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Research Paper

Advanced Circadian Phase in Mania and Delayed Circadian Phase in Mixed Mania and Depression Returned to Normal after Treatment of Bipolar Disorder

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ABSTRACT

Disturbances in circadian rhythms have been suggested as a possible cause of bipolar disorder (BD). Included in this study were 31 mood episodes of 26 BD patients, and 18 controls. Circadian rhythms of BD were evaluated at admission, at 2-week intervals during hospitalization, and at discharge. All participants wore wrist actigraphs during the studies. Saliva and buccal cells were obtained at 8:00, 11:00, 15:00, 19:00, and 23:00 for two consecutive days. Collected saliva and buccal cells were used for analysis of the cortisol and gene circadian rhythm, respectively. Circadian rhythms had different phases during acute mood episodes of BD compared to recovered states. In 23 acute manic episodes, circadian phases were ~7 hour advanced (equivalent to ~17 hour delayed). Phases of 21 out of these 23 cases returned to normal by ~7 hour delay along with treatment, but two out of 23 cases returned to normal by ~17 hour advance. In three cases of mixed manic episodes, the phases were ~6–7 hour delayed. For five cases of depressive episodes, circadian rhythms phases were ~4–5 hour delayed. After treatment, circadian phases resembled those of healthy controls. Circadian misalignment due to circadian rhythm phase shifts might be a pathophysiological mechanism of BD.

1. Introduction

Bipolar disorder (BD) is a common mental disorder characterized by episodic mood symptoms of mania or depression. Episodic relapses of BD are very common, and therefore BD is one of the major leading causes of disability around the world (Goldberg and Harrow, 2004). Numerous etiologies for BD have been proposed, but there is no conclusive evidence.

Humans exhibit an orchestration of circadian rhythmicity with respect to the light-dark cycle (Reppert and Weaver, 2002), involving regulation of physiological processes such as the autonomic nervous system, hormone secretion, and sleep-wake cycles (Dijk and Czeisler, 1995). Circadian rhythms can be entrained by both photic and nonphotic stimuli, however light plays the primary role in the entrainment of the human circadian pacemaker to the environment (Lavie, 2001). The hypothalamic suprachiasmatic nuclei (SCN) are a master clock for the orchestration of circadian rhythmicity. The SCN synchronize peripheral oscillators to ensure temporally coordinated physiology, while the peripheral oscillators interact among themselves and communicate back to the SCN (Schibler and Sassone-Corsi, 2002). The endogenous circadian rhythmicity affects timing for sleep-wake cycles and biochemical rhythms. The circadian regulation of the sleep-wake cycle is thought to be mediated by multisynaptic projections from the SCN to sleep-wake centers of the brain (Deurveilher and Semba, 2005; Saper et al., 2005). Biochemical rhythms such as cortisol concentrations are also thought to be affected by endogenous circadian timing systems (Bremner et al.,

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1983). Time coordination of functions affected by endogenous circadian rhythmicity may result from predictive regulation of function rather than being entirely reactive, for example, body temperature and plasma cortisol increase prior to waking from sleep (Fuller et al., 2006).

Disruptions of circadian rhythms have long been proposed as a fundamental cause of BD (Gonzalez, 2014). Some research has suggested that the intrinsic circadian pacemaker of BD was shorter than a close-to-24-hour period (Wehr et al., 1985). Other hypotheses emphasized phase shifts as the primary circadian rhythm disturbances in BD (Salvatore et al., 2008; Wood et al., 2009). Another formulation suggested that instability in the behaviors of BD patients were keys to disruption of circadian rhythms (Lee et al., 2013). There are many studies suggesting an association between variations in circadian genes and BD as well as specific clinical subphenotypes (Maciukiewicz et al., 2014). Both lithium and valproic acid, used to treat BD, have been shown to influence the rhythmic expression of circadian genes and the rhythmic properties of molecular clocks, especially via inhibition of glycogen synthase kinase-3β (GSK-3β) (Li et al., 2002). There are a wide diversity of reported circadian abnormalities and many unresolved questions.

First, are there characteristic sequential changes in circadian rhythms related to the exacerbation of BD symptoms? So far, studies about the disturbances of circadian rhythms related to BD have been almost entirely cross-sectional (Nurnberger et al., 2000; Wood et al., 2009). If we identify sequential changes of circadian rhythms with the clinical transitions from severe mood states (such as mania or depression or mixed states) to euthymic states, it will provide a deeper understanding of circadian rhythms associated with BD.

Second, how should we interpret the variations of circadian rhythm shifts within studies of BD (Nurnberger et al., 2000; Salvatore et al., 2008)? As highlighted by the subphenotypes in genetic studies of BD (Craddock and Sklar, 2009), we speculate that there could be several subphenotypes correlated with distinctive changes of circadian rhythms within BD.

Third, are there inconsistencies in disorders when measuring circadian rhythm variables of different body systems at the same time, so-called internal desynchronization? Most of the studies have been analyses of independent variables such as hormonal, genetic, or physical activity (Nurnberger et al., 2000; Salvatore et al., 2008). However, these variables may differ in sensitivity to reflect aspects of human circadian rhythm systems. If we compare several circadian rhythm variables of different systems at the same time, it might distinguish dysregulation of circadian coordination in these systems.

To clarify the questions mentioned above, we serially measured behavior and biochemical circadian rhythms in BD during hospitalization from severe states at admission to euthymic states at discharge, and compared them with those of healthy controls.

2. Materials & Methods

2.1. Participants

The patients with BD were recruited from inpatients at the Department of Psychiatry, Korea University Anam Hospital, Seoul, Republic of Korea. Included in the study were 26 manic episodes of 22 Bipolar I disorder (BD-I) patients (12 male and 10 female) who were hospitalized from May 2012 to June 2014, 5 depressive episodes of 5 BD patients (2 male and 3 female, 2 BD-I and 3 BD-II) who were hospitalized from June 2014 to March 2015, and 18 healthy subjects (11 male and 7 female) were assessed from September 2012 to November 2012. The ages of the participants [mean ± SD] were 30.42 ± 10.88 years for patients and 23.00 ± 3.57 years for healthy controls. One BD patient was observed in both manic and depressed episodes during different hospitalizations. In sum, 31 mood episodes requiring hospitalization of 26 BD patients were analyzed. There were no significant differences with respect to characteristics including age and sex among groups (Table 1).

Diagnoses were determined by two psychiatrists (H.-J.L and C.-H.C) according to DSM-IV-TR criteria using the Korean version of the Mini International Neuropsychiatric Interview (Yoo et al., 2006). Patients with BD who needed to be hospitalized because of the aggravation of mood symptoms, were recruited for the study. Inclusion criteria of the participants were: 1) Diagnosis of BD according to DSM-IV-TR criteria and 2) Acute mood episode requiring hospitalization for intensive psychiatric treatment. Patients or controls with intellectual disability, organic brain injury, or other major psychiatric disorders were excluded from the present study. All participants underwent screening to exclude past or present major medical disorders such as cardiovascular disease, metabolic disease (including diabetes mellitus), hormonal disease (including thyroid disease), and cancer. Clinical symptoms were evaluated with the Young Mania Rating Scale (YMRS) (Young et al., 1978), the 17-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1980), and the Clinical Global Impression-Bipolar Version (CGI-BP) (Spearing et al., 1997).

Through in-depth interviews by a psychiatrist (H.-J.L) with all volunteers, we confirmed that controls had no personal or familial psychiatric history. All participants completed questionnaires regarding their sleep conditions to exclude controls who had irregular or disturbed sleep/wake patterns. Controls were excluded if working night shifts or reporting sleep patterns suggestive of circadian rhythm phase disorders. The mood disorder questionnaire (MDQ) was used to assess subthreshold bipolarity (Hirschfeld et al., 2000). Only those with MDQ scores <7 were included in the control group.

Participants were informed about the purpose and procedures of the study and all participants provided informed written consent prior to enrollment after a full explanation and thorough understanding of this study. The study protocol was approved by the Institutional Review Board of Korea University Anam Hospital and was conducted in accordance with the Declaration of Helsinki.

2.2. Protocol

Patients were hospitalized during treatment and wore Actiwatch-L activity recorders on a non-dominant wrist (Philips Respironics, Bend, OR, USA). The sleep habits of hospitalized subjects were controlled by the regular ward routine, i.e., they went to bed at 22:00 h and were

Table 1
Demographic data of study population.

	Patients with bipolar disorder	Healthy controls	P value
Number of subjects	26	18	–
Age (mean ± SD), years	30.42 ± 10.88	23.00 ± 3.57	0.083
Sex (M/F), N	13/13	10/8	0.717
Bipolar type (I/II), N	23/3	N/A	–
Education (mean ± SD), years	13.85 ± 1.95	14.39 ± 2.33	0.407
Age of onset (mean ± SD), years	21.19 ± 7.68	N/A	–
Total number of mood episodes (mean ± SD)	7.62 ± 5.87	0	–
Family loading of mood disorder, %	57.7	0	–
Total number of psychiatric hospitalizations (mean ± SD)	3.62 ± 2.43	0	–

N, number of subjects.