a relapse occurs, repeating sleep deprivation and treatment with a thymoleptic
drug can usually bring about a remission.
7. The effectiveness of sleep deprivation is of use also in making a
differential diagnosis as it suggests endogenous depression.
8. Lastly one should point out that the very impressive change in the
clinical symptoms and signs which can be observed and measured during
the course of 24 hours, are a particularly suitable subject for research,
both neurophysiological and biochemical, aimed at widening our understanding
of the nature of depression.

Sleep: Physiology, Biochemistry, Psychology, Pharmacology, Clinical Implications.

The Effect of REM Deprivation on Depression

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Introduction

Our pilot work in this area consisted of uncontrolled ‘non-blind’
studies of the hypothesis that the symptoms of depression will be relieved
by increased rapid eye movement (REM) pressure produced by REM sleep
depression via awakenings [Vogel et al., 1968; Vogel and Traub, 1968a].
We defined increased REM pressure to be present during administration of
an agent which decreases REM sleep, such that following withdrawal of
the REM decreasing agent there is more REM sleep than before its administration.
For example, monoamine oxidase (MAO) inhibitors [Wyatt et al,
1971; Akindele et al, 1970; Wyatt et al., 1969]; tricyclic antidepressants,
[Hartmann, 1968c; Lewis and Oswald, 1969] and REM deprivation by
awakenings at the start of each REM period [Dement, 1960] increase
REM pressure. Our pilot uncontrolled studies found that during REM
depression by awakenings 5 of 8 moderate to severely depressed, hospitalized
patients improved markedly, 1 patient improved slightly, 2

1 This study was aided by Federal Grant No. ROI MH18391.

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patients did not improve. The patients with little or no improvement had little or no build-up of REM pressure in response to REM deprivation; i.e., little or no REM rebound despite 10-14 consecutive nights of REM deprivation by awakenings alone. For this reason we hypothesized that increased REM pressure rather than REM deprivation was the depression-relieving variable. In contrast to our previous uncontrolled studies, the present preliminary report concerns a double-blind controlled study of our hypothesis. The results concern 24 hospitalized patients with a minimum Hamilton depression score of 25; i.e., with moderate and severe depressive syndromes which occurred in the absence of schizophrenia, organic brain disease or drug abuse.

Method

We classified the depressed patients into two main classes: endogenous or reactive depression by the independent assessment of two psychiatrists. The criteria for endogenous or reactive depression were taken from recent factor analytic studies of depression (Kiloh and Garside, 1963; Rosenthal and Klerman, 1966; Mendels and Cochrane, 1968). In these studies, compared with reactive depressions, endogenous depressions tend to have the following cluster of symptoms: age older than 40 years; precipitant absent or precipitant insufficient to account for depth of depression; lack of reactivity of depression to environmental changes; severe depression (more than 4 on a 7-point global scale); psychomotor retardation; obsessional rather than hysterical premorbid personality; feelings of guilt and remorse rather than of self-pity; middle-of-the-night and early morning insomnia rather than sleep-onset insomnia; visceral symptoms; weight loss of 7 lb or more. When patients had symptoms of each syndrome, we weighed the factors of reactivity to environmental change, obvious precipitant, psychomotor retardation and severity of depression more heavily than the others. Surprisingly, independent agreement on diagnosis occurred in 23 of the 24 cases.

Patients were hospitalized in a private room on a psychiatric inpatient unit. At the time of hospitalization all previous medications were stopped, and no drugs were given during the study other than occasional bedtime chloral hydrate for insomnia, usually 500-1,000 mg; or occasional chlorpromazine, usually 25-75 mg/day for agitation. The patients were observed clinically and their uninterrupted sleep monitored from their rooms by conventional recordings for 6-10 consecutive baseline (B) nights. During the B period patients were randomly assigned to experimental (X) or control (Ç) groups. Following the B period the experimental patients were REM-deprived by awakening them at the onset of each REM period by calling them by name on an intercom and keeping them awake by EEG criteria for three consecutive minutes. REM deprivation was performed on consecutive nights until the patient reached 30 awakenings in a single night or until 6 consecutive nights of REM deprivation, whichever came first. Patients then had a single night of uninterrupted sleep. On the next night the same sequence beginning with
REM deprivation was repeated and this was done continuously for several weeks until discharge from the study. Over the first three weeks of increased REM pressure the average patient had a night of uninterrupted sleep every 4.14 nights. Thus, by allowing an occasional night of uninterrupted sleep, the procedure kept the number of awakenings from becoming inordinately great while it simultaneously permitted sustained periods of several weeks of increased REM pressure. The average patient had increased REM pressure for 5.6 weeks with a range of 2.1-13.6 weeks.

C patients were awakened from NREM sleep instead of REM sleep. Each C patient was matched with an X patient in the same depressive group (endogenous or reactive), awakened the same number of times on each ordinal night as his experimental match and given the same intermittent night of uninterrupted sleep. Awakenings in C patients were made immediately after the end of REM periods. This was done [1] to minimize any reduction of REM sleep from the awakenings, and [2] since REM deprivation awakenings tend to cluster about the time of REM periods, this was done to make X and C groups somewhat equivalent in temporal distribution of awakenings over the night. The first C patient had 13 consecutive C nights following the B period. Thereafter, all C patients had 21 consecutive C nights following the B period. Thus, X and C groups were to be compared at the end of this 21-day post-B period. In addition, after the 21-day C period, a cross-over design was used so that the C patients were REM-deprived like the X patients. Thus, for each control patient we were able to compare the response of his depression to NREM awakenings with his later response to REM deprivation.

Patients were evaluated by several tests every Monday, Wednesday and Friday. Both patients and testers (with the exception of testers for the psychomotor speed) were ignorant of the identity of the X and C group members. Tests were given in the morning to avoid the confusion of diurnal mood change. The tests were the Hamilton depression rating scale and a 7-point global disability scale, both administered by the psychiatrists for the first 9 patients and, thereafter, the global scale was administered by the psychiatrist and the Hamilton scale by two trained people working without knowledge of the other’s results; the Zung self-rating depression scale (which we now administer only once each week), and certain tests of psychomotor speed, attention and concentration administered by the sleep laboratory technicians (viz., the digit symbol and digit span subtests of the WAIS and a letter cancellation test (LCT). About 60% of our unlabeled, coded sleep recordings of 1,530 nights have been scored and tabulated. Mean REM percent on B = 24%; on experimental deprivation (XD) = 8.3%; on experimental recovery (XR) = 37.0%; on control deprivation (CD) = 28.2%; and on control recovery (CR) = 28.0%. B vs. XD, B vs. XR, XD vs. CD and XR vs. CR differences are significant at p 0.01, and B vs. CD differences are nonsignificant at p 0.2 level. The results will be reported in terms of the Hamilton depression scale. We measured the test intercorrelations for the first 19 patients and found the scores on the Hamilton correlated significantly by rank
order correlation with the global, WAIS and LCT for the endogenous depressive, and with Global, Zung and LCT for the reactive depressives. 40 patients have entered the project. 10 left during B: 3 because of improvement; 3 because of change in diagnosis, and 4 because on reconsideration they refused awakenings. Three patients left during C awakenings and 3 patients are in progress. Incidentally, please note that no patients left or became schizophrenic during REM awakenings. Thus, the results of this report concern the 24 patients (12 endogenous and 12 reactive) who have completed the study.

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Results

In the endogenous group (7 X and 5 C) by the end of the first 21 post-B days, the mean X Hamilton decreased from 46.5 to 29.8 (35.3% decrease) while the mean C Hamilton was unchanged (46.4 to 47.4 %). Thus, the endogenous X patients had a 35-percent decrease in mean percent Hamilton while the endogenous C patients had no change. This X-C difference in percent Hamilton change was significant at the 0.001-level (Mann Whitney U - one-tailed, when U = 0). In terms of individuals, 5 of the 7 X patients improved substantially while none of the 5 C patients improved. Three of the 5 C patients then improved with the cross-over REM awakenings over the next three weeks, two substantially and one mildly. Thus, during the initial three weeks of REM deprivation 7 of 12 endogenous depressives improved substantially (mean Hamilton from 45.2 to 28.7 - a 36.6-percent decrease) and two patients improved mildly with a 15-percent Hamilton decrease. After the first three weeks of increased REM pressure, REM deprivation was continued as before, either until improvement sufficient for hospital discharge or until, after a total of 4-6 weeks of increased REM pressure, it became obvious that no change was occurring. With the prolonged increased REM pressure 3 patients did not improve, one relapsed, one showed mild improvement (20% Hamilton decrease), and 7 had a progressive improvement to hospital discharge (mean Hamilton 12.3 in a mean of 5.9 weeks after the start of REM deprivation). After discharge, without antidepressant drugs, the 7 patients either maintained or increased their improvements. It should be noted that consistent sustained improvement in all of the endogenous depressive patients began at about 2.5 to 3.5 weeks after sustained elevations of REM pressure. This, of course, is quite consistent with the timing of improvement on administration of tricyclics and of MAO inhibitors. Three of the four unimproved endogenous depressives, after the failure of REM deprivation, were treated with imipramine in large doses for more than one month and again failed to improve. All four were treated with ECT and three improved satisfactorily for hospital
discharge, while the fourth, still in treatment, is improving with electroconvulsive therapy (ECT).

In the reactive group (8 X and 4 C) by the end of the first 21 post-B days the mean Hamilton decreased from 31.7 to 25.6% (a 19-percent decrease), while the mean C Hamilton decreased from 36.1 to 26.9% (a 25-percent decrease). The smaller decrease in the mean X Hamilton reflected the fact that two of the 8 X reactives became worse during the

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first 21 days on increased REM pressure, while none of the controls became worse. Otherwise, in terms of individuals, there was substantial improvement (Hamilton decreased 30% or more) in 4 of 8 X and in 1 of 4 C; moderate improvement (Hamilton decreased 20-29%) in 1 X and 1 C; and little or no improvement in 2 C. In the first three weeks of the crossover from C awakenings to increased REM pressure, the two previously unimproved C had substantial improvement. Thus, in the first three weeks of increased REM pressure of 12 reactive depressives 9 had moderate to substantial improvement, one had no change, and 2 got worse. With REM deprivation after the first three weeks of increased REM pressure, 8 of 12 reactive patients improved sufficiently for hospital discharge (mean Hamilton from 35.2 to 14.9, a 56% change). After a 4-week mean of increased REM pressure, one improved moderately, one patient remained worse, and 2 patients were unchanged from the B. We have post-discharge follow-up on 6 of the C discharged patients. Two have been rehospitalized and the other 4 have had a variable but usually improved course without antidepressant drugs.

Conclusion

We conclude that these results give preliminary support to the hypothesis that deprivation of REM sleep relieves the symptoms of endogenous depression, and perhaps of some reactive depressions. We suggest that REM pressure may be the mechanism of action of the major antidepressant drugs.

Summary

This study is a preliminary double-blind test of the hypothesis that deprivation of REM sleep will relieve the symptoms of moderate to severe depression. X patients were REM-deprived, by awakenings alone, usually for 3-6 weeks, with an intermittent night of uninterrupted sleep usually every fourth night. C patients were awakened from NREM sleep. The results were that in 12 endogenous depressives, X improved significantly more
than C who did not change, while in 12 reactive depressives there was no difference between mean X and C values, although some X patients had substantial improvement.

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