Tracers for Brain Imaging

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Positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging use positron and gamma-emitting radioisotopes that can easily be incorporated into biological molecules and thus allow the measurement of functional parameters (physiological and/or pharmacological interactions) of tissue rather than just providing the anatomical definition of structures. Both techniques are exceptionally sensitive (PET more than SPECT) and can detect picomolar or even femtomolar concentrations of radiolabelled compound and enable the dynamic acquisition of relatively fast kinetics (of the order of seconds for PET). With these properties, PET/SPECT can facilitate the quantitative measurement of rapid physiological/pharmacological processes of bio molecules in the living brain.

For the tracer (radiopharmaceutical) to be able to enter the CNS (brain), it has to cross BBB (blood brain barrier). It is therefore prerequisite that that radiotracer posses the capacity (proper physiochemical properties) of crossing the BBB, by free diffusion or by specific transport mechanisms.

Depending on the brain target of the imaging and therewith needed properties, tracers for the brain imaging can be divided in several groups: rCBF tracers, metabolic tracers, tracers targeting neurotransmission and receptors, tracers targeting amyloid, tracers for brain tumor imaging.

Physiological properties needed by the radiopharmaceutical to be used for the measurement of brain perfusion are as follows; they must be able to cross BBB (blood-brain barrier), their extraction must approximate unity and must be independent of blood flow, as a consequence their initial distribution will be proportional to regional cerebral blood flow (rCBF). They also must be retained within the brain in their initial distribution long enough for diagnostic tomographic images to be obtained. (eanm guide,3). Ideally, tracer uptake should show no redistribution, initial tracer uptake reflecting rCBF at fast time window after injection, then remains almost unchanged for several hours. Result is image independent of rCBF variations occurring after the fixation time. Today there are two tracers used for evaluation of rCBF in routine clinical practice: ^{99m}Tc-HMPAO (exametazime) and ^{99m}Tc-ECD (bicisate). Other tracers available like ^{123}I-IMP and $H_2{}^{15}O$ are today still used mainly for research purposes. Main metabolic substrates of the brain are oxygen and glucose. Both metabolic pathways are studied with specific tracers. Glucose metabolism is studied with analogues of glucose. [^{18}F]FDG (2-(18F)Fluoro-2- deoxy-D-glucose) today represents the working horse of imaging in several fields of PET Nuclear medicine. [^{18}F]FDG is a glucose analogue and therefore taken up by cells in part by glucose transporters (glucose does not freely cross BBB and cell membrane) and is then phosphorylated by hexokinase into FDG 6-phosphate which cannot be metabolized (unlike glucose) and is consequently trapped in cell. Since FDG accumulates in brain tissue depending on facilitated transport of glucose and hexokinase mediated phosphorylation, it is suitable for imaging of regional cerebral glucose consumption and is currently the most accurate in-vivo method for the investigation of regional human brain metabolism. 15-oxygen is the tracer in research used to study regional cerebral metabolic rate of oxygen (rCMRO2).

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, disease and under the effect of drugs. All three are possible target of imaging with radiolabeled tracers. Dopaminergic system is because of the importance of the brain functions connected with its integrity (movement disorders, Parkinsonism, dementia with Lewy bodies) the most extensively studied neurotransmitter system in brain Nuclear medicine imaging. Several SPECT and PET dopaminergic tracers are now days available for routine clinical practice and research. [^{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). (D_2: [^{11}C]raclopride, [^{18}F]fallypride,...)

Ligands for serotonin receptors ([carbonil-^{11}C]WAY-100635),...) and/or transporters can be applied to the study of neurodegenerative disorders such as Alzheimer's disease (AD) and neuropsychiatric disorders such as depression.

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 ([^{11}C]flumazenil, [^{123}I]iomazenil) 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.

Amyloid plaques and neurofibrillary tangles are pathological markers found in Alzheimer disease (AD) post-mortem brains. Recently, several PET tracers have been developed that bind to amyloid plaques and hence can be used as amyloid imaging agents ([11C]BIP, [^{11}C]SB-13). Further analogues of the tracer such as [18F]flutemetamol are currently being introduced into clinical practice.

Radiolabelled amino acids offer significant improvement in the diagnostic evaluation of cerebral tumors in comparison with conventional anatomical imaging. Increased amino acid transport in brain tumor cells results from over expression of the transporter systems and is related to alterations in the tumor vasculature and tumor cell proliferation. Several radiolabelled amino acids are available, the most frequently used being (methyl-11C)-L-methionine (MET), 3-(123I)iodo-α-methyl-L-tyrosine (IMT) and *O*-(2-(18F)fluoroethyl)-L-thyrosine (FET).

As the number of PET/SPECT centers grows, applications of use in clinical neurology will increase for early and/or presymptomatic diagnosis of diseases and more target-specific radiotracers and ligands will be developed.