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SYNTHESIS AND IN VITRO AND IN VIVO EVALUATION OF IODINE-124-LABELED PSMA PEPTIDES: POTENTIAL THERANOSTIC RADIOPHARMACEUTICALS FOR PROSTATE CANCER

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Receptor-targeted radiopharmaceuticals have shown promises in improvement of the specificity and sensitivity of nuclear medicine imaging and therapy procedures. The prostate specific membrane antigen (PSMA) is a transmembrane protein with significantly elevated expression in prostate cancer (PCa) cells compared to benign prostatic tissue. Several radiotracers have been used for molecular imaging of PCa including choline as a marker of membrane cell proliferation. However, there have been numerous studies reporting a low sensitivity and specificity of these radiotracers. Therefore, different gallium-68 and fluorine-18 PSMA-targeted PET tracers have been developed, utilized and demonstrated a high diagnostic efficacy. However, the short half-life of these radiotracers may limit distribution to distant imaging centers.

Thus, as part of our on-going research effort to develop theranostic radiopharmaceuticals, we here report the synthesis and preclinical evaluation of new 123/124/131I-PSMA conjugates. The synthetic approaches for the preparation of [123/124/131I]iodobenzene and pyridine rhodamine conjugates entailed sequence of reactions. The key precursors N-hydroxysuccinimide 3-tri-n-butylstannyl-benzoate and 3-tri-n-butylstannyl-pyridine carboxylate were radioiodinated using classical method involving 0.1% acetic acid/methanol, iodogen and NaI (123/124/131I, 50 MBq) at room temperature. The N-succinimidyl-p-[I]-iodobenzoate ([123/124/131I]-SIB) and N-succinimidyl-m-[I]-iodopyridine carboxylates ([123/124/131I]-SIP) were purified using Sep-pak silica cartridge. PSMA peptide was then reacted with [123/124/131I]-SIB and [123/124/131I]-SIP, then purified using C18 Sep-pak cartridge to furnish [123/124/13I]-SIB- and [123/124/131I]-SIP-PSMA peptide conjugates. Radiochemical yields were >75% and synthesis times were ˜45 min. Radiochemical purity was always >99% without HPLC purification. The metabolic stability of [123/124/131I]-SIB- and [123/124/131I]-SIP-PSMA peptide conjugates were determined in human plasma and revealed that these radioconjugates remained stable during incubation at 37oC for at least 24 h. In vitro tests on LNCaP cell line has shown that the significant amount of the radioconjugate associated with cell fractions. In vivo characterization in normal Balb/c mice revealed rapid blood clearance of these radioconjugates with excretion predominantly by the renal system. Initial in vivo biological characterizations in nude mice bearing LNCaP cell line xenografts, demonstrated significant tumor uptake. The uptake in the tumors was blocked by excess injection of PSMA peptide, suggesting a receptor-mediated process. These results demonstrate that these radioconjugates may be useful as precise theranostic radiopharmaceuticals for PSMA receptor-positive cancers and their metastasis. However, further evaluation is warranted.

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