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EFFECTS OF 4-(3-INDOLYL-ALKYL)PIPERIDINE DERIVATIVES ON UPTAKE AND RELEASE OF NORADRENALINE, DOPAMINE AND 5-HYDROXYTRYPTAMINE IN RAT BRAIN SYNAPTOSOMES, RAT HEART AND HUMAN BLOOD PLATELETS

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Abstract—4-(3-Indolyl-alkyl)piperidine derivatives (LM 5005, LM 5008, LM 5015) strongly inhibited 5-HT accumulation into rat brain synaptosomes and human blood platelets *in vitro* but were weaker inhibitors of NA and DA uptake. These new compounds inhibited, like clomipramine, the neuronal membrane active transport whereas reserpine blocked the synaptic vesicle storage process of biogenic amines. They had no effect on 5-HT release from human blood platelets. The duration of 5-HT uptake inhibition *in vivo* by LM 5015 was equal to that observed with clomipramine (about 3 hr) and longer for LM 5008 and LM 5005. The piperidine derivatives did not inhibit 5-HT uptake into synaptosomes from specific regions of rat brain in the same manner. Unlike the tricyclic antidepressants, LM 5005 and LM 5008 did not block the *in vivo* uptake of NA into rat heart and LM 5015 was a weak inhibitor. These results suggest that 4-(3-indolyl-alkyl)piperidine derivatives represent a new class of potent and selective inhibitors of 5-HT uptake into rat brain synaptosomes and human blood platelets.

The mechanism principally responsible for the rapid inactivation of released biogenic amines in the synaptic cleft is their re-uptake by the presynaptic membranes. This process is blocked mainly by tricyclic antidepressants [1, 2, 3]. Despite the fact that tertiary amines (imipramine, clomipramine) are more active on 5-hydroxytryptamine (5-HT) uptake, there is no real selective activity with such drugs, perhaps because of the *N*-demethylation of tertiary amines into secondary amines (desipramine, chlordesipramine) [4, 5], *in vivo*, which are potent noradrenaline (NA) uptake inhibitors [6, 7, 8].

Studies with brain synaptosomes [9, 10] and blood platelets [11, 12] demonstrate that these preparations can serve as an excellent model for analysing the effects of agents on biogenic amine uptake and release processes.

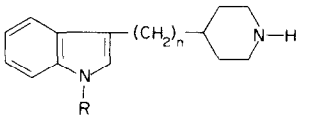
The lack of selectivity of tertiary amine containing tricyclic antidepressants has led us to search, using these methods, for compounds which would possess a more selective inhibitory action on 5-HT uptake.

In the present report we describe the *in vitro* and *in vivo* properties of new 4-(3-indolyl-alkyl)piperidine derivatives (Fig. 1) which selectively inhibit the uptake of 5-HT in rat brain nerve endings and human blood platelets.

MATERIALS AND METHODS

Chemicals. All reagents used were analytical grade. DL-[methylene-^{14}C] noradrenaline bitartrate (53 mCi/m-mole), [ethylamine-1-^{14}C]dopamine hydrochloride (52 mCi/m-mole) and 5-hydroxy[side chain 2-^{14}C]-tryptamine creatinine sulfate (58 mCi/m-mole) were supplied by the Radiochemical Centre Amersham. Radioactivity was measured in a Packard Tricarb liquid scintillation spectrometer (Model 3320) with 15 ml of scintillation fluid (Instagel Packard). All drugs were used as aqueous solutions of their hydrochloride salts.

Uptake of biogenic amines into synaptosome suspensions. The method used for measuring the uptake of monoamines into synaptosomes was similar to the procedure of Kannengiesser *et al.* [13] with slight modifications. All operations were performed at 0.4°. Immature female rats (19–21 days), Charles River strain, were killed by decapitation and the whole brains were immediately removed, weighed and homogenized in 9 vol. of 0.32 M sucrose according to the method of Whittaker [14]. After centrifugation at 900 *g* for 15 min, the supernatant was diluted to 100 ml with 40 mM Na phosphate buffer at pH 7, containing 100 mM NaCl, 4 mM KCl and 11 mM D-glucose. Aliquots (5 ml) of this preparation were incubated for 5 min at 37° with the labelled biogenic amines (10^{-7} M) in the presence or absence of the psychotropic agents. Control samples were incubated at 0° to determine the non-specific uptake. The difference between uptake at 37° and uptake at 0° was taken as a measure for the high affinity transport activity which was inhibited by the antidepressant drugs. After incubation the reaction was stopped by cooling the samples in ice, an aliquot (100 μl) was removed for radioactivity measurement and the remainder was centrifuged (Beckman, model L5 50,



	R	n
LM 5005	CH_3	2
LM 5008	H	2
LM 5015	H	1

Fig. 1.

rotor 50 Ti) at 100,000 *g* for 10 min. The pellet was rinsed twice with cold phosphate buffer (5 ml) and extracted with 0.4 N perchloric acid (300 μl). After centrifugation the radioactivity of the acidic extract was measured. Four or five concentrations of the drugs were used in duplicate to determine the IC_{50} values (concentration of drug that inhibits the uptake of the monoamines by 50 per cent). Proteins were estimated by the method of Lowry [15]. In some experiments on drug treated animals (10 mg/kg i.p.), we used synaptosomes isolated either from the whole brain or from different parts of the brain, obtained by dissection according to Glowinski and Iversen [16].

Uptake and release of 5-HT by human blood platelets. Plastic syringes and tubes were used throughout the experiment to prevent platelet aggregation. 30 ml of blood were taken by venepuncture from each volunteer and put into a centrifuge tube containing 3 ml of anticoagulant (citrate at 3.8 per cent). Platelet rich plasma (PRP) was obtained by centrifugation of blood at 400 *g* for 15 min; platelets were counted and adjusted to about 2×10^{-8} ml^{-1} by appropriate dilutions with autologous platelet poor plasma (PPP) obtained by centrifuging blood at 3000 *g* for 15 min. PRP was dispersed in 1 ml aliquots and the tubes were incubated at 37° in a water bath. They were allowed to equilibrate for 2 min before adding the inhibitor and [^{14}C] 5-HT (10^{-7} M). The uptake was stopped by placing the test tubes in melting ice after 1 min incubation at 37°. The samples were centrifuged at 3,000 *g* for 15 min and the PPP collected. Radioactivity of 0.2 ml of PRP (after adding 0.1 ml of Triton X 100, 20 per cent) and PPP was counted and the uptake of [^{14}C] 5-HT calculated by the formula of Buczko *et al.* [17].

The release of [^{14}C] 5-HT by platelets was measured by the method of David *et al.* [18]. Samples of 1 ml of PRP were incubated with [^{14}C] 5-HT (10^{-7} M) for 15 min; to induce release of the accumulated 5-HT, 0.1 ml of the different drug solutions was added to the samples which were further incubated at 37° for 15, 60 or 120 min. The radioactivity of the PRP was counted as described above. The release induced by the different drugs was then calculated from the difference between the samples incubated with and those incubated without addition of the drugs under the same experimental conditions.

Uptake of NA and DA by rat heart in vivo. Male rats (80 g), Charles River strain, in groups of 5, were treated (i.p.) with either saline or the different drugs at various doses for 45 min. 100 nCi/rat of [^{14}C] NA or [^{14}C] DA were injected intravenously and the animals were killed by decapitation 15 min afterwards. Hearts were immediately removed, rinsed and solubilised in 1 ml of Soluene (Packard). Radioactivity of the samples was then counted.

RESULTS

Uptake of NA, DA and 5-HT into rat brain synaptosomes in vitro. The kinetic analysis of NA, DA and 5-HT uptake into rat brain synaptosomes was performed according to the method of Lineweaver and Burk [19]. The concentrations of biogenic amines used were 0.5, 1, 1.5, 2, 2.5×10^{-7} M (each point in duplicate). The very low apparent K_m indicated that the neuronal uptakes of NA ($K_m = 2.70 \pm 0.22 \times 10^{-7}$ M, $V_m = 7 \pm 1 \times 10^{-12}$ M/mg protein/5 mn), DA ($K_m = 0.80 \pm 0.13 \times 10^{-7}$ M, $V_m = 5 \pm 0.5 \times 10^{-12}$ M/mg protein/5 mn) and 5-HT ($K_m = 1.05 \pm 0.15 \times 10^{-7}$ M, $V_m = 4 \pm 0.5 \times 10^{-12}$ M/mg protein/5 mn) were mediated by high affinity transport systems. These values, which are the means of at least 3 determinations, are similar to those found by different authors [13, 20, 21].

LM 5005, LM 5008 and LM 5015, like clomipramine, strongly inhibited [^{14}C] 5-HT accumulation but were weaker inhibitors of NA and DA uptake. LM 5005 was four times and LM 5008 twice more potent than clomipramine in inhibiting the uptake of 5-HT. LM 5015 was as effective as imipramine (Table 1). The order of activity is: LM 5005 > LM 5008 > clomipramine > LM 5015 > imipramine > desipramine.

Uptake of 5-HT into rat brain synaptosomes in vitro *in the presence of an IMAO.* In order to determine the site of action (neuronal membrane or synaptic vesicle) of LM 5005, LM 5008 and LM 5015, we measured the incorporation of [^{14}C] 5-HT into synaptosomes in the presence or absence of an IMAO: iproniazid [13] (Table 2). Iproniazid at 10^{-3} M has no effect on 5-HT uptake.

The inhibitory action of reserpine was less marked in the presence of the IMAO because [^{14}C] 5-HT remaining unmetabolized did not diffuse through the neuronal membranes. On the contrary, clomipramine, LM 5005, LM 5008 and LM 5015 inhibited the uptake of [^{14}C] 5-HT in the same way, whether or not iproniazid was present. These results indicated that 4-(3-indolyl-alkyl)piperidine derivatives, like clomipramine, preferentially inhibit the neuronal mem-

Table 1. Concentrations of drugs (in μM) causing 50 per cent inhibition of [^{14}C] NA, [^{14}C] DA and [^{14}C] 5-HT (IC_{50}) into rat brain synaptosomes *in vitro*—IC_{50} were determined from 4 to 6 concentrations of drugs in duplicate

Drugs	NA	DA	5-HT
Imipramine	16.5	18	0.2
Desipramine	7.5	16	4
Clomipramine	4.5	5	0.07
LM 5005	17	60	0.02
LM 5008	2	4	0.04
LM 5015	0.45	4	0.15

Table 2. Effects of drugs on [^{14}C] 5-HT uptake *in vitro* into rat brain synaptosomes in the presence of an IMAO (Iproniazid)—Iproniazid (10^{-3} M) was preincubated 15 min with the synaptosome preparation and the uptake was measured as described—

Drugs	Concentrations	Uptake (%)
Control	—	100
Iproniazid	10^{-3} M	100
Reserpine	4×10^{-7} M	51 ± 8*
Reserpine + Iproniazid	4×10^{-7} M	80 ± 9
Clomipramine	4×10^{-8} M	42 ± 1
Clomipramine + Iproniazid	4×10^{-8} M	53 ± 8
LM 5005	4×10^{-8} M	37 ± 6
LM 5005 + Iproniazid	4×10^{-8} M	43 ± 9
LM 5008	4×10^{-8} M	39 ± 3
LM 5008 + Iproniazid	4×10^{-8} M	32 ± 8
LM 5015	4×10^{-8} M	45 ± 13
LM 5015 + Iproniazid	4×10^{-8} M	58 ± 2

* Standard deviation, $n = 3$.

brane active transport whereas reserpine blocks the synaptic vesicle storage process.

Uptake of NA, DA and 5-HT into rat brain synaptosomes in vivo. Synaptosomes of whole brain were prepared from control rats and from rats treated with LM 5005, LM 5008, LM 5015 or clomipramine at 10 mg/kg i.p. For all the drugs tested the maximum of inhibition was found 1 hr after injection (Fig. 2). Clomipramine only had a weak but not significant inhibitory effect on NA uptake (32 per cent at 1 hr). None of the drugs had an effect on DA uptake. On the other hand, the administration of desipramine (10 mg/kg i.p., 1 hr) caused a significant decrease in NA uptake (52 per cent of control, $P < 0.01$) but not in DA or 5-HT uptake*.

Figure 2 shows the time course of 5-HT uptake inhibition after administration of the drugs at 10 mg/kg i.p. The uptake of 5-HT was significantly inhibited 15 min after treatment with LM 5005 (76 per cent inhibition, $P < 0.01$), LM 5008 (69 per cent inhibition, $P < 0.01$), clomipramine (70 per cent inhibition, $P < 0.01$) but not with LM 5015; inhibition was maximum after 1 hr with all the drugs. 5-HT uptake returned to normal levels within 3 hr after LM 5015 and clomipramine, 18 hr after LM 5008 and longer after LM 5005 administration.

Uptake of 5-HT into synaptosomes from different regions of rat brain in vivo. The differences between the controls at 37° and those at 0° were significant for all the brain regions, except the cerebellum (Table 3). This result suggests that the uptake processes are active in six regions of the brain and passive in the cerebellum. The order of activity of 5-HT uptake is: midbrain > striatum > medulla + pons > hippocampus > cortex > hypothalamus > cerebellum.

Clomipramine completely antagonized the active uptake of 5-HT in the hypothalamus, hippocampus, midbrain and partially in the cortex, medulla + pons and striatum. The activity of the 4-(3-indolyl-alkyl)piperidine derivatives was very different. In particular they did not affect the uptake of 5-HT in the hypothalamus. LM 5015 was less effective than LM 5005 and LM 5008 except in the striatum. LM 5005 and LM 5008 completely antagonized the 5-HT uptake in the midbrain, hippocampus and medulla + pons. They were less active in the cortex and striatum.

Uptake of 5-HT in human blood platelets. The uptake of [^{14}C] 5-HT by human blood platelets was very rapid; it reached its maximum within 1 min and did not increase after 1 hr of incubation. The very low apparent K_m found ($2.5 \pm 0.6 \times 10^{-6}$ M) suggests a high affinity transport system. No incorporation of [^{14}C] 5-HT occurred at 0°, which indicated the absence of a non-specific uptake. Tricyclic antidepressants were uncompetitive inhibitors more active than *p*-chloroamphetamine (Fig. 3). Tertiary amines (imipramine, clomipramine) were more effective than secondary amines (desipramine) [22] as with the pinched off nerve endings (Table 4). 4-(3-indolyl-alkyl)piperidine derivatives were competitive inhibitors. LM 5005 was a weaker inhibitor of [^{14}C] 5-HT uptake into human blood platelets than into rat brain synaptosomes. The order of activity was: LM 5008 > clomipramine > LM 5005 = imipramine > LM 5015 > amitriptyline > desipramine > *p*-chloroamphetamine. The IC_{50} found were similar to those observed with rat brain synaptosomes for all the drugs, except LM 5005.

Release of 5-HT by human blood platelets. Incubation of labelled platelets with *p*-chloroamphetamine provoked the release of [^{14}C] 5-HT which was time and concentration dependent (Fig. 4). *p*-Chloroamphetamine which was the least effective 5-HT uptake inhibitor was the most potent 5-HT releaser. Tricyclic antidepressants and 4-(3-indolyl-alkyl)piperidine derivatives had no effect on 5-HT release at concentrations which inhibited 5-HT uptake (Table 4).

Uptake of NA and DA into rat heart in vivo. Tricyclic antidepressants which are known to inhibit the uptake of catecholamines into the brain are also potent inhibitors of catecholamine uptake into the

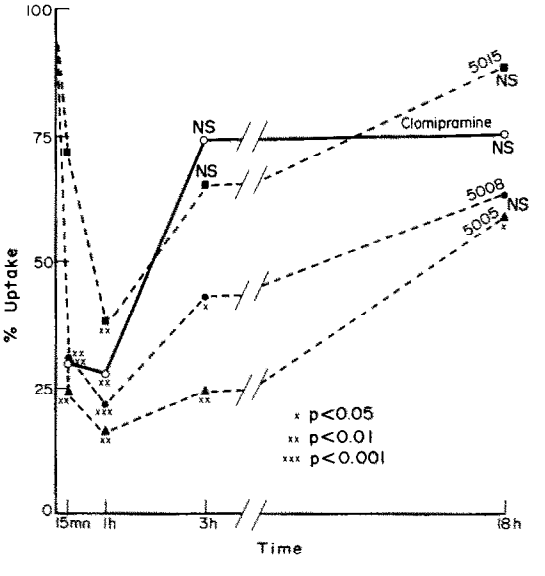


Fig. 2. Time course of [^{14}C] 5-HT uptake into synaptosomes from whole rat brain after administration of clomipramine, LM 5005, LM 5008, LM 5015 at 10 mg/kg i.p.

* Unpublished results.

Table 3. Inhibition of the uptake *in vivo* of [^{14}C] 5-HT into synaptosomes from different regions of rat brain after administration of clomipramine, LM 5005, LM 5008, LM 5015 at 10 mg/kg i.p.—The rats were sacrificed 1 hr after the injection of the drugs and the brains dissected according to the method of Glowinski and Iversen [16]

Drugs	Cerebellum	Medulla + Pons	Striatum	Hypothalamus	Midbrain	Hippocampus	Cortex
Controls 37°	*0.59 ± 0.13	3.34 ± 0.01	3.87 ± 0.01	2.45 ± 0.07	7.93 ± 0.74	2.74 ± 0.21	2.47 ± 0.19
$n = 3$							
Controls 0°	0.49 ± 0.01	1.33 ± 0.03	1.25 ± 0.04	1.48 ± 0.02	1.43 ± 0.09	1.29 ± 0.18	0.86 ± 0.04
$n = 3$	NS	P< 0.001	P< 0.001	P< 0.001	P< 0.001	P< 0.01	P< 0.01
Clomipramine	0.65 ± 0.02	1.85 ± 0.17	2.13 ± 0.01	1.27 ± 0.05	1.94 ± 0.02	1.09 ± 0.02	1.25 ± 0.01
$n = 3$	**0%	74%	66%	100%	92%	100%	76%
	NS	P< 0.001	P< 0.001	P< 0.001	P< 0.001	P< 0.01	P< 0.01
LM 5005	0.39 ± 0.03	1.26 ± 0.06	3.57 ± 0.14	2.46 ± 0.23	1.18 ± 0.04	1.03 ± 0.15	1.38 ± 0.10
$n = 3$	100%	100%	12%	0%	100%	100%	68%
	NS	P< 0.001	NS	NS	P< 0.001	P < 0.01	P < 0.01
LM 5008	0.47 ± 0.01	1.19 ± 0.01	3.41 ± 0.18	2.58 ± 0.19	1.28 ± 0.06	1.03 ± 0.11	1.14 ± 0.07
$n = 3$	100%	100%	18%	0%	100%	100%	83%
	NS	P< 0.001	NS	NS	P< 0.001	P< 0.01	P < 0.01
LM 5015	0.47 ± 0.01	1.24 ± 0.24	2.60 ± 0.17	3.01 ± 0.51	2.11 ± 0.01	1.87 ± 0.17	1.92 ± 0.01
$n = 3$	100%	100%	48%	0%	89%	60%	84%
	NS	P < 0.001	P< 0.01	NS	P< 0.001	P< 0.05	P< 0.01

* pMoles 5-HT/mg protein/5 mn.
** % inhibition.

Table 4. Effect of various drugs on release and uptake of [^{14}C] 5-HT by human blood platelets

Drugs	% release of 5-HT (t = 120 mn)		Inhibition of 5-HT uptake (t = 15 mn)			
			Ki × 10^{-7} M			
	5 × 10^{-6} M	5 × 10^{-5} M	CI	UI	% inhibition (1 × 10^{-6} M)	IC_{50} (μM)
p-Chloroamphetamine	6 + 1	51 + 3			8 + 3	12
Imipramine	3 + 1	13 + 3		1.50	71 ± 4	0.4
Clomipramine	7 + 2	7 + 2		0.25	86 + 5	0.07
Desipramine	1 + 1	13 ± 2		12.50	15 + 3	4.5
Amitriptyline	3 + 1	7 + 1		11.00	46 + 4	1.1
LM 5005	4 + 2	10 ± 4	4.9		75 + 5	0.4
LM 5008	5 + 3	22 + 5	0.2		98 + 2	0.05
LM 5015	10 + 4	14 + 5	4.6		65 + 3	0.55

CI = competitive inhibition; UI = uncompetitive inhibition—Values represent the mean (± standard deviation) from 2 to 4 determinations—Only values ⩾ 10% may be considered as a significant effect.

heart [23, 24]. Therefore we compared the *in vivo* potencies of 4-(3-indolyl-alkyl)piperidine derivatives and tricyclic antidepressants to block the NA and DA uptake into rat heart.

Among the tricyclic antidepressants, secondary amines (desipramine) were more active than tertiary amines (imipramine, clomipramine). LM 5005 and LM 5008 did not block NA and DA uptake into rat heart. LM 5015 was a weak inhibitor less effective than clomipramine.

DISCUSSION

4-(3-Indolyl-alkyl)piperidine derivatives represent a new class of pharmacological agents which selectively inhibit the uptake of 5-HT into the neuronal membrane. LM 5005 and LM 5008 are more specific than LM 5015. The apparent selectivity *in vitro* of imipramine and clomipramine on 5-HT uptake does not occur *in vivo* because of their *N*-demethylation by the hepatic microsomal enzymes which produces the respective secondary amines which are potent catecholamine uptake inhibitors [4, 5, 25]. Clomipramine, the most effective tricyclic antidepressant in inhibiting 5-HT uptake, is also a potent catecholamine uptake inhibitor in the rat heart *in vivo*. On the contrary, LM 5005 and LM 5008 do not inhibit catecholamine uptake in rat heart *in vivo* and the IC_{50} of LM 5015 is 3 times higher than that of clomipramine. The duration of 5-HT uptake inhibition is longer with LM 5005 and LM 5008 (18 hr at least) than with clomipramine (3 hr). This phenomenon could be explained by a prolonged presence of these compounds in the brain or by the metabolization of LM 5005 and LM 5008 into very active 5-HT uptake inhibitor metabolites.

In vivo the 5-HT uptake inhibition by 4-(3-indolyl-alkyl)piperidine derivatives is very different from a specific brain region to another. The administration of these drugs to rats causes no or a small 5-HT uptake inhibition in the hypothalamus and striatum which, however, possess high 5-HT uptake activities (Table 3) and contain 5-HT neurones [26, 27]. This

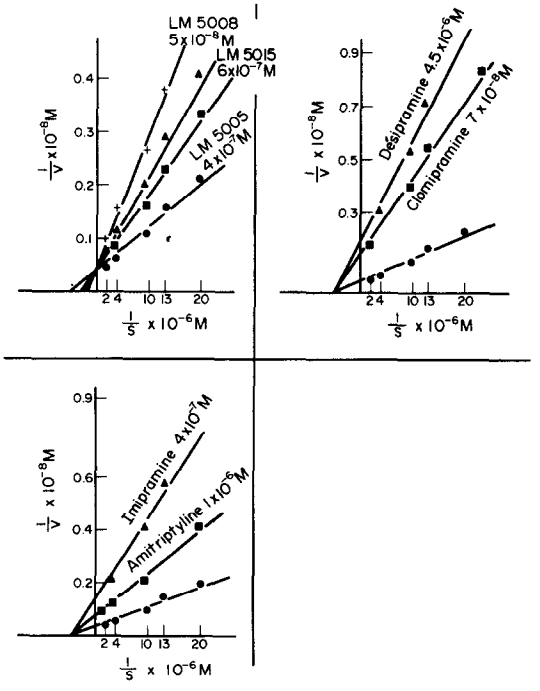


Fig. 3. Kinetic analysis of the inhibition of [^{14}C] 5-HT uptake by human blood platelets according to the method of Lineweaver and Burk [19].

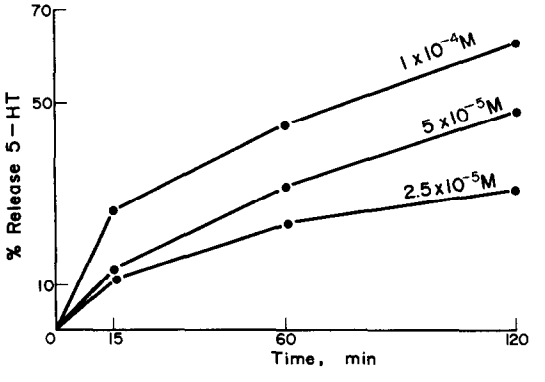


Fig. 4. Effect of *p*-chloroamphetamine on release of [^{14}C] 5-HT from human blood platelets. No release occurred in controls.

Table 5. Inhibition of [^{14}C] NA and [^{14}C] DA accumulations into rat heart by tricyclic antidepressants and 4-(3-indolyl-alkyl)piperidine derivatives

Drugs	Doses (mg/kg i.p.)	% inhibition NA	% inhibition DA	IC_{50} (mg/kg i.p.) NA	IC_{50} (mg/kg i.p.) DA
Desipramine	0.1	25	—		
	1	64	48	0.5	1.1
	5	—	80		
	10	81	—		
Imipramine	1	6	29		
	3	64	—	1.5	2.2
	5	75	70		
	10	83	74		
Clomipramine	5	5	—		
	10	51	2	11	19
	20	75	60		
LM 5005	50	15	29	>50	>50
LM 5008	50	13	24	>50	>50
LM 5015	20	44	41		
	30	46	—	37	45
	50	55	51		

Values represent the mean of 3 determinations.

paradoxical effect was already found with another new selective 5-HT uptake inhibitor, Lilly 110140, which only causes a 20 per cent decrease in 5-HT uptake in the striatum and diencephalon [28]. Moreover, nomifensine, a specific catecholamine uptake inhibitor, has a weaker inhibitory effect on NA uptake in the hypothalamus than in the whole brain *in vitro* [29].

Nevertheless, several hypotheses may be postulated. First, the lack of effect in the hypothalamus and the striatum could be caused by a heterogenous distribution of the drugs in the brain. Second, the uptake sites in the hypothalamus and striatum should be very different from those of the other brain regions, the drugs tested showing no affinity to these sites. Moreover, the "*in vivo*" measurement of the inhibition of 5-HT uptake that we used was in fact and *in vivo*, *in vitro* method. So the lack of effect might be an artefact because of a very reversible binding of the 4-(3-indolyl-alkyl)piperidine derivatives to the hypothalamus and striatum membranes. Further experiments, such as *in vitro* measurements of 5-HT uptake inhibition in different brain regions, or *in vivo* after intracerebral injection of [^{14}C] 5-HT in different species, or determination of the distribution of the labelled 4-(3-indolyl-alkyl)piperidine derivatives, are being carried out, which could elucidate this point.

Whereas tricyclic antidepressants block the reuptake of biogenic amines by the pre-synaptic membranes, reserpine prevents the storage of exogenous monoamines in synaptic vesicles [13]. As only the unbound amines are quickly metabolized by MAO into metabolites which diffuse out through the membrane, the comparison between monoamine uptake in the presence or in the absence of an IMAO could distinguish these two different mechanisms of action. LM 5005, LM 5008 and LM 5015 inhibit in the same way 5-HT uptake whether or not an IMAO is present. Therefore, like tricyclic antidepressants, they are inhibitors of the 5-HT uptake by the pre-synaptic membranes.

The central action of amphetamines is generally attributed to an increase in the concentration of monoamines in the synaptic cleft, which may be achieved by an increase in the release of the amines from pre-synaptic terminals and by an inhibition of the re-uptake of the released amines [30, 31, 32]. For example, *p*-chloroamphetamine, which acts preferentially on 5-HT neurones [33, 34], inhibits 5-HT uptake and provokes a release of 5-HT from human blood platelets. On the contrary, 4-(3-indolyl-alkyl)piperidine derivatives and clomipramine inhibit 5-HT uptake without affecting 5-HT release from human blood platelets.

Thus, because of their specific 5-HT uptake inhibiting property, 4-(3-indolyl-alkyl)piperidine derivatives could exert therapeutic effects in 5-HT dependent mental diseases.

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