ORAL SELF-ADMINISTRATION OF MORPHINE IN RATS

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The operant behavior method has been utilized to ascertain whether certain drugs have the power to reinforce the animal’s operant behavior and also whether the animal can self-administer the drug by means of automatic intravenous or intragastric injections (1–5). Using operant behavior the oral self-administration of morphine has been little studied though the preference for morphine has been reported (6–8). In our present work, the operant discrimination behavior was used with the drug-admixed food method (9, 10) to examine the oral self-administration of morphine.

A Skinner discrimination box (25 x 20 x 30 cm) was used; two sets of levers, food trays and small lights were attached to the inside of the box. Two food dispensers outside the box were connected to the food trays by tubes (developed by our department and Charles River Japan, Inc., Kanagawa). Ordinary pellet food, weighing approx. 45 mg, was from the CLEA Japan, Inc. and the same type of pellet food which was produced by mixing morphine hydrochloride (1 mg/g food) into normal food was prepared in our department.
and by the CLEA Japan, Inc. The former, normal pellet, was supplied from one food tray and the latter, morphine pellet, from the other tray. Six male Wistar rats weighing approx. 250 g were used.

All experiments included a pre-test experiment and a fixed-ratio schedule experiment. In the former, the choice trial and forced trial were included and here the rats could choose between the normal pellet and the morphine pellet food by pressing one or the other lever. In the latter, either lever pressing would supply the morphine pellet, so that rats were forced in every case to take morphine with their food. One choice and two forced trials comprised one experimental session, over the course of three days, and this session was repeated 5 times for a total experiment time of 15 days. After these pre-test experiments, a fixed-ratio schedule was employed, i.e., the fixed-ratio for the drug was increased successively 1, 3, 5 and then 9 while that for the normal pellet remained at 1. Only when the morphine pellet was released did the light above that lever go on. Each trial required 15 hours, from 6:00 p.m. to 9:00 a.m., and for the rest of the day, the rats were provided no food at all (except water). In these experiments, we obtained data on body weight (at 9:00 a.m. and 6:00 p.m.), the number of times the levers were pressed and the number of pellets consumed, the calculated morphine intake and the preference rate (6) for the drug. All the same rats were used throughout the entire experiment.

With progression of the pre-test experiment, the number of morphine pellets consumed rapidly increased while the number of normal pellets decreased and the mean morphine intake at the fifth choice trial was 50.1 mg/kg/day. Thus the preference rate for morphine rapidly increased in the course of pre-test experiment (Table 1). As the fixed-ratio for morphine pellet increased (1, 3, 5 and then 9), the rats pressed that lever a greater number of times.

**Fig. 1.** Relationship between number of times the lever was pressed or number of pellets consumed and the total time in one trial period from 18:00 to 9:00. In A and B, the ordinate represents the cumulative number of times the lever was pressed or of pellets consumed, in B' number of times or number of pellets per unit times. Each plot represents the mean value of 6 rats. MAP: morphine-admixed pellet food. NP: normal pellet food.
<table>
<thead>
<tr>
<th>Choice trial</th>
<th>Body weight (g)</th>
<th>(MAP) Number of lever pressings</th>
<th>(NP) Number of lever pressings</th>
<th>Morphine intake (mg/kg)</th>
<th>Preference rate for MAP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>245.5 ± 25.3</td>
<td>68.3 ± 21.9</td>
<td>68.3 ± 21.9</td>
<td>311.3 ± 71.7</td>
<td>15.6 ± 5.1</td>
</tr>
<tr>
<td>2</td>
<td>255.0 ± 25.0</td>
<td>86.4 ± 15.5</td>
<td>86.4 ± 15.5</td>
<td>240.2 ± 31.8</td>
<td>19.4 ± 5.3</td>
</tr>
<tr>
<td>3</td>
<td>256.0 ± 25.4</td>
<td>233.2 ± 46.1</td>
<td>233.2 ± 46.1</td>
<td>156.8 ± 15.6</td>
<td>39.1 ± 7.6</td>
</tr>
<tr>
<td>4</td>
<td>252.0 ± 23.9</td>
<td>249.8 ± 33.8</td>
<td>249.8 ± 33.8</td>
<td>136.2 ± 40.4</td>
<td>45.2 ± 7.3</td>
</tr>
<tr>
<td>5</td>
<td>268.2 ± 25.2</td>
<td>296.0 ± 36.1</td>
<td>296.0 ± 36.1</td>
<td>161.3 ± 51.1</td>
<td>50.1 ± 5.1</td>
</tr>
</tbody>
</table>

(MAP) (NP)

<table>
<thead>
<tr>
<th>FR schedule</th>
<th>1 vs. 1</th>
<th>284.0 ± 20.4</th>
<th>360.0 ± 37.0</th>
<th>360.0 ± 37.0</th>
<th>96.3 ± 13.4</th>
<th>96.3 ± 13.4</th>
<th>57.2 ± 5.9</th>
<th>77.0 ± 3.9</th>
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</thead>
<tbody>
<tr>
<td>3 vs. 1</td>
<td>281.2 ± 16.2</td>
<td>1013.9 ± 175.3</td>
<td>333.5 ± 56.0</td>
<td>140.9 ± 51.6</td>
<td>140.9 ± 51.6</td>
<td>53.7 ± 9.7</td>
<td>75.1 ± 5.6</td>
<td></td>
</tr>
<tr>
<td>5 vs. 1</td>
<td>304.1 ± 15.3</td>
<td>1939.7 ± 187.9</td>
<td>382.2 ± 36.1</td>
<td>91.4 ± 19.5</td>
<td>91.4 ± 19.5</td>
<td>57.7 ± 7.8</td>
<td>81.1 ± 3.7</td>
<td></td>
</tr>
<tr>
<td>9 vs. 1</td>
<td>312.3 ± 17.0</td>
<td>3359.1 ± 271.5</td>
<td>366.4 ± 29.2</td>
<td>139.0 ± 27.1</td>
<td>139.0 ± 27.1</td>
<td>55.1 ± 4.3</td>
<td>75.2 ± 5.0</td>
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</tbody>
</table>

The data are expressed in a form of mean ± S.E. of 6 rats.

MAP: morphine admixed food pellet  NP: normal food pellet

of times and the number of morphine pellets was constant throughout the fixed-ratio schedule (Table 1, Fig. 1A, B). In 4 non-drug-treated rats, the lever was not pressed when the fixed-ratio was increased to 9 while they did press the other lever which remained at the fixed-ratio 1. With analyzation of these data by unit time (1 hour), we obtained figures which show the relationship between the number of times the lever was pressed and the total times in one trial period (Fig. 1B').

These findings suggest that: 1) The rats could discriminate the morphine pellets from the normal pellets as shown in Table 1. 2) The morphine-treated rats in the pre-test experiment pressed more often for the morphine pellets. Thus we conclude that morphine reinforced the lever pressing behavior of rats when the drug was ingested orally. 3) As shown in the fixed-ratio schedule experiment, despite an increase in the ratio for morphine 1, 3, 5 and 9 successively, the rats obtained relatively a constant dose of morphine. Thus, the rats may be ingesting a maintenance-level dose of morphine.

It should now be possible to use an increased fixed-ratio schedule to measure the extent to which the rats will go to maintain their drug dependence.

REFERENCES