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1-ARYL-PIPERAZINE AS ACTIVE METABOLITES OF DRUGS WITH AN ARYL-PIPERAZINE SIDE-CHAIN

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Many drugs acting mainly on the central nervous system contain an aryl-piperazine moiety in the side-chain of their chemical structure. A common metabolic pathway of such drugs is cleavage of the side-chain with the formation of 1-aryl-piperazines (1). These metabolites are centrally active (2-4) and their formation may therefore be a pharmacologically significant pathway. Hence our interest in studying the time-course of the production and elimination of 1-aryl-piperazines after administration to rats of representative compounds of this class.

MATERIALS AND METHODS

Male CD-COBS rats (Charles River, Como, Italy) weighing about 200 g were used. They were treated orally with the test compound (10–100 mg/kg) and killed at various times after administration. Blood was collected in heparinized test-tubes, centrifuged and the plasma stored at -20°C until assay. Brains were immediately removed and stored at -20°C. Plasma and brain concentrations of 1-aryl-piperazines were determined by electron-capture gas liquid chromatography as previously described (1). The areas under the plasma or brain concentration-time curves (AUC) were calculated by the trapezoidal rule to the last measured concentration and then extrapolated to infinity.

RESULTS AND DISCUSSION

Plasma and brain concentration-time curves of 1-aryl-piperazines after oral administration (25-100 mg/kg) to rats of compounds with a phenyl-(oxypertine, millipertine, antrafenine, niaprazine, enpiprazole, mepiprazole and etoperidone), thiazolyl-(S-3608), pyridyl(azaperone) or pyrimidinyl-(piribedil)piperazine side-chain are shown in Fig. 1. 1-aryl-piperazine formation was apparently rapid and extensive with the newly developed sedative niaprazine (4) azaperone, a butyrophenone of the 4-aryl-piperazine type, oxypertine and millipertine, two antipsychotic agents belonging to the 1-(indolylalkyl)-4-arylpiperazine class. Plasma concentrations of the respective metabolites, 1-(p-fluorophenyl)- (pFPP), 1-(2-pyridyl)- (PdP), 1-phenyl- (PP) and 1-(o-methoxyphenyl)- ($oOCH_3PP$)piperazine, rose rapidly, becoming significant within hours after the administration of the parent drug (25 mg/kg). Brain concentrations of the metabolites were almost parallel but much higher than the plasma concentrations in all cases. Thus brain to plasma AUC ratios were always in excess of unity ranging from about 5 for $oOCH_3PP$ to about 16 for pFPP (Table 1). With antrafenine the reaction was apparently limited and only trace amounts of the metabolite 1-(m-trifluoromethylphenyl)-piperazine (mCF_3PP) were detected in plasma. This metabolite however, concentrated more than other 1-aryl-piperazines in the central nervous system, the brain-to-plasma AUC ratio being approximately 74. With enpiprazole the reaction was even more limited and even after a large dose (100 mg/kg) concentrations of only a few nmoles/g were observed in rat brain. No 1-(o-chloropheyl)-piperazine (oClPP) could be detected in rat plasma (<0.05 nmoles/ml) but this is not surprising as this and previous studies with trazodone and its structurally related compounds etoperidone and mepiprazole have indicated that halogenated phenyl-piperazines may reach brain concentrations several times those in plasma (ref.5 and Table 1). The dopaminergic agent piribedil and its analog S-3608 (100 mg/kg) yielded only trace amounts of the corresponding metabolite, 1-(2-pyrimidinyl)-piperazine (PmP) and 1-(2-thiazolyl)-piperazine (TzP) respectively. Buspirone, an antianxiety agent (6) had been previously found to form significant

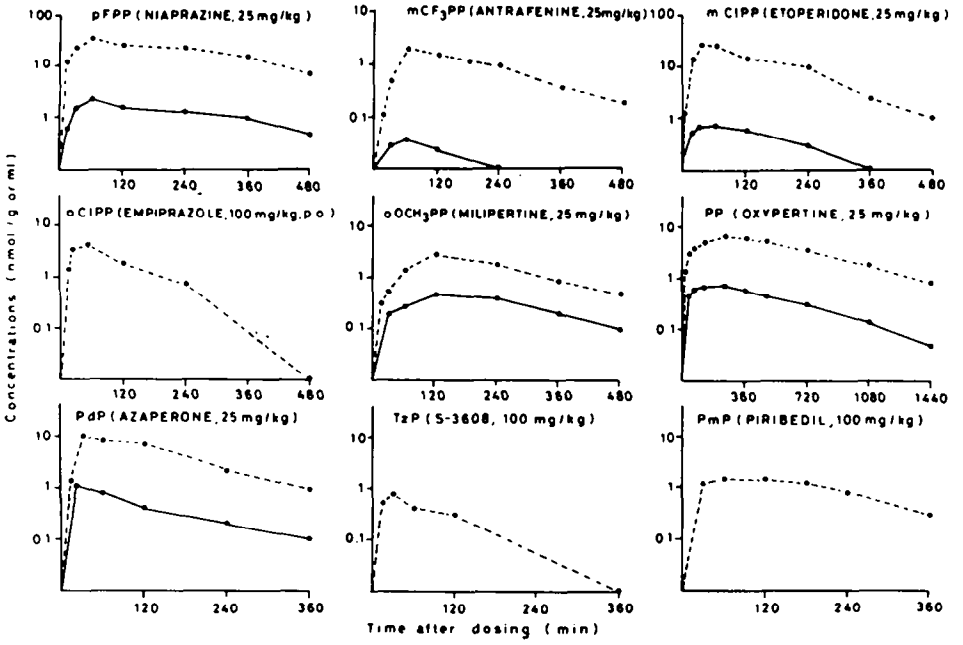

Fig. 1. Plasma (●-●) and brain (●--●) concentration-time curves of 1-aryl-piperazines after oral administration of the corresponding parent drug (see parenthesis).

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amounts of PmP; this metabolite reached brain concentrations 4-5 times those in plasma, expressed as AUC (ref. 7 and Table 1).

Table 1. Plasma and brain area under the curve (AUC) of 1-aryl-piperazines after oral administration of the corresponding parent drug.

Parent drug	Dose (mg/kg p.o.)	Metabolite	AUC (nmoles/ml x min) Plasma	AUC (nmoles/ml x min) Brain	Brain to plasma ratio
Trazodone	25		51	1336	26
Etoperidone	25	1-(m-chlorophenyl)-piperazine	163	4978	27
Mepiprazole	23		27	657	24
Enpiprazole	100	1-(o-chlorophenyl)-piperazine	N.D.	567	(17)*
Niaprazine	25	1-(p-fluorophenyl)-piperazine	681	11442	16
Antrafenine	25	1-(m-trifluoromethylphenyl)piperazine	6	445	74
Millipertine	25	1-(o-methoxyphenyl)-piperazine	156	841	5
Oxypertine	25	1-phenyl-piperazine	210	1920	8
Azaperone	25	1-(2-pyridyl)-piperazine	123	1331	10
S-3608	100	1-(2-thiazolyl)-piperazine	N.D.	83	(6)*
Piribedil	100	1-(2-pyrimidinyl)-piperazine	N.D.	474	4
Buspirone	10		350	1525	

*calculated from i.v. experiments with 1-aryl-piperazines. N.D.: not detectable (<0.05 nmoles/ml)

In summary, drugs belonging to different chemical and pharmacological classes but all having the aryl-piperazine moiety in the side-chain of their molecule form 1-aryl-piperazines to differing extents during biotransformation in the rat. As a general rule these metabolites tend to concentrate in the brain, reaching concentrations 4-74 times those in plasma, depending on which 1-aryl-piperazine is given. These findings, together with the fact that 1-aryl-piperazines are centrally active (2-), suggest that 1-aryl-piperazine formation may be a pharmacologically significant pathway, at least in the rat.

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