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Motor-Activity Markers of Circadian Timekeeping Are Related to Ketamine's Rapid Antidepressant Properties

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ABSTRACT

BACKGROUND: The rapid clinical antidepressant effects of the glutamatergic modulator ketamine may be due to its ability to restore synaptic plasticity and related effects on sleep-wake and circadian systems. Preclinical studies indicate that ketamine alters expression of circadian clock–associated molecules, and clinical studies of ketamine on plasticity-related biomarkers further suggest an association with sleep slow waves and sleep homeostasis.

METHODS: Wrist-activity monitors were used to examine the pharmacologic and rapid antidepressant effects of ketamine on markers of circadian timekeeping (amplitude and timing) in mood disorders. Circadian amplitude and timing of activity at baseline, postinfusion day 1 (D1), and day 3 (D3) were measured in 51 patients with major depressive disorder or bipolar disorder.

RESULTS: Compared with either placebo or baseline, a mood-independent decrease of the central circadian value (mesor) was present on D1 after ketamine treatment. Mood-associated circadian effects between rapid (D1) responders and nonresponders were found at baseline, D1, and D3. At baseline, a phase-advanced activity pattern and lower mesor distinguished subsequent responders from nonresponders. On D1, ketamine nonresponders had a lower mesor and a blunted 24-hour amplitude relative to baseline. On D3, patients with a persisting clinical response exhibited a higher amplitude and mesor compared with nonresponders.

CONCLUSIONS: The findings are the first to demonstrate an association between ketamine's clinical antidepressant effects and circadian timekeeping. The results suggest that traitlike circadian activity patterns indicate rapid mood response to ketamine, and that mediators of continuing ketamine-induced mood changes include altered timing and amplitude of the circadian system.

Keywords: Clock genes, Neuroplasticity, Sleep deprivation, Slow wave sleep, Wrist activity

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Sleep deprivation (SD) and ketamine treatment both rapidly relieve symptoms in patients with major depressive disorder (MDD). The fact that both interventions affect sleep homeostasis and circadian processes suggests that the circadian and sleep-wake systems and their interactions are associated with rapid mood effects. Understanding the separate and interacting effects of these processes may provide useful clues for developing novel rapid antidepressant therapies for mood disorders.

Preclinical studies have noted that both SD and ketamine affect central circadian clock–associated molecules (1). Further, clinical ketamine studies suggest that this agent affects sleep, slow waves, and synaptic plasticity (2–4). In healthy subjects, sleep quality interacts with the circadian system to affect the temporal organization of the human transcriptome (5). Taken together, these studies suggest that interventions that restore and normalize sleep quality—such as ketamine—could correct interactions between disrupted sleep and circadian systems to enhance temporal organization of the circadian sleep-wake system and ultimately improve mood and behavioral health.

Ketamine exerts its initial rapid antidepressant properties via a prolonged change in glutamatergic signaling resulting in increased synaptic strength and plasticity. Changes in glutamatergic transmission affect downstream structural changes in dendritic spines and local synaptic protein synthesis (6), including transport and release of brain-derived neurotrophic factor (BDNF) (7). BDNF secretion, activation of tropomyosin receptor kinase B, and downstream trafficking lead to further dendritic structural complexity, spine and BDNF synthesis, and synaptic plasticity (7,8). Ultimately, changes in critical local neuronal circuits that converge via enhanced synaptic plasticity and neuronal synchronization would hypothetically produce rapid antidepressant effects, particularly in areas involved in mood and behavior (8,9). Notably, ketamine-induced changes in BDNF levels correlate

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with both sleep slow waves (SWSs) and mood changes, as well as with improved sleep quality in individuals with treatment-resistant depression (2,4). Numerous interactions between sleep homeostatic and circadian systems are possible, such as ketamine's effects on clock genes to influence circadian timing and on BDNF and SWSs to affect sleep quality.

Wrist activity is a useful indirect measure of central circadian timekeeping (10), which may be an important transdiagnostic measure of circadian function. To advance translational research, the National Institute of Mental Health (NIMH) Research Domain Criteria (https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml) includes circadian rhythms as a core construct within the Arousal and Regulatory System domain, and actigraphy-monitored rest/activity rhythms as a paradigm to evaluate this construct. Because changes in activity levels have been linked to circadian rhythm disorders (11), seasonal affective disorder (12), and bipolar disorder (BD) (13–15), as well as current (10,16), subsyndromal (17), and euthymic (18) MDD, the relationship between activity and specific diagnoses is likely complex. For example, activity patterns are phase-delayed and blunted in seasonal affective disorder (12) as well as blunted in both at-risk bipolar spectrum disorder (19) and in persons with elevated manic-depressive symptoms (as assessed by the Young Mania Rating Scale) (20). Furthermore, an evening circadian chronotype, regardless of delayed sleep phase syndrome, conveys risk for anxiety, depressive, or substance use disorders (21).

Indeed, dysregulated circadian timekeeping measures (amplitude, phase, day vs. night levels) often contribute to mood symptom severity. Correlations between clinical ratings and nighttime activity in MDD (22), as well as daytime activity in melancholic depression (23), indicate that day-night patterns of activity vary with symptom severity (24). For instance, severity of depression has been associated with amplitude and timing, particularly low amplitude and/or delayed daily peak activity (25), or circadian rhythm misalignment (26,27). In addition, specific markers of circadian timekeeping are often associated with effective antidepressant intervention. For example, activity patterns are phase advanced after SD (28) and bright light (12) therapies, and altered 24-hour amplitude is often associated with increased day and decreased night activity following treatment interventions (12,29–32).

In addition, clock gene variants are often associated with diurnal preference [reviewed in (33)] and have been explored in the pathogenesis of mood disorders (34). Preclinical and clinical evidence suggests that both *CLOCK* (35,36) and *Per* (37,38) mutations are associated with mood disorders. The altered motor activity patterns present with these mutations (36,39) are consistent with the possibility that mood-related temporal variations of activity are associated with genetic variants of clock-related molecules. Furthermore, disrupted patterns of activity are linked to clock-gene mutations associated with mood disorders (37,40–42). The observations that circadian clock genes also interact to affect sleep homeostasis (43–45), and that mistimed sleep affects circadian regulation of the human transcriptome (5,46), suggests that ketamine's effects on sleep timing and clock gene expression might ultimately improve the underlying molecular disorganization of the circadian system.

The present study is the first to investigate the effects of a single ketamine infusion on circadian rhythm expression and clinical response in treatment-resistant mood disorders (both MDD and BD). Specifically, we analyzed the clinical evidence for ketamine's effects on 24-hour activity patterns over the course of five days in individuals with mood disorders. The specific objectives of the study were to 1) identify ketamine's circadian timekeeping effects relative to placebo treatment and 2) assess whether ketamine's rapid antidepressant effects (e.g., its effects on mood and relapse parameters) were associated with altered patterns of circadian timekeeping.

METHODS AND MATERIALS

This study was conducted using data drawn from different investigations (under protocol 04-M-0222) exploring ketamine's antidepressant mechanism of action in patients with treatment-resistant mood disorders (2,47,48). The studies were conducted at the NIMH Clinical Research Center Mood Disorders Research Unit in Bethesda, MD, and were approved by the Combined Neuroscience Institutional Review Board of the National Institutes of Health; specific details have been previously reported (2). One study investigated the clinical effects of ketamine in MDD patients who subsequently received riluzole (another glutamatergic modulator) in an effort to extend ketamine's antidepressant effects (47), and a second study investigated ketamine's antidepressant effects in MDD and BD patients, some of whom received maintenance mood stabilizers. A continuing study is examining ketamine's effects in MDD and BD in a placebo-controlled, crossover study.

Participants

Fifty-one subjects (29 women, 22 men), 20 to 65 years old (mean age ± SEM = 42.6 ± 11.8 years) with confirmed clinical diagnoses of either MDD ($n = 30$) or BD ($n = 21$) were pooled in the analysis. All subjects had a Montgomery–Åsberg Depression Rating Scale (MADRS) score of ≥20 and were experiencing a current major depressive episode lasting at least 4 weeks. In addition, all subjects had previously not responded to at least one adequate antidepressant trial [as assessed by the Antidepressant Treatment History Form, modified (49)]. BD patients were required to not have responded to a prospective open trial of a mood stabilizer while at the NIMH (either lithium or valproate for at least 4 weeks at therapeutic levels; serum lithium, 0.6–1.2 mEq/L; or valproic acid, 50–125 μg/mL). Exclusion criteria included the presence of psychotic features, a DSM-IV diagnosis of drug or alcohol abuse or dependence in the last 3 months, or the presence of an unstable, serious, medical illness. Women could not be pregnant or nursing. Participants were free of all psychotropic medications for 2 to 5 weeks before the assessment, with the exception of mood stabilizers among some BD patients (14 of 21 patients were receiving lithium, 5 of 21 patients were receiving valproic acid, and 2 of 21 patients were drug free). Cigarette use was permitted during the clinical trial, but alcohol use was not. Participants were not allowed to nap