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

H. Maecke (Basel)

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, 111In-DTPA-octreotide (OctreoScan) and 99mTc-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(111In) and, nuclear physical properties.

New developments: Partially because of the above mentioned drawbacks, new conjugates for labelling with 99mTc, 67Ga, 111In and 123I for SPECT and planar imaging; 18F, 11C, 68Ga, 64Cu, 86Y and 124I 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 99mTc, still one of the working horses in nuclear medicine, especially two strategies were followed: 1) The HYNIC (2-hydrozinonicotinic acid) approach. This 99mTc-chelator was coupled to [Tyr3]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 radionuclides, most importantly the therapeutic radiometals 90Y, 177Lu and 211Bi but also radiogallium and 64Cu. The development of DOTA-TOC and DOTA-TATE allowed the stable labelling with 90Y and 177Lu and a multitude of clinical studies which showed very promising therapeutic results. Another success story is the use of 68Ga-DOTA-TOC and 68Ga-DOTA-NOC (NOC = [1-Nal3]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 68Ge (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 111In for imaging and 90Y for therapy. In addition gastrin derivatives were modified again with HYNIC and tetraamines for 99mTc-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