369P THE EFFECT OF MONOAMINE OXIDASE INHIBITORS ON DIMETHYLTRYPTAMINE-INDUCED HYPERACTIVITY IN MICE

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Mice pretreated with pargyline at a dose which inhibits both monoamine oxidase (MAO) isoenzymes, exhibited hyperactivity following systemic administration of N,N-dimethyltryptamine (DMT; Jenner et al, 1980; Morinan & Collier, 1981). In the present study, the effect of selective (clorgyline and selegiline) and non-selective (tranylcypromine) MAO inhibitors on DMT induced hyperactivity was investigated.

Male CFLP mice (25-35g) were injected (i.p.) with 0.9% saline (CON), or MAO inhibitors (all at 5mg/kg), 90 min before DMT 4mg/kg. The locomotor activity of pairs of mice was recorded (Panlab Actisystem) over the 3h period following the first injection.

Tranylcypromine and selegiline reduced activity during the first 90 min, but only in the former group was there evidence of DMT induced hyperactivity (Table 1). Tranylcypromine and clorgyline inhibited MAO-A activity by 95%, increased 5-HT concentration by 66%, and decreased 5-HIAA by 40-50% in the brain (Table 1).

Table 1. EFFECT OF MAO INHIBITORS ON BEHAVIOUR AND NEUROCHEMISTRY.

	Locomotor Activity 0-90 min	90-180 min	MAO Activity nmol/mg/h	5-HT ng/g	5-HIAA ng/g
CONTROL	2795 ± 446	190 ± 45	49.3 ± 4.2	292 ± 15	189 ± 4
TRANYLCYP.	1590 ± 327*	982 ± 305*	4.5 ± 2.0*	486 ± 17*	92 ± 9*
CLORGYLINE	2289 ± 393	283 ± 49	5.2 ± 0.7*	484 ± 26*	120 ± 8*
SELEGILINE	1211 ± 105*	377 ± 95	49.6 ± 11.1	289 ± 13	187 ± 10

Each value represents the mean ± s.e.m. of n=7 (columns 1 & 2) or n=6 (columns 3,4 & 5). *P < 0.05(vs. CON).

These data show that both MAO-A and -B must be inhibited before DMT induced hyperactivity is observed. A similar effect of selective MAO inhibitors on l-tryptophan induced behaviour has also been reported by Sleight et al (1988).

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370P STRUCTURAL REQUIREMENTS FOR HIGH BINDING AFFINITY TO THE 5-HT TRANSPORTER FOR β-CARBOLINES

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Specific 5-HT uptake inhibitors are known to bind to the 5-HT transporter with high affinity (Raisman *et al.*, 1979). Both [^{3}H]-citalopram and [^{3}H]-imipramine can be displaced from their binding sites at the 5-HT transporter by β-carbolines, especially by an endogenous one, pinoline (6-methoxytetrahydro-β-carboline). The binding affinity studies were based on the inhibition of [^{3}H]-imipramine binding in chicken retina (Kari *et al.*, 1988) and [^{3}H]-citalopram binding in human platelets. Structures of the 5-HT uptake inhibitors were calculated using the semi-empirical molecular orbital package MOPAC at the AM1 level. Molecular electrostatic potentials were calculated with the CHEMX software using the VSS program. Conformation analyses were made using molecular mechanics and the CHARM force field. Based on both electronic and steric properties a QSAR study was developed using eight tetrahydro-β-carbolines for [^{3}H]-imipramine binding (James, 1988). Mapping of the binding site was based on the superimposition of the pharmacophore of several specific 5-HT uptake inhibitors including citalopram and imipramine (Marshall, 1987). Pinoline had the highest binding affinity to [^{3}H]-citalopram and [^{3}H]-imipramine binding sites of all the compounds tested. Also according to the QSAR study pinoline was predicted to have the highest affinity to the binding site. The methoxy group at the C-6 position of the β-carboline structure seemed essential for high affinity. Further substitution, substituents at other positions or dehydrogenation reduced affinity. However, the binding affinity of 1,2-dehydro-pinoline to the [^{3}H]-citalopram binding site in human platelets was half that of pinoline, the IC_{50} values were 110 nM and 50 nM, respectively. Pinoline as well as the other β-carbolines did not fit perfectly to the model of the binding site. This model includes two hydrophobic pockets, an anionic site and a couple of sites for electrostatic interactions. β-carbolines can interact with this binding site by the protonated nitrogen of the tetrahydropyridine ring and by the electrostatic properties. They can occupy only one of the two hydrophobic pockets because of their rigid ring structure. This may result in different binding mechanisms and reduced binding affinity in comparison to citalopram. It seems that both steric and electronic properties of β-carbolines determine their binding affinity to the 5-HT transporter.

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