In vivo Evaluation and PET Imaging of [^{11}C]Harmine in Baboon Brains

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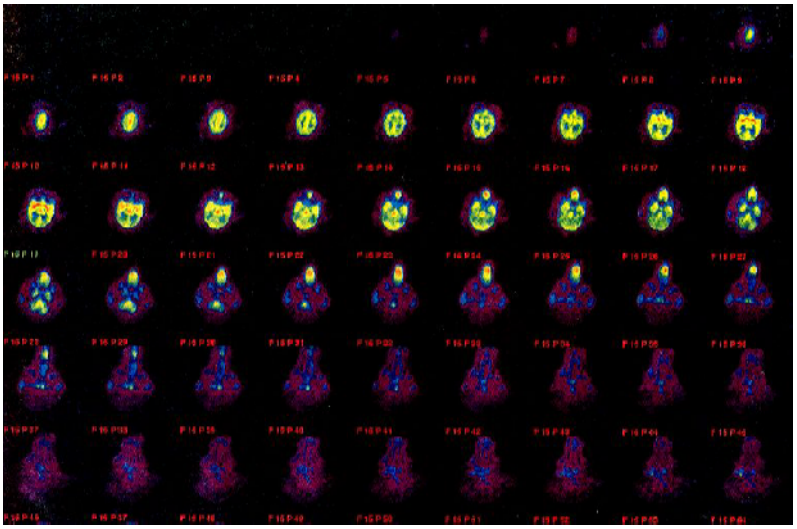

Fig. 1: Uptake of [^{11}C]harmine in a baboon showing specific and heterogeneous uptake in various brain areas

Introduction:

MAO (Monoamine-oxidases) are enzymes which participate in the oxidative deamination of monoamines. They exist in two different forms. Each form (MAO A and MAO B) is characterized by its substrate selectivity, spezificity and its sensitivity to inhibitor substances.

Positron Emissions Tomography (PET) is a molecular imaging tool which allows the non-invasive and detailed observation of tracer kinetics *in vivo*. One of the requirements for the metabolic evaluation of drugs is the development of analogue radiotracers which are able to show quantitatively the distribution in tracer amounts inside the body.

For MAO B various radiopharmaceutical tracers are existing. L-[^{11}C]deprenyl and L-[^{11}C]deprenyl-D2 are used in PET-studies with high sensitivity in regions of high MAO B concentration. L-deprenyl is highly selective for MAO B but leaving MAO A intact. It is used in the treatment of Parkinson's disease, Alzheimer's disease, Schizophrenia and cocaine- and smoking-addiction [1].

However, in contrary to the large amount of MAO B-tracers used for PET, there are only few radiotracers for MAO A available to date. Although for example [^{11}C]chlorgyline is able to bind to MAO A in the human body, there is a lack of specific binding in rhesus monkeys. A group at the Uppsala University, Sweden has already developed another radiotracer, [^{11}C]harmine, with which they could get images of the *in vivo* uptake in rhesus monkeys [2].

In this report, the synthesis of [^{11}C]harmine is described and first *in vivo* images of baboon brains are illustrated.

Synthesis of [^{11}C]harmine:

0.471mmol harmine was dissolved in glacial acetic acid and heated subsequently to the addition of 48% hydrobromic acid overnight under refluxing. The evaporated residue was suspended in water and dissolved by addition of diluted potassium hydroxide. The aqueous solution was washed with methylene chloride and diethyl ether. The product was precipitated with ammonium chloride and gave, after drying under reduced pressure, 77.2 mg (82%) precursor (desmethylated harmine) (1).

[^{11}C]methyl iodide was added to a mixture of 1.5 mg precursor (1) in 200 µl DMF and 3 equivalents of sodium hydroxide (4.5 µl). The reaction mixture was heated at T = 80°C for 5 minutes and then diluted with 500 µl 50 mM ammonium formate/acetonitrile (70:30).

Purification and Analysis:

Semi-preparative HPLC: Luna C_{18} ODS 2, 5 µm, 250x10.00 mm); eluted with 50 mM ammonium formate/acetonitrile (70:30); flow 6 ml/min; UV-detection at 254 nm; retention time 13 min;

Analytical HPLC: Phenophere C18 ODS 2, 5 µm, 250x4.60 mm) eluted with 50 mM ammonium formate/acetonitrile (60:40); flow 2.2 ml/min; UV-detection at 254 nm; retention time 8.2 min.

TLC (methylene chloride / ethylacetate / methanol / ammonium hydroxide [3 M] (20:20:10:1), Rf-value 0.75.

Conclusion:

The precursor for the production of [^{11}C]-harmine was synthesized with 82% yield using [^{11}C]methyl iodide. The compound was injected to a baboon and imaged using PET. [^{11}C]-harmine is a useful tracer for the observation of MAO A metabolism *in vivo*.

References:

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