Pharmacology Biochemistry and Behavior, Vol. 57, Nos. 1/2, pp. 361–365, 1997

0091-3057/97 $17.00 + .00

PII S0091-3057(96)00304-8

Effects of Dopamine Antagonists on Changes in Spontaneous EEG and Locomotor Activity in Ketamine-Treated Rats

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Received 25 July 1995; Accepted 11 June 1996

YAMAMOTO M., Y. MIZUKI, M. SUETSUGI, Y. OZAWA, M. OOYAMA AND M. SUZUKI. *Effects of dopamine antagonists on changes in spontaneous EEG and locomotor activity in ketamine-treated rats.* PHARMACOL BIOCHEM BEHAV **57**(1/2), 361–365, 1997.—We investigated the effects of dopamine antagonists on spontaneous cortical and hippocampal electroencephalographic (EEG) changes, and on hyperlocomotion in ketamine-treated rats. Ketamine (20–60 mg/kg IP) synchronized cortical EEG and desynchronized hippocampal EEG in a dose-dependent manner indicating that the drug induced a dissociation between the cortical and hippocampal EEG. These EEG changes were accompanied by an increase in spontaneous locomotor activity, which involved lack of focused direction, stereotypy, irritability and other abnormalities. Dopamine antagonists, such as haloperidol (0.3–1 mg/kg IP) and nemonapride (0.3–1 mg/kg IP), reversed the dissociation between the cortical and hippocampal EEG in ketamine (60 mg/kg IP)-treated rats. Ketamine-induced hyperlocomotion was also decreased by administration of haloperidol (0.3 and 1 mg/kg IP) or nemonapride (0.1–1 mg/kg IP). Thus, it was found that dopamine antagonists reversed the EEG alterations and behavioural changes in ketamine-treated rats. © 1997 Elsevier Science Inc.

EEG Locomotor activity Ketamine Dopamine antagonists Haloperidol Nemonapride Delirium

DELIRIUM is often observed in patients with organic brain syndromes including senile dementia, cerebrovascular disease and head injury. It may also be induced by various drug such as hypnotics (30), minor tranquilizers (35) and cholinolytics (31,35). About 15% of hospitalized aged patients experienced delirium (17). Delirium is classified into two types on the basis of the following characteristics: (1) the hyperaction-hyperalert variant showing abnormal behavior accompanied by hallucination and excitation; and (2) the hypoaction-hypoalert variant, showing disorientation and sedation (18).

The pathogenesis of delirium has been studied with regard to EEG findings (15,16). Patients exhibiting delirium show significant decreases in alpha activity and an increase in theta and delta activities in the cerebral cortex (15). A moderate correlation existed between the degree of EEG abnormality and the degree of confusion or level of arousal (16). Recently, it was reported that stage 1 REM sleep may be related to delirium in patients who do not show inhibition of muscle activity (8). In biperidine (cholinolytic)-treated cats, stage 1 REM sleep was also observed during delirious behavior, manifested as 'hallucination-like' aggressive behavior (14). Somatosensory evoked potentials were altered in delirious patients, with the differences from control values being significant (32). Thus, changes in electrical activity at both cortical and subcortical levels, including the limbic system where emotional function is regulated, may be involved in delirium. Therefore, it may be important to measure changes in electrical activity of both cortical sites and limbic system sites, such as hippocampus, in the study of delirium.

Two animal models, the atropine-treated rat (34) and the biperidine-treated cat (14) have been utilized in investigating the pathogenesis of delirium. Nevertheless, no current animal model is available for evaluating the effect of drugs on delirium. We therefore tried to develop a delirium model for evalu-

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ating drug effects using ketamine-treated rats. Ketamine is an anesthetic agent which is characterized by a rapid onset of action, analgesic properties, and lack of cardiorespiratory depression (38). However, emergence from ketamine anesthesia is often accompanied by sings of delirium such as restlessness, altered mood, psychomotor agitation and hallucination in humans (6,38). The present studies therefore described ketamine-induced EEG and behavioural changes in rats and the effects of the dopamine antagonists, haloperidol (7,12,25) and nemonapride (36,39), currently used for treatment of delirium, on these ketamine-induced changes.

MATERIALS AND METHODS

Animals

Male Wistar rats weighing about 250 g (Japan SLC. Inc., Hamamatsu, Japan) were used. They were kept in a temperature-controlled room at 23 ± 1°C under a 13 h light–dark cycle (light on 1730–2030 h) and given laboratory chow and water ad libitum. Behavioral and EEG studies were performed between 900–1730 h. This study was carried out following approval from the Committee of Animal Experimentation, Yamanouchi Pharmaceutical Co. Ltd.

Spontaneous EEG

Under pentobarbital anesthesia (40 mg/kg IP), electrodes were implanted on the surface of the sensory cortex (A: 0.27, L: 0.20) and hippocampus A: −0.38, L: 0.20, V: −0.28) according to the rat brain atlas of Paxinos and Watson (1986). At least 2 weeks were allowed after surgery before the rats were used for experiments. Ketamine and test drugs were administered concurrently via the intraperitoneal route. Spontaneous EEG was recorded every 10 min for 40 min after the administration of the drugs and analyzed automatically for delta (2–3.75 Hz), theta (4–7.75 Hz), alpha (8–12.75 Hz) and beta (13–30 Hz) bands using a data analysis apparatus (ATAC 450, Nihon Kohden). The effects of the test drugs were evaluated by comparing the appearance rate of the delta and alpha bands of each 10 min time bin for 40 min after drug administration to the appearance rate of those bands after vehicle administration. The data analysis apparatus yielded 100% as the total appearance rate of four bands including the delta, theta, alpha and beta bands for each 10 min time bin. Therefore, the total appearance rate of four bands for the 40 min following drug administration sums to 400%.

Spontaneous Locomotor Activity

Spontaneous locomotor activity, consisting mainly of locomotion and rearing, was measured every 5 min for 60 min following drug administration using an Animex counter (Animex IIIa, Shimadzu Co., Japan) which reacts to change in electric volume according to animal's movement. To adapt the rats to the new environment, each rat was placed in a perspex cage (40 × 40 × 20 cm) at least 60 min before drug administration. Ketamine and test drugs were administered intraperitoneally at the same time. The effects of test drugs were evaluated by comparing the locomotor activity for 40 min after drug administration to locomotor values following vehicle administration.

Statistical Analysis

Locomotor activity data and EEG data were analyzed using Student *t*-tests or One way ANOVAs followed by Dunnett-test. Values of $p < 0.05$ were considered significant.

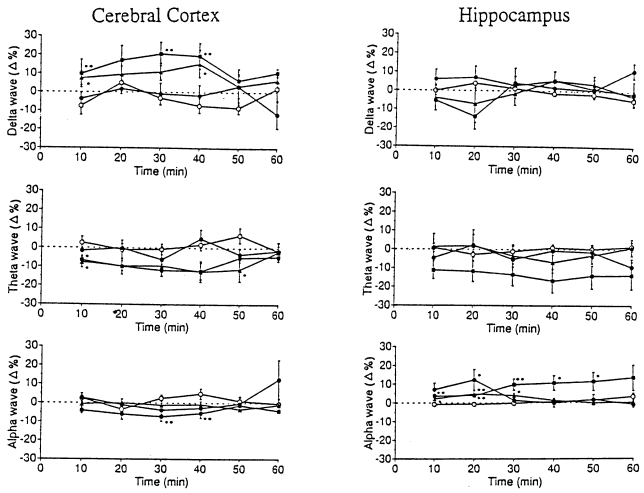

FIG. 1. Effects of ketamine on spontaneous EEG in rats. Each value represents the mean ± SE from 7–8 rats. -○- :vehicle, -●- :ketamine (20 mg/kg IP), -▲- :ketamine (40 mg/kg IP), -■- :ketamine (60 mg/kg IP), Changes in percentage at each time point were determined by comparing appearance rate at each time point with that proceeding drug administration for 10 min. *$p < 0.05$, **$p < 0.01$, Significantly different from the vehicle-treated group (One-way ANOVA followed by Dunnett-test).

Drugs

Nemonapride synthesized at Yamanouchi Pharmaceutical Co., Ltd., and haloperidol (Wako Pure Chemical Industries, Ltd.) were dissolved in lactic acid and diluted with distilled water. Thereafter, they were used after adjustment of the pH to 4 with sodium bicarbonate and administered intraperitoneally in a volume of 1 ml/kg. Ketamine was commercially obtained from Parke Davis Sankyo Co., Ltd.

RESULTS

Spontaneous EEG

Ketamine (20, 40 and 60 mg/kg IP) increased the delta wave component and decreased the alpha wave component in the cerebral cortex, and increased the alpha wave component in the hippocampus ($p < 0.05, p < 0.01$ One way ANOVA followed by Dunnett–test) (Fig. 1). All above mentioned ketamine-induced effects were dose-dependent (20, 40 and 60 mg/kg IP) (Fig. 1). The dopamine antagonists had various effects of ketamine-induced changes. In rats treated with ketamine (60 mg/kg IP), haloperidol (0.3–1 mg/kg IP) decreased the ketamine-induced increase in appearance rate of the alpha wave component in the hippocampus ($p < 0.05$, One way ANOVA followed by Dunnett-test) (Fig. 2). Nemonapride (0.3–1 mg/kg IP) increased the delta wave component ($p < 0.05$) and decreased the ketamine-induced increase in the alpha wave component in the hippocampus ($p < 0.01$, One way ANOVA followed by Dunnett-test) (Fig. 2).

In vehicle-treated rats, haloperidol (1 mg/kg IP) and nemonapride (1 mg/kg IP) had little effect on the spontaneous EEG (One way ANOVA followed by Dunnett-test) (data not shown).

Spontaneous Locomotor Activity

Ketamine (40–80 mg/kg IP) increased spontaneous locomotor activity (vehicle and 60 mg/kg IP in Figs. 3 and 4, $p <$

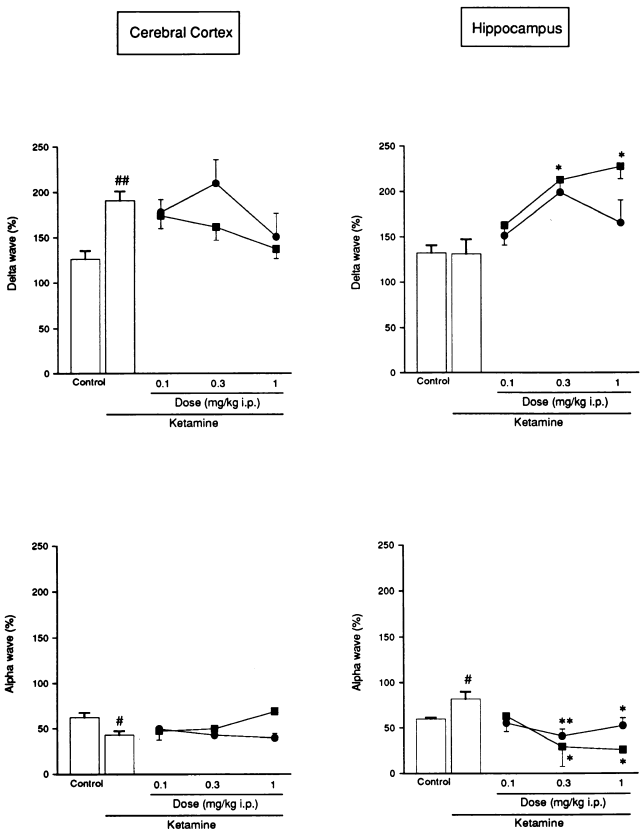

FIG. 2. Effects of haloperidol and nemonapride on spontaneous EEG in ketamine (60 mg/kg IP)-treated rats. Each value represents the mean ± SE from 4–5 rats. -●- :haloperidol, -■- : nemonapride; Spontaneous EEG was observed for 40 min after drug administration and the appearance rate of delta, theta and alpha components was analyzed. The vertical figure indicates the total percentage of the appearance rate of each component every 10 min for 40 min. #$p <$ 0.05, ##$p < 0.01$, Significantly different from the vehicle-treated group (Student *t*-test). *$p<0.05$, **$p < 0.01$, Significantly different from the ketamine and vehicle-treated groups (One-way ANOVA followed by Dunnett-test).

0.01, Student *t*-test; vehicle, 40, 60 and 80 mg/kg IP, data not shown, One way ANOVA followed by Dunnett-test). The rats showed lack of focused direction, stereotypy, irritability and other abnormalities. Haloperidol (0.3 and 1 mg/kg IP) (Fig. 3) and nemonapride (0.1-1 mg/kg IP) (Fig. 4) decreased ketamine (60 mg/kg IP)-induced hyperlocomotion in a dose-dependent manner ($p < 0.01$, One way ANOVA followed by Dunnett-test).

In vehicle-treated rats, haloperidol (0.03–1 mg/kg IP) and nemonapride (0.03–1 mg/kg IP) had little effect on spontaneous locomotor activity (One way ANOVA followed by Dunnett-test) (Table 1).

DISCUSSION

The present study demonstrated that ketamine increased the appearance rate of the delta wave component in the cerebral cortex and of the alpha wave component in the hippocampus. Thus, ketamine synchronized cortical EEG and desynchronized hippocampal EEG indicating that the drug caused a dissociation between the cortical and hippocampal EEG.

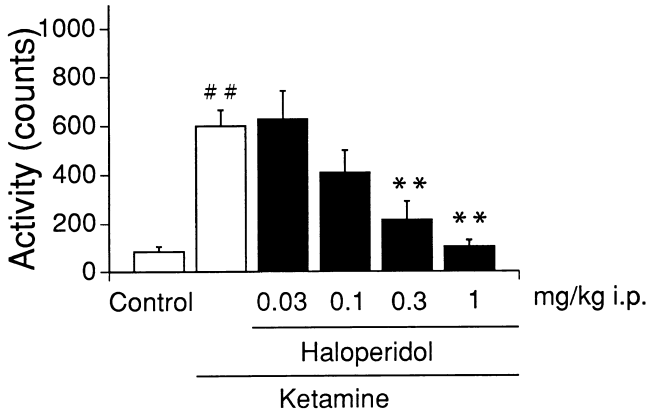

FIG. 3. Effects of haloperidol on spontaneous locomotor activity in ketamine (60 mg/kg IP)-treated rats. Each values represents the mean ± SE for 6 rats. Locomotor activity was observed for 40 min after drug administration. ##$p < 0.01$, Significantly different from the vehicle-treated group (Student *t*-test). **$p < 0.01$, Significantly different from the ketamine and vehicle-treated groups (One-way ANOVA followed by Dunnett-test).

Furthermore, ketamine increased in spontaneous locomotor activity (Fig. 3 and 4). Ketamine-perturbed activity was characterized by lack of focused direction, irritability and fluctuating levels of activity, in agreement with the observations of Hetzler and Wautlet (1985). Emergence from ketamine anesthesia is often accompanied by restlessness, mood changes, psychomotor agitation and hallucination in humans (6). These behavioural changes may be regulated, in part, by electrical activity of the cerebral cortex and hippocampus. The dissociation of cortical and hippocampal EEG, and the increase in spontaneous locomotor activity and abnormal behavior seen after administration of ketamine to rats may be equivalent to the delirium state in patients.

Ketamine is a non-competitive *N*-methyl-d-aspartate (NMDA) antagonist which acts on the phencyclidine site of the NMDA receptor (3,19,32). Phencyclidine is well known to induce behavioral changes such as stereotypy and abnormal

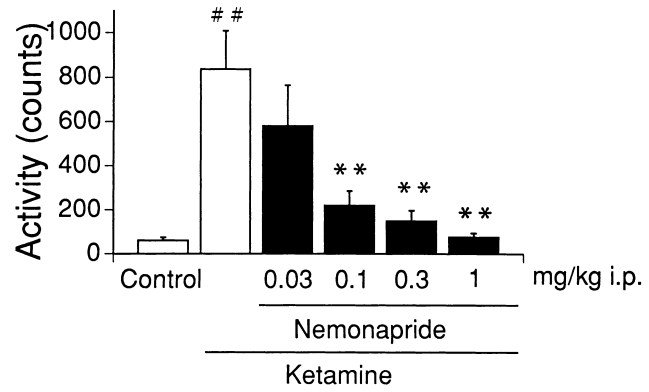

FIG. 4. Effects of nemonapride on spontaneous locomotor activity in ketamine (60 mg/kg IP)-treated rats. Each value represents the mean ± SE from 6 rats. Notations as in Fig. 3. ##$p < 0.01$, Significantly different from the vehicle-treated group (Student *t*-test). **$p < 0.01$, Significantly different from the ketamine and vehicle-treated group (One-way ANOVA followed by Dunnett-test).

TABLE 1

EFFECTS OF NEMONAPRIDE AND HALOPERIDOL ON LOCOMOTOR ACTIVITY IN RATS

Drug	Dose (mg/kg/IP)	Locomotor Activity (counts)
Control		60 ± 14
Nemonapride	0.03	127 ± 18
	0.1	125 ± 27
	0.3	68 ± 17
	1	67 ± 16
Control		83 ± 22
Haloperidol	0.03	70 ± 20
	0.1	67 ± 14
	0.3	61 ± 8
	1	61 ± 9

Each value represents the mean ± SE from 6 rats. One-way ANOVA followed by Dunnett-test is used for statistical analysis.

behavior in rats (24). The effects of phencyclidine on behavior and spontaneous EEG were similar to the effects of ketamine on those parameters in rats (20). It has been reported that both competitive and non-competitive NMDA antagonists increase locomotor activity (33), and that nerve terminals secreting excitatory amino acids are located in the nucleus accumbens (4) a brain site associated with motor function. In addition to hyperlocomotion, ketamine also induces rotation (21) and stereotypy (13). In biochemical studies, ketamine has been shown to influence on not only glutaminergic but also monoaminergic activity. Ketamine changes the levels of brain monoamines and their metabolities in rats (37,40) and primates (1), increases dopamine and norepinephrine release from striatal and cortical slices, respectively (26,28). Further, ketamine inhibits dopamine (11) and norepinephrine (27) uptake into striatal and cortical synaptosomes, respectively. It has been suggested that during recovery from ketamine anesthesia, increases in norepinephrine content in the whole brain, and increases in dopamine turnover in the striatum, may be associated with postanesthesia excitement in rats (40). Recently, Irifune et al. (1991) reported that ketamine may have an indirect dopamine agonist action and that ketamine-induced hyperlocomotion may be mediated by nerve terminals of dopamine neurons in the nucleus accumbens in mice. The effects of the NMDA antagonists MK-801, ketamine and PCP on EEG activity may be mediated through dopaminergic mechanisms (5). These biochemical and behavioral properties of ketamine may have induced the EEG changes observed in the present study.

Dopamine antagonists are now used for the treatment of delirium in patients with organic brain syndrome (7,12,25). In the present study using ketamine-treated rats, haloperidol and nemonapride synchronized the hippocampal EEG, thereby ameliorating the dissociation between the spontaneous cortical and hippocampal EEG (Fig. 2). In vehicle-treated rats, haloperidol and nemonapride had no significant effect on spontaneous locomotor activity (Table 1) and EEG. Ketamine-induced hyperlocomotion was decreased by administration of haloperidol and nemonapride. Haloperidol antagonized phencyclidine-induced hyperlocomotion (29) and fast EEG (23) in rats, suggesting that NMDA antagonists and haloperidol are acting at the PCP/sigma site. The antagonistic effects of haloperidol on both EEG changes and behavioral changes may be the experimental counterpart of the clinical efficacy of haloperidol against PCP-induced delirium and psychosis. It has been shown that droperidol, a dopamine antagonists, significantly decreases the incidence of restlessness, crying, screaming, hallucination and vomiting associated with recovery from ketamine anesthesia in men (2). This finding is supported by the pharmacological data suggesting that ketamine-induced hyperlocomotion may be mediated by nerve terminal of dopamine neurons in the nucleus accumbens, where ketamine inhibits dopamine uptake and provokes a slight dopamine release (10). The pharmacological actions of haloperidol and nemonapride on ketamine-induced EEG changes and/or behavioral changes may be ascribable, in part, to inhibition of ketamine-induced facilitation of central dopaminergic activity.

Appearance of stage 1 REM sleep corresponds to delirium in biperidine-treated cats (14). However, this model may not be appropriate for evaluating drug actions since the preparation of this model seems rather complex. In the ketamine-treated rats used in the present study, dissociation of the spontaneous cortical and hippocampal EEG was ameliorated by administration of dopamine antagonists, which are now used for the treatment of delirium. Since the present model is easy to prepare and is appropriate for the quantitative analysis of drug action, it may, therefore, be suitable for evaluating drug action. In order to establish a delirium model for evaluating drug action, the effects of some cholinomimetics, also used for the treatment of delirium, on ketamine-induced EEG changes are now being investigated.

In conclusion, the ketamine-treated rat may be regarded as a conventional model for investigating the pathogenesis of delirium and for evaluating drug action, although further pharmacological studies are necessary. At present, the model may, at least, provide a promising tool to investigate non-cholinergic mechanisms of dissociation between neocortical and hippocampal EEG activity and increase the understanding of the neurochemical basis of delirium.

ACKNOWLEDGEMENTS

We are indebted to Dr. M. Yamada, Dr. S. Tachikawa, Dr. S. Higuchi and Mr. H. Ida for their invaluable advice.

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