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Dopaminergic augmentation of sleep deprivation effects in bipolar depression

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Abstract

Total sleep deprivation (TSD) has been used in association with lithium salts and with serotonergic and noradrenergic antidepressants, leading to sustained improvements in patients affected by major depression. Current theories on the neurobiological mechanism of action of TSD propose a major role for enhanced dopamine activity. To test the clinical relevance of dopaminergic enhancement in TSD, we treated a homogeneous sample of 28 bipolar depressed patients with three cycles of TSD combined with placebo or with the dopaminergic antidepressant amineptine. Changes in mood over time were rated with self-administered visual analogue scales and with the Montgomery–Åsberg Depression Rating Scale. Patients showed improved mean daily-mood scores after TSD, an effect that was highest at the first cycle and decreased with treatment repetition. Amineptine enhanced the effects of TSD on perceived mood during the first two TSD cycles, but patients in the placebo and amineptine groups showed comparable results at the end of the treatment. Despite its theoretical importance, the clinical usefulness of combining TSD with a dopaminergic agent must be questioned.

Keywords: Sleep deprivation; Depression; Bipolar disorder; Amineptine; Dopamine

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1. Introduction

The rapid mood amelioration caused by total sleep deprivation (TSD) in patients affected by a major depressive episode is usually followed by a symptomatological relapse soon after restoration of the normal sleep-wake cycle (Wu and Bunney, 1990; Leibenluft and Wehr, 1992). In an attempt to prevent this short-term relapse, TSD has been successfully applied in association with lithium salts (Benedetti et al., 1999; Colombo et al., 2000) and antidepressants with serotonergic (Benedetti et al., 1997; Neumeister et al., 1998; Smeraldi et al., 1999), noradrenergic (Shelton and Loosen, 1993; Szuba et al., 1994) and mixed serotonergic–noradrenergic (Elsenga and Van den Hoofdakker, 1982/1983; Kuhs et al., 1996) mechanisms of action. Moreover, recent studies have shown a favorable interaction between sleep deprivation and bright light therapy (Neumeister et al., 1996; Colombo et al., 2000). The synergistic interaction between TSD and antidepressant agents observed in these clinical studies is consistent with a major role for monoamines in the neurobiological mechanism of action of TSD (Wirz-Justice and Van den Hoofdakker, 1999).

A new psychostimulant theory implicates brain dopamine (DA) in the mechanism of action of TSD (Ebert and Berger, 1998). Several lines of evidence showed that TSD is associated with an increase in the activity of brain DA pathways, and that changes in brain DA may be relevant for the clinical effect of TSD. Lower levels of homovanillic acid in the cerebrospinal fluid before TSD were associated with better clinical effects of TSD (Gerner et al., 1979). Plasma levels of prolactin, which is inhibited by DA agonists, were reported to decrease after TSD (Kasper et al., 1988; Baumgartner et al., 1990), and TSD responders and non-responders showed a different prolactin response to sulpiride (Ebert et al., 1993). Single photon-emission computed tomography before and after TSD showed a significantly different D2 receptor occupancy in responders and non-responders, thus suggesting an enhanced dopamine release in responders (Ebert et al., 1994). An increase in eye-blink rate after sleep deprivation, suggesting DA activation, was reported to be proportional to the clinical effects of sleep deprivation (Ebert et al., 1996). Finally, animal research suggested a major role for enhanced DA activity in the behavioral effects of sleep deprivation (e.g. Gessa et al., 1995).

If an enhancement of the activity of brain DA pathways during sleep loss plays a clinically relevant role in the effect of TSD, the addition of a dopaminergic drug to TSD should enhance its clinical effect. In the only previous study to test this hypothesis (Benedetti et al., 1996), we combined TSD with the double-blind administration of placebo or amineptine, an antidepressant drug that enhances dopaminergic transmission by inhibiting presynaptic DA reuptake (Bonnet et al., 1987; Kapur and Mann, 1992; see Appendix A). We observed an effect opposite to that expected, with TSD showing lesser clinical effects in amineptine-treated than in placebo-treated patients. Since amineptine treatment began 6 days before the first application of TSD, we explained this negative interaction by hypothesizing a kind of 'ceiling effect', or a down-regulation of presynaptic and postsynaptic DA receptors due to amineptine pretreatment (Ceci et al., 1986). According to this hypothesis, a positive interaction of amineptine and TSD should be observed with a contemporaneous beginning of the two treatments.

The purpose of the present study was to test the hypothesis that the contemporaneous administration of TSD and amineptine would lead to better clinical effects in bipolar depression than the administration of TSD and placebo.

2. Methods

2.1. Subjects and treatment

Since 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; Barbini et al., 1998), the study was conducted on a homogeneous group of bipolar depressed patients.