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President
J. Christian Gillin, M.D

President Elect
Wallace Mendelson, M.D

Past President
Adrian Morrison, DVM

Section Heads
Basic Mechanisms: Dennis McGinty, Ph.D
Circadian Rhythms: Charles Czeisler, M.D., Ph.D
Normal and Pathological Excessive Daytime Sleepiness: Mary Carskadon, Ph.D
Sleep and Behavior: David Dinges, Ph.D

President’s Column

TO MERGE OR NOT TO MERGE

The Sleep Research Society has historically championed the scientific study of sleep in all its varied manifestations. It has been either the home or the guest house for basic and clinical scientists from many fields, including neurobiologists and neurologists, psychologists and psychiatrists, psychoanalysts and pharmacologists, and clinicians and chronobiologists. More than most scientific societies, the Sleep Research Society has used its limited resources to develop the next generation of scientists.

Although the Sleep Research Society took its current name in the early 1980’s, it is the direct lineal descendent of the Association for the Psychophysiological Study of Sleep (the “first APSS”), which formed about 1961. In those early days, the APSS embraced both scientists and clinicians in many fields of interest. The field was dominated by a relatively small, young, talented group, a band of siblings, not without their rivalries but all were clearly identified as members of the same family, the sleep community. Many of the founders are still active or only recently retired. Many of their children, among whom I count myself, share that same family identity.

One measure of the founders’ success was the growth of sleep disorders medicine in the late 1970s and 1980s. Growth and success, however, often occasion new problems. The sleep field was not spared these growing pains. The APSS split into clinical and research wings, the American Sleep Disorders Association and the Sleep Research Society. Wise people still disagree whether this split was necessary but none can deny that the sense of family, which previously prevailed, was diminished. As has been said, a house divided against itself cannot stand. At times, the two wings of the family failed to communicate or cooperate except for the most basic functions. The “first APSS” was renamed the Association of Professional Sleep Societies, an umbrella over the two societies, perhaps, but certainly neither a house nor a home for the fields of sleep. During these years, the leadership of the field often fell to or was seized by a few visionary and energetic individuals rather than by the APSS, ASDA, or the SRS, which were unable or unwilling to provide institutional, organizational leadership.

When I became President-Elect of the SRS nearly two years ago, I was astonished to find there was no official
communication between the leadership of the SRS and ASDA. The Joint Operations Committee (JOC) had been established to oversee the shared activities of the two societies, specifically, the journal and annual meeting. The JOC implemented policy but was not, in theory, given the authority to decide it. The senior leadership of the two societies were not members of the JOC and they had no mechanism by which to decide policy. In reality, the leadership of the two societies was in danger of abdicating their responsibilities for issues of great importance to the field of sleep, including even the journal and the annual meeting.

Beginning with Adrian Morrison's SRS Presidency in late 1995, some of these problems with the JOC were remedied by adding the senior officers of both societies to the JOC. The JOC now has a monthly conference telephone conference call to discuss issues affecting the whole field of sleep. It has been slowly taking on new responsibilities.

As a result of this new cooperation, the SRS and ASDA have achieved considerable success this year in addressing the needs of the sleep fields and the joint interests of the two societies. Many small issues are dealt with quickly and efficiently. Moreover, many big problems have been addressed for the first time through the cooperation of the SRS and ASDA. Take, for example, the threat of reduced federal funding for biomedical research. In an important first societal effort to increase NIH support for sleep research, the SRS worked with the Government Affairs Committee of the ASDA to formulate the goals of the Sleep Walk in Washington, May 29, 1996. More than a thousand sleep researchers, clinicians, students, sleep disorder patients, and citizen activists lobbied nearly every member of Congress to implement the National Sleep Disorders Research Plan, which was signed by the Director of the National Institutes of Health this spring. We asked the Congress to support the NIH budget for basic and clinical sleep research and research training. To follow up this initial effort, SRS is represented on an informal coordinating committee to establish the goals and ways to implement them. Had the SRS been left out during the planning stages, the research funding issues would not have been major goals of the March and the SRS's main interests would not have been presented to policy makers.

In addition, in the spirit of cooperation, the ASDA contributed $5000 this year for the first time to supplement the $30-35 thousand the SRS has contributed each year to bring students to the annual meeting. As a result, more than 100 students attended the meeting for the first time.

Representatives from SRS and ASDA are also discussing the possibility of a joint Research Committee with a staff member at the APSS headquarters to promote high quality sleep research.

Finally, I was invited to join ASDA leaders to help select the new Executive Director of the APSS office in Rochester, Minnesota. As a result, Jerry Barrett, who came officially on board in August 1996, understands that sleep research is one of the field's top priorities. He is committed to helping both societies.

The question, now, is how can we best insure the future of the fields of sleep? Our times offer great opportunities for progress on many fronts, including basic sleep research, clinical practice of sleep disorders medicine, and practical applications. Nevertheless, these are also perilous times for medicine and research in general. Resources are shrinking or threatened in nearly all areas. For the research community, competition is fierce for federal biomedical research and training grants. Since the crisis of the federal budget deficit will probably continue for years to come, federal grant support is not likely to increase appreciably in the near future. Biomedical researchers have to fight for every cent they get from the federal government and for their special interests. Moreover, the NIH peer-review process is currently undergoing dramatic changes. The important NIMH peer-review committees dealing with sleep grants may be merged with other committees in the National Institutes of Health. If so, sleep related grants will probably receive a colder reception than in the past. For the clinical community, sleep disorders medicine faces many challenges under managed health care. For example, the future of the clinical sleep disorder's laboratory is in doubt because of high costs. New research and technology may be necessary to reduce costs, save the field, and serve the patient.

It is my firm belief that we will not survive as a field of sleep experts in a house divided. The professional sleep researchers, the sleep disorder clinicians and their patients, the students, or the public will not be well served if the ASDA and SRS go their separate ways. Both sleep societies are too small and too vulnerable to the vicissitudes of the times. Besides, each has much to offer to the other. Do we really want a major clinical discipline without a strong preclinical and clinical research wing? Will basic researchers really flourish.
without the scientific puzzles and the public support which come with clinical problems? Can either field survive or progress without attracting bright, well-trained students in both the clinical and the basic disciplines who are excited by the mysteries of sleep and its disorders? Can either the clinicians or the researchers achieve their own goals if they stand alone before the public and the policy makers in and out of government?

We need an organizational structure which supports the broad interests of the sleep fields. At the Annual Meeting in Washington, D.C. in May/June in 1996, both the SRS Executive Committee and the members at the annual Business Meeting voted to investigate the possibility of a closer relationship between the SRS and the ASDA. The leadership of the ASDA also wants to bring the two societies closer together. The current issue under discussion is what organizational model is most appropriate. One possibility would be a total merger at this time, in which both the ASDA and the SRS would cease to exist but would meld into a single organization. Another possibility would be a "federal model," that is, a central power with defined and limited authority to determine policy in the areas of transcendent interest to both "states." Neither the SRS nor the ASDA leadership has committed them to either of these or any other models at this time. Rather, we favor a gradually strengthening relationship at this time between the two societies. Time and experience will be our guides as we explore the relationships.

The leadership of the two societies continues to work well together in many areas. For example, David White, M.D., President of the ASDA, and I plan to visit the Directors of four or five NIH Institutes in mid-September to represent our interests and to strengthen the relationship between the two societies and the government agencies with responsibilities related to sleep. We very much encourage individuals to join both societies if they have both research and clinical interests. We also plan to have a leadership meeting in the fall to discuss other ways we can cooperate for the benefit of the field and for each other.

We may never recreate the intimate sense of the nuclear family which united clinical and basic researchers in the 1960's, but perhaps we can stand together as siblings and cousins within the family of sleep experts, living or visiting in the same home, at the dawn of the new century. Then we can say we sustained and nourished, even saved, a new discipline, dedicated to functions, mechanisms, and disorders associated with the third of our lifes we spend asleep.

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**Letters to the Editor**

William Fishbein, Memory Consolidation in REM sleep: Making Dreams Out of Chaos.
A Response to R.P. Vertes.

Robert Vertes has published a variety of studies that would lead one to assume he would be a leading champion of the theory of memory consolidation in REM sleep. Despite his important contributions he does not believe the collected evidence supports it (SRS Bulletin 1995, 1(2) 27-32).

His primary reason revolves around an essential point regarding the function of the hippocampus. During waking, learning involves systematic selection and delivery of information -- theta waves -- from sensory receptors to the hippocampus (and neocortex), time-locked to the behavioral experience. However, during REM sleep, theta wave flow to (and especially from) the hippocampus is triggered by random, stimulating processes generated from the pons. Therefore the continuous theta activity of the hippocampal system during REM sleep would appear to be neurobiological chaos. Vertes questions whether random, unrelated events can have any functional value in the long-term memory encoding process. The REM sleep-memory consolidation theory is constructed on the long standing belief that the hippocampus is a storage depot for newly acquired information. In this view the hippocampus functions as a 'way-station' transferring unstable memory traces -- during REM sleep -- into more efficient and stable long-term memories (neocortex). Therefore, interference with the occurrence of REM sleep should produce memory impairments; and to a large measure, the bulk of experiments is supportive of this hypothesis. Despite these reassuring findings, recent research has not supported the way-station idea of hippocampal function. This development raises new questions and calls for new interpretations of old ideas.

In the waking state, to learn and remember, independent perceptual and sensory-response behaviors do not require an intact hippocampal system. This is supported by countless lesion studies showing that in most tasks animals (and humans) can learn normally and remember normally without a functional hippocampus. In short, the hippocampus is neither a
temporary storage place for long-term memories, nor is it necessary for the retrieval of long-term memories. It is also not the location of short-term memories.

Then what is the function of the hippocampus? Information comes into the hippocampal system from all regions of the cerebral cortex, including the visual, auditory, sensory cortices and motor cortex. It also receives information from the amygdala concerning odors, unsafe stimuli, and information about the animal’s emotional state: whether it is sexually excited, hungry, frightened, and so forth. Recent accumulated evidence, in a manner, suggests that the function of the hippocampus is to tie together or relate all the things happening at the time the memory was stored. Many experiments suggest that the role of the hippocampus is to construct representational relationships between these various forms of experience, including the order in which events take place. Therefore, lesions of the hippocampus, or REM deprivation (which might be considered a reversible hippocampal lesion) would be expected to interfere with the gathering together of disparate pieces of information, thereby producing deficits in the ability to recover the complex relations. Not surprisingly the amnesic deficits reported in humans, and REM deprivation experiments in humans and animals are mostly found in tasks that are complex and more difficult to learn.

Then what is the function of REM sleep in the memory consolidation process? Certainly the very fact that we dream in itself represents reactivating preexisting memories. From the perspective that the hippocampus gathers endogenous pieces of representational information, REM sleep theta waves may serve to reactivate (or retrieve) memories of sequential episodic patterns of activity in many different parts of the brain. Behavioral dreaming, then, is the simultaneous playing out of these complex relational patterns. A separate yet ancillary aspect of this behavior is the reactivating and strengthening of encoded neocortical memory traces acquired at the time of learning. Absent REM sleep, the individual pieces of information cannot be put together into a meaningful activity pattern, and with time natural decay of the neocortical traces follows.

Therefore, the random, unrelated series of events that Vertes considers as having no functional value may be the very mechanism activating the hippocampus to produce the outflow of disconnected percepts; herein lies the creation of the bizarreness of dream mentation. At the same time, distant memory traces located in different parts of the brain are reactivated and consolidated.

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Reply to William Fishbein’s follow-up commentary on the issue of memory consolidation and REM sleep.

Robert P. Vertes, Center for Complex Systems, Florida Atlantic University, Boca Raton, FL 33431

Much of Dr. Fishbein's commentary involves a discussion of the role of the hippocampus in memory formation. He claims that older notions that the hippocampus serves as a temporary storehouse for memories (short term memory) or that it transfers memories from short to long term stores (way station) have largely been replaced by the view that the hippocampus primarily serves to "construct representational relationships" between information received over several modalities. Accordingly, lesions of the hippocampus (or REM deprivation) would interfere with this process and produce deficits in the ability to form complex relationships between stimuli or events.

Although, as Fishbein indicates, the hippocampus may be involved in forming relationships between diverse sensory events, we believe that few would concede that the hippocampus is not critical for short term memory and/or its transfer into long term stores.

With respect to the present concerns, however, the important issue (and one only briefly addressed by Fishbein) is "what is the function of REM sleep in the memory consolidation process." In addressing this issue, Fishbein appears to assign a different (or an additional) role for the hippocampus in sleep than in waking; in waking the hippocampus was thought to integrate information, in REM to reactivate or retrieve it. For example, Fishbein proposes that in REM sleep the hippocampus (or the theta rhythm of the hippocampus) reactivates specific pieces of information from different parts of the brain, that, during waking (and with the aid of the hippocampus), formed a coherent pattern. The reactivation of the diverse bits of information strengthens the overall pattern. Without REM, the individual items of information from various regions of the brain would remain disconnected and consequently fade with time. Dream bizarreness may in part reflect the fact that only small fragments of larger patterns reach consciousness.
The proposal by Fishbein is a variant (albeit an interesting one) of the theme that events are reactivated, and hence strengthened, in REM sleep. As we previously indicated, a major problem with such proposals is that they do not adequately explain mechanisms whereby some events and not others are reactivated in REM and hence singled out for consolidation. What is the selection process in REM sleep? It would surely seem to be the case that REM sleep is not a mere recapitulation of the day's events; a simple re-play of the day's events. If so, all events would be equally weighted and hence equally strengthened, which is contrary to basic workings of memory. The alternative, of course, is that only "significant" events of the day undergo consolidation, presumably by replaying them, during sleep. This presupposes sleep-related mechanisms for distinguishing significant from non-significant events, sorting the two and in some manner selectively strengthening the former (significant) but not the latter (non-significant). A tall order for REM sleep. Even if some such mechanism were operative in sleep, it would not seem that a single nightly replay (if that is the primary process for strengthening traces) of the day's "significant" events would in itself markedly enhance their storage. A true strengthening would seem to involve repeated "re-plays" of an event, possibly several times during a night or over several nights. In this case, the tasks performed in REM become even more demanding; that is, accessing, retrieving, sorting, and consolidating information of the day together with that of previous days, months or possibly years. The demands/decisions of the "REM consolidator" continue to multiply: how many "repetitions" are sufficient for consolidating a particular event: 10 or 1,000? Is there a linear relationship between number of repetitions and strength of memory? Are spaced or condensed repetitions more advantageous? Obviously, these are complicated issues involving memory consolidation per se, not solely memory consolidation in REM. We would argue, however, these issues will be resolved with reference to conscious rather than unconscious processes.

Fishbein states that dreams undoubtedly involve reactivating preexisting memories. We very much agree, but would add that this reactivation is not critical for cementing these memories but merely reflects the fact that these events occupy a strong place in memory; if not, they would not be subject to recall in dreams. We dream of significant events; the dream itself does not make them significant -- or add significance.

In summary, we restate our original position. We disagree with the views that the useless information is eliminated or useful information is consolidated in REM sleep; we believe that information is essentially not acted upon in sleep.

Articles

ON THE DISTRIBUTION OF DELTA ACTIVITY DURING SLEEP IN DEPRESSION

Roseanne Armitage and Robert Hoffmann
The University of Texas Southwestern Medical Center at Dallas

INTRODUCTION
Although computer analyses of sleep EEG frequencies have been available for more than three decades, the recent advances in microcomputer technology have expanded availability of this technology to virtually every sleep laboratory. There are several discrepancies in the results of studies using quantitative EEG methodologies that warrant an evaluation of the potential contributing sources of these differences. In the following paper we discuss potential sources of difference, classified in two basic areas: 'Data Quantification Variables' and 'Subject Variables'.

DATA QUANTIFICATION VARIABLES
PAA and PSA
The two most popular techniques for evaluating sleep microarchitecture are power spectral analysis (PSA) and period amplitude analysis (PAA). PSA is based on the fast-Fourier transform (FFT), a mathematical transformation that generates a sin/cosine decomposition of EEG signals that vary in magnitude and phase. Each frequency subcomponent is assigned a power (energy under the curve) value that is the square of the FFT. PSA is a frequency domain analysis. PAA is a time-domain approach that computes the time spent in each frequency band, defined on the basis of successive zero-crossing events (polarity changes from
positive to negative or vice-versa) or first-derivative events (inflections that do not cross zero). Zero-cross analysis is more sensitive to slow-frequency EEG activity, whereas first-derivative analyses preferentially quantify fast-frequency EEG. Amplitude is derived from the cumulative voltage of zero-crosses in each frequency band. Both techniques have been applied extensively to the study of sleep EEG in normal controls. The study of sleep microarchitecture in patients with major depressive disorders (MDD) has been more recent.

A fairly large body of literature has emerged over the past decade indicating that PSA and PAA have been more successful than traditional visual sleep stage analysis in differentiating patients with MDD from normal controls and from other psychiatric groups. Sleep EEG frequency analysis, or so-called sleep microarchitecture, may provide more sensitive and specific markers of MDD than variables such as REM latency. Sleep microarchitectural abnormalities in MDD include increased fast-frequency EEG activity (primarily in beta bands), increased hemispheric asymmetry in all sleep stages, decreased coherence in 80-120 minute rhythms between and within the two hemispheres, and decreased delta activity compared to normal controls. (For a review, see Armitage, 1995; Reynolds & Kuper, 1987).

Although there has been much discussion over the differences and similarities between PSA and PAA, we do not believe that the choice of quantification procedures accounts for the discrepancies between studies. With some exception (Geering et al., 1993), PSA and PAA should produce comparable results in control subjects, provided a complete PAA algorithm is used (Armitage et al., 1995). With depressed patients, however, the overlap in variance between the two techniques is less than 50% even for delta frequencies. This suggests that PSA and PAA are quantifying different aspects of EEG in patients with MDD. However, since there is as much discrepancy among studies that use the same algorithm as there are among those that use different algorithms, we think individual difference variables and subject selection procedures will provide more plausible explanations of the differences in findings.

DELTA and MDD: Amplitude Criterion

The majority of work on sleep microarchitecture in MDD to date has focused on delta frequency bands. In one of the earliest studies, Borbely et al. (1984) showed lower delta and alpha PSA power in patients with MDD compared to controls. This was later replicated by Kupfer and colleagues (1989a; 1989b). However, Mendelson et al. (1987) did not find lower delta PSA power in patients with MDD. The work from Kuper’s group has also shown consistently fewer delta wave counts in MDD, particularly in the first NREM period, using a modified PAA procedure designed to detect high-amplitude delta counts. Their work has suggested that delta wave counts are higher in the second than in the first NREM period in MDD, in contrast to normal controls. However, we were unable to replicate higher delta counts in the second NREM period in MDD patients, and did not find consistently higher delta incidence or amplitude in the first NREM period in control subjects.

This failure to find more delta in the first NREM period in controls was puzzling to us, given the widely held view that delta declines systematically across NREM periods. Several studies by Dijk and Borbely and colleagues indicate that the decline in delta is exponential (Dijk et al., 1989a; 1989b; 1990a; 1990b). Feinberg et al.’s data on the other hand show strong linear trends in delta across the night (cf Feinberg, 1994). In a study of the distribution of PAA delta activity across the night in normals, we found that about 62% of recording nights fit an exponential trend for delta incidence, increasing to 81% for delta amplitude. However, the rate of decay was considerably slower than previously reported. For some subjects, both an exponential and a linear trend fit the data (Armitage & Roffwarg, 1992). Surprisingly, the linear decline in delta amplitude and incidence was not as dramatic as that found by Feinberg and colleagues. In addition, we did not find more delta in the first NREM period than in the second, in support of our previous study.

Moreover, it has also been argued that although high-amplitude delta is preserved in women but not men with MDD, the distributions of delta across the night is similar for depressed men and women. In this view, slow-wave sleep regulatory mechanisms are equivalent for men and women with MDD. But the PAA algorithm used by the Pittsburgh group quantifies only high amplitude delta (≥ 75 μV), equivalent to visually-scored Stage 4 sleep. As such, the conclusion of Reynolds et al. requires some modification, in our view. Feinberg, Dijk, Borbely, our own group, and others, for example, have pointed out that the distribution of EEG frequencies when epochs are classified by visual stage-scoring is likely to differ from stage-independent analyses.
While there are a number of discrepancies in data collection procedures between studies of both normal controls and patients with MDD, a strong case cannot be made that these constitute the major source of difference between labs.

**SUBJECT VARIABLES**

**Sex**

One major consideration has influenced our view of the distribution of delta activity in normal controls and patients with MDD, namely sex differences. Our own work has consistently shown sex differences in patients with MDD in a variety of frequency bands. Moreover, these sex differences are significantly stronger than those observed for normal controls. In a more recent study of relatively young patients and controls (< 40 years of age), we evaluated sex differences in the distribution of delta activity. Delta periods were defined as ≥ 4 consecutive epochs in which delta half-wave zero-cross exceeded the mean plus 20 percent. The length of the period, the number of intrusions (epochs that fell below criteria), and the average delta amplitude and incidence were defined for each delta period. Data were then coded for age and sex and submitted to repeated-measures analysis of variance. In general, patients with MDD had more delta periods across the night with more intrusions. Delta incidence was lower in patients with MDD, to a greater degree among depressed men. Delta amplitude, however, was only lower in men with MDD. Depressed women showed the highest delta amplitude of all groups, both in the first delta periods and across the whole night, but did not differ significantly from men and women in the control group. Additionally, the distribution of delta in women with MDD did not differ from normal control men. This suggests that delta regulatory mechanisms are preserved in depressed women. Age did not account for a significant portion of the variance, probably due to the relatively young age of all subjects and the fact that patients and controls were age-matched.

These findings support the view that sex differences are more pronounced in patients with MDD than those observed in controls. Moreover, they strongly indicate that sex effects should be evaluated statistically. Unfortunately, since women are twice as likely to develop MDD, most study samples have considerably more women than men and either, do not or cannot, evaluate sex differences. From our perspective, the coordination of ultradian rhythms between and within the two hemispheres is more disrupted in women with MDD than in men.

Together these findings imply that the pathophysiology of depression is different in men and women. We believe that sex differences in MDD are considerably stronger than the literature suggests, due to the failure to take this individual difference variable into consideration.

**Age And Sex Interactions**

Recently, Reynolds et al. (1990) evaluated the influence of age and sex on delta wave counts in patients with MDD. They reported significant age and sex interactions on delta wave counts, provided alcohol history was used as a covariate. In general, men with MDD had lower delta wave counts than women with the highest delta counts in young men (20-29 years). Age effects, however, were quite different for men and women, and neither group showed systematic decreases in delta counts across decades of age. For example, women with MDD in the 60-69 year age group showed equivalent delta counts to the 20-29 year old women. The reader is also reminded that the PAA algorithm used by the Pittsburgh group includes an amplitude criterion on delta waves. While age effects are implied, a much more detailed examination of this variable is needed before any concrete conclusions can be made.

**Patient Diagnosis**

Diagnostic differences among MDD patients may also contribute to differences between studies. The patients in the Borbely and Kupfer studies were unipolar and for the most part, nonpsychotic MDD, whereas the Mendelson study included mostly bipolar patients. It is entirely likely that the biology of unipolar and bipolar illness is distinctly different. Bipolar patients may also be a more homogenous group. The bipolar group used by Mendelson et al. also showed unusual sleep macroarchitectural features, namely longer REM latency than the control group. Although it is unlikely that this contributed to the delta differences per se, it does suggest that they may have been an unusual group of patients.

The distinction between endogenous and nonendogenous subtypes may also be relevant. Research suggests that endogenous patients not only have more abnormal sleep characteristics, but also show stronger neuroendocrine, temperature and neurotransmitter abnormalities. In short, MDD in endogenous patients is viewed as more biological, and thus may be associated with stronger delta abnormalities. Unfortunately, sample sizes in most sleep studies are generally too small to evaluate statistically the contribution of endogeneity. In the patients studied in our own laboratory, shortest REM...
latency, and lowest coherence are usually found among the endogenous patients. To date, however, we have not systematically evaluated the impact of depression subtypes. It remains a potential contributing factor to the discrepancies between studies.

Subject Life Habit Variables
Additionally, all subjects in our studies maintain individualized sleep schedules. If they sleep from midnight to six am at home, they follow the same routine in the lab. Some, if not all, of the studies from the Pittsburgh group keep all subjects on the same fixed schedule in the lab, from 11 pm to 7 am, for example. Although it is unclear whether fixed or individualized schedules influence the distribution of delta activity, it is conceivable that if the schedule is quite different from the subjects’ usual routine that delta distributions could be altered.

Selection of Control Subjects
Although the details of subject screening are not always reported, most normal controls are selected from university populations and are not screened for personal or family history of psychiatric illness. Since there is evidence that MDD has a genetic link, with higher risk among those who have positive family histories, this may be an important difference. Work from our group suggests that 25% of individuals with a positive family history for depression show decreased EEG coherence with values in the range of symptomatic MDD patients. Thus, the failure to screen out these individuals potentially obscures differences between patients and controls.

However, the subject selection procedures between the Pittsburgh and the Dallas labs are very similar, screening normal controls for medical and psychiatric wellness and negative family histories of psychopathology. Thus, differences in normal control selection procedures cannot explain the differences in delta between Kupfer’s group and our own. It should be noted that these control subjects are not really “normal”. They have very clean medical and psychiatric histories, keep very regular sleep wake schedules (as verified by weekly home diaries), do not engage in shift work, are not students, and abstain from alcohol and caffeine for 5-7 days prior to study.

Regularity Of Sleep Habits
Perhaps differences in subject selection procedures offers a partial explanation regarding differences between our controls and those used by Borbely, Dijk, Feinberg and colleagues. Both the individualized rise and bedtimes established and the maintenance of very regular sleep habits of all of our subjects may diminish the decline in delta across successive NREM periods. The potential contribution of subject screening procedures and regularity of sleep habits was alluded to, but not fully explicated, in Armitage and Roffwarg (1992). We suspected that the more regular the sleep habits, the less likely that delta would show a strong decline across the night.

To test this hypothesis, we asked four of our research assistants, unscreened for personal or family history of psychiatric illness, to sleep in the lab after completing three or four nights of running subjects, and to return to the lab once they had re-established regular, diurnal sleep patterns. As expected, delta declines across NREM periods were substantially stronger following the “night shift”. Moreover, delta incidence and amplitude was considerably higher in the first half of the night, in keeping with other reports. On nights following the re-establishment of regular sleep habits, the linear trends in delta were considerably less pronounced. Although this study was by no means controlled, it suggests to us that the irregularity of sleep habits and partial sleep deprivation can contribute to the distribution of delta activity. The studies of sleep deprivation effects also support this suggestion. The changes in delta across NREM periods are stronger on recovery nights that those observed prior to deprivation. Additionally, irregularity of sleep habits may also contribute to findings of exponential decays in delta in some studies and linear trends in others. We are currently conducting a larger, more systematic study to see if this finding can be replicated.

CONCLUSION
The discrepancies among studies of both normal controls and patients with MDD may arise from factors that include: subject selection procedures, failure to take individual difference variables such as age and sex into account and methodological differences. In fact, it appears that the major sources of difference among labs arise from procedures for the selection and testing of subjects rather than from the data quantification procedures employed in different labs. These factors may effect the likelihood of obtaining statistically reliable results.

REFERENCES
Sixty-seven years after Berger’s publication "Über das Elektroencephalogramm des Menschen" (Berger, 1929) the application of the EEG in psychiatry still appears to be a neglected field. While the EEG continues to be an essential tool in neurology, in psychiatry it is mostly considered only as a means to exclude organic disease or severe drug side effects. As a matter of fact, no typical EEG changes that are pathognomonic for a psychiatric disease have yet been reported. Nevertheless, on the basis of group statistics, differences to healthy controls become obvious, especially if we include specialized EEG applications such as polysomnography, and more sophisticated methods of data analysis such as power spectra analysis.

This review deals with the EEG findings in schizophrenia and affective disorders which are considered as endogenous psychiatric disorders. For both diseases, we will first concentrate on findings in EEG recordings with the routine international 10-20 system of electrode placement, and then discuss the value of the above mentioned specialized examinations. We will exclude the field of organic abnormalities as infectious disease or neurodegenerative disorders like Alzheimer’s disease, where a broader spectrum of literature already exists, and which are also discussed in this issue.

**EEG in affective disorders**

Looking at topographic and dynamic aspects, Blanc and Lairy (1960) distinguished between two characteristic patterns of the routine resting EEG in patients with depression. Patients with endogenous depression showed a high percentage of monotonous alpha rhythm with the tendency of anterior spreading, defined as a pattern of dynamic rigidity (DR, Bente 1981). Patients with neurotic depression tended to exhibit a more discontinuous alpha rhythm with changing topographic preference, defined as dynamic lability (DL, Bente 1981). In a retrospective study of 314 depressed patients, DR was observed in 42% of endogenous, but only in 20% of non-endogenous depressed patients (according to RDC-Criteria, Spitzer et al., 1975).

In endogenous, phasic depression, these characteristics were reproduced in a number of studies. Typically, the EEG shows a pronounced alpha activity, which is slightly slower compared to controls with a tendency to anterior spreading (Shagass et al., 1982, Pollock and Schneider, 1989). A decreased variability of amplitudes is also described (d’Elia and Perris, 1973, Swartzburg and Chodrey 1977).
Correlating DR with clinical symptomatology, Ulrich and Brand (1993) found a significant correlation to psychomotor rigidity. The question of whether DR is a state or rather a trait marker in those patients in which it is exhibited remains to be seen.

Another finding is an increased beta activity in depressives. Matousek (1991), correlating EEG characteristics with different subtypes of endogenous depression, found a higher percentage of beta activity associated with recurrent depression.

Switching to more sophisticated EEG analysis, power spectra analysis is applied from a number of groups. All together, results are varying, which may be caused by choosing different sites for the reference electrode (Dierks et al., 1993). Consistent findings are also a higher Beta 1 power over parietal and occipital, and a higher Beta 2 power over frontal regions in depressives with a high anxiety score compared to controls and depressives with symptoms of retardation (Yamada et al., 1995). On the other hand, high scores in motor retardation correlate with low EEG activity (increased theta 2/alpha 1 bands, Nieber and Schlegel, 1992).

Switching from the EEG in an awake, but resting state to sleep recordings, Armitage (1995) notes as a common feature in depressed patients a decreased delta amplitude or incidence, particularly in the first 100 minutes of sleep, and an increase of fast frequencies, especially in the right hemisphere.

By far the most stable results concerning typical biological abnormalities in depression have been gained by polysomnography. This method combines EEG with measurements of eye movements, muscle tone, ECG and breathing frequency. This allows us to divide sleep into different stages, stages 1-4 and REM sleep, each uniquely characterized by these parameters (Rechtschaffen and Kales, 1968). Finally, as we don't look at EEG abnormalities per se, but instead abnormalities of sleep patterns, this chapter is given only brief consideration.

Consistent findings in depressives are sleep-continuity disturbance, reduction of sleep stages 2 and 3, and shortened REM latency (Gillian et al., 1984; Mendlewicz and Kerkhofs, 1991, Kuperf et al, 1991). Most studies also show an increased REM latency (Coble et al., 1976; Kuperf and Foster, 1978; Feinberg and Carroll, 1984). These phenomena appear homogenous in middle-aged depressives, whereas results are contradictory in adolescents and young adults (Piccinin and Anseaus, 1991; Emslie et al, 1994; Riemann et al., 1995). During remission, REM density decreases first and may be a valuable state marker, while decreased REM latency and diminished slow wave sleep still persist. This effect is not due to drugs, as it is also documented in unmedicated patients treated with cognitive behavioral therapy (Thase et al., 1994). Especially changes in REM sleep may be markers of an underlying muscarinic hypersensitivity in depression, as cholinergic REM induction tests pronounce decreased REM latency (Riemann et al., 1994).

**EEG changes in Mania**

Data on EEG changes in mania are rather poor, and not conclusive. Again, we find no diagnostically pathognomonic characteristics in the EEG of manic patients. Many authors describe an EEG pattern which otherwise resembles drowsiness, the difference being that the patient appears clearly awake (Liberson, 1944; Bonnet and Bonnet, 1960). A similar observation was made by van Sweden (1986) describing beta spindle activity in two fully awake manic patients, whereas it normally occurs in sleep stage 2. Furthermore, the EEG often shows a higher percentage of sudden switches to low amplitude slow activity, which was characterized as dynamic lability (Ulrich 1994). Clinical improvement, therefore, leads to an increased continuity of alpha activity.

Looking at signs of disorganization in the power distribution of the alpha band, manics have an intermediate position for both hemispheres between depressives (lowest) and schizophrenics (highest) (Flor-Henry and Koles, 1984).

In polysomnography, manics share many characteristics with depressive and schizophrenic patients, namely decreased time spent asleep, shortened REM latency and increased REM density (Hudson et al., 1988). This may point to common pathophysiological mechanisms in all three disorders.

**EEG in schizophrenia**

Schizophrenia is, clinically, quite a heterogeneous disorder. Looking for common features in the routine EEG at rest, Davis (1939,1942) described "choppy activity" as highly specific for schizophrenia. By "choppy activity" she meant an EEG with prominent low voltage, desynchronized fast activity. This may correlate to a trait marker, as suggested by Itel et al.(1975). Considered as a sign of high functional disintegration, mostly preceding clinical remission,
many authors describe signs of paroxysmal dysthyemic activity, characterized as an intermittent occurrence of slow, high amplitude waves (Huber and Penin, 1968; Helmchen, 1968, Isermann, 1973), most prominent in the frontal region for delta, and in the occipital region for the theta band (Takizawa et al., 1994). This finding was repeated by Sponheim et al. (1994), comparing 102 schizophrenics with an equivalent number of controls. Within the schizophrenic group, both first episode and chronic schizophrenics showed this pattern of increased slow activity. This suggests that these EEG changes are not related to treatment history, but are genuine to the disorder. However, it should be noted that Clementz et al. (1994) reported similar findings not only in schizophrenics, but also in patients with bipolar disorder. On the one hand this shows the nonspecificity of this finding for schizophrenia, but on the other it most likely points to common aspects of pathophysiology. A decrease in alpha peak frequencies was evident in the schizophrenic group of this study, and was also found in the patients’ healthy female relatives, suggesting a probable trait marker.

Schizophrenia research has developed into a main field of power spectral analysis over the last 20 years, generating results which are not always clear-cut. This may be caused by the forcing of such a heterogenous disorder as schizophrenia into group statistics, neglecting different subtypes and activity of a schizophrenic process. One stable finding is the increased beta power (e.g., ItI et al., 1972, 1977; Cembalo et al., 1981), resembling the findings of Davis in a more sophisticated visualization. Gattaz et al. (1992) also showed increased band power for delta and fast alpha and beta bands in first onset, neuroleptic naive schizophrenics. In these studies, the best separating variable between schizophrenics and controls was increased left frontal delta power (electrode position F7). Correlating clinical symptomatology to the EEG, they report a significant positive correlation between the Brief Psychiatric Rating Scale (BPRS) scores for “anxiety-depression” and “activation” and increased power in the fast bands, and a negative correlation between “anergia” and beta power. On the other hand, negative symptoms correlated positively with the amount of delta power, especially over temporal regions.

To further locate neuronal populations responsible for these changes in power bands, Dierks et al. (1995) used successive center-of-gravity-dipole calculations to exclude reference dependence of the power analysis data. They found more anterior and superficial equivalent-dipoles in the beta bands of schizophrenic patients. With increased severity of symptoms as measured by BPRS, the beta 1 band equivalent-dipoles moved in an anterior direction. The authors suggest that beta activity in schizophrenics is generated by a different neuronal population compared to controls.

For the alpha band, lower alpha-2 band amplitude has been described in the resting EEG. During 10 Hz photic stimulation, which reflects the intrinsic thalamic EEG spindle generation, schizophrenics showed a rather uniform topographic profile in the EEG for the alpha band with a decreased amplitude of the photic driving response. Significant group differences compared to controls were confined to the left posterior hemisphere (Wada et al., 1994, 1995). In a study of Jin et al. (1995), lower photic driving was also found in the high alpha frequency band, although group differences were primarily located in the mid-frontal, central and parietal areas. Both authors suggest a dysfunction in the mechanism underlying alpha generation in schizophrenics, probably with thalamic origin.

Using again the EEG in the context of characterizing behavioral state in polysomnography, different groups characterized sleep abnormalities in schizophrenics. As in depressives, a shortening of the REM latency was confirmed, both in chronic and in first-episode patients (Zarcone et al., 1987, Tandon et al., 1988, Tandon and Greden, 1989, Tandon et al., 1992). Relating REM characteristics to clinical symptomatology, negative symptoms seem to correlate with decreased REM latency (Taylor et al., 1991) and lower REM density (Tandon et al., 1992, Riemann et al., 1994). Testing for cholinergic hypersensitivity with a cholinergic challenge test, schizophrenics showed similar results as depressives in respect of a shortened REM-latency (Riemann et al., 1994). This may again point to common pathophysiological aspects both in schizophrenia and affective disorder.

Conclusion
This article is meant as a short overview regarding EEG findings in psychiatric diseases, and should encourage further reading. We have concentrated on findings in the routine EEG, because these observations can be easily followed up in one’s own patients during clinical practice. As shown, discrete changes in frequency distribution as well as in their topography can be observed. While these observations lack mostly specificity, it is clear that more sophisticated data recording and analysis techniques will be needed for pathophysiological conclusions, e.g., analyzing
nonlinear dynamical properties. But it should not be forgotten that these more extensive techniques follow up on what was originally observed decades ago in routine EEG. Although the EEG will never play as essential a role in psychiatric patients as it does in neurology, with careful observation it can obviously tell us more than mere exclusion of gross organic disorders.

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Adenosine and Sleep

Why Adenosine and Sleep?

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Back in 1973 I read Haulica et al., (1973) paper on a possible hypnotic effect of intracerebroventricularly administered adenosine to dogs. The authors tried to explain adenosine’s somnogenic effect via serotonergic mechanisms (which was a way to think about sleep induction then) but I could not find any link between...
serotonin and adenosine. Mainly for that reason but also because of my firm belief in the monoamine sleep theory which we were testing in cats and rats, I did not think that the experiment should be repeated on other species. Thus, over the years, I forgot about Haulica et al. Paper.

Then in 1982 while working on my lecture on CNS stimulants in a regular pharmacology course for medical students, I found a paper by Snyder et al. (1981) describing the newly observed mechanism of action of methylxanthines. The authors said that methylxanthines, i.e., caffeine and theophylline, produce behavioral excitation not by blocking the enzyme phosphodiesterase (as had been universally accepted) but by blocking adenosine receptors. The authors found that micromolar concentrations of theophylline are sufficient to block adenosine receptors and produce behavioral excitation whereas millimolar concentrations of theophylline are needed to block phosphodiesterase.

I had no idea what adenosine may be doing in the CNS and my library search produced papers by Phillis et. al. (1979), Phillis and Wu (1981) and Stone (1981) which showed that general neurophysiological effects of adenosine were inhibitory. Then, in the middle of my lecture to M-2 students I thought: If methylxanthines produce behavioral excitation by blocking adenosine receptors, would stimulation of adenosine receptors produce sleep? I could hardly wait for my lecture to end, dashed to see Richard Green, a professor in our department who had worked on nucleosides for more than a decade, and asked him if he had some metabolically stable adenosine analogs (plasma half-life of adenosine is only 10 secs) that we could test for potential hypnotic effects in rats. His answer was positive. He picked three adenosine analogs from his drawer: L-PIA, CHA and NECA, which we tested in rats and obtained indications for their hypnotic actions (Radulovacki et al., 1984). Then, when I was writing that paper I re-visited Haulica et al.’s (1973) earlier work and incorporated it in the manuscript. Since then, my laboratory has tested the effects on sleep of adenosine, adenosine deaminase inhibitors, adenosine A1 and A2 agonists and antagonists, and adenosine transport blockers. All this makes an extensive list of publications and would refer an interested reader only to two book chapters that I recently wrote:


Future Directions

For me, works of other authors in this issue of the SRS Bulletin are inspiration for future research of adenosine’s role in sleep. I advise all young scientists interested in adenosine to them carefully.

References


As a candidate sleep factor, adenosine has one major piece of evidence in its favor. Caffeine, the most common psychostimulant, used regularly by 3/4 of the world's population to combat sleepiness, works primarily by blocking adenosine receptors. Not surprisingly, interest in the involvement of adenosine in sleep dates from the discovery that caffeine is an adenosine antagonist. The fact that blockade of adenosine receptors promotes waking indicates that endogenous adenosine is being released in normal individuals and increases the tendency to sleep. This does not necessarily mean that the adenosine is being released specifically as a sleep promoter, but in the absence of other well-documented endogenous sleep promoters it is promising.

The discovery that caffeine blocks adenosine receptors led investigators (most notably Miodrag Radulovacki and his colleagues) to characterize the effects on sleep of other adenosine antagonists and agonists. They have demonstrated that adenosine agonists selectively increase deep nonREM sleep (S2 in rats), and antagonists increase waking. These effects are dose-dependent except that the highest doses of adenosine agonists actually decrease sleep time.

We became interested in adenosine as a result of our interest in homeostatic regulation of EEG slow-wave activity (SWA) in nonREM sleep. Over the past 20 years, Alexander Borbely and his colleagues have used Fourier analysis to quantify the earlier observation that EEG slow waves in nonREM sleep are most pronounced early in the rest period and are further increased following sleep deprivation. Their extensive studies have built a strong case for the idea that nonREM-sleep EEG SWA is reflective of the amount of accumulated sleep need. The implication of this finding is that sleep need (whatever that may be) proportionally promotes the expression of SWA in the EEG.

Many investigators have used EEG SWA as a quantifiable indicator of the level of accumulated sleep need. They have thereby investigated the interactions between sleep homeostasis and circadian rhythms, the time course of accumulation and discharge of sleep need in humans or rats, the possibility that sleep need may sometimes accumulate at different rates in different brain regions, and many other important phenomena. But the neurochemical basis of this link between sleep need and EEG SWA is still unknown. Establishing such a link may have dramatic consequences for our understanding of the function of sleep.

As we all know, sleep is a homeostatically regulated behavior. Other homeostatically regulated behaviors, such as eating, drinking, and thermoregulation, are directed towards maintaining a physical variable within an acceptable range. Studying the biochemical mechanisms of these regulatory systems is greatly aided by the fact that the variable being regulated is known. In the case of sleep, we just do not know what is being regulated. We do not know why sleep occurs or what is being restored. This remarkable fact should be at the forefront of any consideration of sleep mechanisms. It is frustrating, because there is still considerable uncertainty as to what that function might be, but it cannot be ignored.

One promising avenue for discovering the physiological variable that controls sleep behavior is to determine how increased sleep need potentiates EEG SWA. Based in part on the work of Steriade, McCormick and their respective colleagues, a strong case can be made that increases in the amplitude and prevalence of EEG slow waves in nonREM sleep occur as a result of increased membrane hyperpolarization in neurons of the cerebral cortex and thalamus, and that such hyperpolarization is most likely mediated via increases in K+ conductance (see McCormick, 1992; Steriade et al. 1993). This train of thought is outlined in our recent article Restoration of Brain Energy Metabolism as the Function of Sleep (Benington and Heller, 1995).

The increases in EEG SWA that are seen following sleep deprivation do not appear to depend critically on electrode placement. Moreover, similar increases in SWA were seen when electrodes were implanted in a number of subcortical structures (Lancel et al. 1992). These findings imply that whatever neurotransmitter(s) are responsible for these changes must be released more or less throughout the brain and must predominantly increase K+ conductance in all areas. Based on our survey of candidate neurotransmitters, we concluded that adenosine is the only one known to satisfy these
criteria. The primary action of adenosine in most brain regions is a g-protein-coupled increase in K+ conductance, mediated by activation of A1 adenosine receptors. A1 adenosine receptors are fairly homogeneously distributed throughout the forebrain.

We tested the hypothesis that adenosine mediates sleep deprivation-induced increases in EEG SWA by administering CPA, a highly selective A1 adenosine agonist to rats. In agreement with our predictions (and with the suggestive findings of Radulovacki et al. (1984)), CPA produced a dose-dependent increase in EEG SWA, and the power spectrum of changes in EEG activity closely paralleled that produced by sleep deprivation (Benington et al. 1995). CPA was effective when administered either centrally or systemically. Landolt et al. (1994) have also shown that caffeine administration in humans produces a corresponding decrease in EEG SWA in subsequent nonREM sleep, suggesting that endogenous adenosine does in fact potentiate normal EEG SWA.

These findings suggest that increased adenosine release is capable of potentiating EEG SWA. It is an attractive hypothesis that adenosine is the primary mediator of the increases in EEG SWA that occur following sleep deprivation, but more data are needed to confirm that possibility. If adenosine is in fact the neurochemical mechanisms of these effects of sleep deprivation, then the key question is what causes adenosine release to be increased (it is important to note that increases in extracellular adenosine can only result from increases in the rate of adenosine release as opposed to accumulation of adenosine because adenosine is metabolized rapidly in body tissues).

Although adenosine works as a neurotransmitter by activating g-protein coupled receptors, it is not released at nerve terminals by a chemically distinct class of neurons. Instead it is released by facilitated transport from both neurons and glia as a function of the rate of adenosine synthesis (White and Hoehn, 1991). Adenosine is synthesized by three major pathways (Meghji, 1991). The synthesis pathway that appears to be primarily responsible for stimulus-induced adenosine release involves synthesis from 5'-AMP by the enzyme 5'-nucleotidase. Adenosine synthesis (hence release) by this pathway is a simple function of cellular AMP concentration. AMP is produced in the reaction ADP + ADP >> ATP + AMP. In other words, AMP concentration and adenosine release are dependent on the cellular ATP/ADP ratio.

By this mechanism, adenosine release is increased when metabolic demand is increased or metabolic supply is decreased. Adenosine functions in many body tissues as a signal of insufficient metabolic supply relative to demand. In tissues such as heart and muscle, adenosine acts as a local hormone to reduce cellular excitability, hence energy requirements. In the brain, such a function is accomplished by receptor-mediated increases in neuronal K+ conductance.

We view this link between adenosine and brain energy metabolism as an exciting lead to a potential function of sleep. Among the possible forms that cerebral restoration might take, restoration of energy metabolism seems like an obvious possibility. Surprisingly, although energy conservation has been a prominent candidate as a sleep function, restoration of brain energy metabolism has barely even been considered. Instead, biochemical approaches to the restorative function of sleep have tended to focus more on protein synthesis. While protein synthesis is integral to repair and modification of tissues, it is not obvious exactly how a "need" for additional protein synthesis could be expressed on the cellular level by a molecular feedback mechanism. Energy metabolism, on the other hand, is tightly regulated by a host of homeostatic feedback mechanisms.

In the brain, maintenance of optimal energy metabolism is critical because rapid, appropriate response to environmental challenges are key to an organism's survival. It may be that certain processes in restoring energy deficits cannot efficiently take place during waking without compromising the organism's ability to respond optimally. Since constant activity across all 24 hours of the day is neither required nor in fact adaptive, sleep may have evolved to permit energy deficits to be restored when animals are not engaged in active behavior. We propose that loss of consciousness in sleep occurs because energy restorative processes take place most efficiently when neurons are less active, hence less involved in analyzing sensory input.

The above schematic of a restorative function involving restoration of brain energy metabolism could apply to a number of elements of energy metabolism. As an example of a specific restorative function, we have hypothesized that brain glycogen stores are depleted during waking and replenished during sleep. Because the adult brain under normal conditions depends exclusively on glucose as an energy substrate, glycogen is the brain's sole energy reserve. Glycogen synthesis and breakdown in brain are regulated by
receptor-mediated increases in cyclic AMP in astrocytes. Neurotransmitters that increase astrocytic cAMP (and thereby promote glycogen breakdown) include norepinephrine, serotonin, and VIP. These neurotransmitters are released at maximal levels during waking and contribute to making forebrain neurons more active and excitable in that state.

In this way, activation of the brain during waking and mobilization of a supplementary source of glucose are linked by the same neurochemical mechanisms. A potential consequence may be that glycogen stores cannot be replenished as long as the brain is activated by norepinephrine and these other neurotransmitters. The cost of this hypothesized regulatory program is that animals must withdraw periodically and replenish brain glycogen by sleeping. The advantage is that a supplementary energy source is constantly mobilized during waking, reducing the likelihood of transient, local insufficiencies in metabolic supply. This hypothesis (described in more detail in Benington and Heller, 1995), is internally consistent and testable, but it is just one example of a restorative function of sleep relating to brain energy metabolism. Other components of brain energy metabolism should also be considered as possible substrates of sleep restoration.

Regardless of the specific biochemical process being restored in sleep, if prolonged waking results in deficits in brain energy metabolism, adenosine is a promising candidate as a feedback molecule to promote sleep. By inhibiting neuronal activity and responsiveness throughout the brain, adenosine should underlie both the behavioral and neurophysiological phenomena of increased sleep drive. These include a decrease in sleep latency, decreased motivation, impaired performance of repetitive tasks, appearance of EEG slow waves in waking, increased arousal threshold in recovery sleep, and increased depth of nonREM sleep.

References


Adenosine control of cholinergic arousal populations

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Adenosine (AD) possesses a number of compelling characteristics of an endogenous physiological sleep factor. AD is found throughout the CNS along with its anabolic and catabolic enzymes. AD receptors with well characterized inhibitory electrophysiological activity are found on cortical, thalamic and brainstem neurons. Similar to other putative sleep factors, AD or AD agonists, when administered IV, are capable of inducing slow wave and REM sleep (Radulovak, et al, 1984). Finally, as the backbone molecule for ATP, AD may provide a homeostatic link between electrophysiological activity and metabolic activity (reviewed in Greene and Haas, 1991) and thus provide a link between behavioral state and metabolic state that suggests a function (but not an exclusive function) for sleep.

The mechanism for the inhibitory action of exogenous adenosine has been characterized for a number of CNS regions (for review, see Dunwiddie, 1985; Greene and Haas, 1991). Phillips and his colleagues (1975; 1981) have shown that neuronal firing rates are reduced by
exogenous adenosine and, in the cortex, this inhibitory effect is due to both pre- and post-synaptic effects. The most efficacious (but not the most potent) post-synaptic AD inhibition is mediated by an increase in steady-state potassium current (in the CA1 region of the hippocampus the GK is voltage insensitive but in other areas such as the laterodorsal tegmental nucleus (LDT; Rainnie, et al, 1994) and in culture preparations (Trussel and Jackson, 1985) it is inwardly rectifying. AD can also increase the long duration calcium-dependent potassium current responsible for adaptation and the long duration AHP (Haas and Greene, 1984). Most recently, a sensitive effect of AD to decrease the hyperpolarization-activated current, IH, was described by Pape (1992) in thalamic neurons and in LDT cholinergic neurons (Rainnie, et al, 1994). Pape suggested that this AD-mediated decrease of IH would enhance delta wave oscillations in this region and Bennington and Heller (1995) have shown that exogenous AD administered IV, can indeed, selectively increase delta power.

The most potent effect elicited by AD, described in the cortex (for review see Dunwiddie, 1985), is a pre-synaptic inhibition of excitatory input. In the hippocampus this effect is selective for glutamate transmission with no apparent inhibition of gabaergic transmission (Yoon and Rothman, 1991). The mechanism(s) for the pre-synaptic inhibition is controversial and may involve, at least in part, a calcium-independent inhibition of synaptic release (Scanziani, 1992). In the CA1 region of the hippocampus, a tetanus applied to the schaeffer collateral glutamatergic input is sufficient to cause a release of endogenous AD that depresses excitatory synaptic transmission immediately following the tetanus (Mitchell, et al, 1993; Manzoni, et al, 1994). This effect is NMDA-dependent and probably is not directly related to cellular metabolism, but rather to a NMDA-mediated release AD or an AD precursor such as cAMP or AMP (Craig and White,1993). The release does appear to be dependent on interneuron firing. It was suggested that AD release following a tetanus results from feedforward activation of interneurons which in turn causes an increase in extracellular AD (Manzoni, et al, 1994).

It is difficult to reconcile AD’s electrophysiological actions with its putative actions as a sleep factor for several reasons. First, although AD is ubiquitous in cells and A1 receptors that mediate AD-dependent inhibition are found on cortical, thalamic and brainstem neuronal elements, the control of AD release is dependent on local factors. Thus, a global reduction of neuronal activity consistent with the onset of sleep would require a global organization of the control of AD release throughout the cortex and thalamus(Bennington and Heller, 1995). A potential solution to this problem was provided by the observation that endogenous AD exerts a powerful tonic inhibition of cholinergic neurons in the basal forebrain and in the LDT/PPT nuclei of the brainstem (Rainnie, et al, 1994). An increase in extracellular AD in the basal forebrain or LDT/PPT regions that appears to accompany increased waking can inhibit the cholinergic neurons in these regions thus reducing cholinergic tone at the target sites of these neurons which includes most of the CNS. To the extent that cholinergic activity is responsible for arousal, the local increase in AD in the cholinergic nuclei will decrease arousal and promote sleep. Local control of extracellular AD release may thus be related to behavioral state.

Another problem with AD as a sleep factor relates to the control of AD release. There is a large body of evidence that AD release into the CNS extracellular space is related to the metabolic state of neuronal tissue (Pull and McIlwain, 1972; Berne, et al, 1982; McIlwain and Poll, 1986). There is speculation, further, that this relationship holds true even within physiological limits so that AD might provide a physiological negative feedback link between electrophysiological and metabolic state (Greene and Haas, 1985 &1991; McIlwain and Poll, 1986). This same relationship for AD can be extended to global arousal and metabolic state through the inhibitory actions of AD on cholinergic neurons (Rainnie, et al, 1994) or on thalamic and/or cortical neurons (Bennington and Heller, 1995). However, the link between extracellular AD levels and physiological metabolic states is not established. Two potentially physiological mechanisms of release, shown to cause AD-mediated inhibition, have been described; 1) by repetitive excitatory input activation, mentioned above, and 2) through stimulation of cAMP (Rosenberg, et al, 1994; Gereau and Conn, 1994). A number of pathological circumstances that all involve increased metabolic demand relative to metabolite availability (reviewed in Greene and Haas, 1991) can cause an increase in electrophysiologically active AD release. These mechanisms are not consistent with the action of AD as a physiological sleep factor that relates CNS metabolism to behavioral state. In the case of the tetanus evoked release, the time course of the effects is too rapid. In the case of the slower metabolically challenged release, the release is not related to metabolism under physiological conditions.
Finally, the cAMP evoked release would require a yet to be described behavioral-state related mechanism that accounts for its increase during the transition from waking to sleep.

Nevertheless, endogenous AD does exert a tonic inhibitory tone on cholinergic neurons similar to that observed in the hippocampus that is Ca++ independent and controlled at least in part by a bidirectional facilitated transport system (Linden, 1994). The flux is primarily inward as blockade of the transport with nitrobenzylthioionosine results in an increase of AD-mediated inhibition. Recently we have observed a similar effect in the LTD/PPT region (Grunze and Greene, unpublished). Once inside the cell, the AD is rapidly metabolized primarily (but not exclusively) to AMP by adenosine kinase which is then phosphorylated to ADP and ATP. Antagonism of this enzyme by iodotubercidin can profoundly inhibit neurons in the hippocampus (Pak, et al. 1994) and LDT (Grunze and Greene, unpublished) by reducing the metabolism of AD with the result that intracellular AD levels increase and AD is transported from inside to outside of the cell. The relatively large increase in AD requires only a small shift in the equilibrium between AD and ATP since ATP is present intracellularly in millimolar concentrations. Thus, it is conceivable that extracellular levels of AD might be significantly affected by physiological metabolic demands that result in only small changes in ATP levels. Bennington and Heller(1995) have suggested that this might occur in direct correlation to the energy storage molecules of glycogen that are depleted over the course of the day although there is no direct evidence for this relationship. Nevertheless, this raises an interesting possibility that AD levels may not fluctuate until a threshold depletion of glycogen occurs. Then, with continued metabolic demand, the extracellular AD might rapidly increase and rapidly increase the probability of a transition to sleep. Slow wave sleep, with its associated decrease in neuronal activity, may then lead to decay of AD levels as a replenished metabolic equilibrium is reestablished and the decay of AD levels is associated correlated with an increased likelihood of a transition to waking. At present, this is an entirely speculative scenario. However, recent preliminary observations by Pooka-Heiskanen, Strecker, Thakkar, Greene and McCarley (unpublished) of extracellular AD levels in the cholinergic nuclei, determined by microdialysis show that they are relatively high during waking and decrease with slow wave sleep. If these findings are substantiated, they will provide, within the context of our knowledge of AD’s actions, the most compelling evidence to date for a particular sleep factor or, more particularly, a fatigue factor.

Adenosine (AD) possesses a number of compelling characteristics of an endogenous physiological sleep factor. AD is found throughout the CNS along with its anabolic and catabolic enzymes. AD receptors with well characterized inhibitory electrophysiological activity are found on cortical, thalamic and brainstem neurons. Similar to other putative sleep factors, AD or AD agonists, when administered IV, are capable of inducing slow wave and REM sleep (Radulovski, 1984). Finally, as the backbone molecule for ATP, AD may provide a homeostatic link between electrophysiological activity and metabolic activity (reviewed in Greene and Haas, 1991) and thus provide a link between behavioral state and metabolic state that suggests a function (but not an exclusive function) for sleep.

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Another problem with AD as a sleep factor relates to the control of AD release. There is a large body of evidence that AD release into the CNS extracellular space is related to the metabolic state of neuronal tissue (Pull and McIlwain, 1972; Berne, et al, 1982; McIlwain and Poll, 1986). There is speculation, further, that this relationship holds true even within physiological limits so that AD might provide a physiological negative feedback link between electrophysiological and metabolic state (Greene and Haas, 1985 & 1991; McIlwain and Poll, 1986). This same relationship for AD can be extended to global arousal and metabolic state through the inhibitory actions of AD on cholinergic neurons (Rainnie, et al, 1994) or on thalamic and/or cortical neurons (Bennington and Heller, 1995). However, the link between extracellular AD levels and physiological metabolic states is not established. Two potentially physiological mechanisms of release, shown to cause AD-mediated inhibition, have been described: 1) by repetitive excitatory input activation, mentioned above, and 2) through stimulation of cAMP (Rosenberg, et al, 1994; Gereau and Conn, 1994). A number of pathological circumstances that all involve increased metabolic demand relative to metabolite availability (reviewed in Greene and Haas, 1991) can cause an increase in electrophysiologically active AD release. These mechanisms are not consistent with the action of AD as a physiological sleep factor that relates CNS metabolism to behavioral state. In the case of the tetanus evoked release, the time course of the effects is too rapid. In the case of the slower metabolically challenged release, the release is not related to metabolism under physiological conditions. Finally, the cAMP evoked release would require a yet to be described behavioral-state related mechanism that accounts for its increase during the transition from waking to sleep.

Nevertheless, endogenous AD does exert a tonic inhibitory tone on cholinergic neurons similar to that observed in the hippocampus that is Ca++ independent.
and controlled at least in part by a bidirectional facilitated transport system (Linden, 1994). The flux is primarily inward as blockade of the transport with nitrobenzylthioionosine results in an increase of AD-mediated inhibition. Recently we have observed a similar effect in the LTD/PPT region (Grunze and Greene, unpublished). Once inside the cell, the AD is rapidly metabolized primarily (but not exclusively) to AMP by adenosine kinase which is then phosphorylated to ADP and ATP. Antagonism of this enzyme by beautifulcin can profoundly inhibit neurons in the hippocampus (Pak, et al, 1994) and LTD (Grunze and Greene, unpublished) by reducing the metabolism of AD with the result that intracellular AD levels increase and AD is transported from inside to outside of the cell. The relatively large increase in AD requires only a small shift in the equilibrium between AD and ATP since ATP is present intracellularly in millimolar concentrations. Thus, it is conceivable that extracellular levels of AD might be significantly affected by physiological metabolic demands that result in only small changes in ATP levels. Bennington and Heller (1995) have suggested that this might occur in direct correlation to the energy storage molecules of glycogen that are depleted over the course of the day although there is no direct evidence for this relationship. Nevertheless, this raises an interesting possibility that AD levels may not fluctuate until a threshold depletion of glycogen occurs. Then, with continued metabolic demand, the extracellular AD might rapidly increase and rapidly increase the probability of a transition to sleep. Slow wave sleep, with its associated decrease in neuronal activity, may then lead to decay of AD levels as a replenished metabolic equilibrium is reestablished and the decay of AD levels is associated with an increased likelihood of a transition to waking. At present, this is an entirely speculative scenario. However, recent preliminary observations by Porka-Heiskanen, Strecker, Thakkar, Greene and McCarley (unpublished) of extracellular AD levels in the cholinergic nuclei, determined by microdialysis show that they are relatively high during waking and decrease with slow wave sleep. If these findings are substantiated, they will provide, within the context of our knowledge of AD’s actions the most compelling evidence to date for a particular sleep factor or, more particularly, a fatigue factor.

References:
News and Comments

International Symposium
Sleep and Sleep Disorders:
From Molecule to Behavior

The 9th Takeda Science Foundation Symposium on
Bioscience entitled "Sleep and Sleep Disorders: From
Molecule to Behavior" will be held on December 5-7, 1996,
at Kyoto Century Hotel, Kyoto, Japan.
This international symposium is composed of 26 invited
lectures by prominent scholars in sleep science and sleep
medicine. The speakers will present a broad scope of sleep
and sleep-related topics like An impact of sleep research -
models from molecule to behavior, Neuronal activities during
sleep, Evolution of sleep, Homeostasis and aging of sleep,
Hormones and sleep, Host defense and sleep, Molecular
biological approach to sleep research, Genetics of sleep
disorders, Cognitive functions of dreaming brain, and Brain
mechanisms of sleep regulation.

Since this symposium is a semi-closed meeting and the total
number of participants will be limited to about 200, you are
kindly requested to register beforehand. Registration is free of
charge. For further information, please contact immediately:
Symposium Secretariat, Takeda Science Foundation, 2-17-85,
Jusohonmachi, Yodogawa-ku, Osaka 532, Japan. Phone:
+81-6-308-7418, Fax: +81-6-300-6634.

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CLUB HYPNOS

Society for Neuroscience 26th Annual Meeting
Satellite/Ancillary Event
CLUB HYPNOS:

Location: Renaissance Washington DC Hotel
Room: Room 2
Date: Tuesday, November 19, 1996
Time: 5:30 p.m. - 7:30 p.m.
Setup: Reception

2nd Congress of the Asian Sleep Research Society
August 24-29, 1997
Jerusalem, Israel

Further Information: Congress Secretariat
Dan Knassim
PO Box 1931
Ramat Gan 52118, Israel
Student Essay Awards

The SRS takes pleasure in announcing the awardees in the 1996 Essay Awards Program. High school students from 23 states and Canadian Provinces submitted entries. All essays were judged on the basis of content, scientific application and originality.

Five first place awards were presented to:

**Julie Berstein**
Toll Gate High School, Warwick, RI
"Wandering Through Somnambulism"

**Mi-Mi Chen**
Ursuline Academy, Dedham, MA
"Sleep Deprivation"

**Helen Florez**
Cooper City High School, Cooper City, FL
"Even If You Sleep, You're Still At Risk"

**Eric Johnson**
Richard Montgomery High School, Rockville, MD
"Learning While You're Asleep"

**Francine Posillico**
Cold Spring Harbor High School, Cold Spring Harbor, NY
"Sleep and Dreams"

Students submitted essays from the following schools:

- Brookfield High School, Ottawa, Ontario, Canada
- Oakwood Collegiate Institute, Toronto, Ontario, Canada
- Robert F. Hall Secondary School, Caledon East, Ontario, Canada
- Little Rock Hall High School, Little Rock, AR
- Bear Creek High School, Stockton, CA
- Sheridan Middle School, Englewood, CO
- Edwin O. Smith High School, Storrs, CT
- Woodstock Academy, Woodstock, CT
- Cooper City High School, Cooper City, FL
- Fayette County High School, Fayetteville, GA
- Perry High School, Perry, GA
- Central Noble High School, Albion, IN
- Shawnee Mission East High School, Prairie Village, KS
- Paducah Tilghman High School, Paducah, KY
- Ursuline Academy, Dedham, MA
- Queen Anne's County High School, Centreville, MD
- Richard Montgomery High School, Rockville, MD
- Seneca Valley High School, MD
- Hartland High School, Hartland, MI
- North Community High School, Minneapolis, MN
- John F. Kennedy Memorial High School, Iselin, NJ
- Academy of Mount Saint Ursula, Bronx, NY
- Academy of Our Lady of Good Counsel, White Plains, NY
- Aardsley High School, Aardsley, NY
- Beaver River Central School, Beaver Falls, NY
- Cold Spring Harbor High School, Cold Spring Harbor, NY
- Garden City High School, Garden City, NY
- Harborfields High School, Greenlawn, NY
- Manhattan Center for Sciences and Mathematics, New York, NY
- Midwood High School, Brooklyn, NY
- Penn Yan Academy, Penn Yan, NY
- The Clarkson School, Potsdam, NY
- Hawken High School, Gates Mills, OH
- Muncy High School, Muncy, PA
- Strath Haven High School, Wallingford, PA
- Toll Gate High School, Warwick, RI
- Ball High School, Galveston, TX
- Coronado High School, Lubbock, TX
- Friona High School, Friona, TX
- Lewisville High School, Lewisville, TX
- M. B. Lamar High School, Arlington, TX
- Nimitz High School, Irving, TX
- Vines High School, Plano, TX
- James Madison High School, Vienna, WA
- Henry Foss High School, Tacoma, WA
- North Thurston High School, Olympia, WA
- Dohgeland High School, Juneau, WI

In recognition of this achievement, a cash award of $250 and a certificate of excellence will be awarded to each of these students. Additionally, the text, The Encyclopedia of Sleep and Dreaming, is awarded to each student's high school library, on behalf of the awardee. Teachers of all students receive a copy of Basics of Sleep Behavior, and all entrants receive a sleeping brain T-shirt.

1996 marks the fifth consecutive year that the SRS has awarded scholarships to high school students, amounting to $6,000 in cash awards. This year 276 entries were received, the highest total in the five-year history of the program. The 276 entries is nearly two times as many as in 1995.

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MOLECULAR BIOLOGY AND GENETICS OF
SLEEP AND SLEEP DISORDERS

NIH GUIDE, Volume 25, Number 29, August
30, 1996

RFA: HL-96-015

National Heart, Lung, and Blood Institute
National Institute on Mental Health
National Institute on Child Health and Human
Development

Letter of Intent Receipt Date: January 6, 1997
Application Receipt Date: March 13, 1997

PURPOSE
The purpose of this initiative is to advance our
understanding of the molecular and genetic basis
of sleep and sleep disorders. Specifically, the
program is designed to stimulate studies on basic
molecular correlates of sleep, cellular mechanisms
responsible for restorative processes during sleep,
the interactions between sleep and circadian
systems controlling sleep and wakefulness at a
molecular level, the genetic basis of sleep
disorders, and the molecular neurobiology of sleep
and sleep disorders.

This RFA is a one time solicitation. Future
unsolicited competing continuation applications
will compete with all investigator initiated
applications and be reviewed according to
 customary peer review procedures.

SPECIAL REQUIREMENTS
The primary focus of proposed studies must be on
the molecular or genetic basis of sleep and sleep
disorders. Studies of the circadian system must be
tightly coupled to mechanisms of sleep control.
Psychobiological, neurophysiological, anatomical,
or polysomnographic studies which do not include
molecular or genetic approaches to understanding
sleep will be considered unresponsive to this RFA.
Pharmacological studies that investigate the
efficacy of sleep promoting agents but not the
underlying molecular mechanisms will also not be
acceptable. Studies proposing the use of
nonmammalian species should clearly establish the
relationship of these models to the goals set forth
in this RFA. Applicants are encouraged to contact
the program officials listed under INQUIRIES for
further information.

INQUIRIES
Inquiries concerning this RFA are encouraged.
The opportunity to clarify any issues or questions
from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

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National Center on Sleep Disorders Research
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