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PET and SPECT-labelling of peptides

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During the last decade, radiolabelled peptides have emerged as an important class of radiopharmaceuti-}

cals for diagnosis and therapy. New insights in the molecular biology of cancer have resulted in the}

discovery of a number of receptor systems that can be utilized as molecular targets for peptide based}

genes. Peptides have many key properties including high target specificity and affinity, rapid tissue}

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penetration, fast clearance, and low immunogenicity making them very interesting for tracer develop-

ment. Most prominent members yet, are radiolabelled somatostatin derivatives which are already used}

for diagnosis and therapy of neuroendocrine tumours. But also for a variety of other target structures}

radiolabelled peptides are currently studied (1). This includes cholecystokinin/gastrin and GLP-1 ana-

logues for neuroendocrine tumours, bombesin and neuropeptide-Y derivatives for prostate or breast}

cancers, and RGD-containing peptides for imaging angiogenesis.

There are a great variety of labelling strategies available. Due to the larger size of peptides compared}

with small molecular weight ligands (e.g. amino acids, FLT, choline) chelating systems can normally be}

introduced without effecting the binding properties. This enables labelling not only with halogens but}

also with a great variety of radionuclides. Thus, most commonly used isotopes are F-18, Ga-68, and Cu-64}

for PET and In-111 and Tc-99m for SPECT (2). Radioiodine isotopes which can easily be introduced if}

thyroglobulin is found in the sequence or by using the Bolton-Hunter reagent are mainly used for first eva-

luation of new tracer concepts but are, due to low metabolic stability of the iodine bond, not often used}

as labelling strategy for tracers in clinical settings.

A variety of F-18-labelled peptides are described. Almost all labelling is carried out via prosthetic groups}

(3). Most well known is succinimidyl 4-[F-18]fluorobenzoate. Another is 4-nitrophenyl-2-[F-18]fluoro-

propionate. All these react with amino functions within the peptide sequence. However, synthesis of}

these activated ester is complex and time consuming, generally involving HPLC for isolation of the F-18-

labelled prosthetic group. Thus, other strategies are currently evaluated. This include amino-oxy func-

tionalized peptides for labelling with aldehydes [e.g. 4-[F-18]fluorobenzaldehyde], thiol-reactive groups}

as well as Cu-catalysed 1,3 cycloaddition of azides and alkynes (click chemistry). It has been shown that}

introduction of carbohydrates may improve pharmacokinetics. Most recently, approaches are discussed}

which use [F-18]FDG as precursor for prosthetic groups, allowing introduction of the radioactive label}

and the carbohydrate in one step (4).

For labelling of peptides with radiometals usually chelating systems are conjugated with the peptide}

(5). One of the most prominent members is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid}

(DOTA), which is used with different peptides and for complexing a variety of isotopes including Ga-68,}

Cu-64 and In-111. Despite the good tracer properties of [Ga-68]DOTA-TOC, DOTA is not the optimal}

chelating system for Ga-68. Due to the smaller ion radii compared to In-111 Ga-68 would better fit in}

9-membered ring systems as found in 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) derivatives.

It seems to have no effect on DOTA-TOC stability, but studies with other peptides (e.g. RGD-peptides)

showed a negative effect on tracer properties compared with corresponding In-111 labelled analogues}

(6). Similar results are found for Cu-64 labelled DOTA-peptides. The use of alternative chelating systems}

is studied to improve Cu-64 complex stability.

Tc-99m labelling of peptides can be carried out via a variety of different chelating systems (7). Good}

results concerning stability and also pharmacokinetics are found for HYNIC-derivatives. An advantage}

of this chelator is that pharmacokinetics can be modified/optimized by using the appropriate co-ligand}

(e.g. EDDA). Other strategies use Tc-99m-carbonyl approaches, Tc-99m-nitrido-cores or N3S-ligands for}

labelling. The “click-to-chelate” approach was introduced to form triazole containing ligands for the Tc-

99m-carbonyl approaches (8). This is an interesting alternative to other methods for the incorporation of}

metal chelating systems into biomolecules, as the reactions are almost quantitative and do not require}

protecting group chemistry.
References