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Yasuyuki Ichimaru[*] Yutaka Gomita[†]

Yasunori Araki[‡] Minehiro Moriyama[**]

[*]Okayama University,
[†]Okayama University,
[‡]Okayama Univresity,
[**]Okayama University,

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Yasuyuki Ichimaru, Yutaka Gomita, Yasunori Araki, and Minehiro Moriyama

Abstract

Effects of HR-592, a new derivative of indole, on conditioned avoidance and intracranial self-stimulation behavior were investigated in rats using a shuttle box and a Skinner box, respectively. The oral administration of HR-592 at doses of 3-10 mg/kg caused a dose-dependent suppression of the conditioned avoidance response. Even the escape response was slightly suppressed in the group administered 10 mg/kg of HR-592. The self-stimulation behavior was suppressed dose-dependently from 1 to 8 h after the administration of 6-10 mg/kg of HR-592. These results indicate that the action of HR-592 on conditioned avoidance response and intracranial self-stimulation behavior is similar to the action of neuroleptics.

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Effects of HR-592, a New Derivative of Indole, on Conditioned Behavior

Yasuyuki Ichimaru, Yutaka Gomita[a,*], Yasunori Araki[a] and Minehiro Moriyama

Department of Pharmacology, Daiichi College of Pharmaceutical Sciences, Fukuoka 815, and [a]Department of Hospital Pharmacy, Okayama University Medical School, Okayama 700, Japan

Effects of HR-592, a new derivative of indole, on conditioned avoidance and intracranial self-stimulation behavior were investigated in rats using a shuttle box and a Skinner box, respectively. The oral administration of HR-592 at doses of 3-10 mg/kg caused a dose-dependent suppression of the conditioned avoidance response. Even the escape response was slightly suppressed in the group administered 10 mg/kg of HR-592. The self-stimulation behavior was suppressed dose-dependently from 1 to 8 h after the administration of 6-10 mg/kg of HR-592. These results indicate that the action of HR-592 on conditioned avoidance response and intracranial self-stimulation behavior is similar to the action of neuroleptics.

Key words : **HR-592, indole derivative, avoidance, hypothalamic self-stimulation, rats**

HR-592 is a new derivative of indole with a Cl radical at the 5-position of indole (Fig. 1). It is well known that various compounds containing indole, such as reserpine, bufotenine and psilocybin, have characteristic actions like an influence to monoaminergic nerve system, and/or drug addiction and abuse (1, 2). We have found HR-592 to be pharmacologically similar to neuroleptics, in that it causes suppression of spontaneous activity, muscle relaxation and disturbance in motor coordination, is synergistic with anesthetics, and has cataleptogenic and anti-methamphetamine activities (unpublished data). And these results indicate a possibility that HR-592 has an antipsychotic activity.

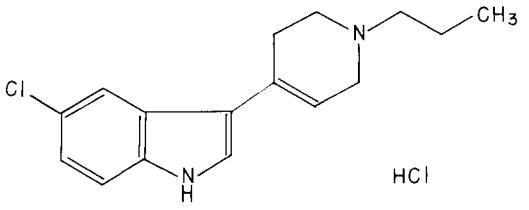

Fig. 1 Structure of HR-592.

It is well known that neuroleptics suppress conditioned behavior, especially the conditioned avoidance behavior (3-5). In addition, intracranial self-stimulation (ICSS) behavior is specifically suppressed by neuroleptics, and the detection of this activity is employed in the screening of neuroleptics (5). In the present study, we investigated the effects of HR-592 on conditioned avoidance and on the lateral hypothalamic ICSS behaviors.

Materials and Methods

Animals. The body weights and number of male Wistar rats used in the present experiments are described for each experiment. Throughout the study, the animals

* To whom correspondence should be addressed.

were housed 3–4 to a plastic cage (30 × 35 × 18 cm) in a breeding room maintained at 22 ± 2°C and illuminated from 9:00 to 21:00. Food and water were provided *ad libitum*.

HR-592 (pure powder; supplied by Hoechst Co.) was suspended in purified water containing 1% Tween 80. The concentration of the test drug was adjusted so that a volume of 0.1 ml could be administered per 100 g of body weight. The vehicle, 1% Tween 80 solution, was administered to the control animals.

Conditioned avoidance responses (CARs). Male Wistar rats weighing 200–250 g (at the beginning of the experiment) were used. The effects of HR-592 on the CARs were investigated by the shuttle box method (6). The apparatus was a plastic two-compartment shuttle box (69 × 28 × 31 cm). The grid floor of one compartment was 5 cm higher than that of the other. The test conditions of the conditioned avoidance behavior were as follows: The animal was exposed to a pure tone of 800 Hz, approximately 70 db, for 5 sec as a conditioned stimulus (CS). If the animal moved into the other compartment in response CS, it was termed CAR. When moved within 5 sec of the CS, the CS was immediately stopped. If the animal did not move to another compartment during the CS, 1 mA current was applied through the floor grid as an unconditioned stimulus (UCS). If the animal moved after an onset of UCS, it was termed escape. The interval between each trial was variable (30, 40 or 50 sec, mean of 40 sec), and one session consisted of 20 trials. After the training, animals which showed 16 or more CARs per session (20 trials) for 3 succesive days were assigned to groups of 4–5 animals. The tests were carried out 1, 2, 4, 8 and 24 h after the oral administration of the test drug. A wash-out period of at least one week was allowed to elapse between each administration when the same animal was to be used more than once. The data were statistically analyzed by a two-tailed Mann-Whitney U-test (7).

Lateral hypothalamic self-stimulation. Male Wistar rats weighing 200–250 g (at the time of surgery) were used. Under pentobarbital-Na anesthesia, the head of the animal was fixed on a stereotaxic apparatus. Using the de Groot's atlas (8), bipolar electrodes (0.25 mm in diameter, insulated except at the tip) were bilaterally implanted into the lateral hypothalamus (A; 5.4, L; + 1.8, V; −3.0). The electrode and a connecting socket were fixed to the skull with two screws and dental cement. After the surgery, 150,000 units of penicillin G were injected intramuscularly. At least 10 days were allowed for the recovery from the surgical operation before the ICSS training. The animal was placed in a Skinner box, and trained in ICSS lever pressing with a constant current (sine wave, 60 Hz, 0.2 sec, 10–200 μA). In a continuous reinforcement schedule, the animals were trained for 15 min (1 session) per day. Animals which showed at least 1,500 lever pressing responses (LPRs) within 15 min for 3 successive days were assigned to groups of 3–5 animals. The tests were carried out for a 15 min period 1, 2, 4, 8 and 24 h after the oral administration of the test drug. At least one-week was allowed to elapse between each administration when the animal was to receive two or more administrations. The data were statistically analyzed by a two-tailed Mann-Whitney U-test (7).

Results

Conditioned avoidance response. Fig. 2 shows the effects of HR-592 on the CARs and the escape responses. In the group treated with 3 mg/kg of HR-592, the CARs were slightly suppressed. The degree of the suppression of the CARs was greater in the 6 mg/kg-treated group than in the 3 mg/kg-treated group, and a significant difference ($p<0.05$) was observed at 4 h after the administration. In the 10 mg/kg treated group, the CARs were suppressed with significant differences ($p<0.01$) from 1 to 8 h after the administration. In this group, even the escape responses were slightly suppressed by approximately 20–25%.

Lateral hypothalamic self-stimulation. Fig. 3 illustrates the representative cumulative curves of the lateral hypothalamic ICSS after the oral administration of HR-592 at 6 mg/kg. In this case, the LPRs were markedly decreased 1 and 2 h after the administration, and considerable decreases in LPRs were observed even 4 and 8 h after the administration.

Fig. 4 shows the effects of HR-592 on the lateral hypothalamic ICSS. The LPRs were slightly reduced in the group treated with 3 mg/kg of HR-592, whereas, the LPRs were significantly suppressed ($p<0.01$) from 1 to 8 h after the administration of 6 mg/kg and 10 mg/kg of HR-592. The LPRs were almost completely

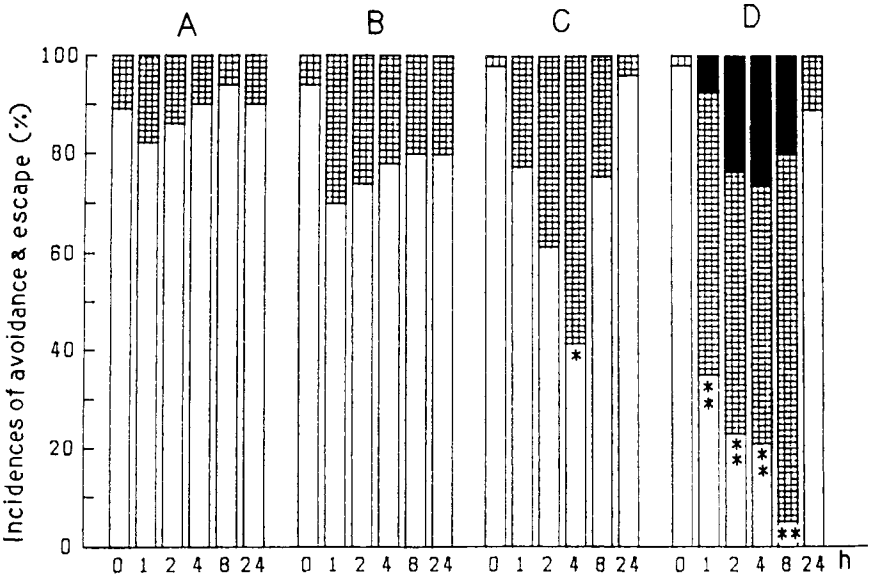

Fig. 2 Effect of HR-592 on conditioned avoidance and escape responses of rats in a shuttle box. An animal was able to shuttle alternately between two compartments in the box for avoiding or escaping the foot-shock as unconditioned stimuli. The drug was orally administered at dosages of 3–10 mg/kg. A, Vehicle group; B, HR-592 3 mg/kg group; C, HR-592 6 mg/kg group; D, HR-592 10 mg/kg group; ▦, inhibition of avoidance response; ■, inhibition of escape response. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

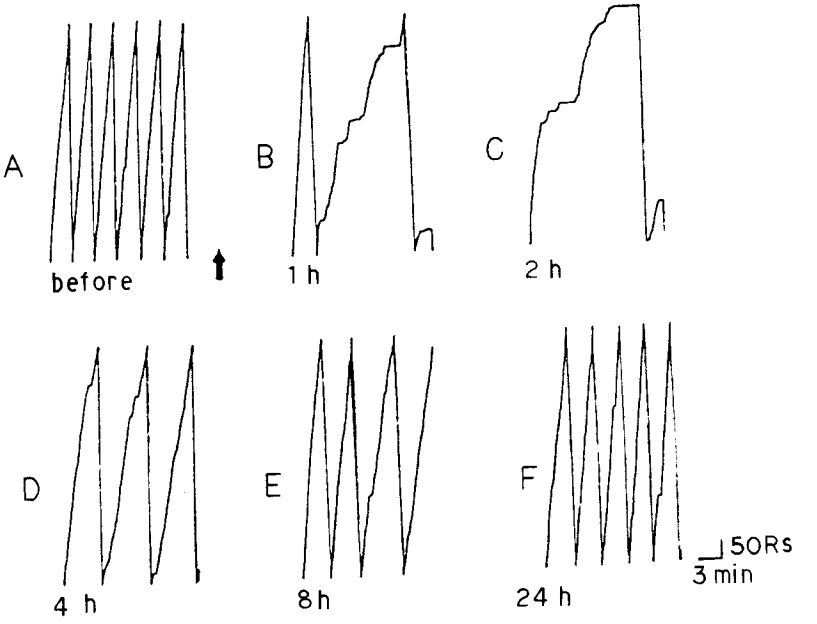

Fig. 3 Representative cumulative records of the lateral hypothalamic self-stimulation behavior when HR-592 was administered at a dose of 6 mg/kg to the rat. The arrow in the figure indicates the administration of HR-592. Rs, responses.

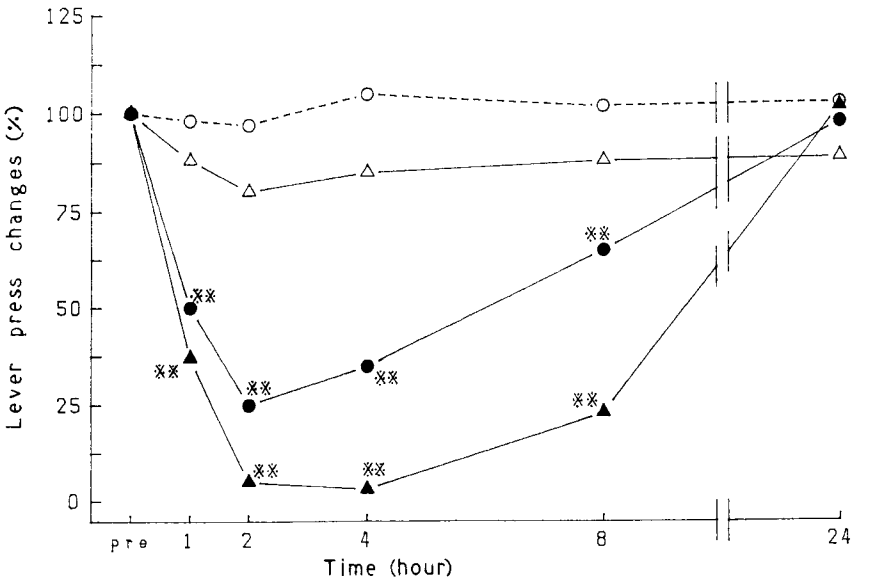

Fig. 4 Effect of HR-592 on lateral hypothalamic self-stimulation behavior in rats. ○—○, vehicle group; △—△, HR-592 3 mg/kg group; ●—●, HR-592 6 mg/kg group; ▲—▲, HR-592 10 mg/kg group. pre, before the drug administration. **, $p<0.01$.

suppressed 2 and 4 h after the administration of 10 mg/kg of HR-592.

Discussion

The effects of HR-592, a new derivative of indole thought to have neuroleptic-like activity, on the CARs and the ICSS were investigated in rats. It was found that the oral administration of 6 mg/kg or more of HR-592 caused statistically significant suppression of both the CARs and the ICSS. From some reports (3–5), it may be concluded that neuroleptics like phenothiazines, butyrophenones and reserpine particularly inhibit conditioned avoidance and intracranial self-stimulation behaviors. We have observed that the oral administration of 30 mg/kg or more of HR-592 resulted in a suppression of locomotor activity in mice, and the 10 mg/kg or more administration resulted in an appearance of catalepsy in rats and a suppression of rota-rod performance in mice (unpublished data). To produce complete muscle relaxation or catalepsy, the oral administration of 30 mg/kg or more of HR-592 was necessary. Therefore, it is difficult to think that the suppression of the CARs and the ICSS is due entirely to its muscle-relaxing or cataleptogenic activity. Accordingly, it seems reasonable to surmise that the suppression of the CARs and the ICSS in the present experiment is a specific activity of HR-592, suggesting the possibility that this drug has neuroleptic-like activity.

In conclusion, the findings of the present experiments provide further evidence to support the possibility that HR-592 has neuroleptic-like activity. To clarify the characteristics of the action of HR-592, biochemical research such as receptor binding assays must be carried out in the future.

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