

Functional imaging of neuroendocrine tumours with PET

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Abstract Several pathophysiological attributes of neuroendocrine tumours (NET) can be addressed by specific radiolabelled probes. This paper provides an overview on the different radiopharmaceuticals that have been developed for Positron Emission Tomography (PET) of neuroendocrine tumours. A review of the literature on 18F-fluorodeoxyglucose (FDG), biogenic amine precursors, somatostatin analogues and hormone syntheses markers is presented. Due to the highly specific tracers that lack any clear anatomical landmarking the advantages of integrated PET/CT are obvious. Amine precursors should be employed in most gastroenteropancreatic NET, FDG should be preserved for more aggressive, less differentiated NETs. Somatostatin analogues are the most promising tracers, since they can improve dosimetry in cases in which radiopeptide therapies are planned. In conclusion, the individual diagnostic approach using PET or the integrated PET/CT should be tailored depending on the histological classification and the differentiation of the tumour.

Keywords Molecular imaging · PET · Neuroendocrine tumour

Introduction

Neuroendocrine tumours are a heterogeneous group of tumours that derive from endocrine cells. These cells have in common that they contain secretory granules and have the capacity to produce biogenic amines and polypeptides [1].

The neuroendocrine cells have the ability to take up and decarboxylate amine precursors such as dihydroxyphenylalanine (DOPA) and hydroxytryptophane and were classified as APUD (amine precursor uptake and decarboxylation) cells. Tumours deriving from these cells were consequently called APUDomas [2]. It was shown that the aromatic amino decarboxylase is upregulated in medullary thyroid cancer and other neuroendocrine tumours [3]. Furthermore, there is evidence that DOPA can temporarily inhibit the endocrine hormone release [4].

Like other tumours neuroendocrine tumours express several different peptide receptors in high quantities [5]. The most investigated peptide receptors are the somatostatin receptors (SSR). SSR are transmembranously segmented heptahelical G-protein coupled glycoprotein receptors [6]. Up to now there are five subtypes cloned, subtype two is divided in two slightly different types that differ in the spliced C-terminals [7]. All subtypes are functionally coupled with an inhibition of the adenylate cyclase [8]. Another commonality is the activation of a phosphotyrosine kinase and a modulation of the mitogen activating protein kinase (MAPK) via a G-protein coupled mechanism [9]. Like all G-protein coupled receptors, the activated SSR is internalized to reach a resensibilisation of the phosphorylated receptor [10].

Since the anatomical origin of the neuroendocrine tumours seemed to influence the way they metastasised and their clinical appearance these tumours were first divided into foregut, midgut and hindgut tumours [11]. This classification was abandoned lately [12] and replaced by a classification that mainly takes into account the size of the tumour and the proliferation rate. There are three classes: Type 1a are well-differentiated neuroendocrine tumours (Ki 67 < 2%), type 1b are well-differentiated neuroendocrine carcinomas (Ki67 2–10%), and type 2 are poorly differentiated neuroendocrine carcinomas.

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A major difference of neuroendocrine tumours and carcinomas (NET) with respect to most other tumours is that they can have a pronounced clinical effect despite the small size of the tumour due to the storage and release of hormones. Therefore conventional anatomic imaging can fail to visualize the primary tumour or its metastases and most importantly cannot depict their specific endocrine features. Gastroenteropancreatic NET, bronchial carcinoids, medullary thyroid carcinomas and pheochromocytomas and paragangliomas belong to this group of tumours. Functional and molecular imaging probes for these tumours have been developed over the past decade [13]. The focus of this review will be on the data that has been gathered with positron emission tomography (PET).

Basically there are at least four different radiopharmaceutical classes that address the different metabolic pathways or molecular properties of these tumours. First the most commonly used PET agent, the glucose derivate [¹⁸F]-fluorodeoxyglucose (FDG), secondly the biogenic amine precursors such as [¹¹C]-hydroxytryptophan (HTP), [¹¹C]-, [¹⁸F]-dihydroxyphenylalanine (DOPA) or [¹⁸F]-fluorodopamine (dopamine). Recently the [⁶⁸Ga] labelled somatostatin analogs have gained a significant importance since they improved the diagnostic approach of somatostatin receptor scintigraphy [14] due to the higher intrinsic resolution and higher sensitivity of PET. Also the synthesis, storage, and release of hormones was addressed, employing mostly [¹¹C]-hydroxyephedrine (HE) or the enzyme inhibiting substrate [¹¹C]-metomidate. Metomidate is a potent inhibitor of 11 β -hydroxylase, a key enzyme in the synthesis of cortisol and aldosterone in the adrenal cortex [15].

FDG

FDG is the most common tumour imaging agent in PET. It is taken up via a glucose transporter (Glut-1) and phosphorylated [16]. Due to the presence of the fluorine atom in the C-2 position, 5-fluoro-2-deoxyglucose does not undergo further glycolysis but is metabolically trapped in the cell. Several studies have investigated its usefulness in different NET [17–23].

Most pheochromocytomas accumulate FDG. However, uptake is found in a greater percentage of malignant than benign pheochromocytomas. In a comparative study on 21 consecutive patients [17] it was concluded that FDG PET is especially useful in defining the distribution of those pheochromocytomas that fail to accumulate metaiodobenzylguanidine (MIBG).

In one study FDG-PET was directly compared to somatostatin receptor scintigraphy (SRS). In the few patients that were studied, PET imaging of gastroenteropancreatic neuroendocrine tumours (GEP-NET) revealed increased glu-

cose metabolism only in less-differentiated GEP tumours with high proliferative activity and metastasising medullary thyroid carcinomas (MTC) associated with rapidly increasing CEA levels. The authors conclude that additional FDG PET should be performed only if SRS is negative and that it might be reasonable to include it as a diagnostic tool in those patients with poorly differentiated NET [18, 19].

Another group found comparable results [20]. In a comparative study it was concluded that FDG PET seemed to be useful to identify those NETs characterized by rapid growth or aggressive behaviour. The authors speculate that FDG uptake by the tumour may be related to a worse prognosis. Furthermore, FDG-PET contributed to better staging of advanced disease.

In a series of carcinoid tumours ($n = 17$) SRS and FDG PET findings were correlated to Ki-67 expression [21]. Most tumours were typical carcinoids with low Ki-67 expression and there was no correlation between the histological features and FDG uptake. The authors concluded that FDG PET should be reserved to patients with negative results on SRS [21].

In a multicenter study on MTC, conventional radiological and nuclear medicine diagnostic procedures were compared to FDG PET [22]. In the studied patients FDG PET showed the highest lesion detection probability for MTC tissue, with a high sensitivity and specificity, and therefore it was concluded that FDG PET is a useful method in the staging and follow-up of MTC [22]. Another group presented comparable results in a unicenter trial [23].

In conclusion, FDG seems to be reasonable in fast-growing NET with rather higher growth fraction as expressed with Ki-67 immunostaining that are poorly differentiated. In most well-differentiated tumours and carcinomas STS or MIBG scintigraphy seem to be superior.

Amine precursors

Since NET derive from the APUD system [2] it seemed logical to develop radiolabelled amine precursors for PET imaging. Labelling of HPT as well as DOPA was first done for neuroimaging studies [24, 25]. Furthermore, one group evaluated ¹⁸F labelled dopamine in paragangliomas [26].

One of the first studies demonstrated uptake of HTP in serotonin producing carcinoids [27]. The same group demonstrated that during treatment with somatostatin analogs the uptake of the precursor can be altered, showing a close correlation between the changes in HTP transport rate and urine hydroxyindolaminoacid (U-HIAA) during treatment [28]. This indicated the potential of HTP PET to monitor therapy. In a further study the specific uptake, decarboxylation and storage in the intracellular vesicles was shown [29]. Inhibiting the peripheral decarboxylation can enhance

tumour accumulation of HTP [30]. The group demonstrated that the decarboxylase inhibitor carbidopa, given as per oral premedication, decreased the renal excretion 6-fold and at the same time increased the tumour uptake 3-fold, hence improving the visualization of the tumours [31]. It was shown in a series of 42 patients that HTP PET is sensitive in imaging small NET lesions, such as primary tumours, and can in a majority of cases image significantly more tumour lesions than SRS and CT [32].

In several other studies the amine precursor DOPA, either labelled with ^{11}C or ^{18}F was used. A selective position labelling of DOPA demonstrated that significant decarboxylation occurred in an endocrine pancreatic tumour [33]. Interestingly, an increased retention of radioactivity occurred after treatment with somatostatin analogs. The authors hypothesized that this is a reflection of a reduction of exocytosis which is induced by this treatment [33]. Several NET tumour entities were investigated using DOPA [34–37]. DOPA PET was superior to FDG PET, STS and conventional diagnostic imaging procedures in gastrointestinal carcinoid tumours [34] and in MTC patients with elevated calcitonin levels [35]. DOPA PET was highly sensitive and specific for detection of pheochromocytomas and superior to MIBG scintigraphy [36]. The same was shown for glomus tumours, another variant of paragangliomas [37].

Dopamine PET was found to be a superior imaging modality with regard to MIBG scintigraphy in patients with metastatic pheochromocytoma; most of the visualized lesions were also seen on CT or MRI, but the specificity was higher in dopamine PET [38].

Taken together, biogenic amine precursors are superior to FDG. They address a neuroendocrine specific metabolic pathway that seems to be superior to SRS. It might be reasonable to include amine precursor PET into the diagnostic workup. However a direct and technically adequate comparison between STS PET and HPT or DOPA PET has not been published up to now.

Somatostatin analogues

The somatostatin receptors that are expressed in large quantities in most neuroendocrine tumours were the first peptide receptors that were addressed for in vivo targeting of human cancers [39]. Beside the diagnostic impact of the in vivo receptor scintigraphy for the localization of tumours and their metastases, there is also a therapeutic impact of radiolabelled somatostatin analogues that has been shown in some clinical trials in somatostatin receptor positive tumours [40]. In order to improve the in vivo molecular imaging of STS positive tumours, several radiolabelled somatostatin analogs for PET imaging have been introduced [41–54].

One of the first presented PET compounds was a derivative of octreotide labelled with ^{68}Ga [55]. In other studies, fluorinated as well as ^{86}Y labelled somatostatin analogues were investigated in animal models [41–43]. One group focused on ^{64}Cu labelled compounds [44–46]. Another group developed a fluorinated compound that was also explored in patients with metastasised neuroendocrine tumours [48, 49]. However, most clinical applications have used ^{68}Ga labelled DOTATOC [47, 50–52]. In a recent study the role of DOTATOC PET for target definition for fractionated stereotactic radiotherapy of intracranial meningiomas was evaluated [53]. In all 26 patients the authors could demonstrate that DOTATOC PET delivered additional information concerning tumour extension. In one patient only PET could delineate the exact tumour localisation [53]. A promising somatostatin analogue with higher affinity to the receptor subtypes two and five was recently presented [54]. Clinical data and comparative studies are lacking, however, since small cell lung cancer expresses subtype five more often; this analogue is potentially of high clinical potential.

Directly comparing the conventional octreotide planar or SPECT scintigraphy with DOTATOC PET, the latter seems to be superior in detecting small tumours or tumours expressing somatostatin receptors only in a low density. DOTATOC PET offers excellent imaging properties and very high tumour to background ratios [51].

In our own experience, the sensitivity of the integrated DOTATOC PET/CT outperforms that of DOTATOC PET due to two factors: first, the high resolution of multidetector CT images allows to identify also very small lesions that might be overseen with PET alone, and second, the improved CT based attenuation correction of the PET images improves the intrinsic resolution.

Hormone syntheses

So far mainly the specific hormonal synthesis of adrenocortical tumours, as well as pheochromocytomas, was addressed. HE is a radiotracer that concentrates in adrenergic nerve terminals, and therefore beside its application in cardiac nuclear imaging, it was evaluated in pheochromocytomas [56]. In a series of patients it was demonstrated that HE has a high sensitivity and specificity in pheochromocytomas [57]. This finding was confirmed by another study that demonstrated a higher sensitivity and specificity with regard to MIBG scintigraphy [58].

The enzyme inhibiting radiotracer [^{11}C]-metomidate was first tested in non-human primates [15] and later validated in patients with adrenocortical tumours [59]. It was shown that this tracer has the potential to differentially characterize adrenal masses with the ability to discriminate lesions

of adrenal cortical origin from noncortical lesions [59]. In a series of patients with adrenal masses FDG PET was compared to metomidate PET. The authors concluded that metomidate is superior in identifying incidentalomas of adrenocortical origin, whereas FDG should be reserved for patients with a moderate to high likelihood of neoplastic disease [60]. The largest population investigated so far ($n = 212$) correlated the PET findings with the histopathological findings in 73 patients. A sensitivity of 89% and specificity of 96% for metomidate PET in proving adrenocortical origin of the lesions was found, whereas pheochromocytomas, metastases to the adrenal gland, and nonadrenal masses were all metomidate negative [61].

Metomidate PET is a highly selective and potentially promising approach of adrenocortical tumours that has been introduced in only few PET centres up to now.

Conclusion

Since the introduction of combined PET and computed tomography (CT), or PET/CT, this integrated approach has been one of the fastest growing diagnostic tests [62]. The lack of anatomic landmarks on PET images, when highly specific tracers such as biogenic amines, somatostatin analogues or hormone synthesis markers are used, makes a consistent fusion to cross-sectional anatomic data extremely helpful. In several FDG PET studies it was shown that addition of CT to PET improves specificity foremost, but also sensitivity, and the addition of PET to CT adds sensitivity and specificity in tumour imaging [63]. PET/CT is more accurate than either of its individual components. So far no prospective trials on PET/CT in NET have been published, therefore this review focused on the available PET literature. Despite the fact that in general NET have a rather good prognosis, in almost all cases surgery is the only curative approach. Therefore an exact tumour delineation in cases with elevated tumour markers is warranted.

FDG PET/CT should be saved for poorly differentiated NET. Biogenic amine precursors like HTP or DOPA showed the best performance of all specific imaging probes in NET.

DOPA or dopamine PET/CT should be used in pheochromocytoma since the exact diagnosis is critical since patients may be cured completely by surgery.

Especially in MTC, DOPA PET/CT is a promising approach, since also small lesions of few mm could be detected.

In cases in which a specific therapy with somatostatin analogues is planned, DOTATOC or possibly DOTANOC PET/CT will provide superior information with regard to conventional octreotide scintigraphy. The development of other new somatostatin analogues with a broader spectrum of receptor affinity [64] will potentially further enhance this approach. Additionally the tomographic data of PET could

be used to improve dosimetry for [^{90}Y] or [^{177}Lu] DOTATOC radiolabeled peptide therapies [65].

The broad spectrum of NET requires tailoring of the individual diagnostic approach using PET or the integrated PET/CT, depending on the histological classification and the differentiation of the tumour.

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