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Circadian Rhythm of Brain Susceptibility to Haloperidol During Chronic Administration

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NAGAYAMA, H., A. TAKAGI, S. YOSHIMOTO, H. MINAMI, K. NISHIWAKI AND R. TAKAHASHI. *Circadian rhythm of brain susceptibility to haloperidol during chronic administration.* PHARMAC. BIOCHEM. BEHAV. **16**(2) 311–314, 1982.—Circadian fluctuation has been reported to exist to the effects of haloperidol after acute administration. In an attempt to clarify the viability of chronotherapy with haloperidol, the antiapomorphine effect of haloperidol after chronic administration was investigated in the present paper. Haloperidol was administered once daily at the same time for 21 consecutive days to rats which were kept under 12 hr lighting conditions with light onset at 19:30. Then the chronology of the antiapomorphine effect was investigated. The antiapomorphine effect was significantly stronger in the group treated at 19:30 than that treated at 13:30. These data agreed with the results found after the acute administration of the drug. After chronic administration, no difference was found in the plasma and brain level of haloperidol due to the time of administration. These experimental results seem to suggest that a circadian rhythm in the brain susceptibility to haloperidol exists even during chronic administration.

Haloperidol Chronic administration Circadian rhythm Antiapomorphine effect

CIRCADIAN fluctuation has been shown to exist to the sedative and antiapomorphine effects of haloperidol after acute administration [17]. The fact that the brain and plasma concentrations of the drug were not different following either time of administration suggests that the fluctuation might be due to a time related variation in the brain's susceptibility to the drug. These data suggest the existence of a circadian fluctuation in the susceptibility of brain dopamine receptors to blockade by haloperidol [17–19].

Haloperidol's antiapomorphine effect is thought to be closely related to its antipsychotic action [3,24]. The presence of the circadian fluctuation in the antiapomorphine effect [16,20] suggests the viability of chronotherapy (i.e., a method of therapy utilizing the biological rhythms) with haloperidol in the clinical setting. However, our previous study [17–19] was limited to antiapomorphine effect of haloperidol 1 hr after acute administration.

The main purpose of the present paper therefore is to report a study conducted to clarify whether or not circadian fluctuation in the chronological change of antiapomorphine effect of haloperidol exists after acute and chronic administration.

METHOD

Adult male S.D. rats weighing 300–400 g were used. They were kept in an animal house under 12 hr lighting conditions with light onset at 19:30 and in an ambient temperature of 24–26°C. Two rats were housed in a cage and were given food and water ad lib. The animals were kept under these conditions for at least 5 weeks, and were accustomed to handling several days before the experiment. The experiments were conducted according to the schedule described below. Five rats per group were assigned to the behavioral experiment, and 4 rats per group were studied to determine the drug level in the plasma and brain. Apomorphine or saline was administered only once to each rat.

Chronological Changes of Antiapomorphine Effect of Haloperidol after Acute Administration

One rat was placed in a cage 24–48 hr prior to the experiment in order to minimize the influence of others. This cage was placed in a room which was maintained under the same conditions as the animal house. Haloperidol (0.01% solution) 0.25 mg/kg, which approximates the clinical dose, was administered IP. The dopamine agonist apomorphine hydrochloride (apomorphine), 0.2% solution, was administered SC at the dose of 5 mg/kg 1, 6, 12, 18, 24, 30 and 36 hr after the administration of haloperidol. The dosage of apomorphine was determined based on the results of our previous experiment [16]. The apomorphine solution was used within 100 min after preparation. The control group was given saline instead of haloperidol. After the administration of apomorphine, apomorphine-induced stereotyped behavior (AISB) was assessed according to Nagayama *et al.*'s method [16]. The rats were observed for 20 sec by a small sized flashlight at 5 min intervals following administration of apomorphine. Observation in all cases was made by the same laboratory worker who was kept blind to the kinds of solution given and the time after the last administration. The administration times for haloperidol were either 19:30 or 13:30, which gave

the maximum and minimum antiapomorphine effect, respectively, 1 hr after acute administration as observed in a previous study [17–19].

Chronological Changes of Antiapomorphine Effect of Haloperidol after Chronic Administration

Haloperidol 0.25 mg/kg was chronically administered IP once daily at the same time for 21 consecutive days. Apomorphine 5 mg/kg was administered SC 1, 6, 12, 18, 24, 30 and 36 hr after the last administration of haloperidol. Saline, instead of haloperidol, was administered chronically to the control group. The other procedures were the same as those followed in the experiment of acute administration [17].

Chronological Changes of Haloperidol Concentration in the Plasma and Brain after Chronic Administration of the Drug

Haloperidol 0.25 mg/kg was chronically administered IP at the same time daily for 21 consecutive days. The time of administration was 13:30 or 19:30. Rats were decapitated at 1, 6, 12, 18, 24, 30 and 36 hr after the last administration. The plasma was separated from the blood collected at decapitation and the whole brain was rapidly removed on ice and, excluding the medulla and cerebellum, was used to determine the chemical composition. The measurement of haloperidol was carried out by the method presented by Suzuki *et al.* [25].

RESULTS

Chronological Changes of Antiapomorphine Effect of Haloperidol after Acute Administration

As the details of AISB have been described previously [16], only a brief description will be given here. AISB consisted of three behaviors: sniffing (which was observed for a period longer than 10 sec within the observation period of 20 sec), licking, and/or gnawing. The duration of AISB was the period extending from the time when one of the three indicators was exhibited twice in succession (in the case of the sniffing behavior the criterion was three times in succession) to the time when that indicator failed to be exhibited twice consecutively as noted in observations carried out in 5 min intervals. Inhibition percentages of AISB were calculated by comparing the duration periods of AISB between saline and haloperidol treated groups. These values were obtained after two different times of administration and at various periods after each administration.

As shown in Fig. 1, the inhibition percentage of AISB was significantly different according to the time of administration (ANOVA, $F(1,56)=7.66$, $p<0.01$ between times of administration, $F(6,56)=6.27$, $p<0.005$ in interaction). Period of inhibition of AISB was between 12 and 18 hr in the group treated at 19:30, but between 1 and 6 hr in the group treated at 13:30 hr. The degree of inhibition of AISB was significantly stronger in the 19:30 group than the 13:30 group.

Chronological Changes of Antiapomorphine Effect of Haloperidol after Chronic Administration

As shown in Fig. 2, antiapomorphine effect of haloperidol was significantly different according to the time of administration after chronic administration (ANOVA, $F(1,56)=12.95$, $p<0.001$). When the two curves are divided into three parts, in the first 12 hr (ANOVA, $F(1,24)=5.96$, $p<0.005$) and in the last 12 hr (ANOVA, $F(1,24)=10.44$, $p<0.005$) significant differences were observed according to the time of administration, but in the middle 12 hr no difference was observed (ANOVA, $F(1,24)=0.12$, n.s.).

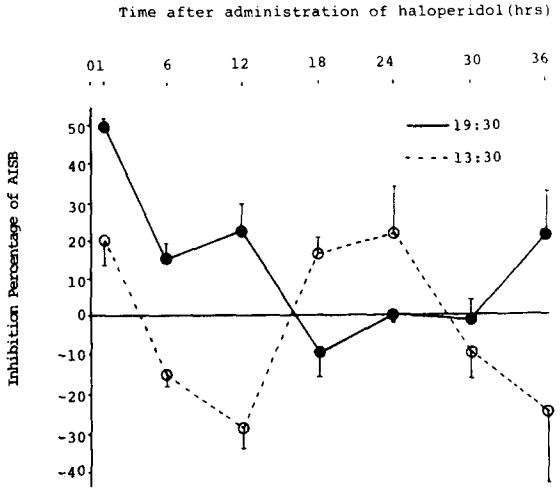

FIG. 1. Effect of haloperidol given at different times of day on apomorphine-induced stereotyped behavior (AISB) after acute administration (0.25 mg/kg IP). Each point is the mean ± SE of 5 animals. Significant difference between the two curves (ANOVA, $F(1,56)=7.66$, $p<0.01$ between times of administration, $F(5,56)=6.27$, $p<0.005$ interaction).

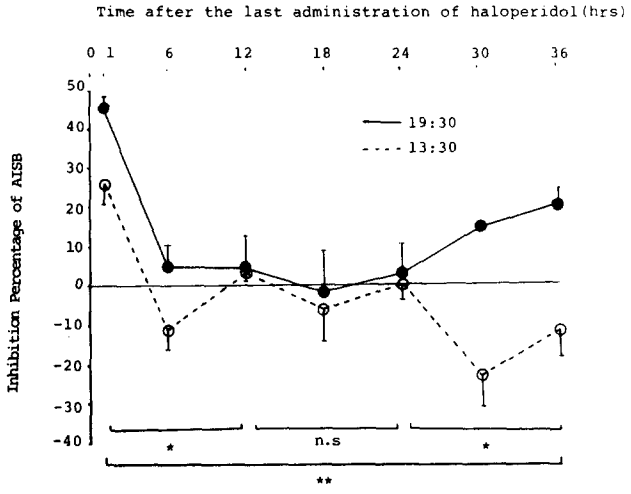

FIG. 2. Effect of haloperidol given at different times of day on apomorphine-induced stereotyped behavior (AISB) after chronic administration (0.25 mg/kg IP for 21 consecutive days). Each point is the mean ± SE of 5 animals. Significant difference between the two curves (ANOVA). *$p<0.005$, **$p<0.001$. (Details can be seen in the text.)

Chronological Changes of Haloperidol Concentration in the Plasma and Brain after Chronic Administration

As shown in Figs. 3 and 4, plasma and brain levels of

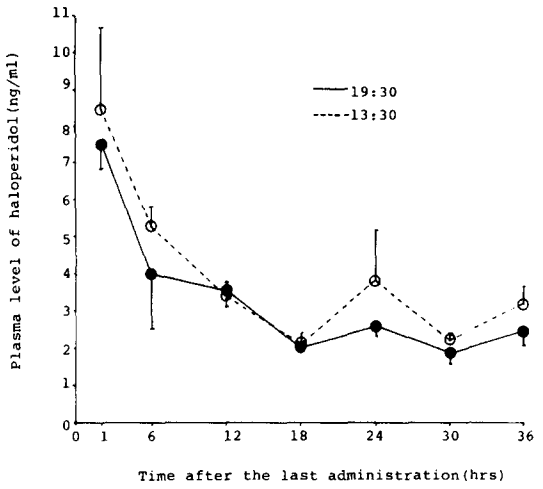

FIG. 3. Plasma levels of haloperidol given at different times of day after chronic administration (0.25 mg/kg IP for 21 consecutive days). No significant difference between the two curves at any points (Student's t). One curve is the mean of levels detected in rats administered haloperidol at 19:30 and one for rats treated at 13:30. Each point is the mean ± SE of 4 animals.

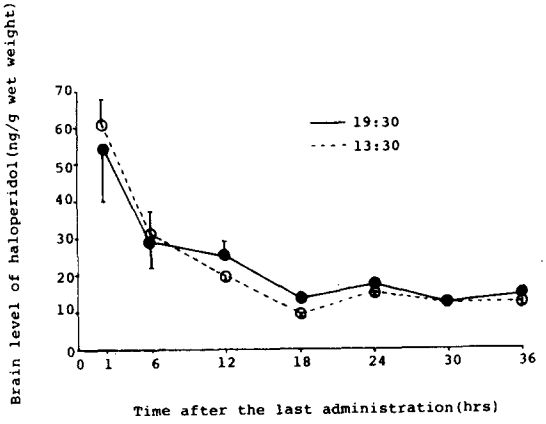

FIG. 4. Brain level of haloperidol given at different times of day after chronic administration (0.25 mg/kg IP for 21 consecutive days). No significant difference between the two curves at any points (Student's t). One curve is the mean of levels detected in rats administered haloperidol at 19:30 and one for rats treated at 13:30. Each point is the mean ± SE of 4 animals.

haloperidol took the same course regardless of the time of administration. That is, no significant difference between groups was observed in plasma and brain levels of haloperidol (Student's t, $p<0.05$). The plasma level of the drug in steady state was 2–4 ng/ml, which is very similar to the clinical level [7].

DISCUSSION

Chronological changes in haloperidol's antiapomorphine effect after acute administration differ significantly according to the time of administration. The difference is not only quantitative but also qualitative (i.e., in the 19:30 group haloperidol inhibited AISB for 12 hr but in the 13:30 group augmented AISB). This suggests that hypersensitivity of dopamine receptors occurs several hours after acute administration at 13:30, and that clinical extrapyramidal hyperkinesias such as akathisia may be more likely to occur early after haloperidol administration at 13:30.

Haloperidol's antiapomorphine effect also differs significantly according to its time of administration after chronic neuroleptic administration. The fact that there is no difference in changes of the plasma and brain levels of haloperidol according to the time of administration suggests that the difference of the effect might not be due to any peripheral factor but due to the difference of sensitivity of the brain dopamine receptors to the drug.

Combining the results reported in the present paper with those reported previously [17], it seems that there is circadian susceptibility rhythm to haloperidol after acute and chronic administration with the peak at 19:30 and nadir at 13:30. Consequently the degree and duration of effect of haloperidol has circadian fluctuation with the same pattern. Considering the fact that the antiapomorphine effect is closely related to its antipsychotic action [3,24], the results suggest that 19:30, i.e., the time prior to going to bed, might be best for administering haloperidol. But clinical investigations are necessary before applying this to clinical practice. In this case although rats are nocturnal, the clock hours in the present experiment can be considered relevant to the human situation, because, in the experimental situation, light-dark rhythm was reversed from the natural one for the rat.

The results recorded 24–36 hr after the administration of haloperidol warrant some emphasis in this discussion. The results at these hours might correspond to the clinical case in which a patient to whom haloperidol is being administered chronically and then is withdrawn abruptly. AISB were inhibited in the 19:30 group, but tended to increase in the 13:30 group. In the former the effect still continues after withdrawal, but in the latter it is not only ineffective but also tends to develop akathisia or dyskinesia.

Many behavioral-pharmacological studies [4, 5, 9–11, 14, 21–23, 26, 27] and neurochemical studies [1, 6, 8, 12, 15] have implicated the hypersensitivity of dopamine receptors induced by chronic administration of haloperidol, which is considered as a model of tardive dyskinesia in some studies [1, 12, 15, 21]. Results reported in these papers suggest that both administration of haloperidol for a long period of time and some period after withdrawal are necessary for hypersensitivity to be induced (i.e., repeated administration for at least 5 days and at least 48 hr after withdrawal). Only Christiansen *et al.* [2] and Martres *et al.* [13] reported that hypersensitivity occurred within the next day of acute administration. In the present experiment, the results show that hypersensitivity occurred only 6 hr after acute administration in the 13:30 group. This finding could only be discovered using a chronopharmacological study.

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