Preparation of new technetium-99m NNS/X complexes and selection for brain imaging agent

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Received April 21, 2004

Abstract Based on excellent experiment results of \(^{99m}\text{TcO-MPBDA-Cl}\), two new ligands MPTDA and MPDAA are synthesized. Then series of \(^{99m}\text{TcO}^{3+}\) complexes are prepared through adding different halide anions, followed by tests of physical chemistry qualities and biodistribution experiments. And results of these experiments show that complexes formed with MPTDA and MPDAA have better lipophilicity than those formed with MPBDA, still maintain the good brain retention ability of this type of compounds, but radioactivity uptake in blood is higher than that of \(^{99m}\text{TcO-MPBDA}\) and ratios of brain/blood are reduced. Obvious affections are fetched out on brain uptake and retention if fluoride, bromide or iodide anions are added. Results of experiments can be explained in reason with theoretic computation. It is confirmed that \(^{99m}\text{TcO-MPBDA-Cl}\) has potential to develop a new type of brain imaging agent considering integrated factors such as brain uptake, retention and toxicity.

Keywords: \(^{99m}\text{Tc}\), brain perfusion imaging agent, MPBDA, MPTDA, MPDAA.

DOI: 10.1360/03yb0030

Quantification of regional cerebral blood flow (rCBF) plays an important role in the diagnosis of various cerebrovascular and neurological diseases. In nuclear medicine, brain perfusion imaging can provide situation of whole or regional cerebral blood flow perfusion (CBF or rCBF) to neurologists, help to find abnormality of cerebral blood flow before cerebrovascular and neurological diseases induce pathological changes in configuration or structure of brain. They offer important information for forepart diagnosis, therapy, curative effects observe and prognosis.

At present, \(^{99m}\text{Tc}\) brain perfusion imaging agents developed overseas, \(^{99m}\text{TcO-D,L-HMPAO}\) and \(^{99m}\text{TcO-L,L-ECD}\) have been broadly applied in the domestic clinical work. But they do have certain disadvantages. It is an urgent affair to develop \(^{99m}\text{Tc}\) radiopharmaceuticals with our own intelligent property rights whose characteristics are equal to the advanced levels abroad. In 1998 a new NNS ligand MPBDA was synthesized, then \(^{99m}\text{TcO-MPBDA}\) was prepared and found have good initial brain uptake and retention ability\(^{[1,2]}\). This study (i) tries to modify MPBDA ligand, add methyl or methoxy group on phenyl moiety to gain better lipophilicity of complexes and then increase brain uptake, (ii) changes anions participating in complexes formation to improve brain uptake and retention, finds out optimal complexes. In succession of biological experiments, a series of quantum chemistry computation are made to probe into structure-effect relationship of these compounds, furthermore to provide a theoretic basis for designing this kind of radiopharmaceuticals.
1 Experimental

1.1 Synthesis of ligands

Synthesis of ligand MPBDA has been published in ref. [1]. Steps of synthesizing MPTDA are as follows: 1.4 g (0.019 mol) of propylene sulfide is added dropwise into a solution of 3.0 g (0.025 mol) of 3,4-diaminobenzene in 20 mL absolute ethanol. The reaction mixture is refluxed under nitrogen. Reaction is inspected by silica gel thin layer chromatography (TLC) with mixture \( \text{anhydrous ether} : \text{petroleum ether} = 1 : 2 \) as fluid phase. \( R_f \) value of the material is 0.1. The new compound with \( R_f = 0.3 \) can be seen after about 2.5 h. Almost all solvent is removed under the reduced pressure and the residue is dissolved in 100 mL of anhydrous ether. The ether solution is extracted 3 times with 20 mL NaOH solution (0.5 mol \( \cdot \) L\(^{-1} \)). Water solution is adjusted to pH = 7 with hydrochloric acid, then reversed extraction is processed with anhydrous ether. Effect of the extraction is checked by TLC until there is no trace of production in water. The ether is incorporated and condensed under the reduced pressure. The thick residue is purified through silica gel column (\( \text{anhydrous ether} : \text{petroleum ether} = 1 : 2 \)). Dry hydrogen chloride gas is bubbled into the collected solution to give white deposit. The precipitated solid is collected under suction and blown to dry in nitrogen gas. 0.6 g white powder was gained (16.1% yield), with melt point of 135—137°C. Synthesis of ligand MPDAA has analogy with that of MPTDA, but the yield is 12.8% and melt point is 80—83°C.

1.2 Preparation of complexes with \( ^{99m}\text{TcO}^3+ \) core

1.0 mg of MPBDA and 1.0 mg of \( \gamma \)-cyclodextrin are dissolved in 1.0 mL distilled water in a 10 mL vial. 0.1 mL of stannous chloride solution (formed by 1 mg of stannous chloride dihydrate in 1 mol \( \cdot \) L\(^{-1} \) hydrochloric acid solution) is injected into the vial continuously. Shaking the vial makes the mixture uniform. After adjusting pH of mixture to 3.2, 1.0 mL (74 MBq) of fresh sodium pertechnetate (Na\(^{99m}\text{TcO}_4\)) is added into the system. The mixture reacts at room temperature (about 20°C) for 15 min. Complex labeling yield is assayed by thin layer chromatography (TLC). The supporter is Xinhua No.1 chromatography strip and fluid is the mixture of methanol/chloroform (\( V/V = 1 : 9 \)). The chromatography separates \(^{99m}\text{TcO-MPBDA} (R_f = 0.9—1.0) \) from \(^{99m}\text{TcO-MPBDA-Br} (R_f = 0—0.1) \) and \(^{99m}\text{TcO}_2 \cdot n\text{H}_2\text{O} (R_f = 0—0.1) \).

If certain halide salt is added to concentration double to [Cl\(^-\)] before adding Na\(^{99m}\text{TcO}_4\), the complex prepared would be \(^{99m}\text{TcO-MPBDA-F}, \ ^{99m}\text{TcO-MPBDA-Br} \) or \(^{99m}\text{TcO-MPBDA-I} \).

Labeling methods of MPTDA and MPDAA resemble that of MPBDA.

1.3 Determination of partition coefficient \( P \)

0.1 mL solution of fresh \(^{99m}\text{Tc} \) complex (approx. 3.7 MBq) is put into a centrifugal tube, then add 1.9 mL phosphate buffer solution (PBS, 0.025 mol \( \cdot \) L\(^{-1} \), pH = 7.4) and 2.0 mL 1-octanol into it. The mixture is surged well at room temperature, then centrifuged at