Effects of Chronic Haloperidol and Chlordiazepoxide Treatment on Lateral Hypothalamic Self-Stimulation Behavior in Rats

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Accepted September 16, 1983

Abstract—The effects of chronic administration of haloperidol and chlordiazepoxide for 14 days on self-stimulation behavior were investigated in rats with electrodes chronically implanted in the lateral hypothalamus. Haloperidol produced a prominent decrease in self-stimulation behavior during chronic treatment, followed by a significant increase in the lever-pressing rate during a 2 week withdrawal period, with a return to the control level about 5 weeks after drug withdrawal. Chlordiazepoxide produced a significant increase in self-stimulation behavior during chronic treatment. However, the lever-pressing rate was not significantly different from the control level during a 3 week observation period following drug withdrawal. These results indicate an increase in the sensitivity of central dopaminergic receptors following chronic haloperidol treatment, but not following chronic chlordiazepoxide treatment.

Intracranial self-stimulation behavior has been widely used as an index for evaluating drug effects on the central nervous system. It has been reported that self-stimulation behavior is attenuated by neuroleptics (1-4) and generally facilitated by anti-anxiety drugs (5-8) when administered acutely. Thus neuroleptics and anti-anxiety drugs act on this behavior in opposite directions. In clinical practice, these psychotropic drugs are commonly used over a long period. It is well accepted that the sensitivity of dopaminergic receptors changes during or after chronic neuroleptic treatment. There have been several reports (9-11) demonstrating supersensitivity on self-stimulation behavior following termination of chronic neuroleptic treatment. However, there have been no reports dealing with the effects of chronic treatment with anti-anxiety drugs on this behavior.

The present experiment was carried out to investigate the effects of chronic treatment with haloperidol, a neuroleptic drug, and chlordiazepoxide, an anti-anxiety drug, on lateral hypothalamic self-stimulation behavior in rats.

Materials and Methods
Experimental subjects were 8 male Wistar rats weighing 300-350 g at the time of surgery. The rats were anesthetized with pentobarbital, and bipolar electrodes were chronically implanted in the medial forebrain bundle. The stereotaxic coordinates were A: 5.5, L: 1.7 and H: -2.5 mm according to the atlas of König and Klippel (12). Electrodes were made of stainless steel wire, 0.20 mm in diameter, insulated except for the tip. Two weeks after surgery, the rats were trained to press a lever for brain stimulation on a continuous reinforcement schedule. Each response provided a 0.25 sec stimulus train of 60 Hz A.C. The rats were given a 30 min training session daily for about 1 month. During the training sessions, stimulus intensity was adjusted on an individual basis in order to bring each animal's lever-pressing rate to approx. 2000 responses per 30 min. After the training sessions, stimulus intensity was determined for each rat as the lowest intensity maintaining a moderately high constant lever-pressing rate for 15 min. These stimulus intensities varied between 16
and 24 µA and were individually maintained for each rat throughout subsequent experiments. After establishment of stimulus intensities, the lever-pressing rate during a 10 min period was recorded once a day. The test drugs used were haloperidol and chlordiazepoxide, which were synthesized in our laboratories. These drugs were suspended in a 0.5% methylcellulose solution. The rats were treated orally with 1 mg/kg of haloperidol once a day for 14 days. Three months after the haloperidol treatment, the same animals were treated with 5 mg/kg of chlordiazepoxide by the same procedure. After completion of the experiment, the location of the electrode tip was examined histologically. Statistical significance was calculated by one-way analysis of variance followed by the t-test.

Results

The rats used in this experiment were subjected to histological examination. The electrode tips of 6 rats were located at the lateral hypothalamic nucleus; those of the remaining 2, however, were not identified accurately. Stimulus intensities and lever-pressing rates of these 2 were almost identical to those of the others, so that the data from these 2 were not discarded.

The results of the chronic haloperidol treatment are presented in Fig. 1 and summarized in Table 1. The lever-pressing rate was fairly constant during a 6 day period preceding the drug administration. During the haloperidol treatment period, the lever-pressing rate measured 1 hr after each administration (on days 1, 3, 5, 7, 10 and 14) was reduced by about 70-80% of the control level. This reduction did not fluctuate significantly during this period. The lever-pressing rate measured 24 hr after each administration (on days 2, 4, 6 and 8 and day 1 after withdrawal) did not completely recover to the control level. Following termination of the chronic haloperidol treatment, the lever-pressing rate on day 1 was almost the same as the control level. However, on day 3 an increase was observed which lasted for 2 weeks. During this period the increase in responses was significant. Five weeks after withdrawal, the lever-pressing rate was no longer significantly different from the control level.

The results of the chronic chlordiazepoxide treatment are presented in Fig. 2 and summarized in Table 2. The lever-pressing rate was fairly constant during a 6 day period preceding the drug administration. During the chlordiazepoxide treatment period, the lever-pressing rate measured 1 hr after each administration (on days 1, 3, 5, 7, 10 and 14)

Fig. 1. Effect of chronic administration of haloperidol (1 mg/kg for 14 days) on lateral hypothalamic self-stimulation behavior in rats. Each point represents the mean response of 8 animals.
Fig. 2. Effect of chronic administration of chlordiazepoxide (5 mg/kg for 14 days) on lateral hypothalamic self-stimulation behavior in rats. Each point represents the mean response of 8 animals.

Table 1. Summary of effect of chronic administration of haloperidol on lateral hypothalamic self-stimulation behavior in 8 rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean lever-pressing rate per 10 min ±S.E.</th>
<th>Number of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before administration (Control)</td>
<td>945 ± 25</td>
<td>48</td>
</tr>
<tr>
<td>During administration (After 1 hr)</td>
<td>286 ± 44**</td>
<td>48</td>
</tr>
<tr>
<td>During administration (After 24 hr)</td>
<td>925 ± 27*</td>
<td>40</td>
</tr>
<tr>
<td>Withdrawal (During a 2 week)</td>
<td>990 ± 28**</td>
<td>48</td>
</tr>
<tr>
<td>Withdrawal (From 5 to 6 weeks)</td>
<td>947 ± 29</td>
<td>48</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01 vs Control

Table 2. Summary of effect of chronic administration of chlordiazepoxide on lateral hypothalamic self-stimulation behavior in 8 rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean lever-pressing rate per 10 min ±S.E.</th>
<th>Number of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before administration (Control)</td>
<td>951 ± 30</td>
<td>48</td>
</tr>
<tr>
<td>During administration (After 1 hr)</td>
<td>1042 ± 28**</td>
<td>48</td>
</tr>
<tr>
<td>During administration (After 24 hr)</td>
<td>917 ± 34**</td>
<td>40</td>
</tr>
<tr>
<td>Withdrawal (During a 3 week)</td>
<td>954 ± 31</td>
<td>48</td>
</tr>
</tbody>
</table>

**P<0.01 vs Control
increased significantly over the control level. The lever-pressing rate measured 24 hr after each administration (on days 2, 4, 6 and 8 and day 1 after withdrawal) showed a slight but significant decrease. Following termination of the chronic chlordiazepoxide treatment, the lever-pressing rate was not significantly different from the control level during a 3 week observation period.

Discussion

It has been well established that neuroleptics which block the dopamine receptors are potent inhibitors of self-stimulation behavior. In the present experiment, the effect of chronic haloperidol treatment on self-stimulation behavior was investigated in rats with electrodes chronically implanted in the lateral hypothalamus. During chronic haloperidol treatment, self-stimulation behavior measured 1 hr after each administration was inhibited on every day of the treatment period. In order to determine whether tolerance would develop during this period, daily responses were compared with each other. There were no significant differences between them, indicating no development of tolerance.

It has been reported that tolerance toward both cataleptogenic action and acceleration of dopamine metabolism easily develops during chronic treatment with "classical" neuroleptics (13) and that this is related to a loss of sensitivity of the striatal dopaminergic neurones to neuroleptics (14). Therefore, it seems unlikely that the striatal dopaminergic neurones play an important role in the mediation of self-stimulation behavior inhibition produced by neuroleptics.

In the present study, a significant increase in lever-pressing rate was seen during a 2 week period following termination of the chronic haloperidol treatment. This behavioral withdrawal effect is in agreement with previous findings of Simpson and Annau (9), Ettenberg and Milner (10) and Seeger et al. (11) who found significant increases in the lever-pressing rate during withdrawal from chronic treatment with chlorpromazine, pimozide and haloperidol, respectively. Withdrawal from chronic neuroleptic treatment produces an enhanced response to dopaminergic agonists and an increase in the binding of tritiated dopaminergic ligands (13). These withdrawal effects are considered to be due to chemical denervation supersensitivity of the dopaminergic receptors (15). The increase in responses seen in the present experiment might be explained as an increase in the reinforcing properties of the stimulation due to the development of supersensitivity of the dopaminergic receptors. Increased responses returned to the control level about 5 weeks after withdrawal. It is considered that supersensitivity of the dopaminergic receptors returned to normal at that time.

It has been reported that benzodiazepines facilitate self-stimulation behavior. In the present experiment, the facilitatory action of chlordiazepoxide during chronic administration was observed on day 1 as well as on the other days tested. The results indicate that neither tolerance nor accumulation occur in the facilitatory effect of chlordiazepoxide on self-stimulation behavior.

It is well known that amphetamine facilitates self-stimulation behavior. Simpson and Annau (9) reported that amphetamine produced an increase in self-stimulation behavior during chronic administration, followed by a significant decrease after the drug was discontinued. In the present study, the lever-pressing rate after termination of the chronic chlordiazepoxide treatment was almost the same as the control level. On the basis of this difference, it seems likely that the bases for facilitation of the two drugs involve different mechanisms. Conceivably, the facilitatory mechanism of chlordiazepoxide might not involve a change in the sensitivity of receptors. Tarsy and Baldessarini (16) reported that the behavioral responses to apomorphine did not change following chronic administration of diazepam, indicating that receptor supersensitivity did not occur. It is considered that sensitivity of the dopaminergic receptors does not change following chronic treatment with benzodiazepines.

References

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