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Labelling and stability of tri- and tetraaza macrocyclic complexes of ^{44}Sc

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Introduction

^{44}Sc ($t_{1/2}$=3.92h), is an ideal β^+ emitter for PET diagnosis. It can be produced by $^{44}Ca(p,n)^{44}Sc$ nuclear reaction in small cyclotrons or as a daughter of long lived ^{44}Ti ($t_{1/2}$=60,4y) from $^{44}Ti/^{44}Sc$ generator.

The goal of our work was to find the best ligands for attaching scandium radionuclides with biomolecules. Due to formation of thermodynamically stable and kinetically inert complexes the macrocyclic ligands were choosen: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), 1,4,7-triazacyclononane-1,4,7 triacetic acid (NOTA), 1,4,7-triazacyclodecane-1,4,7 triacetic acid, (10 ane) 1,4,8-triazacycloundecane triacetic 1,4,8 acid (11 ane) and 1,5,9-triazacyclododecane 1,5,9 triacetic acid (11 ane).

Experimental

DOTA was obtained from Macrocyclic Company, the other ligands were synthesized by reaction of triaza rings with bromoacetic acid. For reasons of availability we used in part of our experiments the ^{46}Sc ($T_{1/2}$=83.8 d) - carrier added nuclide instead of ^{44}Sc. Stability constants of scandium complexes were determined using HPLC method.

The charges of Sc complexes were determined by paper electrophoresis. The kinetics of Sc-DOTA and Sc-NOTA complexes were measured at pH=6.0. Complex formation was determined by instant thin layer chromatography method using ITLC-SG strips developed with the mobile phase: H_2O/NH_3 (25/1).

Results and Discussion

Sc^{3+} forms more stable complexes with DOTA ligand than Lu^{3+}. Also complexes of Sc with DOTA ($\log K_{Sc\text{-}DOTA}$= 27.5) are stronger by a few orders of magnitude than complexes with NOTA ($\log K_{Sc\text{-}NOTA}$=17.6) and 10 ane ($\log K_{Sc\text{-}10ane}$=14.8) ligands. The radiochemical yield of labeling (5.5 nmol of Sc^{3+} and 55 nmol of ligands) - for Sc-DOTA is about 99% and it is much higher than for the Sc-NOTA complex (80%).

The formation of the Sc-NOTA complex is faster than for Sc-DOTA complex. After 10 minutes the equilibrium for Sc-NOTA was reached, while for Sc-DOTA 30 minutes is needed for attaining equilibrium.

Sc-DOTA and Sc-NOTA complexes exhibit high stability in human serum at 37^0C. After 120 hours of incubation in the serum more than 97% of Sc-DOTA remains in solution. In 0,01M PBS buffer Sc-DOTA is stable but in the case of Sc-NOTA, Sc-10 ane, Sc-11ane and Sc-12 ane complexes phosphates exchange ligands in first coordination sphere.

It was found by HPLC method that Sc(DOTA) complex is more hydrophilic than Lu(DOTA) and Sc(NOTA), suggesting different coordination spheres in this complexes.

The lipophilicity studies of ^{46}Sc labelled octreotide indicate that ^{46}Sc-DOTATE has identical lipophilicity as ^{177}Lu-DOTA-TOC, while ^{68}Ga is more hydrophilic.

Conclusion

The presented results show that DOTA complexes of ^{44}Sc radionuclide are perspective precursors for PET radiopharmaceuticals.