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Comparison of different chelating systems for the synthesis of Ga-68 labelled peptides for molecular imaging using RGD-peptides as model compound

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Introduction: Due to its increasing availability Ga-68 attracts increasing interest in molecular imaging with PET. Moreover, due to the straightforward labelling protocols especially for labelling of peptides this is an interesting alternative to F-18 labelling strategies. Here the imaging properties of c(RGDfK) conjugated to different chelating systems are compared.

Methods: Peptides were synthesised using standard SPPS protocols. After cyclisation in solution and selective deprotection of the amino function of the lysine the chelating moieties were conjugated via in situ activation. The chelating systems include 1,4,7,10-tetraazacyclododecane-1,4,7,10-acetic acid (DOTA), a 1,4,7–triaaza-10-oxocyclododecane-1,4,7-acetic acid derivative (B505), 1,4,7-triaazacyclononane-4,7-acetic acid-1-2-glutaric acid (NODAGA), and a tris(2-mercaptoethyl) amine derivative (NS3). Labelling was carried out using the fractionated elution method in sodium acetate or phosphate buffer, respectively. In vitro evaluation included determination of the partition coefficient, protein binding properties, metabolic stability, binding affinity, and cell uptake characteristics. *In vivo* evaluation was carried out using nude mice bearing alpha(v)beta3-positive and alpha(v)beta3–negative tumours. For all tracer biodistribution data were collected. For the most promising also small animal PET imaging was carried out.

Results: All peptides could be labelled with Ga-68 in good radiochemical yields. Labelling of NODAGA-RGD could be achieved even at room temperature. Whereas labelling of NS3-RGD has to be followed by Seppak separation to obtain the product in high radiochemical purity. The compounds showed comparable partition coefficients, binding affinity for the alpha(v)beta3 integrin as well as receptor specific uptake. However, great differences were found in the protein binding properties. Out of the four peptides tested only NODAGA-RGD showed low protein binding. This is also reflected in the biodistribution data. Lowest activity concentration in blood and best tumour/background ratios were found for NODAGA-RGD. Subsequent small animal imaging showed best imaging properties for NODAGA-RGD, which seems to be comparable with F-18-Galacto-RGD.

Conclusions: In this series NODAGA-RGD revealed most promising properties for molecular imaging applications. Easy radiolabelling at room temperature, low amount of protein bound activity and the resulting lower activity concentration found in blood compared to the other compounds makes it to an interesting alternative to F-18-Galacto-RGD for imaging alpha(v)beta3 expression. However, the general advantage of NOTA derivatives for imaging purposes have to be confirmed by additional studies using other peptide structures.