EFFECTS OF QUINIDINE AND CIMETIDINE ON METHAMPHETAMINE STEREOTYPY IN RATS

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The effects of quinidine and cimetidine on methamphetamine-induced stereotyped behavior were studied in rats. Quinidine (10, 30 and 50 mg/kg) and cimetidine (100, 250 and 500 mg/kg) were administered orally 60 min prior to subcutaneous injection of a fixed dose of methamphetamine (5 mg/kg). It was found that quinidine and cimetidine very markedly potentiated the intensity of methamphetamine stereotypy. The duration of the stereotypy in the group pretreated with either drug was 2.3—4.0 times longer than that in the control group. Furthermore, the urinary pH levels of rats were measured after administrations of methamphetamine alone and of methamphetamine following the drugs in question. Urinary pH was not changed by pretreatments with those drugs, suggesting that the enhancing effects of quinidine and cimetidine on methamphetamine-induced stereotyped behavior are not derived from a change in urinary pH level. The enhancement of methamphetamine-induced stereotyped behavior may be explained by inhibitory effects of quinidine and cimetidine on the metabolism of methamphetamine.

Keywords — methamphetamine stereotypy; quinidine; cimetidine; drug interaction

INTRODUCTION

Drug interaction of methamphetamine with other drugs has been poorly documented except with psycholeptics,1) in spite of the spread of methamphetamine abuse. A marked enhancement of methamphetamine-induced stereotypy by quinine was found in previous papers.2,3) This enhanced behavior was derived from an inhibitory effect of quinine on the metabolism of methamphetamine.3) On the other hand, it is known that cimetidine, a drug widely used for the treatment of peptic ulcers, poses an important problem in clinical use due to drug interaction.4—8) In the present study, the effects of quinidine, a diastereoisomer of quinine which is often used as an antiarrhythmic drug, and cimetidine on stereotyped behavior induced by methamphetamine were investigated.

MATERIALS AND METHODS

Animals — Male Sprague-Dawley rats (Tokyo Laboratory Animals Co., Tokyo), weighing 155—180 g, were used in the experiments. Laboratory chow (MF, Oriental Yeast Co.) and tap water were freely available to the animals which were maintained under a 12 h light/dark cycle in a temperature-controlled room (22 ± 1 °C). They were fasted for 18 h prior to the experimental dosing. Each rat was used only once.

Drugs and Treatments — The following drugs were used: quinidine sulfate (Tokyo Chemical Industry Co., Tokyo), cimetidine (Sigma Chemical Co., St. Louis, Mo., U.S.A.) and methamphetamine hydrochloride (Dainippon Seiyaku Co., Osaka). Quinidine and cimetidine were suspended in 1% carboxymethylcellulose sodium (CMC) aqueous solution, and were administered p.o. in a volume of 5 ml/kg body weight. Methamphetamine was dissolved in saline, and was injected s.c. in a volume of 1 ml/kg. Quinidine and cimetidine were administered 60 min prior to the injection of methamphetamine. The control group received 1% CMC aqueous solution instead of quinidine or cimetidine in the same volume.

Procedure — The rats were placed separately in wire-mesh cages (21 × 25 × 15 cm) and were acclimated to the new environment for 30 min prior to drug administration. Ten rats were observed in each experimental session. Following the injection of methamphetamine, the behavioral change of each rat was observed continuously for 8 h or longer. The observer was blind to the drug which was given to each rat. The intensity of behavioral excitation including stereotyped behavior was assessed at a 10 to 30 min interval.
with the rating described previously\(^2\): 0 — asleep, 1 — awake, usually not moving, 2 — short-lasting locomotion and periodic sniffing, 3 — continuous locomotion, rearing and sniffing, 4 — continuous sniffing and/or repetitive head and limb movement, 5 — periodic gnawing, biting or licking, 6 — continuous gnawing, biting or licking. The latency of onset, and the duration of stereotyped behavior induced by methamphetamine were also determined according to the method employed previously.\(^2\)

**Urinary pH** — Animals were housed individually in metabolic cages after drug administration. The urine samples were collected over a period of 3 h. During this period, the rats were given water ad libitum but no food. Urinary pH was measured with a pH-meter (Model F-8E; Horiba Co., Kyoto).

**Statistical Analysis** — Data are shown as mean ± S.E. and analyzed with the Student’s t-test, except for the maximum intensity of stereotyped behavior which was analyzed with Mann-Whitney’s U-test.

**RESULTS**

**Effects of Drugs on Stereotyped Behavior**

The time courses of behavioral changes induced by methamphetamine (5 mg/kg, s.c.) in rats pretreated with 1% CMC aqueous solution (control) or with various doses of quinidine (10, 30 and 50 mg/kg, p.o.) and cimetidine (100, 250 and 500 mg/kg, p.o.) are shown in Figs. 1 and 2. Methamphetamine, 5 mg/kg, s.c., produced stereotyped behavior in all the animals tested. A few min after the injection, the rats exhibited a brief period of continuous locomotion, rearing and sniffing (below score-3), which was followed by the onset of stereotyped behavior (above score-4). Most animals in the methamphetamine control group showed the stereotypy of score-4. The behavioral effect of methamphetamine was markedly enhanced in all the animals pretreated with quinidine. This agent not only significantly prolonged the duration but also significantly increased the intensity of methamphetamine stereotypy. Likewise, pretreatment with cimetidine resulted in a marked enhancement of methamphetamine stereotypy as did quinidine. The latency to onset, the duration and the maximum intensity of methamphetamine stereotypy observed in a combination of methamphetamine with quinidine or methamphetamine with cimetidine are shown in Table I. The enhancing effects of quinidine and cimetidine on the stereotyped behavior induced by methamphetamine were, as a whole, dose-dependent. Howev-

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**FIG. 1. Time Course of the Behavioral Changes Induced by Methamphetamine in Rats Pretreated with Quinidine**

Each symbol represents the mean of 10 rats. Animals were pretreated with 1% CMC aqueous solution (as control) (—), or quinidine 10 mg/kg (— □ —), 30 mg/kg (— ◯ —) and 50 mg/kg (— ● —) orally 60 min prior to methamphetamine (5 mg/kg, s.c.).

**FIG. 2. Time Course of the Behavioral Changes Induced by Methamphetamine in Rats Pretreated with Cimetidine**

Each symbol represents the mean of 10 rats. Animals were pretreated with 1% CMC aqueous solution (as control) (—), or cimetidine 100 mg/kg (— □ —), 250 mg/kg (— ◯ —) and 500 mg/kg (— ● —) orally 60 min prior to methamphetamine (5mg/kg, s.c.).
TABLE 1. Effects of Quinidine and Cimetidine on Methamphetamine-Induced Stereotyped Behavior in Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment dose (mg/kg)</th>
<th>Latency to onset (min)</th>
<th>Duration (min)</th>
<th>Max. intensity (score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1% CMC + methamphetamine (5)</td>
<td>24.8 ± 0.8</td>
<td>128.5 ± 6.9</td>
<td>4.5 ± 0.9</td>
</tr>
<tr>
<td>2</td>
<td>Quinidine (10) + methamphetamine (5)</td>
<td>23.5 ± 1.0</td>
<td>367.0 ± 12.6a)</td>
<td>6.0 ± 0.0a)</td>
</tr>
<tr>
<td>3</td>
<td>Quinidine (30) + methamphetamine (5)</td>
<td>24.2 ± 0.8</td>
<td>439.0 ± 14.0ab</td>
<td>6.0 ± 0.0a)</td>
</tr>
<tr>
<td>4</td>
<td>Quinidine (50) + methamphetamine (5)</td>
<td>23.8 ± 0.8</td>
<td>511.9 ± 12.4ac</td>
<td>5.8 ± 0.1a)</td>
</tr>
<tr>
<td>5</td>
<td>Cimetidine (100) + methamphetamine (5)</td>
<td>24.4 ± 0.3</td>
<td>289.3 ± 17.1a)</td>
<td>6.0 ± 0.0a)</td>
</tr>
<tr>
<td>6</td>
<td>Cimetidine (250) + methamphetamine (5)</td>
<td>25.0 ± 0.4</td>
<td>420.0 ± 14.5ab</td>
<td>5.9 ± 0.1a)</td>
</tr>
<tr>
<td>7</td>
<td>Cimetidine (500) + methamphetamine (5)</td>
<td>25.2 ± 0.5</td>
<td>431.2 ± 17.6ab</td>
<td>6.0 ± 0.0a)</td>
</tr>
</tbody>
</table>

Animals were pretreated with quinidine, cimetidine or 1% CMC solution (control) orally 60 min prior to methamphetamine s.c. injection. Each value represents the mean ± S.E. of 10 rats.

a) p < 0.01 vs. group 1, b) p < 0.01 vs. group 2 or 3, c) p < 0.01 vs. group 3. Numerals following the drugs indicate their doses (mg/kg).

er, neither quinidine nor cimetidine by itself exhibited obvious behavioral symptoms. Additionally, the latency to onset for methamphetamine-induced stereotyped behavior was not affected by quinidine or cimetidine.

Influences of Drugs on Urinary pH

The results obtained on urinary pH levels of the samples (N=6 in each group) were as follows: methamphetamine (5 mg/kg, s.c.) alone, 7.9 ± 0.2, quinidine (50 mg/kg, p.o.) alone, 8.2 ± 0.4, and cimetidine (500 mg/kg, p.o.) alone, 7.6 ± 0.4. Moreover, the pH levels were 7.3 ± 0.1 in the group of methamphetamine following quinidine and 7.7 ± 0.2 in the group of methamphetamine following cimetidine.

DISCUSSION

As seen from the data represented, quinidine pretreatment prominently enhanced the stereotyped behavior evoked by methamphetamine both in duration and intensity. The enhancing effect of quinidine on methamphetamine stereotypy almost resembled that of quinine which was reported previously. 2,9

It is well known that p-hydroxylation reaction is the major metabolic pathway of methamphetamine and amphetamine in rats. 9,12 Recently, we found that this metabolic reaction of methamphetamine can be selectively inhibited by pretreatment of rats with quinine. 3 In addition, quinidine and quinine, which are diastereoisomers, are known to be hydroxylated by hepatic microsomal enzymes. 13,16 Based on these facts, it is considered that quinidine, like quinine, would inhibit the p-hydroxylation of methamphetamine and its N-desmethyl metabolite, amphetamine, with a resultant enhancement of the stereotyped behavior induced by methamphetamine. This concept is supported by the finding that quinidine increased the concentrations of both methamphetamine and amphetamine in rat brain. 17

The present results also indicate that pretreatment of rats with cimetidine distinctly potentiated and prolonged the stereotyped behavior induced by methamphetamine, like with quinidine. A number of studies on drug interactions have demonstrated that a histamine H2-receptor antagonist, cimetidine, increases the actions of drugs such as theophylline, diazepam, warfarin, quinidine and lidocaine which can be metabolized by cytochrome P-450 dependent path-
ways.4–8) The facts mentioned above are explained by the high binding affinity of cimetidine for liver cytochrome P-450 of humans and several animals18,19 which, in turn, causes an inhibition of hepatic drug metabolism. Therefore, it would be reasonable to explain that the enhancing effect of cimetidine on methamphetamine-induced stereotypy behavior is, at least in part, attributable to its increasing effects on the levels of methamphetamine and its metabolite, amphetamine, in the rat brain.17)

On the other hand, methamphetamine is excreted in a higher amount at acidic urinary pH than at alkaline pH.20,21) The present data, however, showed that the urinary pH after methamphetamine following quinidine or cimetidine was not significantly different from the pH level of methamphetamine alone. These results suggested that the enhancing effects of quinidine and cimetidine on methamphetamine stereotypy are not due to a change in the urinary pH level.

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REFERENCES