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# 1-*m*-Chlorophenylpiperazine is an active metabolite common to the psychotropic drugs trazodone, etoperidone and mepiprazole

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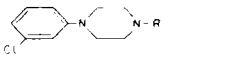
In the course of studies on the mechanism of action of trazodone, an antidepressant agent recently introduced into clinical practice (Silvestrini et al 1968; Silvestrini & Lisciani 1973; Brogden et al 1981), it was found that in rats the drug produced the pharmacological effects of a 5-hydroxytryptamine antagonist at low doses but of an agonist at higher doses (Maj et al 1979). Subsequent studies revealed that the latter effect was due to the formation of 1-*m*-chlorophenylpiperazine (mCPP) (Melzacka et al 1980; Cervo et al 1981) a metabolite resulting from hydrolysis and oxidation in the side-chain of trazodone (Melzacka et al 1979; Caccia et al 1981a,b). This metabolite acts as a direct 5-HT receptor agonist (Samanin et al 1979; Fuller et al 1980; Rokosz-Pelc et al 1980; Invernizzi et al 1981) and after oral trazodone it accumulates in the rat brain at concentrations comparable to those found after pharmacologically and biochemically effective doses of mCPP (Caccia et al 1981b; Cervo et al 1981). These data, together with the fact that in volunteers given trazodone the metabolite reaches measurable plasma concentrations (Caccia et al 1982), suggest that mCPP contributes to, or even accounts for, the antidepressant action of the parent drug.

Recently, other compounds containing a chloro-substituted phenylpiperazine have been introduced in psychopharmacology. Examples are etoperidone and mepiprazole (see Fig. 1 for chemical structures) which so far have not been studied from the metabolic point of view. Etoperidone, a triazoloderivative, resembles trazodone in its chemical structure and pharmacological profile (Lisciani et al 1978; Ramacci et al 1979), while



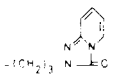
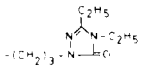
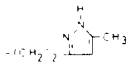
| Compound | R |
|---|---|
| 1-*m*-chlorophenyl-piperazine | -H |
| Trazodone |  |
| Etoperidone |  |
| Mepiprazole |  |

Fig. 1. Chemical structure of 1-*m*-chlorophenyl piperazine, trazodone, etoperidone and mepiprazole.

* Correspondence.

mepriprazole, a pyrazole derivative, is currently used as a minor tranquillizer in various emotional and psychosomatic conditions (Gonçalves 1972; Dotevall & Groll 1974; Pöldinger 1975) although there are also indications that it might be useful in the treatment of depression (Fuxe et al 1976; Seyfried et al 1976).

The fact that these derivatives display 5-HT antagonists and agonist properties in rats, depending on the dose and pharmacological test used (Przegalinski & Lewandowska 1979; Fuxe et al 1976; Seyfried et al 1976; Maj & Sypniewska 1980), suggested the utility of investigation whether the latter effect is attributable to formation of the active metabolite mCPP. mCPP has been identified in body fluids of rats treated with etoperidone (Melzacka et al 1980) but not in urine of mepiprazole-treated rats (Maj & Sypniewska 1980). Kinetic studies comparing the time course of the metabolite concentration in rat plasma or brain have not yet been reported, despite the fact that the metabolite's target organ is the brain where it reaches concentrations several times those found in body fluids (Caccia et al 1981a b; 1982).

*Method*

Male CD-COBS rats (Charles River, Italy), 200 g, were treated orally with equimolar doses (61·3 μmol $kg^{-1}$) of trazodone hydrochloride (25 mg $kg^{-1}$), etoperidone hydrochloride (25·4 mg $kg^{-1}$) and mepiprazole dihydrochloride (23·1 $mgkg^{-1}$) and were killed at various times after administration. mCPP was extracted from plasma and brain homogenate and detected by electron-capture gas liquid chromatography as previously described (Caccia et al 1981a).

*Results and discussion*

The results of the plasma and brain analyses indicated that hydrolysis and oxidation in the side-chain giving mCPP was a common metabolic pathway for these drugs. Gas-chromatography-mass spectrometry was used to confirm the presence of the metabolite in plasma and brain extracts. Comparison of the plasma concentration-time curves of mCPP (see Fig. 2) however, showed that the reaction occurred to a different degree for the three parent compounds. It was apparently rapid and extensive for etoperidone; peak plasma concentrations ($C_{max}$) of the metabolite were found within 30 min ($T_{max}$) compared with the 2 h $T_{max}$ with trazodone. The $C_{max}$ value for etoperidone was also significantly higher (0·89 ± 0·20 nmol $ml^{-1}$) than

Table 1. Brain concentrations (nmol $g^{-1}$ ± s.e.m.) of 1-*m*-chlorophenylpiperazine, after oral administration of equimolar doses (61 μmol $kg^{-1}$) of trazodone, etoperidone and mepiprazole to rats.

| Time after administration | mCPP brain concentrations (nmol $g^{-1}$ ± s.e.m.) Etoperidone | Trazodone | Mepiprazole |
|---|---|---|---|
| 5 min | 1·71 ± 0·15 | 1·42 ± 0·17 | <0·15 |
| 15 min | 18·93 ± 0·33 | 2·62 ± 0·18 | 1·17 ± 0·59 |
| 30 min | 31·70 ± 3·46 | 5·45 ± 0·26 | 1·31 ± 0·28 |
| 1 h | 26·97 ± 5·60 | 5·52 ± 0·72 | 2·61 ± 0·73 |
| 2 h | 14·71 ± 5·09 | 5·96 ± 0·49 | 1·22 ± 0·31 |
| 4 h | 10·53 ± 3·82 | 2·05 ± 0·02 | 2·58 ± 0·84 |
| 6 h | 2·44 ± 0·53 | 0·82 ± 0·05 | 0·70 ± 0·16 |
| 8 h | 1·10 ± 0·21 | 0·42 ± 0·02 | 0·50 ± 0·07 |
| AUC (nmol $g^{-1}$ $h^{-1}$) | 87·76 | 22·90 | 12·70 |

Each point is the mean of 4–6 rats. Brain areas under the curve (AUC) were calculated by the trapezoidal rule and extrapolated to infinity.

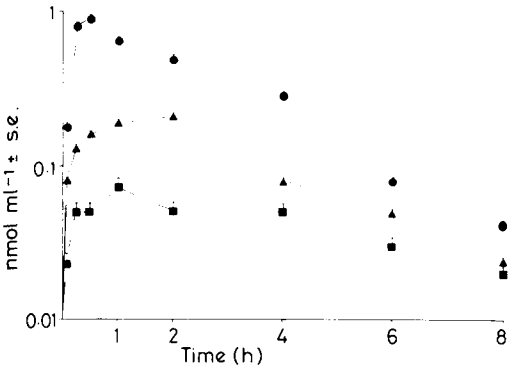



FIG. 2. Plasma concentrations-time curve of 1-*m*-chlorophenyl -piperazine after oral administration (61 μmol $kg^{-1}$) of etoperidone (●), trazodone (▲) and mepiprazole (■) to rats.

trazodone (0·22 ± 0·01 nmol $ml^{-1}$). With mepirazole this reaction apparently occurred to a limited degree and the metabolite rose to $C_{max}$ within 1–4 h, but never reached 1/3 of the mCPP plasma concentration attained with trazodone.

Like the $C_{max}$ values, the plasma areas under the curve (AUC) for mCPP followed the order etoperidone > trazodone > mepirazole with an approximate ratio of 6:2:1. These findings were reflected in the brain (see Table 1), where mCPP reached concentrations expressed as AUC about 30 times those in plasma. The highest $C_{max}$ and AUC values for mCPP were observed with etoperidone, while mepiprazole gave the lowest.

Comparison of these kinetic parameters with those observed in rats after different doses of mCPP (Caccia et al 1981b) shows that the oral doses of the compounds tested in this study (61 μmol $kg^{-1}$—about 25 mg $kg^{-1}$) correspond to about 10, 2·5, and 1 mg $kg^{-1}$ of mCPP respectively for etoperidone, trazodone, mepiprazole.

Whether these differences are important in determining differences in these drugs' pharmacological activity remains to be investigated. It should be underlined, however, that mCPP has pharmacological and biochemical effects compatible with a stimulatory action on 5-HT receptors in a dose range of 0·25–2·5 mg $kg^{-1}$ (Samanin et al 1979; Invernizzi et al 1981; Cervo et al 1981). Thus, the possibility of the metabolite contributing to or accounting for the pharmacological effects of all its parent compounds is conceivable from our results.

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