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Biotransformation of Benzyl trans-2-phenylcyclopropanecarbamate to Tranylcypromine in Rat*

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Abstract □ A metabolic study was performed in order to characterize the *in vivo* MAO-inhibitory activity of benzyl trans-2-phenylcylopropanecarbamate which was reported to be twice as potent as the tranylcypromine. In the rat urine which was obtained after the administration of the benzyl trans-2-phenylcyclopropanecarbamate(40mg/kg) through oral route, a metabolic product, tranylcypromine as well as the intact drug was detected by GC/MS.

Keywords □ Monoamine oxidase inhibition, Tranylcypromine, Benzyl trans-2-phenylcyclopropanecarbamate, Metabolic study.

Tranylcypromine (trans-*dl*-2-phenylcyclopropylamine, TCP) has been used as a model compound to study mechanism of the monoamine oxidase (MAO) inhibition.[1] Two carbamate analogs of TCP, ethyl trans-2-phenylcy clopropanecarbamate (ethylcarbamate analog) and benzyl trans-2-phenylcyclopropanecarbamate(benzylcarbamate analog) were first synthesized by Kaiser *et al.*[2]. According to Zirkle *et al.*[3] who determined *in vivo* MAO-inhibitory activity of the carbamate analogs using tryptamine potentiation test, relative potencies of the ethylcarbamate analog and the benzylcarbamate analog to that of TCP were 0.1 and 2.0, respectively and the activities were assumed, without an experimental evidence, to be due to the *in vivo* hydrolysis of the carbamate analogs to TCP.

Most recently, Baker *et al.*[4] reported in their studies on the carbamate prodrugs of phenylethylamines that the MAO-inhibitory activity of ethylcarbamate analog of TCP is entirely due to the metabolic formation of TCP. The result was supported by the fact that the degree of *in vitro* MAO inhibition by 9.0μM of TCP which is equivalent to the TCP concentration found in the rat brain 1 hour after the administration of ethylcarbamate analog(0.1mmol/kg) through *i.p.* route was comparable to that of *in vivo* MAO inhibition by the ethylcarbamate analog.

In our studies to elucidate mechanism of the MAO inhibition by 2-phenylcyclopropylamines, we have intended to find an evidence of the reactive metabolites as the molecular entities finally acting on MAO. In relation to this attempt, we have reported that the primary metabolites of TCP detected in the rat urine were N-acetyl and arylhydroxy N-acetylTCP[5] and that TCP has a marginal pKa of 8.15[6]. In addition, before the Baker et al.'s report[4], we had carried out the experiment to determine metabolic conversion of the ethylcarbamate and benzylcarbamate analogs to TCP by analyzing rat urine samples after dosing the carbamate analogs. In fact, the carbamate analogs were found to be excreted as intact drugs and the metabolic product, TCP. On the basis of these results, a study is ongoing to determine a sele-

* Mechanism of the Monoamine Oxidase Inhibition by 2-Phenylcyclopropylmines III

ctive transport of the carbamate analogs to the active sites of the brain. In this communication, we report a preliminary finding, from the study, on the detection of intact benzylcarbamate analog and TCP from the benzylcarbamate analog-dosed rat urine.

The benzylcarbamate analog was synthesized by the method of Kaiser *et al.*[2]. The compound was dissolved in a small volume of EtOH and suspended in 5% CMC. The suspended compound was administered to three male Sprague Dawley rats (40mg/kg) by the method of oral intubation. The urine sample (40ml) obtained over 36 hours from the rats in a metabolism cage was centrifuged to remove solid substances and pH adjusted to pH 3 using 0.5N H_2SO_4. The solution was then extracted twice with two volumes of $CHCl_3$ (pH 3 fraction). The extracted urine was made to pH 9.5 using 10% ammonia water and extracted twice with two volumes of $CHCl_3$ (pH 9.5 fraction). Final samples were prepared by evaporating the $CHCl_3$ and concentrating the solution under N_2 to dissolve the residues in 0.1~0.2ml MeOH. Blank samples were also prepared by following the same procedures using control urine. The samples were analyzed using GC/MS in the same analysis conditions as described in the previous report[5].

Fig. 1A represents TIC profile of the pH 3 fraction. A peak at scan number 1091 was from the intact benzylcarbamate as determined by the mass spectrum (Fig. 2A) and retention time, which were consistent with those of an authentic compound. Fig. 1B shows TIC profile of the pH 9.5 fraction in which a peak at scan number 230 was from the tranylcypromine as confirmed by the mass spectrum[5] and retention time of the authentic compound obtained in the same analysis conditions. Unexpectedly, we

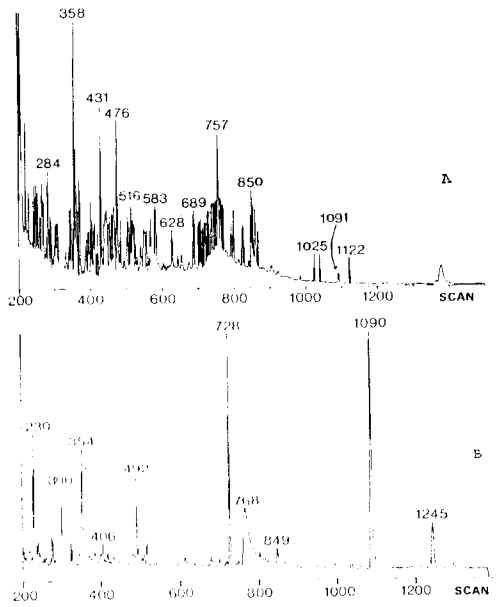

Fig. 1. Total ion current profile of (A) pH 3.0 fraction and (B) pH 9.5 fraction.

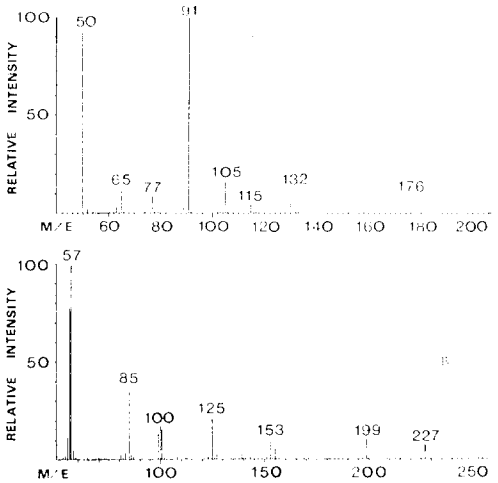

Fig. 2. Mass spectra of (A) benzylcarbamate analog and (B) endogenous material.

found that a peak at scan number 1090 of the pH 9.5 fraction (Fig. 1B) was from an endogenous material (Fig. 2B) indicating that the intact benzylcarbamate analog which comes out at the same scan number 1091 of the pH 3 fraction could not be detected by one alkaline

extraction of the urine samples. The N-acetyl and arylhydroxy N-acetyltranylcypromine which can be formed through the continued metabolic pathways of the metabolite, TCP were not detected in the present study.

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