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Vesa Oikonen

NET and [^{18}F]FDOPA PET: Literature review

Somatostatin receptor scintigraphy (SNS) with ^{111}In-labelled somatostatin receptor analog is a standard procedure for the detection and staging of neuroendocrine tumors (NETs, APUDomas). NETs can be small and situated almost throughout the body. This heterogeneous group of tumors take up amino acids, transform them into biogenic amines (dopamine and serotonin) by decarboxylation, and store the amines in vesicles; this is the so-called APUD (amino precursor uptake and decarboxylation) concept. L-Dihydroxyphenylalanine (L-DOPA) is a precursor of catecholamines (dopamine, noradrenalin and adrenalin). Its conversion to dopamine is catalysed by the aromatic amino acid decarboxylase (AADC).

Pancreatic islet cells take up L-DOPA where AADC converts it to dopamine (Borelli et al. 1997). Ahlström et al. (1995) were the first to visualize pancreatic NETs with [^{11}C] –L-dihydroxyphenylalanine ([^{11}C]DOPA) PET, and the same group also demonstrated that the *in vivo* uptake was due to decarboxylation (Bergström et al. 1996).

In whole body [^{18}F]FDOPA PET for detecting gastrointestinal carcinoid tumors, the primary tumors were well localized (Hoegerle et al. 2001b). Comparison with the histologic and immunohistochemical findings shows that serotonin-expressing tumors especially take up [^{18}F]FDOPA (Hoegerle et al. 2001b). [^{18}F]FDOPA PET of pancreas has also been shown to distinguish between focal and diffuse forms of hyperinsulinism (HI) in infancy (Ribeiro et al. 2005). Preliminary results suggest that [^{18}F]FDOPA PET may not be optimal for imaging of small cell lung carcinoma (SCLC), although these carcinomas express neuroendocrine markers (Jacob et al. 2003). In detecting medullary thyroid carcinoma (belongs to NET group) [^{18}F]FDOPA PET was found to perform better than SRS or [^{18}F]FDG, although not with adequate diagnostic certainty without morphological imaging (Hoegerle et al. 2001a). [^{18}F]FDOPA whole-body PET was found to be highly sensitive and specific for detection of pheochromocytomas (Hoegerle et al. 2002).

[^{18}F]FDOPA accumulation is very high in the kidneys and urinary bladder (Ribeiro et al. 2005), which may be a problem in studying the tail of the pancreas.

[^{18}F]FDOPA accumulation in HI in pancreas could not be detected (scan started at 50 min) if the patient was pre-treated with AADC inhibitor carbidopa (Ribeiro et al. 2005). This suggests that the late accumulation phase would be specific to decarboxylation. It is still possible that the initial uptake may be increased, if cell transport is also up-regulated, but [^{18}F]FDOPA is soon released from the tissue if it cannot be decarboxylated.

Normal uptake of [^{18}F]FDOPA in pancreatic β-cells can not be observed in the images, because islets constitute only about 1% of the pancreatic mass; it is estimated that for quantifying β-cell mass (BCM) the PET tracer should accumulate in ratio 100:1 in β-cells compared to other pancreatic tissue (Sweet et al. 2004); this hardly can be achieved with any dopamine related compound, because also exocrine cells produce and store DOPA and dopamine (Mezey et al. 1996). It may be possible to improve the pancreas-to-surrounding tissue ratio somewhat by pretreating the patients with COMT inhibitor (Bergström et al. 1997).

Alternative but related tracers

[^{11}C]-5-hydroxytryptophan ([^{11}C]-5-HTP) is specifically taken up by carcinoid serotonin-producing tumors, decarboxylated by AADC, and stored in vesicles as [^{11}C]serotonin. [^{11}C]-5-HTP provided in some cases higher SUV than [^{18}F]FDOPA (Ahlström et al. 1995) and was shown to be more sensitive in imaging small NET lesions (Örlefors et al. 2005). Contrast of the uptake images could be further enhanced by concomitant administration of AADC inhibitor carbidopa (Örlefors et al. 1998 THIS IS NOT CORRECT REFERENCE).

6-[^{18}F]Dopamine ([^{18}F]DA) has been shown to be highly sensitive and superior to scintigraphy (Ilias et al. 2003).

Data analysis methods

Hoegerle et al. (2001b) analysed static images visually. Becherer et al. (2004) computed SUV images from static scans. SUV images were then evaluated visually without ROI analysis. Ribeiro et al. (2005) calculated SUVs and draw ROIs over the pancreas, liver, kidneys and lungs.

Ribeiro et al. (2005) showed that the radioactivity concentration in pancreas, liver and lung remained rather constant (although small decrease can be observed) between 50 and 80 min after injection of [^{18}F]FDOPA. This suggests that dynamic PET scanning is not useful, but a static 5-min scan between 45 and 90 min should be informative enough (Becherer et al. 2004, Ribeiro et al. 2005). Although the concentration decrease with increasing time was small, it suggests that reversible uptake models (e.g. Logan graphical analysis) measuring distribution volume (DV) would be more appropriate for the analysis than irreversible uptake models (e.g. Gjedde-Patlak graphical analysis). If arterial plasma curve is not measured, a tissue-to-reference tissue (preferably tissues with high perfusion and blood content but low AADC activity) ratio approach may be related to distribution volume and be proven useful.

For [^{11}C]-5-HTP the Gjedde-Patlak graphical analysis has been applied (Örlefors et al. 1998), although the plots did not reach linear phase during the PET scan (0-45 min); the arterialized plasma curve was not corrected for metabolites.

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