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Comparative Study of ^{99m}Tc Labelled Somatostatin Analogs for Targeting the Somatostatin Receptor *in vivo*

A. Nikolopoulou[1], B. Nock[1], T. Maina[1], C. Tsipra[1], M. Poppe[1], H. Mäcke[2] and E. Chiotellis[1]

1. Institute of Radioisotopes-Radiodiagnostic Products, *Dimocritos*, Agia Paraskevi, Athens, Greece
2. Institute for Nuclear Medicine, University Hospital, Basel, Switzerland

A recent development in Oncology involves the use of metabolically stabilized peptide hormone analogs labeled with metallic radionuclides for the diagnosis or therapy of malignant disease. This approach was successfully applied for the first time in the visualization of somatostatin (SMS) positive tumors and their metastases with ^{111}In-DTPA-octreotide. In an effort to obtain a ^{99m}Tc SMS receptor affine radioligand we describe herein the synthesis, radiochemistry and preliminary biological evaluation of three novel ^{99m}Tc labeled SMS analogs, N_4-G-Tyr^3-octreotide, *1*, N_4-RC-160, *2*, and N_4-S-octreotide, *3*. In these compounds a tetramine bifunctional unit was covalently attached to the N-terminal (D)Phe^1 of the peptide chain using BOC-protection strategies. The peptide conjugates were purified by high performance liquid chromatography (HPLC) and characterized by UV/Vis and ES-MS spectroscopies. As revealed by HPLC, ^{99m}Tc labeling was quantitative under mild conditions, leading to a single ^{99m}Tc species in high specific activities. Affinity of ^{99m}Tc-*1* and ^{99m}Tc-*3* for the SMS receptor, as determined by in vitro binding assays in rat brain cortex membranes, was found unaffected by the presence of the bulky metal chelate. The binding properties of ^{99m}TC-*2* could not be determined by this assay due to an extremely high non-specific binding of this radioligand, a result of its increased lipophilicity. Tissue distribution in healthy mice revealed, that the two octreotide analogs, ^{99m}Tc-*1* and ^{99m}Tc-*3*, are washed out mainly through the kidneys and the urinary tract, whereas ^{99m}Tc-*2* shows a high accumulation in the liver due to its high lipophilicity. Analysis of urine samples by HPLC showed, that ^{99m}Tc-*1* is excreted integer from the body of mice, while ^{99m}Tc-*2* is totally transformed to an unidentified hydrophilic metabolite in vivo. In vivo blocking experiments using animals pretreated with 50 µg octreotide prior to injection of the radioligand demonstrated, that accumulation of the radioactivity in SMS binding sites in vivo (e.g. pancreas, adrenals), is specific.