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EDITORIAL COMMENTARY

^{18}F-Labelled exendin to image GLP-1 receptor-expressing tissues: from niche to blockbuster?

Otto C. Boerman · Martin Gotthardt

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Since the discovery of radiolabelled octreotide and the successful introduction into clinical practice of Octreoscan®, it has been expected that radiolabelled peptides would become a new class of radiopharmaceuticals for cancer imaging. Indeed, a series of receptor binding peptide analogues, such as cholecystokinin (CCK)/gastrin, bombesin, vasoactive intestinal protein, neurotensin and others, has been tested for imaging receptor-expressing tumours in animal models. However, clearly their introduction into clinical practice is still awaited. In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Kiesewetter et al. describe the feasibility of imaging insulinoma with ^{18}F-labelled exendin [5], which could be considered as a major step forward in the development of another peptide-based tracer for tumour imaging. Exendin was tested more than a decade ago for the first time to image tumours expressing the glucagon-like peptide (GLP-1) receptor on their cell surface [4]. Exendin is a 39-amino acid peptide found in the saliva of the Gila monster, which binds to the incretin hormone receptor, GLP-1R. This receptor is expressed generally in low amounts in specific tissue compartments of several organs, such as pancreas, intestine, lung, kidney, breast and brain [7]. The endogenous ligands of the GLP-1R, GLP-1 and gastric inhibitory peptide are rapidly degraded by the enzyme dipeptidyl peptidase IV [8]. Therefore, the GLP-1 analogue exendin was proposed for targeting GLP-1R-expressing tumours. Among others, the GLP-1R is especially expressed in insulinomas, particularly the more common benign tumours [7]. Although insulinomas are a rare tumour type with an incidence estimated at one to four new cases per million people per year, the clinical relevance of insulinoma imaging lies in the exact preoperative localization of the tumours. This could help the surgeon in planning accurate resection, thus potentially reducing surgical complications [9].

In Rip1Tag2 mice that spontaneously develop GLP-1R-expressing insulinomas, Wicki et al. [11] have shown that ^{111}In-labelled exendin-4 extremely efficiently targeted the insulinoma lesions: uptake in the lesions exceeded 200%ID/g. Despite the high intrinsic kidney uptake of the tracer (190%ID/g), they showed that high doses of ^{111}In-exendin-4 (28 MBq/mouse) inhibited the growth of the lesions. More importantly, the same group showed that ^{111}In-exendin-4 accurately visualized the localization of insulinomas in patients [12]. Exendin-4 was also labelled with ^{99m}Tc by C-terminally conjugating HYNIC [13], which could make the peptide even more attractive for imaging insulinoma with single photon emission computed tomography (SPECT) in patients.

The new challenge is to develop an exendin-based positron emission tomography (PET) tracer for insulinoma imaging, which would allow more accurate determination of the localization and extent of the insulinoma. DOTA-conjugated exendin-3 could be labelled with high efficiency with ^{68}Ga and the in vivo characteristics of this tracer were determined by microPET imaging of nude mice with s.c. GLP-1R-expressing INS xenografts [2]. For PET imaging of insulinomas an ^{18}F-labelled tracer would have additional advantages over a tracer labelled with ^{68}Ga: (1) the option to acquire images beyond 2 h post-injection due the longer

O. C. Boerman (✉) · M. Gotthardt
Department of Nuclear Medicine – 756,
Radboud University Nijmegen Medical Centre,
PO Box 9101, 6500 HB Nijmegen, The Netherlands
e-mail: o.boerman@nucmed.umcn.nl

half-life of ^{18}F and (2) higher resolution of the images due to the lower positron energy. However, the development of an ^{18}F-labelled version of exendin is a challenge, particularly because a tracer with a high specific activity is required. In mice with s.c. INS tumours it has been shown that optimal tracer uptake in the GLP-1R-expressing tumours could only be obtained at a peptide dose of 22 pmol (=0.1 μg) or lower per mouse, indicating that for microPET a specific activity of 200 GBq/μmol would be required for imaging at the optimal peptide dose. In the study presented in the present issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Kiesewetter et al. [5] succeeded in producing a tracer that met this requirement. They elegantly exploited the very efficient reaction between a maleimide and a thiol group, by reacting the ^{18}F-labelled FBEM with [Cys40]-exendin-4 with a 35% yield. Using this synthetic route ^{18}F-labelled exendin-4 could be produced with a specific activity of 45 GBq/μmol. The tracer was stable in blood and had a high affinity for the GLP-1R (IC_{50}=1.2± 0.1 nmol). Upon i.v. injection in nude mice, the tracer accumulated rapidly in the GLP-1R-expressing s.c. insulinoma xenografts (7.2%ID/g), whereas uptake in GLP-1R-negative tumours was tenfold lower. The tracer could be synthesized within 1 h, opening the way for PET imaging of insulinoma in patients.

Potentially this tracer could be applied much more widely, as the GLP-1R is also expressed on the insulin-producing beta cells in the pancreas. Recently, it was shown that radiolabelled exendin could also be used to monitor the survival of transplanted beta cells [1, 9]. Beta cell transplantation currently is an experimental therapy for patients with type I diabetes. However, survival of the transplant is limited because of immunological rejections as well as metabolic stress factors following transplantation. ^{18}F-Exendin could potentially be used to longitudinally monitor the viability of transplanted beta cells. In addition, the tracer could be used to determine the beta cell mass in the pancreas. In type 1 diabetes, autoimmune destruction of pancreatic beta cells leads to an absolute deficiency of insulin secretion with hyperglycaemia as a consequence. It has been shown that there is a reserve capacity of beta cells and that type 1 diabetes only becomes clinically apparent when the beta cell mass drops under a critical threshold (< 30%) [6, 10]. The beta cell mass also changes during the development and course of type 2 diabetes [3]. If ^{18}F-exendin could be used to quantitatively determine the pancreatic beta cell mass in vivo, this would allow studies that give further insight into the pathogenesis and development of type 1 and 2 diabetes. If clinical studies will show that the beta cell mass could be accurately quantitatively determined with PET with ^{18}F-exendin in patients developing diabetes, after radiolabelled octreotide, ^{18}F-labelled exendin might be the second peptide-based tracer that could be applied widely in the clinical setting.

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