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Drug-related Sleep Stage Changes: Functional Significance and Clinical Relevance

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Introduction

With the discovery of rapid eye movement (REM) sleep by Aserinsky and Kleitman in the early fifties and the description of the NREM-REM cycle by Dement it became clear that sleep is not a unitary state. Sleep is organized into distinct brain states (REM) and NREM, each having identifiable and characteristic physiological patterns, which vary cyclically across the night. While significant reductions or disruptions of a sleep stage is inevitably followed on a recovery night by a rebound in the disrupted sleep stage, the functional significance and clinical relevance of sleep stage variations is still not clear. Newer drugs are being developed that have been shown to enhance NREM, specifically slow wave sleep, as well as REM sleep. The purpose of this chapter is to review and discuss the clinical relevance and functional significance of drug-related sleep stage effects.

Normal Sleep Staging

Polysomnographic (PSG) studies, which refers to the simultaneous recording of multiple electrophysiological parameters [i.e., electrooculogram (EOG), electromyogram (EMG), and electroencephalogram (EEG)] during sleep, have demonstrated that sleep is a complex, highly organized biological state composed of two distinct brain states, rapid eye movement (REM) and non rapid eye movement (NREM) sleep (1,2). In terms of EEG activity, NREM sleep is characterized by EEG slowing and increased voltage relative to the low voltage (10–30 microvolts) and fast frequency (16–26 Hz) of activated wakefulness. Relaxed

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wakefulness with eyes closed exhibits an alpha (8–12 Hz) EEG pattern of 20–40 microvolts, which further slows to 3–7 Hz and decreases in amplitude during drowsy, stage 1 NREM, sleep. Stage 2 NREM sleep is characterized by phasic events of sleep spindles (12–14 Hz) and K-complexes (negative sharp waves of 0.5 Hz and greater) and elevated arousal thresholds relative to stage 1 NREM sleep. When arousal threshold is highest, the EEG of NREM stage 3 and 4 sleep has 0.5 – 2 Hz waves of 75 microvolts and greater, termed slow waves. NREM stages 3 and 4 are merely differentiated by the quantity of slow wave activity (SWA) on a given epoch (20–50% vs >50%) and often to maintain scoring reliability are not differentiated in visual sleep scoring. The EEG of REM sleep, in dramatic contrast, reverts to the low-voltage, mixed frequency pattern seen in stage 1 NREM sleep. The EOG of REM displays bursts of rapid eye movements, for which this stage is named. In contrast to this aroused EEG, the EMG shows a total atonia of voluntary muscles.

Sleep is entered through NREM stage 1, which normally lasts 1–7 min before the sleep spindles and K-complexes of NREM stage 2 appear (1,2). As stage 2 progresses a gradual appearance of high-voltage slow wave activity occurs, eventually reaching criteria for scoring stage 3 and 4 NREM sleep. This first episode of NREM stages 3 and 4 lasts approximately 10–30 min, depending of age, and sleep lightens to stage 2 before the initiation of the first REM episode, which occurs 90–120 min after sleep onset. NREM and REM sleep continue to cycle in this manner for 4–5 cycles per eight hours. Each cycle is about 90 minutes, but the sleep stages in those cycles change across the night. The duration of each episode of NREM stage 3 and 4 decreases each cycle and the duration of each REM episode increases with each cycle. During the third and fourth NREM-REM cycles there is minimal delta wave activity and REM periods are of 20–30 min duration.

The observation that slow wave sleep diminishes progressively across NREM-REM cycles over the night led to the hypothesis that slow wave sleep/slow wave activity is precisely controlled, reflecting the operation of a sleep homeostat (3). This hypothesis was established and supported with many studies using both visual scoring and various quantitative EEG methods such as spectral analysis. Quantitative EEG methods yield several indicies of slow wave activity that prove to be more sensitive than visual scoring of slow wave sleep. Numerous studies, that have deprived sleep, extended sleep, or added daytime naps, have shown that slow wave sleep and slow wave activity increase and decrease in the predicted directions (i.e., the index increases with increasing hours of wake and decreases with increasing hours of sleep), as one would hypothesize for a sleep homeostat. One important caveat is that all of these studies involved acute, not chronic, manipulations of sleep. Given this hypothesis and the extensive data supportive of the hypothesis, drugs which enhance slow wave sleep should have important functional and clinical significance.

Drug Effects on Sleep Stages

Benzodiazepine Receptor Agonists

The major class of drugs indicated for the treatment of insomnia is the benzodiazepine receptor agonists (BzRAs). The class includes benzodiazepines and non-benzodiazepines that act at the benzodiazepine receptor. Benzodiazepines are known to reduce stage 3–4 sleep. For example, estazolam 2 mg in 35 yr old insomniacs reduced stage 3–4 sleep from 4% to 1% (4). Temazepam 15 and 30 mg in 38 yr old insomniacs reduced stage 3–4 sleep from 8% to 5% (5). Both drugs reduced percentage of stage 1 sleep from 11% and 16% to 9%. In elderly insomniacs (60–85 yrs), triazolam 0.125 mg had no effect on sleep stages; % stage 1 was 22% and % stage 3–4 was 5% on both placebo and active drug (6). In each of the studies total sleep time was increased and where measured, self-reported sleep was improved. Additionally, in the elderly study cited above the improved sleep time was associated with an improvement in daytime sleepiness as measured by the Multiple Sleep

Latency Test (MSLT). This improved MSLT was found with 22% stage 1 sleep the previous night in the elderly subjects. These benzodiazepine data highlight the importance of caution in interpreting the significance of sleep stage changes and the biology associated with them. For example, it is known that in humans stage 3–4 sleep is associated with the highest arousal threshold. Yet, while benzodiazepines decrease stage 3–4 sleep, they also increase arousal threshold (7). Given the known action of these drugs on the cortex, one has to question whether these declines represent a drug effect on stage 3–4 sleep or on the ability of the cortex to produce high amplitude slow waves, which is our surrogate measure of stage 3–4 sleep.

On the other hand, the non-benzodiazepine BzRAs do not appear to consistently alter sleep stages (8). In one study of healthy 21–35 yr old normals, zolpidem 0–20 mg did not affect stage 1 or stage 3–4 (9). The high dose reduced REM sleep. Zopiclone 0–15 mg in middle-age insomniacs reduced stage 1 from 12% to 8% (10). At the high dose it reduced stage 3–4 (9% to 4%) and REM sleep (20% to 18%). The S-isomer, eszopiclone (0, 1, 2, 3, 3.5 mg), in healthy volunteers did not alter stage 3–4 or stage 1 sleep at any dose (11). In these studies all the BzRAs, both Bz and non-Bz, that were studied improved sleep time or efficiency, and where assessed, improved self-reports of sleep. Finally, none of these drugs, at clinical doses, suppress REM sleep, although there are reports of increases in latency to REM sleep. GABA Reuptake Inhibitor:

Tiagabine a selective GABA reuptake inhibitor indicated for epilepsy has been studied for its effects on sleep. In a study of the effects of tiagabine, 0,2, 4, 8 mg, on the sleep of older adults, the 4 and 8 mg doses increased slow wave sleep by approximately 15 and 40 min, respectively. It did not reduce sleep latency and had inconsistent effects on sleep time and self-ratings of sleep (12). In another study of healthy elderly 5 mg tiagabine doubled the minutes of slow wave sleep, while also improving sleep efficiency, but not self-reported sleep quality (13). It should be noted sleep efficiency was relatively low, 78%, in the placebo group and time-in-bed was unrestricted, making it difficult to interpret these results. In a study of elderly insomniacs receiving 0, 2, 4, 6, and 8 mg, the 4–8 mg doses increased slow wave sleep, the 6 and 8 mg doses reduced stage 1 sleep and number of awakenings, but had no effect of sleep efficiency or self-reported sleep (14). In middle age adults with insomnia tiagabine 0, 4, 6, 8, 10 mg again increased slow wave sleep in a dose-related manner, but had no effects on sleep latency, wake after sleep onset, or total sleep time (15). Finally, in another study of middle age insomniacs, tiagabine 0, 4, 8, 12, 16 mg increased percent of 3–4 sleep from 7% to 29%, but did not consistently improve sleep latency, wake after sleep onset, or sleep time (16).

One study has attempted to assess the functional significance of slow wave sleep enhancement with tiagabine in healthy normals during sleep restriction, which is known to impair next-day function. Healthy volunteers were randomized to placebo or 8 mg tiagabine before sleep over four nights during which bedtime was restricted to 1–6am (17). Relative to placebo tiagabine increased slow wave sleep by about 30 min and the sleep restriction associated impairment of psychomotor vigilance performance was diminished by the drug. The amount of slow wave sleep during the restriction was positively correlated with average daily sleep latency on the MSLT, that is greater slow wave sleep was correlated with longer latencies on the MSLT (i.e., less daytime sleepiness). One caution, many other outcome measures of daytime function in the study did not show this relation with stage 3–4 sleep. The study also has implications for the use of sleep restriction in insomnia therapy in that the depth of sleep may be enhanced through increased stage 3–4 sleep (see discussion sleep stage variations in insomnia below).

$GABA_A$ Agonist

Gaboxadol, is a selective extrasynaptic $GABA_A$ agonist that was being developed as a hypnotic, but was abandoned in 2007 due to an inadequate therapeutic-safety ratio. An early study of healthy adults showed that 20 mg gaboxadol increased slow wave sleep time relative to placebo from 56 to 80 min (18). Another study of healthy adults introduced a 4–6pm nap, which typically will reduce subsequent nocturnal slow wave sleep and 20 mg garboxadol administered before the nocturnal sleep increased slow wave sleep relative to placebo from 54 to 78 min (19). In two large studies of healthy, middle-aged, volunteers undergoing a 4-hr phase advance, which was used as a model of transient insomnia, doses of 0, 5, 10, and 15 mg were administered (20,21). The 10 and 15 mg doses increased slow wave sleep and increased total sleep time, primarily by reducing wake after sleep onset. These doses also improved self reports of sleep time. In healthy elderly without sleep complaints gaboxadol 15 mg increased stage 3 and 4 sleep and reduced stage 1 sleep (22). It also improved sleep time and wake after sleep onset as well as self-reported sleep time and sleep quality. In two studies of middle-aged insomniacs at does of 0, 10, 15, 20 mg gaboxadol increased stage 3 and 4 sleep and at the 15 and 20 mg doses it also increased sleep time by primarily reducing wake time after sleep onset. (23,24). Finally in elderly patients with insomnia gaboxadol 10 mg increased stages 2, 3, and 4 and reduced wake after sleep onset, but had no effect on sleep latency (25).

As with tiagabine, a study used the sleep restriction paradigm to investigate the capacity of gaboxadol to enhance slow wave sleep during sleep restriction and thereby reduce the performance impairing effect of the restriction (26). In this study of healthy volunteers slow wave sleep was increased by 17 min relative to placebo and while a positive correlation of slow wave sleep to MSLT was found, psychomotor vigilance was not improved relative to placebo. The failure to reverse the performance impairing effect of sleep restriction may be due to a lessoned effect of gaboxadol on slow wave sleep (17 vs 30 min increase) compared to the tiagabine study.

$GABA_B$ Agonist

Gamma–hydroxybutyrate (GHB) and the sodium salt of GHB, sodium oxybate, have a long history of study for their sedative effects. GHB is present in the CNS synthesized from GABA as its active metabolite. When administered orally in supraphysiological doses, as GHB or sodium oxybate, it is thought to act specifically, but weakly, at the $GABA_B$ receptor, hence the need for supraphysiological doses (27). In healthy people, 23–63 years old, a single GHB 2.25 g dose administered 15 min prior to sleep increased percentage of slow wave sleep from 10.5% to 13.6%, but it did not increase total sleep time (28). In healthy, young men 2.5, 3.0, and 3.5 g GHB increased the minutes of slow wave sleep in a dose-related manner and reduced initial sleep latency, but did not increase total sleep (29). The slow wave sleep effects in these studies were limited to the first third of the night, hence the need for a second nightly dose when treating narcolepsy, its current FDA indication.

In narcolepsy, early studies used relatively low total doses (50–60 mg/kg) of GHB given before sleep and 3–4 hrs later. In 20 patients with narcolepsy GHB 50 mg/kg increased slow wave sleep and decreased stage 1 sleep (30). It reduced the number of awakenings, but did not increase total sleep time and had no impact on the excessive sleepiness of the narcopletics as measured by the Multiple Sleep Latency Test (MSLT). In a study of 24 narcoleptics GHB 60 mg/kg, in divided doses, increased slow wave sleep and reduced the number of awakenings and it improved self-rated daytime sleepiness (31).

Showing therapeutic potential to improve both sleep and daytime sleepiness, a number of larger multi-site clinical trails of sodium oxybate, the sodium salt of GHB, were conducted.

Sodium oxybate was administered to narcoleptics in a titrated dosing schedule of 4.5, 6, 7.5, and 9 g (32). The 7.5 and 9 g doses increased stage 3 and 4 sleep in the second half of the night and delta power across the night. Accompanying the nocturnal changes were improvements in daytime alertness as measured by the Maintenance of Wakefulness Test (MWT). In a larger multi-site trial of sodium oxybate in narcoleptics, 4.5, 6, and 9 g doses were administered and stage 3 and 4 sleep was increased in a dose related manner and stage 1 sleep was reduced at the 6 and 9 g doses (27,33). Again MWT scores were improved.

Alpha 2 Delta Ligands

Several antiepileptic drugs with a unique mechanism of action have been explored for their sleep effects. These drugs do not bind at $GABA_A$, $GABA_B$, or BZ receptors, but rather at the alpha 2 delta subunits of voltage-gated calcium channels. Pregabalin with a wide range of therapeutic indications was evaluated for its effects on the sleep of healthy volunteers. Pregabalin 450 mg was compared to alprazolam 3 mg and placebo all administered before sleep (34). Relative to placebo pregabalin increased stage 3 and 4 sleep, while alprazolam reduced stage 3 and 4 sleep. Pregabalin also reduced the number of awakenings, but it did not increase sleep time in these normal volunteers. Both drugs improved ratings of sleep quality and ease of falling asleep. In patients with controlled epilepsy, but remaining self-reported sleep disturbance, pregabalin 300 mg taken twice daily (not specifically before sleep) had no effect on stage 3 and 4 sleep, but it did reduce the number of awakenings relative to placebo (35).

Another alpha 2 delta acting drug, gabapentin, has indications for epilepsy and neuropathic pain. In healthy volunteers gabapentin was titrated to a 1,800 mg daily dose, taken in divided doses in the am, midday, and before sleep (36). It increased the percentage of slow wave sleep from 8% to 13%, but did not affect other sleep stages. No differences in self-reported sleep or daytime sleepiness were observed. The sleep of patients with localization-related epilepsy controlled with various single anti-epileptic drugs (AED) was compared to that of patients discontinued from their AEDs (37). Gabapentin 900 mg increased slow wave sleep (19%) relative to the control patients (11%), but it did not alter other sleep stages or increase sleep time. The effect of gabapentin 300 and 600 mg was studied in healthy middle age adults, whose sleep was disrupted with a pre-sleep 4 oz dose of 40% alcohol (38). The 600 mg dose, relative to placebo and alcohol, increased slow wave sleep, while both doses reduced stage 1 sleep and the number of awakenings and increased sleep efficiency.

Serotonergic Antagonists and Inverse Agonists

Serotonergic antagonists also increase stage 3–4 sleep, but do not consistently improve sleep time or insomnia related symptoms. Ritanserin, a $5\text{-}HT_{2A/2C}$ receptor antagonist with an approximately 40 hr half-life, is one such drug. In healthy volunteers ritanserin 5 mg, administered in the morning increased the amount of subsequent nightltime slow wave sleep by almost 50%, but there was no relation of the increased slow wave activity to any daytime performance measures, or reports about the efficiency or quality of sleep (39). Also, it did not increase sleep time or decrease sleep latency. In a dose study of ritanserin 1, 3, 10, and 30 mg administered in the morning to healthy volunteers, relative to placebo ritanserin increased slow wave sleep duration in a dose related manner (40). Again no effects on sleep time or self-rated sleep measures were observed. A study in healthy volunteers compared ritanserin 5 mg to 20 and 40 mg ketanserin, which has less affinity to $5\text{-}HT_{2C}$ receptors than ritanserin (41). Both drugs were administered 90 min before sleep and ritanserin increased slow wave sleep relative to placebo and the increase was larger than that of ketanserin. Ketanserin reduced number of awakenings and wake after sleep onset to a greater extent than ritanserin. Given the daytime administration of ritanserin, it's effects on driving performance and subsequent nighttime sleep was compared to that of lorazepam (42).

Lorazepam 1.5 mg and ritanserin 5 mg, both given bid (1100 and 1700 hr), had differential effects on driving and sleep. Lorazepam impaired driving and increased daytime sleepiness as measured by the Multiple Sleep Latency Test, while ritanserin had no effects on sleepiness and driving performance. Ritanserin increased nocturnal slow wave sleep, while lorazepam had no effects on stage 3–4 sleep.

Ritanserin has also been studied in poor sleepers and other patient groups. In a study of young healthy volunteers, self-described as poor sleepers, 5 mg ritanserin increased slow wave sleep and delta EEG power spectra and it also increased REM and total sleep times and self-rated sleep quality (43). In middle age poor sleepers, ritanserin 5 mg, administered after dinner, doubled the amount of slow wave sleep and reduced the amount of stage 1 sleep (44). It did not alter sleep time or rating of sleep quality. In middle age patients with dysthymic disorder ritanserin 10 mg vs placebo taken at breakfast doubled the percentage of stage 3 and 4 sleep (45). It also reduced the number of sleep stage shifts, but had no effects on sleep time or self-rated sleep. Finally, a study assessed the effects of ritanserin 5 and 10 mg on the sleep of patients with narcolepsy (46). Both doses increased stage 3 and 4 sleep and the 10 mg dose decreased stage1 sleep, but neither dose improved daytime sleepiness.

Several 5-HT_{2A} inverse agonists have been assessed as potential treatments for insomnia. The drug, SR46349B (eplivanserin), in a 1 mg dose administered 3 hr before bedtime to healthy adults, increased stage 3 and 4 sleep from 19% to 32% and increased delta power spectra, but did affect self-reported sleep quality (47). In a dose-ranging study 1, 10, or 40 mg eplivanserin in healthy adults increased slow wave sleep time by about 30%, but not in a dose-related manner (48). Additionally, relative to placebo it improved sleep efficiency and reduced the number of awakenings.

A recent study of a selective 5-HT_{2A} inverse agonist, nelotanserin, suggests potential slow wave sleep enhancement and sleep consolidation(49). At doses of 10, 20, and 40 mg administered to healthy adults before an afternoon nap, slow wave sleep was increased in a dose-related manner with the increase being from 47 to 82 min at the 40 mg dose. Total sleep time and the other sleep stages were not affected, but the number of awakenings, sleep stage shifts, and micro-arousals were all reduced.

Summary

The Bz and non-Bz agonists all improve insomnia; the Bzs mildly, but consistently, reduce stage 3–4 sleep and the non-Bz agonists do not affect stage 3 and 4 sleep. Thus, clinically these drugs improve insomnia, but some reduce stage 3 and 4 sleep. On the other hand, some of the serotonergic antagonists and inverse agonists and GABA reuptake inhibitors increase stage 3 and 4 sleep, but do not consistently improve measures of insomnia. Finally, a $GABA_A$ agonist appears to both increase stage 3 and 4 sleep and improve various measures of insomnia, and a $GABA_B$ agonist increases stage 3 and 4 sleep, consolidates sleep by reducing sleep stage shifts and awakenings and improves the daytime sleepiness associated with narcolepsy.

Thus, modulations of stage 3–4 sleep have no consistent relation to improving insomnia. On the other hand, GHB/sodium oxybate increases stage 3–4 sleep and improves daytime alertness in narcolepsy. Stage 1 sleep reductions are reported with some of the drug classes discussed above, but not consistently so. These inconsistencies raise the question as to whether the functional significance of drug-related sleep stage alterations relate to the specific nature of sleep stage deficiencies in a given sleep disorder.

Sleep Stage Variations in Sleep Disorders

Primary Insomnia

There have been many studies over the years that have attempted to document PSG differences in the sleep of people with insomnia compared to those without insomnia. Most studies have failed to find differences in measures of onset and maintenance (i.e., sleep latency, wake after sleep onset) or in sleep stage distribution (50–52). An early, and the most frequently referenced study, is that of Carskadon et al, 1976, in which 122 drug-free insomniacs did not differ in PSG sleep from non insomniacs (53). Plots of the distribution of sleep efficiency in the two groups showed considerable overlap. Among those studies showing PSG differences, increased wake time after sleep onset and less stage 3 and 4 sleep in insomniacs relative to controls has been reported (54,55). Studies using EEG spectral analyses have compared patients with primary insomnia to age-matched controls. Some studies have failed to find substantial differences in EEG power in the delta and theta bands (56), while others have reported differences (57). One consistent finding reported in several studies is an increase in beta and gamma EEG activity in patients with insomnia compared to age-matched controls (57,58).

Given the inability to find consistent PSG deviations from normal controls, particularly in total sleep times, a distinction between insomniacs showing objective sleep disturbance and those with no objective sleep disturbance was incorporated in the diagnostic nomenclature. The International Classification of Sleep Disorders (ICSD) includes the diagnostic entity “sleep state misperception” to account for those reporting disturbed sleep, but showing normal PSGs. Given many studies were for 1–2 nights, which may be an inadequate assessment, a study of patients with sleep state misperception sampled their sleep for two nights on each of three occasions separated by two weeks (59). This study found sleep state misperception patients had an elevated percentage of stage 1 sleep relative to age-match controls (14% vs 11%). Spectral analyses of the sleep EEG of patients with sleep state misperception have found lower delta and greater alpha, sigma and beta activity than controls (60). As mentioned above. it is not clear whether the observed changes in sleep stages, when observed, were inherent to the condition or secondary to pathophysiological events like apneas and hypopneas which cause EEG arousals.

Sleep Apnea and Periodic Leg Movement Disorders

The characteristic impact of these primary sleep disorders is the fragmentation of sleep with brief EEG arousals (i.e., 3–15 sec) and or awakenings that follow each apnea or leg movement event. The impact on sleep stages of these primary sleep disorders is an increase in the percentage of stage 1 sleep to 50–60% in patients with severe obstructive sleep apnea syndrome (OSAS) or to 25% and more in patients with periodic leg movements (61,62). Further, percentage of stage 3–4 sleep is reduced to 3% and less. While controls were not included in these particular studies, the degree of stage 1 elevation and stage 3–4 reduction, corrected for age, would be considered “abnormal”. Furthermore, the degree to which sleep is fragmented, as documented by brief EEG arousal indices and secondarily reflected in the sleep stage deviations, relates to objective assessments of daytime sleepiness and the daytime sleepiness complaints of these patients. Treatment of OSAS, whether by surgery or continuous positive airway pressure, reduces the number of brief arousals and normalizes the sleep stage deviations and improves the daytime sleepiness (63). Similarly, treatment of periodic leg movements improves sleep continuity and the daytime symptoms (64,65).

The functionally impairing and sleep disruptive effects of primary sleep disorders has been modeled in healthy normals by fragmenting sleep with auditory tones producing brief EEG arousals. In one such study, the sleep of healthy young adults was disrupted with brief

arousals on average 14 times per hour of sleep, which clinically would be considered a mild to moderate arousal index (66). The consequent impact on sleep stages was to increase stage 1 sleep from 10% to 19% and to reduce stage 3 and 4 sleep from 19% to 5%. This fragmentation of sleep produced mild daytime sleepiness, reducing the average sleep latency on the Multiple Sleep Latency Test (MSLT) from 14 min to 9 min.

Narcolepsy

The classic tetrad of symptoms in narcolepsy is excessive daytime sleepiness, cataplexy, sleep paralysis, and sleep onset hallucinations with many considering disturbed nocturnal sleep a fifth symptom. Studies generally have shown reduced sleep efficiencies in patients with narcolepsy compared to age-matched healthy controls and some have shown elevated stage 1 sleep (67). In drug-free narcoleptics percent stage 1 sleep was elevated (21% vs 14%), but percent stage 3 and 4 (10%) was the same in both groups (67). In another small study, drug-free narcoleptics compared to age-match controls showed a greater percentage of stage 1 (17% vs 9%) and lessoned (11% vs 15%) percentage of 3 and 4 (68). On the other hand, a larger study found no differences in any sleep stages between narcoleptics and controls (69). Finally, a study that conducted EEG spectral analyses in narcoleptics found no differences from age-matched controls in visually scored stage 3 and 4 sleep, but did find diminished slow wave activity and power (70).

Summary

Insomniacs do not show consistent disturbance of sleep stages, but when present, the most disturbance seen is a mild elevation in stage 1 sleep (10–15%). Functional daytime impairment occurs in patients with primary sleep disorders (i.e. apnea, periodic leg movements) due to the fragmentation of sleep by brief EEG arousals, which is then also reflected in higher percentages of stage 1 sleep and reductions of stage 3 and 4 sleep. Sleep stages 3 and 4 of patients with narcolepsy are not consistently abnormal, while stage 1 appears elevated in most studies of narcoleptics. The major pathologic sign of narcolepsy is sleep onset REM periods. Overall, the data from patients with various sleep disorders suggest that in the absence of frequent EEG arousals and sleep fragmentation which tends to increase stage 1 sleep and reduces stages 3 and 4, there are no systematic changes in sleep stage distribution. The final question then is, what are normal variations in sleep staging and what are the functional consequences of sleep stage manipulation in healthy normals.

Sleep Stage Variations in Non-Patients

Age and Sex Variations

Beyond the sleep stage changes of the first decade of life, the major variation in sleep stages occurs with aging. NREM stages 3 and 4 decline with age from approximately 20% in young adults to 10% in the fourth decade and to 6% in the sixth decade in one study (71). Computer analyses of the delta wave activity of stage 3 and 4 sleep suggest that the age-related decline can be attributed to a reduction in delta wave amplitude and not specifically in the number of delta waves (72). Because sleep-disordered breathing (SDB), which fragments sleep thereby increasing stage 1 and reducing stages 3 and 4 sleep, increases with age, valid data on age-dependent variations in sleep stages have to include concurrent assessment of SDB events, which was done in the cited data above. In contrast REM sleep time shows little variation across the life span after the first year.

The other major variation in sleep stages is related to sex. Sex differences in the sleep of elderly volunteers have been well described (72). The most prominent and consistent sex-related finding has been a reduction in the percentage of visually scored stage 3–4 sleep in elderly men (73), which has been extended using computer scoring of slow wave activity

(74). Whether this delta wave sleep difference reflects a sex-related anatomical difference that alters the electrophysiological signal (e.g., greater male skull thickness and increased dead space between the skull and cortex, thereby attenuating the signal), a differential prevalence of sleep pathologies that fragment and suppress delta wave activity (i.e., a higher prevalence of SDB in men), or a homeostatic sleep process difference between men and women is not clear. Related to the discussion of insomnia above, it is interesting to note that while the decline in sleep wave sleep with age is more pronounced in men, the age related increase in the prevalence of insomnia is more pronounced in women.

Recent small clinical studies of young to middle-aged adults (20–50 yrs) have confirmed the sex-related difference in delta wave sleep, using either visual or computer scoring (74–79). Computer analyses of the sleep EEG in samples of young and middle-age adults suggest that the delta wave difference between men and women is related to an anatomical difference that produces an electrophysiological difference in signal amplitude. Power density differences in sleep EEG were found across a wide frequency range in NREM sleep (i.e., were not limited to delta wave frequency bands), were found in the REM sleep EEG, and also were shown in the frequency of sleep spindles (74–79). Men had smaller power densities and lower spindle frequency, likely due to their thicker skulls.

The above studies had small samples of convenience. In a population-based sample of older persons (mean age 61 yrs) sex differences in sleep were reported (80). Men had more wakefulness during sleep and more stage 1 sleep and less stage 3–4 sleep than women. Given that SDB increases with age, the lighter sleep of the men in this population-based sample could be attributed to a higher prevalence of SDB. A recent study assessed sex differences in a younger (31–40 yrs old), large community-based sample with concurrent assessment of SDB (81). After correcting for SDB in these younger men, no stage 3–4 differences between men and women were found, but the men had greater percentage of stage 1 sleep (i.e., 13%).

A number of studies have attempted to relate variations in sleep stages to measures of daytime function. Studies of night-to-night variations in REM sleep have shown positive correlations with memory function (i.e., greater REM time is associated with better memory), although the REM-memory relation is controversial (82). Beyond studies of a REM-memory relation, the functional significance of stage 3 and 4 sleep has received research attention. For example, in young men slower reaction times were related to lesser amounts of visually scored stage 3 and 4 sleep (83). But, the majority of studies, most of which have been conducted in elderly, have shown no relation between stages 3 and 4 sleep and measures of cognitive function (84–87). Several more recent studies have used spectral EEG analyses to quantify delta activity (88,89). On 1 or 2 of the half-dozen performance measures assessed, greater power in the 2–4 Hz frequency band was predictive of better performance. However, inclusion of 2–4 Hz frequency as delta, which is more typical of stage 1 than delta sleep, and unusually high percentages of visually scored stage 3 and 4 sleep (i.e. about 20% in 50 and 60 year olds) raise questions about these studies.

Studies of Selective Sleep Stage Deprivation and Recovery

In an attempt to understand the functional and clinical relevance of variations in sleep stage distribution, selective sleep stage deprivation studies have been conducted. While the majority of selective sleep stage deprivation studies have focused on REM sleep, a few early selective delta sleep deprivation studies were conducted. The acute within-night response to loss of stage 3–4 sleep (i.e., a rapid return to stage 3–4 sleep and increasingly higher arousal thresholds), makes stage 3–4 deprivation studies difficult to conduct (90). In contrast, REM deprivation at least for a few days is easier to achieve (91). These early studies found that when stage 4 sleep was deprived by arousing the sleeping individual immediately upon entry

to stage 4 sleep, subsequent entries to stage 4 sleep increased within the night and over subsequent nights (91,92). When uninterrupted sleep was permitted, a rebound in stage 4 sleep was observed.

Daytime performance has been tested after selective stage 4 or REM sleep deprivation and decrements specific to sleep stage were not found after as many as 7 nights of the selective sleep stage deprivation (91–93). Interestingly, in recent long term partial sleep deprivation studies, restricting bedtime to 5 hours a night leads to an increase in stage 3–4 sleep and daytime performance decrements. . However, this stage 3–4 compensation disappears after 1–2 days, but the performance decrements associated with the sleep restriction continue to accumulate (94). It was concluded from all of these approaches that the major predictor of performance decrement was total sleep time and not time spent in specific sleep stages (95).

As mentioned, when recovery sleep is allowed after sleep deprivation, a rebound in stage 3 and 4 sleep is observed. It has been shown repeatedly that visually-scored stage 3 and 4 sleep, or slow wave activiity measured by EEG spectral analysis, is increased during recovery sleep as a function of the number of hours of prior waking (96). Furthermore, without prior sleep deprivation, within the night, the amount of delta activity declines over successive NREM-REM cycles. It is hypothesized and generally accepted that delta activity is reflective of a sleep regulatory process, termed process S (96). But one has to be cautious because enhanced delta activity does not necessarily reflect the restorative processes of sleep. Post sleep deprivation recovery of EEG delta activity does not relate to the recovery of daytime behavioral function in correlational studies. This hypothesis was tested by comparing restoration of daytime function after selective deprivation of delta sleep during the recovery night following total sleep deprivation to a non-disturbed night of recovery sleep (97). Recovery sleep restored performance, and importantly, there was no difference between recovery sleep with and without delta sleep. It is critical to note that all of these sleep deprivation studies were acute and the sleep stage recovery associated with long term sleep deprivation in humans is not well documented.

Summary

Studies of sleep stage variations in healthy volunteers have reported considerable changes in sleep stages as a function of age and sex. The major changes observed are an age-related reduction of stage 3 and 4 sleep which is more pronounced in men than women. There also is some evidence of an increase in stage 1 sleep with age in men. Selective sleep stage deprivation studies do not find a functional significance associated with the loss and recovery of specific sleep stages.

Conclusions

Slow wave sleep changes as a function age and more rapidly in men than women and stage 1 sleep increases slightly with age in men. After controlling for primary sleep disorders, which also increase with age, no functional or clinical significance is found with these changes. Similarly, in healthy normals, selective sleep stage deprivation studies have not found functional impairment associated with the loss and recovery of specific sleep stages. Large changes in sleep stages that are associated with functional impairment are found in some primary sleep disorders, but these changes are likely secondary to the fragmentation of sleep by brief arousals. Often the fragmentation is associated with an elevation in stage 1 sleep. To date no consistent sleep stage changes such as deficiencies of stage 3–4 sleep or elevations of stage 1 sleep have been reported in insomniacs.

Given the observation of these normal reductions in slow wave sleep and often elevations in stage 1 sleep with age and the absence of clear sleep stage changes in insomnia, the

functional significance and clinical relevance of drug related changes in stage 3–4 sleep still remains to be demonstrated. Studies showing that enhancement of slow wave sleep in healthy older adults is also associated with improved daytime function such as memory or vigilance, will be an important step. Similarly, studies showing that the usual impairing effects of sleep time reductions can be reversed, such as the studies attempted with tiagabine and gaboxadol, will be of further importance. In patients with insomnia, the data for many of these agents suggest that while sleep onset is not reduced, sleep maintenance may be improved, possibly through the reduced arousability associated with the enhanced stage 3 and 4 sleep.

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