Enhancement of Prolactin-Secreting Effect Produced by Repeated Administration of Haloperidol in the Avoidance Situation and Dopamine Neurons in Rats

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Accepted August 25, 1988

Abstract—Male Wistar strain rats subcutaneously administered haloperidol at the dose of 0.035 mg/kg at 3-4 days interval, 10 times, in the avoidance situation. Enhancement of the prolactin-secreting effect of haloperidol was observed when it was given in the home cages at the 10th day after termination of the repeated administration. In these animals, 3H-spiperone binding sites in the pituitary significantly increased, while the DOPAC/DA ratio in the hypothalamus significantly decreased. The enhancement phenomenon may be produced by a decrease in the activity of dopamine neurons in the hypothalamus.

The behavioral effects of drugs acting on the central nervous system (CNS-acting drugs) are often modified by repeated administration. We have demonstrated that repeated administration of CNS stimulants such as d-amphetamine, methamphetamine, morphine, methylphenidate, cocaine, ephedrine or mazindol at fixed intervals of 1-7 days produced marked enhancement of their acute effects on the ambulatory activity of mice and rats (1). The similar enhancing behavioral effects of CNS depressants such as antipsychotic (2) or antianxiety drugs have also been reported by us. For example, enhancement of the lever-press avoidance-suppressing effect of haloperidol was produced by its repeated administration at fixed intervals of 1-7 days (2). These experiments suggested that the enhancing effect might not be associated with either an accumulation or change in the absorption of haloperidol, but closely related to the environmental situations to which the animals had been exposed under the drug effect. In the present experiment, the effect of repeated administration of haloperidol in the avoidance situation on prolactin secretion was investigated in rats.

Animals used were male rats of the Wistar strain, weighing 260-270 g, supplied by the Institute of Experimental Animal Research of Gunma University School of Medicine.

The rats were trained to avoid an electric shock by pressing a lever according to warning stimuli (buzzer and small lamp) in an operant chamber. The avoidance schedule consisted of a 25 sec intertrial interval and a 5 sec presentation of the warning stimuli. The electric shock of 110 V, 0.5 mA, 50 Hz AC for 5 sec (training period) and 0.5 sec (drug-test period), respectively, was delivered through the stainless steel floor grid.

After establishment of the avoidance response, the animals were divided into two groups of 35 each. Group I was repeatedly given s.c. with haloperidol (HPD) at 0.035 mg/kg at 3-4 days interval for a total of 10 times. According to our experiences, the dose tested was optimum for suppressing the avoidance response without any cataleptic symptom in the Wistar strain male rats when the drug was repeatedly given. Group II was prepared as a control for Group I, and these animals were repeatedly given saline at 1 ml/kg under the same conditions. The avoidance response was observed for 90 min immediately after the drug administration.

The animals were given HPD at 0.025-0.05 mg/kg, s.c., including saline in the home cage at 10 days after termination of the
repeated drug administration. At 90 min after acute drug administration, the animals were sacrificed by decapitation and blood samples were collected for the prolactin assay. Prolactin was assayed by double antibody radioimmunoassay according to the recommendations supplied with the NIAMDD kit.

The \(^3\)H-sperone (SPP) binding test was performed on the pituitary at 10 days after termination of the repeated drug administration, essentially as described by Usdin et al. (3).

The animals were decapitated after enzyme inactivation by microwave irradiation at 5 kW for 1.5 sec in the 10th day after termination of the drug repetition. Regional levels of dopamine (DA) and 3,4-dihydroxyphenylacetic acid (DOPAC) were measured by high-performance liquid chromatography with electrochemical detection using the technique of Keller et al. (4).

The discrete avoidance response (DAR) in Group I was scarcely suppressed in the first administration of HPD. However, progressive enhancement of the DAR-suppressing effect was produced when the drug was repeatedly given as reported previously by us (2). No similar enhancement phenomenon was observed in Group II after repeated saline.

Serum prolactin levels in Groups I and II increased in a dose-dependent manner when HPD was given (Fig. 1). In particular, the levels in Group I increased more markedly than those in Group II, and the levels obtained after saline and HPD at 0.035 and 0.05 mg/kg in Group I were significantly different from those obtained in Group II. Group I (33.4±2.6 fmol/mg protein) showed a significant increase in the specific binding of \(^3\)H-SPP in the pituitary as compared with that in Group II (19.9±3.3 fmol/mg protein) (P<0.05, Student’s t-test).

No significant difference in DA level in the hypothalamus was observed between Groups I and II. However, the DOPAC level in this region significantly decreased in Group I when compared with that in Group II, and as the result, the DOPAC/DA ratio significantly decreased in Group I (Fig. 2).

The present experiment demonstrated that enhancement of the prolactin-secreting effect of HPD was observed in the animals given the drug repeatedly in a discrete avoidance situation. These results suggest that the enhancing effect is detectable not only for behavioral effects of many CNS-acting drugs but also for the prolactin-secreting effect of an antipsychotic drug if appropriate experimental determinants are provided.

According to our experience, the enhancement of the prolactin-secreting effect was not produced when the animals were given HPD repeatedly in their home cages without exposure to the avoidance situation (5). This fact suggests that the enhancement phenomenon is closely related to the environmental situation to which the animals have been exposed under the drug effect.

A number of reports have suggested that no changes in prolactin level are observed in animals and man when antipsychotic drugs are given repeatedly (6, 7). However, a progressive increase in serum prolactin secretion was also reported to be produced by...
repeated administration of the drugs in schizophrenic patients (8-10), and these differences in prolactin responses are supposed to be due to differences in the administration schedules.

In the present experiment, no significant change in DA level was observed in the hypothalamus in Group I. However, the DOPAC level in this significantly decreased, and as the result, the DOPAC/DA ratio also decreased. On the other hand, significant increase in the specific D₂-dopamine binding sites in the pituitary was detected in Group I in which a marked enhancement of the prolactin-secreting effect of HPD was seen.

Prolactin secretion from the anterior pituitary gland is believed to be mediated through the tubero-infundibular dopamine neurons (11). Prolactin secretion is inhibited by dopamine or its agonists such as L-dopa (12), apomorphine (13) and amphetamines (12); and on the contrary, it is stimulated by dopamine blocking agents such as antipsychotic drugs (14), reserpine (15), α-methyl-p-tyrosine (12) in animals and man. The biochemical data obtained in the present experiment and factors mentioned above, therefore, suggest that the enhancement of the prolactin-secreting effect may be produced by a decrease in the activity of dopamine neurons in the hypothalamus.

Fig. 2. Effects of repeated administration of haloperidol on dopamine turnover in the hypothalamus. Repetition of the drug decreased dopamine turnover (**P<0.001, Student's t-test). —— Saline-repeated (Group II) (N=10). —— Haloperidol-repeated (Group I) (N=10) (0.035 mg/kg/3–4 days x10).

References
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