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Synthesis of ^{131}I and ^{99m}Tc labelled compounds of indoleacetic acid and derivatives. Study of their properties as brain radiotracers

Arturo A. Vitale[1], Carlos O. Cañellas[2], Jorge Ciprian-Ollivier[3], Silvia G. de Castiglia[4] and Alicia B. Pomilio[1]

[1] PROPLAME (UBA and CONICET), Departamento de Química Orgánica, Pabellón 2, Ciudad Universitaria, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, 1428 Buenos Aires, Argentina.
e-mail: aavitale@sinectis.com.ar
[2] Tecnonuclear s.a., Argentina.
[3] Unidad Académica Moyano-Facultad de Ciencias Médicas, Universidad de Buenos Aires, Argentina.

Introduction

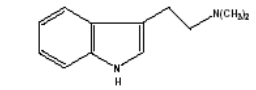
Human brain contains neurons connected together to form a complex network. Interconnection is done through the release of specific neurotransmitters.

Neurotransmission in brain function is one of the most difficult fields of study, not only because of the tiny amounts that constitute the metabolism of neurotransmitters, but also because they are difficult to isolate. The monoamines norepinephrine, dopamine and serotonin are those neurotransmitters of best known distribution.

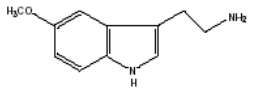
Serotonin or 5-hydroxytryptamine (5-HT) has an important role in the central nervous system. Disorders of its metabolism are associated with psychiatric disorders, such as uni- and bipolar depression, obsessive - compulsive phobic pathologies, schizophrenias, endogenous psychoses particularly eating disorders, and tendency to addictive behaviour (Jimerson *et al*., 1990; Meltzer, 1990; Abi-Dargham *et al*., 1996; Jarry and Vaccarino, 1996).

In a previous research carried out in our laboratories on the biological role of *N*,*N*-dimethyltryptamine (*N*,*N*-DMT) (**1**), which is the dimethylation product of a metabolic precursor of serotonin, we based on the reported occurrence of a higher concentration of this molecule in the urine of non-medicated psychotic patients in critical phase, *versus* the non-presence in the urine of normal patients (Pomilio *et al*., 2003), as well as the development of the experimental psychosis model obtained by the intake of Ayahoasca, which is a *N*,*N*-DMT-rich potion of shamanistic use (Pomilio *et al*., 1999). Under these assumptions, and especially due to its chemical-structural features, we inferred its potential usefulness and extended these studies to other derivatives, such as tryptamine (**2**), 5-methoxytryptamine (**3**) and indoleacetic acid (**4**).

N,*N*-DMT and the I-131-labelled derivative have already been synthesized in our laboratories (Sintas and Vitale, 1997), and the same approach was applied to prepare I-131-labelled derivatives of other indole compounds. ^{99m}Tc-Complexes of these



1 **2**



3 **4**

compounds were also prepared for the first time, thus the structures of the covalent compounds as well as the charge and lipophilicity of the ^{99m}Tc-complexes being determined. Radiochemical purity was also assessed, and the compounds were administered into biological models in order to determine the biodistribution, target organs, metabolic routes, and especially the use for visualization of serotoninergic areas in brain.

Methodology

Labelling with (^{131}I Na): The compounds were labelled with a solution of sodium iodide (^{131}INa) of high specific activity without carrier nor reducing agent, using chloramine-T in water as oxidant.

Labelling with ^{99m}Tc: Labelling was developed using nitrogenous solutions, protected from light. The reducing agent was stannous tartrate, being ligand/reducing agent rate at pH 10. The solution of sodium [^{99m}Tc]-pertecneciate was added to the reducing agent, and the ligand was labelled with the obtained radioactive solution.

The radiochemical purity of the labelled complexes was determined by ITLC chromatography (SG) with methylethylketone

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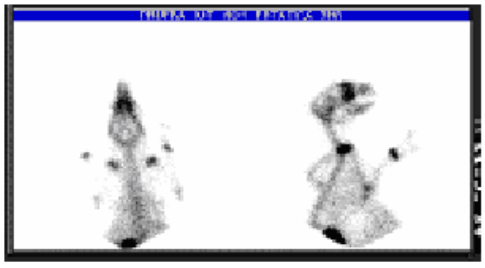
and saline solution. The hydro- and/or lipophilicity of the complexes were determined by the *n*-octanol/water partition coefficient. Charge was determined by electrophoresis in Whatman 1 paper at 300 V for 45 minutes with 5 mM phosphate buffer solutions at pH 6.5, 6.8, 7.3 and 7.5 (under conditions similar to those of plasma and brain compartments).

Results

Labelling with ^{131}I: Radiochemical purity was higher than 95%, Rf values of the ^{131}I-labelled compounds providing the same fluorescence as that of indole nucleus under UV light. Molecules showed to be lipophilic on the basis of *n*-octanol/water partition coefficients.

Labelling with ^{99m}Tc: Radiochemical purity was higher than 90%, Rf values of the ^{99m}Tc-labelled compounds being the same as that of fluorescence due to indole nucleus under UV light. Molecules were hydrophilic on the basis of *n*-octanol/water partition coefficients, whereas their neutrality was shown by electrodeposition at different pH values.

Biological behaviour of [^{131}I]-*N,N*-DMT and [^{99m}Tc]- *N,N*-DMT: Upon administration of [^{99m}Tc]- *N,N*-DMT to inbred rabbits, a concentration of 15.2 ±1.5% of the injected dose (ID) was detected in brain within 10 minutes, which decreased to 5.4 ± 0.9% ID at 60 minutes, at which time the excretion was 78.6 ± 5.5% ID. Concentration in brain at 180 minutes post administration is shown in the figure.



Conclusions

The iodination of the indolic compounds allowed to obtain a high radiochemical purity that, according to the method previously reported (Sintas and Vitale, 1997) avoided subsequent purification steps.

The main modification of the method was to carry out the reaction on the water:chloroform surface, just to overcome the problems caused by the use of an oxidant as chloramine-T on the indole ring, which not only acts on the ^{131}I- but also on the substrate.

Based on the fact that both ^{131}I- and chloramine-T are soluble in the aqueous layer, while biogenic amines are soluble in the chloroform layer, the ^{131}I-labelled product can be separated out, thus preventing that the reaction continues until substrate degradation. Therefore, a product with a purity higher than 98% was obtained.

The development of the ^{99m}Tc-labelling led us to use a controlled reducing system, thus obtaining a V oxidation state of the radioisotope. The use of stannous tartrate, pH 10, lack of oxygen and a proper ligand:reducing agent mass relationship allowed to achieve these controlled conditions.

From the point of view of the biological behaviour, the fact that both radiopharmaceuticals crossed blood-brain barrier with striking ease was demonstrated, thus going in and out the brain compartment in spite of being neutral and hydrophilic compounds.

This condition allows their rapid body excretion demonstrated by minimum circulating activity within few minutes after injection.

For [^{131}I]- *N,N*-DMT brain uptake was 20% at 5 minutes, being effectively excreted, thus finding 2.1% at 60 minutes.

In the case of [^{99m}Tc]- *N,N*-DMT the analysis of the biological results allowed us to infer the biological complex stability in brain compartment, being the wash-out slow, which is an index of the possible expression of an intense and durable activity at the level of receptors.

These agents constitute the first compounds of a new generation of radiopharmaceuticals with stable affinity for brain receptors, which structurally are not tropane derivatives, and further allow to carry out both PET and SPECT studies.

Note: This study was presented at the "XXVI Congreso Argentino de Química" , San Luis, Argentina, 2006

References

- Abi-Dargham A., Laruelle M., Charney D. and Krystal J. (1996) Serotonin and schizophrenia: a review. *Drugs Today* **32**, 171-185.
- Jarry J. L and Vaccarino F. J. (1996) Eating disorder and obsessive-compulsive disorder: neurochemical and phenomenological commonalities. *J. Psychiatry Neurosci.* **21**, 36-48.

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- Jimerson D. C., Lesem M. D., Kaye W. H., Hegg A. P. and Brewerton T. D. (1990) Eating disorders and depression: is there a serotonin connection? *Biol. Psychiatry* **28**, 443-454.

- Meltzer H. Y. (1990) Role of serotonin in depression. *Ann. N.Y. Acad. Sci.* **600**, 486-500.

- Pomilio A., Vitale A., Ciprian-Olliver J., Cetkovich-Bakmas M., Gómez R. and Vázquez G. (1999) *Ayahoasca*: an experimental psychosis that mirrors the transmethylation hypothesis of schizophrenia. *J. Ethnopharmacol.* **65**, 29-51.

- Pomilio A., Vitale A. and Ciprian-Ollivier J. (2003) Cult-Hoasca: A Model for schizophrenia. *Mol. Med. Chem.* **1**, 1-4.

- Sintas J. A and Vitale A. A. (1997) I-131 Derivatives of indolealkylamines for brain mapping. *J. Label. Compound Radiopharm.* **39**, 677-684.