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Development, characterisation and in vivo evaluation of two 68Ga-labelled NPY analogues as potential tracers for breast cancer imaging.

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Introduction: Receptor targeting with radiolabelled peptides has gained attention in Nuclear Medicine since these are over-expressed in many proliferative processes. In particular, researchers found that Neuropeptide Y (NPY) type 1 receptor is over- expressed in 90% of breast carcinomas.
Objective: The aim of the present study was to develop and characterise two 68Ga-labelled NPY analogues with potential application in breast cancer imaging. Two peptides were used (L1, L2), both having the active sequence (Tyr-Arg-Leu-Arg-BPA-Nle-Pro-Asn-Ile-OH), NOTA as a chelator and a molecule of lysine as a spacer.
The amino acid sequences of both peptides are identical but L2 has an acetyl group (–COCH3) in the amino residue of the spacer (L1: H-Lys(NOTA)-Tyr-Arg-Leu-Arg-BPA-Nle-Pro-Asn-Ile-OH) (L2: Ac-Lys(NOTA)-Tyr-Arg-Leu-Arg-BPA-Nle-Pro-Asn-Ile-OH).
Methodology: Each peptide (100 µg, 5.85x10-5 mmol) was incubated with [68 Ga]GaCl3 (60-100MBq, 0.2 mL), at pH 4.5 and 95ºC for 10 minutes. Physicochemical characterisation included: radiochemical purity (RCP) assessed by RP-HPLC, lipophilicity (through partition coefficient between octanol and phosphate buffer pH 7.4), plasmatic protein binding (PPB) by size exclusion. Stability in plasma and in labelling milieu was assessed up to 2 hours. Challenge with 100 molar excess of diethylenetriaminepentacetic acid (DTPA) was performed by HPLC. Biological behaviour was evaluated in accordance to University Ethics Committee regulations, in female nude mice bearing MCF7 cancer xenograft induced with 1x106 cells injected subcutaneously into the right hind leg. Tumour was allowed to grow 4 weeks up to an average mass of (0.07+0.02)g. Biodistribution was determined one hour post injection of each tracer.
Results: Both complexes were obtained with RCP higher than 95% and were stable in plasma and in reaction milieu. Log P values were (68Ga-L1=- 3.2+0.1) and (68Ga-L2 =-2.6+0.1). Protein binding values were (31.7+0.4)% for 68Ga-L1 and (20.1+0.3)% for 68Ga-L2. Challenge with DTPA, in both cases showed high stability and no trans-chelation of the gallium for up to 2 hours.
Both complexes showed low blood and muscle uptake and high renal excretion., 68Ga-L2 higher uptake in liver and kidneys compared to 68Ga-L1 . The target/non target ratio expressed as % of injected dose/gram) was (3.5+0.4)% for 68Ga-L1 and (4.7+0.4)% for 68Ga-L2.
Conclusions: Labelling strategy was adequate for obtaining both complexes with high RCP and remarkable in vivo stability. Even though both complexes showed similar behaviour, 68Ga-L2 was less hydrophilic and had lower PPB value compared with 68Ga-L1, probably due to the addition of the acetyl group to the amino group of the spacer. Biodistribution studies showed that renal elimination is the main route of excretion in both cases. Although tumour uptake is moderate favourable T/nT ratio encourages performing further studies in cell lines in order to conclude about the potentiality of both tracers as promising radiopharmaceutical for breast cancer imaging.

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