Are REM-Sleep Abnormalities in Depression more than an Epiphenomenon?


Introduction

Although shortened REM latency as an expression of REM sleep disinhibition at the beginning of the night is one of the most robust biological findings in major depressive disorders, it has not been clarified whether it is more than an epiphenomenon. Some recent findings contradict the assumption that shortened REM latencies are specific markers for primary or endogenous depression. For example, such abnormalities also occur in neurotic or situational depression (1, 2) and additionally in experimental manipulations like reduced behaviour activity in normal subjects (3). On the other hand, there are some arguments supporting the pathogenetic relevance and specificity of REM latency shortenings in depression, especially the results of the arecoline REM-induction-test (RIT) of Gillin and Sitaram (4, 5). They found that the direct muscarinic agonist arecoline, infused during the second non-REM period, could provoke a significantly more rapid onset of the following REM period in acutely depressed and in remitted depressed patients compared with healthy controls. As this increased susceptibility of the REM sleep regulating system to a cholinergic stimulus also occurred in a state of psychic wellbeing, this was regarded as state independent, i.e. trait-marker for depression. Assuming that REM latency is inversely related to the ratio of cholinergic to aminergic central nervous transmitter activities — the reciprocal interaction model postulated by Hobson et al. (6, 7) —, the authors interpreted these data as supporting the cholinergic/aminergic imbalance hypothesis of affective disorders (8). They additionally stated that depression seems to be associated with a trait-related muscarinic supersensitivity and a state-related aminergic deficiency.

This hypothesis, however, is still limited by the fact that the arecoline-RIT has not been tested in a larger sample of patients with different non-depressive psychiatric disorders. Furthermore, the procedure of the arecoline-RIT acts on the length of the second non-REM period, although in depression it is the first non-REM period that is shortened. Arecoline has also some marked experimental disadvantages that may confound results: arecoline causes unpleasant peripheral side-effects, making the i.m. administration of a peripheral antidote like methscopolamine necessary. It has only a very short half-life of maximally 30 minutes and must therefore be applied during sleep by infusion. Both these experimental aspects may lead to possible sleep disturbing effects.

Therefore the introduction of RS 86 in sleep research by Spiegel (9) seems to provide a more adequate tool for testing the cholinergic hypothesis of REM sleep abnormalities in affective disorders. The spiropiperidyl derivate RS 86, which passes the blood-brain barrier, is a direct, orally acting muscarinic agonist with a half-life of about eight hours. As it causes only minor peripheral side-effects, a peripheral antidote such as methscopolamine is unnecessary. It has already been demonstrated that RS 86 stimulates REM sleep in healthy controls of both sexes and different ages (9, 10).
We therefore investigated whether the RIT with RS 86 supports the results of the arecoline-RIT, that means reveals an increased sensitivity also of the first REM period to this cholinergic stimulus in acute and remitted depressives in comparison with healthy controls. Additionally, we focused on the question, whether non-depressive psychiatric disorders can be differentiated from depressives by the RS 86-RIT, i.e., whether an abnormal RS 86-RIT is specific for depression.

Study Design

We studied 16 patients with a major depressive disorder (DSM III), six men, ten women, mean age 38 ± 14 years, with a mean 21-item Hamilton-scale score of 28 ± 6 and compared them with 16 age-and gender-matched healthy controls.

Nine patients, three men and six women, aged 37 ± 14 years, were studied in a complete state of remission. They had suffered from a major depressive disorder at least half a year ago. Their 21-item Hamilton-scale score was zero.

Additionally we investigated 20 patients, eight men and 12 women, mean age 24 ± 5 years with other psychiatric disorders like anorexia nervosa (N = 6), bulimia (N = 6) obsessive compulsive disorder (N = 1), somatization disorder (N = 1), and personality disorders (N = 6).

All subjects were drug-free for at least one week, the remitted depressives for at least four months.

The RS 86-RIT was preceded by an adaptation night in the sleep lab. In depressed patients one placebo night preceded the night with the RS 86 application. In all other subjects the adaptation night was followed randomly either by the placebo night or the RS 86-RIT-night. All subjects were blind to the placebo-drug-regime. The subjects were given RS 86 in capsule form at 10.00 p.m. Polysomnographies were performed between 11.15 p.m. and 6.30 a.m.

Results

As shown in Fig. 1 RS 86 led to a highly significant shortening of the first non-REM period in the 16 depressives from 65.4 to 15.8 minutes. The REM sleep shortening effect was much more pronounced than in the 16 healthy controls. In this group REM latency, however, was also reduced significantly from 74.1 to 50.0 min. The REM sleep cumulation curve revealed this REM sleep provoking effect to be limited to the beginning of the night, although RS 86 has a half-life of about eight hours. Slow-wave sleep was not significantly decreased by RS 86 in depressives, but was reduced significantly in healthy subjects (p < 0.05). In remitted depressives, however, RS 86 only caused a nonsignificant shortening of REM latency from 73.7 to 64.6 min. Only two patients exhibited a REM latency shorter than 25 min whereas the acutely depressed patients exhibited REM latencies ≤ 25 min in 14 out of 16 cases after RS 86.

In the 20 psychiatric patients with non-depressive disorders (Fig. 2) the effect of RS 86 was very similar to that in healthy subjects, both in the patients with eating disorders as well as in the group of other psychiatric diseases. Regarding the whole patient sample there was a significant reduction of REM sleep latency, which however was significantly less pronounced than in acutely depressed patients.

Discussion

Our results support the data of Gillin and Sitaram (4, 5) regarding the increased susceptibility of the REM sleep system to a cholinergic stimulus in depression. The RS 86-RIT, however gave
Age-and gender-matched Depressives (N = 16)
Healthy Controls (N = 16)

Depressives (N = 16)
Remitted Depressives (N = 9)

Fig. 1: REM latencies of 16 depressed patients and 16 age- and gender-matched healthy controls and of 9 patients completely remitted from a major depressive disorder. Arrows mark medians.
no hint that such a hypersensitivity persists during remission. That means the present data are in agreement with the assumption of a state- but not of a trait-marker. The investigations in non-depressed psychiatric patients seem to prove the specificity of an abnormal RIT for depression. Especially patients with eating disorders did not show a supersensitivity of the REM-sleep system to a cholinergic stimulus. It has to be mentioned, however, that those 20 patients were not age- and gender-matched with the depressives and that for example schizophrenic or schizoaffective patients were not included in the sample.

Our data support the assumption that during depression there is a disturbance in the regulation of REM-sleep which seems to be promoted by cholinergic and inhibited by aminergic neurons. The disinhibition of REM-sleep can be demasked by the cholinergic drug RS 86 if there is no REM-sleep abnormality under baseline conditions. Although this result seems to contradict the assumption that REM latency shortening is only an epiphenomenon in depressive disorders, the pathogenetic basis of this phenomenon is still unclear. Is it a hypersensitivity of muscarinic receptors during depression as Gillin and Sitaram hypothesize (4, 5), or is it the consequence of an impaired inhibiting effect of the aminergic systems during depression as Vogel (11) and Beersma et al. (12) hypothesized, based on computer simulation experiments? Further results in healthy subjects under conditions of experimentally induced muscarinic supersensitivity or impaired aminergic activity seem to be necessary to answer this question. Our investigation in general, however, confirms the heuristic value of the RS 86-REM-induction test for research in depression.
References


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