Tuesday, April 5, 2005

S-44. Symposium: Sleep, depression and antidepressants

Chairperson(s): Axel Steiger (München, Germany), Edith Holsboer-Trachsler (Switzerland)
08.30 - 10.00, Gasteig - Black Box

S-44-01

Sleep debt, reasons and consequences

J. Hetta, J.-E. Broman. *Karolinska institutet Neurotec/Psychiatry, Stockholm, Sweden*

Objective: Chronic sleep debt affects many individuals in our society. Sleep debt may also increase the prevalence and severity of depression. This study examined the prevalence and relations of sleep debt in a ten-year perspective

Methods: A questionnaire on sleep habits and sleep complaints was sent to a randomly selected sample of 1962 inhabitants, aged 20-59 years, in Uppsala Municipality, Sweden. The questionnaire included questions from the Uppsala Sleep Inventory and the Hospital Anxiety and Depression (HAD) Scale. The results were compared to a similar study in 1993.

Results: Criteria for Persistent Insufficient Sleep (PIS), a condition of a substantial sleep loss on a chronic basis, were fulfilled by 11.5% of the responders in 1993 and by significantly more women than men (13.8% vs. 9.0%; 2=7.1; p<0.01). In 2003 these criteria were fulfilled by 18.6% and by significantly more women than men (21.8% vs. 14.4%; 2=11.0; p<0.001). One-half of subjects with PIS reported concomitant sleeping difficulties. In subjects with PIS without sleeping difficulties, the most conspicuous causes of insufficient sleep were work-related factors and simply too little time for sleep. According to the HAD Scale, definite cases of anxiety had increased from 10.2% in 1993 to 15.4% in 2003, while definite cases of depression had increased from 2.9% to 6.5%.

Conclusion: In the last ten years there are more individuals reporting chronic sleep debt and there is a parallel increase in the prevalence of depression.

S-44-02

The role of peptides and steroids in normal and disturbed sleep regulation

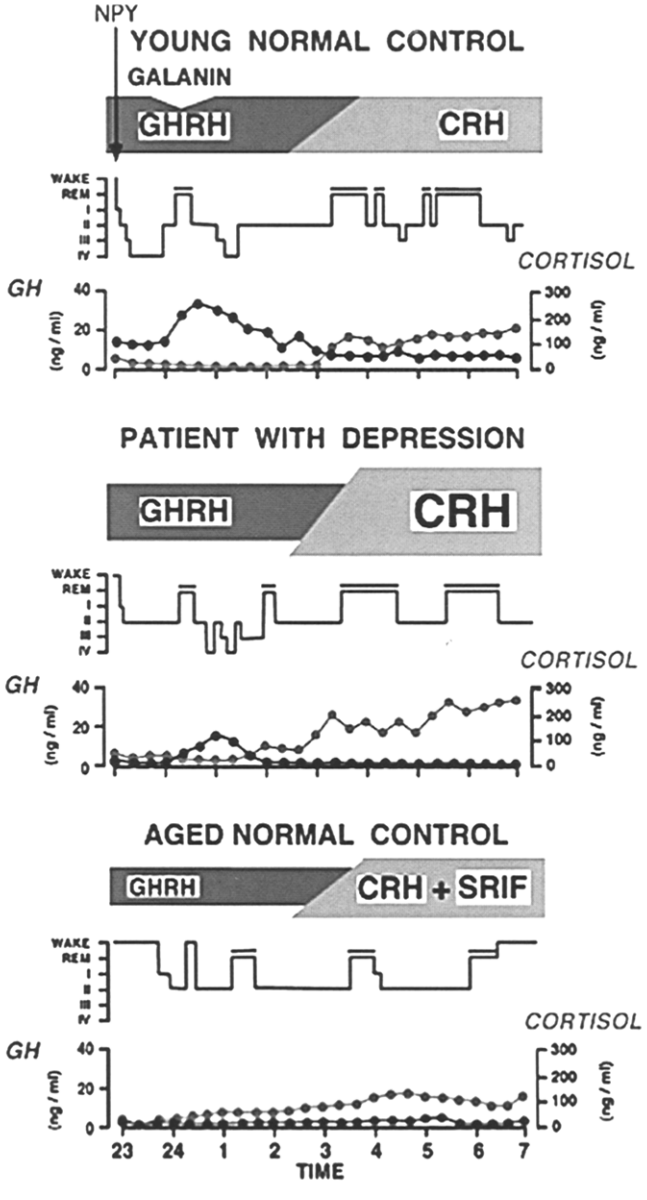
A. Steiger. *Max Planck Institut Abt. für Psychiatrie, München, Germany*

Objective: During depression and ageing similar changes of sleep-endocrine activity (decreases of SWS and growth hormone [GH], desinhibition of REM sleep and hypercortisolism) occur. We elucidated the role of peptides and steroids in normal and pathological sleep regulation.

Methods: Sleep EEG and hormone secretion were investigated simultaneously in patients and controls after various peptides and steroids.

Results: In young males after pulsatile iv GH-releasing hormone (GHRH) SWS and GH increased and cortisol decreased. Corticotropin-releasing hormone (CRH) exerted opposite effects. Also ghrelin, galanin and neuropeptide Y promoted sleep. Vasoactive intestinal polypeptide (VIP) decelerated sleep cycles. In the elderly GHRH exerted weak effects, whereas somatostatin disturbed sleep. In depressed patients and matched controls we found a sexual dimorphism in the effects of GHRH. In females GHRH impaired sleep. CRH-1-antagonism lead to a normalisation of sleep in depression. The glucocorticoid methylprednisolone induced in patients with multiple sclerosis depression-like changes of sleep. In menopausal women estrogens and progesterone improved sleep.

Conclusion: Our data show a complex network of endocrine factors in sleep regulation (see figure). Quality of sleep appears to depend distinctly from a reciprocal interaction of GHRH and CRH, at least in males. Changes in the GHRH/CRH balance in depression (CRH overactivity) and ageing (reduced activity of GHRH) explain the aberrances of sleep during these states. Beside of peptides elevated glucocorticoid levels appear to contribute to sleep-EEG changes in depression. We suggest that CRH antagonism leads to normalisation of the disturbed sleep pattern in depression.



Model of peptidergic sleep regulation

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S-44-03

Sleep EEG and HPA axis regulation changes under antidepressant treatment and prediction of long-term outcome

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Objective: In acute depression characteristic changes in EEG sleep measures are well documented findings. However, the course and the predictive value of these alterations for long-term course of depression still warrants clarification. Therefore, we examined whether the previous clinical course of depression, and the long-term outcome in follow-up are associated with abnormal EEG sleep parameters. Since the hypothalamic-pituitary-adrenocortical (HPA) system seems to play a crucial role in treatment outcome and course of depression, we evaluated HPA system function as well.

Methods: 15 patients with depression were enrolled in the study. HPA system assessment using the combined DEX/CRH test and sleep EEG studies were conducted at baseline, after a 6 week antidepressant treatment period (trimipramine), and at follow-up (after 2 to 10 years of the index episode).

Results: The previous clinical course as reflected by the number of episodes until baseline correlated significantly with EEG sleep measures i.e. sleep continuity values and slow wave sleep (SWS). During treatment sleep continuity values improved and the correlation with the previous long-term course disappeared. However, the correlation with SWS persisted. In the prospective long-term outcome SWS and REM density variables were related to the occurrence of recurrences in follow-up. These identified sleep EEG markers correlated closely with HPA system regulation.

Conclusion: In conclusion, the previous and the prospective long-term course of depression are related to sleep EEG variables during the acute depressed state. Among them SWS and REM density measures seem to reflect predictive markers for the long-term course of depression. These markers are associated with HPA system regulation.

S-44-04

Sleep EEG alterations as surrogate markers of serotonin and noradrenaline neurotransmission in healthy subjects: Relationship to the neurobiology of depression

L. Staner, F. Cornette, D. Osbild, C. Staner, C. Gilles, R. Luthringer. *FORENAP, Rouffach, France*

Objective: Dysfunctions of the central monoaminergic system have been implicated in the neurobiology of depression and since both serotonin and noradrenaline are involved in sleep regulation processes, it has been proposed that sleep EEG alterations observed during major depression could reveal these monoaminergic dysfunctions. In the present study, we investigate whether the effects of a serotonergic antidepressant (citalopram) on sleep EEG parameters could be differentiate from those of a noradrenergic antidepressant (reboxetine). These effects were compared relative to those of placebo and of a non antidepressant drug enhancing noradrenergic transmission (yohimbine).

Methods: 16 healthy male volunteers aged 27 +/-6.3 years were included in a double-blind placebo-controlled 4-way cross-over study including 4 sessions each separated by at least a 8-day wash-out period. Each subject received either citalopram 40mg, reboxetine 8mg, yohimbine 40mg or placebo. Difference from baseline values were analyzed on the per protocol set allowing for subjects, sequence, periods and treatment.

Results: The results of the present study demonstrated the dramatic effects of a single administration of citalopram or reboxetine on sleep -continuity, - architecture and -profile in comparison to those induced by yohimbine. Both antidepressant drugs displayed REM suppressing properties but differed in terms of their effects on wake propensity. The effects of yohimbine were modest and consisted of a sleep disrupting effect comparable to those of reboxetine but without influence on REM sleep.

Conclusion: The present results study bring some support to the idea that polysomnographic recordings could distinguish noradrenergic from serotonergic reuptake blocking properties of an antidepressant drug.

Tuesday, April 5, 2005

S-47. Symposium: Relationship between dose and response in trials of antidepressants

Chairperson(s): Per Bech (Hillerod, Denmark), Lars F. Gram (Odense C, Denmark)
08.30 - 10.00, Holiday Inn - Room 2

S-47-01

Pharmacokinetics and -dynamics in dose-response trials with antidepressants

L. F. Gram. *Univ. Southern Denmark IST, Clinical Pharmacology, Odense C, Denmark*

Objective: Dose-effect studies with antidepressants define, in groups of patients, the probabilty of a certain degree of therapeutic response and/or tolerability problems for different doses and duration of drug therapy. Such studies thus describe the inter patient variability and the therapeutic range of the drug.

Methods: Systematic reviews and a 5-dose study with clomipramine (DUAG 1999) have shown that for both tricyclic and SSRI antidepressants, the dose effect curves for therapeutic response and tolerability are flat and overlapping. High doses yield better response, but with higher risk of tolerabilty problems.

Results: The clomipramine study (DUAG 1999) suggested that all doses may be effective, but that high doses (125 - 200 mg/d) result in faster reponse than the low doses (25 - 50 mg/d). Genetic polymorphism and dose dependent kinetics for clomipramine enhanced the inter patient variation from a factor 8 for dose to a factor 100 for steady state blood concentrations (clomipramine + desmehtylclominpramine). However the correlations for dose versus rating score and concentration versus rating score were not significantly different (R(S) about - 0.25, p= 0.01 - 0,05).

Conclusion: In conclusion clinical dosing should be based on a judgement of the individual patient's need for rapid and effective cure against the importance of good tolerability. Dose is an important, but not the only determinant of the clinical effects of antidepressant drugs. However, for further studies on the other factors of importance including pharmacokinetics, the dose-effect study design remains essential.

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