

## Full Paper

## Characteristic Effects of Anti-dementia Drugs on Rat Sleep Patterns

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Received September 1, 2008; Accepted January 21, 2009

**Abstract.** The present study was undertaken to clarify the effects of anti-dementia drugs on sleep pattern in rats. Electrodes were chronically implanted into the frontal cortex and the dorsal neck muscle of rats for the electroencephalogram (EEG) and electromyogram (EMG), respectively. EEG and EMG were recorded with an electroencephalograph. SleepSigh ver. 2.0 was used for analysis of the sleep–wake state. Total times of waking, non-rapid eye movement (non-REM) sleep, and rapid eye movement (REM) sleep were measured from 10:30 to 16:30. Galantamine had no significant influence on the sleep pattern. On the other hand, donepezil and memantine showed significant increases in sleep latency and total waking time and a decrease in total non-REM sleep time. Furthermore, memantine decreased total REM sleep time. To investigate the characteristics of non-REM sleep in detail, non-REM sleep was classified as stage 1, 2, or 3 according to the depth of sleep. Different from donepezil and galantamine, memantine significantly decreased stage 1 and increased stage 3 in non-REM sleep. From these findings, it can be concluded that galantamine caused no sleep disturbance, different from donepezil and memantine.

**Keywords:** donepezil, galantamine, memantine, sleep–wake pattern, dementia

## Introduction

Alzheimer's disease (AD) is the most common form of dementia. The pathology of AD is a neurodegenerative disorder, regardless of age, characterized by cognitive dysfunction, including loss of memory, judgment, and comprehension. These symptoms are accompanied by behavioral and mood disturbances. In addition, insomnia is also often observed in patients with AD (1, 2). It seems likely that insomnia in AD occurs by damage to the neuronal pathways that participate in the initiation and maintenance of sleep. It is clear that sleep disorders influence the social life of patients and caregivers by decreasing their quality of life (QOL).

In general, acetylcholinesterase inhibitors are widely used for the treatment of mild or moderate AD. Donepezil is a centrally acting selective, competitive, and reversible acetylcholinesterase inhibitor (3). Galantamine, a tertiary alkaloid extracted from the several species of *Amaryllidaceae*, is an acetylcholinesterase inhibitor that also acts

as an allosterically potentiating ligand on nicotinic acetylcholine receptors (4, 5). On the other hand, memantine is well known to act as an antagonist on *N*-methyl-D-aspartic acid (NMDA) receptors and has a protective effect against neuronal damage induced by excess glutamic acid (6). Clinically, memantine is used for the treatment of moderate or severe AD, especially in developed regions, including the USA and Europe (7).

It is well recognized that donepezil causes sleep disturbance in humans (8, 9). In addition, Wisor et al. (10) confirmed that donepezil caused a significant increase of sleep latency in a transgenic mouse model of AD. On the other hand, it has been reported that galantamine caused no significant changes in the sleep–wake pattern in humans (11); however, there is no report about the effect of galantamine on the sleep–wake pattern in animals. As for memantine, there is as yet little information as to whether the drug influences the sleep–wake pattern.

The present study was therefore performed to clarify the characteristic properties of sleep–wake patterns induced by donepezil, galantamine, and memantine in rats.

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Published online in J-STAGE  
doi: 10.1254/jphs.08229FP

## Materials and Methods

### *Animals*

Male Wistar rats weighing 220–350 g (Japan SLC, Shizuoka) were used. All animals were maintained in an air-conditioned room with controlled temperature ( $24 \pm 2^\circ\text{C}$ ) and humidity ( $55 \pm 15\%$ ). They were housed in aluminum cages with sawdust and kept under a light-dark cycle (lights on from 07:00 to 19:00). The animals were allowed free access to food and water, except during the experiments. All procedures involving animals were conducted in accordance with the Guidelines for Animal Experiments at Okayama University Advanced Science Research Center.

### *Surgery*

The animals were anesthetized with pentobarbital sodium (Nembutal<sup>®</sup>, 35 mg/kg, i.p.; Abbott Laboratories, North Chicago, IL, USA) and then fixed to a stereotaxic apparatus (SR-5N; Narishige, Tokyo). For electroencephalogram (EEG) recording, a stainless steel screw electrode (800  $\mu\text{m}$  in diameter) was chronically implanted into the right frontal cortex (A: 0.5, L: 3.0), according to the atlas of Paxinos and Watson (12). A stainless steel screw fixed in the left frontal bone served as a reference electrode. To record the electromyogram (EMG), stainless steel wire electrodes (200  $\mu\text{m}$  in diameter) were implanted into the dorsal neck muscle. The electrodes were connected to a miniature receptacle, and the whole assembly was fixed to the skull with dental cement. At least 7 days were allowed for recovery from the surgery.

### *EEG and EMG recordings*

EEG and EMG were recorded with an electroencephalograph (Model EEG 4314; Nihon Kohden, Tokyo) for 6 h (10:30–16:30). The recording was carried out according to the previously described method (13–15). The signals were amplified and filtered (EEG, 0.5–30 Hz; EMG, 16–128 Hz), digitized at a sampling rate of 128 Hz, and recorded using the data acquisition program SleepSign ver. 2.0 (Kissei Comtec, Nagano). EEG and EMG of the rat were measured in a cylindrical plastic cage (diameter, 26 cm; height, 31 cm) with a floor covered with sawdust. The observation cage was placed in a sound-proof and electrically shielded box (70  $\times$  60  $\times$  60 cm).

### *Sleep–wake state analysis*

Sleep–wake states were automatically classified by 10-s epochs as awake, non-rapid eye movement (non-REM), or rapid eye movement (REM) sleep by SleepSign ver. 2.0, according to the previously described criteria

(16, 17). As a final step, the defined sleep–wake stages were examined visually and corrected if necessary. Each state was characterized as follows: wakefulness, low-amplitude EEG and high-voltage EMG activities; non-REM sleep, high-amplitude slow or spindle EEG and low-voltage EMG activities; REM sleep, low-voltage EEG and EMG activities. Sleep latency was defined as the time from the start of the experiment up to the first 12 consecutive 10-s epochs of sleep.

### *Classification of sleep stages*

Non-REM sleep was classified as stage 1, 2, or 3 according to the following criteria: Stage 1, light stage of sleep, was defined as the state including only spindles. Stage 2, intermediate stage of sleep, was defined as the state including spindles and delta waves. Stage 3, deep stage of sleep, was defined as the state including only delta waves. The spindle (9–16 Hz) and delta waves (0.5–4 Hz) were analyzed by SleepSign ver. 2.0. The percentage of each sleep stage was calculated by the following equation: Percentage of sleep stage (%) = stage 1, 2, or 3 sleep time / non-REM sleep time  $\times$  100.

### *Calculation of delta activity during non-REM sleep*

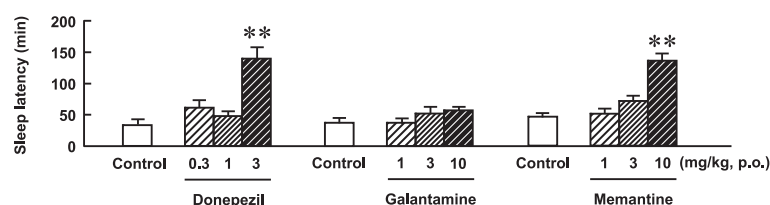
Delta activity during non-REM sleep was determined using SleepSign ver. 2.0. The power spectrum densities, integrated and averaged, could be divided into 4 frequency areas: delta wave (0.5–4 Hz), theta wave (4–8 Hz), alpha wave (8–13 Hz), and beta wave (13–30 Hz). Delta activity (%) was calculated by the following equation: Delta activity (%) = delta wave power density in the drug administration period / delta wave power density in the vehicle administration period in each animal  $\times$  100.

### *Drugs*

The following drugs were used: donepezil hydrochloride (Toront Research Chemicals Inc., North York, ON, Canada), galantamine hydrobromide (Janssen Pharmaceutical KK, Tokyo), and memantine hydrochloride (Sigma, St. Louis, MO, USA). Donepezil, galantamine, and memantine were dissolved in distilled water. The drugs were administrated orally at 10:30, and EEG and EMG were measured for 6 h after drug administration. Drugs were administrated at intervals of 7 days when the same rats were used for repeated experiments. Each rat was subjected to experimentation four times, and the doses of each drug were administered using a crossover design.

### *Data analyses and statistics*

Values shown are the means  $\pm$  S.E.M. One-way analysis of variance (ANOVA) with Dunnett's test was



**Fig. 1.** Effects of anti-dementia drugs on sleep latency. Columns and vertical bars represent the means  $\pm$  S.E.M. ( $n = 8$ ). Drugs were administrated orally. \*\* $P < 0.01$ : significantly different from the control group.

used to estimate drug effects. A  $P$ -value  $< 0.05$  was considered significant.

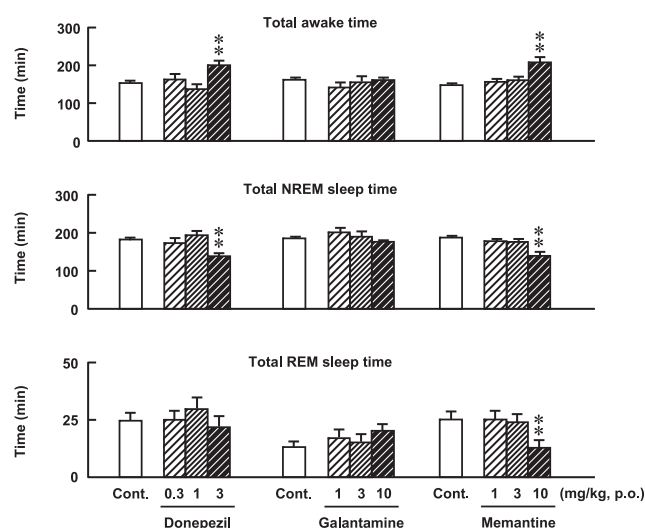
## Results

### Effect on sleep latency

Donepezil and memantine at a dose of 3 and 10 mg/kg, respectively, caused a significant increase of sleep latency. On the other hand, galantamine caused no significant increase of sleep latency even at a dose of 10 mg/kg (Fig. 1).

### Effect on total times of wakefulness, non-REM sleep, or REM sleep

Donepezil and memantine at a dose of 3 and 10 mg/kg, respectively, caused a significant increase in the total awake time and decrease in the total non-REM sleep time. In addition, memantine at a dose of 10 mg/kg caused a significant decrease in the total REM

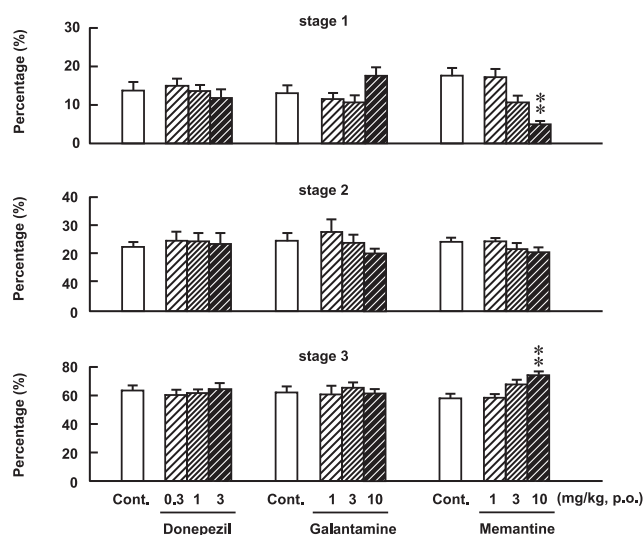


**Fig. 2.** Effects of anti-dementia drugs on total awake, total non-REM sleep, and total REM sleep times. Columns and vertical bars represent the means  $\pm$  S.E.M. ( $n = 8$ ). Drugs were administrated orally. \*\* $P < 0.01$ : significantly different from the control group.

**Table 1.** Effects of anti-dementia drugs on hourly non-REM sleep time

	non-REM sleep time (min)					
	0–1 h	1–2 h	2–3 h	3–4 h	4–5 h	5–6 h
Donepezil (mg/kg, p.o.)						
Control	20.1 $\pm$ 2.0	31.0 $\pm$ 2.3	31.8 $\pm$ 1.8	32.9 $\pm$ 1.9	34.5 $\pm$ 1.3	32.2 $\pm$ 1.6
0.3	14.6 $\pm$ 2.1	30.0 $\pm$ 3.8	30.9 $\pm$ 2.4	33.3 $\pm$ 2.4	32.6 $\pm$ 2.3	31.3 $\pm$ 3.1
1	18.8 $\pm$ 3.2	31.1 $\pm$ 2.3	35.1 $\pm$ 1.4	35.8 $\pm$ 1.6	36.6 $\pm$ 2.5	36.5 $\pm$ 2.9
3	9.2 $\pm$ 1.1**	13.8 $\pm$ 1.9**	19.1 $\pm$ 3.3**	23.3 $\pm$ 2.4*	34.7 $\pm$ 3.1	37.8 $\pm$ 2.0
Galantamine (mg/kg, p.o.)						
Control	20.8 $\pm$ 2.8	30.8 $\pm$ 1.7	32.0 $\pm$ 1.7	32.6 $\pm$ 2.1	35.9 $\pm$ 1.9	33.3 $\pm$ 2.1
1	20.6 $\pm$ 3.2	34.1 $\pm$ 2.7	37.0 $\pm$ 2.1	36.8 $\pm$ 2.4	36.4 $\pm$ 2.1	36.8 $\pm$ 1.7
3	18.7 $\pm$ 4.9	27.7 $\pm$ 2.8	32.6 $\pm$ 1.9	37.0 $\pm$ 1.9	39.5 $\pm$ 2.3	35.0 $\pm$ 3.6
10	14.9 $\pm$ 0.8	26.3 $\pm$ 0.9	33.2 $\pm$ 1.6	33.7 $\pm$ 1.2	35.0 $\pm$ 1.4	33.6 $\pm$ 1.3
Memantine (mg/kg, p.o.)						
Control	18.3 $\pm$ 2.2	33.9 $\pm$ 2.2	29.9 $\pm$ 1.6	35.4 $\pm$ 1.8	34.5 $\pm$ 1.8	35.9 $\pm$ 1.6
1	16.8 $\pm$ 2.5	32.0 $\pm$ 2.4	32.2 $\pm$ 1.7	33.8 $\pm$ 1.5	35.0 $\pm$ 1.3	28.7 $\pm$ 1.8
3	13.6 $\pm$ 0.9	26.9 $\pm$ 3.7	29.6 $\pm$ 1.9	36.8 $\pm$ 1.8	37.4 $\pm$ 1.8	31.6 $\pm$ 1.9
10	5.2 $\pm$ 1.7**	8.6 $\pm$ 2.0**	14.6 $\pm$ 3.5**	34.9 $\pm$ 4.9	36.3 $\pm$ 2.4	39.9 $\pm$ 3.1

Each value represents the means  $\pm$  S.E.M. of 8 rats. \*\*\*: Significantly different from the control group at  $P < 0.05$  and  $P < 0.01$ , respectively (Dunnett's test).



**Fig. 3.** Effects of anti-dementia drugs on percentage of sleep stages of non-REM sleep. Columns and vertical bars represent the means  $\pm$  S.E.M. ( $n = 8$ ). Drugs were administrated orally. Percentage (%) = stage 1, 2, or 3 sleep time / non-REM sleep time  $\times 100$ . \*\* $P < 0.01$ : significantly different from the control group.

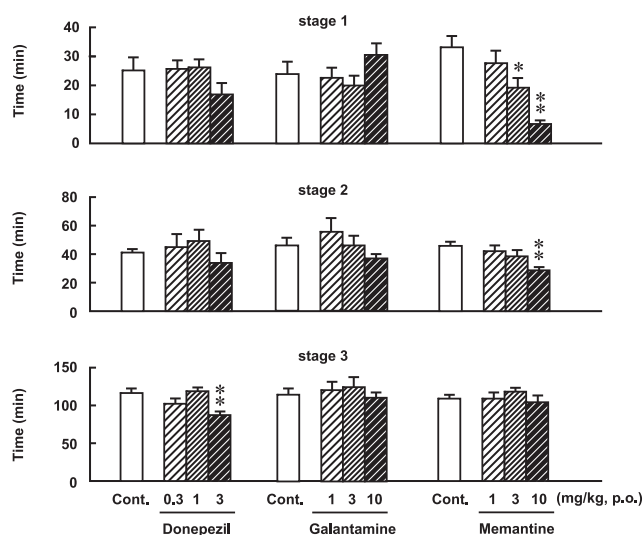
sleep time. On the other hand, galantamine caused no significant changes in total awake, total non-REM sleep, or total REM sleep times (Fig. 2).

#### Effect on hourly non-REM sleep time

Donepezil and memantine at a dose of 3 and 10 mg/kg, respectively, caused an increase in hourly non-REM sleep and these effects lasted for 4 or 3 h, respectively. On the other hand, galantamine caused no significant changes in hourly non-REM sleep time during 0–6 h (Table 1).

#### Effect on sleep stages of non-REM sleep

We examined three sleep stages (stage 1, 2, and 3) of non-REM sleep as an indicator of sleep quality after drug administration. Donepezil at a dose of 3 mg/kg caused a significant decrease in real time of stage 3. Galantamine caused no significant changes in all sleep stages of non-REM sleep. On the other hand, memantine at doses of 3 and 10 mg/kg caused significant decreases in real time of stage 1. Memantine at a dose of 10 mg/kg showed a significant decrease in percentage of stage 1 and real time of stage 2 and a significant increase in the percentage of stage 3 (Figs. 3 and 4). Although memantine at a dose of 10 mg/kg caused no significant changes in real time of stage 3 at 0–6 h, a significant decrease in real time of stage 3 at 0–3 h and a significant increase in real time of stage 3 at 3–6 h were observed (data not shown).



**Fig. 4.** Effects of anti-dementia drugs on real time of sleep stages of non-REM sleep. Columns and vertical bars represent the means  $\pm$  S.E.M. ( $n = 8$ ). Drugs were administrated orally. \* $P < 0.05$ , \*\* $P < 0.01$ : significantly different from the control group.

#### Effect on delta activity during non-REM sleep

Next, we calculated delta activity as an indicator of sleep quality and intensity after drug administration. Donepezil at a dose of 3 mg/kg showed a significant decrease in delta activity at 1–2 h. In contrast, memantine at a dose of 10 mg/kg caused a significant increase in delta activity at 3–6 h. On the other hand, galantamine caused no significant changes in delta activity during non-REM sleep (Table 2).

#### Discussion

It has been reported that donepezil at a dose of 2.5 mg/kg improved amyloid  $\beta$ -induced memory impairment in rats (18). Galantamine is reported to improve scopolamine-induced amnesia in rats at doses of 0.3–3 mg/kg (19). As for memantine, there are reports that the drug is effective in long-term spatial memory failure and amyloid  $\beta$ -induced memory impairment at a dose 5–7.5 and 20 mg/kg, respectively (19, 20). In the present study, therefore, we used the same dose levels as effective in the rat memory dysfunction model.

As shown in Fig. 1 and Table 1, it was found that donepezil caused significant increases in sleep latency and awake time and a decrease of non-REM sleep time in rats that lasted for 4 h. Almost the same findings were reported by Wisor et al. (10); that is, donepezil at doses of 2 and 4 mg/kg caused a significant prolongation of sleep latency in mice, although no significant effect was observed in the sleep–wake cycle. From these findings,

**Table 2.** Effects of anti-dementia drugs on delta activity during non-REM sleep

	Delta activity (%)					
	0 – 1 h	1 – 2 h	2 – 3 h	3 – 4 h	4 – 5 h	5 – 6 h
Donepezil (mg/kg, p.o.)						
Control	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
0.3	107.3 ± 16.2	90.4 ± 13.3	104.3 ± 11.2	104.9 ± 8.1	104.2 ± 9.3	103.1 ± 14.4
1	107.0 ± 16.1	90.6 ± 11.2	105.6 ± 12.2	117.4 ± 8.3	117.5 ± 12.9	106.3 ± 8.5
3	77.3 ± 13.5	50.1 ± 4.0**	125.7 ± 44.7	104.4 ± 7.1	139.9 ± 18.8	135.6 ± 19.1
Galantamine (mg/kg, p.o.)						
Control	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
1	85.7 ± 8.7	135.9 ± 18.9	110.6 ± 6.1	130.0 ± 13.3	113.0 ± 8.3	108.7 ± 8.4
3	99.3 ± 15.3	95.5 ± 13.2	109.0 ± 11.4	125.4 ± 8.5	110.9 ± 12.0	119.0 ± 16.1
10	84.6 ± 12.8	79.9 ± 8.6	108.8 ± 12.0	89.4 ± 7.1	91.4 ± 14.1	90.3 ± 10.0
Memantine (mg/kg, p.o.)						
Control	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
1	110.7 ± 22.5	108.8 ± 9.6	127.7 ± 17.1	110.1 ± 15.8	110.2 ± 16.6	82.5 ± 7.4
3	113.9 ± 33.2	117.3 ± 13.3	130.1 ± 7.3	132.2 ± 4.4	123.5 ± 4.5	111.5 ± 9.6
10	65.7 ± 9.2	86.7 ± 23.7	137.3 ± 20.4	184.3 ± 17.9**	153.7 ± 11.6**	158.2 ± 15.5**

Each value represents the means ± S.E.M. of 8 rats. Delta activity (%) = delta wave power density during the drug administration period / delta wave power density during the vehicle administration period in each animal × 100. \*\*: Significantly different from the control group at  $P < 0.01$  (Dunnett's test).

it is reasonable to conclude that donepezil caused sleep disturbance in animals. On the other hand, in a clinical study, Ancoli-Israel et al. (8) showed that donepezil tended to worsen the Pittsburgh Sleep Quality Index (PSQI), used as an indicator of sleep quantity and quality; therefore, we studied the effect on delta activity during non-REM sleep to investigate sleep quality in rats (15, 21). As shown in Table 2, donepezil caused a significant decrease in delta activity at 1 – 2 h. As shown in Figs. 3 and 4, we found that donepezil decreased the real time of stage 3 (deep stage of non-REM sleep). The percentage and the real time of stages in non-REM sleep are the index meaning the frequency of light or deep sleep similar to slow-wave sleep in the previous report (21). On the other hand, delta activity during non-REM sleep means the depth of sleep. From these findings, it became clear that donepezil caused not only a decrease in non-REM sleep time but also deterioration of sleep quality in rats. There are some reports that acetylcholinesterase-inhibiting activity is responsible for sleep disturbance in both humans and animals. For instance, rivastigmine significantly increased the number of awakenings at night in an older human group (22), and physostigmine significantly decreased total sleep time in humans (23). In animals, Wisor et al. (10) reported that donepezil caused a prolongation of sleep latency in mice; therefore, it is reasonable to presume that the arousal effect of donepezil is revealed through its

acetylcholinesterase-inhibiting action.

In the present study, galantamine showed no significant effects on sleep patterns in rats. It has also been reported that galantamine had no remarkable effect on the sleep–wake pattern in humans (11, 24). Geerts et al. (25) and Ogura et al. (26) reported that the acetylcholinesterase-inhibiting action of galantamine is weaker than those of donepezil, rivastigmine, and physostigmine; therefore, it seems likely that the differences in sleep patterns among these drugs may be due to the potency of acetylcholinesterase-inhibiting activity.

As shown in Fig. 1, similar to donepezil, memantine caused significant increases in sleep latency and total wakefulness time and decreases of total non-REM sleep time and total REM sleep time in rats. In addition, these effects induced by memantine lasted for 3 h. As shown above, memantine had NMDA-antagonistic activity. It is well known that MK-801, a drug showing NMDA-receptor antagonistic activity, caused hyperlocomotion in rats (27). Almost identical results were obtained with NPC 12626, an NMDA-receptor antagonist, in rats (28). Spanagel et al. (29) reported that memantine at a dose of 10 mg/kg enhanced dopamine release in the prefrontal cortex of the rat. It is well known that dopaminergic stimulation makes relatively large contributions to the arousal effect (30). Furthermore, it has been reported that an NMDA-receptor antagonist, MK-801, and phencyclidine stimulate locomotor activity by dopamine

neurotransmission (31); therefore, it is logical to believe that memantine disturbed sleep via the dopaminergic system. As shown in Fig. 3, we found that memantine decreased the percentage of stage 1 (light stage of non-REM sleep) and increased the percentage of stage 3 (deep stage of non-REM sleep). Almost the same results were observed in real time of stages of non-REM sleep. As shown in Fig. 4, memantine decreased the real time of stage 1 and stage 2. In addition, the drug caused a significant increase in delta activity at 3–6 h, a significant decrease in real time of stage 3 at 0–3 h, and a significant increase in real time of stage 3 at 3–6 h. The increase of sleep quality at 3–6 h induced by memantine may be due to the compensatory action of its insomnia effect representing an increase in sleep latency and decrease in deep stage of non-REM sleep at 0–3 h.

From these findings, it can be concluded that galantamine may be a useful anti-dementia drug that does not cause sleep disorders, different from donepezil and memantine. In addition, it was clarified that donepezil decreased sleep quality and that memantine decreased sleep quality at 0–3 h and increased sleep quality at 3–6 h.

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