Improvement of a patient's circadian rhythm sleep disorders by aripiprazole was associated with stabilization of his bipolar illness

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Keywords
aripiprazole, biological oscillator, bipolar disorder, circadian rhythm sleep disorders, suprachiasmatic nucleus

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Accepted in revised form 9 December 2016; received 20 September 2016

DOI: 10.1111/jsr.12496

SUMMARY
Splitting of the behavioural activity phase has been found in nocturnal rodents with suprachiasmatic nucleus (SCN) coupling disorder. A similar phenomenon was observed in the sleep phase in the diurnal human discussed here, suggesting that there are so-called evening and morning oscillators in the SCN of humans. The present case suffered from bipolar disorder refractory to various treatments, and various circadian rhythm sleep disorders, such as delayed sleep phase, polyphasic sleep, separation of the sleep bout resembling splitting and circabidian rhythm (48 h), were found during prolonged depressive episodes with hypersomnia. Separation of sleep into evening and morning components and delayed sleep-offset (24.69-h cycle) developed when lowering and stopping the dose of aripiprazole (APZ). However, resumption of APZ improved these symptoms in 2 weeks, accompanied by improvement in the patient's depressive state. Administration of APZ may improve various circadian rhythm sleep disorders, as well as improve and prevent manic–depressive episodes, via augmentation of coupling in the SCN network.

INTRODUCTION

Sleep deprivation and bright light therapy are highly effective as non-pharmacological therapies for depressive episodes in bipolar disorder and depression. These therapies are thought to have an antidepressant effect by improving circadian rhythm disorders.

The present patient suffered from a prolonged depressive state with hypersomnia and various circadian rhythm sleep disorders. Administration of aripiprazole (APZ) improved circadian rhythm sleep disorders associated with impairment of suprachiasmatic nucleus (SCN) coupling, and simultaneously improved the patient's depression. His manic–depressive episodes were prevented for 3 years on APZ.

CASE HISTORY

The patient is a Japanese male in his 40s who was diagnosed with bipolar I disorder. His mother suffers from major depressive disorder. He had been engaged in programming-related work at a major information technology (IT) company.

Treatment for affective disorder began in March 2000. He was hospitalized for treatment of manic and depressive episodes. Due to these episodes, he was not able to live on his own. In July 2005 he began visiting a daycare centre, spending 6 h in the daytime with 30 people every day, and he received treatment at our clinic. The patient's condition was characterized by prolonged mild depressed mood, hypersomnia, diminished ability to think and hypobulia. The patient had a strong desire to see the treatment succeed. He had recorded a sleep journal daily without fail for approximately 6.5, years beginning in 2009. His sleep journal revealed two normal sleep periods (each lasting approximately 3 months) and a depressive period with hypersomnia lasting 27 months in total during the 33 months prior to administration of APZ. No abnormal findings were seen on physical examinations and head magnetic resonance imaging (MRI).

Written informed consent was obtained from the patient for this case report. Note that some modifications have been made to the text to protect the anonymity of the patient.

Details of the circadian rhythm sleep disorders

Prior to administration of APZ, a period with polyphasic sleep, a period during which the sleep phase was delayed, and circabidian rhythm were seen during the hypersomnia period (duration: 463 days) in his sleep journal.

Separation of sleep into evening and morning components, and separation of the sleep bout into two sleep bouts of antiphase (approximately 12 h), were seen in the present patient.

TREATMENT

Pharmacotherapy

Using sodium valproate 800 mg as the base drug, an atypical antipsychotic (olanzapine 20 mg or quetiapine 300 mg) and an antidepressant (mianserin 30 mg, trazodone 75 mg or fluvoxamine 50 mg) were administered as add-on drugs. With the exception of APZ described below, none of the above drugs was effective for the patient's depression or circadian rhythm sleep disorders.

Treatment for circadian rhythm sleep disorders

Bright light therapy, social rhythm therapy and chronotherapy were effective at times, but none of them provided a stable effect. A melatonin agonist (ramelteon) was ineffective.

Aripiprazole administration was initiated early in April 2012. The circadian rhythm sleep disorders improved rapidly, together with the patient's depressed mood, after administration of APZ (18–24 mg). APZ was stopped temporarily due to a suspected adverse reaction to the high dose of APZ, when he complained of emotional despondency and hypobulia. The patient's sleep and mood as recorded by himself in a journal were subsequently checked (Fig. 1). However, it was concluded that they were not adverse reactions to APZ. Withdrawal of APZ was associated with exacerbation of depression symptoms and onset of circadian rhythm sleep disorders, such as marked delays in the timing of sleep relative to the day–night cycle, a marked lengthening of the period of the sleep–wake cycle and separation of sleep into evening and morning components, culminating in circabidian (48-h) sleep–wake cycles. Resumption of APZ administration reversed these effects completely. Since resuming APZ, manic/depressive episodes and circadian rhythm sleep disorders, including hypersomnia, have not recurred for 3 years. This patient was originally a night owl who would get up late in the morning, but while on APZ his sleep offset advanced to a slightly early time, i.e. 06.21 ± 01.25 h (n = 182), and total sleep time at night became slightly shorter, i.e. 07.41 ± 01.65 h (n = 182).

Chronotherapy and separation of sleep bout resembling 'splitting'

Czeisler *et al.* (1981) first reported the efficacy of this treatment (called chronotherapy) for patients with delayed sleep phase syndrome. With this treatment, the initiation of sleep time is delayed by approximately 3 h every day. In the present patient, this chronotherapy was provided several times prior to administration of APZ. It improved depressive episodes with hypersomnia, and these effects lasted for less than 3 months. Once during this procedure, however, the sleep bout separated into two bouts of antiphase (approximately 12 h) for only 5 days, and fused again (Fig. 2). This phenomenon resembled 'splitting'.

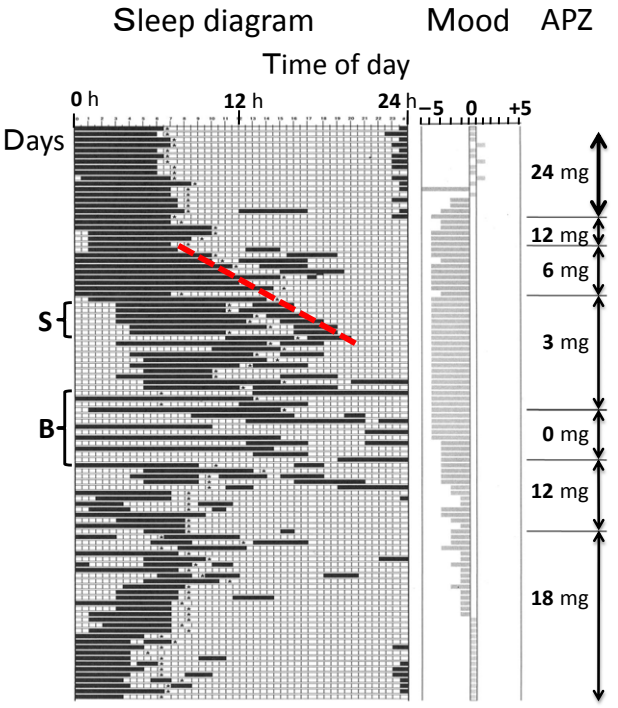

Figure 1. Effects of withdrawal of aripiprazole (APZ) on sleep–wake cycle and mood. Sleep diagram, mood of the patient based on 11-point scale (from −5 to 0 to +5) and the dose of APZ administration are illustrated. S: Separation of sleep into evening and morning components; B: circabidian rhythm; ★: time of taking APZ (once a day), red oblique dashed line: sleep offset (circadian period: 24.69 h). After reducing the dose of APZ, separation of sleep into evening and morning components appeared, and then the circabidian rhythm appeared. After resuming APZ, sleep offset converged 08:00 hours after previously being irregular and unstable, and gradually advanced to 07:00 and 05:00 hours thereafter. Meanwhile, sleep onset began to advance subsequent to the above. As a result, total sleep time shortened and re-entrainment with the external light–dark cycle was established. In addition, the patient's depressed mood and hypobulia improved quickly with the recovery of sleep offset.

DISCUSSION

The time–course of emergence of segmentation of the sleep bout in the present patient was very similar to that observed in the free-running rhythm of the activity bout that emerged immediately after AVP-Bmal1$^{-/-}$ mice with SCN coupling disorder were transferred from a normal light–dark cycle to a

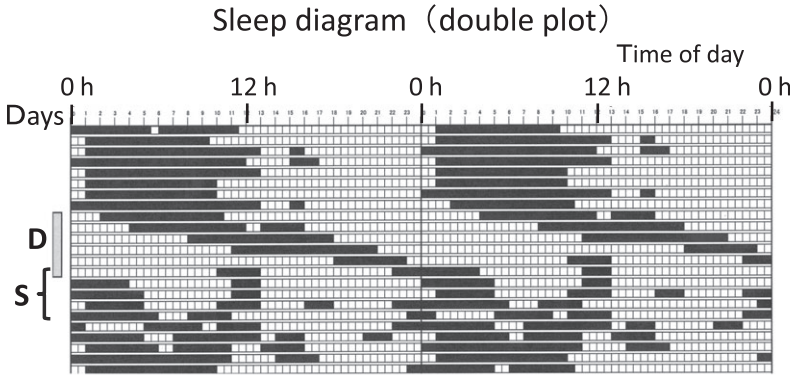

Figure 2. Separation of the sleep bout into two bouts of antiphase (approximately 12 h). Five months after beginning his hypersomniac state, the patient experienced delay of sleep onset and waking in the afternoon. Therefore, the sleep phase was delayed by means of forcing the patient to go to bed 3 h later each day for 6 successive days (indicated by D on the left side). The horizontal axis of the figure is 48 h (double plot) to make it easier to determine changes in the sleep phase. On the 5th day, the patient fell asleep at 18:00 hours, but he slept for only 5 h. On the 6th day, he slept for 3 h around noon. The sleep bout separated into two bouts of antiphase (approximately 12 h) for only 5 days (indicated by S on the left side)**.** This phenomenon resembled 'splitting'. A hypersomnia phase then appeared.

constant dark environment (Mieda *et al*., 2015). In addition, separation of the sleep bout into two bouts of antiphase (approximately 12 h) was also seen in the present patient, and this was very similar to 'splitting of activity bout', which is induced by bilateral coupling disorder of SCN under constant light conditions in hamsters (Golombek and Rosenstein, 2010), but its duration lasted for only 5 days. Wehr (1991) claimed that splitting of the activity phase in nocturnal animals was probably the same phenomenon as splitting of the sleep phase in diurnal animals. Based on these findings and suggestions the present author judged that, as in rodents, so-called morning and evening oscillators of SCN, which drive the appearance of morning and evening sleep bouts, were present in the this patient, and that he suffered from an SCN coupling disorder.

Regarding treatment, APZ improved the various circadian rhythm sleep disorders and depressive state, and prevented the recurrence of manic–depressive episodes for 3 years. While reducing APZ, at APZ 6 mg the sleep offset was delayed every day with a circadian period of 24.69 h (possibly a free run), and at APZ 3 mg the delay of sleep onset began. Sleep offset delay and sleep onset delay were not parallel. Separation of sleep into evening and morning components then occurred. From these, it was understood that there was a difference between morning and evening sleep components in terms of the reactivity to APZ and dose-dependent effects. These circadian rhythm sleep disorders improved rapidly with resumption of APZ. Based on this, it is surmised that APZ exhibited these effects by improving the SCN coupling disorder. However, the precise mechanism of the action of APZ is unknown. As for the pharmacological actions of APZ, it has a partial agonistic effect on 5-HT1A/2C/7 receptors (Shapiro *et al*., 2003), up-regulates release of histamine in the anterior hypothalamus (Murotani *et al*., 2011) and inhibits GSK3β (Park *et al*., 2009). It is known that these pharmacological actions have non-photic and photic-like phase advance effects (Cote and Harrington, 1993; Cuesta *et al*., 2009; Sprouse *et al*., 2005). Aripiprazole also has an activation effect on BMAL1 and a shortening effect on the period of circadian rhythm (Hirota *et al*., 2008). These effects were associated with earlier sleep offset, shortened total sleep time, advanced sleep phase and functional augmentation of SCN coupling.

Administration of APZ may improve various circadian rhythm sleep disorders, as well as improve and prevent manic–depressive episodes, via augmentation of coupling in the SCN network.

LIMITATIONS

It has not been confirmed whether the SCN coupling disorder in this patient was induced by accentuation of the underlying depression with hypersomnia or was a sporadic occurrence unrelated to the underlying disease. In the present case, separation of sleep into evening and morning components was associated with the depressive state. Kripke *et al.* (2015) have suggested that bifurcation of the sleep phase is associated with the manic state. Separation of sleep into evening and morning components and bifurcation of the sleep phase may be similar phenomena, but similarities and differences in their pathophysiological mechanism have not been elucidated.

ACKNOWLEDGEMENTS

I express my deep gratitude to Dr Yasuo Hishikawa, Professor Emeritus of Akita University, for proofreading this paper, and Dr Tetsuo Shimizu, Professor of Akita University, for providing valuable advice.

CONFLICT OF INTEREST

The author has no conflicts of interest.

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