in the other groups, and likelihood of psychological distress was significantly higher for Whites than for the other racial/ethnic groups (Bromberger et al., 2001). More recent cross-sectional analyses of the SWAN data (Kravitz et al., 2003) indicated that difficulty sleeping was reported overall by 38% of the women, but that the age-adjusted rates were significantly the highest amongst the perimenopausal (45.4%) and surgically menopausal (47.6%) groups.

Unfortunately many older adults see poor sleep quality as a part of normal aging. This is likely not the case. Although sleep does change across the life span, complaints about sleep by older adults should not be discounted. The underlying causes of sleep complaints may be risk factors for other health complications. The effects of poor sleep on quality of life should not be ignored. However, the old dogma that poor sleep is a natural part of aging has not been supported. Data indicate that age itself does not predict insomnia, even in the presence of a decrease in sleep efficiency and decreased proportion of slow wave sleep (Vitiello et al. 2002). Rather, the prevalence of insomnia and other sleep disorders is high in the population due to a variety of factors common in late life (Foley et al., 1995). These changes begin in midlife, as do many of the diseases and disorders associated with aging. The prevalence of insomnia and other sleep disorders is high in the population due to the growing numbers of elderly and the associated comorbidities, disease, changes in environment, or concurrent age-related processes common in late life that affect sleep.

INSOMNIA

Insomnia is a subjective complaint of insufficient or non-restorative sleep, which can generally be divided into two different types of complaints depending upon the duration of the sleep difficulty. Insomnia may be either short-term (transient/acute) or chronic. In the elderly, transient insomnia may be caused by bereavement, adjustment to medical difficulties and physical limitations. By definition, transient insomnia is short in duration, and will generally improve without intervention or with short-term hypnotic medication therapy. Chronic insomnia, however, can have

serious impact on daily functioning and can result in impaired functioning and reduced quality of life in older adults (Roth and Ancoli-Israel, 1999; Zammit et al., 1999). The result of a 1,000 telephone-interview of randomly selected U.S. adults indicated that the prevalence of occasional insomnia did not change with age, however, the prevalence of chronic insomnia was highest (20%) in adults age 65 and over (Ancoli-Israel and Roth, 1999). This suggests that, although occasional sleep complaints may not be associated with age, older adults experience chronic sleep difficulties more often than by younger adults. A similar poll of 1500 older Americans (aged 55+) found that 67% reported trouble sleeping and that only one in eight had discussed these problems with their physicians (Lamberg, 2003).

While there is agreement that total sleep loss is harmful to the health of humans, the field of sleep research is not unanimous in whether small decreases of the sleep period have an effect on the human brain and body. Some researchers divide sleep into “core sleep” which is the slow wave sleep and “optional” or “buffer” sleep that consists of stage 2 sleep and some REM sleep. Furthermore, some epidemiological studies have suggested that insomnia, paradoxically, is associated with prolonged life (Kripke et al., 2002). However, most population-based epidemiological studies indicate that both short and long duration sleep patterns are significant predictors of death (Cappuccio et al., 2010). One possible mechanism for the increased mortality associated with short sleep is an increased incidence of coronary artery calcification (King et al., 2008).

Self-reported sleep problems tend to be lower amongst African-Americans (AA) than Caucasian groups. This has been found previously in a large AA cohort developed within the five counties in the North Central Piedmont of North Carolina (Foley et al., 1999). The largest differences were in waking during the night wherein the prevalence of wakeful sleep among the AA was almost 60 percent that of the C. Similar results were found in a biracial community study in Brooklyn, New York (Jean-Louis et al., 2001), although the prevalence rates for each race were higher in Brooklyn than in North Carolina. Further analysis of this population for within-ethnic group differences showed that English-speaking Caribbean-born AA reported fewer sleep complaints than did U.S.-born AA, and Haitian-born AA were intermediate between these two groups (Zizi et al., 2002).

Insomnia appears not only to affect mental health, i.e., insomnia is a significant risk factor for depression (Paudel et al., 2008), but also to be associated with physical problems, i.e., hypertension. The increasing prevalence of insomnia in midlife (ages 40-50 years) appears to some extent to be secondary to weakening sleep mechanisms, i.e., loss of slow wave sleep associated with the aging process. Furthermore, insomnia appears to be associated with hypercortisolemia and a daytime shift of IL-6 and TNF α secretory patterns, conditions that may lead to multiple health problems including visceral obesity, insulin resistance, hypertension, and osteoporosis that, in turn, may affect longevity (Vgontzas et al., 2003).

Insomnia in older adults is not benign. A number of research studies have shown, both cross-sectionally and longitudinally, that insomnia has a negative impact on cognitive functioning and quality of life (Roth and Ancoli-Israel, 1999; Zammit et al., 1999; Lichstein et al., 2001; Katz and McHorney, 2002). Insomnia patients were found to have slower reaction time, poorer balance,

and were more likely to forget numbers in the digit span test than carefully matched controls. Furthermore, these deficits were seen even after the insomnia patients spontaneously experienced a subjectively good night of sleep (Hauri, 1997). Individuals with insomnia complaints were found to have overall poorer quality of life than the J.n individuals without insomnia (Zammit et al., 1999) and individuals with insomnia endorsed more symptoms of depression and anxiety. It is, therefore, unclear whether depression and anxiety lead to both sleep disturbance and impaired life quality, or whether the sleep disruption leads to the impaired quality of life and psychiatric difficulties. However, few studies have been done on the effect of insomnia on quality of life specifically in older adults. In one of the few such studies, it was found that older adults with secondary insomnia had worse quality of life than those with primary insomnia (Lichstein et al., 2001), while another study (Alapin et al., 2000) examined poor sleep in older adults and found that poor sleepers reported more difficulty functioning during the day and experienced more tension and depression. In a cohort of non-depressed and non-demented older adults, self-reported excessive daytime sleepiness was associated with moderate impairments in daily functions, such as housework, sports, and general activity levels (Gooneratne et al., 2003).

SLEEP-DISORDERED BREATHING

Sleep-Disordered Breathing (SDB) encompasses obstructive sleep apnea (OSA), hypopnea (shallow breaths), and upper airway resistance syndrome. Patients with OSA or hypopnea may have frequent and repetitive episodes of oxygen desaturation, and all SDB patients have frequent arousals from sleep and resultant sleep deprivation. The clinical symptoms include loud snoring and excessive daytime sleepiness. The intermittent hypoxemia and episodes of brain activation (arousal) are associated with abrupt increases in systemic blood pressure, and SDB patients do not demonstrate the expected nocturnal dip in blood pressure (Morrell et al., 2000; Peppard et al., 2000b; Loreda et al., 2001). It has been observed that older AA have at least a two-fold greater risk of clinically undiagnosed severe SDB than do Caucasians (C) (Ancoli-Israel et al., 1995; Redline et al., 1997), independent of age, gender, or body mass index (BMI). The prevalence of hypertension, which is higher in AA than C, is associated with SDB (Nieto et al., 2000), and severe SDB is associated with a significant increase in cardiovascular events (Wolk et al., 2003). For many older individuals with hypertension, blood pressure does not fall the expected amount at night (dipping). This non-dipping is more frequent in AA than C, and the difference was not accounted for by BMI, gender, mean arterial blood pressure, or SDB (Ancoli-Israel et al., 2002). Thus non-dipping specifically was not a result of SDB, but independently related to race. However, while in both races non-dipping was most likely found in those older individuals with SDB and hypertension, the SDB was significantly more likely to be severe among AA with hypertension. These results suggest that AA with hypertension and who are non-dippers should be screened for SDB.

The most important risk factor for SDB is overweight and obesity, suggesting that its incidence is likely to increase dramatically with the recent epidemic of overweight and obesity. A prospective study from the Wisconsin Sleep Cohort documented the role of weight gain in increasing incidence and progression of SDB, and

weight loss in slowing its progression (Peppard et al., 2000b). Previous studies of weight loss and SDB have been in samples of morbidly obese patients; the importance of this study lies in demonstrating that even modest body weight changes affect SDB, and the findings offer hope for prevention and reduction of SDB. The most common, effective treatment for SDB (continuous positive air pressure or CPAP) is palliative and not curative. Many studies indeed suggest that prevalence is very high in people ages 65 and older, but interestingly there does not appear to be a distinct linear increase after that (Ancoli-Israel et al., 1991; Young et al., 2002) although other data support a linear trend with increasing age (Newman et al., 2005; Bliwise et al., 2010).

The breathing pauses of SDB clearly cause acute cardiovascular abnormalities; the uncertainty lies only in whether these events cause sustained, chronic disease. Apnea and hypopnea episodes during sleep cause acute, transient blood pressure perturbations, inducing elevations of 30 mmHg or more in mean arterial pressure, fluctuations in heart rate and rhythm, increased sympathetic nerve activity, arousal and sleep fragmentation, and swings in intrathoracic pressure. Even minimally elevated AHI at baseline was significantly associated with an increased odds of developing hypertension over a 4-year period. A dose-response relation was observed, with an odds ratio (OR) of 2.9 for AHI ≥ 15 vs. AHI = 0 events/hour (Peppard et al., 2000a). Several clinic-based studies and a cross-sectional analysis of self-reported cardiovascular disease in the Sleep Heart Health Study (SHHS) support a significant association. In the SHHS, those in the upper quartile of AHI (≥ 11.0 events/hour) had a 42% greater odds of prevalent CVD (including coronary heart disease, stroke, and congestive heart failure) compared with participants in the lowest quartile (AHI < 1.3 events/hour), after adjusting for multiple potential confounders (Shahar et al., 2001). Additional analyses examining the association of SDB and CVD along the entire spectrum of SDB severity suggested that most of the elevation in risk of CVD occurs as the AHI rises from 0 to 10 events/hour (Nieto et al., 2000), including adjustment for hypertension, suggesting that hypertension is not the only mechanism by which the risk of cardiovascular sequelae is heightened in persons with SDB. The SHHS found a stronger association between stroke and SDB than between total CVD and SDB; the OR of prevalent stroke in persons in the upper SDB quartile compared to those in the lowest quartile.

Sleep-Disordered Breathing has been linked with considerable behavioral morbidity (including excessive daytime sleepiness, decreased cognitive function, motor vehicle accidents, depression) and decreased quality of life (Young et al. 2002). Excessive daytime sleepiness is a cardinal feature of clinically recognized SDB. Clinic patients are unrepresentative of subjects with elevated AHI in the general population, as asymptomatic individuals are less likely to be evaluated for the presence of SDB than are those who complain of sleepiness. However, in the Wisconsin Sleep Cohort, 23% of women and 16% of men with AHI ≥ 5 reported frequent occurrence of three manifestations of sleepiness compared with only 10% of women and 3% of men with AHI < 5 (Young et al., 1997). In the SHHS, there was a significant, progressive increase in Epworth Sleepiness Scale (ESS) score with increasing AHI, from a mean of 7.2 in subjects with AHI < 5 to 9.3 in subjects with AHI ≥ 30 (Gottlieb et al.,

1999). The percentage of subjects with excessive sleepiness, defined as an ESS score ≥ 11 , increased from 21% in subjects with AHI < 5 to 35% in those with AHI ≥ 30 .

RESTLESS LEGS SYNDROME

Restless Legs Syndrome (RLS) is a sensori-motor disorder characterized by an unremitting urge to move the legs during periods of rest, especially during bed time that interferes with sleep onset and disrupts sleep. It is estimated to occur in 10% of adults, increasing in prevalence with increasing age (Phillips et al., 2000; Rothdach et al., 2000; Allen et al., 2003). Clinical interventions for RLS have focused upon dopaminergic agonist therapies. However, it appears that RLS patients have an underlying deficiency in serum and cerebrospinal fluid (CSF) ferritin levels resulting in a problem of iron utilization (Allen and Earley, 2001). Dopamine synaptic integrity is dependent upon Thy-1, a glycoprotein that is expressed on T-cells and highly expressed in the brain. Thy-1 mRNA is modulated by iron (Ye and Connor, 2000), and Thy-1 protein levels are markedly decreased in RLS brains. Neuropathological examination of brains from RLS patients revealed no histopathological abnormalities, but did show that iron, ferritin, and transferrin receptor staining all were markedly decreased in substantia nigra cells, while transferrin staining was increased and tyrosine hydroxylase was present at normal levels, suggesting that RLS may be a functional disorder of iron processing in these neuromelanin cells that impairs the dopaminergic system (Connor et al., 2003).

SLEEP AND METABOLISM

Poor sleep may play a significant role in the metabolic syndrome, defined as a cluster of three or more of the following measurements: abdominal obesity, elevated triglycerides, low level of high-density lipoprotein cholesterol, high blood pressure and high serum glucose. Sleep disturbances are implicated in changes in other body systems, especially the production of appropriate levels of hormones. Emerging data show impaired sleep as a risk factor for obesity and also for hallmarks of diabetes, such as insulin resistance and impaired glucose tolerance (Knutson et al., 2007). Older men and women (mean ages 76.4 and 83.6 years, resp.) in the MrOs and SOF cohorts whose sleep was evaluated by wrist actigraphy and were short sleepers (5 h or less) were significantly more likely to be obese than those sleeping 7 to 8 h (OR of 3.70 and 2.26, resp.), while those sleeping between 5 and 7 h also were significantly at risk for obesity (OR of 1.51 and 1.29, resp.) (Patel et al., 2008). Further study of these cohorts indicated that independent of sleep duration, the proportion of time spent in slow wave sleep was inversely associated with weight and BMI (Rao et al., 2009). Indeed, a systematic review of a number of published studies found that short sleep was independently associated with weight gain, especially for the younger age groups (Patel and Hu, 2008). This association was uniformly found in longitudinal studies. A number of studies have shown that sleep loss can lead to impairments in glucose metabolism and insulin resistance as possible precursors to Type 2 diabetes, and to alterations in the hormones leptin and ghrelin which then lead to inappropriate appetite increases leading to increased food consumption (Knutson, 2007).

Midlife is associated with an increased prevalence of common sleep disorders, i.e., OSA and insomnia. The increased prevalence of sleep apnea in middle age is associated with increased weight gain from early adulthood to midlife and concomitant increase of immune and metabolic abnormalities such as hypercytokinemia, hyperleptinemia, and insulin resistance. Epidemiological studies, such as the Adult Health and Behavior Project at the University of Pittsburgh, using self-reported sleep durations, have shown that metabolic syndrome and central adiposity are significantly associated with short sleepers, i.e., less than 7 h average over a week, aged 30–54 years (Hall et al., 2008). It is possible that chronic sleep loss, commonly practiced in our modern society by people during their productive age, via “low grade” inflammation and insulin resistance contributes to the epidemic of obesity, diabetes, and sleep apnea in our society, conditions associated with increased morbidity and mortality.

SLEEP AND COGNITION

A number of research studies, both cross-sectional and longitudinal, have shown that disturbed sleep has a negative impact on cognitive functioning and quality of life. An analysis of the Established Populations for Epidemiologic Studies of the Elderly (EPESE) data examine whether self-reported symptoms of insomnia independently increase risk of cognitive decline in older adults (Cricco et al., 2001). Among non-depressed men, those reporting symptoms of chronic insomnia had a significant adjusted OR of 1.49 for cognitive decline, relative to those with no insomnia. Men with incident insomnia were not at increased risk (OR = 1.16). These relationships were not found in women. Therefore, while chronic insomnia independently predicted incident cognitive decline in older men, no associations between insomnia and cognitive decline were found in women.

Population-based studies of the effect of SDB on cognitive function are few and the existing findings are somewhat weaker than results from clinic-based studies. This is not surprising because of selective referral. In the Wisconsin Sleep Cohort Study AHI was significantly but weakly related to diminished psychomotor efficiency, a factor reflecting the coordination of fine motor control with sustained attention and concentration. SDB was not related to the memory factor. Extrapolating the regression findings, the effect of an increase in AHI of 15 was approximately equivalent to the effect of 5 years of aging on psychomotor function. Weak but significant associations of SDB and neuropsychological function were also found in a study of 100 self-reported snorers recruited from public advertisements and clinic referrals, screened to exclude comorbidity related to cognitive function (Adams et al., 2001). In a study to assess the association between SDB and cognitive functioning in an elderly cohort of Japanese-American men between 79 and 97 years of age, less than 30% of the men had no SDB (AHI < 5) and nearly one-fifth (19%) had severe SDB (AHI ≥ 30). Severe SDB was associated with higher BMI, habitual snoring, and daytime drowsiness, but no association was found between SDB and cognitive functioning, including measures of memory function, concentration, and attention (Foley et al., 2003).

There is a large and increasing research literature on the cognitive deficits associated with sleep apnea. Cross-sectional studies of normal populations have typically found small or no

relationship between SDB and cognitive functioning. However, in the Honolulu-Asia Aging Study of Sleep Apnea, where less than 30% of the men had no SDB (AHI < 5) and nearly one-fifth (19%) had severe SDB (AHI ≥ 30), severe SDB was associated with higher BMI, habitual snoring, and daytime drowsiness. No association was found between SDB and cognitive functioning; including measures of memory function, concentration, and attention on standardized cognitive tests used to screen for Alzheimer disease and other dementias in older persons. Because a healthy-participant effect may have contributed to this finding, more extensive cognitive testing may be necessary to reveal more subtle deficits resulting from SDB (Foley et al., 2003).

The molecular processes underlying the role of sleep in the consolidation of long-term memory are being examined using specific phosphorylated cAMP-responsive element binding protein (CREB)-mutant mice (Graves et al., 2001). Results indicate that like sleep deprivation, inhibition of protein kinase A (PKA) or protein synthesis disrupts memory consolidation only at discrete times following training and these times vary depending upon the strength of the training protocol. Total sleep deprivation in mice from 0–5 h, but not 5–10 h, after training impairs retention of contextual fear conditioning (in which an animal learns to fear a new environment), a hippocampus-dependent task when tested at 24 h or 12 days after training. This does not occur with retention of cued-fear (when an animal learns an association between a cue, such as a tone, and a shock) training, a hippocampus-independent but amygdala-dependent task (Graves et al., 2003a). Levels of cAMP response element (CRE)-mediated transcription oscillate in the SCN in a circadian fashion; CREB levels within forebrain are higher in waking than in sleep. CREB mutant mice had increased levels of sleep parameters (NREM, REM, total sleep time, less time awake) than wild type, indicating that CREB protein contributes to the mechanisms by which wakefulness is maintained. CREB mutants also do not have the induction of CRE-mediated gene expression in the hippocampus following sleep deprivation, indicating the critical role played by CREB in its induction following sleep deprivation (Graves et al., 2003b). Protein-dependent processes are necessary components of the incorporation of memories into long-term storage (Scharf et al., 2002). Thus sleep may preferentially affect hippocampus-dependent and not amygdala-dependent memory consolidation, in a fashion similar to that of the PKA signaling pathway that is crucial for long-term memory storage.

Sleep deprivation and sleep fragmentation also have been shown to inhibit neurogenesis in the adult hippocampus, which may or may not be totally dependent upon elevated stress-related corticosteroids (Mirescu et al., 2006; Guzman-Marin et al., 2007). In a rat model, acute total sleep deprivation (48 h) as well as chronic sleep restriction (4-h sleep for each of 7 days) elevated the activity of the hypothalamic-pituitary-adrenal axis (HPA) resulting in increased levels of plasma adrenocorticotrophic hormone (ACTH) and the glucocorticoid corticosterone (Meerlo et al., 2002).

SLEEP AND CIRCADIAN RHYTHMS

Aging is characterized by changes in both sleep and circadian rhythms (Dijk et al., 2000). Complaints of non-specific sleep disturbances and awakenings during the night, daytime sleepiness, and the use of hypnotic medications increases significantly with

age. Sleep disorders such as sleep-disordered breathing, restless legs, and periodic limb movement disorder increase in prevalence with age. Increasing evidence also suggests that medical conditions such as diabetes, nocturia, cardiovascular disease, respiratory disorders and chronic pain contribute to poor sleep in the elderly (Bliwise et al., 1992; Foley et al., 1995; Maggi et al., 1998). Other factors associated with aging, such as disease, changes in environment, or concurrent age-related processes may contribute to problems of sleep in older persons (Ancoli-Israel and Cooke, 2005). In the absence of external time cues, healthy older adults (ranging in age between 60 and 76 years), in comparison to healthy younger adults (ranging in age between 18 and 32 years) showed lower capacity for sleep (as measured polysomnographically) with asymptotic Total Sleep Time duration of 7.4 h versus 8.9 h, and lower daytime propensity (as measured by the Multiple Sleep Latency Test). Older subjects also had significantly less NREM and REM sleep under conditions allowing for maximal sleep opportunity (Klerman and Dijk, 2008).

Several factors have been implicated to produce sleep fragmentation in the elderly, including sleep disorders, compensation for lost sleep, and increased total time in bed, lack of social constraints and disruption of the circadian system. Studies on young adults have shown that entrainment of the circadian timing system can be achieved with much lower light intensities than was previously estimated. Duffy has demonstrated that light of indoor intensity can have a significant phase-shifting effect on the circadian pacemaker, and can suppress plasma melatonin secretion (Duffy and Wright, 2005). Thus, awakening early in the morning, such as when associated with nocturia (nighttime voiding), and turning on a lamp, may lead to an earlier entrainment of the circadian clock and contribute to the early morning awakenings of older individuals.

Our current understanding of the regulation of the human sleep-wake cycle indicates that sleep and wake behaviors are generated by a complex interaction of sleep homeostatic and endogenous circadian processes, as well as environmental factors. The sensation of sleepiness, propensity to fall asleep and depth of sleep are hallmarks of the compensatory response to sleep loss (Dijk and Czeisler, 1994). This drive toward sleep and the tendency to sleep longer and more deeply after sleep deprivation is referred to as "sleep homeostatic process". The sleep homeostatic process regulates the amount of slow wave sleep and depth of sleep. It has been postulated that the sleep homeostatic process is regulated by sleep factors that increase during wakefulness and decline during sleep. Recent studies suggest that adenosine may play an important role in this physiological drive. With increased wakefulness, brain energy stores decrease and adenosine accumulates (Basheer et al., 2001) resulting in increased neuronal membrane depolarization and inhibition of neuronal transmission (Basheer et al., 2000). In support of the model that sleep is required for the restoration of brain energy metabolism (Benington and Heller, 1995; Benington, 2000), levels of brain glycogen decreased significantly by about 40% in brains of rats deprived of sleep for 12 or 24 h while recovery sleep of 15-h duration after 12-h sleep deprivation reversed the decreases in glycogen (Kong et al., 2002). The glycogen was found to be concentrated in white matter (predominantly localized to GFAP-positive astrocytes), but also found in gray matter. No changes specifically related to sleep deprivation were found in the

activity of any of the major metabolic adenosine enzymes in any brain region, although they were generally higher during periods of activity. Thus, changes in adenosine with sleep deprivation are not a consequence of alterations in adenosine enzyme activity. These data suggest that sleep deprivation produces a gradual depletion of brain ATP and higher adenosine levels in some brain regions (striatum and hippocampus) and that different regulatory mechanisms control adenosine levels in these areas compared to the cortex. The effects of sleep deprivation however, are not uniform in all strains of mice (Franken et al., 2003), indicating that brain glycogen level *per se* is dependent upon genetic factors. A recent review of this energy hypothesis can be found in Scharf et al. (2008).

An interesting recently discovered molecule is orexin/hypocretin (Hcrt), a hypothalamus-specific peptide that is restricted to neuronal cell bodies in the dorsal and lateral hypothalamic areas. Two forms have been identified, Hcrt1 and Hcrt2, with the latter proposed as a peptide neurotransmitter. The brain cells that secrete the hypocretins make connections with many of the brain regions involved in regulating the sleep-wake cycle. The hypocretins may act as chemical signals involved in the mechanisms of homeostasis and alertness. Its functions have been proposed as involved in coordination of autonomic functions and homeostasis, including feeding, blood pressure regulation, neuroendocrine regulation, thermoregulation, and the sleep-wake cycle. In young rats and monkeys, levels of Hcrt1 are highest at the end of the wake-active period and lowest toward the end of the sleep period. The effects of age on the diurnal rhythm of Hcrt1 levels in the CSF determined by radioimmunoassay (Desarnaud et al., 2004). In old rats there was a 10% decline in CSF Hcrt1 over the 24-h period, compared to young adult rats. Functionally, if there was less Hcrt1, and there also was a decline in Hcrt receptor mRNA, as had been previously found. The overall consequence in aging would be diminished action of Hcrt at target sites. This would diminish the waking drive, which in the elderly could contribute to the increased tendency to fall asleep during the normal wake period.

A key role to the regulation of sleep homeostasis was the finding of cells within the ventrolateral preoptic nucleus (VLPO) that are contain the inhibitory transmitters gamma-aminobutyric acid (GABA) and galanin, and which are active during sleep and inhibit the arousal histaminergic and adrenergic systems. In turn, VLPO is inhibited by the arousal systems. Thus there is a switching between sleep and wake (Saper et al., 2001).

Little is known about the molecular mechanisms underlying sleep. The induction of key regulatory proteins in a cellular protective pathway involves the unfolded protein response (UPR). It has been found that in cerebral cortex, the protein expression of BiP/GRP78, a chaperone and classical UPR marker, increased with increasing durations of sleep deprivation. UPR helps the endoplasmic reticulum (ER) restore function in response to cellular stress by up-regulating the expression of chaperones and promoting preventing the aggregation of misfolded proteins and helping to properly fold the protein. PERK, the transmembrane kinase responsible for attenuating protein synthesis, which is negatively regulated by binding to BiP/GRP78, is activated by dissociation from BiP/GRP78 and by autophosphorylation leading to phosphorylation of the elongation initiation factor 2 α and alteration in ribosomal function, all components of the UPR. These changes

are first observed after 6 h of sleep deprivation following the onset of the dark cycle when the mice normally would sleep. The longer the length of sleep deprivation (up to 12 h), the greater was the expression of BiP/GRP78. Thus, prolonging wakefulness induced the UPR indicating that extending wakefulness produces ER stress (Naidoo et al., 2005), and aging appears to impair the adaptive UPR and lead to increased expression of proapoptotic proteins (Naidoo et al., 2008). Other approaches that are becoming utilized are expanding our understandings of the how sleep deprivation alters the brain's structure. Proteomic analyses of cerebral cortices from young (2.5 m) and older (24 m) mice have identified classes of proteins that are altered with sleep deprivation and age, involving cell signaling, maintenance of the cytoskeleton, metabolism, pre-synaptic exocytosis involved in Ca^{2+} -mediated processes, heat shock proteins, mRNA, and serum proteins (Pawlyk et al., 2007).

With age, circadian rhythms are advanced or shifted earlier relative to clock time. This can result in the internally driven sleep period moving earlier than the desired sleep period. Older adults commonly report that they can hardly stay awake until bedtime, but are awake before the sun rises in the morning. The fact that older adults are likely to complain of sleep difficulties in the latter half of the night suggests that the endogenous timing of the sleep/wake cycle may contribute to the sleep difficulties. The relationship between sleep timing and the timing of the circadian rhythm of plasma melatonin secretion was investigated in a group of healthy young and older subjects without sleep complaints (Duffy et al., 2002). The timing of sleep and the phase of the circadian melatonin rhythm were earlier in the older subjects, although the duration of sleep was similar. Consequently, the older subjects were waking at a time when they had higher relative melatonin levels, in contrast with younger subjects, whose melatonin levels were relatively lower by wake time. This cannot be explained by a shortening of the circadian period, since it has been reported that the free-running period of young and very health elderly subjects did not differ (24 h 11 min) (Czeisler et al., 1999) and that circadian rhythm amplitude can be well preserved in the "super healthy" older person (Monk and Kupfer, 2000). However, while the relationship between the circadian period and wake time is significantly correlated in younger healthy persons, this relationship is absent in healthy older adults (Duffy and Czeisler, 2002). These findings indicate that aging is associated not only with an advance of sleep timing and the timing of circadian rhythms but also with a change in the internal phase relationship between the sleep-wake cycle and the output of the circadian pacemaker.

At the cellular and molecular level, it has been shown that there are age-associated changes in afferent and efferent pathways of the suprachiasmatic nucleus (SCN), the biological clock that controls the circadian patterning of many neural, endocrine, and behavioral functions. The clock mechanism of the SCN depends upon several genes and their associated protein products that work together through a transcriptional and translational feedback loop to circadian signal. The first mammalian clock gene (the *Clock* gene of mice) was identified and cloned in 1994. It recently has been reported that the encoded factor CLOCK and another factor BMAL1 are two members of bHLH-PAS-containing family of transcription factors that represent the positive elements of circadian autoregulatory feedback loop that activate transcription of other

circadian rhythm genes, period (*per*) and cryptochrome (*CRY*) that code other circadian proteins (Konratov et al., 2003). Age alters the 24-h expression profile of CLOCK and its binding partner BMAL1 in the hamster SCN, but there is no effect of age on the 24-h profile of either Per1 or Per2 proteins when hamsters are housed in constant darkness. Light pulses, which induce smaller phase shifts in old animals than in young, lead to decreased induction of Per1, but not of Per2, in the SCN of old hamsters (Kolker et al., 2003). The only difference between SCN rhythmicity in young and old rats is a small but significant age-related shortening of the free-running period.

Circadian rhythmicity is not limited to the SCN, but also is found in other tissues, such as the liver (Turek and Allada, 2002; Hida et al., 2009). To investigate the organization of a mammalian circadian system, a transgenic rat line was constructed in which luciferase was rhythmically expressed under the control of the mouse Per1 promoter. Light emission from cultured SCN of these rats was invariably and robustly rhythmic and persisted for up to 32 days *in vitro*. Liver, lung, and skeletal muscle also expressed circadian rhythms, which damped after two to seven cycles *in vitro* (Yamazaki et al., 2000). Circadian rhythmicity in some peripheral tissues was unaffected by aging, whereas rhythmicity in other tissues was either phase advanced relative to the light cycle or absent. Those tissues that were arrhythmic could be induced to oscillate by application of forskolin, a compound that activates cyclic adenosine monophosphate (cAMP) activity independent of the membrane receptors, suggesting that they retained the capacity to oscillate but were not being appropriately driven *in vivo*. Aging seems to affect rhythms in some but not in all tissues and may act primarily on interactions among circadian oscillators, perhaps attenuating the ability of the SCN to drive damped oscillators in the periphery (Yamazaki et al., 2002).

Using *Drosophila*, it has been established that a null mutation (*cyc⁰¹*) in a clock gene, *cycle*, as well as for the *Jerk* mutant of *Clock*, is related to a deficient rest phenotype; rest was specifically and significantly reduced without marked effects on locomotor activity (Hendricks et al., 2000; Koh et al., 2006). That is, the animals were not generally hyperactive but rested less while having normal or slightly decreased locomotor activity. In microarray studies, the *cycle* mutants had reduced ability to respond to oxidative stress (a normal response in sleep-deprived flies), and were significantly short-lived compared to their wild type background, suggesting that a mechanism links sleep abnormalities and shortened lifespan. Similarly, it was found that modafinil, a drug that reduces rest, also leads to early mortality (Hendricks et al., 2003). Long-lived *methuselah* flies did not show the same decrease in sleep rebound after deprivation with age that is seen in wild type flies, suggesting that long-lived mutants may have abnormally robust homeostatic mechanisms. In contrast, short sleeping mutant flies (*Hyperkinetic* mutations which code for the beta subunit of *Shaker*) had shortened lifespans, independent of activity changes or age, compared to wild-types (Bushey et al., 2010). Another gene identified in *Drosophila* is *sleepless* which encodes a protein SLEEPLESS the loss of which causes marked sleep reduction. More moderate reductions result in reduced sleep recovery following sleep deprivation, and this protein appears to be a signaling molecule for the homeostatic sleep drive that lowers neuronal membrane excitability through enhanced K^+ channel activity (Koh et al., 2008).

NURSING HOMES

Sleep disturbances and decline in neuropsychological performance are common in older adults. Reduced social and physical activity, commonly seen in nursing homes and assisted care facilities, is likely a contributing factor for these age-related changes in sleep and cognition. Relatively simple social modifications (Benloucif et al., 2004), such as a single daily morning or evening activity session (sessions consisted of stretching, low-impact aerobics, and game playing) for 2 weeks improved sleep and neuropsychological function (a neuropsychological test battery) over baseline levels. Subjective sleep quality ratings, measured by the Pittsburgh Sleep Quality Index, improved following activity sessions in either the morning or the evening, although objective measures of sleep did not improve when measured by actigraphy or polysomnography. Similar findings were seen in a larger nursing home study (Alessi et al., 2005) of 118 residents randomized to a multidimensional, non-pharmacological intervention versus usual care, which found a significant decrease in daytime sleeping compared to usual care controls, which may translate to an improvement in quality of life. These results suggest that short-term exposure to either morning or evening social and physical activity improves objective measures of neuropsychological performance and subjective sleep quality in the elderly. Increasing exposure to social and physical activity may be a useful intervention to improve sleep quality and daytime function in older adults.

SUMMARY

Although there is a growing body of research on the aging circadian system, relatively little exists on the aging sleep homeostatic mechanisms. The brain mechanisms underlying age-dependent changes in the sleep homeostatic mechanisms are beginning to be understood. New studies are pursuing leads into the genetics of sleep. The relevance of the genetics of sleep to the problems of the older individual needs further stimulation. Similar to other recent findings that neuronal loss is not an inevitable consequence of aging, these data indicate that there is little evidence of an age-related loss of neurons that have been identified as playing a key role in the maintenance of sleep homeostasis. Thus, the age-related alterations in the control of sleep appear to not be due to loss of critical neurons but to subtle changes within the cells and in their interactions with other brain cells involved in the control of sleep and alertness. The elucidation of these factors, such as the role played by adenosine in the induction of sleep, can lead to the development of more effective and targeted pharmacological approaches to alleviate some of the problems of sleep that afflict over half of our older population.

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Research also needs to be directed at the development of new and more effective therapeutic modalities that are targeted at correcting the underlying pathological mechanisms of sleep disorders rather than treating them symptomatically. However, until that time, clinical trials on the safety and efficacy of hypnotic and somnolent agents are needed.

A large proportion of older nursing home residents have problems in nighttime sleep and daytime wake. They often are treated for their sleep problems with hypnotic agents that may put them at risk for falls and confusion. Behavioral and environmental approaches may be more effective at dealing with these sleep problems, along with the identification of undiagnosed sleep apnea that could underlie some of these problems.

Research needs to further elucidate how the state of sleep debt is associated with decreased glucose tolerance and insulin sensitivity, elevated evening cortisol levels, and increased sympathetic activity. It appears that there are distinct changes in sleep quality that occur through the adult age span, and these changes also mark specific alterations in hormonal systems that are essential for metabolic regulation. Sleep loss may increase the stress load, possibly facilitating the development of chronic conditions, such as obesity, diabetes, and hypertension, which have an increased prevalence in low socioeconomic groups.

Another exciting area of newly developing research is the understanding of the relationships between sleep and cognitive functioning. This may be especially important in the older individual, given the increased risks for disturbed sleep and disturbed cognition. This is an exciting window of opportunity as research on the relationships between sleep, cognition, aging, and the neurophysiologic and molecular mechanisms is just beginning to coalesce.

Despite our recent advances that connect sleep loss to both brain and bodily functions, much more research is needed to understand the complex associations between sleep, inflammation, stress hormones, metabolic function, obesity, cardiovascular morbidity, and aging. The recent findings need to be replicated and expanded, controlling for age, gender, and racial effects. Indeed, some hints that women sleep better than men, and that this may be one of the factors explaining why women live on average several years longer than men, needs to be addressed in systematic experimental and epidemiological studies. In addition, development of strategies for prevention and improved treatments of sleep disorders that affect large proportions of middle-aged individuals, such as sleep apnea and insomnia, are necessary if we are going to improve the quality and the length of human life. Furthermore, the understanding of the biological substrate of aging associated sleep deterioration should take a priority and may lead to new strategies for a better and longer life.

Sleep is a pillar of health!

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