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Peptides and radionuclides for imaging and therapy of NET: current status and future developments

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Introduction: Radiolabeled peptides for the imaging and targeted radionuclide therapy of neuroendocrine tumours have been successfully developed and were shown to be valuable in nuclear oncology in the last 1-2 decades. Several G-protein coupled receptors were shown to be overexpressed on neuroendocrine tumours, most importantly the somatostatin receptors, but also the CCK2 (cholecystokinin) receptor and the GLP-1 (Glucagon-like-peptide 1) receptor. There are two registered radiopeptides, ^{111}In-DTPA-octreotide (OctreoScan) and ^{99m}Tc-Neo-Tect; the latter being registered for the assessment of solitary pulmonary nodules. Both compounds have drawbacks with regard to receptor binding affinity and/or pharmacokinetics as well as price(^{111}In) and, nuclear physical properties.

New developments: Partially because of the above mentioned drawbacks, new conjugates for labelling with ^{99m}Tc, ^{67}Ga, ^{111}In and ^{123}I for SPECT and planar imaging; ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{86}Y and ^{124}I for PET and 90Y, 177Lu, 213Bi for targeted radiotherapy were developed. For this purpose new chelator-somatostatin analogues were developed which specifically bind the radiometals and chemical ligation methods were designed for the specific binding of the respective radiohalogens. For ^{99}mTc, still one of the working horses in nuclear medicine, especially two strategies were followed: 1) The HYNIC (2-hydrozinonicotinic acid) approach. This ^{99}mTc-chelator was coupled to [Tyr^3]octreotide (TOC) and [Tyr3,Thr8]octreotide (TATE). Kit formulations with EDDA and/or tricine as coligands were developed and both radioligands showed remarkable clinical results. 2) Similar image quality and pharmacokinetics were obtained with a bifunctional tetraamine chelator coupled to TOC and TATE.

DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) was proposed as 'universal' chelator for a multitude of radiometals, most importantly the therapeutic radiometals ^{90}Y, ^{177}Lu and ^{213}Bi but also radiogallium and ^{64}Cu. The development of DOTA-TOC and DOTA-TATE allowed the stable labelling with ^{90}Y and ^{177}Lu and a multitude of clinical studies which showed very promising therapeutic results. Another success story is the use of ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-NOC (NOC = [1-Nal^3]octreotide, a sst2, 3 and 5 binding peptide) potentially allowing to target a broader spectrum of tumours. Gallium-68 is a generator-produced metallic positron emitter with a long lived mother nuclide ^{68}Ge (T1/2 = 271 d). Additional parallel synthetic methods, modifying the peptide sequence helped to further develop somatostatin based peptides with a broader affinity profile or even pan-somatostatin character.

Cholecystokinin 2 receptors (CCK2) have been shown to be overexpressed on some neuroendocrine tumours, on small cell lung cancer and particularly on medullary thyroid cancer. A variety of gastrin- and CCK-related peptides were developed and investigated preclinically and clinically. They were coupled with stabilized derivatives of DTPA (diethylenetriaminepentaacetic acid) and labelled with ^{111}In for imaging and ^{90}Y for therapy. In addition gastrin derivatives were modified again with HYNIC and tetraamines for ^{99m}Tc-labeling and used successfully in clinical studies.

An interesting new development is the targeting of the GLP-1 receptor which is overexpressed in insulinoma and gastrinoma. Peptides based on Exendin-4 and GLP-1 were radiolabeled and studied in animal models.

Future developments: A new and exciting development was recently reported for peptides targeting the somatostatin receptors 2 and 3. It was shown that somewhat unexpected receptor antagonists show a distinctly higher tumour uptake in vitro and in vivo when compared with agonists. This appears to be a change in paradigm as it was common sense that agonists along with their receptor triggering internalisation are needed for efficient and persisting tumour targeting.

References

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