—Review—

Positron Emission Tomography for Brain Research

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Abstract

Positron emission tomography (PET) is a nuclear medicine imaging technique. Through the use of various radiopharmaceuticals, PET allows *in vivo* imaging of regional cerebral functions, including cerebral blood flow, molecular metabolism, and receptor binding capacity. PET is useful not only for diagnosis and therapeutic planning but also for neurological science research.

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Key words: Parkinson's disease, Alzheimer's disease, stroke, neuroimaging

Introduction

Positron emission tomography (PET) is a nuclear medicine imaging technique that allows imaging and quantifying of cellular and molecular processes in humans. The PET scanner detects pairs of γ-rays emitted indirectly by positron-emitting radioisotopes that are introduced into the body along with a radiopharmaceutical. Thus, PET allows *in vivo* imaging of regional cerebral functions, including cerebral blood flow, molecular metabolism, and receptor binding capacity (**Table 1**). In this review, the role of PET as a powerful tool for brain research is discussed.

Cerebral Blood Flow and Cerebral Metabolism of Oxygen

Imaging techniques have been developed and applied to evaluate brain hemodynamics[1]. PET and ^{15}O-labeled gasses allow *in vivo* imaging of regional cerebral functions, including cerebral blood flow (CBF), cerebral blood volume, and oxygen metabolism. Chronic cerebrovascular disorders are the most frequent indications for the measurement of CBF and the oxygen extraction fraction (OEF). In patients with chronic internal carotid artery occlusion, elevated OEF values are considered key indicators of impending infarction and for determining indications for bypass surgery[2–5].

When cortical areas become activated, regional cerebral blood flow increases. [^{15}O]H_2O PET allows repeated measurement of CBF under different conditions, because the half-life of ^{15}O is extremely short ($t_{1/2}$=2 minutes). Brain PET activation has been used to reveal regional cortical neural activity involved in language and visual processing in the living human brain[6–9]. Moreover, PET has also been used for planning surgical treatment[10], and monitoring recovery from motor aphasia after ischemic stroke[11].

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Table 1 Radiopharmaceuticals for brain PET

Radiopharmaceutical	Application
[^{15}O]CO_2, [^{15}O]H_2O	Cerebral blood flow
[^{15}O]O_2	Cerebral oxygen consumption
[^{15}O]CO	Cerebral blood volume
[^{18}F]FDG	Glucose metabolism
[^{11}C]deprenyl	Monoamine oxidase
6-[^{18}F]DOPA O-[^{11}C]methyl-L-tyrosine	Dopamine synthesis
[^{11}C]CFT	Dopamine transporter
[^{11}C]DTBZ	Vesicular monoamine transporter 2
[^{11}C]NMSP [^{11}C]raclopride	Dopamine D_2 receptor
[^{11}C]SCH23390	Dopamine D_1 receptor
[^{11}C]flumazenil	Central benzodiazepine receptor
[^{11}C]PK11195	Peripheral benzodiazepine receptor
[^{11}C]SA4503	Sigma$_1$ receptor
[^{11}C]3NMPB	Muscarinic acetylcholine receptor
[^{11}C]doxepin	Histamine H_1 receptor
[^{11}C]MPDX	Adenosine A_1 receptor
[^{11}C]TMSX	Adenosine A_{2A} receptor
[^{11}C]verapamil	P-glycoprotein
[^{11}C]PIB [^{11}C]BF-227	Amyloid β protein
[^{11}C]methionine	Amino acid metabolism

Cerebral Metabolism of Glucose

Cerebral glucose metabolism is thought to reflect regional neuronal activities[12–14]. The glucose analog 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) accumulates in the brain at a rate proportional to the regional metabolism of glucose. Therefore, [^{18}F]FDG PET images reflect regional brain dysfunction. We have reported the relationship between each task of the Mini-Mental State Examination (MMSE) and regional glucose hypometabolism in patients with Alzheimer's disease (AD)[15]. That study demonstrated that in patients with AD, the distribution of hypometabolism in the resting state is related to clinical symptoms and that MMSE scores reflects brain dysfunction in the left hemisphere. This study also showed that the correlation between statistical parametric mapping (SPM) and [^{18}F]FDG PET is useful for objectively evaluating the results of cognitive tests and diagnostic scoring.

[^{18}F]FDG PET is especially useful for the differential diagnosis of early-stage neurological diseases[16–28]. In patients with AD, [^{18}F]FDG PET and statistical image analysis techniques, such as SPM and 3-dimensional stereotactic surface projections, have shown that cerebral glucose metabolism is reduced in the parietal lobe and in the posterior cingulate gyrus[16,17,29]. Some studies have revealed that glucose metabolism is reduced in the occipital lobe in patients with Parkinson's disease (PD), **Fig. 1**[18,19], as well as in patients with dementia with Lewy bodies (DLB)[20]. Previous studies using region-of-interest analysis have found that the cerebral metabolism of glucose was reduced in the basal ganglia, brainstem and cerebral cortex, and,

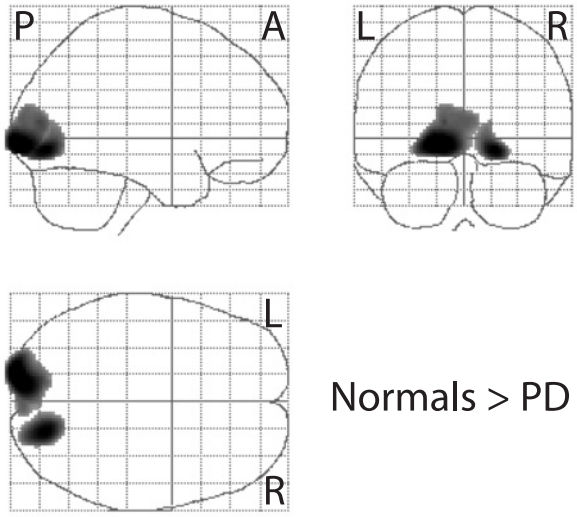

Fig. 1 SPM analysis of representative brain regions with a significant decrease of cerebellar normalized FDG uptake in 14 patients with PD without dementia as compared with 24 control subjects. A statistical map is displayed with a voxel threshold probability of 0.001 and an extent threshold of 500 contiguous voxels per cluster (uncorrected for multiple comparison). The FDG uptake in PD was significantly reduced in the bilateral occipital cortices.

particularly, in the frontal lobe of patients with progressive supranuclear palsy (PSP)[21–25]. SPM has revealed hypometabolism of the midbrain in PSP, which is independent of clinical deterioration[26]. Hypometabolism of glucose is observed in the bilateral putamen of patients with multiple system atrophy with predominant parkinsonian features (MSA-P, previously called striatonigral degeneration) and in the cerebellum and pons of patients with multiple system atrophy with predominant cerebellar features (MSA-C, previously called olivopontocerebellar atrophy)[30,31]. [^{18}F]FDG PET has demonstrated asymmetrical hypometabolism in the striatum and cerebral cortex of patients with corticobasal degeneration (CBD)[31–33].

Approximately 40 to 60 minutes after injection, [^{18}F]FDG accumulates in the brain in a manner reflecting regional glucose metabolism. Therefore, [^{18}F]FDG PET is suitable for demonstrating changes in regional cerebral metabolism associated with walking before the subject is immobilized in the PET scanner. An activation study with [^{18}F]FDG PET has shown differences in regional brain function between healthy control subjects and patients with MSA-C[34].

Dopaminergic System

PET allows the acquisition of *in vivo* images of regional cerebral functions, which include blood flow, and metabolism, and receptor-binding capacity[35]. PD is a progressive degenerative neurological disorder characterized by resting tremor, bradykinesia, cogwheel rigidity, and postural instability. These symptoms result primarily from the loss of dopaminergic neurons in the substantia nigra. PET has enabled the acquisition of *in vivo* images of dopamine metabolism in patients with PD **(Fig. 2)**[36]. [^{18}F]DOPA PET has demonstrated that presynaptic dopaminergic function in the dorsal putamen is reduced to almost 50% of normal in patients with PD[37]. The distribution of presynaptic membrane dopamine transporter (DAT) in the human brain can be shown by means of PET with [^{11}C]2β-carbomethoxy-3β-(4-fluorophenyl) tropane ([^{11}C]CFT) **(Fig. 3)**[38]. Uptake of DAT-ligand PET is thought to be more sensitive for detecting dopaminergic dysfunction in early PD than is [^{18}F]DOPA PET because of a compensatory down-regulation of DAT to maintain dopamine levels at the synapses[39]. PET with [^{11}C]raclopride ([^{11}C]RAC) and N-[^{11}C]methylspiperone ([^{11}C]NMSP) has shown that the number of dopamine D_2 receptors is increased in the putamen in PD **(Fig. 3)**. In patients with MSA-P, the number of both DAT and dopamine D_2 receptors is decreased in the putamen[40].

The binding of [^{11}C]RAC depends on the concentration of endogenous dopamine, because [^{11}C]RAC has a weak affinity for dopamine D_2 receptors. This property of [^{11}C]RAC enables the use of [^{11}C]RAC PET in receptor-activation studies to investigate whether physiological stimulation induces dopamine release[41].

Adenosine A_1 and A_{2A} Receptors

Adenosine is produced by conversion of

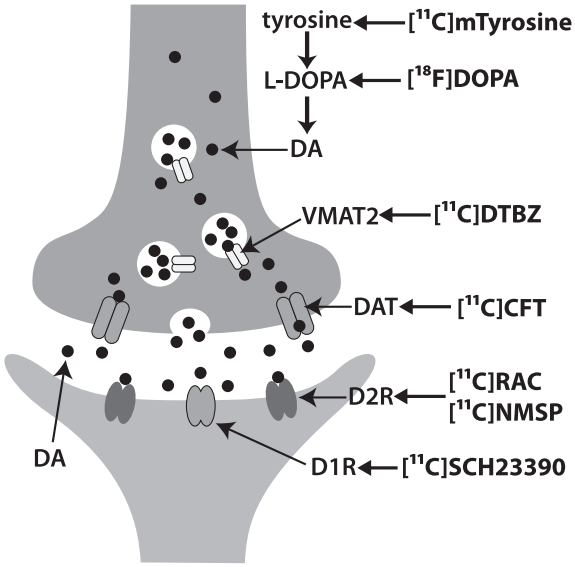

Fig. 2 Dopaminergic synapses and radiopharmaceuticals. Tyrosine hydroxylase catalyzes the conversion of L-tyrosine to 3,4-dihydroxy-L-phenylalanine (L-DOPA), which is converted to dopamine (DA) by aromatic L-amino acid decarboxylase. The turnover of dopamine can be evaluated PET and [^{18}F]fluoro-L-DOPA ([^{18}F]DOPA). Dopamine is transported from the cytoplasm into synaptic vesicles by the vesicular monoamine transporter 2 (VMAT2), and stored in synaptic vesicles. [^{11}C]Dihydrotetrabenazine ([^{11}C]DTBZ) binds to VMAT2. Membranes of the synaptic vesicles coalesce with the cytoplasmic membrane upon depolarization of the axon terminal, and dopamine is released from the synaptic vesicles into the synaptic cleft. The released dopamine binds to dopamine receptors (D_1, D_2, D_3, D_4, D_5, and their variants), and interacts at the level of second messengers and beyond. N-[^{11}C]methylspiperone ([^{11}C]NMSP) and [^{11}C]raclopride ([^{11}C]RAC) have affinity for the dopamine D_2 receptor, whereas [^{11}C]SCH23390 has affinity for the dopamine D_1 receptor. The released dopamine also binds to dopamine transporters (DAT), which reuptake dopamine from the synaptic cleft into dopaminergic neurons. The distribution of presynaptic membrane DAT in the human brain can be investigated with PET and [^{11}C]2β-carbomethoxy-3β-(4-fluorophenyl) tropane (CFT).

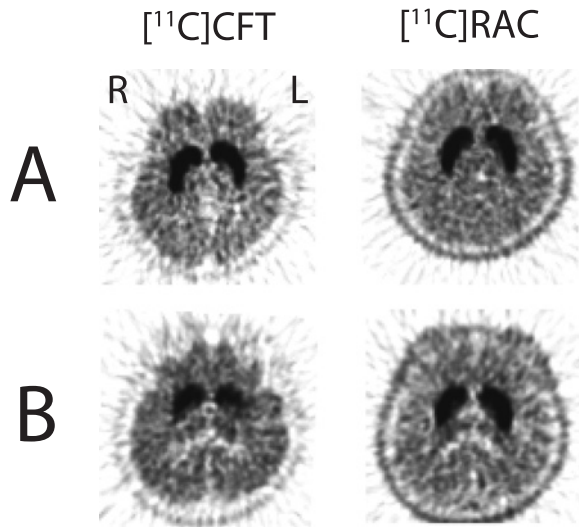

Fig. 3 Dopaminergic PET in a healthy 54-year-old man (A) and in a 60-year-old patient with PD (B). Both [^{11}C]CFT and [^{11}C]RAC accumulated in the putamen and head of the caudate nucleus in the healthy subject. In the patient with PD, however, PET images demonstrated low density of the dopamine transporter and high density of dopamine D_2 receptors in the putamen.

intracellular and extracellular adenine nucleotides, and plays a role as an endogenous modulator of synaptic functions in the central nervous system[42–44]. The effects are mediated by at least four receptor subtypes: A_1, A_{2A}, A_{2B}, and A_3[45].

Adenosine A_1 receptors are widely distributed throughout the entire brain, they inhibit adenyl cyclase[46,47], and interact negatively with dopamine D_1 receptors in direct pathway neurons[48,49].

[1-methyl-^{11} C] 8-dicyclopropylmethyl-1-methyl-3-propylxanthine (MPDX) is thought to be a promising PET ligand with selective and high affinity for adenosine A_1 receptors in the central nervous system[47,50–52]. An animal study of occlusion and reperfusion has found that decreased MPDX binding to adenosine A_1 receptors after reperfusion was a sensitive predictor of severe ischemic damage[53].

Adenosine A_{2A} receptors are abundant in dopamine-rich areas of the brain, such as the basal ganglia[54]. These receptors are known to stimulate adenyl cyclase, and interact negatively with dopamine D_2 receptors at the level of second messengers and beyond[54]. Adenosine A_{2A} receptor antagonists have recently attracted attention as the nondopaminergic treatment of PD. The selective adenosine A_{2A} receptor antagonist istradefylline has

been developed as a novel nondopaminergic agent for PD and provides an antiparkinsonian benefit without causing or worsening dyskinesia, which is one of the most inconvenient side effects of dopaminergic therapy[55,56]. A postmortem study has suggested that adenosine A_{2A} receptors were increased in patients with dyskinesia following long-term levodopa therapy[57]. Therefore, adenosine A_{2A} receptors may be involved in the development of side effects of antiparkinsonian agents. Although adenosine A_{2A} receptors have attracted much attention, until quite recently there has been little information regarding their presence in the living human brain. We developed the PET ligand, [7-methyl-^{11}C] - (*E*) -8- (3,4,5-trimethoxystyryl) -1,3,7-trimethylxanthine ([^{11}C]TMSX) for mapping adenosine A_{2A} receptors[58,59] and have successfully visualized the receptors in a living human brain by means of [^{11}C]TMSX PET[60,61]. Our studies have demonstrated that the binding potential is greatest in the anterior and posterior putamen, followed by the head of the caudate nucleus and thalamus, but is low in the cerebral cortex, especially the frontal lobe[60,61]. [^{11}C]TMSX PET has also shown a large binding potential in the striatum where adenosine A_{2A} receptors are abundant, as found in postmortem and nonhuman studies, but the binding potential of [^{11}C]TMSX is greater in the human thalamus than in other mammals.

Studies for adenosine A_1 and A_{2A} receptors in PD with extraction of the time activity curve of plasma using independent component analysis (EPICA)[62–65], [^{11}C]MPDX and [^{11}C]TMSX without arterial blood sampling are now underway in our laboratory.

Sigma$_1$ Receptors

The sigma receptor has been established as a distinct receptor, although it was initially proposed as a subtype of opioid receptors[66]. It is classified into at least two subtypes: sigma$_1$ and sigma$_2$[67]. Sigma$_1$ receptor is believed to be involved in aging[68,69] and various diseases, such as schizophrenia[70], depression[71] and ischemia[72].

In patients with AD, a postmortem study has shown that the sigma$_1$ binding sites are reduced in the hippocampus[73]. Sigma$_1$ receptor agonists are expected to improve cognitive deficits in AD patients[74]. Ishiwata et al.[75] have developed the PET ligand [^{11}C]SA4503 for mapping sigma$_1$ receptors, and have successfully visualized them in the living human brain[76–81]. Using [^{11}C]SA4503 PET, we found that the density of cerebral and cerebellar sigma$_1$ receptors is reduced in early-stage AD[82].

Some studies have suggested that sigma$_1$ receptors were involved in modulating the synthesis and release of dopamine[83,84]. In patients with PD, we have found that the binding potential of [^{11}C]SA4503 is significantly lower on the more-affected side than on the less-affected side of the anterior putamen, although there is no significant difference with respect to binding potential between patients and control subjects[85].

Benzodiazepine Receptors

The distribution of central benzodiazepine receptors (BZRs) in the human brain can be shown with PET and [^{11}C]flumazenil (FMZ), a highly specific benzodiazepine antagonist. These receptors belong to the γ-aminobutyric acid type A ($GABA_A$) receptor complex. Because these receptors are widely distributed in the cerebral cortex, it was assumed that [^{11}C]FMZ PET could demonstrate the neural density of the cerebral cortex[86]. Thus, they have been used to investigate the neural density in various diseases, including AD[87,88], cerebellar degeneration[89], chronic alcoholism[90], Huntington's disease[91] and temporal lobe epilepsy[92–94]. In a [^{11}C]FMZ PET study of AD, Ohyama et al. have shown that BZRs in the association-cortex are less impaired than is neuronal function, as assessed on the basis of the cerebral blood flow and glucose metabolism[88]. [^{11}C]FMZ PET is of value in determining an epileptogenic focus[92–94]. We have shown that the time for [^{11}C]FMZ PET static scaning to obtain semiquantitative images of BZR distribution is 20 to 40 minutes after injection, which is almost proportional to the BZR binding capacity and sufficiently useful for clinical studies[93,95,96]. Furthermore, using the static scan method we have demonstrated that synaptic elimination may be

independent of visual experience in the GABAergic system of the human visual cortex during visual development and have indicated that GABAergic inhibitory activity must be involved in the neural plasticity of the visual system[96].

Microglia are involved in immune surveillance in the intact brain and become activated in response to inflammation, trauma, ischemia, tumor, and degeneration of neurons. PET images with [^{11}C]PK 11195, a specific ligand for peripheral BZRs, reflect microglial activation and be used to study various diseases, such as ischemic stroke[97,98], AD[99], PD[100,101], MSA[102], PSP[103] and CBD[104].

Amyloid Imaging

Senile plaques and neurofibrillary tangles are hallmark pathologic features accompanying the degeneration involved in AD, and amyloid β peptide is a major constituent of senile plaques[105]. Studies are underway to determine whether amyloid PET would be a useful tool for the early diagnosis of AD[106–108] and DLB[109,110]. Amyloid imaging is also expected to be useful for assessing the efficacy of antiamyloid therapy[107].

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