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Sleep deprivation hastens the antidepressant action of fluoxetine

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Abstract Among ten bipolar depressed patients admitted to our psychiatric ward, five patients were treated with fluoxetine alone and five subjects were treated with fluoxetine in association with total sleep deprivation (TSD) in order to evaluate the effect of the interaction between the administration of the serotonergic antidepressant compound fluoxetine and repeated cycles of TSD. Patients treated with fluoxetine plus repeated TSD showed a faster amelioration of depressive symptomatology compared with the other group. We discuss our findings hypothesizing an enhancement in dopaminergic and possibly in serotonergic transmission due to repeated TSD adding to the increase in serotonergic transmission due to fluoxetine medication.

Key words Sleep deprivation · Fluoxetine · Depression
Dopamine · Serotonin

Introduction

The purpose of the present study was to evaluate the interaction between serial repetition of total sleep deprivation (TSD) and the administration of the antidepressant drug fluoxetine in the treatment of acute episodes of major depression in patients affected by bipolar disorder.

Total sleep deprivation is known to be a powerful antidepressant treatment for patients affected by mood disorders: It acts rapidly and with a response rate of nearly 60% (e.g., Wehr 1990), but the abrupt mood improvement is followed by an early relapse into depressive symptomatology (e.g., Wu and Bunney 1990).

Potentially useful clinical applications of sleep deprivation come from its association with other chronotherapeutic treatments, such as bright-light therapy (e.g., Neumeister et al. 1996) and sleep-phase advancement (e.g., Berger et al. 1995; Riemann et al. 1995; Riemann et al. 1996), and from its association with antidepressant drugs, at the beginning of treatment, in order to hasten the onset of action of the medication. Taken together, the available results on this subject are promising (Leibenluft and Wehr 1992), but the effect of the combined treatment seems to depend on the kind of administered drug: Positive interactions have been reported with lithium, nortryptiline, clomipramine, desipramine, and amitriptyline (e.g., Elsenga and Van den Hoofdakker 1983; Baxter et al. 1986; Shelton and Loosen 1993; Szuba et al. 1994; Kuhs et al. 1996), whereas a negative interaction has been observed with trimipramine and amineptine (Holsboer-Trachsler et al. 1994; Benedetti et al., in press).

Fluoxetine is a selective serotonine reuptake inhibitor which has been proved to be an effective antidepressant treatment with an onset of action of approximately 3–4 weeks (Montgomery 1989).

Partial sleep deprivation has been successfully associated with fluoxetine treatment in outpatients who remained chronically depressed despite being on medication with fluoxetine alone for at least 3 months (Leibenluft et al. 1993). We investigated the possible positive interaction of repeated TSD cycles and fluoxetine drug treatment in acutely depressed patients.

Subjects and methods

Because a major problem in previous studies on the effect of sleep deprivation was diagnostic heterogeneity (Leibenluft and Wehr 1992), and high response rates to sleep deprivation have been reported in bipolar-I patients (Szuba et al. 1991), the study was conducted on a homogeneous group of bipolar depressed patients. The sample included 10 subjects consecutively admitted to our Research Center for Mood Disorders for a major depressive episode, according to DSM-III-R criteria. Axis-I diagnosis was bipolar disorder, depressed. All subjects were free of any psychotropic medication for at least 1 week before the admission. An informed consent was obtained from each subject.

At the outset of the study, patients were enrolled and randomly assigned to the two treatment groups. Beginning from day 1, the

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Table 1 Clinical and demographic characteristics of the subjects. *HDRS* Hamilton Depression Rating scale

Variable	Group 1 ($n = 5$)[a]	Group 2 ($n = 5$)[b]
Gender		
Age (years)	40.0 ± 12.1	42.0 ± 9.7
Age at onset (years)	29.2 ± 11.5	27.0 ± 5.9
Duration of illness (years)	16.8 ± 12.3	15.0 ± 10.0
Duration of current episode (weeks)	7.8 ± 4.3	9.4 ± 4.9
HDRS score at outset	25.2 ± 3.6	26.2 ± 8.5

NOTE: Values are means ± standard deviations. No difference between the two groups is statistically significant (Student's *t*-test, two tailed $p > 0.10$ for all comparisons)
[a] Two males and three females
[b] One male and four females

dosing schedule of drug for all subjects was fluoxetine 20 mg o.d. (given per os at 8 a.m.).

Group-1 subjects ($n = 5$) were administered three TSD cycles composed of a night of TSD followed by a recovery night. On days 6, 8, and 10 patients were totally sleep deprived and had to stay awake for 36 h (from 7 a.m. until 7 p.m.) of the following day. They were then allowed to sleep during the nights of days 7, 9, and 11. Compliance of the subjects with the TSD procedure was ensured by nursing staff. The TSD treatment was started 6 days after the beginning of fluoxetine treatment because of the delay to reach the steady state, which has been reported to vary between 5 and 15 days (Altamura and Montgomery 1990).

Group-2 subjects ($n = 5$) received the same drug treatment as group-1 subjects, but were not sleep deprived. Clinical and demographic characteristics of the sample, divided according to the two therapy groups, are summarized in Table 1. No difference between the two groups was statistically significant (Student's *t*-test, two tailed, $p > 0.05$ for all comparisons).

Severity of depression and mood change were assessed on the mornings of the outset, days 7, 14, 21, and 28 by external raters who were blind to the experimental conditions, with the Hamilton Depression Rating scale (HDRS; Hamilton 1960). Levene's test of homogeneity of variances was performed on HDRS scores at day 0. Mean scores of the two groups at the same day were compared through Student's *t*-test. To assess the clinical effects of the treatment, a two-way repeated measures analysis of variance (ANOVA) was performed on HDRS scores from the outset to day 28, with Fisher's test of least significant difference (LSD) as the post hoc range test.

Results

Mean HDRS scores of the two groups are plotted in Fig. 1. Homogeneity of variances at the outset was successfully tested (Levene's test; $F = 1.88$, df 1,8, $p = 0.21$); the mean HDRS scores of the two groups did not significantly differ (Student's $t = 0.24$, df 8, two-tailed test $p = 0.81$).

Repeated-measures ANOVA performed on HDRS scores showed a significant time effect ($F = 20.23$, df 4,32, $p < 0.0001$), a nonsignificant group effect ($F = 0.42$, df 1,8, $p = 0.58$), and a nonsignificant time × group interaction ($F = 0.86$, df 4,32, $p = 0.49$).

The LSD test showed that the two groups significantly differed at day 7 ($p = 0.016$) and at day 14 ($p = 0.044$) with group-1 subjects having significantly lower HDRS scores than group-2 subjects in both comparisons (see Fig. 1). The HDRS scores at days 21 and 28 were not significantly different.

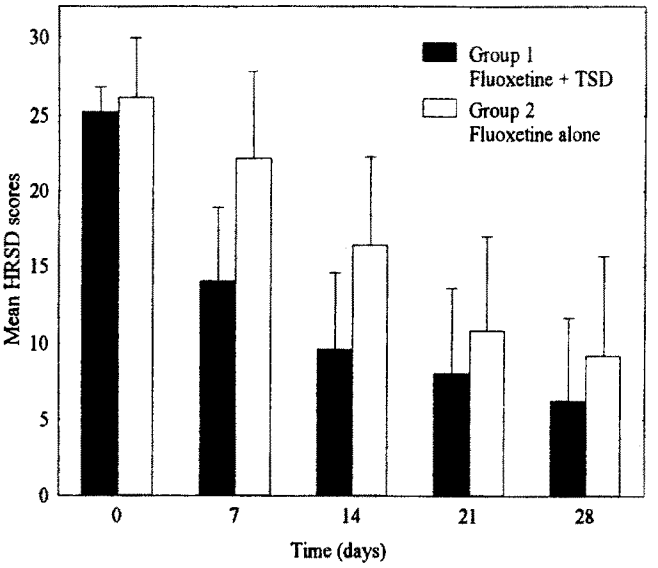

Fig. 1 Mean Hamilton Depression Rating scale (HDRS) scores and standard errors in the two groups. Scores are significantly different at days 7 and 14 (Fisher's least significant difference test; see text for details)

Discussion

In our experimental conditions, the association of repeated TSD cycles with fluoxetine antidepressant treatment resulted in a faster reduction in depressive symptomatology in acutely depressed bipolar patients. At days 7 and 14 the mean HDRS scores of sleep-deprived patients fell to 55.6 and 38.0%, respectively, of their basal levels, whereas in patients treated with fluoxetine alone, they slowly decreased to 84.7 and 62.6%, respectively, of the baseline. The previous association of TSD had no effects on the overall course of the episode: HDRS scores of the two groups did not significantly differ after 3 and 4 weeks of treatment, and repeated-measures ANOVA confirmed the absence of significant time × group interactions. Although these results must be considered preliminary because of the small sample size, they suggest that repeated cycles of TSD may be a useful tool to decrease the intensity of depressive symptomatology at the beginning of the antidepressant drug treatment.

The neurochemical mechanism by which TSD may potentiate the action of fluoxetine needs further research to be explained. Little is known about the mechanism of the antidepressant action of TSD (Kuhs and Tolle 1991), and several hypotheses have been proposed (e.g., Vogel et al. 1980; Wu and Bunney 1990; Haug 1992; Bouhuys et al. 1995). Recent findings suggest an involvement of the brain dopaminergic system, with a strong enhancement of the activity of the brain dopaminergic pathways during sleep loss (e.g., Zwicker and Calil 1986; Fratta et al. 1987; Kasper et al. 1988; Lauterbach 1994). Several reports sug-

gest that changes in dopaminergic function seem to be related to the antidepressant effect of TSD (Ebert and Kaschka 1995): Plasma levels of prolactin, a hormone which is known to be inhibited by dopamine agonists, decrease after TSD (Kasper et al. 1988; Baumgartner et al. 1990), and the prolactin response to sulpiride is different in TSD responders and nonresponders (Ebert et al. 1993); lower levels of homovanillic acid in the spinal fluid before TSD have been associated with a greater antidepressant response (Gerner et al. 1979); and single-photon-emission computerized tomography before and after TSD showed a significantly different D_2 receptor occupancy in responders and nonresponders, thus suggesting an enhanced dopamine release in responders (Ebert et al. 1994). Moreover, preclinical studies show an enhancement in serotonergic transmission following sleep deprivation (e.g., Wesemann et al. 1983; Asikainen et al. 1995), and the involvement of serotonergic transmission in the clinical effect of TSD has been preliminarily evaluated (Blier et al. 1987; Salomon et al. 1994).

It is hypothesizable that an enhancement in dopaminergic transmission and possibly in serotonergic transmission due to repeated TSD, adding to the increase in serotonergic transmission due to fluoxetine medication, could have produced a faster antidepressant effect; the fast amelioration could then have been maintained by fluoxetine drug treatment alone. In this respect it should be noted that our subjects were bipolar-I patients, which have been reported to show higher response rates to sleep deprivation (Szuba et al. 1991), possibly because of the similarities between the mechanism of the antidepressant action of sleep deprivation and the onset of mania (e.g., Wehr 1987). Ongoing research of the interplay between dopaminergic and serotonergic systems (e.g., Ferre 1994), of the interaction between sleep deprivation and dopaminergic drugs (e.g., Benedetti et al., in press), and of the effect of sleep deprivation on brain serotonergic activity (e.g., Salomon et al. 1994) will help clarify this point.

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