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Review

PET in neurological research and diagnostics

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Abstract

From its inception in the mid 70's, PET has been a major tool for basic and clinical neuroscientists. Today,PET continues toplay a critical role in preclinical fundamental research both for the understanding of brain disease pathophysiology and for drug development. But PET is also routinely used for the diagnostic and the theranostic of many neuropathologies, including major social impact brain diseases such as stroke, neurodegenerative disorders, including Alzheimer and Parkinson diseases, and epilepsy.
Key words: PET, neurology, brain imaging

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Introduction

Positron emission tomography and neurology share a long story that started in the 1950's when the first PET prototype devices were designed. Because PET is ideally suited to look at physiology rather than at anatomy, it was clear from the beginning that a complex organ such as the brain could clearly benefit from this new technique. After years of technical development, the technique has 100 cubic millimeter spatial resolution and nanomolar sensitivity, two key technical features that make it unique in the spectrum of neuroimaging technique. Today, PET is used for diagnosis and research in several neuropathologies and particularly for dementia, movement disorders, and stroke, because these diseases sharing a number of special features. Matter-of-factly, these diseases:

— are major healthcare issues in all countries;
— have late life clinical expression;
— are diagnosed on the basis of clinical symptoms;
— have so far no treatment, or treatments loosing efficiency over time;
— have pathophysiology's that areuncompletely understood;
— result from molecular events starting much earlier in life;

In this paper, we briefly describe how PET is currently used for improving the diagnosis and searching for therapeutic tools for these pathologies.

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Tracing neurobiological processes with PET

Because of its intrinsic exquisite sensitivity, and thanks to the wide spectrum of high specificity available radiotracers, PET can be used for the assessment of many neurophysiological and neuropathophysiological processes in vivo (Table 1). For instance, parameters of regional cerebral energy supply and consumption parameters can be quantitatively estimated, including blood flow (with ^{15}O-water or ^{15}O-butanol), glucose (with ^{18}F-deoxyglucose or FDG) and oxygen metabolism (with $^{15}O_2$, ^{18}F-misonidazole or FMISO) and used to evaluate neural cell degeneration. Similarly, brain protein synthesis and turnover can be locally measured with labeled amino acids (^{11}C-Methionine, ^{11}C-Leucine, ^{18}F-Tyrosine, alpha^{11}C-Methyl-Tryptophan or AMT) or nucleoside (^{18}F-Thymidine or FLT), allowing the assessment and follow-up of brain cell division. Even more interesting for research purposes, is the unique ability of PET to allow the investigation of brain neurotransmission systems. The regional distribution, kinetic parameters and metabolism of neurotransmitters and membrane receptors can so be quantified for the dopaminergic (^{11}C-Raclopride, ^{18}F-DOPA), serotoninergic (^{18}F-Altanserin, ^{18}F-CWAY), cholinergic, gabaergic-A central (^{11}C-Flumazenil, FMZ), peripheral benzodiazepine (^{11}C-PK1185), and opioid (^{11}C-Carfentanyl) systems, to name the most important of them.

For several brain disorders (Table 1 and Table 2), such PET tracers are extremely useful: 1. for the understanding of their pathophysiology at the molecular level, thereby allowing the identification of specific therapeutic targets, and 2. for designing optimal PET diagnostic and theranostic tools. Last but not the least, PET is also the technique of choice for the evaluation of beta-amyloid aggregation and neuritic plaque formation (using ^{11}C-PIB, ^{18}F-florbetapir or ^{18}F-flutemetamol), two processes thought to be at the core of the pathophysiology of neurodegenerative disorders, including Alzheimer disease (AD).

Table 1. Key PET tracers in neurological research and diagnostic

	Pathophysiological process	Key biologicalparameters	PET tracers	Diagnostic use	Research use
Stroke	Oligemia	Blood flow	^{15}O H_2O		
	Ischemia	Oxygenmetabolism	$^{15}O_2$		✓
Alzheimer	Neurodegeneration	Glucose metabolism	^{18}F FDG		
	Proteinaggregates	A-beta plaque density	^{18}F florbetapir	✓	✓
Epilepsy	Hyperexcitabilty	Glucose metabolism	^{18}F FDG		
		GABA receptordensity	^{11}C flumazenil	✓	✓
Parkinson	Loss of DA neurons	DA synthesis			
		Monoamine transport	^{18}F DOPA		✓
			^{18}F DBZT		

Table 2. FDA approved PET radiopharmaceuticals for clinical use in neurology

Tracer	Biological target	Indication	Year approved
^{18}F-FDG	Glucose metabolism	Epilepsy	1994
^{18}F-FDG	Glucose metabolism	Alzheimer disease	2005
^{18}F-florbetapir	Amyloidb accumulation	Alzheimer disease	2012

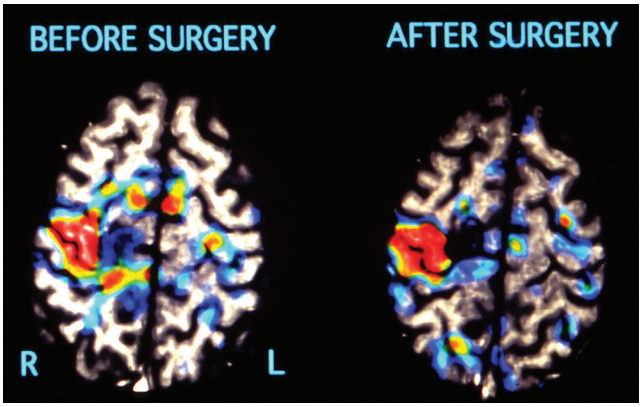

Figure 1. $H_2{}^{15}O$ PET activation study of the cortical network involved in left hand movement in a patient before (left) and after surgical resection of a cavernoma located in the close vicinity of the left hand motor area. Each image is the difference between 60 sec duration scan acquired after intravenous infusion 6 mCi of $H_2{}^{15}O$ either with or without movement of the left hand fingers. Difference images are superimposed on the subject structural MRI. Note that the surgery spared the hand motor area but an activation focus on the midline disappear after surgery showing that premotor area has been disconnected from the motor area. (R, right; L, left). Courtesy GIN, CEA, Orsay

PET diagnostic and theranostic of neuropathologies

Alzheimer disease and other neurodegenerative disorders

This is the domain where PET is the most useful inboth the research and clinical routine areas, one major pathology being extensively investigated with PET, namely Alzheimer disease. AD, the most common cause of dementia and an important challenge for healthcare systems, is initially characterized by memory complaints, evolving later on towards severe cognitive decline. At the molecular/cellular level, AD is characterized by the presence of amyloid-beta (A-beta) plaques, neurofibrillary tangles and activated microglia, resulting in neuronal cell loss. These neuropathological changes are thought to precede cognitive symptoms by many years, which justifies the use of PET using both FDG and A beta markers (such as ^{11}C-PIB or newly developed ^{18}F-labeled tracers, see above) in order: 1. to make an early detection of the disease, 2. to predict whether or not a subject with mild cognitive impairment (MCI) will end up having AD, 3. to make differential diagnosis with other diseases such as Lewy body dementia or fronto-temporal dementia (FTD), 4. to assess treatment outcome. Other PET tracers, including for various neurotransmitter systems, are used to progress in the knowledge of AD pathophysiology.

Cerebrovascular disease (CVD)

CVD results from an imbalance of the normal relationship between the cerebral vasculature and the brain parenchyma, sometimes resulting in stroke. PET should be the technique of choice for investigating stroke, being the only technique able to provide quantitative and reliable estimates of cerebral blood flow ($H_2{}^{15}O$), blood volume ($C^{15}O$), and oxygen ($^{15}O_2$) and glucose (FDG) metabolisms. However quantitation and the use of short-lived positron emitters (123 sec for ^{15}O) makes its use restricted to the preclinical or clinical research area. Nevertheless, PET has been found to be invaluable for the understanding of the compensatory responses of the brain to reductions in perfusion pressure and their associated changes in blood flow and metabolism, paving the way for the design of new treatment strategies. Moreover, although functional magnetic resonance imaging (fMRI) is by and large the technique of choice for studying the neural bases of cognitive processes and their disorders, $H_2{}^{15}O$ and PET are still used when

absolute quantitation of hemodynamic parameters are mandatory or when fMRI cannot be performed due to safety (presence of implants, see Figure 1) or nuisance (noise) reasons.

Epilepsy

Epilepsy is a chronic disorder characterized by recurrent and unprovoked seizures. Epilepsy is controlled with drugs in 70% of the cases. When seizures cannot be controlled, surgery is considered and interictal PET with FDG is used to localize the seizure onset zone to be resected. In preclinical research GABAA opioid, and serotoninergic neurotransmission are being investigated with PET as existing or possible therapeutic targets.

References

1. Goffin K, Dedeurwaerdre S, Van Laere K, Van Paesschen W. Neuronuclear assessment of patients with epilepsy. Semin Nucl Med 2008; 38: 227–239.
2. Jagust WJ. Amyloid imaging. Arch Neurol 2011; 68: 1377–1378.
3. Nordberg A, Rinne JO, Kadir A, Langström B. The use of PET in Alzheimer disease. Nat Rev Neurol 2010; 6: 78–87.
4. Powers WJ, Zazulia AR. PET in cerebrovascular disease. PET Clin 2010; 5: 1–37.
5. Vallabhajosula S, Vallabhajosula B. A broad overview of positron emission tomography radiopharmaceuticals and clinical applications: what is new? Semin Nucl Med 2011; 41: 246–264.