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PET radiopharmaceuticals for neuroreceptor imaging

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Abstract Routine clinical PET radiopharmaceuticals for the noninvasive imaging of brain receptors, transporters, and enzymes are commonly labeled with positron emitting nuclides such as carbon-11 or fluorine-18. Certain minimal conditions need to be fulfilled for these PET ligands to be used as imaging agents *in vivo*. Some of these prerequisites are discussed and examples of the most useful clinical PET radiopharmaceuticals that have found application in the central nervous system are reviewed.

Key words PET radiopharmaceuticals, Brain receptors, Carbon-11, Fluorine-18

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1 Introduction

Positron emission tomography (PET) is an imaging modality that allows studying of physiological, biochemical, and pharmacological functions at a molecular level. The PET methodology permits the measurement of absolute values of physiological parameters such as blood flow or receptor concentrations. In addition, the method allows obtaining quantitative information on the pharmacokinetics and pharmacodynamics of a biomolecule in living animals.

The main constituents of most biological molecules are carbon, nitrogen, and oxygen. The incorporation of positron-emitting nuclides such as carbon-11, nitrogen-13, or oxygen-15 with physical half-lives of 20, 10, and 2 minutes, respectively, into pharmaceuticals thus leads to PET radiopharmaceuticals, which are chemically indistinguishable from their nonlabeled counterparts. Fluorine-18 with a physical half-life of 110 minutes is another frequently used positron-emitting nuclide. Since not many bio-organic compounds contain a fluorine atom, radiolabeling with fluorine-18 is mainly done by nonisotopic substitution, for example, as with L-^{18}F-6-fluorodopa or with the most widely used routine PET ligand, 2-^{18}F-fluoro-deoxyglucose (^{18}F-FDG). Over the years, a number of biologically interesting PET ligands have been developed and used in PET investigations to study the various biochemical functions in healthy and diseased subjects, and in recent years to evaluate drug effects and receptor occupancies in the living human brain [1,2]. In this article, the most common PET radiopharmaceuticals that are currently used for the brain imaging of receptors, transporters, and enzymes are reviewed.

2 Some properties of the brain imaging radiopharmaceuticals

Establishing the use of a PET ligand for human applications requires the expertise of several scientists including radiochemists, pharmacologists, and clinicians who work in close collaboration in an interdisciplinary environment. The PET imaging of the central nervous system (CNS) receptors in the human brain is an expanding area and for PET radiopharmaceuticals to be useful as *in vivo* imaging agents, a number of prerequisite criteria have to be fulfilled. These conditions are briefly discussed below.

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2.1 Selectivity/High affinity for the receptor (K_i or $K_d \leq 10^{-9}$M)

The equilibrium dissociation constant (K_d) of a drug–receptor complex is the concentration of the drug that occupies or binds to 50 % of the available receptor population. By definition, affinity is the reciprocal of the equilibrium dissociation constant and is ideally the highest for the target site to be imaged. Considering that the concentration of binding sites (B_{max}) for most brain receptors is rather low (nano- to femtomoles per milligram tissue), PET ligands should have binding affinities in the subnanomolar range. But a very high affinity can render a PET radiopharmaceutical useless because its uptake may become blood flow-dependent instead of being dependent on the rate of binding.

2.2 Specific radioactivity

Specific radioactivity refers to the amount of radioactivity per unit mass of a radiopharmaceutical. Unlike radioligands used only for *in vitro* binding assays, radioligands used for *in vivo* brain receptor imaging must be prepared in high specific radioactivity so that only a small percentage of the total number of available binding sites is occupied by the radioligand. A low specific radioactivity may lead to the saturation of the binding sites, which may result in pharmacological effects or toxicity.

2.3 Metabolism and position of the label

Since PET cannot discriminate between the signals from the parent radioligand and the radiolabeled metabolites, it is essential that PET ligands do not undergo rapid metabolism over the period of PET measurements. Therefore, it has to be verified that radioactive metabolites that are formed in the course of data acquisition do not contaminate the PET signals. The position of the radiolabel in a molecule is also another crucial factor and has to be considered very carefully during the planning of the synthetic approach because the loss of the radiolabel in a molecule by metabolic degradation will limit its usefulness as a PET ligand.

2.4 Blood–brain barrier permeability

For a CNS radiopharmaceutical to be useful as an imaging agent, it must be lipid soluble and should readily pass the blood–brain barrier (BBB). The octanol/water partition coefficient, *P*, is often used as a predictor for BBB penetration. The *P* values can be computed or experimentally measured and the log *P* values between 2 and 3 are generally considered optimal. This criterion necessarily holds for diffusion-mediated transport systems but not for specialized active transport systems as in the case for amino acids.

2.5 Clearance rate and binding to proteins

Rapid clearance rates from the blood and nonspecific binding sites are also important. A low binding of the radioligand to the plasma proteins is essential since only the free fraction of the radioligand in the plasma is available for diffusion out of the vascular space.

3 PET radioligands for imaging neuroreceptors and monoamine transporters

A large number of ^{11}C- and ^{18}F-labeled PET ligands have been developed for imaging in neurology but until now only a few have found application as *in vivo* imaging agents in humans. The dopaminergic system has been the most extensively studied and not surprisingly, the dopamine D2 receptor system was the first receptor to be examined by PET in humans [3]. The involvement of this receptor system in numerous brain disorders such as schizophrenia, Parkinson's disease and other movement disorders has prompted an intense research in this field. Although high-affinity PET ligands exist for imaging the postsynaptic dopamine D1 and D2 receptors in humans (Table 1), there are as yet no selective radioligands for the dopamine D3 and D4 receptor subtypes. Of all the benzamide derivatives reported till date, ^{11}C-Raclopride [4] is the most widely used PET ligand for the investigation of striatal D2 receptors in humans. ^{18}F-Fallypride, also a benzamide and a structural analog of raclopride is well suited for the *in vivo* visualization of extrastriatal D2 receptors [5]. For the presynaptic dopamine transporters (DATs), a series of cocaine congeners labeled with either ^{11}C or ^{18}F have been developed [6,7]. Some of these compounds (Table 1) including ^{11}C-PE21 [8] and

^{18}F-β-CFT [9] have found routine application as imaging agents for the DAT. In addition to being used as diagnostic agents, these DAT PET ligands have also been employed as surrogate markers in the development of novel drugs for use in the therapy of brain disorders in which the dopaminergic system is implicated.

Table 1. Some routine PET ligands for the dopaminergic and serotonergic systems (D = dopamine receptor, DAT = dopamine transporter, VMAT= vesicular monoamine transporter).

Receptor	Ligand	Refs
D1	^{11}C-SCH 23390	[22]
	^{11}C-NNC 112	[23]
D2	^{11}C-Raclopride	[4]
	^{11}C-FLB 457	[24]
	^{18}F-Fallypride	[5]
DAT	^{11}C-PE21	[8]
	^{18}F-ß-CFT	[9 ,25]
	^{18}F-ß-CIT-FP	[26]
	^{18}F-FECNT	[27]
	^{18}F-FECNT	[40]
VMAT2	^{11}C-DTBZ	[41]
5-HT$_{1A}$	^{11}C-DWAY	[10]
	^{11}C-NAD-299	[40]
	^{18}F-FCWAY	[28]
	^{18}F-p-MPPF	[11]
5-HT$_{2A}$	^{11}C-MDL 100907	[12]
	^{18}F-Altanserin	[13]
	^{18}F-Setoperone	[14]
SERT	^{11}C-McN-5652	[15]
	^{11}C-DASB	[16]
	^{11}C-MADAM	[17]
	^{11}C-AFAM	[18]
	^{11}C-ADAM	[19]

The serotonergic system is implicated in a number of neurological and psychiatric disorders such as depression, anxiety, schizophrenia, and Alzheimer's disease. Although more than 16 receptor subtypes for this system are known, PET ligands exist only for the 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor subtypes, which are found in high densities in the hippocampus and neocortical regions of the brain. ^{11}C-DWAY [10] and ^{18}F-pMPPF [11] (Table 1) are some examples of 5-HT$_{1A}$ PET ligands currently used for the visualization of 5-HT$_{1A}$ receptors in humans. For the PET imaging of the 5-HT$_{2A}$ receptor, PET ligands such as ^{11}C-MDL100907 [12], ^{18}F-Altanserin [13], and ^{18}F-Setoperone [14] are available.

The first promising tracer developed for the imaging of the serotonin transporter (SERT) was (+)-^{11}C-McN 5652 [15]. Although (+)-^{11}C-McN 5652 labels the SERT in the human brain, it also exhibits high nonspecific binding and slow kinetics. Recently, a highly promising diarylsulfide class of compounds, namely, ^{11}C-DASB [16], ^{11}C-MADAM [17], ^{11}C-AFM [18], and ^{11}C-ADAM [19] have been developed as putative PET ligands for the *in vivo* imaging of the SERT in humans. Using (+)-^{11}C-McN 5652 as a SERT PET ligand, a significant increase in the SERT density in the thalamus of patients with depression was observed.

For other CNS receptors and enzymes such as benzodiazepine receptors or monoamine oxidases, a number of successful PET ligands are in clinical use (Table 2).

Table 2 Some routine PET ligands for other brain receptors and enzymes (MAO = monoamine oxidase, GABA = gamma-aminobutyric acid, nAChR = nicotinic acetylcholine receptor).

Receptor/ Enzyme	Ligand	Refs
MAO-A	^{11}C-Clorgyline	[29]
MAO-B	^{11}C-Deprenyl	[30]
	^{11}C-Deprenyl-D2	[31]
GABA$_A$	^{11}C-Flumazenil	[32, 33]
	^{18}F-Fluoroethyl-flumazenil	[34]
nAChR	^{18}F-A-85380	[35,36]
Opiate	^{11}C-Diprenorphine	[37]
	^{18}F-Cyclofoxy	[38]
	^{11}C-Carfetanil	[39]
Adenosine A1 receptor	^{18}F-CPFPX	[42]

4 Outlook

At present, attempts are being made to develop useful PET ligands for the imaging of the norepinephrine transporter (NET) in humans, but currently no optimal PET ligand exists for this purpose. Over the course of years, many attempts have been made by several research groups to develop PET pharmaceuticals for neuroreceptor systems that might be targets for therapeutic intervention. But despite strenuous efforts, only a handful of PET radioligands currently exist, and suitable PET ligands for a vast majority of neurotransmission systems are still lacking.

This is especially true for the glutamate receptors (both ionotropic and metabotropic), a receptor system

that is implicated in a wide variety of brain diseases. Three new radiopharmaceuticals for the PET imaging of the metabotropic glutamate receptor subtype 5 (mGluR5) have been described in a recent publication, but it is not clear whether these compounds can be used for the PET imaging of mGluR5 in humans [20]. Recently, Ametamey, *et al.* [21] reported on a novel, selective, and high-affinity mGluR5 antagonist, which shows promise as a PET radioligand for the imaging of the mGluR5 in humans. This new compound, ^{11}C-ABP688, displayed an *in vivo* distribution pattern consistent with the known regional density of mGluR5. Fig.1 shows an *ex vivo* autoradiographic illustration of the ^{11}C-ABP688 uptake in a rat brain.

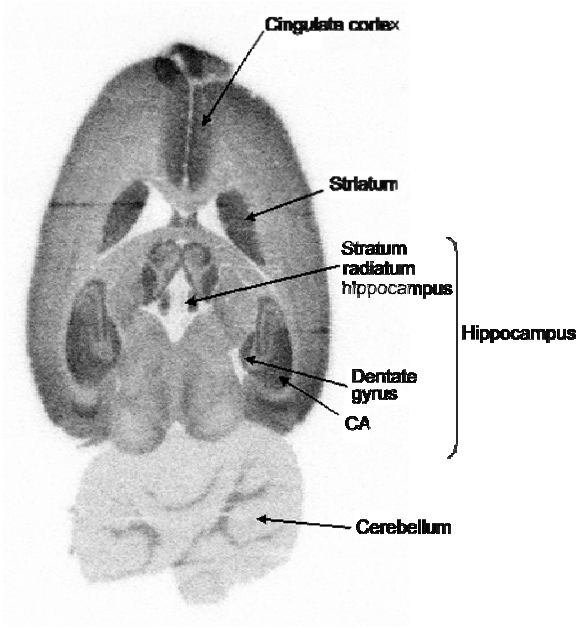

Fig.1 Unwashed horizontal slice of a rat brain 8 min after intravenous injection of ^{11}C-ABP688.

As mentioned above, a vast majority of neurotransmission systems lack PET imaging agents, and therefore there is an urgent need to develop selective and useful PET radioligands to aid in the diagnosis or staging of a variety of disease states in which neuroreceptors are functioning abnormally. Radiochemists are therefore challenged to develop more useful PET imaging agents, bearing in mind that PET radiopharmaceutical development is an iterative process that requires a lot of efforts. Although all the guidelines and criteria needed for a successful ligand may be followed, there is no guarantee that a successful tracer for human application will be the end product and obviously no successful radiopharmaceutical can fulfill all the requirements.

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