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INTRODUCTION

Recent Advances in Sleep and Chronobiology

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The hows and the whys of sleep and chronobiology remain among the leading scientific challenges to a full comprehension of the central nervous system and its behaviors. Nearly all but the "lowest" organisms exhibit daily periods of repose and action. Cycles of rest and activity or sleep and wakefulness are carefully regulated by both endogenous circadian "clocks" and homeostatic processes. The circadian system adjusts the timing of sleep or activity over the 24-hour day. Homeostatic processes reflect both the increased propensity to sleep with extended duration of wakefulness and the recovery or recuperative benefits of sleep itself. In most mammals, three important processes regulate states of consciousness and behavior: the circadian system, the homeostatic system, and ultradian rhythm of NonREM and REM sleep.

The basic and clinical sciences of sleep and chronobiology have been the beneficiaries of recent advances in neuroscience, including molecular neurobiology and genomics, cellular physiology, functional brain imaging, computational neuroscience, topographical EEG, immunology, and neuropsychopharmacology. The new findings and methodologies have important implications for understanding the pathophysiology and treatment of neuropsychiatric disorders. This special issue of *Neuropsychopharmacology* contains 18 invited papers on recent advances in basic and clinical research, especially in sleep and, to a lesser extent, in chronobiology.

One of the most dramatic recent discoveries in neuroscience is the identification of the hypocretin/orexin neuropeptide system and its role in the pathophysiology of narcolepsy. In 1998, two groups (L. De Lecea et al., T. Sakurai et al.) independently identified this peptide system in the lateral hypothalamus. In the next year, two groups published papers in *Cell* within weeks of each other, linking abnormalities in the hypocretin/orexin system to narcolepsy. In the first paper, a team headed by Emmanuel Mignot reported a mutation of the hypocretin/orexin receptor 2 (Hcrtr 2) in canine narcolepsy (L. Lin et al.); in the second paper, the team headed by M. Yanagisawa reported that hypocretin/orexin knockout mice appeared to have narcolepsy (R.M. Chemelli et al.). In this issue, **Emmanuel Mignot**, who directed for the past 15 years the only dedicated research laboratory on the pathophysiology of narcolepsy, comments on the neurobiology of the hypocretin/orexin system. His paper reviews the diagnosis, treatment, neuropsychopharmacology, and genetics of human narcolepsy. Finally, he speculates on the role of hypocretin/orexin in sleep, sleep deprivation, and other physiological issues. **Jerry Siegel and colleagues**, who have studied the electrophysiology of canine narcolepsy for many years, discuss the role of hypocretin/orexin in symptom variability, regulation of brainstem motor systems, and control of the locus coeruleus and nucleus magnocellularis. Both groups independently examined autopsied human narcoleptic brains and reported low numbers of hypocretin/orexin cells in lateral hypothalamus, but with some differences. In a third paper in this issue, **Rafael Salin-Pasqual and colleagues** summarize the role of the whole hypothalamus in the regulation of sleep and wakefulness. They also venture some conjectures about the role of hypocretin/orexin in depression, the night eating syndrome, and obstructive sleep apnea.

A fundamental question has been whether behavioral states—sleep, wakefulness, sleep deprivation, NonREM sleep, and REM sleep—affect gene expression. **Giulio Tononi and Chiara Cirelli** have investigated thousands of transcripts in the brains of rats and, more recently, fruit flies, which appear to sleep according to accepted behavioral criteria. Their results suggest that most of the genes upregulated during wakefulness or sleep deprivation are known; in contrast, most of the genes upregulated during sleep are unknown at this time.

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NEUROPSYCHOPHARMACOLOGY 2001–VOL. 25, NO. S5
© 2001 American College of Neuropsychopharmacology
Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/01/$–see front matter
PII S0893-133X(01)00335-9

Two papers address the role of neurotransmitters which may regulate sleep. **Wally Mendelson and Anthony Basile** review the data on oleamide, an endogenous fatty acid amide, which is synthesized in the mammalian brain, interacts with cannabinergic, serotonergic, and GABAa receptors, and which may be an endogenous sleep-inducing compound. **Polly Moore and colleagues** confirm that ipsapirone, a $5HT1_A$ receptor agonist, inhibits REM sleep in normal volunteers but fails to replicate an earlier paper indicating that rapid tryptophan depletion (RTD) with the tryptophan free amino acid drink disinhibits REM sleep. The latter finding may suggest individual different responses to the RTD.

Michael Irwin reviews the intriguing relationships between sleep, sleep deprivation, and immune processes and nocturnal secretion of cytokines. Moreover, his data suggest for the first time that alcohol dependence and African-American ethnicity jointly contribute to the reduction of Stages 3 and 4 sleep (low frequency, high amplitude EEG measured also by spectral analysis), reduced natural killer (NK) and stimulated NK activity, reduced pro-inflammatory cytokine IL-6, and increased Th2 IL-10. Since sleep deprivation is common in our 24-hour society and in many psychiatric, sleep, and medical illnesses, the question arises whether sleep disturbance is associated with clinically significant impairment in immune functioning.

Monte Buchsbaum and colleagues present a reanalysis of their pioneering quantitative study of local cerebral glucose metabolism in wakefulness, nonREM sleep, and REM sleep in normal volunteers, showing dramatic global and regional differences among the three different stages of consciousness.

Applying new methods for topographical EEG (27 EEG derivations) in normal volunteers before and after sleep deprivation for 40 hours, **Luca Finelli and colleagues** demonstrate that the EEG power distribution in nonREM sleep has a characteristic pattern ("finger print") for each individual. Furthermore, power in specific EEG frequency bands increased or decreased in different cortical regions during recovery sleep after sleep deprivation compared with normal sleep without prior sleep deprivation; this observation suggests that the recuperative functions of sleep may vary between anatomically specific cortical areas. **Hans-Peter Landolt and Lieselotte Posthuma de Boer** studied three depressed patients with MAOI-induced near total suppression of REM sleep for 6–18 months, the longest such published study. At a time when several research groups have suggested that memory consolidation may occur during REM sleep, these observations pose a cautionary note. These patients did not complain of cognitive impairment.

One of the paradoxes of experimental sleep deprivation for a night is that it impairs cognitive performance in normal subjects but improves depressive symptoms in depressed patients. **Sean Drummond and Greg Brown** review the limited literature on the effects of sleep deprivation on performance in normal controls who undergo functional brain imaging studies. Their own studies with functional magnetic resonance imaging (FMRI) suggest that sleep deprivation may be associated with adaptive cerebral responses during some but not all cognitive tasks. **Joe Wu and colleagues** review the functional imaging literature of sleep deprivation in depression. The studies more or less consistently report that metabolic activity in ventral anterior cingulate and medial orbital prefrontal cortex is elevated prior to sleep deprivation and normalized in association with the antidepressant effects after sleep deprivation. **Camellia Clark and colleagues** describe a potential FMRI method for quantitative cerebral perfusion and illustrate its usefulness in two depressed patients and one control subject before and after sleep deprivation.

Erich Seifritz provides a brief overview of the sleep disturbances associated with depression and their potential contributions to understanding the neurobiology of depression and sleep. In a 4-year longitudinal follow-up survey of 1176 adolescents with notable depressive symptoms at baseline conducted by **Christi Patten and colleagues**, persistent depressive symptoms were associated with female gender, changes in sleep problems and cigarette smoking, and other variables.

In a more chronobiological perspective, **Kurt Kräuchi and Anna Wirz-Justice** present physiological data supporting their new hypothesis that the onset of sleep depends upon a circadian upregulation of the distal to proximal skin temperature gradient, followed by decreased core body temperature. For many years **Ray Lam and colleagues** have studied seasonal affective disorder (SAD), a disorder which may have a chronobiological basis. In their current paper, catecholamine depletion induces a clinical relapse during the untreated, summer-remitted, state in these patients. In their review paper, **Barbara Parry and Ruth Newton** argue that chronobiological disturbances may occur in premenstrual dysphoric disorder, pregnancy and post-partum depression, and menopause and that all of these disorders respond to sleep deprivation, in some cases for long periods of time.

The future of sleep and chronobiology depends upon basic and clinical neuroscience. Powerful new tools promise historic discoveries in many scientific disciplines. The recent discovery of orexin/hypocretin has lessons for investigators in many areas. It illustrates the importance of the bi-directional perspective in "translational" research: communication between the bench and the bedside must go both ways. Yanagisawa's group made an orexin/hypocretin knockout mouse because they hypothesized that this protein regulated feeding, but a clinician in that group recognized the signs of human narcolepsy in these mutant mice. At the same time, Mignot's group, after a long search through the dog genome, found a mutation in the

hypocretin/orexin receptor associated with canine narcolepsy which suggested the mechanism but not the exact pathophysiology of human narcolepsy. Whether one attributes such success to serendipity or the "prepared mind," we can hope for more "breakthroughs" in the future. In the field of sleep and chronobiology, we should anticipate further advances in understanding the molecular basis of sleep, sleep deprivation, biological rhythms, and genetics. Recent studies, for example, have suggested the genetic and molecular basis of the advanced phase sleep syndrome. Indeed, sleep and/or circadian rhythm could be among the first complex behaviors in mammals to be well understood at a basic level. Functional brain imaging, neuropsychology, cellular neurophysiology, genetics, and computational neuroscience have much to contribute to understanding basic and clinical issues. Sleep and chronobiology are slowly but surely giving up some of their secrets.

ACKNOWLEDGMENTS

The papers in this special issue resulted from a Festschrift for J. Christian Gillin, M.D., on October 28–29, 2000 at the School of Medicine, University of California, San Diego (UCSD) and VA San Diego Healthcare System. The meeting was proposed and organized by Dr. Lewis Judd, M.D., Chairman of Psychiatry, UCSD, and Sonia Ancoli-Israel, PhD, Professor of Psychiatry, UCSD. The organizers and Dr. Gillin thank the contributors to this special issue; Robert Lenox, MD, Editor-in-Chief of *Neuropsychopharmacology;* Council, the American College of Neuropsychopharmacology (ACNP); William E. Bunney, Jr, MD, for editorial review and suggestions; Sheila Neely, Kathy Stuart, and Jady Psek, for administrative assistance, and the UCSD General Clinical Research Center (Michael Ziegler, MD, Director), the American Academy of Sleep Medicine, the Sleep Research Society, Bristol-Myers-Squibb, Ely Lilly and Company, ResMed, Wyeth Ayerst Laboratories, and Ambulatory Monitoring Company for unrestricted educational grants to support the Festschrift and this special issue.