*Full Paper***Effects of Some Antipsychotics and a Benzodiazepine Hypnotic on the Sleep-Wake Pattern in an Animal Model of Schizophrenia**Takayuki Ishida¹, Yoshihito Obara¹, and Chiaki Kamei^{1,*}¹*Department of Medicinal Pharmacology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 1-1-1 Tsushima-Naka, Okayama 700-8530, Japan**Received May 10, 2009; Accepted July 6, 2009*

Abstract. We studied the effects of antipsychotics and a hypnotic on sleep disturbance in schizophrenia using an animal model of the disease. Electrodes for the electroencephalogram (EEG) and electromyogram (EMG) were chronically implanted into the cortex and the dorsal neck muscle of rats. EEG and EMG were recorded with an electroencephalograph for 6 h (10:00 – 16:00). SleepSign ver. 2.0 was used for EEG and EMG analysis. Haloperidol and olanzapine had an antagonizing effect on the increases in sleep latency and total awake time and the decrease in total non-rapid eye movement (NREM) sleep time induced by MK-801. Olanzapine also antagonized the decrease in total rapid eye movement (REM) sleep time induced by MK-801. Aripiprazole antagonized only the increase in sleep latency induced by MK-801, whereas, risperidone, quetiapine, and flunitrazepam had no effect in the changes of sleep-wake pattern induced by MK-801. Olanzapine increased delta activity and decreased beta activity during NREM sleep. In contrast, flunitrazepam had an opposite effect. It was clarified that haloperidol and olanzapine were effective for decrease of sleep time in this animal model of schizophrenia. In addition, aripiprazole showed a sleep-inducing effect in schizophrenia model rat. On the other hand, flunitrazepam showed no beneficial effect on sleep disturbance in schizophrenia model rat.

Keywords: antipsychotic, benzodiazepine hypnotic, sleep-wake pattern, MK-801, schizophrenia

Introduction

Haloperidol is a representative typical antipsychotic drug and has potent dopamine receptor antagonistic activity; however, various atypical antipsychotics have been developed recently and classified into three groups: serotonin-dopamine antagonists (risperidone), multi-acting receptor-targeted antipsychotics (olanzapine and quetiapine), and a dopamine system stabilizer (aripiprazole). These antipsychotics are recommended for use according to each symptom observed in schizophrenia patients. It is usually recognized that schizophrenia patients suffer from insomnia. For instance, polysomnographic sleep studies on schizophrenia patients have revealed a number of abnormalities, including decreased total sleep time and sleep efficiency, reduced slow-wave sleep, and prolonged sleep latency (1 – 3). Although it is

clear that sleep disturbance deteriorates the social life of patients and care givers, there is little information about the characteristic properties of antipsychotics in the sleep-wake pattern of schizophrenia patients.

Abnormalities in several neurotransmitters have been found in the brain of patients with schizophrenia, and much attention has focused on the roles of dopamine and glutamate neurotransmission underlying the disease. As for glutamate neurotransmission, dysfunction of the *N*-methyl-D-aspartic acid (NMDA) receptor is believed to be associated with a number of neuropsychiatric disorders, including schizophrenia. Recently, animal models of schizophrenia have been established and used for the development of new antipsychotic drugs. For example, an NMDA-receptor antagonist MK-801 caused schizophrenia-like symptoms such as impaired pre-pulse inhibition, hyperlocomotion, social interaction deficits, and spatial memory deficits in rats (4 – 6). On the other hand, there are some reports regarding the correlation between symptom clusters of schizophrenia and electroencephalogram (EEG) abnormalities in rats

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and humans (7, 8). However, little work has been done on not only the sleep-wake pattern in an animal model of schizophrenia but also the effects of antipsychotics on the sleep-wake pattern in MK-801-treated animals. At present, benzodiazepine derivatives are widely administered for the treatment of insomnia in schizophrenia (9).

In the present study, therefore, we studied the effect of MK-801 on the sleep-wake pattern and the effects of haloperidol, risperidone, olanzapine, quetiapine, aripiprazole, and flunitrazepam on the changes in sleep patterns induced by MK-801. Sleep latency, total awake, non-rapid eye movement (NREM), and rapid eye movement (REM) sleep times were used as sleep parameters. In addition, cortical EEG power spectrum was used for detecting sleep quality and sleep characteristics.

Materials and Methods

Animals

Male Wistar rats weighing 220–350 g (Japan SLC, Shizuoka) were used. There are no significant changes of weight gain in some drug-treated rats compared with non-treated rats. 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®, 35 mg/kg, i.p.; Abbott Laboratories, North Chicago, IL, USA) and then fixed to a stereotaxic apparatus (SR-5N; Narishige, Tokyo). For EEG recording, a stainless steel screw electrode (800 μm in diameter) was chronically implanted into the left frontal cortex (A: +1.0, L: -2.0) according to the atlas of Paxinos and Watson (10). 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 μm 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 electro-

encephalograph (Model EEG 4314; Nihon Kohden, Tokyo) for 6 h (10:00–16:00). The recording was carried out according to a method described previously (11, 12). The signals were amplified and filtered (EEG, 0.5–30 Hz; EMG, 16–128 Hz) and then 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 its floor covered with sawdust. The observation cage was placed in a sound-proof and electrically shielded box (70 × 60 × 60 cm).

Sleep-wake state analysis

The sleep-wake states were automatically classified by 10-s epochs as awake, NREM, or REM sleep by SleepSign ver. 2.0, according to the previously described criteria (13, 14). 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; NREM 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.

Calculation of delta and beta activity during NREM sleep

Delta activity during NREM 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 (%) and beta activity (%) were calculated using following equation: Delta (beta) activity (%) = [delta (beta) wave power density in the drug administration period] / [delta (beta) wave power density in vehicle administration period in each animal] × 100.

Drugs

The following drugs were used: MK-801 (Sigma, St. Louis, MO, USA), haloperidol (Serenace®; Dainippon Sumitomo, Osaka), risperidone (Risperdal®; Janssen Pharmaceutical K.K., Tokyo), olanzapine (Zyprexa®; Eli Lilly Japan K.K., Tokyo), aripiprazole (Ebilify®; Otsuka, Tokyo), quetiapine (Seroquel®; Astellas, Tokyo), and flunitrazepam (Silece®; Eisai, Tokyo). MK-801 was dissolved in physiological saline and intraperitoneally injected just before oral administration of antipsychotics or a hypnotic. The drugs, except for MK-801, were suspended in 0.5% carboxymethylcellulose solution

and administered orally at 10:00. EEG and EMG were measured for 6 h immediately after drug administration. Drugs were administered at intervals of 7 days when the same rats were used for repeated experiments.

Data analyses and statistics

Values shown are the mean $\pm$ S.E.M. One-way analysis of variance (ANOVA) with Dunnett's test was used to estimate the drug effects. The paired *t*-test was used to estimate delta or beta activity during NREM sleep. A *P*-value less than 0.05 was considered significant.

Results

Effect of MK-801 on the sleep-wake pattern and hourly awake time

MK-801 at doses of 0.05 and 0.1 mg/kg caused significant increases in sleep latency and total awake time and decreases in total NREM sleep and total REM sleep times. In addition, MK-801 caused a significant increase in hourly awake time (0.05 mg/kg, 0–1, 1–2, and 2–3 h; 0.1 mg/kg, 0–1, 1–2, 2–3, 3–4, and 4–5 h) (Fig. 1 and Table 1).

Effects of antipsychotics and flunitrazepam on changes in the sleep-wake pattern induced by MK-801 during the 6-h recording period

Haloperidol at doses of 0.3 and 1 mg/kg caused a significant antagonizing effect on an increase in sleep latency induced by MK-801. The drug at a dose of 1 mg/kg also antagonized an increase in total awake time and decrease in total NREM sleep time induced by MK-801. Risperidone caused no antagonization of the sleep disturbance induced by MK-801 (Fig. 2A). Olanzapine at doses of 2 and 5 mg/kg caused a significant antagonizing effect on the increase in total awake time and decrease in total NREM sleep time induced by MK-801. The drug at a dose of 5 mg/kg also significantly antagonized the increase in sleep latency and the

decrease in total REM sleep time induced by MK-801. Quetiapine even at a dose of 30 mg/kg caused no antagonization of the sleep disturbance induced by

Fig. 1. Effect of MK-801 on the sleep-wake pattern. Columns and vertical bars represent the mean $\pm$ S.E.M. ($n = 8$). Drug was injected intraperitoneally. *, **: Significantly different from the control group at $P < 0.05$ and $P < 0.01$, respectively (ANOVA with Dunnett's test). Sleep latency, total awake time, total NREM sleep time, and total REM sleep time: $F_{4,35} = 23.75, 19.02, 14.87$, and 8.65 , respectively.

Table 1. Effect of MK-801 on hourly awake time

	Time (min)					
	0–1 h	1–2 h	2–3 h	3–4 h	4–5 h	5–6 h
MK-801 (mg/kg, i.p.)						
Control	37.4 $\pm$ 2.3	25.6 $\pm$ 2.6	17.1 $\pm$ 2.1	13.4 $\pm$ 1.4	15.3 $\pm$ 1.2	18.9 $\pm$ 2.3
0.01	44.7 $\pm$ 1.8	20.9 $\pm$ 1.3	16.5 $\pm$ 1.5	17.9 $\pm$ 2.1	18.3 $\pm$ 2.7	19.8 $\pm$ 1.8
0.02	40.2 $\pm$ 3.7	26.0 $\pm$ 2.5	18.4 $\pm$ 2.6	17.7 $\pm$ 2.1	19.0 $\pm$ 1.8	16.9 $\pm$ 1.8
0.05	51.9 $\pm$ 2.9**	45.5 $\pm$ 2.3**	31.5 $\pm$ 2.0**	21.5 $\pm$ 2.9	20.6 $\pm$ 2.2	18.1 $\pm$ 1.4
0.1	49.6 $\pm$ 3.3*	48.0 $\pm$ 3.2**	44.4 $\pm$ 3.8**	36.7 $\pm$ 3.6**	27.9 $\pm$ 3.7**	20.7 $\pm$ 3.0

Each value represents the mean $\pm$ S.E.M. of 8 rats. *, **: Significantly different from the control group at $P < 0.05$ and $P < 0.01$, respectively. (Dunnett's test). $F_{4,35} = 4.47, 25.93, 23.67, 12.75, 3.66$, and 0.49 .

Fig. 2. Effects of antipsychotics and flunitrazepam on changes in the sleep-wake pattern. A: Effects of haloperidol and risperidone on the sleep disturbance induced by MK-801. Columns and vertical bars represent the mean $\pm$ S.E.M. ($n = 8$). Antipsychotics were administered orally, and MK-801 was injected intraperitoneally. *: Significantly different from the control group at $P < 0.05$ (ANOVA with Dunnett's test). Sleep latency, total awake time, total NREM sleep time, and total REM sleep time: haloperidol-treated group, $F_{3,28} = 5.13, 3.70, 4.05$, and 1.43 , respectively; risperidone-treated group, $F_{3,28} = 0.10, 0.54, 0.63$, and 2.70 , respectively. B: Effects of olanzapine and quetiapine on the sleep disturbance induced by MK-801. Columns and vertical bars represent the mean $\pm$ S.E.M. ($n = 8$). Antipsychotics were administered orally, and MK-801 was injected intraperitoneally. *, **: Significantly different from the control group at $P < 0.05$ and $P < 0.01$, respectively (ANOVA with Dunnett's test). Sleep latency, total awake time, total NREM sleep time, and total REM sleep time: olanzapine-treated group, $F_{3,28} = 7.73, 19.86, 18.90$, and 7.61 , respectively; quetiapine-treated group, $F_{3,28} = 0.47, 0.72, 0.67$, and 0.91 , respectively. C: Effects of aripiprazole and flunitrazepam on the sleep disturbance induced by MK-801. Columns and vertical bars represent the mean $\pm$ S.E.M. ($n = 8$). The antipsychotic and hypnotic were administered orally, and MK-801 was injected intraperitoneally. *: Significantly different from the control group at $P < 0.05$ (ANOVA with Dunnett's test). Sleep latency, total awake time, total NREM sleep time, and total REM sleep time: aripiprazole-treated group, $F_{3,28} = 3.48, 1.45, 1.97$, and 0.13 , respectively; flunitrazepam-treated group, $F_{3,28} = 0.55, 0.56, 0.42$, and 0.81 , respectively.

MK-801 (Fig. 2B). Aripiprazole at doses of 10 and 20 mg/kg significantly caused an antagonistic effect on the increase in sleep latency induced by MK-801.

Flunitrazepam even at a dose of 5 mg/kg caused no antagonistic effect on the sleep disturbance induced by MK-801 (Fig. 2C).

Table 2. Effects of antipsychotics and flunitrazepam on the changes of hourly awake time induced by MK-801

	Time (min)					
	0–1 h	1–2 h	2–3 h	3–4 h	4–5 h	5–6 h
Haloperidol (mg/kg, p.o.) + MK-801 (0.05 mg/kg, i.p.)						
Control	54.2 ± 1.2	41.4 ± 1.9	29.7 ± 3.5	24.7 ± 1.6	18.7 ± 2.1	22.7 ± 1.5
0.3	47.3 ± 3.1	27.0 ± 3.3**	17.5 ± 2.8*	19.0 ± 2.7	19.8 ± 1.9	19.9 ± 2.7
1	42.6 ± 2.2**	28.9 ± 2.5*	15.3 ± 2.3	16.5 ± 2.7	16.5 ± 2.7	19.1 ± 2.7
Risperidone (mg/kg, p.o.) + MK-801 (0.05 mg/kg, i.p.)						
Control	51.7 ± 1.5	48.6 ± 1.6	33.0 ± 2.8	25.7 ± 3.0	17.3 ± 2.6	19.2 ± 2.4
1	48.0 ± 2.6	45.3 ± 1.6	33.7 ± 2.8	28.4 ± 4.6	15.0 ± 3.0	14.7 ± 1.6
3	38.6 ± 2.8**	35.4 ± 3.8*	34.5 ± 3.9	31.4 ± 1.9	20.9 ± 3.3	20.0 ± 3.2
Olanzapine (mg/kg, p.o.) + MK-801 (0.05 mg/kg, i.p.)						
Control	54.0 ± 1.4	49.9 ± 1.8	35.9 ± 3.4	20.0 ± 2.5	20.4 ± 2.4	15.3 ± 2.3
2	46.8 ± 2.2	32.5 ± 3.9**	22.8 ± 3.4*	20.2 ± 2.5	20.4 ± 2.2	16.8 ± 2.5
5	34.3 ± 4.6**	19.9 ± 2.2**	10.8 ± 1.7**	11.1 ± 1.4	12.4 ± 1.8*	12.8 ± 1.0
Quetiapine (mg/kg, p.o.) + MK-801 (0.05 mg/kg, i.p.)						
Control	52.3 ± 1.3	43.3 ± 1.7	29.6 ± 2.5	23.7 ± 2.8	25.6 ± 1.8	23.3 ± 1.6
10	45.2 ± 2.4	37.9 ± 4.0	31.8 ± 3.5	22.6 ± 2.1	22.1 ± 1.8	22.7 ± 2.7
30	45.2 ± 2.6	40.0 ± 1.5	27.6 ± 3.9	27.7 ± 2.6	22.9 ± 1.3	22.4 ± 3.0
Aripiprazole (mg/kg, p.o.) + MK-801 (0.05 mg/kg, i.p.)						
Control	53.2 ± 0.7	47.3 ± 1.7	30.4 ± 3.6	20.8 ± 3.0	19.1 ± 2.2	18.0 ± 1.9
10	47.7 ± 2.6	33.3 ± 3.9*	19.1 ± 2.2	18.9 ± 1.9	18.2 ± 2.9	21.1 ± 1.4
20	47.3 ± 3.3	28.4 ± 5.8**	28.4 ± 5.3	22.3 ± 3.6	23.1 ± 3.6	22.3 ± 2.0
Flunitrazepam (mg/kg, p.o.) + MK-801 (0.05 mg/kg, i.p.)						
Control	51.8 ± 1.2	37.7 ± 2.3	28.2 ± 1.6	24.4 ± 1.6	24.4 ± 1.2	23.6 ± 3.3
2	47.4 ± 4.1	38.3 ± 2.8	29.3 ± 3.0	28.6 ± 2.5	30.3 ± 2.7	28.8 ± 2.9
5	44.5 ± 2.5	37.3 ± 1.9	30.9 ± 2.8	26.7 ± 3.3	27.6 ± 2.7	30.1 ± 2.4

Each value represents the mean ± S.E.M. of 8 rats. *, **: Significantly different from the control group at $P < 0.05$ and $P < 0.01$, respectively. (Dunnett's test). Haloperidol group, $F_{3,28} = 4.66, 5.34, 2.54, 1.82, 0.92$, and 0.48 ; risperidone group, $F_{3,28} = 7.11, 3.55, 0.06, 1.91, 1.07$, and 0.92 ; olanzapine group, $F_{3,28} = 7.31, 21.3, 12.4, 2.05, 2.76$, and 1.25 ; quetiapine group, $3.31, 0.91, 0.56, 0.86, 0.90$, and 0.54 ; aripiprazole group, $F_{3,28} = 2.06, 5.21, 1.83, 0.29, 0.52$, and 2.26 ; flunitrazepam group, $F_{3,28} = 2.47, 0.47, 0.49, 1.30, 1.25$, and 0.90 .

Effects of antipsychotics and flunitrazepam on the changes of hourly awake time induced by MK-801

Haloperidol caused a significant antagonizing effect on the increase in awake time induced by MK-801 (0.3 mg/kg, 1–2 and 2–3 h; 1 mg/kg, 0–1 and 1–2 h). Risperidone significantly antagonized the increase in hourly awake time induced by MK-801 (3 mg/kg, 0–1 and 1–2 h). Olanzapine caused a significant antagonizing effect on the increase in hourly awake time induced by MK-801 (2 mg/kg, 1–2, 2–3 h; 5 mg/kg, 0–1, 1–2, 2–3, and 4–5 h). Quetiapine even at a dose of 30 mg/kg showed no antagonization of the increase in hourly awake time induced by MK-801. Aripiprazole significantly antagonized the increase in hourly awake time induced by MK-801 (10 mg/kg, 1–2 h; 20 mg/kg, 1–2 h). Flunitrazepam even at a dose of 5 mg/kg had no significant antagonizing effect on the

increase in hourly awake time induced by MK-801 (Table 2).

Effects of antipsychotics and flunitrazepam on delta and beta activities during NREM sleep in MK-801-treated rats

Next, we examined delta and beta activities as an indicator of depth of sleep after drug administration. MK-801 even at a dose of 0.1 mg/kg caused no significant changes of delta and beta activities (data not shown); however, to test the drug's effect, MK-801 (0.05 mg/kg)-treated rats were used. Haloperidol and olanzapine caused a significant increase of delta activity in MK-801-treated rats (haloperidol at 1 mg/kg, 0–1 h; olanzapine at 5 mg/kg, 0–1 h). Risperidone and flunitrazepam caused a significant decrease of delta activity in MK-801-treated rats (risperidone at 3 mg/kg, 2–3

Fig. 3. Effects of antipsychotics and flunitrazepam on delta and beta activities during NREM sleep in MK-801-treated rats. Power value of the control was normalized to 100%, and then power values of haloperidol at 1 mg/kg (open circle), risperidone at 3 mg/kg (closed circle), olanzapine at 5 mg/kg (open triangle), quetiapine at 30 mg/kg (closed triangle), aripiprazole at 20 mg/kg (open square), and flunitrazepam at 5 mg/kg (closed square) group were converted to relative power data, respectively. Columns and vertical bars represent the mean $\pm$ S.E.M. ($n = 8$). The antipsychotic and hypnotic were administered orally, and MK-801 was injected intraperitoneally. *, **: Significantly different from the control group at $P < 0.05$ and $P < 0.01$, respectively (paired t -test).

and 3–4 h; flunitrazepam at 5 mg/kg, 2–3, 3–4, 4–5, and 5–6 h). Quetiapine and aripiprazole had no significant effect on delta activity in MK-801-treated rats. On the other hand, flunitrazepam caused a significant increase of beta activity in MK-801-treated rats (flunitrazepam at 5 mg/kg, 0–1, 1–2, and 2–3 h). Risperidone, olanzapine, and quetiapine caused a significant decrease of beta activity in MK-801-treated rats (risperidone at 3 mg/kg, 4–5 and 5–6 h; olanzapine at 5 mg/kg, 3–4, 4–5, and 5–6 h; quetiapine at 30 mg/kg, 2–3, 3–4, and 5–6 h); however, haloperidol and aripiprazole had no significant effect on beta activity in MK-801-treated rats (Fig. 3).

Discussion

It was found that MK-801 at doses of 0.05 and 0.1 mg/kg caused significant increases in sleep latency and total awake time and significant decreases in total

NREM sleep and REM sleep times, indicating that MK-801 had a sleep disturbance effect. We recognized that the sleep disturbance caused by MK-801 showed both difficulty in falling asleep (increased sleep latency) and waking up often during the night (decreased total NREM and REM sleep times). It has been reported that in a novel environment, MK-801 at a dose of 0.3 mg/kg increased locomotor activity in mice (15). Hanania and Zahniser (16) and Monti et al. (17) described that an increase in locomotor activity induced by MK-801 is responsible for dopaminergic stimulation, which contributes to the arousal effect in mammals. From these findings, it is reasonable to presume that MK-801 caused sleep disturbance by elevating dopamine levels in the rat brain. It is well known that activities of daily living are impaired by insomnia in humans. As shown in the present study, the sleep disturbance during the light phase was induced by MK-801 in rats. Although no investigation of sleep-wake pattern during the dark

phase was performed, the following result should be predictable: the activity of the rats during the dark phase may be impaired to some extent because excessive sleepiness was observed after sleep deprivation in rats as reported by Andersen et al. (18) and Machado et al. (19).

Levin et al. (4) reported that MK-801 at a dose of 0.05 mg/kg caused a disturbance of pre-pulse inhibition that is widely used to estimate the effect of antipsychotic drugs. MK-801 at a dose of 0.05 mg/kg showed changes in sleep-wake pattern without causing an increase in general behavior in the present experimental condition; therefore, a dose of 0.05 mg/kg was used to investigate the effects of antipsychotics and a hypnotic on sleep disturbance induced by MK-801. It has been reported that haloperidol (0.1 mg/kg), risperidone (0.3 mg/kg), olanzapine (3 mg/kg), quetiapine (20 mg/kg), and aripiprazole (10 mg/kg) remarkably attenuated the disruption of pre-pulse inhibition in rodents (20–23). In the present study, therefore, we used the effective dose levels in rodent schizophrenia models. As shown in the results, haloperidol at a dose of 1 mg/kg significantly antagonized the increases in sleep latency and total awake time and the decrease in total NREM sleep time induced by MK-801. Olanzapine at a dose of 5 mg/kg also had an antagonizing effect on the increases in sleep latency and total awake time and decreases in total NREM sleep and REM sleep times induced by MK-801. Aripiprazole at doses of 10 and 20 mg/kg significantly antagonized the increase in sleep latency induced by MK-801. Almost identical findings were observed in hourly awake time with haloperidol, olanzapine, and aripiprazole. On the other hand, risperidone at a dose of 3 mg/kg significantly antagonized the increase in hourly awake time at 0–1 and 1–2 h induced by MK-801, although the drug showed no effect on total times of wakefulness, NREM sleep, and REM sleep times. The reason why risperidone showed a significant antagonizing effect on hourly awake time at 0–1 and 1–2 h may be as follows: the effect of risperidone was relatively short acting or the drug showed a depression in the early phase (0–2 h) and stimulation in the late phase (2–6 h). Quetiapine and flunitrazepam even at a high dose had no significant effect on the changes of the sleep-wake pattern induced by MK-801.

It is well known that both typical and atypical antipsychotics showed a dopamine D_2 -receptor antagonistic effect. On the other hand, it has been reported that raclopride and remoxipride (D_2 -receptor antagonist) showed no effect on sleep stages (24). Therefore, the differences of hypnotic effects in some antipsychotics found in our present study may be difficult to explain by their D_2 -receptor antagonistic effects. Haloperidol is known to have an antagonistic effect on α_1 -adreno-

receptors, which is closely related with the regulation of the sleep-wake pattern (25). In addition, Mathe et al. (26) reported that an α_1 -receptor antagonist, prazosin, inhibited the increase of locomotor activity induced by MK-801; therefore, it was thought at the time that the antagonistic effect of haloperidol on sleep disturbance induced by MK-801 may be due to its α_1 -receptor antagonistic activity. As shown in the present study, the effect of olanzapine is similar to that of haloperidol, except for total REM sleep. There are some findings that olanzapine had antagonistic effects against 5-HT_{2A}, H₁, and M₁ receptors (5, 27–30). Richelson et al. (30) reported that olanzapine is a more potent drug for H₁ and M₁ receptors, which make large contributions to the hypnotic effect, than risperidone and quetiapine. We have reported that a 5-HT_{2A}-receptor antagonist, cyproheptadine, caused an increase in REM sleep time and a decrease in total awake time in rats (31); therefore, it is reasonable to assume that the 5-HT_{2A}-receptor antagonistic activity of olanzapine may be responsible for antagonizing the MK-801-induced decrease in total REM sleep time. Aripiprazole antagonized only the increase in sleep latency induced by MK-801. Aripiprazole is well known to have both partial D_2 -receptor and 5-HT_{1A}-receptor agonistic activities; in other words, the drug caused an inhibition or activation of the dopaminergic or serotonergic system under different conditions. As mentioned above, dopaminergic function was considered to be activated by MK-801. Therefore, it is reasonable to presume that aripiprazole inhibits dopaminergic function in MK-801-treated rats. In addition, Hirase et al. (11) reported that a 5-HT_{1A}-receptor agonist, tandospiron, caused a decrease in sleep latency in sleep-disturbed rats; therefore, it is reasonable to consider that the antagonistic activity of aripiprazole on the increase in sleep latency induced by MK-801 was exhibited via the 5-HT_{1A} receptor. As shown previously, risperidone caused an antagonizing effect on the increase in hourly awake time induced by MK-801, although the duration was relatively short. It is well known that risperidone has an antagonistic effect on 5-HT_{2A}; therefore, it was thought at the time that risperidone exerted this effect through the 5-HT_{2A} receptor.

Another point of interest is sleep quality. It is well known that benzodiazepines decrease delta activity and increase beta activity in both animals and humans, and this sleep pattern is considered unphysiological sleep (32, 33). Different from flunitrazepam, olanzapine significantly increased delta activity and decreased beta activity in MK-801-treated rats, indicating that the drug increased the quality of sleep. As for the mechanism, it is well known that the 5-HT_{2A} receptor is closely related with the regulation of slow-wave sleep. For

Table 3. The efficacy of antipsychotics and a benzodiazepine hypnotic on MK-801-induced sleep disturbance

	Haloperidol	Risperidone	Olanzapine	Quetiapine	Aripiprazole	Flunitrazepam
Sleep latency	↓	—	↓	—	↓	—
Awake	↓	—	↓	—	—	—
NREM sleep	↑	—	↑	—	—	—
REM sleep	—	—	↑	—	—	—
Delta activity	↑	↓	↑	—	—	↓
Beta activity	—	↑↓	↓	↓	—	↑

instance, Kantor et al. (34) and Sharpley et al. (35) reported that a 5-HT_{2A}-receptor antagonist, ritanserin, increased the deep stage of sleep and delta activity of the cortical EEG power spectrum in rats; therefore, olanzapine seems to increase sleep quality via 5-HT_{2A} receptors. On the other hand, with the result that flunitrazepam deteriorated sleep quality, it is well known that benzodiazepines bind to the GABA_A receptor benzodiazepine-binding site directly. In the present study, however, flunitrazepam had no effect on the sleep-wake pattern, although the drug decreased delta activity and increased beta activity during NREM sleep. From these results, it can be considered that the mechanism of a benzodiazepine hypnotic is different between the sleep-inducing effect and sleep quality-deteriorating effect. In summary, we showed the efficacy of drugs used in the present study on MK-801-induced sleep disturbance (Table 3).

From the present results, it is concluded that haloperidol, risperidone, olanzapine, and aripiprazole had a sleep-inducing effect, different from quetiapine and flunitrazepam. In addition, olanzapine enhanced sleep quantity and quality in contrast to flunitrazepam.

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