Lurasidone Suppresses Rapid Eye Movement Sleep and Improves Sleep Quality in Rats

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Abstract. Patients with psychiatric disorders, including schizophrenia, are reported to suffer from sleep disorders. In this study, we investigated the effects of lurasidone, an atypical antipsychotic, on sleep architecture in rats using sleep electroencephalography. The course of sleep in rats was classified into 3 stages: WAKE, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. Lurasidone shortened REM duration and prolonged the mean duration of one bout in WAKE and NREM. Quantitative frequency band analysis during NREM sleep revealed that lurasidone increases slow waves and decreases fast waves. These results suggest that lurasidone ameliorates sleep disorders associated with psychosis.

Keywords: lurasidone, antipsychotic, sleep

Lurasidone, a new antipsychotic drug approved by the FDA in 2010, exhibits strong dopamine D₂ and 5-hydroxytryptamine (5-HT)₂A receptors antagonistic activity as well as 5-HT₁A receptor partial agonistic activity and 5-HT₇ receptor antagonistic activity. As such, lurasidone is classified as a serotonin–dopamine antagonist (SDA) (1). Lurasidone has been shown to enhance cognitive function and improve psychosis in rodents and non-human primates (2–4). Recent clinical studies confirmed that lurasidone alone, or in combination with valproate or lithium, is effective for the depressive state of bipolar disorder type I (5, 6). Based on these findings, a request for expansion of indication was submitted to the FDA and was subsequently approved in June 2013.

Sleep problems, including prolonged sleep latency, fragmented sleep, and early-morning awakening, have been reported in patients with mood disorders such as schizophrenia and bipolar disorder (7, 8). Especially, researchers have found a correlation between increased rapid eye movement (REM) sleep and the severity of depressive state (9, 10). Thus, amelioration of sleep in these patients can improve quality of life.

In the present study, we investigated the effects of lurasidone on non-REM (NREM) and REM sleep in rats using electroencephalography (EEG). The amount and quality of sleep were assessed based on the number and duration of bouts in each sleep stage and the ratio of frequency bands (delta to gamma) during NREM.

All experimental procedures for the use of animals were reviewed and approved by the Institutional Animal Care and Use Committee of Sumitomo Dainippon Pharma, Co., Ltd. Seven adult male Wistar rats (Charles River Laboratories Japan, Kanagawa) were used in this study. The animals were housed in an air-conditioned room (temperature of 20°C–26°C and humidity of 40%–70%) with a 12:12 h light/dark cycle (light on at 7:00) and allowed access to food and tap water ad libitum.

The rats were anesthetized with sodium pentobarbital (40 mg/kg, i.p.), and a radio transmitter (TL11M2-F40-EET; Data Science International, New Brighton, MN, USA) was implanted subcutaneously in the back. A pair of electrode wires was fed subcutaneously to a small incision on the skull. One wire was implanted on the dura 2-mm anterior to the bregma and 2-mm to the left of the midline, and the other wire was placed 4-mm posterior to the bregma and 4 mm to the right of the midline. A stainless screw was also placed on the skull 2-mm anterior to the bregma and 2 mm to the left of the midline.
Effects of Lurasidone on Sleep in Rats

midline. The EEG electrodes and screw were fixed in place using dental cement. Electromyograms (EMG) were recorded from the dorsal neck muscle using another pair of electrodes. Rats were administered antibiotics and analgesics following wire implantation.

After surgery, the rats were allowed at least 2 weeks recovery in individual plastic cages before EEG/EMG recording. The lighting cycle was changed during this period (light-on: 10:00 – 22:00). Lurasidone or solvent was administered at the start of the light-on period, and EEG/EMG was recorded for 6 h in a soundproof box using Dataquest A.R.T. software (Data Science International). To effectively evaluate the beneficial effect of lurasidone, the animals were used in a crossover design. A minimum one-week washout period was allowed between recordings. Dosing was performed in a pseudo-randomized order.

In sleep stage analysis, in which a 10-s period was regarded as one epoch, WAKE, REM, and NREM were automatically assessed based on EEG and EMG recordings using Sleepsign3 software (Kissei Comtec, Nagano). A condition in which EMG exceeded the threshold was defined as WAKE, that in which the power of delta waves (0.5 – 4 Hz) was 1,500 µV² or greater with no EMG response was defined as NREM, and that in which the power of theta waves (4 – 8 Hz) exceeded 40% of the total power of 0.5 – 80 Hz waves with no EMG response was defined as REM. Total REM duration, NREM duration, and latencies to the initial REM and NREM were calculated. REM and NREM were considered initial when they continued for 2 and 6 epochs, respectively. In addition, the number and mean duration of bouts in every 2-h period were calculated in each stage.

After assessment of each sleep stage, EEG power in each of the following frequency bands during NREM sleep was quantified using Sleepsign3: delta, theta, alpha (8 – 12 Hz), beta (12 – 30 Hz), and gamma (30 – 80). The power ratio of each wave to all waves (0.5 – 80 Hz) was calculated using Sleepsign3.

Lurasidone was prepared in our laboratories, suspended in 0.5% methylcellulose (MC) as a vehicle, and orally administered to rats in a volume of 2 mL/kg. All data are expressed as means ± S.E.M. Differences between groups were determined using Dunnett’s multiple comparison test. Differences in the ratio of each frequency band between each dose and the vehicle were determined with the paired \( t \)-test. A probability level of < 0.05 was considered significant.

Lurasidone increased total NREM duration over the 6-h recording period (3 mg/kg: 251.4 ± 4.1, \( t_{24} = 3.8, P = 0.0024 \); 10 mg/kg: 259.8 ± 2.8, \( t_{24} = 5.28, P < 0.0001 \)), but had no effect on the latency to initial NREM even at 10 mg/kg (Fig. 1: A, B). Moreover, lurasidone decreased the number of bouts in all sleep stages and extended the mean duration of one bout in NREM (Table 1). These results indicate that lurasidone promotes sleep and suppresses its fragmentation. Quantitative frequency band analysis during NREM sleep showed that lurasidone increases delta-wave ratio and decreases alpha-, beta-, and gamma-wave ratios (Table 2).

These findings indicate that lurasidone induces deep
Table 1. Effect of lurasidone on sleep stage count

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>WAKE</th>
<th>REM</th>
<th>NREM</th>
<th>Bout duration (s)</th>
<th>REM</th>
<th>NREM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14.3 ± 0.9</td>
<td>10.4 ± 1.6</td>
<td>21.6 ± 1.6</td>
<td>134.4 ± 17.8</td>
<td>84.3 ± 11.0</td>
<td>214.3 ± 26.3</td>
</tr>
<tr>
<td>1</td>
<td>12.3 ± 1.2</td>
<td>7.4 ± 0.6</td>
<td>17.1 ± 1.6</td>
<td>157.7 ± 16.8</td>
<td>98.9 ± 8.6</td>
<td>281.7 ± 40.7</td>
</tr>
<tr>
<td>3</td>
<td>10.1 ± 2.0</td>
<td>5.7 ± 1.2*</td>
<td>14.3 ± 1.9*</td>
<td>167.7 ± 38.0</td>
<td>91.6 ± 13.3</td>
<td>405.3 ± 58.8*</td>
</tr>
<tr>
<td>10</td>
<td>8.6 ± 1.5*</td>
<td>3.0 ± 1.0*</td>
<td>11.0 ± 1.5*</td>
<td>257.9 ± 62.8</td>
<td>50.5 ± 15.5</td>
<td>530.6 ± 68.9*</td>
</tr>
</tbody>
</table>

The number of bouts and mean duration of one bout in each sleep stage were evaluated over a 2-h period after lurasidone administration. *P < 0.05, significantly different from the vehicle.

Table 2. Effects of lurasidone on frequency bands

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Delta</th>
<th>Theta</th>
<th>Alpha</th>
<th>Beta</th>
<th>Gamma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg</td>
<td>1.07 ± 1.2</td>
<td>0.44 ± 0.4</td>
<td>0.20 ± 0.3</td>
<td>0.27 ± 0.6</td>
<td>0.16 ± 0.2</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>2.34 ± 0.5*</td>
<td>0.09 ± 0.2</td>
<td>0.80 ± 0.1*</td>
<td>1.21 ± 0.2*</td>
<td>0.25 ± 0.1</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>4.55 ± 0.9*</td>
<td>0.25 ± 0.3</td>
<td>1.51 ± 0.3*</td>
<td>2.32 ± 0.6*</td>
<td>0.48 ± 0.2*</td>
</tr>
</tbody>
</table>

Differences in the ratio of each frequency band compared to the vehicle (%) were evaluated. *P < 0.05, significantly different from the vehicle.

sleep. Although benzodiazepine hypnotics also induce sleep, they increase fast wave components (11). The sleep induced by lurasidone, on the other hand, seems to be closer to natural sleep (Table 2). Although this study was performed in the former half of the non-active phase, we intend to expand the measurement time to a whole day in future studies. This will allow better understanding of the effects of lurasidone on sleep.

As shown in Fig. 1C, lurasidone decreased total REM duration in a dose-dependent manner with significant effect at 3 and 10 mg/kg (3 mg/kg: 44.4 ± 5.2, t24 = 2.59, P = 0.042; 10 mg/kg: 35.0 ± 3.2, t24 = -4.24, P = 0.0008). In addition, lurasidone slightly prolonged REM latency (10 mg/kg: 79.8 ± 17.2, t24 = 2.41, P = 0.061; Fig. 1D). It has been reported that REM sleep increases in the depressive state and that antidepressants ameliorate REM sleep concomitant with depressive symptoms. As some antidepressants also suppress REM sleep even in healthy subjects and naïve animals, it is believed that REM suppression may be a useful biomarker for antidepressant effect (9, 10, 12). Indeed, paroxetine at a dose of 10 mg/kg significantly decreased REM sleep duration and prolonged REM sleep latency under the current experimental conditions (data not shown). Thus, our results in this study indicate that lurasidone might have antidepressant effect. Lurasidone has already been shown to be effective in animal models of depression (1) and in patients with bipolar disorder (5, 6). The results of this study add to this profile by supporting the efficacy of lurasidone for depressive symptoms.

The sleep-inducing effect of lurasidone might be caused by its antagonism of the 5-HT2A receptor. As described by Morairty et al. (13), MDL100907, a 5-HT2A receptor–selective antagonist, increased NREM sleep and delta power during NREM sleep. Those effects are consistent with the current results. However, MDL100907 did not affect REM sleep. With regard to REM suppression, 5-HT1A receptor activation and 5-HT7 receptor inhibition might be candidate mechanisms. Indeed, Monti et al. reported that administration of buspirone or ipsapirone, both of which are 5-HT1A receptor partial agonists, suppresses REM in rats. In addition, the 5-HT7 receptor antagonists, SB-269970 and JNJ-18038683, have been reported to exhibit REM-suppressive and antidepressant-like effects in animals and humans (12, 14, 15). Consistent with these findings, our unpublished data show that tandospirone, a 5-HT1A receptor partial agonist, and SB-258741, a 5-HT7 receptor antagonist, suppress REM sleep (data not shown). As several neurotransmitters and receptor subtypes control sleep in a complex way, the effects of lurasidone on sleep architecture in this study may have resulted from a combination of mechanisms involving 5-HT2A, 5-HT1A, and 5-HT7 receptors. To clarify the exact contribution of each receptor, direct experiments aimed at inhibiting the effects of lurasidone on sleep are needed.

In conclusion, analysis of rat sleep EEG in the non-active phase revealed that lurasidone induces sleep and suppress its fragmentation. Our results also show that lurasidone suppresses REM sleep, which served as an index of antidepressant effect. These findings suggest that lurasidone can improve sleep disorders associated with psychosis, including schizophrenia and bipolar disorder.

Conflicts of Interest

All authors are employees of Sumitomo Dainippon Pharma Co., Ltd., and there are no known conflicts of interest associated with this publication.
References


