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Contribution of Sleep Physiology to Depressive Pathophysiology

Erich Seifritz, M.D.

Among the best characterized neurobiological changes in mood disorders are specific alterations in electroencephalographic (EEG) sleep, including disinhibited rapid eye movement (REM) sleep and suppressed slow wave sleep. A strong link between mood disorders and sleep is that depressive symptoms are alleviated by one night of sleep deprivation and reoccur after sleeping. Sleep underlies homeostatic and circadian mechanisms that interact in complex ways. These relationships have been formalized in electrophysiological, neurochemical and neuroendocrinological models that extend to the pathophysiology of affective illness. Sleep research as a pathophysiological window to the brain has contributed extensively to the understanding of the neurobiology of depression and has been a substantial guide for the advancement of model-driven clinical and preclinical research. Pharmacological probes of normal and depressed sleep play an important role. It is anticipated that the combination of novel topographical EEG and neuroimaging techniques with traditional experimental methods will provide us with further insight into the neurobiology of sleep and depression.
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KEY WORDS: *EEG sleep; REM sleep; Slow wave sleep; Serotonin; Acetylcholine; Pharmacological probes; PET; fMRI*

Sleep disturbances are among the most prevalent clinical problems and physical signs of depression and are chiefly characterized by increased REM sleep (Benca et al. 1992) and reduced slow wave sleep measures. These changes are not specific for mood disorders, but they may be used for experimental studies probing sleep-regulatory mechanisms as a pathophysiological window to the brain (Gillin and Borbély 1985). The focus of this minireview is on studies examining the relationship between sleep, serotonin (5-HT) and acetylcholine, and their mutual interactions in depression.

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Aspects of Sleep Regulation

Sleep underlies both homeostatic and circadian factors interacting in complex ways that have been formalized in the 2-process model of sleep regulation (Borbély 1982). Neurochemically, some characteristics of the two processes are associated with interactions between aminergic and cholinergic neurotransmission (for review see Steriade and McCarley 1990) and the regulation of neuropeptides (Ehlers and Kupfer 1987) and other systems. The basic mechanisms unraveled in animals are at least partially paralleled in human studies combining EEG sleep with pharmacological probes. For instance, REM sleep is suppressed following systemic 5-HT_{1A} agonists (Gillin et al. 1994; Seifritz et al. 1996) and promoted following cholinergic agonists (Sitaram et al. 1976; Berger et al. 1985; Gillin et al. 1991b; Seifritz et al. 1998). Muscarinic receptor antagonists, on the other hand, partially suppress REM sleep (Gillin et al. 1991a), and the depletion of central serotonin enhances REM sleep (Bhatti et al. 1998; Moore et al. 1998, 2001; Voderholzer et al. 1998). In depression, it was found that cho-

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linergic REM induction was exaggerated as compared with healthy control subjects (Sitaram et al. 1980; Berger et al. 1989a,b; Gillin et al. 1991b) and suggested cholinergic supersensitivity associated with depression.

Cholinergic activation leads to a suppression of slow wave activity and to an enhancement of higher EEG frequencies during sleep (Berkowitz et al. 1990). This is consistent with the depolarization of thalamocortical cells after stimulation of cholinergic nuclei (Steriade et al. 1991) and corticothalamic 5-HT_2 receptors (McCormick and Wang 1991).

Antidepressant Action of Sleep Deprivation

Probably the most impressive link between mood disorders and sleep regulation is illustrated by the fact that depressive symptoms are acutely alleviated by one night of sleep deprivation and that the initial symptoms reoccur after one night of recovery sleep (Wu and Bunney 1990; Wirz-Justice and Van den Hoofdakker 1999) or even after microsleep episodes (Hemmeter et al. 1998). In terms of the 2-process model, the time-course of depressive symptoms parallels the time-course of delta sleep that is low after sleep and high after wakefulness. This relationship translates into an electrophysiological conception to understanding sleep deprivation's antidepressant properties (Borbély and Wirz-Justice 1982). It has also been postulated that the depressiogenic mechanisms during sleep are somehow related to REM sleep. This view has been supported by the finding that most antidepressants suppress REM sleep, and that suppression (Vogel et al. 1975) or displacement (Berger et al. 1997) of REM sleep relieves depressive symptoms.

The antidepressant effects of sleep deprivation are at least partially associated with modifications of 5-HT system function. In brief, sleep deprivation in laboratory animals enhances the turnover of 5-HT (Asikainen et al. 1995), increases the concentration of 5-hydroxyindoleacetic acid during recovery sleep (Borbély et al. 1980), increases the firing rate of serotonergic neurons in the DRN (Gardner et al. 1997), and downregulates 5-HT_{1A} somatodendritic autoreceptors (Prévot et al. 1996). The selective deprivation of REM sleep augments the behavioral response to serotonergic stimulation (Mogilnicka 1981), decreases the sensitivity of dorsal raphe nuclei (DRN) 5-HT_{1A} autoreceptors (Maudhuit et al. 1996), and modifies the activity of central monoamine oxidases (Thakkar and Mallick 1993). Whereas sleep deprivation modifies some measures of central 5-HT activity (Benedetti et al. 1997; Seifritz et al. 1997a) in healthy humans, the prolactin secretion upon 5-HT stimulation is enhanced after sleep deprivation (Salomon et al. 1994) and may predict clinical response to sleep deprivation (Kasper et al. 1988) in depressed patients. Sleep deprivation's efficacy may be amplified by 5-HT enhancing drugs (Wirz-Justice et al. 1976; Benedetti et al. 1997; Smeraldi et al. 1999) and appears to be related with a functional polymorphism within the promoter of the serotonin transporter gene (Benedetti et al. 1999). Interestingly, tryptophan depletion does not reverse sleep deprivation's antidepressant effects but rather prevents depressive relapse after one night of recovery sleep (Neumeister et al. 1998).

DISCUSSION

Sleep research has provided us with an impressing body of data linking basic neuroscience with pathophysiological concepts of the neurobiology of depression. The translational crosstalk between clinical and preclinical sleep research has stimulated fascinating progress in both fields. Many questions have been solved but many others remained open and warrant further research. For instance, whereas the earlier studies have consistently shown disinhibition of REM sleep in depression (Benca et al. 1992) more recent studies do not necessarily confirm these findings. Furthermore, studies using arecoline (e.g. Gillin et al. 1991b) or RS-86 (e.g. Berger et al. 1989a) as cholinergic probes demonstrated exaggerated REM induction in depressed patients and suggested muscarinic receptor supersensitivity, but studies using pilocarpine could not confirm these findings (Lauriello et al. 1993; Seifritz et al. 1998). It is of note that exaggerated REM induction was only shown in those studies in which the depressed patients had enhanced REM sleep parameters at baseline (Figure 1). A similar situation has been obtained for the 5-HT system: whereas evidence suggests that 5-HT_{1A} agonists such as ipsapirone produce differential neuroendocrine and temperature responses in depressed compared with normal subjects (Maes and Meltzer 1995), ipsapirone did not suppress REM sleep more in depressed patients than in normal control subjects (Gillin et al. 1996). Furthermore, some evidence even suggested opposite relationships and did not show intraindividual correlations between serotonergic REM suppression and cholinergic REM induction in depressed and healthy subjects (Seifritz et al. 1998). In the same vein, the initially reported REM enhancing effects (Moore et al. 1998) of serotonin depletion by means of a tryptophan-free amino acid challenge was not replicated in a second study carried out with virtually the same experimental parameters (Moore et al. 2001).

A fundamental problem of systemic pharmacological probes in human subjects, even with very specific receptor-selective drugs, is that it cannot be directly distinguished whether a drug's action is mediated by pre-, post-, auto-, or heteroceptors, or by a combination of them (e.g. Seifritz et al. 1997b). One promising lead in

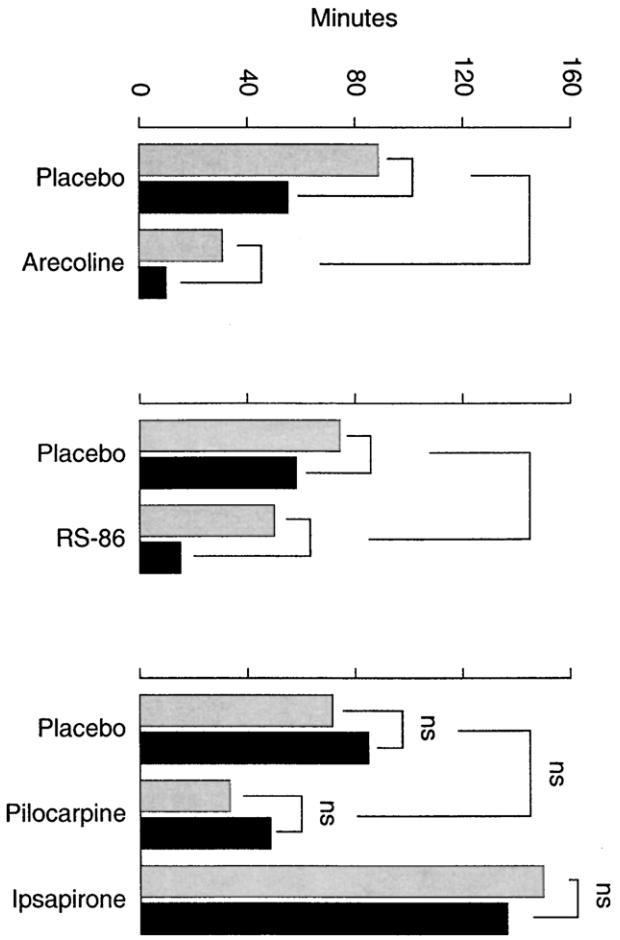

Figure 1. Effect of systemic cholinergic stimulation on REM latency in depressed patients and normal controls. Gray bars = healthy subjects, black bars = patients with major depression; * = $p < .05$, ns = not significant. Whereas the cholinergic drugs arecoline (Gillin et al. 1991b, top panel) and RS-86 (Berger et al. 1989b, middle panel) produced an exaggerated REM sleep induction in depressed patients compared with normal controls, the REM latency shortening induced by pilocarpine (Seifritz et al. 1998, bottom panel) was not different between patients and controls (note: in the study with arecoline, the latency from the first to the second REM sleep period was used). Interestingly, baseline REM latency (placebo) was not different in the pilocarpine study. There was also no difference in REM latency effects of the 5-HT_{1A} agonist ipsapirone in normal versus depressed subjects. Data are replotted with authors' permission.

depression research using sleep regulation as a model of the functional neuroanatomy of depression may in the application of topographic EEG and neuroimaging techniques combined with pharmacological probes.

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