Principles of Functional Brain Imaging with Radiotracers

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Tracers

Radiotracers for CNS examinations enters the CNS crossing the blood brain barrier (BBB). Their prerequisite is the capacity of crossing the BBB or with free diffusion or by specific transport mechanisms.

rCBF tracers

The detection of the local level of blood supply to the brain derives from the application of the Fick's principle, based on the use of freely diffusible substances. In consequence, tracers for studying rCBF are freely diffusible. Some of them freely return back from brain to blood (back diffusion), others after crossing the BBB are transformed in non-diffusible species that allow an easy and efficient investigation of their regional distribution. Basically, the concentration of such tracers in the brain is proportional (either not linearly) with rCBF. The most commonly used tracers are trapped in the brain for times sufficiently long to allow an efficient SPECT detection. They are often referred as "chemical microspheres". Indeed, their behavior is quite different from that of microspheres, which are trapped in the brain 'linearly' with rCBF. These tracers are 'flow limited' but not 'flow linear'. It is important to bear this in mind whenever looking at SPECT rCBF images. Linearization procedures have been proposed but none with sound theoretical basis. In the most precise terms, the brain distribution of these 'chemical microspheres' reflects the local value of the 'steady state influx constant', a parameter dimensionally expressed as ml/min/g, connected to flow by a complex expression. Nevertheless the performance of these tracers can cope with research and clinical requests efficently. Since their appearance more than 1000 scientific papers have been published and their use is recommended by several scientific associations (see below).

Metabolic tracers

As already said, the main metabolic substrates of the brain are oxigen and glucose. Both metabolic pathways are studied with specific tracers. 15-oxigen (positron emitter hal life 110 sec) is the tracer used to study regional cerebral metabolic rate of oxigen (rCMRO2) but clinical use of this method is not done. Glucose metabolism is studied with analogues of glucose, mainly labeled 2-deoxy-glucose. This analogue has the characteristic of sharing with glucose the affinity for the membrane specific glucose transporter (glucose does not freely cross BBB and cell membrane) and the first glycolythic step (hexokinase transform of glucose to glucose 6-P). Phosphoglucoso isomerase, the next enzyme in glycolytic pathway, does not recognize 2-D-glucose-6P, which consequently accumulates inside the cells. The cells that accumulates 2-DG inside the CNS are mainly astrocytes which physiologically carry on the glycolytic reactions. The level of glucose demand is regulated by neuronal-astrocyte interactions, recently reviewed. The amount of glucose imported by the cells is also dependent of the level of oxigen supply. A great deal of effort has been spent in developing physical and mathematical models of the brain kinetics of 2-Dglucose. These models have been made operative by the reduction to easily computable expression, as that proposed by C. Patlak with his graphical analysis or by Blomquivst with his linearization.

Radiopharmaceutical	Function	Indication	Availability
[^{99m}Tc]HMPAO	rCBF	See guidelines	Clinical
[^{99m}Tc]ECD	rCBF	See guidelines	Clinical
[^{123}I]IMP	rCBF	CVD	Research/Clinical in some countries (Japan)
[^{18}F]FDG	Glucose metabolism	See guidelines	Clinical
$H_2{}^{15}O$	rCBF	Quantitative rCBF measurement	Research
O_2	Oxygen extraction fraction	CVD	Research

Neurotransmission and receptors

Synaptic cleft is the place where interactions between cells take place. The neurotransmitter released by the presynaptic neuron reaches the postsynaptic cell membrane where receptors are present and initiates the neurotransmission chain of events. The transmitter can also reenter in the presynaptic neuron via the reuptake channels, which actively participate in modulating the intracleft concentration. All the constituents of the synaptic transmission chain, i.e. transmitter, receptors and reuptake channels, can be modulated by functional requests, as a consequence of local physiology as well disease and under the effect of drugs. The three components listed above are all possible target of imaging with radiolabeled tracers. At the research level the entity of synthetic activity and of intracellular transport, and the density of postsynaptyc receptors and presynaptic reuptake sites have all been investigated. At the moment the most extensive practice has been done with dopaminergic system tracers, mainly cyclotron labeled products. Dopaminergic system has been chosen as the preferential target for this studies because of the importance of the brain functions connected with its integrity, and also because the spatial distribution of the system is adequately known and segregated as to be well investigated with the spatial resolution of PET/SPECT instrumentation. The field of neuroreceptor investigation is now becoming more of clinical availability, with the market appearance of several reliable and easy to use receptorial tracers.

PET/SPECT radiopharmaceuticals for neurotransmitter systems

Ligands for the dopaminergic system are the tracers most frequently used in the clinical setting. These tracers have been widely used for the assessment of patients with Parkinson's disease (PD) and related movement disorders. [^{18}F]fluorodopa and cocaine derivatives labeled with ^{123}I and ^{99m}Tc ([^{123}I]beta-CIT, [^{123}I]FP-CIT and [^{99m}Tc]TRODAT-1) are the most frequently used tracers for the study of the nigrostriatal dopaminergic dysfunction in PD. Other dopaminergic ligands, such as those for the dopamine receptors, have been used for the identification of post-synaptic dopaminergic deficit in parkinsonian neurodegenerative disorders (D_2 receptor ligands), for the assessment of neuroreceptor/neurochemical changes and drug occupancy in psychiatric disorders (D_1 and D_2 receptor ligands) and for pharmacological studies on endogenous dopamine changes (D_2 receptor ligands).

Ligands for serotonin receptors and/or transporters can be applied to the study of neurodegenerative disorders such as Alzheimer's disease (AD) and neuropsychiatric disorders such as depression. New ligands for serotonin transporters are under evalution in humans. Tracers for the cholinergic system can be used for the study of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Lewy-body dementia, and progressive supranuclear palsy.

Tracers for the central benzodiazepine (BZD) receptors have been used in patients with epilepsy to identify the epileptogenic focus characterized by a focal decrease of BZD receptor density, for the study of neuronal loss in AD, and for the study of BZD receptor density in schizophrenic patients and post-traumatic stress disorder (PTSD). [^{11}C]PK 11195, a ligand for the peripheral BZD receptor, has been used for the in vivo imaging of microglial activation in stroke and AD. New ligands 'disease-specific', such as probes for amyloid plaques ([^{11}C]PIB, [^{11}C]SB-13) or neurofibrillary tangles will be likely used in the near future for the assessment of patients with mild congitive impairment and AD.

Table showing some of the available radiopharmaceuticals for brain receptors, transporters and enzymes

(see also Halldin C, Gulyás B, Langer O, Farde L. Brain radioligands - State of the art and new trends. Q J Nucl Med 2001; 2001;45:139-52)

	Dopamine	
D1 receptors	*D2 receptors*	*Dopamine transporter*
[^{11}C]SCH 23390	[^{11}C]raclopride	[^{11}C]PE2I, [^{123}I]PE2I
[^{11}C]NNC 112	[^{11}C]FLB 457	[^{11}C]ß-CIT-FE
	[^{11}C]NMSP	[^{11}C]methylphenidate
	[^{18}F]fallypride	[^{18}F]ß-CFT
	[^{18}F]fluoroethylspiperone	[^{18}F]ß-CIT-FP, [^{123}I]ß-CIT-FP
	[^{123}I]IBZM	[^{123}I]ß-CIT
	[^{123}I]epidepride	[^{123}I]altropane
		[^{99m}Tc]TRODAT-1
VMAT2	*L-aromatic amino acid decarboxylase (AADC)*	
[^{11}C]DTBZ	[^{18}F]6-F-dopa	

	Serotonin	
5-HT1A receptors	*5-HT2A receptors*	*Serotonin transporter*
[carbonil-^{11}C]WAY-100635	[^{11}C]MDL 100907	[^{11}C]MADAM, [^{11}C]DADAM
[^{11}C]DWAY	[^{11}C]NMSP	[^{11}C]McN5652
[^{18}F]FCWAY	[^{18}F]altanserin	[^{11}C]DASB
[^{18}F]*p*-MPPF	[^{18}F]setoperone	[^{123}I]ADAM, [^{123}I]b-CIT, [^{123}I] nor-b-CIT

	Acethylcoline	
Muscarinic receptors	*Nicotinic receptors*	*Acethylcolinesterase*
[^{11}C]NMPP, [^{123}I]IQNB	[^{18}F]2-F-A-85380, [^{18}F]6-I-A-85380	[^{11}C]PMP
	[^{123}I]5-F-A-85380	[^{11}C]MP4A

Opiate receptors	GABA receptors/central benzodiazepine receptors	Peripheral benzo-diazepine receptors
[^{11}C]carfentanil	[^{11}C]flumazenil	[^{11}C]PK 11195
[^{11}C]diprenorphine	[^{123}I]iomazenil	
[^{18}F]cyclofoxy		

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