Cerebral Glucose and Dopa Metabolism in Movement Disorders

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ABSTRACT: The development of positron emission tomography (PET) has enabled us to perform in vivo measurements of certain aspects of regional cerebral function. Regional cerebral glucose metabolism may be readily quantified with [18F] fluoro-2-deoxyglucose (FDG) and presynaptic dopaminergic function may be studied with the labelled dopa analog 6-[18F] fluoro-L-dopa. We have applied a model to the analysis of 6-FD/PET data with which in vivo age-related changes in dopaminergic function may be demonstrated in normal subjects. With this technique, we have studied a series of asymptomatic MPTP-exposed subjects and have shown evidence of subclinical nigrostriatal pathway damage. Studies of regional cerebral glucose metabolism with FDG in early Huntington’s disease have shown a characteristic impairment in caudate function which precedes the development of caudate atrophy. In addition, some asymptomatic individuals who are at risk for HD have caudate hypometabolism. We feel that, at the present time, PET provides information which is complementary to the clinical examination in establishing a diagnosis of HD. In the future these studies may also help in the investigation of at risk individuals.


Our understanding of the pathophysiology of disorders of muscle tone in man has been based largely on studies of post-mortem brain tissue, and on animal models of specific neurological disorders. X-ray computed tomography (CT) and magnetic resonance imaging (MRI) have made it possible to correlate in vivo structural abnormalities with disease processes and this has provided for some improvement in our knowledge of pathophysiology. These methods, however, do not provide direct information concerning cerebral function. With the development of positron emission tomography (PET) has come the ability to study cerebral function, on a regional basis, with anatomical resolution sufficient to separate major subcortical structures such as the thalamus, caudate and putamen.

PET is a quantitative imaging technique which permits regional measurement of radioactive activity following the administration of radioactive isotopes which decay by emitting positrons. By utilizing appropriately labelled compounds and by applying the principles of tracer kinetic analysis, local cerebral physiological and biochemical processes may be studied. In particular, regional cerebral blood flow and the regional metabolism of oxygen and glucose may be measured. In addition, it is now possible to assess abnormalities of both pre-synaptic and post-synaptic neurotransmitter function with PET.

PRESYNAPTIC DOPAMINERGIC FUNCTION

Labelling of presynaptic dopaminergic nerve endings with 6-[18F] fluoroL-dopa (6-FD) has been demonstrated in vivo in both human and monkey brain.1,2 Fluorodopa behaves as an analog of L-dopa; it is a substrate for aromatic L-amino acid

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decarboxylase\textsuperscript{3} and is thought to be decarboxylated to fluoro-dopamine (FDA) within dopaminergic nerve endings. The accumulation of radioactivity within the striatum is inferred to be related to the decarboxylation of 6-FD to FDA and, in part, to the physiological “trapping” of FDA within intraneuronal vesicles. Significant quantities of FDA have been demonstrated in the striata of rats administered 6-FD.\textsuperscript{4} Evidence that this is contained within vesicles comes from demonstrations that striatal activity decreases following administration of reserpine\textsuperscript{2} and contained within vesicles comes from demonstrations that striatal vesicles. Significant quantities of FDA have been demonstrated related to the decarboxylation of 6-FD to FDA and, in part, to accumulation of radioactivity within the striatum is inferred to be the striatum of animals given 6-FD.\textsuperscript{4,6}

The interpretation of 6-FD/PET studies is complicated by the presence of significant “background” activity throughout the brain. In carbidopa-treated animals this consists of 6-FD and 3-0-methy!-6-FD (3-OMFD) formed by catechol 0-methyl transferase.\textsuperscript{4} When the neutral amino acid transport system is saturated by infusing amino acids following administration of 6-FD, there is a marked reduction of cerebral uptake in all brain regions implying that 6-FD and 3-OMFD are transported into the brain by this system.\textsuperscript{7}

These complexities of cerebral and peripheral 6-FD metabolism have made it difficult to produce precise quantitative information concerning the kinetics of presynaptic dopamine synthesis and turnover. Attempts to apply tracer kinetic principles to the analysis of 6-FD uptake data have been reported.\textsuperscript{8} We have adapted a general model for the analysis of unidirectional tracer uptake data\textsuperscript{9} for use with 6-FD/PET studies. To apply this model, we first developed a method to correct for the presence of labelled metabolites in plasma to determine the true 6-FD input function.\textsuperscript{10,11} This method is easily applied to patients who have been pretreated with carbidopa because the only labelled 6-FD metabolite in plasma is 3-OMFD.\textsuperscript{11} In patients who have not received carbidopa, a more complex HPLC-based method of plasma analysis is required to determine the plasma 6-FD time-activity curve. With this model, we calculate a “striatal influx constant” which describes the rate of transfer of the radioactive label from blood to striatum. This influx constant includes several independent physiological processes, including transport across the blood-brain barrier, uptake into neurons, decarboxylation to FDA, and trapping within neuronal vesicles. Calculation of this index provides a quantitative index of presynaptic dopaminergic function. With this model, we have demonstrated in vivo an age-related decrease in the striatal influx constant which is similar in degree to the age-related decrease in nigral cell counts.\textsuperscript{12}

Methods such as this have not yet been applied widely to the analysis of 6-FD/PET data. Nevertheless, general conclusions can be drawn from studies which show decreased striatal 6-FD uptake. Since the retention of radioactivity within the striatum is related to the presence of normally functioning dopaminergic terminals, decreased radioactivity suggests impaired dopaminergic function.

Parkinson’s disease

Presynaptic dopaminergic pathways have been studied with 6-FD in normal individuals and in patients with Parkinson’s disease (PD). In purely unilateral PD, reduced radioactivity was reported in the putamen contralateral to the affected limbs; caudate activity was normal.\textsuperscript{13} In slightly more advanced PD, i.e. patients with bilateral involvement but still significant clinical asymmetry, we observed a mild symmetric decrease in isotope accumulation in the caudate which was accompanied by a more markedly decreased accumulation in the putamen.\textsuperscript{14} The reduced putamen activity, although bilateral, was most marked contralateral to the most severely affected limbs. In patients with “on/off” reactions, a further decrease in striatal activity has been described.\textsuperscript{15} The observation that putamen is affected more than caudate is consistent with neurochemical data concerning the distribution of dopamine depletion in PD.\textsuperscript{16} In addition, these findings support the hypothesis that the putamen is more involved in the control of movement than is the caudate.

MPTP-induced parkinsonism

The association between 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and the symptoms of classical parkinsonism in animals and human subjects is well established.\textsuperscript{17,18,19} A group of subjects who received intravenous injections of MPTP without developing extrapyramidal signs or symptoms has been identified by Dr. J.W. Langston and his co-workers. These subjects provide a unique resource to test the hypothesis that exposure to a toxin can produce subclinical damage to the nigrostriatal pathway. This is critical to the threshold hypothesis of Calne and Langston\textsuperscript{20} that PD may result from the combination of environmentally induced subclinical damage to the pars compacta followed by normal age-related loss of additional nigral neurons until a critical level of dopamine depletion is reached.

We have used the 6-FD/PET technique to study dopa metabolism in these individuals to seek evidence supporting this hypothesis.\textsuperscript{21,22} We found a progressive decrease in 6-FD derived striatal radioactivity from normals (n = 7) through MPTP-exposed subjects (n = 6) to PD patients (n = 13). In MPTP subjects, caudate activity was significantly depressed compared to normals but was indistinguishable from that seen in patients with PD. Putamen values did not differ significantly from normals although there was a trend to depressed activity in the MPTP-exposed putamen.

These results support the hypothesis that exposure to an environmental toxin may give rise to subclinical nigrostriatal damage. By following these patients clinically and with repeated PET studies, we hope to establish the presence of a critical level of striatal activity for the earliest manifestation of clinical signs.

Cerebral Glucose Metabolism

The distribution of regional cerebral metabolism of glucose (rCMRG) and oxygen (rCMRO\textsubscript{2}) is thought to be related to neuronal and synaptic functional activity. This is because the major energy expenditure in the brain is for the ion transport systems responsible for maintaining the electrochemical gradients across neuronal membranes which are necessary for the generation of action potentials. Because aerobic glucose metabolism is responsible for most of the necessary energy production, mapping of rCMRG provides an image of brain functional (i.e., metabolic) activity. Glucose metabolism is measured with PET by using [\textsuperscript{18}F] fluorodeoxyglucose (FDG) and a three com-
The measurement of cerebral metabolism with PET has been particularly useful in situations characterized by the presence of impaired cerebral function in the absence of major structural change. Huntington’s disease (HD) is characterized by widespread neuronal loss affecting mainly the caudate and putamen. In advanced HD, this neuronal loss produces caudate atrophy which may be visualized with structural imaging techniques. In early HD, however, CT or MRI abnormalities are usually absent in spite of the presence of definite clinical signs and symptoms.

Pioneer studies of rCMRG in HD were performed by Kuhl and co-workers. They reported a relative decrease in caudate metabolism which they considered to be characteristic of the disease. They postulated that these metabolic changes preceded bulk tissue loss, although many of their patients already had CT evidence of ventricular dilatation and caudate atrophy. To help clarify the relationship between HD and striatal disease, they measured rCMRG with the FDG/PET technique in patients with mild but definite clinical manifestation and a positive family history. We excluded patients with significant caudate atrophy to minimize the potential artifactual hypometabolism that may occur because of the partial volume effect induced by tissue loss. We found definite caudate hypometabolism in all patients with no overlap between normal controls and affected HD patients. Young and colleagues found that the reduction in caudate and putamen metabolism correlates with functional capacity and with all the motor abnormalities of HD except dystonia. They also noted that thalamic metabolism is increased in comparison with normal subjects and found this increase to be correlated with dystonia.

Although caudate metabolic depression has been present in all reported asymptomatic patients with HD, it does not appear to be specific for HD. Some patients with benign hereditary chorea have similar changes as do some with the Lesch-Nyhan syndrome. Furthermore, caudate hypometabolism does not appear to be the functional substrate of chorea. Chorea has been observed in the absence of caudate hypometabolism in lupus and in some patients with benign hereditary chorea.

The measurement of caudate glucose metabolism with PET does seem to provide useful confirmation for the early diagnosis of Huntington’s disease in appropriate patients. If PET is to be diagnostically helpful, however, proper patient selection is important. Further studies are required to determine the functional substrate of chorea.

Is there evidence of impaired caudate function, as reflected by impaired metabolism, prior to the development of clinical symptoms? If so, measurement of rCMRG with PET would be a useful test in the assessment of symptomatic individuals with a family history of HD. In their original study, Kuhl and colleagues reported caudate hypometabolism in 6 of 15 asymptomatic at risk subjects. Over the following two years, three of these hypometabolic subjects developed clinical signs of HD. More recently, the UCLA group has reported on results from 23 asymptomatic at risk individuals in whom graded reductions in caudate metabolism were observed.

Findings contrast with those of Young and colleagues who found no evidence of caudate abnormalities in at risk individuals.

We have studied 12 individuals at risk for HD with both PET and a polymorphic human linked DNA marker. By performing DNA polymorphism studies we determined that eight of these persons had a 95% probability of being asymptomatic heterozygotes for HD. Four of these eight had caudate glucose utilization which was more than two standard deviations (SD) below that of age-matched controls. In the other four presumed heterozygotes, caudate metabolism was only mildly depressed. Four persons with a 5% likelihood of having inherited the abnormal gene had normal caudate metabolism. These findings suggest that although metabolic abnormalities may appear in the striatum prior to the onset of clinical symptoms, the hypometabolism probably occurs relatively close to the clinical onset so that patients studied several years previously will not have significant PET abnormalities. We hope to confirm this hypothesis by following these patients clinically, and performing serial PET studies to determine when abnormalities appear.

Further studies are required to clarify the relationship between caudate hypometabolism and the clinical abnormalities of HD. Possible explanations for the apparent disagreement among groups studying at risk individuals include the fact that different methods of PET data analysis have been used. In addition, it may be that clinical evaluation of patients differs significantly between groups.

**CONCLUSIONS**

The work presented in this review represents only the tip of the iceberg of the potential of PET. As new radioligands and appropriate tracer kinetic methods are developed, additional information concerning brain function will become available to the investigator. In particular, the development of methods to study receptors with PET is a high priority. Dopamine receptors have received significant attention in several centres and this work is of obvious interest to movement disorder research. Once the quantitative methodology has become fully established for this work, studies on these receptors in health and disease will no doubt ensue.

**REFERENCES**


