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Neurophysiological Factors in Depression: New Perspectives*

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Summary. Within the last decade, the application of neurophysiological and neuroendocrine techniques has led directly to the identification of specific psychobiological correlates of depression. More recent efforts have attempted to establish linkages between mechanisms of action by antidepressants and such psychobiological factors. EEG sleep investigations, conducted with various antidepressants, have focused on the "specificity" of REM suppression or slow-wave sleep alterations. To date, results point to a greater commonality of action for REM suppression, lack of sedative effect as a necessary condition for clinical improvement, and the need for greater emphasis on slow-wave sleep research in relation to clinical recovery. The need for integrated theories of neurophysiological and neuroendocrine factors in depression is stressed.

Key words: Slow-wave sleep – REM sleep – Antidepressants – Biological rhythms

The major aim of this report is to indicate how the tools of sleep physiology and neuroendocrinology may be useful in understanding how antidepressants initiate their clinical effect. Such types of studies may also contribute to a more precise insight into the pathophysiology of depression itself. Initially, it was assumed that the effects of antidepressants on sleep would reflect specificity of action in which only certain types of neurotransmitter mechanisms would, for example, be involved in REM suppression or the sedative response of antidepressants. However, it appears that the sedative action on an antidepressant is not required for antidepressive efficacy (Kupfer et al. 1987). Second, that there appears to be a commonality of overall REM suppression regardless of which antidepressant is used, and, furthermore, the distribution of delta sleep through the night may also represent a common feature in the action of antidepressants. While one aspect of our current work has involved the examination of *acute* changes of antidepressants on sleep, more recently we have been actively involved in examining long-term recovery changes in specific groups of recurrent depressed patients. Prior to reviewing studies in these two treatment areas, we will briefly summarize the current consensus on EEG sleep correlates of depression.

At this time four major areas of consensus on the most characteristic EEG sleep changes in depression have emerged from clinical sleep research in the 1970s (Kupfer 1982). The majority of depressed patients demonstrate *hyposomnia* (a sleep continuity disturbance usually associated with increased wakefulness and frequent early morning awakening) (Fig. 1). A minority of depressed patients (15%–20%) shows hypersomnia, a feature usually associated with other psychophysiological phenomena such as anergia. Thus, nearly all depressed patients demonstrate a change in their sleep continuity. Second, considerable agreement has now emerged that a *reduction in slow-wave sleep* is found in depressed states, usually reported as a reduction or absence of manually scored stages 3 and 4 sleep. More recent data have demonstrated that delta wave sleep, as measured by computerized procedures, is lower in depressed patients than normals. First, in young adult and middle-aged depressives reduction both in the absolute number of EEG delta waves during non-REM (NREM) sleep and in the

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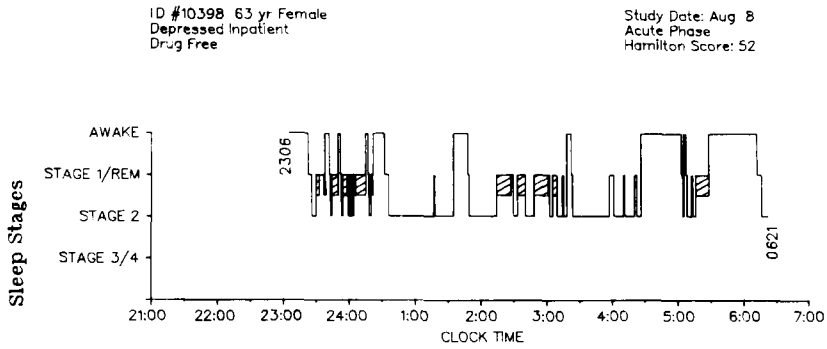

Fig. 1. Sleep patterns – EEG sleep stages of a patient with endogenous depression

rate of production of such delta wave activity occurs[1] (Kupfer et al. 1986b). While these reductions may be characteristic of all NREM periods during sleep, the most pronounced changes occur in the first NREM sleep period. Secondly, while nondepressed healthy controls show a linear decrease in the rate of production of slow-wave activity across consecutive NREM sleep periods, by contrast an altered temporal distribution of slow-wave activity is often evident in NREM sleep of major depressives. Depressed patients show a reduction in delta activity, particularly during the first NREM sleep period, compared with the second (Kupfer et al. 1986b; Reynolds et al. 1985a). Reduced slow-wave activity, particularly in the first NREM period, is also interesting in that the length of the first NREM period defines the shortened REM latency in the majority of patients with depressive illnesses, especially the endogenous forms (Rush et al. 1982). The two changes, redistribution of slow-wave activity from the first to the second NREM period and the increased rate of production of REMs in the first REM period, are relatively more specific to endogenous depression compared, for example, with Alzheimer's dementia (Reynolds et al. 1985b) and schizophrenia (Ganguli et al. 1987). The next finding (one that has become most prominent because of its considerable replicability and the relative ease with which it can be scored and interpreted) has been a *shortened interval to the first REM period.* While this finding is somewhat contingent upon the criteria used to determine sleep onset, in the majority of patients with clinically significant depression the REM latency (or first NREM sleep period) is shortened. The distribution of REM latency is determined by several independent but probably interactive factors including the age range of the sample studied, the severity of the depressive symptoms, length of episode, especially the early stages (Kupfer et al. 1988), and finally the subtype of depressive illness. Thus, very abbreviated REM sleep latencies (i.e., < 20 min) have been found in association with delusional depression (Thase et al. 1986; Coble et al. 1981), but also in association with elderly nondelusional depression (Reynolds et al. 1985b). Finally, a recent finding that has received considerable attention has been *REM sleep temporal distribution.* In addition to our contributions in this area, the work of Gillin et al. (1979) and Vogel (1981) has also demonstrated an abnormal distribution of REM sleep compared with both normal controls and patients suffering from other psychiatric illnesses or sleep disorders. While an increased amount of REM sleep in the first third to first half of the night is present, it is even more apparent that depressed patients show a marked increase in the total number of rapid eye movements. It may be that the most significant REM sleep alteration is a change in the REM density (concentration of eye movements) in the sleep of these depressed patients. With respect to REM sleep, the major change in depressive states may be the redistribution of REM activity in all age groups. However, only in older depressives is a predictable absolute increase in REM density and number of REM movements routinely found. These conclusions, based on the application of automated procedures which tend to be more precise than visual estimates, represent the areas of consensus among sleep investigators in both the United States and Europe.

Our current studies demonstrate that at least one (and usually more) of these abnormalities is found in 90% of all patients with major depressive disorder (Kupfer et al. 1982; Kupfer and Reynolds 1983). This constellation of changes is apparently distinct from that which is found in other kinds of insomnia, sleep deprivation, free-running conditions, and different psychiatric illnesses. As other disorders show only one or two of these abnormalities (e.g., narcolepsy is associated with a reduced REM latency), the constellation of changes is probably not a nonspecific effect mental illness, but must point in some way to pathogenetic changes in depression. How these constellations of sleep changes are altered by antidepressant

[1] Average delta wave count represents the number of slow waves per minute of NREM sleep

drugs, either in therapeutic dosages or in smaller doses as pharmacological probes, remains a key focus of our clinical research efforts.

The widespread efficacy of tricyclic antidepressants (TCAs) in the treatment of depression has stimulated increased investigative interest in the search for specificity of mechanism of drug action. While neurochemical and "receptor" studies have received most attention, researchers are also examining the immediate and long-term effects of TCAs on various neurophysiological systems. It has previously been suggested that in order to discriminate among potential neurochemical influences on EEG sleep, it is important to separate effects related to sedation (sleep continuity effects) from those related to REM sleep (Kupfer et al. 1987). Our own data support the notion that the sedative effects of antidepressants seem to be related to anticholinergic and serotonergic effects, especially anticholinergic effects. The action of amitriptyline, in contrast to that of zimelidine or desipramine, illustrates this point (Shipley et al. 1984, 1985). It is appealing to assume that the REM sleep abnormalities seen in depression are associated with decreased norepinephrine (NE) and increased acetylcholine (ACh). Therefore, the administration of drugs that either increase NE or decrease available ACh would alter the balance between these two neurotransmitter systems.

A second strategy of using EEG sleep investigations to understand the clinical recovery process in depression has been based on a prediction derived from Borbély's (1982) two-process model of sleep regulation. If the S-process (sleep propensity or ability) is indeed deficient in depression, then one would predict increased slow-wave sleep (SWS) following successful treatment with antidepressants, as shown by either total delta wave counts or average delta wave counts per minute of NREM sleep. Recovery from sleep deprivation has been shown to be associated with increased SWS in normals and a transient mood improvement in many depressed subjects (Van den Hoofdakker et al. 1986; Gillin and Borbély 1985). One would also predict that patients who respond to TCA treatment might show a greater change than nonresponders in these measures of SWS. In our investigations to date, however, we have found no evidence for dramatic changes in average delta sleep production during the first 4 weeks of an acute treatment trial for depression, although the temporal distribution of slow-wave activity was altered towards normal, with greater SWS intensity in the first NREM period (Kupfer et al. 1987).

As part of a major study on recurrent depression, we have had an opportunity to perform a pilot study on the sleep of ten depressed patients prior to treatment, during the first night of active drug treatment, and several *months* later in a continuation phase of treatment. These ten patients, with a mean age of 34 years, in the substudy all met criteria for recurrent major depression (Table 1). The seven females and three males showed a mean Hamilton depression rating of almost 19 prior to active treatment, but following several months of treatment had a Hamilton depression score of less than 5. The group had a mean age of onset of 26 years with a median number of 4 previous episodes. During continuation treatment, these patients were treated successfully with interpersonal psychotherapy and a stable dose of imipramine. All of them went on to enter the maintenance phase of the study.

Table 1. Clinical characteristics of ten patients

Sex	3 males; 7 females	
	Mean ± SD	Median
Age (years)	34.0 ± 10.5	31.5
Hamilton rating scale for depression at baseline	18.7 ± 3.9	17.5
Hamilton rating scale for depression at continuation	4.9 ± 3.0	3.5
Age of onset (years)	26.3 ± 11.7	20.5
Number of previous episodes	7.0 ± 6.1	4.0
Duration of index episode (weeks)	14.9 ± 10.3	10.5

Both manual and automated scoring of EEG sleep were performed in this group of patients at three points in their clinical course. With respect to sleep continuity measures (Table 2), there were no significant changes in sleep maintenance, time spent asleep, and only a trend toward an increase in sleep latency in the continuation phase. With respect to sleep architecture, only a significant increase in percent of stage 2 sleep was noted. No alterations in manually scored percent of stage 3 or 4 (delta) sleep were noted. Even though there was only one night's administration of imipramine, the average number of REM periods was significantly decreased by 50% from the baseline nights to the imipramine night (3.6 to 1.8) and remained reduced at 2.1 ± 0.9 REM periods at the continuation phase study. A rapid reduction in REM activity occurred with a single dose of imipramine which had recovered to some extent at continuation. Percent of REM time was reduced from 24% at baseline to 6% on the night of imipramine administration and recovered to 12% at continuation. REM latency increased in the group of patients from 74 min at the baseline nights to 173 min on the night of imipramine administration and remained extended at 164 min at continuation. The REM suppressant effect appeared to be present throughout the night and was reflected

Table 2. Manual sleep measures

	Baseline		50 mg IMI (I)	Continuation (C)	ANOVA *P*	A'posteriori results
	Night 1	Night 2[d]				
Sleep continuity						
Sleep latency[a]	16 ± 8	20 ± 14	14 ± 8	25 ± 11	0.04	NS
Awake (min)[a]	14 ± 13	34 ± 33	36 ± 34	25 ± 24	0.17	–
Time spent asleep (min)	394 ± 39	385 ± 34	384 ± 28	391 ± 49	0.91	–
Sleep efficiency (%)[b]	93 ± 3	88 ± 8	89 ± 7	89 ± 5	0.27	–
Sleep maintenance (%)[b]	97 ± 3	92 ± 7	92 ± 7	94 ± 5	0.16	–
Sleep architecture						
Stage 1 (%)[c]	3.8 ± 2.5	6.0 ± 3.0	6.2 ± 3.7	8.4 ± 6.3	0.08	–
Stage 2 (%)	65 ± 8	64 ± 8	80 ± 8	71 ± 8	< 0.0001	B < C < I $P < 0.05$
Delta (%)[c]	7.3 ± 8.7	5.8 ± 7.2	8.0 ± 8.1	8.4 ± 9.5	0.33	–
REM measures						
REM latency (min)[c]	70 ± 21	77 ± 37	173 ± 82	164 ± 83	0.0004	B < (C and I) $P < 0.01$
Percent REM[c]	24 ± 4	24 ± 4	6 ± 3	12 ± 5	< 0.0001	I < C < B $P < 0.01$
REM activity (units)[c]	119 ± 39	125 ± 38	23 ± 13	89 ± 44	< 0.0001	I < (B and C) $P < 0.01$
REM density (RA/RT)[c]	1.3 ± 0.4	1.4 ± 0.4	1.0 ± 0.3	1.9 ± 0.6	< 0.0001	I < B < C $P < 0.05$
REM intensity (RA/TSA)[c]	0.30 ± 0.09	0.32 ± 0.09	0.06 ± 0.04	0.24 ± 0.13	< 0.0001	I < (B and C) $P < 0.01$
Number of REM periods	3.7 ± 1.0	3.4 ± 0.9	1.8 ± 0.7	2.1 ± 0.9	< 0.0001	(I and C) < B $P < 0.01$

[a] Transformation used in ANOVA: ln (X + 1)
[b] Transformation used in ANOVA: ln (100 − X + 1)
[c] Transformation used in ANOVA: sqrt (X)
[d] B = average of the two baseline nights

even more in the second REM period than in the first REM period.

When automated REM measures were examined in this sample, the following changes were noted (Table 3). A significant decrease in average REM count throughout the night was found from 8.7 at the baseline nights to 5.6 on the night of imipramine administration, and the total number of REM movements for the entire night of sleep was reduced from 856 to 154 respectively. At continuation, the average REM count had increased significantly from the first drug night (11.7 ± 5.9), and the total REM count had recovered to 712 REM counts per night. With respect to automated measures in individual REM periods, the total number of rapid eye movements in the second REM period decreased from 272 at the baseline nights to 99 on the night of imipramine administration versus REM counts of 158 and 83, respectively, in the first REM period. This trend was also reflected in the average REM counts for the second REM period, which went from 9.5 at the baseline nights to 6.2 on the night of imipramine administration in the second REM period versus 5.7 to 4.6, respectively, in the first REM period.

Automated delta wave measures yielded the following findings (Table 3). Average delta wave count for the entire night increased nonsignificantly from 10.9 at the baseline nights to 12.6 counts/min of NREM sleep on the night of imipramine administration and was similar at continuation to 12.9. In contrast, the total number of delta counts throughout the night increased significantly from 3120 at the baseline nights to 4518 on the night of imipramine administration and only reduced to 3997 counts in the continuation phase. This increase in delta wave counts was reflected in the increase in total delta wave count of NREM1 acutely and maintained during the continuation period. With respect to the distribution of average delta counts, there were no significant differences in the first NREM period across the three time periods; however, major differences occurred in the second NREM period, where the average delta count was reduced from 14 at the baseline nights to 8.3 on the night of imipramine administration and subse-

Table 3. Automated sleep measures

Automated measures	Baseline		50 mg IMI (I)	Continuation (C)	ANOVA *P*	A'posteriori results
	Night 1	Night 2[c]				
Average REM counts whole night[a]	8.5 ± 3.4	8.8 ± 2.8	5.6 ± 3.2	11.7 ± 5.9	0.01	I < C, $P < 0.05$
Total REM counts whole night[b]	842 ± 316	870 ± 268	154 ± 93	712 ± 314	< 0.0001	I < (C and B) $P < 0.01$
Average REM counts in REM 1[a]	5.6 ± 3.3	5.8 ± 2.7	4.6 ± 3.5	11.2 ± 6.5	0.0094	C > (B and I) $P < 0.05$
Total REM counts in REM 1[b]	158 ± 183	155 ± 99	83 ± 84	350 ± 281	0.0054	I < C, $P < 0.01$
Average REM counts in REM 2[a] ($n = 3$)	9.9 ± 3.9	9.1 ± 3.9	6.2 ± 4.1	13.7 ± 10.0	0.24	–
Total REM counts in REM 2[b] ($n = 3$)	286 ± 150	258 ± 128	99 ± 45	410 ± 205	0.03	I < C, $P < 0.05$
Average delta counts whole night[a]	11.3 ± 5.8	10.5 ± 6.2	12.6 ± 6.9	12.9 ± 7.7	0.25	–
Total delta counts whole night[b]	3297 ± 1671	2943 ± 1736	4518 ± 2525	3997 ± 2240	0.0042	B < I, $P < 0.01$
Average delta counts in NREM 1[a]	17.1 ± 8.8	14.3 ± 9.6	19.2 ± 11.6	17.9 ± 11.7	0.17	–
Total delta counts in NREM 1[b]	1220 ± 666	1050 ± 758	3072 ± 2257	2844 ± 1806	< 0.0001	B < (C and I) $P < 0.01$
Average delta counts in NREM 2[a]	14.5 ± 9.1	13.4 ± 9.4	8.3 ± 5.8	7.4 ± 6.8	0.0069	C < B, $P < 0.05$
Total delta counts in NREM 2[b]	1182 ± 705	1184 ± 840	1291 ± 1026	1028 ± 1194	0.13	–

[a] Transformation used in ANOVA: sqrt (X)
[b] Transformation used in ANOVA: ln (X)
[c] B = average of the two baseline nights

Table 4. Means (standard deviations) for data at hourly segments past sleep onset ($n = 10$)

Average delta[a]	1 h	2 h	3 h	4 h
Baseline night 1	17.7 (12.1)	12.9 (9.1)	15.8 (10.0)	7.7 (5.6)
Baseline night 2	18.5 (9.4)	15.4 (9.1)	12.1 (7.9)	9.7 (6.4)
Imipramine night	24.3 (13.9)	19.5 (11.9)	15.9 (8.7)	7.8 (4.4)
Continuation night	18.5 (12.8)	20.8 (12.1)	12.6 (8.3)	8.8 (5.5)

[a] Analyses were run using the square root transformation

quently to 7.4 at continuation. Statistical analyses of the third REM and NREM periods were not carried out because of the reduction in the number of subjects who experienced a third REM-NREM period.

A second technique for examining automated delta wave measures involved analysis of the average delta by minutes after sleep onset. The first 240 min following sleep onset were examined during the three conditions using hourly determinations. As shown in Table 4, in each of the two baseline nights as well as the imipramine and continuation nights a substantial decrease in the average delta sleep occurred over the first 4 h. Utilizing an ANOVA analysis, it was determined that there was a significant change ($P < 0.005$) in the baseline condition versus the acute imipramine condition. This was not true when baseline nights were compared with continuation or the acute imipramine period was compared to the continuation period. In summary, there appeared to be primarily a linear decay in the delta wave sleep at the baseline or acute imipramine period, except at the time of continuation, in which curvilinearity was demonstrated.

Thus, the effects of imipramine on the EEG sleep of depressed patients are rapid and are consistent

with longer-term studies on imipramine which have been carried out for several months (Kupfer et al. 1986a). While the changes in sleep continuity may not be significant over a long period of time, the changes in sleep features with increases in stage 2 and decreases in REM sleep are pronounced and sustained. Specifically, the administration of imipramine is associated with an immediate prolongation of REM latency, reduction in the number of REM periods, and an increase in the total amount of delta wave counts, all of which persist as long as the drug is administered.

When SWS was examined in this investigation, the acute increase in the number and concentration of delta sleep waves in the patients was observed. In addition to an alteration in the distribution and "slope" of delta wave density with one night of administration, a significant increase in the *total* number of delta waves was present at this time. Not surprisingly, this increase in delta wave sleep was associated with a delay of REM onset and a prolonged first NREM/REM cycle. Since the time spent asleep did not change significantly, the increased delta wave count is not a function of increased sleep time. While this redistribution of delta wave sleep into the first 2 h after sleep onset persisted into the continuation phase 4 months later, no evidence of increased SWS density is present.

At this point, it is not yet known whether SWS density change is associated with clinical recovery (Beersma et al. 1986). Recently, Reynolds et al. (1987) demonstrated that the antidepressant action of sleep deprivation is correlated significantly with increases in SWS and improvement in sleep maintenance after sleep deprivation. This finding is in contrast with the results of Van den Hoofdakker and colleagues (1986). This entire issue has been reviewed extensively by Borbély (1987). Preliminary results suggest that antidepressants may not produce a simple linear increase in the average delta count and that antidepressant drugs may affect the SWS patterning differently than transient sleep deprivation. Further analysis, involving the time-course of the slope decay in SWS during various periods of antidepressant administration compared with baseline studies, is necessary to test the applicability of the two-process model of sleep regulation for integrating therapeutic/biological measurements in depression.

The results of our pilot study on imipramine suggest the following. An investigation of the acute effects of imipramine on the sleep of normals is warranted. Further, the acute delta wave effect should be replicated in a second sample of depressed patients. If this effect is present for imipramine, then the next question is whether the finding is generally true for other antidepressants. Finally, the question of whether the extent of increased delta wave count correlates with clinical response remains to be answered.

While this report is not intended to represent a comprehensive overview of sleep, biological rhythms, and affective disorders, the emphasis on SWS also points to the need for integrating data from other biological rhythms with data on SWS. Our own laboratory's recent endeavors in this area have focused on the relationship of selected neuroendocrine changes in depressed patients. Even though it is well accepted that both EEG sleep and neuroendocrine alterations are commonly found in affective disorders, most of the investigations published to date have focused on each area separately, rather than any detailed examination of their interrelationships.

Recently, we reported (Jarrett et al. 1988) that a single dose of imipramine was found to induce shifts of timing (in relation to sleep onset) of several neuroendocrine rhythms. After 50 mg imipramine was administered 60–90 min prior to sleep onset, growth hormone (GH) release occurred prior to sleep onset and the usual night-time cortisol rise time also commenced 80–90 min earlier than expected. The acute administration of imipramine apparently increased the level of dissociation between GH release and slow-wave sleep. Since these neuroendocrine changes occurred prior to any sleep-related effects, it suggests an "override" of the masking action of sleep onset on biological rhythms (Wehr and Goodwin 1983).

While several theories of biological rhythm dysregulation have been advanced, the data on imipramine's "timing" effects on all-night sleep EEG and night-time neuroendocrine rhythms may enable us to test more precisely such theories. Further application of the S-process hypothesis incorporating hypothalamic peptide modulation of EEG sleep in depression also represents an interesting heuristic direction (Ehlers and Kupfer 1987). This particular model is based upon the following empirical findings (Table 5). A considerable body of data on the first part of the night suggests that both SWS and growth hormone are decreased in depressed patients, that the nadir of nocturnal cortisol levels is blunted, and that REM sleep and REM activity distribution are shifted to the earlier hours of sleep. Ehlers and colleagues (1986) have demonstrated EEG effects following intracerebroventricular growth hormone releasing factor (GRF) administration to animals, suggesting that SWS changes may be stimulated by the GRF-GH axis. Further studies on possible alterations in growth hormone secretion would be valuable, especially since the mechanisms for the nocturnal release of growth hormone are probably different from growth hormone release during the day in response to a variety of metabolic

Table 5. CRF/GRF and the two-process model of sleep in depression

	Process S	Process C
Definition:	A sleep-dependent process that builds up during the day and is released at night	A sleep-independent circadian process
Sleep stage relationship	Slow wave sleep-related	REM sleep-related
Neuroendocrine relationship	GRF and/or GRF/CRF ratio	CRF-HPA axis
Alteration in depression	Deficient	Increased
Physiological consequences in depression	GH hyposecretion after sleep onset, decreased delta density, delayed sleep onset, lighter overall sleep pattern	Cortisol hypersecretion over 24-h period, increased REM activity and density

(Adapted from Ehlers and Kupfer 1987)

probes. Thus, our strategies are predicated on the assumption that growth hormone releasing factors may alter sleep EEG patterns and nocturnal growth hormone secretory activity.

As a testable hypothesis, we suggest that both neurohormones, corticotropin releasing factor (CRF) and GRF, may actively participate in the two processes with GRF representing the process S and CRF the process C. Thus, lowered levels of GRF would be seen as inducing a weakened or impaired slow-wave (delta) sleep generator. Growth hormone increases during the day may reflect the increased level of process S during the day in terms of "leakage" and, therefore, may lead to a decrease in process S during sleep time. The increased levels of CRF over the 24-h period would produce not only an elevated and a flattened appearance of the C process, but might also result in increased REM activity and REM density during the night. The CRF/GRF ratio may, in fact, reflect the strength of the S process.

The findings of our acute studies on imipramine suggest an apparent disassociation between growth hormone release and delta sleep (Jarrett et al. 1988). However, we have to realize that this disassociation may already be present prior to the administration of imipramine. Nevertheless, we feel that the onset of the pharmacological action of imipramine is correlated with the following immediate events: (1) growth hormone release is induced independent of sleep onset; (2) there is a delay in REM onset which facilitates increased delta sleep; and (3) the rise of cortisol is moved almost 90 min earlier in the night. This occurs despite the fact that there is no change in the cortisol nadir.

Based on new EEG sleep and neuroendocrine data (Kupfer and Frank 1988), we would now like to further extend this hypothetical model. We would suggest that processes S and C may be affected differentially by antidepressant treatment. Process C, which includes REM sleep, the cortisol releasing factor/hypothalamic pituitary adrenal axis, as well as temperature rhythms and physical activity rhythms, may be affected more rapidly by antidepressant treatment and could change significantly within days or several weeks of acute treatment. The C process may be associated with the initial redistribution of REM/NREM sleep and changes in REM/NREM cycles, especially in the first half of the night. We have recently suggested that the early phase of a depressive episode is more associated with REM sleep changes, such as increased REM sleep percent and REM activity, than in the later phase of the same episode (Kupfer et al. 1988). In contrast, process S may represent a process slow to recover, if at all, during an episode of depression.

This extended model may integrate data that deal with acute pharmacological, the concept of biological scarring and a persistence of biological stigmata. The advantages of studies using this extended model are several-fold: (1) it provides additional experimental tools to test the hypothesis, so that neuropeptide challenge strategies on sleep EEG may be employed; (2) it facilitates the examination of interactions among various biological rhythms; and (3) the application of the model provides an opportunity to make specific predictions concerning the level of dissociation among selected biological rhythms in the depressive state and in the state of clinical recovery.

Since we would assert sleep and neuroendocrine measures are tied into the sleep-wake cycle, we propose that a potential application may be their use as long-term indicators of relapse and perhaps as predictors of new episodes in depressed patients. Evidence is accumulating to support the concept that shifts occur in the normal cycle of both the sleep and neuroendocrine rhythms and that these disturbances may persist following clinical recovery from the illness. Furthermore, such abnormalities may serve as trait characteristics for the illness and thereby signify a level of vulnerability. Indeed, further research may ultimately establish the prognostic value of longitudinally following these measures in remitted recurrent

depressives. The advantage of studying sleep-endocrine interactions is that they both represent circadian rhythm disturbances which may, in turn, be related to changes in neurotransmitter and receptor activity in affective disorders.

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