Effects of Quinidine and Cimetidine on the Methamphetamine Level in the Rat Brain

Tsutomu SUZUKI, Horng-Jen FAN CHIANG and Miwa MISAWA
Department of Applied Pharmacology, School of Pharmacy, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142, Japan

Accepted November 8, 1986

Abstract—The drug interaction between methamphetamine and quinidine/cimetidine was investigated in terms of distribution of methamphetamine to the brain. The concentrations of methamphetamine and amphetamine in the brain after an s.c. injection of methamphetamine were determined in rats pretreated with a single oral dose of quinidine or cimetidine. Both drugs markedly enhanced the increase in the concentrations of methamphetamine and its metabolite, amphetamine. These results suggest that the recent finding of the enhancements of the behavioral effect of methamphetamine by quinidine and cimetidine is due to the increase in levels of methamphetamine and amphetamine in the brain by these pretreatment drugs.

In spite of the spread of methamphetamine abuse, drug interactions of methamphetamine with other drugs have been poorly documented except with psycholeptics (1). The previous studies showed that quinidine enhanced the methamphetamine-induced stereotyped behavior (2), and quinine, its diastereoisomer, has an inhibitory effect on the metabolism of methamphetamine (3). On the other hand, it is known that cimetidine, a widely used drug for the treatment of peptic ulcers, has an important problem in clinical use because of drug interactions with other drugs (4–7). Cimetidine has been shown to inhibit the activity of hepatic microsomal cytochrome P-450 (8, 9) and also to enhance the methamphetamine stereotypy (2). Therefore, the enhancements of the stereotypy of methamphetamine in the rat after quinidine and cimetidine may be due to their inhibitory effects on the metabolism of methamphetamine, which cause increases in the brain methamphetamine. To test this hypothesis, the brain methamphetamine together with amphetamine (N-demethylated metabolite) concentrations were measured after methamphetamine administration in the rat pretreated with either quinidine or cimetidine.

Male Sprague-Dawley rats were fasted for 18 hr before the experimental dosing, and they weighed 145–190 g at the start of the experiment. Quinidine sulfate (Tokyo Chemical Industry Co., Tokyo) and cimetidine (Sigma Chemical Co., St. Louis, MO, U.S.A.) were suspended in 1% carboxymethylcellulose (CMC) aqueous solution. Methamphetamine hydrochloride (Dainippon Seiyaku Co., Osaka) was dissolved in saline and injected s.c. in a fixed dose of 5 mg/kg, 1 hr after oral administration of quinidine (10 and 50 mg/kg) or cimetidine (100 and 250 mg/kg). Control animals received requisite volumes of 1% CMC solution 1 hr prior to the injection of methamphetamine. The doses of quinidine and cimetidine used in the present study are within the range of the doses used for the antiarrhythmic effect of quinidine (15 mg/kg, i.p. and 30 mg/kg, p.o.) (10, 11) and the antiulcer effect of cimetidine (200 mg/kg, i.p. or p.o.) (12, 13).

For the determination of brain concentrations of methamphetamine and its metabolite, amphetamine, groups of animals (each N=6–7) were decapitated at various times after the injection of methamphetamine. The brains were immediately dissected out, and the levels of methamphetamine and
amphetamine were measured by gas chromatography, using an instrument equipped with a nitrogen-phosphorus detector according to the method of Terada (14). Briefly, brain methamphetamine and amphetamine were extracted with acetone-formic acid. After producing pentafluorobenzoyl derivatives of methamphetamine and amphetamine, the products were injected into the gas chromatograph. The recovery ratios of methamphetamine and amphetamine from brain tissues were 94–106%.

Figures 1 and 2 illustrate the methamphetamine and amphetamine concentrations in the brain at various times after the injection of 5 mg/kg of methamphetamine in quinidine, cimetidine or 1% CMC solution (control) pretreated rats. The methamphetamine concentration in the rat brain was increased rapidly after the injection, and reached a peak within 30 min in all the animals tested. In rats pretreated with either quinidine or cimetidine, the concentration of methamphetamine in the brain was significantly increased at almost all the time points as compared with that in the control group. To analyze the degree of enhancement by quinidine or cimetidine, the areas under the brain concentration-time curves (AUC, 0–8 hr) for methamphetamine were calculated. The AUC in the quinidine (Fig. 1) or cimetidine (Fig. 2) pretreated rats was 1.7–2.3 times larger than that in the control group. On the other hand, the level of brain amphetamine reached a peak more slowly than that of methamphetamine (requiring about 1 hr or more). Quinidine or cimetidine pretreatment also produced a significant increase in the brain amphetamine concentration at almost all the time points. The enhancement of increase in the concentrations of methamphetamine and amphetamine by quinidine or cimetidine was stronger at a higher dose.

It has been reported that quinidine like its diastereoisomer, quinine, also enhanced methamphetamine-induced stereotyped behavior both in duration and intensity (2, 3, 15). We also reported that pretreatment of rats with quinine inhibits the p-hydroxylation reaction of methamphetamine and amphetamine (3), which is the major metabolic pathway for them in this species (16–18). Based on these facts, the potentiation of methamphetamine-induced stereotyped behavior in the rat by quinidine (2) may be interpreted by an inhibition of the p-hydroxy-

![Fig. 1](image-url)  
**Fig. 1.** Brain concentrations of methamphetamine (left) and amphetamine (right) in rats pretreated with 1% CMC solution (control) (---), 10 mg/kg quinidine (—–) or 50 mg/kg quinidine (---), orally, 1 hr prior to methamphetamine (5 mg/kg, s.c.). Each point represents the mean with S.E. of 6–7 rats. *P<0.05, **P<0.01 vs. the control group and *P<0.05, **P<0.01 vs. quinidine (10 mg/kg) treated group (Student's t-test).
Fig. 2. Brain concentrations of methamphetamine (left) and amphetamine (right) in rats pretreated with 1% CMC solution (control) (--), 100 mg/kg cimetidine (——) or 250 mg/kg cimetidine (-----), orally, 1 hr prior to methamphetamine (5 mg/kg, s.c.). Each point represents the mean with S.E. of 6-7 rats. *P<0.05, **P<0.01 vs. the control group and *P<0.05, **P<0.01 vs. cimetidine (100 mg/kg) treated group (Student's t-test).

lation reactions of methamphetamine. That is, it is because 1) the brain level of methamphetamine was enhanced by quinidine pretreatment and 2) the level of amphetamine which is produced by the N-demethylation pathway from methamphetamine (not by p-hydroxylation) was also increased. It is known that both methamphetamine and amphetamine produce stereotyped behavior in a similar fashion (1).

The present data also indicated that cimetidine pretreatment caused an increase in the concentrations of methamphetamine and amphetamine in the brain. Cimetidine, a histamine H2-receptor antagonist, inhibits the hepatic microsomal drug metabolism by its high binding affinity for cytochrome P-450 (8, 9). It is therefore suggested that the increased concentrations of methamphetamine and amphetamine in the brain by cimetidine are probably derived from its inhibitory effect on the metabolism of methamphetamine. That is, as in the case of quinidine, cimetidine seems to strongly inhibit p-hydroxylation of methamphetamine, resulting in an increase in the amounts of both methamphetamine and amphetamine. Thus, the enhancing effect of cimetidine on methamphetamine stereotypy (2) can be explained by the increased levels of methamphetamine and amphetamine in the brain as a result of the drug interaction. Furthermore, cimetidine has been reported to influence not only the activity of the central histaminergic system, but also those of serotonergic, GABAergic systems and dopamine autoreceptors (19–21). The possibility that cimetidine might have affected the stereotypy of methamphetamine via modulating the activity of the above-mentioned neurotransmitter systems may also, in part, need to be considered.

Acknowledgement: We wish to thank Dr. M. Terada (School of Medicine, Kyorin University) for his kind advice and technical assistance.

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