Enhancement of Behavioral Effect and Acute Toxicity of Methamphetamine by Quinine in Rats

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Abstract—The behavioral effect and acute toxicity of methamphetamine were tested alone and in combination with quinine in rats. Quinine prolonged and increased the effect of methamphetamine. The enhancement of methamphetamine-induced stereotyped behavior was very marked when quinine was given prior to or simultaneously with methamphetamine. However, the time for onset of methamphetamine-induced stereotyped behavior was not affected by quinine. The mortality of methamphetamine was also potentiated markedly by quinine. The enhancement of the behavioral effect and the toxicity of methamphetamine may be due to inhibition of the metabolism of methamphetamine by quinine.

In our previous report (1), we demonstrated that quinine could markedly increase methamphetamine-induced anorexia in rats. This finding was based on the results that the inhibition of food consumption and the growth curve was greater in the rats given methamphetamine in combination with quinine than those given methamphetamine alone (1). These results suggest that quinine enhances effects of methamphetamine.

Amphetamine-induced behavioral excitation in rats, consisting of increased exploratory behavior, grooming, forward locomotion or various stereotyped behaviors, had been described in detail by Randrup et al. (2). The interactions between amphetamine-like stimulants (amphetamine, methamphetamine, etc.) and various drugs have been reported by many authors in terms of the behavioral changes (3-6). Therefore, the behavioral study is thought to be useful for the investigation of combined effects of amphetamine-like stimulants and other drugs.

The main purpose of this study was to investigate the interactions between methamphetamine and quinine in rats from the viewpoints of behavioral pharmacology. In addition, toxic interactions of methamphetamine and quinine were also examined.

Materials and Methods

Animals: Male Sprague-Dawley rats (Tokyo Laboratory Animals Co., Tokyo) were housed in groups of eight in wire cages in a room maintained at a constant temperature (22±1°C) with preprogrammed 12 hr light and dark cycles (light on at 08:30). Food (CA-1, Clea Japan, Tokyo) was always available, except for fasting for 18 hr prior to the experimental dosing. Tap water was supplied ad libitum throughout the fasting and post-administration periods. Each animal was tested once only.

Drugs and administration schedules: Methamphetamine hydrochloride was obtained from Dainippon Seiyaku Co. and quinine sulfate was purchased from Wako Pure Chemical Industries, Ltd. Methamphetamine was dissolved in physiological saline, and quinine was suspended in 1% carboxymethyl-cellulose sodium (CMC) aqueous solution. The injection volume of methamphetamine was 1 ml/kg and quinine was 5 ml/kg body weight.
Classification of the behavior: Forty rats weighing 161.4±1.2 g at the beginning of the study were used. They were placed in individual steel and wire cages (21×25×15 cm) 30 min before drug administration to allow adaptation to the experimental situation. In this study, the rats were divided into four groups that received drugs as follows: (1) methamphetamine, 5 mg/kg, s.c., alone; (2) quinine, 50 mg/kg, p.o., 60 min before methamphetamine, 5 mg/kg, s.c.; (3) simultaneous administration of methamphetamine, 5 mg/kg, s.c., and quinine, 50 mg/kg, p.o.; and (4) quinine, 50 mg/kg, p.o., 60 min after methamphetamine, 5 mg/kg, s.c. After administration of methamphetamine (given at 13:00), the behavior of each rat was observed for 8 hr or longer. The behavioral change induced by methamphetamine was scored according to a slight modification of that previously used by Scheel-Krüger (6) and by Costall and Naylor (7); it is shown in Table 1. The individual scores for each of the ten rats in a group were noted and averaged every 10 to 30 min for 8 hr after the methamphetamine injection. Three parameters of methamphetamine-induced stereotyped behavior were considered as follows: 1) the latency of onset, 2) the duration, and 3) the maximum intensity. The latency of onset of stereotyped behavior was determined by the occurrence of continuous sniffing, repetitive head and limb movements with the rat sitting in a crouched posture. The termination of stereotyped behavior was evaluated by the animal falling asleep, resting, or entering a phase of hyperactivity. In addition, the behavior after single administration of quinine (50 mg/kg, p.o.) or 1% CMC solution was also studied (six rats in each group). The statistical significance was determined using Student’s t-test for the latency of onset and the duration of stereotyped behavior and Mann-Whitney’s U-test for the maximum intensity of stereotyped behavior.

Acute toxicity: Two hundred rats weighing 202.7±1.4 g were housed individually and divided into twenty groups with ten rats in each group. Ten doses (from 10.5 to 113.4 mg/kg, s.c.) of methamphetamine alone or in combination with a fixed dose (50 mg/kg, p.o.) of quinine were tested. All administrations were carried out between 13:00 and 14:00 to avoid diurnal variations in drug metabolism (8, 9). Deaths were recorded for three days after the drug administration. The lethal dose (LD50) and 95% confidence limits were determined by the Litchfield-Wilcoxon procedure (10) in animals administered methamphetamine alone or in combination with quinine.

Results

Behavior: The time courses of behavioral change induced by methamphetamine alone or methamphetamine combined with quinine are shown in Fig. 1. The latency to onset, the duration and the maximum intensity of methamphetamine-induced stereotyped behavior are shown in Table 2. Methamphetamine (5 mg/kg, s.c.) caused a moderate behavioral excitation such as sniffing and head movement in all rats and continuous licking, gnawing, or biting in a few of them. The behavioral change lasted for 3–4 hr. The effect of methamphetamine was enhanced slightly when quinine (50 mg/kg, p.o.) was given 60 min after the administration. Moreover, quinine, given 60 min prior to or simultaneously with methamphet-

Table 1. Scoring system used for estimation of the intensity of behavioral excitation

<table>
<thead>
<tr>
<th>Score</th>
<th>Description of behavioral excitation</th>
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<tbody>
<tr>
<td>0</td>
<td>Asleep</td>
</tr>
<tr>
<td>1</td>
<td>Awake, usually not moving, occasional grooming and eating</td>
</tr>
<tr>
<td>2</td>
<td>Shortlasting locomotion and intermittent sniffing</td>
</tr>
<tr>
<td>3</td>
<td>Continuous locomotion, rearing and sniffing</td>
</tr>
<tr>
<td>4</td>
<td>Continuous sniffing and/or repetitive head and limb movement (brief periods of locomotor activity may be observed)</td>
</tr>
<tr>
<td>5</td>
<td>Intermittent licking, gnawing or biting of cage or itself</td>
</tr>
<tr>
<td>6</td>
<td>Continuous licking, gnawing or biting of cage or itself (no locomotor activity)</td>
</tr>
</tbody>
</table>
amine administration, potentiated very markedly the effect of methamphetamine both in degree and duration. However, the onset of methamphetamine-induced stereotyped behavior was not altered by quinine. CMC solution (5 ml/kg, p.o.) or quinine (50 mg/kg, p.o.) alone did not produce any behavioral excitation during 6 hr of observation (Fig. 1).

Acute toxicity: Deaths usually occurred 3 hr after the injections of methamphetamine and were characterized by hyperpnea and convulsions. However, all data are presented as the number of deaths recorded 72 hr after the injection. Figure 2 shows the mortality in rats after administration of methamphetamine singly and combined with a fixed dose (50 mg/kg, p.o.) of quinine. Methamphetamine killed the rats in a dose-dependent manner. The mortality of methamphetamine was markedly enhanced by quinine. The LD50 for methamphetamine alone was estimated to be 79.7 (61.8–120.3) mg/kg, but it was decreased to 21.3 (14.5–28.0) mg/kg by quinine.

Discussion

The present results indicated that quinine enhanced the behavioral excitation (such as increased locomotor activity or development
of stereotyped behavior) induced by methamphetamine. It has been known that quinine at high doses can affect central nervous system functions (11). However, like the solvent (1% CMC solution), 50 mg/kg, p.o. of quinine, tested in this study, it did not produce any change in the behavior. In addition, the onset time of methamphetamine-induced stereotyped behavior was not affected by quinine. These results suggest that the central effect of quinine is scarcely involved in the potentiation and prolongation of the behavior-stimulating effect of methamphetamine.

Furthermore, it was shown that the duration and intensity of methamphetamine-induced behavioral excitation were more pronounced in the rats given the drug prior to or simultaneously with methamphetamine than those given the drug after methamphetamine. These findings indicate the possibility that the enhancing effect of quinine on methamphetamine-induced behavioral excitation is due to inhibition of methamphetamine metabolism.

It has been reported that the excretion rate of methamphetamine in humans was dependent on urinary pH level (12, 13). Methamphetamine is excreted in higher amounts at an acidic urinary pH than at an alkaline pH (12, 13). However, our recent study indicated that the urinary pH in rats was not changed by the combination of methamphetamine with quinine (1). These results suggest that the enhancing effect of quinine on methamphetamine-induced behavioral excitation is not due to a change in the urinary pH level.

The present study also showed that mortality of methamphetamine was markedly increased by quinine at a dose of 50 mg/kg, p.o. However, it had been reported that 50 mg/kg, p.o., of quinine did not kill any rats even after a chronic administration (50 mg/kg/day for 14 days) (1). Moreover, it had also been observed in mice that the mortality of methamphetamine was not affected by quinine (T. Suzuki et al., unpublished data). Such a species difference may be explained by the fact that aromatic hydroxylation of amphetamine at the para position is the major pathway of amphetamine metabolism in rats (14–16), but it is relatively minor in mice (16, 17). In addition, quinine itself is also hydroxylated by the liver microsomal enzymes (18–20). Therefore, quinine may compete with the p-hydroxylation of methamphetamine and thereby delays the metabolism of methamphetamine. However, further studies are required to elucidate such a metabolic interaction between quinine and methamphetamine in relation to potentiation of the pharmacological or toxicological effects of the latter drug.

Fig. 2. Acute toxicity of methamphetamine (MA) given alone or in combination with a fixed dose (50 mg/kg) of quinine (Q). MA and Q were administered simultaneously. Each column represents the mortality of 10 rats during the 72 hr observation period.

References
Interaction of Methamphetamine and Quinine

178–187 (1966)


