



SRS BULLETIN

A PUBLICATION OF THE SLEEP RESEARCH SOCIETY, USA

VOLUME 8
NO. 3
WINTER
2002



BULLETIN

A Publication of the Sleep Research Society, USA
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Westchester, IL 60154



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PRESIDENT'S MESSAGE



As we enter the New Year, I am pleased to report that the Sleep Research Society Board has been hard at work to begin a process of strategic planning as well as to prepare for our upcoming celebration of the 50th anniversary of the discovery of REM sleep. As a first step in looking towards the future, we have focused on creating a structure that will allow the SRS to achieve its primary goal of promoting the field of sleep research.

The Board has begun to review organizational policies and procedures as well as evaluate committee structure and revise committee mandates. Our goal is to energize committees by instituting policies allowing for greater involvement of SRS membership, and by encouraging committees to focus on activities that meet member needs and further the field of sleep research. Committee mandates and rosters are posted on the SRS web site.

The Board has also reviewed the SRS Bylaws and will propose several changes that will emphasize the process of governance and allow the SRS greater flexibility to support programs in the areas of research and education. Proposed changes to the Bylaws will be posted on the SRS web site for review and comment by the membership.

One of our most critical societal needs is to increase our membership. The field of sleep research is growing rapidly, as evidenced by the ever-increasing numbers of publications and NIH-funded investigators, yet our membership has not kept pace with this growth. The SRS needs the talents and energies of members representing all aspects of sleep-related research for our meetings, committees and societal initiatives. For our current members, now is the time to renew your commitment. Many of you have already returned your renewal notices with payment. I encourage the rest of our members to retain the full benefits of Sleep Research Society membership by sending in your dues today.

I also ask you to help us increase our impact on the field by encouraging your colleagues to join. If we would each commit to endorse one new member this year, we could double our membership in 2003 and solidify our position as the premier scientific organization representing sleep research. Membership application forms are available on the SRS web site (www.sleep-researchsociety.org) or from Judy Yore (jyore@aasmnet.org) at the national office.

For the SRS to make greater investments in the field, we will also need greater involvement of our membership in ongoing and new initiatives. I invite you all to share your expertise with the SRS. For volunteer information, contact Judy Yore or visit the SRS web site.

During the next six months, I will be working with President Elect Emmanuel Mignot and the rest of the Board to begin to continue the strategic planning process that will extend beyond my term in office. Since input from SRS members will be vital to our success, we will be asking for your feedback and involvement. As noted in the summer issue of the Bulletin, the SRS will emphasize a number of areas as it plans for the future; following are the highlights of recent SRS activities and future plans in these areas:

1. **Training:** Historically, the most significant investments of the SRS have been made in training programs for students and young scientists. I am appointing a Task Force to assess the training needs of our future scientists and our membership and to recommend programs to meet those needs.
2. **Research:** The SRS continues to promote and support sleep-related research. As part of this effort, we are drafting a response to Dr. Theodore A. Kotchen's request for input regarding the NIH Center for Scientific Review's process to evaluate grant applications in clinical research. We also have SRS representation on the Advisory Counsel that drafted the NCSDR Research Plan. Look for this latest plan on the NIH web site at www.hhlb.nih.gov/about/ncsdr. SRS participation in these efforts is critical to the growth of our profession. In addition, with the onset of the new program year (2003-2004), a Research Committee will be appointed to work on development of new programs to foster sleep research.
3. **Career development:** Last year, we proudly announced that Washington State University was the first recipient of the 3-year J. Christian Gillin Junior Faculty Development Award. This summer, David Rector, Ph.D., will be completing his first year as a junior faculty member at the university. The



JFPD Committee will evaluate the effectiveness of this program and make recommendations regarding future awards.

4. Relationship with the AASM: The SRS recently formed a Limited Liability Corporation (LLC) with the AASM to enhance the effectiveness of our joint ventures such as the APSS Annual Meeting and the journal SLEEP. In addition, the SRS and AASM added a new initiative this year; we will jointly sponsor a research fund-raising dinner at the APSS Annual Meeting. Proceeds from the dinner will be shared equally by the two societies and may be used only for support of research-related initiatives. Please join us on Wednesday, June 4 to show your support for research and to mingle with your colleagues.

Planning is progressing for the APSS 17th Annual Meeting June 3-8 at the Hyatt Regency in downtown Chicago. The meeting will also serve as a joint meeting with the World Federation of Sleep Research Societies. Record-breaking numbers of submissions were received in all presentation categories, including 1,148 abstracts. The SRS will host a special reception on Thursday, June 5 to present some special awards honoring members of the profession and to unveil a plaque that will be placed at the University of Chicago commemorating the 50th anniversary of the discovery of REM sleep by. Visit the APSS web site (www.apss.org) for up-to-date meeting information, and be sure to register early!

Your suggestions and comments regarding Society activities are always welcome. I wish you all a happy and healthy New Year.

Ruth M. Benca, MD, PhD
SRS President

EDITOR'S COLUMN

by Larry D. Sanford, PhD

Research, by its nature, can narrow our focus. Sometimes we only see issues relevant to our immediate situation, whether they regard our particular research problem or the esoteric vagaries of getting and maintaining funding. However, as conveyed in the features in this issue, the field of sleep research is multifaceted.

At the 2002 Lake Arrowhead Summer Sleep Workshop, the focus was on the "interactions and intersections between sleep and other disciplines." Topics such as cardiovascular/pulmonary, depression, epilepsy, memory/learning, neuroinformatics, pain and stress and their link to sleep were explored by established scientists and trainees. Apart from determining basic sleep mechanisms, discerning the relationship of sleep to problems studied in other fields may well be the most important direction that sleep research will take in coming years. This issue includes a "sampler" of topics that were covered.

Improvements in technology have facilitated the sharing of ideas and information across continental borders. As a result, sleep research is becoming more international in nature. This issue highlights laboratories in Brazil, Italy and Uruguay, providing insight into the research and clinical enterprises in these countries. I thank the laboratory leaders, and those who assisted them, for taking time out of their busy schedules to prepare these portraits of their labs and their work.

On a final note, this issue contains a feature highlighting notable news about our members. Please continue to share information regarding promotions, honors, and other noteworthy items. I also encourage my colleagues to contribute articles for publication in future issues. Book reviews, letters to the editor and your thoughts regarding issues facing the sleep professions are welcome.

Discovery
REM 50th Anniversary



JUNE 3-8, 2003, CHICAGO, ILLINOIS

***PRELIMINARY PROGRAM
AVAILABLE MARCH 1, 2003***

Keynote Address

William C. Dement, M.D., Ph.D.

Director, Stanford Center of Excellence in Sleep Disorders
Stanford University
Palo Alto, California

Michel Jouvet, M.D.

Professeur Emeritus
Faculte de Medecine
Universite de Claude Bernard
Lyon, France

VISIT WWW.APSS.ORG FOR MORE INFORMATION



CALL FOR VOLUNTEERS

The SRS invites members to share their expertise and experience by volunteering to serve on committees. Your involvement will help make the SRS a stronger and more vital organization. The SRS is seeking volunteers to staff the following committees for the program year starting in June 2003. Contact Judy Yore (jyore@aasmnet.org) for information regarding committee appointments. We look forward to your participation.

Awards Committee

The Awards Committee solicits nominations for SRS awards, reviews nominations and submits recommendations to the Board. The Committee establishes and evaluates award criteria and proposes the establishment of new award categories, as appropriate.

Educational Program Committee

The Educational Program Committee proposes, plans and develops sleep research related programs, materials and products to meet the continuing education needs of the membership, excluding trainee programs. The Committee recommends and implements a mechanism for the submission and review of educational program proposals. The Committee also advises the Board regarding continuing education activities that will benefit the membership.

Membership Committee

This Committee recommends policy to the Board relating to the building and maintenance of Sleep Research Society membership. The Committee reviews membership applications, develops materials used to attract new members, and suggests programs to retain existing members.

Publications/Web Services Committee

The Publication/Web Services Committee oversees the organizations' printed and electronic communication functions. The Committee has responsibility for making recommendations to the Board relating to printed publications such as *SLEEP* and the SRS Bulletin. The Committee also suggests policy pertaining to the development and maintenance of the SRS web site, ensuring that the content is accurate and relevant to the organization's mission and goals.

Research Committee

This new Committee is responsible for making recommendations to the Board regarding the Society's policies and activities relating to research. The Committee encourages research, coordinates professional responses to research issues, and addresses general research-related matters. In addition, the Committee oversees the implementation and evaluation of the junior faculty development

program to financially support the appointment of junior faculty dedicated to sleep research.

Trainee Education Advisory Committee

The Trainee Education Advisory Committee (TEAC) recommends and reviews trainee related programs and activities, including requests for trainee travel assistance, trainee workshops, and trainee activities scheduled in conjunction with the APSS Annual Meeting. The TEAC will also propose other programs, services and initiatives to meet the needs of the student membership and to promote the profession to this constituency.

SAVE THE DATE! Research Fundraising Dinner



The American Academy of Sleep Medicine and the Sleep Research Society are pleased to announce their first annual research fundraising dinner, "Discovering the Secrets of Sleep." Proceeds will benefit the sleep research initiatives of the two organizations. This event will take place the evening of **June 4, 2003** at the Hyatt Regency Hotel, as part of the APSS Annual Meeting in Chicago.

Enjoy a night of dinner, dancing, and socializing with friends and colleagues amid the busy schedule of APSS events. Look for registration information in the APSS Annual Meeting preliminary program. Please contact Carey Pulvino at (708) 492-0930 or cpulvino@aasmnet.org for further information.

WELCOME NEW MEMBERS

As our numbers grow, we strengthen our impact on the profession. Help us spread the word about the benefits of membership. In 2003, we ask each member to recruit at least one colleague for membership in the Society. Information regarding membership can be found on the SRS web site at www.sleepresearchsociety.org or from Judy Yore, SRS Coordinator at jjore@aasmnet.org.

Join us in welcoming the following new members who recently joined the Society.

FULL MEMBERS

Lee K. Brown, MD
New Mexico Center for Sleep Medicine

Fang-Chia Chang, Ph.D.
China Medical College Hospital

Kelly Dineen, PhD
Evanston Northwestern Healthcare

Christopher Earley, PhD
John Hopkins School of Medicine

Jidong Fang, MD, PhD
Pennsylvania State University College of Medicine

Yehuda Finkelstein
Meir Hospital

Erika Gaylor, PhD
Stanford University School of Medicine

Helene Gaudreau, Ph.D.
Douglas Hospital Research Center

Bruno Giordani, PhD
University of Michigan

Suanne Goodrich, PhD
Lynn Health Science Institute

Daniel Gottlieb, MD, PhD
Boston University School of Medicine

Carl L. Hart, PhD
Columbia University

H. Craig Heller, PhD
Stanford University

Ichiro Kita, PhD
Stanford University

Bernat Kocsis, MD, PhD
Harvard Medical School

Samuel Kuna, MD
University of Pennsylvania

Luis de Lecea, PhD
Scripps Research Institute

Kenneth Lichstein, PhD
University of Memphis

Anthony Liguori, PhD
Wake Forest University School of Medicine

Xianchen Liu, MD, PhD
Arizona State University

Tonya Palermo, PhD
Rainbow Babies and Children's Hospital

Lorraine Potocki, MD
Baylor College of Medicine

Susan Redline, MD
Case Western Reserve University

Charles Reynolds, III, MD
University of Pittsburgh

Masaya Takahashi, Ph.D.
National Institute of Industrial Health

Sigrid C. Veasey MD
University of Pennsylvania

Jamie Rolando Villablanca, MD
UCLA School of Medicine

Alexandros N. Vgontzas MD
Penn State College of Medicine

Carol M. Worthman, PhD
Emory University

ASSOCIATE MEMBERS

Jennifer Kirkby, BS
Rush Presbyterian-St. Luke's Medical Center

Tracey Leigh Signal, MS
Wellington School of Medicine

STUDENT MEMBERS

Geneviève Alain, MS
University of Montreal, Canada

Lavinia Fiorentino, MS
UCSD-VA

Keith Fridel, BA
University of Arizona

Julie Kabat, BS
Rush Presbyterian-St. Luke's Medical Center

Julie Kern, BA
University of Southwestern Medical Center

Jully Kim
University of Southwestern Medical Center

Barrett Klein, BS
University of Arizona

NEW MEMBERS, cont.

Lynne Lamarche
University of Ottawa
Alicia Levin, BA
University of Pennsylvania
Kelly Lewis, BS
University of Texas Southwestern Medical Center
Michael Linn, BS
University of California – San Diego
Louise M. O'Brien, PhD
University of Louisville
Niwat Taepavarapruk, BSc
University of British Columbia
Pornnarin Taepavarapruk, BSc
University of British Columbia
Jennifer Thompson MA
Lynn Health Science Institute
Jamie M. Zeitzer, PhD
Stanford University



APSS 17TH ANNUAL MEETING Sleep Research Comes to Chicago June 3-8, 2003

Plans for the APSS 17th Annual Meeting are well under way and we are looking forward to a stimulating event! The amount of science submitted exceeds all previous meetings. Fourteen courses have been scheduled for June 3 and 4. The APSS Program Committee received 1,148 abstracts and 75 proposals for discussion sessions and symposia. Attending this meeting will bring you up to date on the latest research, technology and clinical practice. We look forward to seeing you in Chicago.

Visit the APSS web site for the latest meeting information:
www.apss.org.

MEMBERS IN THE NEWS

ON THE MOVE

Merrill Mitler, PhD, is leaving the Scripps Research Institute in La Jolla, California to join the staff of the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland. He is replacing Paul L. Nichols as Program Director in the area of Systems and Cognitive Neuroscience.

AWARDS AND HONORS

J. Christian Gillin, MD, University of California, San Diego, was awarded the 2002 Gold Medal Award by the Society of Biological Psychiatry for "pioneering work in biological psychiatry."

Adrian Morrison, DVM,

PhD, has been appointed a Nigerian war chief, charged with combating scientific illiteracy in Africa. He received this appointment in November 2002, when he went to Jos, Plateau State, Nigeria with the World Health Mission as a basic scientist to lecture and advise



on research at the local university and hospital.

Hiroshi Kadotani, MD, PhD, Kyoto University Faculty of Medicine, has just completed his first year as a PREST researcher. This program, supported by the Japanese government, provides research funding to young scientists for up to three years.

Emmanuel Mignot, MD, PhD, was recently appointed a Howard Hughes Medical Institute Investigator. Dr. Mignot was selected through a national competition to appoint 12 outstanding physician scientists. Over 200 candidates were drawn from 119 institutions nationwide. This competition identified researchers whose scientific work was characterized by their interaction with patients and embodying the concept "from bench-to-bedside" transitional research.

Philip R. Geron, DMD, was recognized by *New Jersey Monthly* magazine as one of the top ten best oral and maxillo-facial surgeons in New Jersey. This honor was given to a handful of "top dentists" in their specialty as selected by their peers.

COMMITTEE APPOINTMENTS

Peter Hauri, PhD has been appointed chair of the AASM committee charged to revise the International Classification of Sleep Disorders. Other committee members include: Nancy Collop, MD, Jack Edinger, PhD, Mark Mahowald, MD, Emmanuel Mignot, MD, PhD, Gerald Rosen, MD, R. Bart Sangal, MD, Arthur Walters, MD, Phyllis Zee, MD, PhD.

Edward M. Weaver, MD, MPH, was appointed Chair of the Sleep Disorders Committee of the American Academy of Otolaryngology from 2002 to 2005.

CLUB HYPNOS

Contributors: Eric A. Nofzinger, MD, & Kathy Sexton-Radek, PhD

Club Hypnos events, SRS receptions held in conjunction with the meetings of allied organizations, provide opportunities for colleagues to discuss their interests in sleep research. Guests socialize, share ideas and learn about the benefits of SRS membership. In November 2002, the SRS sponsored two Club Hypnos receptions.

On November 4, Eric Nofzinger, MD, hosted the Club Hypnos held in conjunction with the Society for Neuroscience annual meeting in Orlando, Florida. This reception provided an informal venue for those engaged in sleep and neuroscience research to socialize with other meeting attendees who share an interest in sleep research. In addition to visiting friends and acquaintances, this event presented the opportunity to invite some of the most promising new investigators in the field of neuroscience to join the SRS.

Over the past six years, this Club Hypnos event has been coordinated with the "Sleep and Circadian Rhythms Datablitz" organized by the National Center for Sleep Disorders Research (NCSDR), and cosponsored by the SRS. The coordination of these events provides for a stimulating evening of conversation with some of the leading thinkers in sleep research. It includes a "rapid-fire" series of one-minute oral presentations by innovative new investigators in the areas of sleep and circadian rhythms

research. At the November Datablitz, an astounding array of approximately 30 discoveries in sleep research was relayed in quick succession, amazing everyone present. The evening was capped off by a 2-minute plenary presentation by a distinguished guest speaker. This year, Dr. David Goval, University of Louisville, left the audience breathless by providing new information regarding the brain mechanisms that either result from, or may contribute to, the development of sleep apnea syndrome.

This year's reception lived up to its expectations as one of the liveliest annual events sponsored by the Sleep Research Society. Many distinguished sleep researchers enjoyed the occasion, pronouncing the evening a great success for the area of sleep research.

Our second fall event was held in conjunction with the Association for the Advancement of Behavior Therapy (AABT) meeting in Reno, Nevada. This conference supports the work of Behavior Therapists who are dedicated to understanding human behavior and developing interventions to enhance the human condition. The reception, coordinated by Kathy Sexton-Radek, immediately followed the Insomnia and Other Sleep Disorders special interest group meeting. Attendees had the opportunity to participate in stimulating discussions and the exchange of ideas.

All are welcome to attend future Club Hypnos events. It's a wonderful opportunity to network and maximize your membership in the SRS.



Promoting research in Orlando. Michael Twery, PhD, NHLBI and Carl E. Hunt, MD, Director NCSDR, NHLBI.

STUDENT BITS

The Student BITS segment is an ongoing forum for issues pertaining to sleep and to the training and retention of sleep scientists, from a trainee's perspective. Undergraduate, graduate or postdoctoral trainees are welcome to submit articles for this section of the *Bulletin*. Please contact Jennifer L. Martin, Assistant Editor SRS *Bulletin*, Student BITS and 2002-2003 Trainee Member at Large at jemartin@ucla.edu for upcoming deadlines and information.

STUDENT MEMBERSHIP IN THE SRS

Jennifer L. Martin, PhD

Department of Medicine

University of California, Los Angeles

I encourage all trainees to join the SRS. Take advantage of the resources offered and demonstrate your commitment to the profession. The benefits of membership are substantial, including the following:

- A membership directory, which can be quite helpful in searching for the contact information of faculty members when looking for potential graduate or post-doctoral mentors.
- The SRS Bulletin, which includes a variety of articles and announcements as well as this special section for trainees.
- A subscription to the journal *SLEEP* at a discounted rate **and** free access to the on-line version.
- Information via the "new trainee e-mail network" (formerly known as t-net). This will include job postings and information about upcoming SRS trainee events (including Trainee Day at APSS).
- Student rate to attend the APSS Annual Meeting, the premier meeting for sleep researchers

Since SRS trainee membership is only \$15.00 a year, it's quite a bargain compared to the dues of most other scientific organizations. Joining or renewing your membership for 2003 will make these benefits immediately available to you.

I want to also encourage trainees to visit the SRS website at www.sleepresearchsociety.org. The site contains a host of helpful information including announcements, job postings, sleep-related links, and guidelines for the annual High School Essay Contest. Information about the upcoming Trainee Day at the 2003 APSS Annual Meeting is also posted on this site.



SLEEP MEDICINE EDUCATION AND RESEARCH FOUNDATION

The Sleep Medicine Education and Research Foundation was established in 1998 by the American Academy of Sleep Medicine to support the growth and development of sleep medicine as a medical specialty. The Foundation strives to provide continuing education to physicians, patients, and the public about the diagnosis and treatment of sleep disorders. In addition, its sponsorship of sleep-related research aids in the advancement of the field.

Since its inception, the Foundation has awarded over \$1 million in research funding, with topics spanning all areas of the sleep medicine field. The projects sponsored by the Foundation are paramount to generating further achievements in the field of sleep medicine. Please consider making a contribution to the Foundation today.

Please send your contribution to:

Sleep Medicine Education and Research Foundation

One Westbrook Corporate Center, Suite 920, Westchester, IL 60154 Fax: (708) 492-0943

For additional information, please contact Carey Pulvino, Foundation Coordinator at cpulvino@aasmnet.org.

LAKE ARROWHEAD

2002 Summer Sleep Workshop: Interactions and Intersections Between Sleep and Other Disciplines

Interactions between Sleep and the Cardiovascular and Pulmonary Systems

Fiona C. Baker, PhD, and Janna L. Morrison, PhD

The interaction between the cardiovascular and pulmonary systems (CVPS) with sleep has been thoroughly studied over the past several decades, or so our group thought when we first met together at Lake Arrowhead to prepare our presentation. Over the next couple of days, we debated, discussed, read articles, and questioned our group leaders, Ronald Harper, PhD, Timothy Roehrs, PhD, Christopher Sinton, PhD and Ronald Szymusiak, PhD about many aspects of the CVPS system and sleep, including basic and clinical physiology. This area of research is vast and since we all have very different research backgrounds, each of us approached the interaction between the CVPS and sleep from a different angle. In this way, we combined our expertise with the new information that we had gathered in our group discussions. We discovered that there are many areas of both cardiovascular and pulmonary physiology that require investigation in relation to their impact on sleep. However, for our presentation, we focused on sleep-disordered breathing and the development of chronic heart failure. We presented five different topics:

- 1) Cardiovascular and pulmonary relationships to sleep, especially in heart failure patients.
- 2) The role of the sympathetic nervous system in mediating hypertension in obstructive sleep apnea (OSA) patients.
- 3) Damage to structures in the central nervous system in patients with sleep-disordered breathing.



Monique LeBourgeois, Christopher Sinton, Ronald Szymusiak, Hui (Tory) Gong, Ronald Harper, Aaron Uschakov, Janna Morrison, Fiona Baker

- 4) Sleep-disordered breathing in children: causes and consequences.
- 5) Sleep-disordered breathing in postmenopausal women.

First, Hui Tory Gong, MD, presented some background information about the interaction between the CVPS and sleep. Breathing and cardiovascular function change during normal sleep states (Verrier et al, 1996) and there is also a tight association between the CVPS and sleep in patients with sleep-disordered breathing (Leung & Bradley, 2001). For instance, patients with sleep-disordered breathing may be at an increased risk for cardiovascular disease (Berger et al, 2001). Certainly, sleep disordered breathing is one of the best predictors for poor outcome in heart failure and is present as both obstructive sleep apnea and Cheyne-Stokes breathing in more than half of patients with chronic heart failure (Leung & Bradley, 2001). Heart failure may arise in patients who have prolonged, untreated sleep apnea due to several mechanisms, including the repeated nocturnal episodes of hypoxemia in these patients, which may disturb endothelium-dependent vasodilation (Berger et al., 2001). Sleep deprivation in sleep apneic patients, due to repetitive arousals from sleep, with associated blood pressure elevations and increased sympathetic activity also may be a contributing factor to the development of chronic heart failure.

Next, Aaron Uschakov discussed how the sympathetic nervous system mediates an increase in mean arterial pressure (MAP), which ultimately may lead to heart failure (Leung & Bradley, 2001). Patients with OSA and heart failure also have an increase in sympathetic tone and MAP, possibly due to repeated intermittent hypoxia (Fletcher, 2001; Neubauer, 2001). Uschakov also reviewed some commonly recognized mediators involved in sympathetic increases in MAP. He then focused on potential treatment options for sustained increases in blood pressure, which may be beneficial to sleep apneic patients. Possibly, early treatment of sleep apnea symptoms, with CPAP, might offset the increased sympathetic activity and consequently reduce the likelihood of heart disease. This session highlighted the important need for further research to investigate the involvement of the sympathetic nervous system in the development of sleep apnea.

Until recently, little attention has been given to effects of sleep-disordered breathing on nervous system structure, as described by Janna Morrison, PhD. The characteristics of sleep apnea mentioned previously, such as hypoxia and fluctuating blood pressure, however, may damage neural structures (Macey et al 2002). Recent studies show that patients with heart failure and OSA have gray matter loss in areas of the brain, such as the frontal and

parietal cortex, hippocampus and cerebellum (Macey et al 2002). In addition, brain activity patterns in response to challenge differ between controls and patients with OSA with either underactivation, late activation or overactivation depending on the brain area (Ronald Harper, PhD, personal communication). The cause of these deficits is not known, but may be a consequence of the repeated intermittent hypoxia that characterizes OSA. For example, climbing fibres in the cerebellum are very sensitive to hypoxia and these fibres are damaged in OSA patients (Harper, personal communication). In addition, studies of intermittent hypoxia in rats show an increase in apoptosis in CA1 of the hippocampus (Gozal et al, 2001). Alternatively, neural deficits due to an unknown insult such as fever as an adult or even hypoxic insults during fetal development may predispose individuals to the development of sleep-disordered breathing.

Sleep-disordered breathing has been better studied in adults than in children. But, as Monique LeBourgeois, MS, informed everyone, the incidence of OSA in a pediatric population may exceed 10%. In children, OSA usually occurs secondary to hypertrophied tonsils and adenoids, craniofacial abnormalities, or damage to the cerebellum (an interesting link to the structural changes discussed in another conference session). Children with OSA frequently have movement disorders as well, suggestive of neural structure damage. The developmental years are critical, especially for neural growth. Yet, intermittent hypoxia in children with untreated OSA, could cause long-term cognitive deficits. Also, in the absence of treatment, children with OSA may be at a higher risk of developing cardiovascular disease in later life.

Fiona Baker, PhD went on to point out that other population groups, such as post menopausal women, have an increased risk of sleep-disordered breathing compared to premenopausal women. For example, it is known that the etiology of sleep-disordered breathing in women differs from that of men, with women having more hypopneas (partial obstructive events) that are of a short duration. In addition, there is currently interest in research relating to the involvement of sex steroid hormones in protecting premenopausal women against developing sleep-disordered breathing. Progesterone is a respiratory stimulant, and either alone or combined with estrogen may decrease sleep-disordered breathing (Pickett et al. 1989). Treatment of sleep-disordered breathing in postmenopausal women will be enhanced if we understand better the roles of these steroids in regulating breathing, and the impact of hormone replacement therapy. Another interesting gender difference, which remains unexplained, is that although fifty to sixty percent of male patients with chronic heart failure have Cheyne-Stokes respiration with central apnea, it is seldom seen in female patients (Leung & Bradley, 2001).

Future Directions

At the conclusion of this presentation several ways in which the sleep community could contribute to the fields of cardiovascular and respiratory research were highlighted.

Is OSA a predictor for the future development of chronic heart failure?

We believe that the results from ongoing longitudinal studies in

patients with treated OSA, will provide valuable information about whether treatment of OSA early will improve prognosis for the development of cardiovascular disease.

What are the mechanisms behind sleep-disordered breathing causing heart failure?

It will be important for future research to investigate the relative contributions of the components of sleep-disordered breathing (intermittent hypoxia, arousals, increased sympathetic dysfunction) to the development of hypertension and cardiovascular disease. How the chronically sleepy state, characteristic of OSA patients, influences cardiovascular function also requires additional study.

What is the relationship between sleep-disordered breathing and structural brain deficits?

Many aspects of this question are still unanswered. What comes first? Could a neural insult during fetal life or adulthood eventually cause deficits in centrally-mediated upper airway regulation, which could lead to the development of some forms of sleep-disordered breathing? Or, do the characteristics of sleep-disordered breathing, especially hypoxia, cause neural deficits? Newly available brain imaging techniques may provide information to help answer these questions in the future.

What are the consequences of sleep apnea in children, women and different population groups?

It is vital to find out more about the etiology of OSA in children and the consequences for not only their cognitive and social development, but also their risk of cardiovascular disease in later life. Also, further research about sleep-disordered breathing in women will reveal the protective mechanisms of sex steroids and gender differences in the etiology of OSA, leading to new treatment methods in women and possibly men.

Lake Arrowhead participants learned a lot about the interaction between the CVPS and sleep. Sleep researchers are able to make important contributions to the general understanding of both the normal function and disease states of the cardiovascular and pulmonary systems and their interaction with sleep.

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Sleep and Epilepsy

Margaret N Shouse, PhD, and Charles Wilson, PhD

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Current Status

The age-adjusted incidence of epilepsy (more than two unprovoked seizures) in total population studies of industrialized countries ranges from 27/100,000 to 54/100,000 person years. Onset most frequently occurs in the young (first decade) and the elderly (over 70 years of age). Ninety-seven percent of seizures may be classified into two main categories:

1. Primary generalized (40%), in which onset of EEG seizure discharge occurs simultaneously in diffuse thalamocortical circuits, and clinically evident seizures may be generalized tonic-clonic convulsions, myoclonic seizures or absence seizures, and
2. Localization-related (57%), in which EEG seizure discharge originates in relatively discrete brain regions, and clinically evident seizures are simple-partial (maintaining consciousness) or complex-partial (loss or alteration of consciousness) with or without secondary generalization.

Seizure manifestations are significantly affected by sleep and vice-versa, regardless of the type of seizure disorder. Clinical and animal observations suggest four main interactions (2,3):

1. Seizure discharge propagation is minimal during REM sleep but increases during NREM as well as during transitional arousal states to and from NREM and REM sleep episodes, when compared to waking.
2. Sleep deprivation provokes seizures and increases epileptiform EEG activity between seizures and therefore is commonly employed as a diagnostic aid.
3. Seizure disorders can disrupt sleep and its physiological components reflected by significant changes in sleep architecture.
4. Specific antiepileptic drugs (AEDs) can increase NREM sleep time, reduce REM or have no effect on sleep state percentages. AEDs may influence sleep independently of seizure disorders but, ideally, should allow normal sleep without seizure activity.

Overlapping anatomical and neurotransmitter/neuromodulatory systems provoke or suppress different sleep or arousal states and seizure events. Hypothalamic and brainstem generators of

NREM sleep and arousal project to thalamocortical generators of sleep spindles and spike-wave discharges (SWDs) with which they are affiliated and also to limbic areas (e.g., hippocampus, amygdala, orbital frontal cortex) where complex-partial seizures frequently originate. Norepinephrine, serotonin, acetylcholine, gamma-amino-butyric acid (GABA), galanin and adenosine are implicated in sleep and seizure generation or suppression (e.g., 3,5).

A number of experimental approaches are used in investigations of sleep and epilepsy. Four examples are:

1. *Polygraphic recordings*, particularly EEGs. Both disciplines employ and in fact require EEG records for sleep staging and/or seizure classification. Experimental dissociative procedures have been used to differentiate seizure-prone from seizure-resistant physiological components of different sleep or waking states (e.g., brainstem lesions causing REM sleep without atonia, atropine induced EEG synchronization in REM or waking). Effects of dissociative manipulations on various animal models of primary and secondary generalized seizure disorders suggest that EEG synchronization can facilitate EEG seizure discharge propagation in any state, whereas antigravity tone is essential for seizure-related movement (3).
2. *Genetics*. Autosomal dominant nocturnal familial frontal lobe epilepsy (ADNFLE) is a current area of active investigation in humans. Numerous genetic epilepsy models in rodents are also available, as reviewed by Noebels in *Epilepsy, A Comprehensive Textbook*, 1997. Examples are WAG/Rij, GAERs (genetic absence epilepsy in rodents) and GEPRs (genetic epilepsy prone rodents). The sleep-waking state distribution of SWDs in these models resembles that in human absence seizure disorders (1).
3. *The slice preparation*. Steriade, McCormick and others have successfully used the slice preparation to investigate thalamocortical mechanisms of sleep spindles and SWDs (1). The slice preparation has also been used to study localization-related seizure disorders but not in relation to sleep.
4. *Microdialysis and extracellular unit recordings*. These procedures are used in both fields and have been studied in animals and in surgical candidates with temporal lobe epilepsy (e.g., 4). Seizure discharge is most localized in REM sleep so that sleep recordings with units can be a valuable aid in identifying a seizure focus to be removed (3,4).

New Possibilities for Interaction

To crystallize new possibilities for interaction, our group proposed an experimental strategy. The objective was to employ some of the above mentioned, overlapping mechanisms and research strategies to study the recent developments in extra-thalamic forebrain mechanisms of sleep, particularly EEG synchrony, in the context of seizure activity. Much has been done on EEG synchronization and SWDs in thalamocortical slices, but an in vivo model is needed to follow-up on extrathalamic influences. The WAG/Rij genetic epilepsy model of absence seizure disorders was selected.

Absence seizures represent ~6% of all seizure types and are char-

acterized by paroxysmal episodes of impaired consciousness associated with bilaterally synchronous 3/sec spike-wave discharges (SWDs). There is a genetic component with age related penetrance. Onset is in young children, and the disorder can resolve by adulthood. Like humans, the epileptic rodents display SWDs most often in NREM, drowsiness and transitions into NREM and REM and least often in alert waking and REM (1).

SWDs are thought to develop in the same thalamocortical circuits that generate sleep spindles and, in particular, to represent a transformation of normal synchronizing mechanisms of spindles into abnormal ones (1). Thalamocortical synchronization mechanisms are under inhibitory control from monoaminergic and cholinergic activating systems arising in brainstem and forebrain.

Brain stem monoaminergic activity is determined by mutually inhibitory relationships with the preoptic hypothalamic area (POHA). The POHA contains a population of GABA/galaninergic, sleep-promoting neurons which are localized within the ventrolateral preoptic nucleus (VLPO) and the median preoptic nucleus (MNPO). Cells in these nuclei exhibit state-related c-fos immunoreactivity and a unique sleep-waking state discharge pattern opposite to that of monoaminergic cell groups. Specifically, hypothalamic cell discharge remains elevated throughout NREM and REM, whereas noradrenergic and serotonergic cells decline in NREM and are virtually silent in REM. GABAergic cells of the VLPO and MNPO project to these brainstem monoaminergic areas and to the nonspecific thalamic nuclei. MNPO also projects to cholinergic neurons of the magnocellular basal forebrain. These preoptic basal forebrain cells, together with cholinergic cells of the pontine tegmentum, are implicated in the genesis of EEG desynchronization during alert waking and REM. Collectively, these findings suggest that sleep-active neurons of the POHA could influence thalamocortical synchronization by affecting thalamic membrane potentials directly or indirectly by suppressing hypothalamic or brainstem monoaminergic and possibly cholinergic cell activity.

Preliminary data further show that both low and high frequency electrical stimulation of VLPO induces EEG synchronization in rodents and rabbits. This stimulation also has a low threshold for inducing SWDs in young rabbits.

The aim of the proposed studies is to examine the role the GABAergic/galaninergic, sleep-promoting system of POHA in the generation of absence seizures. Specifically, we propose that dysfunction sleep-promoting neurons of the POHA is one of the pathogenic mechanisms of absence seizure disorders.

The experimental approach is to study sleep and absence epilepsy interactions in intact animals, including both the WAG/Rij absence epilepsy model and non-epileptic rats. Target structures for extracellular unit activity studies include VLPO and VMPO. Hypothalamic unit discharge rates will be measured during chronic polygraphic recordings of cortical and hippocampal EEG synchronization patterns, eye movements and skeletal muscle tone to register unit discharge patterns as a function of sleep-waking states as well as spindle and SWD incidence. Baseline recordings are planned before and after either electrical stimulation or pharmacological manipulations. Low versus high fre-

quency electrical stimulation of VLPO or MLPO would be compared for sleep inducing and SWD inducing effects. Pharmacologic manipulations (microdialysis), including the GABA-A antagonist bicuculline and a benzodiazepine GABA-A agonist are planned to mimic anticipated electrical stimulation effects.

There are three predictions for these experimental phases.

1. *Baseline.* Increased unit activity in VLPO and MNPO will occur in seizure-prone states of drowsiness, transitions to and from NREM and REM and during NREM when compared to alert waking and REM sleep before and after electrical stimulation vs. drug infusion. This outcome is anticipated in control rats (non-epileptic) and in WAG/Rij rats without seizures. Maximum increases should be seen during spontaneous SWDs in WAG/Rij rats.
2. *Electrical stimulation.* Both low and high frequency stimulation of VLPO and MNPO should provoke sleep onset and SWDs in normal and WAG/Rij rats.
3. *Pharmacological manipulations.* Microinfusion of bicuculline should block GABAergic interneurons, thereby increasing the discharge rate of GABAergic projection neurons of VLPO and MNPO in all rats, and should also increase SWDs in WAG/Rij rats. Benzodiazepines should have the opposite effects on cell discharge rates and SWDs.

Anticipated results could lead to further studies to differentiate the roles of VLPO and MNPO in SWD generation and to determine whether GABAergic modulation of the thalamocortical synchronization circuit is direct or via monoaminergic and/or cholinergic systems. Findings might also shed light on extrathalamic mechanisms of SWD generation in states when thalamocortical synchronizing mechanisms are relatively inactive, including drowsiness and REM as well as transitions into REM and from REM to waking.

Recommendations for Future Interactions

The experiment proposed by our group is one example in one seizure model (absence seizures) to show how microdialysis, electrophysiology and behavioral observation can be used to investigate an unexplored topic – hypothalamic mechanisms of the provocative effects of NREM sleep and transitional arousal states versus the antiepileptic effects of REM sleep. A similar experiment was planned to evaluate temporal lobe epilepsy, but time constraints did not permit its inclusion.

There are institutional funding sources and mechanisms for information sharing. For example, the Epilepsy Branch of the National Institute of Neurological Disorders and Stroke issued a program request for research proposals on the relationship of sleep to epilepsy. The American Epilepsy Society (AES) has a special interest group (SIG) on sleep and epilepsy. Beth Malow, PhD, (University of Michigan) is the SIG organizer, which is on the program for the annual AES meeting. Sleep and epilepsy topics should also be included at APSS Annual Meeting sessions.

More basic research is needed to explain the voluminous clinical findings relating sleep and epileptic seizure manifestations. Important advances have been made recently in the neurobiolo-

gy of NREM sleep, and this could be a particularly fertile area for future research.

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Stress And Sleep Interactions

Morten Pilgaard Kristensen, PhD

The following is a brief survey of the current state of knowledge of the interactions between stress and sleep. This brief overview emerged from the plenary presentation and group discussions on the topic at the 2002 Lake Arrowhead Sleep Training Workshop.

Stress is a tremendously effective and useful adaptive coping mechanism, which serves to mobilize body resources to deal with environmental challenges in the acute phase but becomes commensurably detrimental to the organism when stress is very intense, protracted or repeated. Prolonged stress is a pervasive problem in modern human existence, which can have serious effects on health and well-being. In recent years, it has become apparent that elements of the stress response also have profound effects on behavioral state regulation.

However, a key problem plaguing the stress research field is the lack of a universally accepted mechanistic definition of the term "stress". Obviously, the absence of a clear definition hampers progress in elucidating functional mechanisms overlapping with interrelated research fields, including sleep. Contrasting attempts at defining stress have focused on the eliciting factors (stressors) or the organismal responses (neuroendocrine, physiological and/or behavioral). The stress research pioneer, Hans Selye (1936), saw stress as "responses to demands (usually noxious) upon the body." Later definitions changed the scope as recognition grew that more than simple physical aspects of a stimulus could make it a stressor and produce "alterations in psychological homeostatic processes" (Burchfield, 1979). More recent efforts have sought to comprehensively unite the emerging picture of the interplay between stressor characteristics and responses by defining stress as "a state of threatened homeostasis, which is reestablished by a complex repertoire of physiologic and

behavioral adaptive responses of the organism" (Chrousos, 1998).

Although a specific definition remains elusive, a common, central component of the stress response, which is generally agreed upon and encompassed by virtually all definitions, is stereotypic activation of the hypothalamo-pituitary-adrenocortical (HPA) axis. HPA axis activation is initiated by secretion of corticotropin releasing hormone (CRF) into the portal vessels from terminals of paraventricular hypothalamus neuron axons terminating at the median eminence. CRF triggers release of adreno-corticotrophic hormone (ACTH) into the general circulation in the anterior pituitary. ACTH, in turn, elicits glucocorticoid release from the adrenal medulla.

Remarkably strong evidence for the interaction between stress and sleep is that activity of every link in the aforementioned chain of neuroendocrinological events constituting the HPA axis is associated with behavioral state alterations. Administration of ACTH or glucocorticoids impede active sleep (Chastrette et al., 1990; Gillin et al., 1972; 1974), and CRF promotes wakefulness, including as part of the stress response (for review see Opp, 1995). Moreover, medial PVH cell activity levels are state-dependent and increase from wakefulness to quiet sleep and peak during active sleep (Kristensen et al., 1996).

HPA axis activation occurs not only in response to stressors, but is also subject to strong circadian and ultradian fluctuations, which show species-specific timing. Massive release of the HPA axis hormones, ACTH as well as glucocorticoids, occurs around the onset of the active period in diurnal as well as nocturnal animals. Additionally, stress hormone release occurs in phasic ultradian spikes superimposed upon the diurnal cyclicality. It is particularly noteworthy that in humans, the average periodicity of phasic ACTH release is similar to that of the basic activity rest cycle: 90 minutes.

HPA axis activation occurs to a wide range of noxious or potentially threatening stimuli or stressors. Commonly used experimental stressors include ether anesthesia, pain, and exposure to a novel environment, a predator or a dominant con-specific as well as blocking performance of appetitive highly-motivated behavior, such as feeding, drinking or copulation. A common feature of stressors appears to be that they signal a loss of controllability or predictability of the individual's environment. Often the emotional aspects of a stimulus appear to endow it with stressor status. Emotional stimuli are evaluated through limbic structures, such as the amygdala (LeDoux, 2000). Moreover, the central nucleus of the amygdala sends projections, although polysynaptically, to the PVH and shows state-specific discharge patterning.

Stressor-elicited HPA axis activation typically does not occur in isolation. It is usually, but not always, accompanied by other physiological responses, such as increases in sympathetic nervous system outflow, as well as behavioral responses, which may be more stimulus specific. However, even autonomic stress responses may be partially mediated via the PVH, which sends descending projections to parasympathetic and sympathetic control regions, including the nucleus of the solitary tract, which exhibits state-dependent discharge levels. Additionally, the PVH

is reciprocally connected with several brainstem regions, which have been implicated in state regulation, such as the dorsal raphe and locus coeruleus.

Behavioral state control can be viewed as a homeostatically regulated process. To the extent that sleep is an appetitive behavior, thwarting the consumatory phase would be expected to function as a stressor, as does blocking performance of other motivated behavioral elements, e.g., food seeking or predator escape. However, evidence for this hypothesis has not been forthcoming. Indeed, although sleep-deprivation, like stressors, can lead to hypertension and compromise immune function, long-term sleep-deprived rats exhibit none of the three classical hallmarks of prolonged stressor exposure: 1) hypertrophy of the adrenal gland, 2) thymus atrophy and 3) gastric ulceration - even when the deprivation becomes lethal (for review see Rechtschaffen and Bergman, 2002). An obstacle to demonstrating that sleep deprivation can be an acute stressor is the nebulous aspect of stimulus onset, i.e., the relative change in sleep drive is much more gradual than that of other motivating sensations, e.g., fear, pain or even hunger and thirst. Moreover, a confounding factor of such studies is that many methods of sleep deprivation, such as restraint or even handling, can be stressors in their own right in many species, including rats.

The relationship between behavioral state regulation and stress is interesting beyond the potential commonality between the arousal generating circuitry for the two functions in that several disorders may link them. These include a number of psychiatric disorders, which appear to be precipitated or exacerbated by stress, and which are also associated with sleep disturbances, although it is unclear to what extent this under-evaluated component of the etiology precedes or follows the psychological effects. Examples are anxiety, depression and posttraumatic stress disorder (PTSD). The sleep disturbances associated with these disorders are often not properly diagnosed or treated in the face of other pervasive and serious symptoms, even though they may be predictive of future pathology, e.g., for PTSD. However, treating the associated sleep disturbances or otherwise manipulating sleep patterns can ameliorate symptoms in some psychiatric patients as well as other stressor effects in the general population.

Thus, a critical area for further research is the progression of sleep disturbances and underlying mechanisms in stress-evoked models of psychiatric disorders. Identifying the components that mediate the stress- and sleep-related changes may contribute to elucidating the disease mechanisms. Regardless, it has the potential to discover avenues for therapy as well as further describing the links between stress and behavioral state regulation. To this end, it is important that the disease model be as faithful to the circumstances of human stress as possible, e.g., Chronic Mild Stress - especially with regard to triggering the disorder. Several animal models of psychiatric disorders elicited by stressors of disparate types (physical vs. psychogenic), intensity, and timing (single vs. repeated, and duration of, presentations) can be used to evaluate associated sleep disturbances. Such disorder models include acute exposure to an intense stressor for PTSD, and fear conditioning, chronic mild stress or exposure to a novel environment for anxiety, as well as repeated social defeat, inescapable

shock or restraint for depression. Evaluation of the sleep disturbances associated with these models of human psychiatric disorders aid in validation of the models, and may help identify the role of sleep disturbances in the progression of the etiology.

In summary, the area of overlap between the sleep and stress fields is ripe for further, detailed investigation with regard to both basic properties and clinical aspects. This includes mechanisms of interaction, at all levels of HPA axis activation, as well as with other physiological, behavioral and psychological stress responses. The comparable timing parameters of HPA axis activation and vigilance state patterning also deserve further scrutiny. There should also be additional research into the causes of sleep disturbances associated with stress-related disorders. In this context, it will be valuable to investigate effects of individual differences in genetic and gender background, early life experience as well as current social status on sleep and psychiatric consequences of stress.

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INTERNATIONAL LABORATORIES ON VIEW

A Visit to Brazil

Basic and Clinical Research
Sleep Institute
Universidade Federal de São Paulo

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Sleep research in our laboratory began at the end of the 70's aiming at understanding the effects of paradoxical sleep deprivation on brain neurotransmission. In the beginning of the 80's we began polysomnography on an experimental basis, which was performed at the same time that an epidemiological survey on sleep problems took place in São Paulo City. The same survey was repeated in 1995.

A purpose-built facility was opened in 1989. The building housed ten polysomnography apartments and marked the beginning of a clinical group that, in addition to performing research in the fields of neuropsychiatry and breathing disorders, rendered clinical practice.

In the 90's the basic research department, which had been growing steadily in the 80's, implemented a computerized sleep laboratory for twenty rats and twelve mice and a molecular biology/genetic laboratory. In the clinical field a new building was raised with twenty-six apartments for polysomnography. Other specialties including pediatrics, rheumatics and sports medicine were drawn to the center.

The Institute has recently consolidated its existence in a new eighteen-story building of 52,800 square feet with ninety-four apartments for polysomnography with all the necessary infrastructure and organization for clinical research.

Converging on the idea of developing a new chair called Sleep Medicine and Biology in the Universidade Federal de São Paulo-UNIFESP, we offer specialization courses in Sleep Medicine for students and for polysomnography technicians, as well as Master and Ph.D. programs in sleep physiology and disorders.

Sleep Deprivation

The causes, mechanisms and consequences of sleep deprivation (SD) and the physiological basis of the resulting need to sleep constitute the research core of our group. Our goals are to expand scientific understanding of sleep functions by addressing the broad spectrum of consequences of sleep loss, contributing to the development and validation of new diagnostic and therapeutic approaches to sleep-related conditions.

The initial work of our group focused on SD-induced behavioral changes, suggesting that SD affects the functional state of several brain neurotransmitters, such as dopamine (49, 51) and acetylcholine (50). Some of the behavioral alterations induced by SD are manifested by increased genital reflexes (2) alone (4) or in combination with cocaine in adult (3) or in old rats (1).

Neurochemical studies using receptor autoradiography demonstrate relevant changes in dopaminergic (29), cholinergic (30) and noradrenergic (21) systems. Autoradiographic mapping has revealed regionally heterogeneous binding receptor modifications after SD.

A number of studies have shown that depriving animals of sleep prior to training (prior SD) impairs acquisition/learning on a variety of tasks (9,10,12).

The possibility has arisen recently that SD may induce toxic effects in defined neuronal populations. Our group has recently reported changes in glutathione (GSH) levels after 96 hours of SD, suggesting the occurrence of oxidative stress in localized areas of the CNS (11), specifically, in the hypothalamus and thalamus, suggesting the possibility of apoptotic changes in these areas. Using TUNEL analysis to detect breaks in DNA and expression of proteins associated with apoptosis (bcl-2 and bax mRNA) in brain by in situ hybridization (ISH), we did not find SD-induced apoptosis or necrosis (20). The evidence of oxidative stress after SD was also observed systemically, as demonstrated by an increase in plasma oxidative stress index and a decrease in plasma homocysteine levels (31). Our results suggest that oxidative stress observed after SD is not sufficient to induce neural cell death (11,20). The possibility that localized functional deficits, not necessarily associated with cell loss, occur after SD remains to be addressed.

Stress and Sleep

Why do some people develop chronic insomnia after a stressful event whereas others do not? Stress-induced insomnia appears to be associated with individual vulnerability. Stress induces activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the release of CRH, ACTH and corticosterone, hormones that are related to wakefulness and attention directed toward the stressful situation. However, it is unknown whether insomnia-prone individuals also have a hyperactive HPA axis. Our group is trying to answer this question by using animal models that produce an exaggerated response of the HPA axis to stress. These animals are recorded before and after an acute stress. Based on the work of Palma and co-workers (32), we used immobilization in one study (48) and are currently using cold stress. In the near future, we are planning to use a psychological stressor to simultaneously investigate sleep and stress responses in these animals.

A second aspect of the relationship between sleep and stress is the manner in which sleep deprivation, and more specifically, paradoxical sleep deprivation (PSD) alters the stress response. It is possible to attenuate PSD-induced increased activity of the HPA axis. We developed the modified multiple platform method (MMPM) in which 6-10 animals, under social stable conditions, are placed onto 14 platforms, so they can move around and interact (44,47). Although the flower pot technique and the MMPM result in similar ACTH and CORT plasma levels (45), animals deprived by the MMPM exhibit less HPA axis activation in response to the elevated plus maze than do individually-deprived rats. This result indicates that group-PSD may favor a more adequate coping process and, consequently, more adaptive behavioral and hormonal responses (46).

Sleep and Periodic Leg Movements

In order to examine aspects involved in the pathophysiology of Periodic Leg Movements (PLM) during sleep, our group is developing studies in humans and animal models. In humans, the studies explore this disorder in paraplegic individuals and the influence of physical exercise on PLM in both paraplegic and non-paraplegic subjects (22,23-25,27,41-43).

In regard to the animal models, we are currently using spinal cord lesioned rats to identify PLM and the possible influence of physical activity in reducing these movements during sleep.

Somnolence and Accidents in Shift Workers

This service is provided to National companies, which uses irregular or regular shift work and whose workers need to adapt their sleep pattern and biological rhythm to the company's working schedule (26). We are currently developing partnerships with several transportation companies and with industries. This service is based on scientific results and gives support for the development of new studies in this field.

Group of Sleep Respiratory Disorders (SRD)

Since 1992, pneumologists attend an average of fifteen patients per week in the SRD ambulatory; the most frequent disorders

being Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS), Sleep Hypoventilation Syndrome (Obesity Hypoventilation, Chronic Obstructive Pulmonary Disease [COPD], Neurological Disorders), Asthma, among others.

The main research directions of this group are:

1. Pathophysiology of the OSAHS, specifically assessing the respiratory center, ventilation mechanics and exercise capacity. The results of these studies show that OSAHS patients exhibit a discrete reduction of the ventilation command that improves with the acute use of CPAP. These patients present preserved respiratory muscle force and exercise capacity (6,28).
2. OSAHS pathophysiology associated to COPD, i.e., Mixed Syndrome. The studies showed that the pulmonary disease limits these patients, who present severe heart arrhythmias that improve with nocturnal use of CPAP associated with nasal oxygen.
3. Sleep and Chiari Malformation: A current project assesses the relationship between cranial size and apnea-hypopnea index (AHI) in order to evaluate the best neurosurgical access route for decompression of the respiratory center (8).
4. Diagnostic approach to OSAHS: The results evidenced an important individual variability of the AHI (7), which should be used with caution as an index of severity and therapeutic prognosis. Currently, a proposal to study other clinical and polysomnographic parameters to classify OSAHS severity is being elaborated.
5. Morbid Obesity and Sleep: A group of candidate patients to undergo bariatric surgeries are being evaluated by polysomnography before and after the surgery.
6. Diurnal Somnolence and OSAHS: Together with the Stanford group, under Dr. Christian Guilleminault's supervision and with the support of Lafon Laboratories in France, we developed a proposal to investigate diurnal residual somnolence (DRS) in OSAHS patients adequately treated with CPAP. In these rare patients, the use of a CNS stimulant subjectively improved DRS with few side effects.

Sleep in Rheumatic Conditions

Sleep in fibromyalgia (FM) is characterized by multiple arousal events, alpha-delta phenomenon (38), altered sleep spindles (Frochtengarten & Roizenblatt, 2001) and cyclic alternating sleep pattern (Mac Farlane et al., 1996; Moldofsky et al., 1975). These data indicate that thalamocortical mechanisms might be impaired in FM (Mountz et al., 1995). Since 1991 we have studied sleep disturbances in fibromyalgia and other chronic pain conditions such as rheumatoid arthritis, juvenile rheumatoid arthritis, low back pain and repetitive strain injury.

Our results show that fibromyalgia patients show distinctive patterns of alpha intrusion in non-REM sleep. The phasic alpha sleep pattern, which is found in patients with severe symptoms is useful in selecting therapeutic modalities and in assessing the response to a specific treatment that might improve sleep quality, pain and fatigue in fibromyalgia (Roizenblatt et al., 2001). The effects of analgesia in sleep were studied after non-pharmacological intervention with interferencial current plus pulsed ultra-

sound applied to the tender points. Despite improving sleep complaints and increasing slow wave sleep, there was no substantial change in alpha activity during slow wave sleep, as shown by FFT analysis (Almeida et al., 2001a).

Common aspects in juvenile and adult fibromyalgia were noted, but the adolescent group exhibited less tender points, higher pain threshold and less prominent sleep complaints and PSG abnormalities. Fibromyalgia in the mothers was detected in about seventy-one percent of the studied sample of thirty-four adolescents (39). Regarding rheumatoid arthritis, sixty percent of the children with polyarticular disease exhibit alpha delta sleep. Ten out of twelve children with alpha delta sleep pattern present concomitant pain complaints at the time of the sleep recording (Roizenblatt et al., 2002).

In basic research, we are undertaking a study on the effect of neonatal pain in adult rats. We observed that not only the rats, when they reach adult life, but also the lactating dams, before and after weaning exhibit evidence of anxiety behavior and also sleep disturbances (Roizenblatt et al., 2002b).

Sleep and Cardiovascular Diseases

We have been carrying out collaborative work with Dr. Christian Guilleminault, from the Stanford Sleep Disorders Center, including studies on several aspects of Sleep Breathing Disorders (SDB) and insomnia (13-18, 36,37).

Promising areas of research interest, in which we have started collecting data, are: sleep disordered breathing (SDB) and pregnancy, and cardiovascular aspects of SDB (19). There has also been collaborative studies with the Department of Cardiology of Universidade Federal de São Paulo on neurocardiogenic autonomic dysfunction and sleep, and coronariography in patients with stable angina during sleep.

Future Directions

Sleep, Physical Exercise and Circadian Rhythms

The group is studying the influence of physical exercise on sleep patterns and efficiency in some sleep disorders. The studies are primarily carried out in humans. We help the national sports teams to adapt to new time zones, when they have to travel to countries with large time differences from Brazil.

Pediatrics

The Pediatric Sleep Clinic of Instituto do Sono has two pediatric sleep specialists: Gustavo A. Moreira and Márcia Pradella-Hallinan. A five-bed sleep laboratory performs polysomnography on infants, children and adolescents aged 0-18 years.

Two recent papers are under submission – acoustic arousal in children with obstructive sleep apnea, and growth hormone and melatonin in children with short stature. The team also studies the characteristics of OSAHS in children with mucopolysaccharidosis, clinical and polysomnographic correlation in children with adenotonsil and OSAHS and the effects of supplemental oxygen on sleep architecture in children with chronic lung disease. We are currently performing data analysis of the microstructure of

sleep in children with major depression, juvenile rheumatoid arthritis and epilepsy, and the ontogenetic evolution of CAP. Pulse transit time and nasal transducer are currently being used for the diagnosis and development of normality data of sleep-disordered breathing in children.

Molecular Genetics of Sleep

Recently we have set up a laboratory to study genetics of sleep and circadian rhythms. In collaboration with the Stanford University Narcolepsy Center we are genotyping polymorphisms in the Hypocretin and Clock genes. Moreover, we are typing HLA DQ0602 in narcoleptic patients. Other projects under development include the association between the allele HLA DQ0602 and depression and the search for mutations or polymorphisms that could affect circadian phenotypes. In the near future we intend to expand our studies to other genes related to sleep and circadian rhythms.

Melatonin

The interest of our group on melatonin is recent and began with the toxicological evaluation of the hormone on healthy volunteers (40). These stimulating results led us to propose a possible therapeutic use of melatonin in menopausal women with sleep complaints under treatment with isoflavone.

Several approaches are being performed by a multidisciplinary group to assess the effects of melatonin on several conditions, including chronic headaches (33,34) circadian rhythms in blind and sighted subjects (35), in addition to exploring its therapeutic potential.

Sleep and Auto-Immune Disease

Using the hybrid NZB/NZW mouse strain which develops spontaneous lupus erythematosus, the groups is currently exploring the effects of PS deprivation on immunological markers, and the role of dopamine and prolactin on the evolution of the disease.

Sleep and Aging

The laboratory is also investing efforts on the study of sleep in pathological aging (e.g., Alzheimer's disease) and the relationship between sleep deprivation and brain markers of pathological aging (e.g., tau protein).

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Sleep Research in Italy

Laboratory of Wake-Sleep Physiology and Neurochemistry
Department of Human and General Physiology
University of Bologna

Academic staff members are Roberto Amici, Christine Jones, Emanuele Perez and Giovanni Zamobni. In addition, on a yearly basis, two to four PhD students or postdoctoral collaborators receive funding through grants or awards.

Basic Activity

The basic activity of the laboratory is to investigate the relationship between the architecture of the wake-sleep cycle and brain biochemical activity (brain activity biochemically assessed). The experimental paradigm is to modify the wake-sleep cycle by changing ambient conditions. Since animals kept in the laboratory have a limited amount of behavioural regulation, a change in ambient conditions would be mainly dealt with by an adaptive change in autonomic activity. However, since wake-sleep cycle stages are characterized by specific changes in autonomic activity, a change in the ambient condition results in a change in the architecture of the wake-sleep cycle. The main example of autonomic changes during sleep is that of the suspension of thermoregulatory control during REM sleep, which may be seen as a suspension of physiological homeostasis. On this ground, the wake-sleep cycle may be viewed as a succession of stages, during which homeostatic regulations are fully integrated at the hypothalamic level (wakefulness and non-REM sleep), and of stages during which they are not (REM sleep).

Thus, biochemical equivalents of behavioural states may be investigated in regions involved in the integration of autonomic control, such as the hypothalamus (anterior hypothalamus-preoptic region for thermoregulatory control). In our laboratory, changes in the accumulation of second messengers have been selected as a biochemical marker of changes in hypothalamic activity.

Results

The main results we have obtained may be summarized as follows.

The suspension of physiological homeostasis which characterizes REM sleep allows the three basic stages of the wake-sleep cycle to be reduced into two, since wakefulness and non-REM sleep may be viewed as a period during which homeostatic regulations are maintained and, thus, together they would form a time interval separating two successive REM sleep episodes (REM sleep interval). The analysis of the wake-sleep cycle in different mammalian species shows that the distribution of REM sleep intervals is bimodal and is composed of a subpopulation of "short" intervals and a subpopulation of "long" intervals.

These two subpopulations are separated by a low frequency class of intervals, which, in the rat, corresponds to that of intervals lasting three minutes. Thus, we have proposed that in this species REM sleep occurs in two forms: one of *single episodes*, when the

intervening intervals are long (greater than 3 minutes) and another consisting of clusters of *sequential episodes*, when the intervening intervals are short (less than or equal to 3 minutes). In the rat kept under normal laboratory conditions, the amount of REM sleep in the form of single episodes is sixty to sixty-eight percent and is thirty-five to forty percent in the form of sequential episodes.

The study of animals, during both a mid term exposure (24-48 hours) to low ambient temperature and the following recovery at normal laboratory temperature, has shown that the reduction and the increase in REM sleep, observed during the exposure and during the following recovery, respectively, is mainly due to corresponding changes in the occurrence of sequential REM sleep episodes. Single REM sleep episodes appear to be much less affected and a change is found only when ambient temperature is brought to a very low level.

The suppression of REM sleep at low ambient temperature may be seen as a behavioural thermoregulatory response the animal is forced to perform since the laboratory condition does not allow more efficient actions such as burrowing, nesting or, eventually, escaping. For example, the low level of efficiency of this thermoregulatory behaviour is shown by the fact that it induces a sleep deprivation. Surprisingly, it has been observed that the recovery of REM sleep, following a forty-eight hour exposure to a very low ambient temperature (-10°C), was lower than that observed following twenty-four hours of exposure to the same ambient temperature, in spite of a larger sleep loss. This was due to a difficulty in the production of the necessary amount of sequential REM sleep episodes during the first hours of the recovery period.

With respect to second messengers, we have observed that at normal laboratory temperature the preoptic-anterior hypothalamic accumulation of cAMP is reduced during REM sleep compared to wakefulness and non-REM sleep. Interestingly, cAMP accumulation does not change in the cerebral cortex. The accumulation of cAMP determined during the wake-sleep stages at low ambient temperature (0°C) shows changes only at the hypothalamic, but not at the cortical level. Compared to normal laboratory temperature, in the cold, hypothalamic cAMP accumulation in both wakefulness and NREM sleep decreases to REM sleep levels, which do not change. Hypothalamic cAMP levels are fully recovered during the first few hours of the recovery period (early recovery). Thus, a general suggestion would be that a perturbation of the wake-sleep cycle, such as that observed with exposure to low ambient temperature, is concomitant with a loss of amplitude of the change in hypothalamic cAMP accumulation observed during the wake-sleep stages at normal laboratory conditions.

In fact, when cAMP accumulation is measured, in wakefulness, at the end of a twenty-four hour or forty-eight hour exposure to a very low ambient temperature and during the early recovery, the findings are that cAMP accumulation is again reduced, at the end of the exposure, at the hypothalamic, but not at the cortical level. However, in the early recovery the control levels are reattained following twenty-four hours of exposure, but not following forty-eight hours.

The possibility that the preoptic-hypothalamic reduction in cAMP accumulation, following the forty-eight hour exposure to a very low ambient temperature, is due to some unspecific metabolic effect is apparently ruled out by the finding that, in contrast to cAMP, inositol 1,4,5 - trisphosphate (IP3) accumulation increases in both the preoptic-anterior hypothalamus and cerebral cortex.

In our opinion, these results suggest that the reduction in cAMP accumulation following a forty-eight hour exposure to a very low T_a is due to mechanisms (perhaps monoaminergic receptor down regulation) that, in order to be re-established, require a period of time. An additional working hypothesis is that the difficulty in providing enough sequential REM sleep episodes to compensate for the REM sleep loss during the exposure, an effect we have observed during the first hours of the recovery following the forty-eight hour exposure to a very low ambient temperature, may be related to such a low hypothalamic level of cAMP. With respect to this, it should be remembered that sequential REM sleep episodes should occur at short intervals and, thus, the occurrence of sequential episodes requires frequent interruptions of the control of physiological homeostasis. It may be that this process is affected by the change in hypothalamic cellular activity that is most likely related to the decrease found in cAMP accumulation.

The issue of the relationship between changes in the wake-sleep cycle and second messengers accumulation at the hypothalamic level has also been addressed pharmacologically, by administering LiCl to animals kept at normal laboratory temperature. Since LiCl affects enzymes (adenylyl cyclase and inositol monophosphatase) involved in the production of cAMP and IP3, both the changes in the wake-sleep cycle and the cerebral accumulation of these two second messengers have been determined at fixed times following the substance administration. The results of these experiments are currently undergoing analysis.

Current Research

At the moment the laboratory is following two lines of research:

The first is a complete study of the wake-sleep cycle in the rat kept for twenty-four hours at four different low ambient temperatures followed through recovery over a four days period. Low ambient temperatures have the advantage to induce a partial deprivation of sleep and, thus, they allow the wake-sleep cycle to be studied during the exposure, which is during deprivation. In this research we have chosen a long period of recovery so as to be able to perform a precise assessment of the relationship between the loss and the recovery of both NREM and REM sleep. Moreover, we have used a full digitalisation of the EEG signals in order to study them in the frequency domain. Also, a vegetative variable, such as hypothalamic temperature, has been recorded in the same form. Eventually, the analysis of digital signals will be used to provide a consistent definition of the transitions from NREM into REM sleep. In fact, we should be able to start the analysis from a population of successful transitions, that should progressively decrease in parallel to the lowering of ambient temperature and, after that, to compare results with those coming from a population of unsuccessful transitions that, in contrast,

should increase in parallel to the lowering of ambient temperature.

The second line of research extends the study of the interaction between thermoregulatory and sleep processes to the analysis of a possible interaction between osmoregulation and sleep. With respect to this, it should be stressed that: 1) osmoregulation is a homeostatic function primarily under hypothalamic control, carried out by the release of antidiuretic hormone (vasopressin) when the osmolality of the extracellular fluid is increased; 2) osmoregulation is phylogenetically older than thermoregulation; 3) thermoregulation and osmoregulation are functionally linked, as suggested by the finding that, in dehydration, osmoregulation prevails over thermoregulation and by the convergence of thermal and osmotic stimuli on the same preoptic-anterior hypothalamic neurons. In this line of research we are assessing the changes in the wake-sleep cycle induced by changes in osmotic regulation and, conversely, how osmotic regulation changes during the wake-sleep cycle.

Equipment

The laboratory is fully equipped for the work we are presently carrying out, both from a behavioural (polygraphs, thermoregulated rooms, digital recording equipment, etc.) and a biochemical (centrifuges, chromatography, traditional and microplate spectrophotometry, microscopes, cryostat, radioactivity counters, etc.) viewpoint.

Funding

Funding is mostly provided by two grant systems. One is local, regulated by the University of Bologna and based on the consistency of research groups and their capacity to publish in internationally acknowledged Journals. The other is nationwide and is controlled by the Minister of University and Research on the basis of an evaluation performed by an international panel of referees. Grants for PhD students and postdoctoral collaborators are mainly provided locally by the University.

Private associations (either profit or not for profit) in Italy provide a limited amount of funds for research on cancer or other diseases and for basic research in molecular biology. They also provide grants for postgraduate education. The tax rebate allowed by the Italian Government for these types of donation is very limited.

The European Union is at the moment pressing more for research that would show substantial applicative results in the foreseeable future. Thus, it is not easy to find financial support for basic research that is not dealing with genetics or molecular biology.

Recent Relevant Papers

1. Since the activity of this laboratory has a direct derivation from the pioneering work of Pier Luigi Parmeggiani, the reader is referred to Parmeggiani, P. L. (1994) The autonomic nervous system in sleep. In: Kryger MH, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine. Philadelphia: W.B. Saunders Company, 1994, 194-203.

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50 Years of Progress in Uruguay

Laboratory of Neurophysiology
University of the Republic

Prof. Ricardo A. Velluti, M.D., D.Sc.
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History

The year 2002 was the fiftieth anniversary of our Neurophysiology laboratory. Its origin, back in 1952, was the result of a meeting of Elio García-Austt, José P. Segundo and Joaquín V. Luco, from Chile, in Montevideo. Since its inception, researchers at the laboratory have continuously investigated various research topics and published new data, even through the harsh political days. As seen in the following citations, sleep and wakefulness has been a research topic from the beginning:

1. Mazzella, H., García-Mullin, R. and García-Austt, E. Effect of carotid sinus stimulation on the EEG. *Acta Neurol. Latinoamer.*, 1957, 3: 361-364. (Cited in the Kleitman's book 1963). Original results on EEG synchronization after carotid sinus stimulation.
2. Segundo, J.P. The Reticular Formation. A survey. *Acta Neurol. Latinoamer.* 1956, 2: 245-281. This review, including original results, was the best one worldwide at the time.

Present Time

Our facility is divided into four different laboratories of animal research and one for human all night sleep recording. Three setups are fully equipped for animal studies during sleep and for sensory -auditory, somesthetic or visual- unitary firing or evoked potentials analysis. There is another set-up also for experimental sleep recording of two simultaneous free animals or restrained guinea pigs or rats (*ATI Delphos Polysomnograph*) in a sound attenuated box. A fifth laboratory is equipped with an *ATI*

Delphos Polysomnograph set to record human sleep. An adjacent bedroom with bath is used for recording human subjects.

The People

The group is comprised of 11 researchers with different backgrounds and ages. Besides myself there are three full-time researchers. Most of the research personnel has received post-doctoral training abroad, e.g., Department of Physiological Science and Department of Physiology, UCLA; Dipartimento di Fisiologia Umana e Generale, Bologna, Italia; Departamento de Anatomía, Universidad Autónoma de Madrid and Ramón y Cajal Hospital, Madrid, España.

In addition to the research staff, there are two EEG-Sleep recording technicians, a mechanic-electrician and a computer technical consultant.

Research Topics

Interactions between auditory input and sleep

- a) Auditory unit responses from the cochlear nucleus up to the primary cortex.
- b) Correlation of evoked auditory unit activity with the hippocampal theta rhythm in sleep and waking. Units from brain stem, thalamic and cortical auditory regions.
- c) Correlation of evoked visual units from the lateral geniculate and hippocampal theta rhythm.
- d) The hippocampal theta rhythm as a timer for heart rate during paradoxical sleep.
- e) Excitatory neurotransmitters at the inferior colliculus level in sleep and waking.
- f) The efferent action of cortical neurons on inferior colliculus unit activity and neurotransmitters in sleep and waking.
- g) Human deaf patients. Sleep analysis (Hypnogram, brain mapping, fast Fourier transform) before and after a cochlear implant.
- h) Analysis of the EEG frequency components during physiological heart and respiratory arrhythmia.

Summary of Research

A recent review summarizes part of this laboratory's research: Velluti & Pedemonte. *Cell Mol. Neurobiol.* 2002, in press.

1. The review analyzes sensory processing during sleep and wakefulness from a single neuronal viewpoint. Our premises are that processing changes throughout the sleep-wakefulness cycle may be at least partially evidenced in single sensory neurons by: a. changes in the phase locking of the response to the hippocampal theta rhythm. b. changes in the discharge rate and firing pattern of the response to sound. c. changes in the effects of the neurotransmitters involved in the afferent and efferent auditory pathways.
2. The first part of our report is based on the hypothesis that the encoding of sensory information needs a timer in order to be processed and stored, and that the hippocampal theta rhythm could contribute to the temporal organization. We have demonstrated that the guinea pig's auditory and visual neuronal discharge exhibits a temporal relationship (phase locking) with hippocampal theta waves during wakefulness and

sleep phases.

3. The concept that the neural network organization during sleep *versus* wakefulness is different and can be modulated by sensory signals is introduced. On the other hand, the sensory input may be influenced by the CNS state, i.e., asleep or awake.

During sleep the evoked firing of auditory units increases, decreases or remains similar to that observed during quiet wakefulness. However, there has been no auditory unit yet that stopped firing as the guinea pig enters sleep. Approximately half of the cortical neurons studied did not change firing rate when passing into sleep while others increased or decreased. Thus, the system is continuously aware of the environment. We postulate that those neurons that changed their evoked firing during sleep are also related to still unknown sleep processes.

4. Excitatory amino acid neurotransmitters participate in the synaptic transmission of the afferent and efferent pathways in the auditory system. In the inferior colliculus, however, the effects of glutamate's mediating the response to sound and the efferent excitation evoked by cortical electrical stimulation failed to show differences in sleep and wakefulness.

Considering that neonates and also infants spend most of the time asleep, the continuous arrival of sensory information at the brain during both sleep phases may serve to 'sculpt' the brain by activity-dependent mechanisms of neural development, as has been postulated for wakefulness.

Moreover, the auditory system provides information throughout the brain including the cortex in both sleep phases. The unitary firing shifts as well as the hippocampal theta rhythm phase-locking are part of the processing that could be used, e.g., as time



Seated, from left to right: Tamara Liberman (Master student), Zulma Rodríguez (Technician), Alejandra Inderkum (MD), Claudia Bentancor (MD), Natalia Goldstein (MD). Standing, from left to right: Marisa Pedemonte (MD, Ph.D), Alberto Rodríguez (technician), Juan P. Gambini (MD, Master), Lucía Pérez-Perera (Master), Pablo D. Torterolo (MD, Master), Giancarlo Vanini (MD), Atilio Falconi (PhD), Ricardo A. Velluti (MD, PhD).

giver in order to organize, at low frequencies, the incoming data. Furthermore, the results may be a necessary first part –auditory input invading the brain during sleep- for a possible sleep auditory learning or memory traces fixation.

Sleep and wakefulness auditory processing: cortical units vs. hippocampal theta rhythm

A physiological approach to the understanding of the central nervous system auditory processing during behavior requires taking into account the mechanisms of perception, attention and sleep/wakefulness generation. The correlation of the neuronal discharge with the hippocampal theta rhythm has been described for motor and sensory modalities. We address the question of the relationship between unitary activity in the auditory cortex (AI) and the hippocampal theta rhythm. We observed that there is a phase-locking between the cortical units and theta waves that was not present after data “shuffling”. It may depend on the power of theta hippocampal field potential. On changing behavioral state, a temporal relationship -phase-locking- was found during wakefulness, slow wave sleep and paradoxical sleep. Besides, this correlation may shift when neurons are acoustically stimulated and, the same neuron could show different correlations for the spontaneous and evoked activities. The influence that attention processes exert on hippocampal activity may indicate a point of interaction between those processes and the changes in the pattern of discharge of auditory neurons in sleep and wakefulness. Our results are indicative of a new approach for sensory processing analysis in relation to behavioral states and particularly with sleep.

-Pedemonte, Pérez-Perera, Peña & Velluti. *Sleep Res. Online*, 4: 52-57, 2001.

The hippocampal theta rhythm synchronizes visual neurons in sleep and waking

The hippocampal theta rhythm was reported to be associated with movements, attention, auditory processing, autonomic functions, learning and memory and postulated as an associator of discontinuous events. Since visual information includes temporal cues, our study was centered on the correlation between hippocampal theta rhythm and lateral geniculate activity. Phase-relationships between hippocampal theta and unit firing were found with both spontaneous and light evoked activity during wakefulness, slow wave and paradoxical sleep. Most important, this temporal correlation was dynamic exhibiting or not phase-locking within seconds, and changes related to the sleep-waking cycle and perhaps to attention shifts. Hippocampal theta rhythm may supply a low frequency temporal dimension to the processing of visual information.

-Gambini, Velluti & Pedemonte. *Brain Res.*, 926: 137-141, 2002.

Human research

At the APSS Annual Meeting in Chicago (2003), our lab will present results on human sleep in: a) deaf people, b) apneic patients and c) normal sleeper’s heart rate variability, in slow wave and paradoxical (REM) Sleep. These studies develop new and very interesting basic results that may be applied for patients’ non-invasive control.

Sleep Research in Our Country

Sleep, in particular, is also studied in two other laboratories. *F.R. Morales*, now Chairman of the Department of Physiology, leads a group working on trigeminal motor neurons and the reticular formation GABAergic synapses in sleep and waking. He is also working and publishing at the UCLA Department of Physiology together with M.H. Chase.

J.M. Monti, at the Department of Pharmacology, is still actively publishing on basic pharmacological approaches to sleep in rats, particularly on serotonin receptors, dopamine and histamine.

A survey of the general state of science in our country can be obtained from a recent report: -H. Suárez & R. A. Velluti, *Research resurgence in Uruguay, The Lancet Perspective*, 2000, p. 356.

A waxing and waning of money for science is a general characteristic in most South American countries. Uruguay is no exception. Although university scientists receive low salaries, considering all fields of basic science, we are doing well. More than ever, we are dependent on external collaborative projects financed by the European Union (Brussels), NIH, NSF, Howard Hughes Foundation (USA), Third World Academy of Science (Italy), etc.

Personally, I am optimistic about our research potential. Difficulties will be solved by researcher activity and creativity as well as the cooperation of national authorities.

SLEEP to Launch Web-based Manuscript Submission and Peer Review

In March 2003, the journal *SLEEP* editorial office will be launching Manuscript Central, a Web-based system for manuscript submission and peer review. Manuscript Central is operated by ScholarOne, a software company that specializes in scholarly publishing applications. The system allows authors, reviewers, editors, and editorial office staff direct access to journal operations through the Web.

Digital workflow will expedite the peer-review process and streamline the journal's administrative tasks. Manuscripts and reviews will be transmitted electronically among authors, the journal office, editors, and reviewers around the world. The system enables authors to submit their manuscripts as Microsoft Word, RTF, PostScript, HTML, and PDF files, and it accepts a wide variety of graphic file types and multi-media formats. Manuscript files are then accessible to reviewers and editors through the journal's Manuscript Central site, which is accessible through <http://www.journalsleep.org>.

Electronic submission of manuscripts eliminates mailing costs, facilitates and encourages global participation, accelerates the peer-review process, and enables authors to access journal operations and check the status of their manuscripts or update their contact information. In addition, a Web-based system allows editors direct access to an extensive database from which to select reviewers by name, areas of expertise, and key words.

Built-in security ensures that editors and reviewers assigned to a particular manuscript can view only that manuscript. Only reviewers, whose identities are kept confidential, have access to the manuscript until they have completed and submitted their reviews.

More detailed information on electronic submission and peer review will be published in upcoming issues of *SLEEP* and on the Web at <http://www.journalsleep.org>.



