《招待講演 I》

Clinical Investigation with Positron Emission Tomography

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Positron Emission Tomography (PET) has provided a method for studying noninvasively brain, heart, lungs or pancreas function. Measurement of regional blood flow, oxygen and glucose metabolism in brain, blood flow and palmitic acid metabolism in myocardium are now widely used in clinical conditions. More recently methods for measuring protein synthesis and intracellular pH in brain have been reported. At least, characterization of several types of neurotransmitter receptors have been achieved and pathological changes in dopamine receptor have been very recently demonstrated for the first time.

Cardiac metabolism and receptors can now be studied in myocardial disease by PET. Three areas of particular interest are decreased blood flow and ischemia, increased cardiac load and cardiomyopathy. ^{11}C-Palmitate and ^{18}F-Deoxyglucose have been proved to be useful in metabolic studies in man. The spatial distribution of ^{11}C-palmitate can be used to delineate qualitative metabolic abnormalities associated with clinical disease. While the initial regional delivery of ^{11}C-palmitate as observed in vivo by PET is proportional to flow and a diminution in initial accumulation in ischemic regions reflects this, there is also diminished utilization due to decreased aerobic metabolism. Parallel studies using ^{18}F-Deoxyglucose showed in contrast increased uptake rates in the initial phases of ischemia but decreased uptake rates in infarcted regions. The progress and extent of ischemia and myocardial infarction can thus be delineated. Substrate imaging by PET is also clinically useful in evaluating the response of the ischemic regions to interventions such as coronary thrombolysis. In cardiomyopathies metabolic images are used to characterize disease states et to visualize the spatially heterogenous accumulation of tracer.

Investigation of cardiac receptors in man by PET is just beginning. Visualization and characterization of muscarinic acetylcholine beta-adrenergic, peripheral-type benzodiazepine and serotoninergic receptors have been demonstrated in man.

As far as brain is concerned, a large amount of data is available concerning cerebrovascular diseases, brain tumors, dementia, epilepsy, mental diseases and movement disorders such as Parkinson's disease and Huntington's disease.

One of the largest contributions of PET to brain pathophysiology so far has been the elucidation of the evolution of cerebral ischaemia to infarction in vivo in man. The normal human brain is characterized by a close coupling between cerebral blood flow and cerebral oxygen consumption. This is reflected by high flow to grey matter and low flow to white matter. The relationship between flow and metabolism is quantified by the arteriovenous oxygen difference or the fractional oxygen

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extraction (i.e. the arteriovenous difference of oxygen divided by the arterial oxygen content). Tomographic scans of the OEF in the human show that the normal fractional extraction of oxygen is at the same level throughout the brain (range 0.35–0.42). Systematic measurement of OEF in patients at various stages after the onset of vascular occlusion have clarified the dynamic nature of CBF: $CMRO_2$ relationships in the natural history of a stroke. The earliest studies have invariably shown an elevation of OEF to very high levels. When patients are studied sequentially a focal depression in OEF in the territory supplied by the initially occluded vessel is observed between 2 and 30 days after the onset of the ischaemic insult. It has been shown that combination of low OEF with low $CMRO_2$ is highly indicative of infarction. The effects of various therapies have also been investigated. Remote effects of infarctions have also been extensively studied; the crossed cerebellar diaschisis is a metabolic depression in the cerebellar hemisphere contralateral to the infarcted cerebral hemisphere. Very recently metabolic depression was observed in the whole cortex homolateral to a small thalamic infarction using oxygen 15 and ^{18}F fluorodeoxyglucose.

PET studies in brain tumors have concentrated so far on measuring regional blood flow, blood volume, oxygen and glucose metabolism. All the tumors have a low OEF, which suggests that, at least on a macroscopic scale, the oxygen supply to tumor tissue is more than enough to meet metabolic demand. This contradicts the theory that tumor growth is associated with tissue ischaemia, as suggested by experimental work. The blood flow in tumors does not correlate with blood volume, as is the case in normal brain and in some pathological conditions. This discrepancy is explained by the increased vascularity of tumors (shunts), as indicated by tumor blood volume, as opposed to tissue perfusion.

Glucose metabolism in tumors has been investigated by several groups. A correlation between human glioma grade and the uptake of ^{18}FDG in vivo has been reported. ^{18}FDG can make a distinction between recurrence of a glioma or post radiation necrosis. This distinction can be difficult to make on clinical or CT-scan evidence. Recurrent glioma apparently takes up ^{18}FDG while radiation necrotic tissue does not. A metabolic uncoupling between regional oxygen consumption and regional glucose consumption has also been observed indicating increased aerobic glycolysis.

Protein synthesis rate has been shown to be increased in brain tumors; the higher the grade of the tumor the larger the increase in protein synthesis independently of the existence of blood-brain barrier breakdown which can be quantified by injecting ^{68}Ga-transferrine.

Several PET studies dealing with dementia have been published. The two main entities within this group of disorders are the dementia of Alzheimer's type and multi infarct dementia. Most of the studies deal with cerebral blood flow, oxygen and glucose utilization; methionine incorporation in proteins in patients with dementia has also been measured. Disturbances of cerebral blood flow and metabolic activity have been observed which can be in part non specific and the consequence of neuronal cell loss.

PET studies about focal epileptic lesions have been reported. It seems that during an ictus glucose metabolism is increased in the affected area, whereas, inter-ictally a zone of hypometabolism is present.

Although the task appears much more difficult PET has been used to map neuronal dysfunction

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in mental diseases, paticularly in schizophrenia. ^{11}C-Methionine and ^{18}F-FDG have been used by several groups. Labeled ligands which bind specifically to receptors will probably bring new information in that field.

FDG studies on Huntington's chorea and Parkinson's disease have also been reported. Recently using L-Dopa labeled with ^{18}F, a reduced uptake of the tracer has been shown in the striatum. L-Dopa study could be coupled to ligands for the dopamine receptor such as ^{11}C-Methylspiperone, ^{76}Br-Bromospiperone or ^{11}C-Raclopride. For the first time a loss of striatal dopamine receptors in patients with progressive supranuclear palsy has been demonstrated in vivo by PET using ^{76}Br-Bromospiperone.

The potential of PET is thus obvious; the present results which are already spectacular are however preliminary. Emphasis is now put on receptor studies and a large number of specific ligands will soon be available. For brain studies one can quote ligands for dopamine, benzodiazepine, serotonine, acetylcholine and opiate receptors. PET studies are not only confined to brain and heart but can also be used to investigate other organs such as pancreas, lungs or kidneys. Thus, even if PET procedures cannot be installed on a large scale in the future, this method produces unique results which cannot be obtained by an other technique including NMR imaging and spectroscopy.

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