Positron Emission Tomography in Parkinson's Disease

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ABSTRACT: Positron emission tomography (PET) allows the study of physiological and neurochemical processes which would otherwise be inaccessible, using radioactive labels on biological compounds to follow their fate in the body. By analysing changes of concentration with time we can measure blood flow, neuronal metabolism and receptor ligand interactions. In Parkinson's disease (PD), PET has been used to examine the dopaminergic deficit and its relationship to motor performance. It has also been shown to detect asymptomatic dopaminergic lesions that have implications for the etiology of PD. In untreated PD there is increased density of D2 binding sites, while in chronically treated PD with motor fluctuations, D2 receptor density is reduced. [18F]-fluorodeoxyglucose studies of demented PD patients show a pattern of cortical metabolism similar to Alzheimer's disease. Activation studies, which measure changes in blood flow during the performance of motor tasks, show reduced activation of medial frontal areas in PD.

RÉSUMÉ: Tomographie par l'émission de positons dans la maladie de Parkinson. La tomographie par l'émission de positons (PET) permet d'étudier des processus physiologiques et neurochimiques inaccessibles par des moyens autres que le marquage et le traçage de composés radioactifs. En analysant les changement de concentration dans le temps, on peut mesurer le débit sanguin, le métabolisme neuronal et les interactions récepteur-ligand. Dans la maladie de Parkinson (MP), le PET scan a été utilisé pour étudier le déficit dopaminergique et sa relation à la performance motrice. On a également pu mettre en évidence des lésions dopaminergiques asymptomatiques qui ont des implications dans l'étiologie de la MP. Dans la MP non traitée, il y a une augmentation de la densité des sites de liaison D2, alors que dans la MP traitée de façon chronique où il y a des fluctuations motrices, la densité des récepteurs D2 est réduite. Des études effectuées au moyen du [18F]-fluorodésoxyglucose chez des parkinsoniens présentant une démence montrent un métabolisme cortical similaire à celui observé dans la maladie d'Alzheimer. Des études d'activation qui mesurent les changements dans le débit sanguin durant l'exécution de tâches motrices, montrent une activation diminuée des zones frontales médianes dans la MP.

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Over the two decades since its introduction, Positron Emission Tomography (PET) has undergone considerable development.[1] PET requires the combined efforts of nuclear physicists, chemists, engineers, biologists, mathematical modellers and physicians. The challenges presented by PET have been worked through to the extent that we are able to produce clinically and scientifically relevant information that cannot be gathered by other means.

The basic principle underlying PET is to attach a radioactive label to a biological compound and follow its fate in the body with a detection system that measures regional radioactivity concentrations. Certain radionucleotides decay by emitting a positron – a positively charged particle with a mass identical to that of an electron. The positron is the electron's antimatter equivalent. This means that when the positron interacts with an electron within the tissue both particles annihilate; their combined mass is converted to energy in the form of two gamma photons. The photons travel away from the annihilation site at 180 degrees to each other. If two radiation detectors facing each other on either side of a positron emitting source detect photons at the same time, then the point of decay should be located on the line between the detectors. By arranging pairs of detectors in a ring around the source of radiation, images of radioactivity concentration can be created using processes similar to those that produce CT and MRI images.

PET can do more than create static images of radioactivity. The scanner can record multiple images following the injection of a radioactive tracer. The temporal pattern of radioactivity accumulation may then be analyzed to derive improved measures of neuronal metabolism, blood flow and ligand-receptor interactions. PET development continues at a rapid pace. The next step forward will be the implementation of scanners that collect data in 3-dimensions as compared with current cameras that only collect radiation from a plane a few millimetres thick. This will greatly improve camera efficiency. We will therefore be able to use lower radiation doses to get results similar to

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those from current scanners, or obtain clearer images from the same radiation doses. The improved quality of these images will be useful for examining complex structures such as the striatum.

The number of compounds labelled with positron emitters continues to increase. Oxygen-15, carbon-11 and fluorine-18 (substituting for hydrogen) all emit positrons, and therefore almost any biological compound can be labelled. An important factor limiting the application of potential compounds is the development of mathematical models that describe metabolic rates and receptor binding. If the labelled compound has a complex metabolic pathway, then it may be too difficult to formulate accurate models that give meaningful results from PET measurements. This issue may be resolved by using compounds that are only partially metabolized such as fluorodeoxyglucose, or enzyme blockers such as carbidopa which simplifies the metabolic pathway of fluorodopa.

[18F]-Fluorodopamine

[18F]-fluorodopamine (FD) is an analogue for levodopa. FD crosses the blood-brain barrier via the large neutral amino-acid transport system. It is decarboxylated to fluorodopamine within the terminals of dopaminergic neurones. A proportion of fluorodopamine is then taken up and stored in nerve terminal vesicles. This storage is stable for 1 - 2 hours, and during this time we can calculate the rate constant for the uptake of FD from the blood into the striatum.[2] FD metabolism bypasses tyrosine hydroxylase. FD therefore does not directly trace the endogeneous dopamine pathway which has tyrosine hydroxylase as the rate-limiting step. The rate-limiting step for FD metabolism, L-aromatic amino-acid decarboxylase, does not appear to be subject to regulatory mechanisms to the same degree as tyrosine hydroxylase. This means that the FD striatal uptake rate is related to the number of dopaminergic neurones present and may be used an an index of damage to the nigrostriatal dopaminergic pathway.

Decreased FD uptake correlates with the motor deficit in Parkinson's disease (PD). Subscores of the Columbia scale for bradykinesia and tremor correlate highly with FD uptake, while there is a weak correlation with rigidity. Motor performance correlates with contralateral but not ipsilateral FD uptake.[3-6]

FD PET images of the striatum in PD show about a 20% reduction of anterior striatal FD uptake and a marked, sometimes complete, reduction in posterior striatal uptake, averaging about 60%.[7] This pattern is consistent with the post-mortem finding in Parkinson's disease of non-uniform reductions in dopamine concentration within the striatum with an anterior-posterior gradient.[8] It is also consistent with pathological observations that substantia nigra pars compacta cell counts are reduced to about 15 - 30% of normal in PD, with the ventro-lateral section that projects to the putamen being most affected.[9] Defining patterns of striatal uptake has applications in two areas. First, other forms of parkinsonism, such as that associated with progressive supranuclear palsy, have a more uniform reduction of FD uptake throughout the striatum.[7] This may be useful diagnostically, especially to classify patients for research purposes. Second, it seems likely that very early striatal lesions affect only subregions of the striatum. These would only be detected by sub-regional analysis as total striatal FD uptake would probably fall within the normal range. This is important if PET is to be used to detect presymptomatic dopaminergic lesions.

Approximately 50% of nigrostriatal dopaminergic neurons and 90% of striatal dopamine, as measured at post-mortem,[10] are lost before symptomatic parkinsonism develops. The patient remains asymptomatic with lesser degrees of loss probably due to a combination of reserve capacity and compensatory mechanisms. Efforts to diagnose early parkinsonism, which may be important for neuroprotective therapy, would preferably detect this asymptomatic state. There are two examples in humans of asymptomatic dopaminergic lesions detected by PET. The first is in subjects who have been exposed to the neurotoxin MPTP. Symptomatic subjects show marked reduction in FD uptake similar to that seen in PD. A group of asymptomatic subjects who had been exposed to MPTP had reduced FD uptake intermediate between normal and that seen in parkinsonism.[11] The second example is found among patients from Guam with the ALS-parkinsonism-dementia complex. Parkinsonian patients have marked reduction in FD uptake. Patients with ALS, but no parkinsonism, who have presumably been exposed to the same environmental agent have an intermediate reduction in FD uptake.[12] Because of the unusual diseases, both these studies were limited to small patient groups. Both also used objective methods for analyzing the PET scans. Designing studies to detect presymptomatic PD is difficult because we cannot define groups with high risk of disease. Scanning a large segment of the normal population would be an enormous undertaking. We have happened upon a subject, recruited as part of a normal control group, who has abnormally reduced FD uptake. He is being watched carefully for the development of clinical parkinsonism.

The effect of aging on the nigrostriatal dopaminergic system has been examined with FD and PET. These studies have explored the hypothesis that an age-related decline in dopaminergic function may play a role in the pathogenesis of PD.[13] Wayne Martin from Vancouver found a significant decline in FD uptake with age in a group of nine subjects.[2] In contrast, the Hammersmith group have reported no significant decline with age in a study using similar methods of analysis.[14] It seems that declining dopaminergic function may not be an inevitable result of aging. On the other hand, there may well be a group of functionally normal subjects who have reduced FD uptake. It is possible that these subjects include those asymptomatic individuals who have Lewy bodies in the substantia nigra at post-mortem. Careful longitudinal studies are necessary to follow patients with reduced FD uptake to identify any increased risk of developing parkinsonism.

Knowledge of the rate of progression of the dopaminergic deficit in PD has important implications for the search for the cause of the disease. We have performed follow-up FD PET scans in both normal subjects and patients with PD at three year intervals. We found a very small, but significant decline of FD uptake.[15] The rate of change was similar in the two groups. These results suggest that the progression of the dopaminergic lesion is very slow once symptoms become established.

FD PET is also useful for monitoring therapy for PD. Patients with adrenal medullary transplants do not show definite changes in FD uptake. Fetal transplants have however shown dramatic increases in FD uptake in the region of transplanted tissue in patients with PD[16] and with MPTP parkinsonism. The increased uptake is not apparent until about six months after

transplantation. In addition, the patients have not shown the same degree of clinical response as the increase in FD uptake. The reason for this is unclear, but may be because neuronal connections have not been re-established between the substantia nigra and the striatum.

Dopamine Receptor Ligands

Ligands have been developed for both the dopamine D1 and D2 receptors. To produce results analagous to *in-vitro* experiments on receptor-ligand interactions, we need to measure both receptor density and receptor affinity. Approaches to measuring receptor affinity usually require repeated measurements with varying specific activities. While this is easily done *in-vitro*, it is difficult to perform a series of 1 - 2 hour PET studies on a subject. Most published studies therefore measure only relative receptor density.

Raclopride, labelled with carbon-11, binds reversibly to dopamine D2 receptors with high selectivity and affinity. This ligand has been used in several studies of parkinsonism. In untreated PD, the absolute density of striatal D2 binding sites falls within the normal range. In patients with hemiparkinsonism, the mean uptake of raclopride was 10 - 15% higher in the putamen contralateral to the symptomatic limbs.[17,18] This implies mild relative upregulation of D2 binding sites in the more deafferented neurons. The studies were however performed on small groups of patients and await confirmation. In patients with PD and motor fluctuations on chronic treatment, D2 binding site density is reduced by about 40% in caudate and putamen.[19] These results are consistent with the post-mortem study that found normal striatal D2 receptor density in treated PD patients with a smooth response to medication and decreased density in patients with fluctuating responses.[20] Poorly levodopa-responsive multiple system atrophy and progressive supranuclear palsy have D2 receptor density reduced by about 10 - 20%. This is less than the reduction in fluctuating PD. If this is the case then it suggests that the poor dopa-responsiveness in these patients is not due to reduced D2 receptor density alone.[19,21]

[18F]-Fluorodeoxyglucose

The uptake of [18F]-fluorodeoxyglucose (FDG) into the brain is an index of neuronal metabolism. Deoxyglucose is transported across the blood-brain barrier and phosphorylated by the same pathway that handles glucose. It does not however progress further down the glucose metabolic pathway because of its anomalous structure. The metabolized tracer is retained in the brain, making the measurement of local metabolic rates of glucose much more simple than if labelled glucose were used.

Striatal FDG metabolism is normal in PD.[22,23] This is in contrast to conditions associated with striatal degeneration such as multiple system atrophy and PSP that show significant falls in striatal glucose utilization.[24-26]

FDG is particularly useful for studying dementia. Alzheimer's disease is associated with a distinctive pattern of reduced posterior parietal and temporal lobe glucose metabolism. Demented patients with PD generally show a similar pattern.[22] This pattern is distinct from the reduced frontal lobe metabolism seen in PSP.[24-26] There have not yet been enough pathological studies to determine whether the low posterior parietal and temporal metabolism seen in demented PD patients represents coexistent AD or whether it can also result from cortical Lewy bodies, or loss of cortical cholinergic, noradrenergic and serotonergic afferents.

Activation Studies

The dynamic nature of PET means it is possible to study focal changes in cerebral blood flow during sensory stimulation or performance of a motor task. These studies tie together function and anatomy of the nervous system. While a strong stimulus may increase regional blood flow by over 20%, the signal obtained from individual patients is often not clear enough to allow accurate determination of anatomical location. To deal with this difficulty, elaborate techniques have been developed to average studies on several subjects.[27] Before such averaging can be performed, the images of the brains must be normalized anatomically to each other or to a stereotactic atlas as well as corrected for differences in global blood flow. Local variations in blood flow must then be assessed for statistical significance. The improved resolution and efficiency of scanners able to detect radioactivity in three dimensions will simplify these processes.

The effect of PD on cortical activation during motor tasks has been studied with these techniques.[28] In control subjects, random movements of the hand are associated with increased blood flow in the primary sensorimotor cortex, premotor cortex, supplementary motor area and anterior cingulate area in the contralateral cortex and bilateral increase in the parietal areas 40. In patients with PD, there is significant activation in the sensorimotor cortex. There is also activation in the supplementary motor area, premotorcortex and cingulate area 24, but the changes are less extensive than in controls. Based on these observations, PD does not seem to be associated with impaired function of the sensorimotor cortex, but there appears to be dysfunction of areas involved in the integration of motor function. These results are from only one study and await confirmation, but they demonstrate PET's ability to study processes otherwise inaccessible by other means.

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