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Reversal of depressant action of trazodone on avoidance behaviour by its metabolite *m*-chlorophenylpiperazine

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m-Chlorophenylpiperazine (CPP) is one of the metabolites of the antidepressant drug trazodone in rat (Melzacka et al 1979) and in man (Caccia et al 1981). CPP has been widely studied for its 5-hydroxytryptamine-mimetic (Maj et al 1979; Samanin et al 1979), anorectic (Samanin et al 1979, 1980) and other pharmacological properties (Maj & Lewandowska 1980; Rokosz-Pelc et al 1980; Cervo et al 1981; Borsini et al 1981). We have found that CPP facilitates the avoidance behaviour of mice (Vetulani et al 1982), while trazodone has been reported to depress avoidance responses in rats (Silvestrini et al 1968; Gatti 1974). We have assessed in mice the effects of trazodone on avoidance behaviour and whether CPP could antagonize a possible depressant action of trazodone. In mice trazodone is metabolized to CPP (Melzacka, unpublished findings).

Method

In the present study trazodone and CPP were tested alone or in combination in trained mice. Male BALB/c mice (25–30 g), purchased from Charles River (Calco Como, Italy) were tested in a shuttle-box apparatus previously described by Bovet et al (1969). It consisted of 8 automatic shuttle-boxes placed in a soundproof cubicle. Each shuttle-box was divided into two 20 × 10 cm compartments, connected by a 3 × 3 cm opening at the floor level. The conditioned stimulus (CS) was a light provided by a 10 W electric bulb placed on the top of each compartment (10 cm above the floor) and switched on alternately in the two compartments for 30 s. Five seconds after the onset of the CS an electric shock, serving as unconditioned stimulus (US), was applied for 25 s to the grid floor through a selenium rectifier (110 V delivered through a 0·5 Mohm resistance). An avoidance response was recorded if a mouse avoided the US by running in to the dark compartment within 5 s after the onset of the CS. If it failed to avoid, the mouse could still escape the US by crossing the opening during the whole 25 s period. Inter trial responses were punished and were seldom present in trained animals.

The mice were trained in the avoidance situation every day; each daily session consisted of 100 trials and lasted 50 min. After daily sessions for 5 or 6 days the mice showing at least 70% of avoidance responses were given the drug before the session (drug session) and the effect of treatment was evaluated by comparing the performance of the mice in the drug session with that in the preceding non-drug (control) session, and expressing the avoidance decrement as a percentage.

Trazodone and CPP, used hydrochlorides, were dissolved in 0·9% NaCl (saline) and injected intraperitoneally in a volume of 10 ml kg^{-1}. If given in combination, they were given in a single injection.

In the experiments in which trazodone or CPP were given alone, the differences between the results of control and drug session were evaluated with the Student's *t*-test. The data from the experiment on drug combinations were evaluated by an overall analysis of variance for each dose of trazodone combined with various doses of CPP, and individual between-group comparisons made, if appropriate, employing the error term of the overall analysis of variance.

Results

Trazodone or CPP alone. Given 15 min before the avoidance test in doses of 5 and 10 mg kg^{-1}, trazodone significantly depressed the response, by 38%

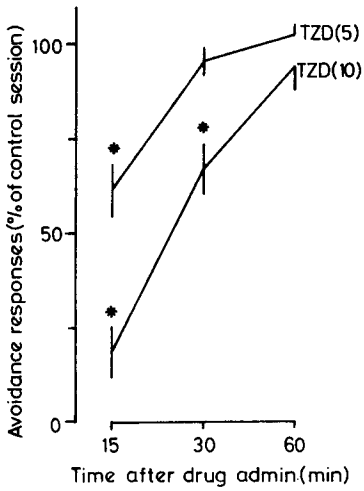

FIG. 1. The effect of trazodone (TZD), 5 and 10 mg kg^{-1}, on avoidance performance in trained BABL/c mice. Each point represents the mean (±s.e.m.) of 16 results. The results are presented as percentage of the performance in the control session. Asterisks denote results significantly different from the control performance (Student's paired *t*-test, $P < 0.05$). Abscissa: time (min) of the beginning of drug session after trazodone administration. Ordinate: avoidance response as percent of the control values.

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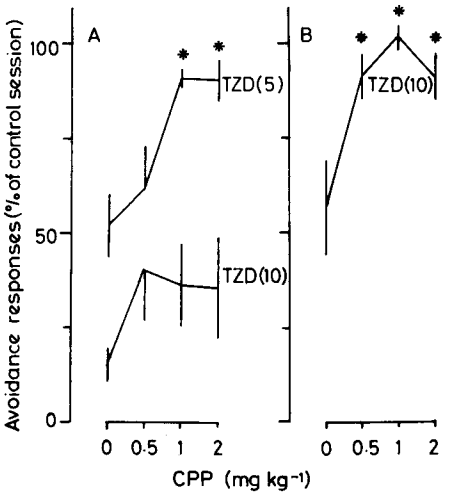

FIG. 2. The effect of *m*-chlorophenylpiperazine (CPP) on the depressant action of trazodone (TZD) on avoidance performance. Each point represents the mean (±s.e.m.) of 8 results. Trazodone and CPP were given in mixed solutions (10 ml kg^{-1} i.p.) 15 (A) or 30 (B) min before the beginning of drug session. Abscissa: CPP dose (mg kg^{-1}). Ordinate: Avoidance response as percent of control value. Analysis of variance has shown significant effect of CPP on the trazodone action: 5 mg kg^{-1} 15 min before test ($F = 6{\cdot}99$, df 3/28, $P < 0{\cdot}01$) and 10 mg kg^{-1} 30 min before test ($F = 6{\cdot}92$, df 3/28, $P < 0{\cdot}01$). Asterisks denote results significantly different from the group receiving trazodone alone ($P < 0{\cdot}01$).

($P < 0{\cdot}05$) and 82% ($P < 0{\cdot}001$) of the pre-drug values, respectively. The depressant action was always stronger in the first half of each session, and was often accompanied by failure to escape. The depressant effect was short-lasting, and only after the high dose was it still present in the session beginning 30 min after the injection (depression by 33%, $P < 0{\cdot}05$). Neither dose of trazodone affected avoidance tested 60 min after dosing (Fig. 1).

CPP, administered at doses of 0·5–10 mg kg^{-1}, 15 or 30 min before the test, did not exert any significant effect. The performance of the trained BALB/c mice precluded facilitating effects which were evident when the same doses of the drug were tested in mice of the same strain during training (Vetulani et al 1982).

Trazodone and CPP combined. CPP given together with a low dose of trazodone, 5 mg kg^{-1}, 15 min before the drug session, or with a high dose of trazodone, 10 mg kg^{-1}, 30 min before the drug session, significantly ($P < 0{\cdot}01$) and dose-dependently reversed the inhibitory effect of trazodone on conditioned avoidance response. In doses up to 2 mg kg^{-1} CPP did not antagonize the inhibitory action of a high dose of trazodone given 15 min before the drug session (Fig. 2).

Discussion

The present findings show that trazodone exerts a short-lasting depressant effect on avoidance behaviour of mice and that such inhibitory action may be reversed by CPP, one of its metabolites. The results suggest that accumulation of CPP in the brain might be responsible, at least in part, for the transitoriness of the avoidance depression produced by trazodone administered alone.

The fact that trazodone is biotransformed to an active metabolite which may antagonize some effects of the parent compound may be of importance for understanding the action of this antidepressant, whose pharmacological profile is so unique that its classification among psychotropic agents poses great difficulties (Al-Yassiri et al 1981).

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