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Diurnal alterations in circadian genes and peptides in major depressive disorder before and after escitalopram treatment

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Summary
Background: Strong links exist between circadian disturbances and some of the most characteristic symptoms of clinical major depressive disorder (MDD). However, changes in the expression of clock genes or neuropeptides related to the regulation of circadian rhythm that may influence the susceptibility to recurrence after antidepressant treatment in MDD have not been investigated.
Methods: Blood samples were collected at 4 h intervals for 24 h from 12 male healthy controls and 12 male MDD patients before and after treatment with escitalopram for 8 weeks. The outcome measures included the relative expression of clock gene mRNA (*PERIOD1*, *PERIOD2*, *PERIOD3*, *CRY1*, *BMAL1*, *NPAS2*, and *GSK-3β*), and the levels of serum melatonin, vasoactive intestinal polypeptide (VIP), cortisol, adrenocorticotropic hormone (ACTH), insulin-like growth factor-1 (IGF-1), and growth hormone (GH).
Results: Compared with healthy controls, MDD patients showed disruptions in the diurnal rhythms of the expression of *PERIOD1*, *PERIOD2*, *CRY1*, *BMAL1*, *NPAS2*, and *GSK-3β* and disruptions in the diurnal rhythms of the release of melatonin, VIP, cortisol, ACTH, IGF-1, and GH. Several of these disruptions (i.e., *PER1*, *CRY1*, melatonin, VIP, cortisol, ACTH, and IGF-1) persisted 8 weeks after escitalopram treatment, similar to the increase in the 24 h levels of VIP and decreases in the 24 h levels of cortisol and ACTH.
Conclusion: These persistent neurobiological changes may play a role in MDD symptoms that are thought to contribute to the vulnerability to recurrence and long-term maintenance therapy.

1. Introduction

Major depressive disorder (MDD) is one of the leading causes of premature death and disability (Murray and Lopez, 1997;

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Lopez et al., 2006). Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. These symptoms can become chronic or recurrent and lead to substantial impairments in the ability to take care of everyday responsibilities. For more than 50 years, drug treatments for MDD have targeted monoamine systems (Hickie and Rogers, 2011). The overall therapeutic value of many of the older tricyclic drugs and most commonly prescribed selective serotonin-reuptake inhibitors (SSRIs) for patients with depression is clear, but they usually require several weeks of administration to achieve clinical efficacy.

Strong links exist between circadian disturbances and some of the most characteristic symptoms of clinical depression, including delayed sleep onset, non-restful sleep, early-morning wakening, daytime fatigue, and blunting or reversal of the normal morning peaks in subjective energy, mood, and alertness (Germain and Kupfer, 2008). The older tricyclic drugs and SSRIs were not initially designed to focus on the disturbances of the circadian rhythmic system in depressive patients. These drugs always led to some adverse effects, such as suppressed rapid-eye-movement (REM) sleep and disrupted slow-wave sleep and REM cycles (at least in the short term), and did not necessarily restore normal circadian function (Dumont et al., 2005) during treatment. In fact, a previous study showed that 10—30% of antidepressive treatment was ineffective (Sackeim, 2001). Even if the antidepressive treatment is effective, it is incomplete or not curative in many MDD patients. Additionally, common side effects of antidepressive drugs also affect treatment compliance. The ineffectiveness of antidepressive drugs in emotional disorder patients has been reported to be as high as 40% (Bhattacharjee, 2007).

Escitalopram is a highly selective SSRI and therapeutically active *S*-enantiomer of citalopram. A recent meta-analysis found that escitalopram-treated patients showed significantly higher response rates and increased mean changes from baseline in total scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) at weeks 1 and 8 compared with citalopram-treated patients (Azorin et al., 2004). A previous study showed that serotonin (5-hydroxytryptamine [5-HT]) was strongly implicated in the regulation of the mammalian circadian clock located in the suprachiasmatic nuclei (SCN), and 5-HT_7 receptor-mediated phase resetting in the SCN is markedly influenced by the degree of postsynaptic responsiveness to 5-HT and photic stimulation (Ehlen et al., 2001). Although the onset of the clinical effect of escitalopram is delayed by 1 week, its onset of clinical effectiveness is one of the fastest among existing antidepressants worldwide. The hypothesis of the present study was that escitalopram may play a regulatory role in disruptions in circadian rhythms in MDD patients associated with significantly higher response rates (Azorin et al., 2004).

We selected specific clock genes because they are important components of the molecular clock mechanism or have been shown to be related to mood disorders. In the same subjects, we also examined circadian rhythms in blood levels of hormones and peptides. Because melatonin is an endocrine output signal by which the circadian clock provides information as an endogenous synchronizer, it is able to stabilize and reinforce circadian rhythms and maintain their mutual phase relationship. Vasoactive intestinal polypeptide (VIP) is a recognized synchronizing factor in the suprachiasmatic nucleus (SCN). A close relationship is well known to exist between the function of the hypothalamic-pituitary-adrenal axis and MDD. The growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis is involved in brain growth, development, and myelination, and plasticity, reflected by neurogenesis (Aberg, 2010). Growth hormone may be involved in the formation of depression and pathological changes (Aberg et al., 2006).

The present study tested the expression of clock genes (*PER1*, *PER2*, *PER3*, *CRY1*, *BMAL1*, *NAPS2*, and *GSK-3*β), neuropeptides, and hormones in peripheral blood to clarify the circadian rhythmic system characteristics of MDD patients and possible reasons for susceptibility to recurrence.

2. Materials and methods

2.1. Subjects and clinical assessment

The clinical sample consisted of 15 male first-attack patients with MDD and 12 age- and gender-matched controls. The patients were consecutively recruited from the local psychiatric hospitals in northern China. Recruitment occurred between February 2009 and March 2012. The patients' ages ranged from 23 to 44 years (mean $\pm$ SD: 32.25 $\pm$ 7.65 years). The 12 patients who completed the study reported no history of any other psychiatric disorders and no history of taking any antidepressants. The patients met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association, 1994), criteria for major depression. The diagnosis was established using the Structured Clinical Interview for DSM-IV disorders (SCID), which was performed by two experienced psychiatrists. A minimum score of 22 points on the 10-item Montgomery and Åsberg Depression Scale (MADS) (Montgomery and Asberg, 1979) was required to be enrolled in the study. The duration of the present depressive episode was in the range of 1—24 months. The exclusion criteria included (1) age $<$18 or $>$45 years, (2) score on the 14-item Hamilton Anxiety Scale (HAMA) (Hamilton, 1976) $>$21, (3) past or present history of psychoactive substance abuse, (4) diastolic blood pressure $<$60 mm Hg or heart rate $<$60 beats per minute, (5) current or past serious physical illness (e.g., active tuberculosis, acute hepatitis, cirrhosis, renal illness, cardiovascular illness, or unstable diabetes), (6) immune disorders, (7) major Axis I psychiatric disorders, and (8) score of suicidal ideation on the MADS $\geq$ 5.

Control participants included 12 physically and mentally healthy male volunteers who were recruited from the local community who were matched for age (age range, 18—45 years; mean $\pm$ SD: 31.15 $\pm$ 10.19 years) and gender. Screening for psychiatric disorders was performed according to the 28-item Global Health Questionnaire (GHQ) and an interview conducted by a physician that provided a full medical history and details on lifestyle and habits. The following exclusion criteria were used: (1) any of the exclusion criteria for the experimental group, (2) past or present DSM-IV Axis I or Axis II disorders, (3) sleep disturbances, (4) shift work, (5) use of any medication within the past 30 days, (6) any current or past physical illness that would be aggravated or reappear if the individual participated in the study.