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 [^{18}F] fluoro-2-deoxyglucose (FDG) and presynaptic dopaminergic function may be studied with the labelled dopa analog 6-[^{18}F] 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.

RÉSUMÉ: Le métabolisme du glucose et de la DOPA dans les désordres du mouvement Le développement de la tomographie par émission de positrons (PET) nous a permis de mesurer in vivo certains aspects de la fonction régionale du cerveau. Le métabolisme régional du glucose dans le cerveau peut être facilement quantifié avec le [^{18}F] fluoro-2-désoxyglucose (FDG) et la fonction dopaminergique présynaptique peut être étudiée avec l'analogue marqué de la dopa, le 6-[^{18}F] fluoro-L-dopa. Nous avons appliqué un modèle à l'analyse des données recueillies dans l'étude 6-FD/PET avec lequel des changements dans la fonction dopaminergique in vivo qui sont en relation avec l'âge peuvent être démontrés chez des sujets normaux. Avec cette technique, nous avons étudié une série de sujets asymptomatiques exposés au MPTP et nous avons démontré l'existence de dommages nigrostriataux subcliniques. Des études du métabolisme régional du glucose cérébral au moyen du FDG dans la maladie de Huntington à ses débuts ont montré une altération caractéristique dans la fonction du noyau caudé, altération qui précède le développement de l'atrophie à ce niveau. De plus, certains individus asymptomatiques, à risque pour la maladie de Huntington, ont un métabolisme diminué au niveau du noyau caudé. Nous croyons que, actuellement, le PET fournit une information qui est complémentaire à l'examen clinique pour établir le diagnostic de MH. Dans l'avenir, ces études pourront également contribuer à l'investigation des individus à risque.

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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 radioactivity 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-[^{18}F] 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[3] and is thought to be decarboxylated to fluorodopamine (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.[4] Evidence that this is contained within vesicles comes from demonstrations that striatal activity decreases following administration of reserpine[2] and that FDA is released by depolarization of dopaminergic neurons.[5] Some of the "trapped" FDA is slowly released during the times typically employed in PET, and further metabolites of FDA (fluoro-DOPAC and fluoro-HVA) have been demonstrated in the striatum of animals given 6-FD.[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-methyl-6-FD (3-OMFD) formed by catechol 0-methyl transferase.[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.[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.[8] We have adapted a general model for the analysis of unidirectional tracer uptake data[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.[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.[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.[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.[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.[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.[15] The observation that putamen is affected more than caudate is consistent with neurochemical data concerning the distribution of dopamine depletion in PD.[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.[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[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.[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 normal 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 ($rCMRO_2$) 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 [^{18}F] fluoro-2-deoxyglucose (FDG) and a three com-

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partment model.[23,24] With this method, regional metabolism may be quantified in mg (or μmole) of glucose/min per 100 gm tissue.

Huntington's disease

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.[25] 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 metabolism, we measured rCMRG with the FDG/PET technique in patients with mild but definite clinical manifestation and a positive family history.[26] 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[27] 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 symptomatic patients with HD, it does not appear to be specific for HD. Some patients with benign hereditary chorea have similar changes[28] as do some with the Lesch-Nyhan syndrome.[29] 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[30] and in some patients with benign hereditary chorea.[28]

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 asymptomatic individuals with a family history of HD. In their original study, Kuhl and colleagues[25] 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.[31] More recently, the UCLA group has reported on results from 23 asymptomatic at risk individuals in whom graded reductions in caudate metabolism were observed.[32] Five of these subjects had values which were more than one standard deviation below normal control values. These findings contrast with those of Young and colleagues[33] 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.[34] 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

1. Garnett ES, Firnau G, Nahmias C. Dopamine visualized in the basal ganglia of living man. Nature 1983; 305: 137-138.
2. Garnett ES, Firnau G, Nahmias C, et al. Striatal dopamine metabolism in living monkeys examined by positron emission tomography. Brain Res 1983; 280: 169-171.
3. Firnau G, Garnett ES, Sourkes TL, et al. [^{18}F]Fluoro-dopa: a unique gamma-emitting substrate for dopa decarboxylase. Experientia 1975; 31: 1254-1255.
4. Cumming P, Boyes BE, Martin WRW, et al. The metabolism of [^{18}F]-6-fluoroL-dopa in the hooded rat. J Neurochem 1987; 48: 601-608.
5. Chiueh CC, Zukowska-Grojec Z, Kirk KL, et al. 6-Fluorocatecholamines as false adrenergic neurotransmitters. J Pharmacol Exp Ther 1983; 225: 529-533.
6. Chiueh CC, Kirk KL, Channing MA, et al. Neurochemical basis for the use of 6F-DOPA for visualizing dopamine neurons in the brain by positron emission tomography. Soc Neurosci Abstrs 1984; 14: 883.
7. Leenders KL, Poewe WH, Palmer AJ, et al. Inhibition of L-[^{18}F] fluorodopa uptake into human brain by amino acids demonstrated by positron emission tomography. Ann Neurol 1986; 20: 258-261.

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8. Garnett ES, Firnau G, Nahmias C, et al. Blood-brain barrier transport and cerebral utilization of dopa in living monkeys. Am J Physiol 1980; 238: 318-327.
9. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metabol 1983; 3: 1-7.
10. Martin WRW, Boyes BE, Leenders KL, et al. Method for the quantitative analysis of 6-fluorodopa uptake data from positron emission tomography. J Cereb Blood Flow Metabol 1985; 5(Suppl. 1): S593-S594.
11. Boyes BE, Cumming P, Martin WRW, et al. Determination of plasma [^{18}F]-6-fluorodopa during positron emission tomography: elimination and metabolism in carbidopa treated subjects. Life Sci 1986; 39: 2243-2252.
12. McGeer PL, McGeer EG, Suzuki JS. Aging and extrapyramidal function. Arch Neurol 1977; 34: 33-35.
13. Nahmias C, Garnett ES, Firnau G, et al. Striatal dopamine distribution in Parkinsonian patients during life. J Neurol Sci 1985; 69: 223-230.
14. Martin WRW, Stoessl AJ, Adam MJ, et al. Positron emission tomography in Parkinson's disease: glucose and dopa metabolism: *In*: Yahr M, Bergmann K, eds. Parkinson's disease. Advances in Neurology, Vol. 45. New York; Raven Press 1986; 95-98
15. Leenders KL, Palmer AJ, Quinn N, et al. Brain dopamine metabolism in patients with Parkinson's disease measured with positron emission tomography. J Neurol Neurosurg Psychiatr 1986; 49: 853-860.
16. Hornykiewicz O. Brain neurotransmitter changes in Parkinson's disease. *In*: Marsden CD, Fahn S, eds. Movement Disorders. London: Butterworth Scientific 1981; 41-58.
17. Davis GC, Williams AC, Markey SP, et al. Chronic parkinsonism secondary to intravenous injection of meperidine analogues. Psychiatr Res 1979; 1: 249-254.
18. Burns RS, Chiueh CC, Markey SP, et al. A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proc Natl Acad Sci 1983; 80: 4546-4550.
19. Langston JW, Ballard P, Tetrud JW, et al. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. Science 1983; 219: 979-980.
20. Calne DB, Langston JW. Aetiology of Parkinson's disease. Lancet 1983; 31: 1457-1459.
21. Calne DB, Langston JW, Martin WRW, et al. Positron emission tomography after MPTP: observations relating to the cause of Parkinson's disease. Nature 1985; 317: 246-248.
22. Martin WRW, Stoessl AJ, Adam MJ, et al. Imaging of dopamine systems in human subjects exposed to MPTP. *In*: Markey SP, Castagnoli N, Trevor AJ, Kopin IJ, eds. MPTP: A neurotoxin producing a parkinsonian syndrome. Orlando: Academic Press 1986; 315-325.
23. Sokoloff L, Reivich M, Kennedy C, et al. The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem 1977; 28: 897-916.
24. Phelps ME, Huang SC, Hoffman EJ, et al. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. Ann Neurol 1979; 6: 371-388.
25. Kuhl DE, Phelps ME, Markham CH, et al. Cerebral metabolism and atrophy in Huntington's disease determined by ^{18}FDG and computed tomographic scan. Ann Neurol 1982; 12: 425-434.
26. Hayden MR, Martin WRW, Stoessl AJ, et al. Positron emission tomography in the early diagnosis of Huntington's disease. Neurology 1986; 36: 888-894.
27. Young AB, Penney JB, Starosta-Rubinstein S, et al. PET scan investigations of Huntington's disease: cerebral metabolic correlates of neurological features and functional decline. Ann Neurol 1986; 20: 296-303.
28. Suchowersky O, Hayden MR, Martin WRW, et al. Cerebral metabolism of glucose in benign hereditary chorea. Movement Disorders 1986; 1: 33-44.
29. Palella TD, Hichwa RD, Ehrenkaufer RC, et al. ^{18}F-fluorodeoxyglucose PET scanning in HPRT deficiency. Am J Hum Genet 1985; 37: A70.19.
30. Guttman M, Lang AE, Garnett S, et al. No consistent abnormality of FDG scanning in SLE chorea: further evidence that striatal hypometabolism is not the correlate of chorea. Neurology 1986; 36(suppl.1): 309.
31. Kuhl DE, Markham CH, Metter EJ, et al. Local cerebral glucose utilization in symptomatic and presymptomatic Huntington's disease. *In*: Sokoloff L, ed. Brain Imaging and Brain Function. New York: Raven Press 1985; 199-209.
32. Mazziotta JC, Phelps ME, Pahl J, et al. Caudate hypometabolism in asymptomatic subjects at risk for Huntington's disease. J Nucl Med 1986; 27: 920.
33. Young AB, Penney JB, Starosta-Rubinstein S, et al. Persons at risk for Huntington's disease: brain metabolism determined with ^{18}F-FDG. J Nucl Med 1986; 27: 920.
34. Hayden MR, Hewitt J, Stoessl AJ, et al. The combined use of positron emission tomography and DNA polymorphisms for preclinical detection of Huntington disease. Neurology 1987 (in press).