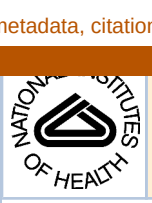

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Cerebral mitochondrial metabolism in early Parkinson Disease

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Abstract

Abnormal cerebral energy metabolism due to dysfunction of mitochondrial electron transport has been implicated in the pathogenesis of Parkinson Disease (PD). However, in vivo data of mitochondrial dysfunction has been inconsistent. We directly investigated mitochondrial oxidative metabolism in vivo in 12 patients with early, never-medicated PD and 12 age-matched normal controls by combined measurements of the cerebral metabolic rate of oxygen ($CMRO_2$) and the cerebral metabolic rate of glucose (CMRglc) with positron emission tomography. The primary analysis showed a statistically significant 24% increase in bihemispheric CMRO2 and no change in CMRO2/CMRglc. These findings are inconsistent with a defect in mitochondrial oxidative phosphorylation due to reduced activity of the mitochondrial ETS. Since PD symptoms were already manifest, deficient energy production due to a reduced activity of the mitochondrial ETS cannot be a primary mechanism of neuronal death in early PD. Alternatively, this general increase in CMRO2 could be due, not to increased metabolic demand, but to an uncoupling of ATP production from oxidation in the terminal stage of oxidative phosphorylation. Whether this is the case in early PD and whether or not it is important in the pathogenesis of PD will require further study.

Keywords

Parkinson Disease; Cerebral oxygen metabolism; Cerebral glucose metabolism; Positron emission tomography; Mitochondrial

INTRODUCTION

Parkinson disease (PD) is a degenerative neurological disease that is manifested by tremor, rigidity, bradykinesia and postural instability (Calne et al, 1992). Although PD is characterized

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DISCLOSURE/CONFLICT OF INTEREST
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neuropathologically by alpha-synuclein-immunopositive Lewy bodies in the substantia nigra and other brainstem structures, there is in increasing recognition that PD is a diffuse brain disease involving both cortical and subcortical structures (Braak et al, 2003). Dysfunction of mitochondrial oxidative metabolism has been implicated in the pathogenesis of PD though a variety of mechanisms including reduced ATP production and generation of free radicals (Abou-Sleiman et al, 2006). Diminished activity in complex I of the mitochondrial electron transport system (ETS) in post-mortem brain tissue has been reported in cortex and substantia nigra.as well as in platelets (Krige et al, 1992; Schapira 1994; Keeney et al, 2006). In vivo evidence of mitochondrial electron transport dysfunction has been inconsistent. Low ATP levels have been reported in the cortex in two studies (Piert et al, 1996; Rango et al, 2006). Overall cerebral oxygen metabolism has been reported to be not different from normal, but with relative increases in the basal ganglia opposite to the most symptomatic side (Wolfson et al, 1985; Leenders et al, 1985). These in vivo studies were performed in patients with mean disease duration of 6–7 years that was clinically advanced enough to have required treatment with L-dopa. If a defect in mitochondrial electron transport is important in the pathogenesis of PD, it will be present early in the course of the disease and prior to the possibly confounding effects of drug therapy.

Dysfunction of the mitochondrial ETS will reduce the cerebral metabolic rate of oxygen (CMRO2). However, since the brain regulates metabolism to match energy demand, both CMRO2 and the cerebral metabolic rate of glucose (CMRglc) are reduced under any condition with diminished energy demand, such as barbiturate anesthesia (Astrup et al, 1981). Specific defects in mitochondrial ETS decrease CMRO2 proportionately more than CMRglc (fewer moles of oxygen consumed per mole of glucose metabolized), thereby producing a reduction in the CMRO2/CMRglc ratio below the normal value of 5.6 (Brierley et al, 1977; Frackowiak et al, 1988). (This is in distinction to the situation during physiological brain activation in which the CMRO2/CMRglc ratio is also below normal, but CMRO2 is not reduced (Dienel et al, 2002).) Therefore, in vivo assessment of mitochondrial energy metabolism requires combined measurement of CMRO2 and CMRglc, which has not previously performed in Parkinson Disease (Frackowiak et al, 1988). To assess the role of defects in mitochondrial metabolism in the pathogenesis of PD, we directly measured $CMRO_2$ and CMRglc in vivo with positron emission tomography (PET) in early, never-medicated participants with PD and compared to age-matched normal controls.

MATERIALS AND METHODS

Participants

Parkinson Disease—Participants with PD were recruited from the Washington University Movement Disorders Center.

Inclusion criteria were:

1. Clinically definite PD:
    - **a.** onset after age 30 years.
    - **b.** Three of the following: rest tremor, rigidity, bradykinesia or postural instability; or two of these features with one of the first three displaying asymmetry (Calne et al, 1992).
    - **c.** Three or more of the following: unilateral onset; persistent asymmetry; rest tremor; or progression (United Kingdom Parkinson Disease Society Brain Bank criteria) (Hughes et al, 1992)
    - **d.** Asymmetric resting tremor (Rajput et al, 1991)

2. Symptomatic for less than 4 years
3. Never taken any anti-parkinsonian medication.

Exclusion criteria were:

1. Any of the following: a history of stroke; history of head injury; history of definite encephalitis, oculogyric crises; previous dopamine receptor antagonist treatment; sustained remission; strictly unilateral features after 3 years; supranuclear gaze palsy; cerebellar signs; early severe autonomic involvement; early severe dementia (within first year of onset) with disturbances of memory, language, and praxis; extensor plantar reflex; any defect on brain imaging; or MPTP exposure.
2. Major neurological or psychiatric disease other than PD or clinically significant lesions on brain imaging that was done prior to enrollment in the study.
3. Regular treatment or exposure in the last 6 months to flunarizine, cinnarizine, reserpine, amphetamines, MAO inhibitors or other medications that might interfere with mitochondrial metabolism.
4. Currently taking chloramphenicol or valproic acid
5. Ever having taken dopaminergic medications for any reason
6. Anticholinergics, amantadine, CoQ10, selegiline and Vitamins E and C must be discontinued for 30 days prior to entry into the study
7. Diabetes mellitus treated by medications
8. Pregnancy

All underwent clinical neurological evaluation by Movement Disorder specialists and were assigned a duration of symptoms and a clinically more involved side of the body based on this examination. They were all followed clinically for at least three years to determine whether each still met the above clinical criteria for idiopathic PD. This determination was made by an investigator blind to the PET data.

Normal controls—Normal controls were recruited contemporaneously by public advertisement and from friends and spouses of patients. All underwent clinical neurological evaluation by a neurologist.

Inclusion criteria were:

1. Disease free by subject's own history including no history of migraine, childhood febrile seizures or head trauma with loss of consciousness
2. Taking no medication by subject's own history
3. No signs or symptoms of neurological disease other than mild distal sensory loss in the legs consistent with age
4. No pathological lesions on MR scan done for this study (see below). Mild atrophy and punctate asymptomatic white matter abnormalities were not considered pathological. Exclusion criteria were the same as for the participants with PD.

Normal controls were recruited as part of a larger study including patients with Huntington's Disease and then retrospectively age matched to the patients with Parkinson Disease without reference to PET measurements (Powers et al, 2007).

Image Acquisition

T1-weighted MR images were acquired with a Siemens Sonata 1.5T scanner (Siemens Medical Solutions USA, Inc., Malvern, PA). A mid-sagittal scout spin-echo sequence was used to position the subject, then a 3-D MPRAGE sequence was acquired (TR/TE/TI=1900/3.93/1100 ms, FA=8°, 7:07 min, 128×256×256 matrix 1.25×1×1 mm voxels). In 10 patients and 11 controls high-resolution MR images were acquired with a Siemens Allegra 3T scanner (Siemens Medical Solutions USA, Inc., Malvern, PA) to permit identification of the substantia nigra. A 2-D turbo spin echo sequence (TR/TE=5540/99 ms, FA=180°, 384×512 matrix 0.5×0.5×2 mm voxels acquired as 21 interleaved, contiguous planes) was co-registered to an MPRAGE image, which, in turn, was co-registered to the MPRAGE image from the 1.5T scanner.

PET images were obtained in the 2-D acquisition mode with a Siemens/CTI ECAT EXACT HR 47 PET scanner (Siemens Medical Solutions USA, Inc., Malvern, PA) with participants lying supine in a quiet dark room. Cerebral blood flow (CBF), cerebral blood volume (CBV), CMRO2 and oxygen extraction fraction (OEF) were measured as previously described (Raichle et al, 1983; Mintun et al, 1984; Martin et al, 1987; Powers et al, 2007). Arterial blood samples for measurement of pCO_2 and oxygen content were collected and analyzed (Instrumentation Laboratory, Lexington, MA). In one PD participant and one control pCO2 measurement were not done because of a broken machine. Dynamic emission PET scans were obtained after slow intravenous injection over 10–20 seconds of 10 mCi of ^{18}F-fluorodeoxyglucose (^{18}FDG) for measurement of CMRglc (Powers et al, 2007). All PET emission scans were reconstructed with filtered back projection using the individual attenuation measurements and scatter correction with a ramp filter cutoff at the Nyquist frequency producing images with a resolution of 4.3 mm full width at half maximum.

Image Analysis

The 1.5 T MR image was segmented into brain and cerebrospinal fluid (CSF) based on voxel intensities. Manual editing was required to remove external tissue where there was insufficient CSF to separate the brain (near sinuses, temporal lobes, eyes, and brainstem), and a single erosion followed by conditional dilation completed the tissue segmentation. The MR image was then edited manually to generate a region of interest encompassing both cerebral hemispheres by removing the cerebellum and brainstem along a plane connecting the posterior commissure and the most inferior point of the interpeduncular fossa.

The substantia nigra was identified on the 3T turbo spin echo sequence (Foster et al, 2007). This region included both the pars compacta and the pars reticulate. Although the pars compacta is the primary site of pathology in PD, the spatial resolution of PET limits the small size of the region from which metabolic measures can be made and components of the pars compacta extend finger-like projections into pars reticulata making anatomic separation of the two not feasible on MRI (Damier et al, 1999).

The putamen was identified on the 1.5T MPRAGE sequences. Medially and anteriorly, the putamen was defined on the coronal view. Where separation from caudate or nucleus accumbens by white matter was not clear, an arbitrary straight line was drawn laterally and inferiorly following the direction of the internal capsule on this section. This rule does not correspond perfectly to anatomic putamen, but represents a necessary compromise, since histologic detail is required to distinguish putamen from caudate or nucleus accumbens accurately. Laterally the claustrum was excluded whenever the external capsule could be partially or completely visualized. The tail of the caudate was excluded by reference to sagittal views.

The globus pallidus was identified on 1.5T transverse MPRAGE images by its lateral border with the putamen and its medial border with the internal capsule. The highest and lowest MRI images that contained visible palllidum nestled against putamen defined its superior and inferior borders.

The volume of the substantia nigra, putamen and globus pallidus for each participant were determined from the number of voxels within each structure and the voxel volume size.

The original segmented MR image plus the three ^{15}O PET images were co-registered to a composite 40–60 minute ^{18}FDG PET image using Automated Image Registration software (AIR, Roger Woods, University of California, Los Angeles, CA) (Woods et al, 1993). Mean counts corrected for partial volume effects due to non-brain structures including CSF were generated for the bihemispheric, substantia nigra, putamen and globus pallidus regions of interest for each of the three ^{15}O PET images and for the dynamic ^{18}FDG PET images (Videen et al, 1999; Powers et al, 2007). Corrected mean counts were converted to quantitative CBF, OEF or CMRO2 (Videen et al, 1987).

For measurement of bihemispheric CMRglc, a modified Marquardt parameter estimation routine was used to derive rate constants for each participant using the partial volume corrected dynamic bihemispheric ^{18}FDG PET counts and arterial whole blood time-radioactivity curves (Powers et al, 2007). For calculation of regional substantia nigra, putamen and globus pallidus CMRglc, we employed a single scan strategy utilizing mean ^{18}FDG counts integrated from 40–60 min post-injection and a single set of rate constants (Phelps et al, 1979). We compared the 4 rate constants derived from bihemispheric parameter estimation in the 12 participants with PD and the 12 age-matched normal controls (see below) and found no difference (all $p > .3$). We therefore used the mean values for the rate constants derived from all 24 participants in the calculation of regional CMRglc. For this study, we calculated from our entire series of 23 normal control subjects ages 26–70 a value for the lumped constant of 0.64 that yielded a mean bihemispheric value for CMRO2/CMRglc equal to the value of 5.6 that has been directly measured from arterial and jugular venous samples in normal adults, ages 21–69 (Gottstein et al, 1963).

Statistical Analysis

The null hypothesis of no difference in cerebral oxygen metabolism in patients with early PD was tested by comparison of bihemispheric CMRO2 between participants with PD and age-matched normal controls by 2–sided unpaired t-test with the criterion for statistical significance set at $p<.05$ (SPSS 15.0 for Windows, SPSS, Inc.) To further understand the pathophysiology of the changes in CMRO2, we performed secondary explanatory analyses of bihemispheric CMRO2/ CMRglc and CMRglc. In addition we analyzed regional CMRO2, CMRO2/CMRglc and CMRglc from bilateral substantia nigra, putamen and globus pallidus. For substantia nigra, these data were only available for 10 controls and 10 participants with PD. Two participants with PD and one control did not undergo 3T MR scanning due to machine unavailability. In one additional control subject, CMRO2 measurements were unreliable due to low counts (calculated CMRO2 was negative). We also analyzed regional/hemispheric ratios of CMRO2 and CMRglc in the putamen and globus pallidus to determine if changes were a reflection of overall bihemispheric changes or were specific to these structures. All of these analyses were performed by unpaired t-tests. Finally, we determined if there were asymmetries in CMRO2 and CMRglc in the putamen and globus pallidus based on the side of the body with the most prominent parkinsonian signs (paired t-test). These data, along with measurements of systemic physiology and bihemispheric PET and MR measurements, are presented with p-values from 2-sided t-tests that are uncorrected for multiple comparisons. Data are presented as mean ± SD, unless otherwise noted.

This protocol received prior approval by the Washington University Human Studies Committee (IRB). Written informed consent was obtained from all participants.

RESULTS

Participants

Twenty-two subjects with PD were initially enrolled. Complete studies were carried out in 12. Eight did not have complete PET and MR studies due to technical problems. Two were determined not to have PD by lack of persisting asymmetry and no motor response to high doses of levodopa.. The 12 participants with PD were ages 44–77 (mean 60). There were 6 men and 6 women. Symptom duration was 8–48 months (mean 22). Hoehn and Yahr stages were: 2 Stage 1, 1 Stage 1.5, and 9 Stage 2 (Hoehn and Yahr 1967). Thirty-three normal control subjects were initially enrolled in the combined study of PD and Huntington's Disease. Ten did not successfully complete PET and MR studies: eight due to technical problems, one had an abnormal MR scan and one withdrew after MR. From the 23 who successfully completed PET and MR studies, 12 were matched by age to the 12 participants with PD without reference to any PET or MR data. Their ages were 45–71 (mean 61) years. There were 6 men and 6 women. Exclusion of subjects for incorrect diagnosis of PD and for technical reasons was independent of diagnosis and performed prior to any group data analysis.

Cerebral Mitochondrial Metabolism

The primary analysis showed a statistically significant 24% increase in bihemispheric CMRO2 in PD (p=.037) (Table 1). This increase is the opposite direction expected for defects in mitochondrial electron transport. Bihemispheric CMRglc was increased by 15% and CMRO2/CMRglc was increased by 10%. Both of these changes are also in the opposite direction expected with defects in mitochondrial electron transport. Examination of the confidence intervals for the differences between the two groups for these latter two measurements demonstrates that there is less than a 6% chance that CMRglc is lower in PD by any amount and only a 10% chance that CMRglc/CMRO2 is reduced by 10% or more.

Similar results, albeit with more measurement imprecision as expected, were found in the substantia nigra. Examination of the confidence intervals for the differences between the two groups demonstrates that there is less than a 20% chance that substantia nigra CMRO2 in PD is lower by more than 10%, that CMRglc is lower by more than 16% and that there is only a 10% chance that CMRglc/CMRO2 is reduced by any amount.

Measurements from putamen and globus pallidus also showed increases in regional CMRO2 and CMRglc (Table 2). Analysis of regional/bihemispheric ratios showed no difference between controls and participants with PD indicating that the increases in regional metabolism were primarily a reflection of overall bihemispheric changes There were no differences in CMRO2 or CMRglc between the structures ipsilateral and contralateral to the side of the body with the greatest signs (data not shown).

Systemic physiological measurements were comparable between the participants with PD and the controls: pCO_2 36 ± 4 vs. 37± 3 mm Hg (p= 0.406), arterial oxygen content 17.3 ± 1.4 vs. 17.0 ± 1.5 ml 100mL^{-1} (p= 0.604) and arterial plasma glucose 4.97 ± 0.45 vs. 4.72 ± 0.38 micromoles mL^{-1} (p=. 159).

There were no differences in volume between the normal controls and the participants for substantia nigra (p = .109), putamen (p = .465) or globus pallidus (p=.966).

DISCUSSION

The CMRO2 method that we have used has been validated for quantitative accuracy in non-human primates across a wide range of CMRO2 (Mintun et al, 1984; Altman et al, 1991). Included in these validation studies were measurements during intra-aortic sodium cyanide infusion, specifically demonstrating the ability of this technique to accurately measure a reduction in CMRO2 under conditions of reduced mitochondrial ETS activity (Altman et al, 1991).

We corrected for artifactual reductions in PET measurements due to partial volume effects from increases in ventricular, cisternal and sulcal CSF volume due to atrophy. The method does not correct for partial volume effects on the globus pallidus and putamen from surrounding white matter, which will worsen with atrophy of these structures (Videen et al, 1988; Videen et al, 1999). These white matter effects cause lower values for CMRO2 and CMRglc when globus pallidus and putamen are smaller. However, we found no difference in the volume of these structures between normal controls and participants with PD so this cannot be the explanation for the increased metabolism in PD

The hypothesis that patients with early PD have a defect in cerebral mitochondrial electron transport was tested by comparison of bihemispheric CMRO2 between participants with PD and age-matched normal controls. This primary analysis showed a statistically significant 24% increase in bihemispheric CMRO2 in PD. Explanatory analyses showed that CMRO2/CMRglc was not reduced. Similar results, albeit with more measurement imprecision as expected, were found in the substantia nigra. Increased CMRO2 with a normal CMRO2/CMRglc is inconsistent with a defect in mitochondrial oxidative phosphorylation due to reduced activity of the mitochondrial ETS (Brierley et al, 1977; Frackowiak et al, 1988). Whereas a finding of normal CMRO2 in PD would not exclude the possibility of dysfunction of mitochondrial ETS since complex I, III and IV activity can be substantially reduced before there is a reduction in CMRO2, dysfunction of the ETS cannot be the explanation for *increased* CMRO2 in PD (Davey et al, 1998). Since PD symptoms were already manifest in these 12 patients, we can exclude deficient energy production due to a reduced activity of the mitochondrial ETS as a pathogenic mechanism of their disease. Thus, while defects in mitochondrial ETS may be present in some patients with PD, the absence of such defects in these 12 patients with early PD indicates that they cannot be essential to the pathogenesis of neuronal death in early PD.

Previous studies of CMRglc in PD have yielded mixed results. In five studies of global CMRglc, four have reported reductions of approximately 20% and one reported no significant difference compared to age-matched controls (Kuhl et al, 1984; Leenders et al, 1985; Eidelberg et al, 1993; Eidelberg et al, 1994; Piert et al, 1996). In one of these studies, reductions in global CMRglc were seen only after L-dopa was administered suggesting that the reduction in metabolism may be at least in part due to medication effects (Piert et al, 1996). Berding et al have suggested that hypometabolism parallels disease duration (Piert et al, 1996). Thus, these reported changes in CMRglc likely reflect a consequence of the PD disease process. We deliberately chose to study patients with very early disease to try to determine if there was metabolic dysfunction that caused PD. The mean disease duration of 22 months in our study was substantially shorter than in these previous studies where it ranged from 4 to 15 years. Our analysis using absolute and relative measurements showing a trend toward increased global CMRglc in very early PD supports the theory that the reported reductions in metabolism are a consequence, not a cause, of the disease.

Basal ganglia metabolism in PD has been reported to be increased, decreased or unchanged (Kuhl et al, 1984; Rougemont et al, 1984; Martin et al, 1984; Wolfson et al, 1985; Leenders et al, 1985; Mohr et al, 1992; Eidelberg et al, 1993; Eidelberg et al, 1994; Eidelberg et al, 1995;

Piert et al, 1996). In these studies, findings are dependent on whether analysis is performed using absolute values, relative values or more sophisticated image analysis techniques such as statistical parametric mapping or scaled subprofile modeling (Eidelberg et al, 1993; Eidelberg et al, 1995; Piert et al, 1996). Increased metabolism in basal ganglia structures has been ascribed to loss of dopaminergic inhibitory pathways (Martin et al, 1984; Wolfson et al, 1985; Eidelberg et al, 1993). Following unilateral 6-hydroxydopamine lesions of the substantia nigra in rats, glucose hypermetabolism is focally restricted to ipsilateral globus pallidus and is transient (Wooten and Collins 1981). We found no evidence that the increases in basal ganglia CMRO2 and CMRglc were focal or related to the more clinically involved side, but we cannot exclude this possibility due to the small sample size and low power. Nevertheless, loss of inhibitory dopaminergic input seems an unlikely explanation for the general increase in hemispheric CMRO2 that we measured. Alternatively, this general increase in CMRO2 could be due, not to increased metabolic demand, but to an uncoupling of ATP production from oxidation in the terminal stage of oxidative phosphorylation. Uncoupling (dysfunction of Complex V ATP synthase) produces an increase in both CMRO2 and CMRglc similar to what we observed (Patel and Brewer 2003; Tretter and Adam-Vizi 2007). Whether uncoupling of oxidative phosphorylation occurs in early PD and whether or not it is important in the pathogenesis of PD will require further study.

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Table 1

Bilateral Cerebral and Substantia Nigra Metabolism in Early Parkinson Disease

	Number	CMRO2	CMRglc	CMRO2/CMRglc
Hemispheric				
Normal Controls	12	115 ± 25	20.7 ± 2.6	5.6 ± 1.3
Parkinson Disease	12	143 ± 36	23.8 ± 4.4	6.15 ± 1.6
t-test		p=.037*	p=.056	p=.39
Substantia Nigra				
Normal Controls	10	110 ± 71	15.9 ± 2.3	6.78 ± 3.91
Parkinson Disease	10	147 ± 91	17.9 ± 3.2	8.36 ± 4.91
t-test		p=.313	p=.122	p=.437

* Primary analysis

CMRO2 - cerebral metabolic rate of oxygen (micromoles $100g^{-1}$ min^{-1}), CMRglc – cerebral metabolic rate of glucose (micromoles $100g^{-1}$ min^{-1}), Values are mean ± SD.

Table 2

Bilateral Basal Ganglia Metabolism in Early Parkinson Disease

	Number	CMRO2	Regional/Hemispheric CMRO2 Ratio	CMRglc	Regional/Hemispheric CMRglc Ratio
Putamen					
Normal Controls	12	138 ± 27	1.21 ± 0.06	24.2 ± 4.1	1.17 ± 0.13
Parkinson Disease	12	175 ± 40	1.23 ± 0.19	29.8 ± 5.0	1.26 ± 0.11
t-test		p=.016	p=.86	p= .007	p=.08
Globus Pallidus					
Normal Controls	12	110 ± 39	0.95 ± 0.19	16.8 ± 2.8	0.81 ± 0.07
Parkinson Disease	12	137 ± 37	0.98 ± 0.23	20.6 ± 2.8	0.88 ± 0.12
t-test		p=..097	p=.702	p=.003	p=..093

CMRO2 - cerebral metabolic rate of oxygen (micromoles $100g^{-1}$ min^{-1}), CMRglc – cerebral metabolic rate of glucose (micromoles $100g^{-1}$ min^{-1}), Values are mean ± SD.