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AN IODINATED DERIVATIVE OF MOCLOBEMIDE AS POTENTIAL RADIOLIGAND FOR BRAIN MAO-A EXPLORATION

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Summary

In vivo evaluation of MAO-A would be of great value for the diagnosis and follow-up of therapy of depression. In order to perform this exploration by SPECT, we developed an iodinated derivative of the reversible MAO-A inhibitor, moclobemide. Ro 11-9900 was synthesized and analysed by IR, NMR and HPLC. Radioiodination was carried out by nucleophilic exchange of [^{125}I] on the brominated precursor, and yielded [^{125}I]-Ro 11-9900 with high specific activity. In vitro experiments on rat brain homogenates showed that Ro 11-9900 had poor inhibitory activity on MAO-A, as already described for moclobemide. By contrast, in vivo biodistribution in the rat brain showed that [^{125}I]-Ro 11-9900 accumulated in a region corresponding to the localization of locus coeruleus known for its high density of MAO-A. Moreover, preinjection of the irreversible MAO-A inhibitor clorgyline (10 mg.kg^{-1}) prevented accumulation of radioactivity by 40 to 60% and we found that the radioactivity in the brain corresponded exclusively to [^{125}I]-Ro 11-9900 and not to a metabolite. [^{125}I]-Ro 11-9900 was highly accumulated in the pineal gland, both on MAO-A and on MAO-B sites. We concluded that the unmetabolized iodinated derivative of moclobemide, Ro 11-9900, preferentially labeled MAO-A in vivo in the rat brain. This compound would therefore be a potential tracer for evaluation of MAO-A by SPECT.

Key Words: moclobemide, Ro 11-9900, monoamine oxidase, SPECT, radioiodination

Monoamine oxidase (MAO, E.C 1.4.3.4), a flavin-containing enzyme, plays an important role in the regulation of monoaminergic transmission in the central nervous system. Indeed, neurotransmitter amines are released in the synapse and there is about 90% reuptake by presynaptic neurons where part may be stored in granules and another part inactivated by deamination by MAO. Two types of MAO have been described, MAO-A and MAO-B, identified

by their different substrate and inhibitor specificity (1, 2): MAO-A preferentially deaminates 5-hydroxytryptamine (5-HT) and is irreversibly and selectively inhibited by clorgyline; MAO-B selectively oxidizes ß-phenylethylamine (PEA) and is irreversibly and selectively inhibited by L-deprenyl. The biodistribution of the two forms of MAO is different according to the animal and the tissue. In the central nervous system, MAO-A is mainly expressed by noradrenergic neurons whereas MAO-B is specifically expressed by serotoninergic neurons and glial cells (3).

It has been shown that the antidepressant effects of several classes of compounds are due to their MAO-A-inhibiting properties. Moclobemide [Ro 11-1163, 4-chloro-N-[2-(4-morpholinyl)ethyl]-benzamide] is a reversible and short-acting preferential MAO-A inhibitor (4) which seems particularly useful in elderly people because of its lack of anticholinergic effects and its possible cognition enhancing properties (5). It therefore could be assumed that in this population, in vivo evaluation of the functionally active MAO-A concentration and of the occupancy of MAO-A sites by drugs would be very valuable. It would be particularly helpful to determine individual adaptation to the antidepressant treatment to obtain the optimal therapeutic effect. Scintigraphic methods are well adapted for such in vivo evaluation and radiolabeled derivatives of clorgyline have already been developed for exploration of MAO-A by PET (6, 7) or by SPECT (8, 9). However, since clorgyline binds irreversibly to MAO-A, a quantitative in vivo method with an equilibrium model cannot be used. A selective reversible ligand is already available for the quantification of MAO-A by the in vitro method (10), but no ligand of this type has been developed for the scintigraphic method yet.

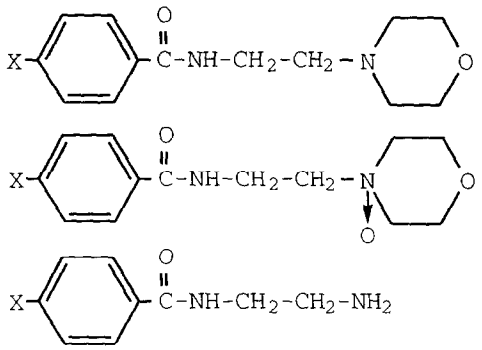
We therefore chose to label the reversible MAO-A inhibitor moclobemide with iodine in order to obtain a tracer for the exploration of MAO-A by SPECT. We describe here the chemical and radiochemical synthesis of an iodinated derivative of moclobemide, designated Ro 11-9900 according to Schoerlin et al. (11). In vitro affinity and specificity for MAO activity of this compound was determined on a rat brain preparation. Cerebral biodistribution and in vivo metabolism studies were performed in rats with the ^{125}I-labeled derivative.

Methods

Synthesis and radiolabeling of Ro 11-9900

Brominated and iodinated analogs of moclobemide (Fig.1) were synthesized at 0-5°C with 4-bromobenzoylchloride (Janssen) or 4-iodobenzoylchloride (Aldrich) and one equivalent of 2-morpholinoethylamine (Lancaster) in the presence of triethylamine (12). The free bases of compounds 2 and 3 (Fig.1) were used for structural characterization whereas the hydrochloride of the compound 2 was used as precursor of the radiolabeled compound and the unlabeled iodinated product 3 was used as standard and for in vitro experiments. Radioiodination was achieved under solid-state conditions enhanced by ammonium sulfate using the brominated precursor, 2, and [^{125}I]NaI (3.7 GBq / ml in 0.1 N NaOH, Amersham, England) at 210°C for 40 min (13).

We synthesized the expected metabolites of Ro 11-9900, the N-oxide iodinated derivative of Ro 12-5637 and the iodinated derivative of Ro 16-6491 (Fig.1). The N-oxide iodinated derivative of Ro 12-5637, compound 5 or 4-iodo-N-[2-(4-morpholinyl)ethyl]N'-oxide, was obtained by oxidation of Ro 11-9900, according to the procedure described by Taylor et al. (14). The iodinated derivative of Ro 16-6491, compound 7 or 4-iodo(2-aminoethyl) benzamide, was obtained according to a previously described method (15).



1:X=Cl, moclobemide
2:X=Br, precursor
3:X=I, Ro 11-9900

4:X=Cl, Ro 12-5637
5:X=I

6:X=Cl, Ro 16-6491
7:X=I

Fig.1
Chemical structures of moclobemide (1), its brominated analog (2), its iodinated analog (3), the known metabolites of 1 (4 and 6), and the expected metabolites of 3 (5 and 7).

In vitro MAO inhibitory activity

The inhibitory activity of RO 11-9900 was assessed by measuring its potency in vitro to inhibit MAO activity in rat brain homogenate with 5-hydroxy [side chain-2-^{14}C]tryptamine creatinine sulfate ([^{14}C]5-HT, Amersham) at a final specific activity of 37 kBq.µmol^{-1} as selective substrate for MAO-A, and phenylethylamine hydrochloride ß [ethyl-1-^{14}C] ([^{14}C]PEA, New England Nuclear) at a final specific activity of 370 kBq.µmol^{-1}, as selective substrate for MAO-B (16). The inhibitory potencies of moclobemide, clorgyline and L-deprenyl were determined as references.

Whole brains of male Wistar rats (200-300 g) were homogenized using an Ultra turrax (T25) homogenizer in 20 vol of 0.1 N sodium phosphate buffer (pH 7.4) and all assays were performed with this crude preparation. A reaction mixture containing 100 µl of crude homogenate, 50 µl of inhibitor (or 50 µl of water for controls) and 250 µl of buffer was preincubated for 20 min at 37°C. The reaction was started by the addition of the substrate (100 µl) and incubation was continued at 37°C for 5 min with [^{14}C]5-HT (625 µmol.l^{-1}) or for 1 min with [^{14}C]PEA (40 µmol.l^{-1}). The reaction was stopped by addition of 200 µl of 4 N HCl. The metabolites formed were extracted with 7 ml of toluene/ethyl acetate mixture (50/50 v/v). After shaking and freezing, the organic phase was

transferred to a counting vial containing a mixture of 10 ml of toluene/2,5-diphenyloxazole (4 $g.l^{-1}$) for determination of the radioactivity. The results were expressed as percentages of residual MAO activity calculated from control values. IC_{50} were calculated graphically from the inhibition curves obtained with inhibitor concentrations ranging from 10^{-4} to 10^{-10} $mol.l^{-1}$.

Biodistribution studies

Experiments in rats were carried out in compliance with applicable guidelines from the "Ministère de l'Agriculture, France". Three groups of male Wistar rats weighing 200 g were constituted. They received an i.v. injection of 0.9% NaCl, 5 $mg.kg^{-1}$ of L-deprenyl or 5 $mg.kg^{-1}$ of clorgyline, respectively. In another set of experiments the three groups received an i.v. injection of 0.9% NaCl, 10 $mg.kg^{-1}$ of L-deprenyl or 10 $mg.kg^{-1}$ of clorgyline, respectively. Twenty minutes after this injection, all the animals received 555 kBq of [^{125}I]-Ro 11-9900 and were sacrificed one hour later. Samples of blood and cerebral regions (pineal gland, frontal cortex, olfactory tubercles, striatum, thalamus, hypothalamus, hippocampus, cerebellum and brainstem) were removed, weighed, and their radioactivity was measured with a gamma scintillation counter (LKB 1282 Compugamma). The uptake was expressed as the percentage of injected dose per gram of tissue. In order to evaluate deiodination of the radioiodinated product in vivo, the thyroid gland of each animal was removed and its radioactivity was measured.

For ex vivo autoradiographical study, rats were injected i.v. with 3.7 MBq of [^{125}I]-Ro 11-9900 and were sacrificed one hour later. Brains were rapidly removed, frozen on dry ice and cut into 20 µm transverse slices. After drying the slices were exposed to a sensitive film (Hyperfilm β-max, Amersham) for four weeks and then developed (Kodak L24 revelator), fixed and dried.

In vivo brain metabolism

Male Wistar rats weighing 200 g received an i.v. injection of 555 kBq of [^{125}I]-Ro 11-9900 and were sacrificed one hour later. Whole brains were removed and radiolabeled compounds were extracted with methanol as previously described (17). After elimination of the solvent, the radioactive extract was analysed by co-injection with RO 11-9900, 5 and 7 on HPLC system (Beckman) fitted with UV (254 nm) and radioactivity detectors.

Results

Synthesis and labeling

Chemical control by IR, NMR and HPLC showed high purity (>95%) for all synthesized compounds. HPLC purification permitted total separation of the precursor and the labeled product [^{125}I]-Ro 11-9900, and the specific activity of the labeled product was therefore comparable to that of the [^{125}I]NaI used (74 $TBq.mmol^{-1}$). The radiochemical purity controlled by HPLC using unlabeled Ro 11-9900 as standard was upper than 95% (Fig.2).

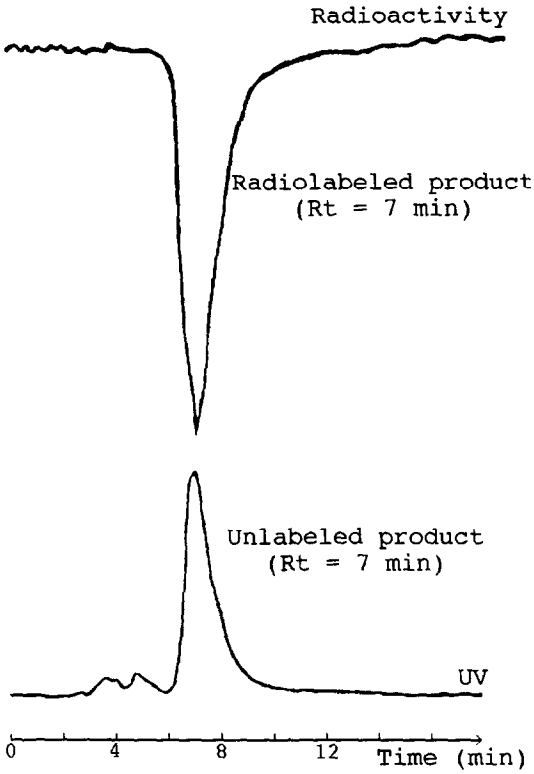


Fig.2
After purification of [^{125}I]-Ro 11-9900, radiochemical purity was controlled on a reversed phase column 10 RP 18 using MeOH/0.025 M Na_2HPO_4 pH 7.4 (60/40, v/v) as the mobile phase.

In vitro MAO inhibitory activity

The IC_{50} of Ro 11-9900 for MAO-A and MAO-B activities as well as those of moclobemide, clorgyline and L-deprenyl for comparison are shown in Table I.

TABLE I

IC_{50} (nM)

Compound	MAO-A	MAO-B
Ro 11-9900	$> 10^4$	$>10^5$
Moclobemide	$> 10^4$	$> 10^5$
Clorgyline	4 ± 2	2650 ± 354
L-Deprenyl	1125 ± 106	13.5 ± 3.5

In vitro MAO-A and MAO-B inhibitory potencies were measured using rat homogenates. Each value represents the mean ± S.D. of 3 to 4 independent determinations.

Biodistribution studies

One hour after i.v. injection of [^{125}I]-Ro 11-9900, the radioactivity measured in the thyroid, which reflects the in vivo deiodination levels of the product, was on average 0.20 ± 0.05% of the injected dose and the radioactivity measured in the blood was on average 0.20 ± 0.02% of the injected dose per gram. The highest accumulation of [^{125}I]-Ro 11-9900 for the control groups was found in the pineal gland, about 0.3% of the injected dose per gram tissue. This accumulation was unmodified by a pre-injection of 5 mg.kg^{-1} of L-deprenyl but was decreased to 20% by a dose of 10 mg.kg^{-1}. In clorgyline pre-treated rats, no significant modification was observed at the dose of 5 mg.kg^{-1} while a 30% decrease was measured at the dose of 10 mg.kg^{-1} (Fig.3).

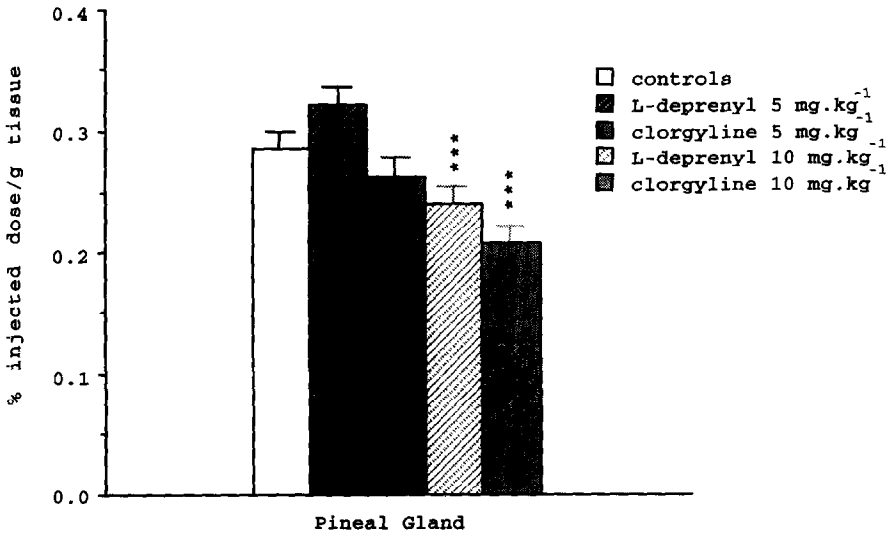


Fig.3
Accumulation of [^{125}I]-Ro 11-9900 in the pineal gland one hour after i.v. injection. The rats received a pre-injection of 0.9% NaCl (controls), 5 mg.kg^{-1} of L-deprenyl or 5 mg.kg^{-1} of clorgyline , 10 mg.kg^{-1} of L-deprenyl or 10 mg.kg^{-1} of clorgyline 30 min before injecting ligand. Results are expressed as the mean percentage of injected dose per gram of tissue ± S.D. and were analyzed by t test for unpaired values. (***), $p < 0.0005$; $n = 5$ for each value.

In cerebral areas in the control groups (Fig.4A and 4B), the highest levels of [^{125}I]-Ro 11-9900 were found in the brainstem. These values were significantly higher than those measured in all other cerebral regions ($p < 0.01$ to $p < 0.0005$, according to the region). Pre-injection of L-deprenyl at the dose of 5 mg.kg^{-1} had no significant effect on the cerebral accumulation of [^{125}I]-Ro 11-9900 (Fig.4A).

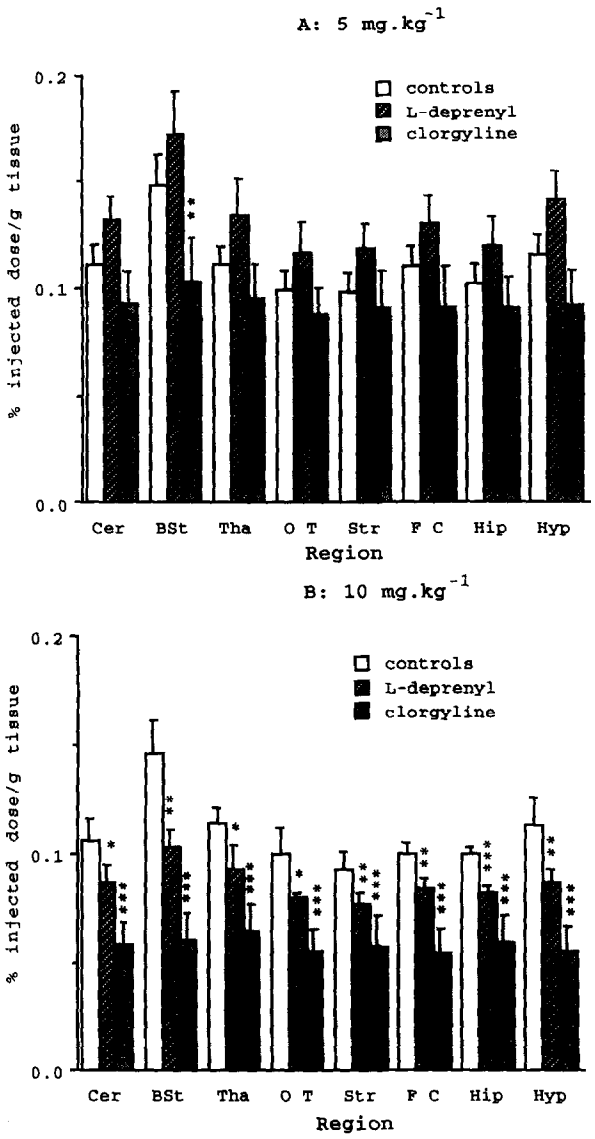


Fig.4
Accumulation of [^{125}I]-Ro 11-9900 1 hour after i.v. injection in cerebral areas: cerebellum (Cer), brainstem (BSt), thalamus (Tha), olfactory tubercles (OT), striatum (Str), frontal cortex (FC), hippocampus (Hip) and hypothalamus (Hyp). The rats received a pre-injection of 0.9% NaCl (controls), 5 mg.kg^{-1} of L-deprenyl or 5 mg.kg^{-1} of clorgyline 30 min before injecting the ligand (A) or a pre-injection of 0.9% NaCl (controls), 10 mg.kg^{-1} of L-deprenyl or 10 mg.kg^{-1} of clorgyline 30 min before injecting the ligand (B). Results are expressed as the mean percentage of injected dose per gram of tissue ± S.D. and were analyzed by t test for unpaired values.(*), $p<0.01$; (**), $p<0.005$; (***), $p<0.0005$ between treated and control rats; n = 5 for each value.

By contrast, a dose of 10 $mg.kg^{-1}$ prevented accumulation of the ligand by 30% in the brainstem (0.102 ± 0.009% ID/g) and by 17 to 24% in other cerebral areas (Fig.4B). A pre-injection of clorgyline at the dose of 5 $mg.kg^{-1}$ significantly prevented accumulation of [^{125}I]-Ro 11-9900 by 30% in the brainstem while no significant decreases were observed in other cerebral regions (Fig.4A). At the dose of 10 $mg.kg^{-1}$, clorgyline prevented accumulation of [^{125}I]-Ro 11-9900 by 60% in the brainstem (0.060 ± 0.012% ID/g) and by 39 to 51% in other regions (Fig.4B).

Fig. 5 shows the distribution of [^{125}I]-Ro 11-9900 using an ex vivo autoradiographical method. A high accumulation in the pineal gland can be observed, and in a specific region of the brainstem which was assumed to be the locus coeruleus.

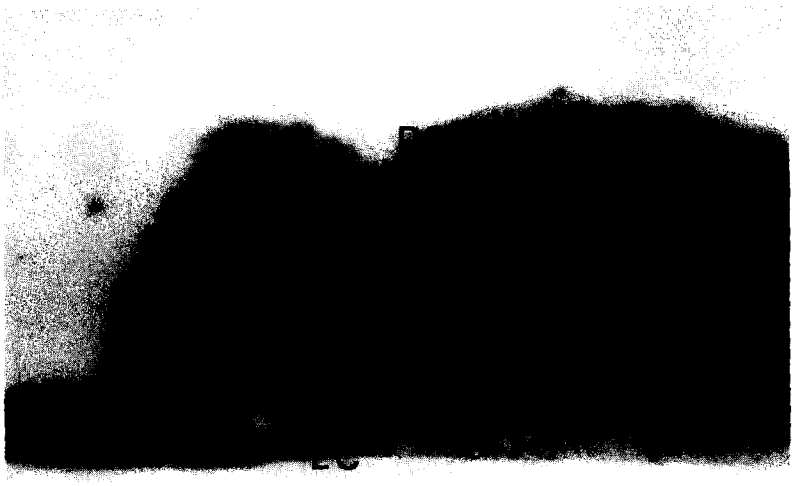


Fig.5
Ex vivo autoradiogram of rat brain sagittal section 1 hour after i.v. injection of [^{125}I]-Ro 11-9900 at the lateral level of 1.40 mm (Atlas of Paxinos and Watson, 1982; 18). High intensities are observed in the pineal gland (P G) and in the locus coeruleus (L C).

In vivo brain metabolism

One hour after i.v. administration of [^{125}I]-Ro 11-9900, HPLC analysis of the brain extract showed that more than 95% of radioactivity was due to [^{125}I]-Ro 11-9900.

Discussion

In vivo evaluation of the functionally active MAO-A concentration and of the occupancy of MAO-A sites by drugs would be of great value in the diagnosis and therapeutic follow-up of

depression. To date, only the irreversible MAO-A inhibitor clorgyline or its derivatives have been labeled for scintigraphic exploration of MAO-A activity by PET (6,7) or by SPECT (8,9), but no reversible and selective radioligands have been available. In order to develop a reversible tracer for MAO-A exploration by SPECT, we synthesized an iodinated derivative of the reversible inhibitor, moclobemide, by substitution of chloride by iodine. We synthesized Ro 11-9900 and its brominated analog and characterized both compounds by conventional spectra. The radioiodinated derivative [^{125}I]-Ro 11-9900 was obtained by exchange between the bromide atom of the bromo-precursor and ^{125}I-iodide, resulting in a no-carrier-added radiolabeled compound with a 50% yield and a very high degree in purity (>95%).

Our in vitro experiments showed that inhibitory potencies of Ro 11-9900 towards MAO-A and MAO-B activities were close to those obtained for moclobemide. Moclobemide and its iodinated derivative were therefore 1000 times less potent in vitro than the irreversible MAO-A inhibitor clorgyline. Similar results have already been shown for moclobemide and several reversible MAO-A inhibitors, whereas other reversible MAO-A inhibitors and irreversible inhibitors had high in vitro activity (4).

In vivo experiments showed that deiodination of [^{125}I]-Ro 11-9900 one hour after injection was low since a low radioactivity level was found in the thyroid gland. In the brain, the radiolabeled iodinated derivative of moclobemide was highly accumulated in the brainstem. Moreover, autoradiographic studies demonstrated that in this cerebral area, the main fixation of [^{125}I]-Ro 11-9900 corresponded to the localization of the locus coeruleus. This is in agreement with the regional concentrations of brain MAO-A measured in the rat both with a histochemical procedure (19,20) and with an autoradiographic method with [^{14}C]-clorgyline (21,17). In vivo fixation of [^{125}I]-Ro 11-9900 in other brain areas was lower than in the bulb and homogeneous between regions. Such a homogeneous distribution was also observed recently with an iodinated derivative of clorgyline in the mouse brain (9).

We therefore showed that the iodinated derivative of moclobemide Ro 11-9900 had a low in vitro inhibitory potency towards MAO-A, but that its biodistribution in the rat brain corresponded to the known distribution of MAO-A sites. It can be therefore hypothesized that biological in vitro and in vivo biodistribution properties of this compound are close to those of moclobemide itself, for which poor in vitro activity and high ex vivo activity in the mouse brain have been described (4). To explain the apparently contradictory results between in vitro and in vivo experiments, it has been proposed that the MAO-inhibiting activity could be attributed to a metabolite of moclobemide (22). However, it has been shown ex vivo that in the rat brain only one of the expected metabolites of moclobemide, Ro 12-5637, inhibited MAO-A activity but less rapidly and less potently than moclobemide, other identified metabolites being completely inactive (4). We therefore studied the in vivo metabolism of [^{125}I]-Ro 11-9900 in the rat. After extraction of brain homogenate, we identified exclusively intact [^{125}I]-Ro 11-9900 as the only radiolabeled compound. In the same way, Cesura et al. did not find any metabolite of moclobemide after a prolonged incubation (48h)

with human placenta membranes (23). It seems therefore that similar discrepancies between in vitro and in vivo results were observed for both Ro 11-9900 and moclobemide. The duration of the in vitro incubation did not seem to be a valuable explanation for the poor in vitro efficiency for both compounds (4). Moreover there is no evidence for in vivo production of an active metabolite. Our results and those of Da Prada, are in favour of the in vivo activity of moclobemide and the in vivo binding of [^{125}I]-Ro 11-9900 themselves and not the forms metabolized in the brain. We therefore hypothesize that as it has been proposed for moclobemide (23), Ro 11-9900 belongs to the class of "slow binding inhibitors" described by Williams and Morrison (24).

Concerning in vivo selectivity of Ro 11-9900 for MAO-A, we observed that the binding of [^{125}I]-Ro 11-9900 in the brainstem was prevented by pre-injection of clorgyline in a dose-dependent way (30% with 5 mg.kg^{-1} and 60% with 10 mg.kg^{-1}), whereas a pre-injection of L-deprenyl had an effect (-30%) only at 10 mg.kg^{-1}. We also observed that [^{125}I]-Ro 11-9900 was accumulated in the pineal gland at a higher level than in the brain, this accumulation being prevented by 20% and 30% by L-deprenyl and clorgyline respectively, both at the dose of 10 mg.kg^{-1}. These results are in favour of preferential MAO-A activity in the brain and mixed MAO-A and MAO-B activity in the peripheral organs such as the pineal gland for Ro 11-9900, as already shown for moclobemide (4). These results could be explained by a peripheral metabolism of moclobemide resulting in a compound, Ro 16-6491, which is more active on MAO-B than the parent compound (4). We found no radioactive metabolite of [^{125}I]-Ro 11-9900 in the brain, but results obtained in the pineal gland could be related to a metabolization of [^{125}I]-Ro 11-9900 to [^{125}I]-Ro 16-6491 in this peripheral tissue. This hypothesis is reinforced by the fact that we have previously demonstrated that [^{125}I]-Ro 16-6491 which binds preferentially to MAO-B in the rat's pineal gland crosses very poorly the blood-brain barrier in this species (15).

To conclude, we have developed Ro 11-9900, an iodinated derivative of moclobemide, which seemed in the rat to be poorly metabolized in vivo and to label preferentially to MAO-A in the brain. The study of the cerebral biodistribution of this product labeled with ^{123}I in the non-human primate by SPECT is therefore envisaged, to determine whether it is suitable for scintigraphic exploration of MAO-A in humans with disease such as depression.

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