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1-(*o*-Methoxyphenyl)piperazine is a metabolite of drugs bearing a methoxyphenylpiperazine side-chain

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Drugs bearing an *o*-methoxyphenylpiperazine (oOCH$_3$PP) moiety in the side-chain of their molecule may form oOCH$_3$PP during biotransformation in-vivo in the rat. This has been verified by combined gas chromatography-mass spectrometry of urine from rats given orally a series of relatively new *o*-methoxyphenylpiperazine-substituted derivatives. The metabolite is reported to be biochemically and pharmacologically active and therefore its formation may have pharmacological significance, at least for derivatives undergoing extensive cleavage of the arylpiperazine side-chain.

1-(*o*-Methoxyphenyl)piperazine (oOCH$_3$PP) has potent hypotensive action in man and this effect is sometimes accompanied by central side-effects such as sedation, disorientation, stupor, nausea and vomiting (Page et al 1959). In animals, besides pronounced antihypertensive and weak adrenolytic activities (Morphis et al 1959), it abolishes the behavioural effects of apomorphine (stereotypy, rotational behaviour) and increases the concentrations of homovanillic acid in the rat brain (Minard et al 1979). Like other phenylpiperazine derivatives (Maj & Lewandowska 1980; Fuller et al 1981; Invernizzi et al 1981) it enhances central 5-hydroxytryptaminergic transmission (Pawłowski 1983) and recent binding studies show that it behaves as a selective 5-HT agonist, displaying affinity for the 5-HT binding site (5-HT$_1$) comparable with that of the recognized 5-HT agonist 1-*m*-trifluoromethylphenylpiperazine (Lyon et al 1986). The oOCH$_3$PP moiety has been incorporated into the structure of many chemically and/or pharmacologically unrelated compounds which, in analogy with structurally related drugs (Caccia et al 1984), can form oOCH$_3$PP by metabolic cleavage of their side chain. Relatively new among the various *o*-methoxyphenylpiperazine substituted derivatives are the novel antihypertensive agent urapidil 6-(3-(4-(*o*-methoxyphenyl)-1-piperazinyl)propylamine)-1,3-dimethyluracil (Schoetensack et al 1977; Kanniainen et al 1985), IP-66, 1-[2-ethoxy-2-(3'-pyridyl)ethyl]-4-(2'methoxyphenyl)piperazine, an experimental compound with marked hypotensive and adrenolytic activities (Bacciarelli et al 1980; Castellucci et al 1984), the potential anxiolytic agent enciprazine (*N*-2-methoxyphenyl-*N'*-[2-hydroxy-3-(3,4,5-trimethoxyphenoxy)-n-propyl]piperazine) (J. Engel, personal communication) and MJ-7378, 8-(4-*o*-methoxyphenyl-1-piperazinylethyl)-8-azaspiro[4,5]decane-7,9-dione, a compound structurally and pharmacologically related to the antianxiety agent buspirone (Wu et al 1972) (see Fig. 1 for chemical structures).

oOCH$_3$PP formation from these derivatives has not yet been reported and it was of interest to ascertain whether this reaction occurred in-vivo in the rat.

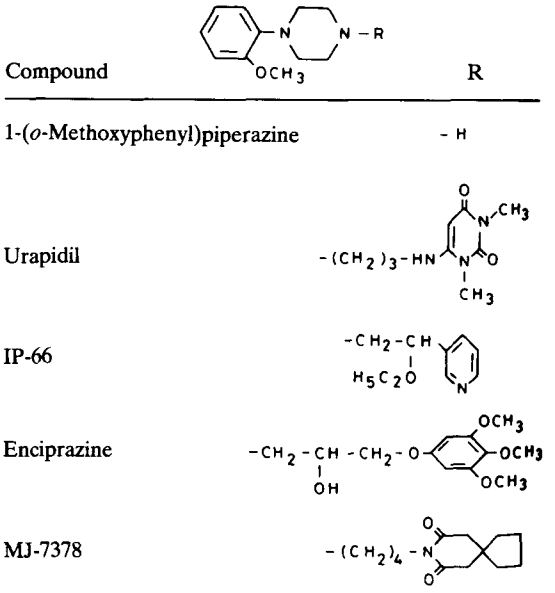

FIG. 1. Chemical structures of 1-(*o*-methoxyphenyl)-piperazine, urapidil, IP-66, MJ-7378 and enciprazine.

Materials and methods

Male CD-COBS rats were treated orally with equimolar doses (50 μmol kg^{-1}) of urapidil (19·4 mg kg^{-1}), IP-66 (17·1 mg kg^{-1}), enciprazine (21·6 mg kg^{-1}) and MJ-7378 (20·7 mg kg^{-1}) and the urine was collected for 24 h in metal metabolism cages, and immediately stored at −20 °C until analysis. The metabolite was extracted from rat urine by a modification of the procedure previously described (Caccia et al 1984) and its chromatographic properties were compared with those of synthetic oOCH$_3$PP. Gas chromatography-mass spectrometry (GC-MS) was used to confirm the specificity of the analysis. An LKB 2091 gas chromatograph-mass spectrometer equipped with an LKB 2130 computer

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data processing system was used. The chromatographic column was a silanized glass tube (2 m × 2 mm i.d.) packed with 80–100 mesh Gas Chrom Q with 3% OV-1 as the stationary phase. The injector port temperature was 250 °C; the oven temperature was kept at 160 °C for 1 min and then programmed from 160 to 230 °C at 8 °C min^{-1}. The carrier gas was helium at a flow rate of 25 mL min^{-1}. The mass spectrometer was operated in the electron impact mode at the following conditions: electron energy 70 eV, trap current 50 μA, ion source temperature 250 °C.

Results

Peaks corresponding to authentic $oOCH_3PP$ (retention time 7 min) were evident from urine extracts of all the compounds investigated. GC–MS of the extracts confirmed the presence of the metabolite. Fig. 2 shows the mass spectrum of $oOCH_3PP$. The ion at *m/z* 192 is the molecular ion. A loss of 42 u produces the base peak at *m/z* 150. This loss is caused by a McLafferty rearrangement, with the expulsion of CH_2=N-CH_2·, and is typical of piperazine derivatives (Budzikiewicz et al 1967). The expulsion of 57 u, probably due to further fragmentation of the piperazine ring, gave the ion at *m/z* 135. The ion at *m/z* 120 is probably produced by the rearrangement proposed in Scheme I. This possible route leading to the ion at *m/z* 120 is suggested in comparison with the similar behaviour of related compounds (Caccia et al 1984).

This study shows that pharmacologically active compounds bearing an *o*-methoxyphenylpiperazine moiety in the side-chain of their chemical structure may form $oOCH_3PP$ during biotransformation in-vivo in the rat. This metabolite has several pharmacological activities (see introduction) and, like other 1-arylpiperazines, reaches concentrations in brain higher than those in plasma (Caccia et al 1985). Therefore its formation may have pharmacological significance but this will depend on the extent of its formation.

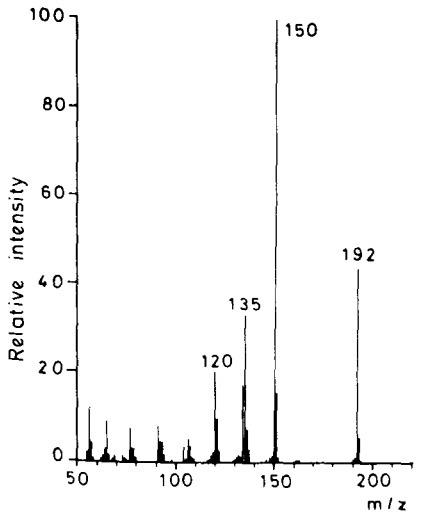
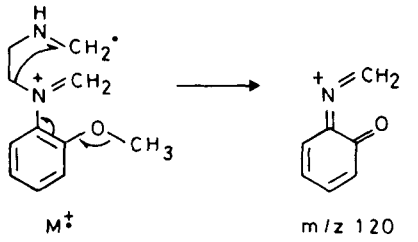


FIG. 2. Mass spectrum of 1-(*o*-methoxyphenyl)piperazine.



SCHEME I. Possible route of fragmentation of 1-(*o*-methoxyphenyl)piperazine, leading to an ion at *m/z* 120.

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