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PET studies of cerebral metabolism in Parkinson Disease

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Abstract A defect in cerebral energy production due to dysfunction of the mitochondrial electron transport system (ETS) has been postulated to be important in the pathogenesis of Parkinson Disease (PD). However, direct in vivo measurements of cerebral mitochondrial function are scant and inconsistent. We directly investigated cerebral mitochondrial function in vivo with positron emission tomography (PET) 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). Instead of the decrease in $CMRO_2$ and $CMRO_2$/CMRglc molar ratio characteristic of defects in mitochondrial oxidative metabolism, there was a statistically significant 24% general increase in $CMRO_2$ and no change in $CMRO_2$/CMRglc. Since PD symptoms were already manifest, reduced oxidative activity of the mitochondrial ETS cannot be a primary mechanism of neuronal death in early PD. This increase in metabolism could reflect the increased energy requirements of an injured brain or an uncoupling of ATP production from oxidation in the terminal stage of oxidative phosphorylation. Which is the case in early PD and whether these metabolic abnormalities are important in the pathogenesis of PD will require further study.

Keywords Parkinson Disease · Cerebral oxygen metabolism · Cerebral glucose metabolism · Mitochondria

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Introduction

Dysfunction of mitochondrial oxidative metabolism has been implicated in the pathogenesis of Parkinson Disease (PD) (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 (Schapira 1994; Keeney et al. 2006). However, in vivo evidence of cerebral mitochondrial electron transport dysfunction is scant and 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 treated 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.

Specific defects in mitochondrial ETS decrease $CMRO_2$ proportionately more than CMRglc (fewer moles of oxygen consumed per mole of glucose metabolized), thereby producing a reduction in the $CMRO_2$/CMRglc molar ratio below the normal value of 5.6 (Brierley et al. 1977; Frackowiak et al. 1988). Therefore, in vivo assessment of mitochondrial energy metabolism requires combined measurement of $CMRO_2$ and CMRglc, which had not previously performed in Parkinson Disease.

PET studies of early PD at Washington University

We directly measured $CMRO_2$ and CMRglc in vivo with positron emission tomography (PET) in 12 early, never-

Table 1 Bilateral cerebral and substantia nigra metabolism in early Parkinson Disease (from Powers et al. 2008)

	Number	$CMRO_2$	CMRglc	$CMRO_2$/CMRglc
Bihemispheric				
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[a]	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

$CMRO_2$—cerebral metabolic rate of oxygen (micromoles 100 g^{-1} min^{-1}), CMRglc—cerebral metabolic rate of glucose (micromoles 100 g^{-1} min^{-1}), Values are mean ± SD

[a] Primary analysis

medicated participants with PD and compared to 12 age-matched normal controls. All participants also underwent magnetic resonance scanning to permit correction of the PET data for brain atrophy and to permit accurate localization of substantia nigra, putamen and globus pallidus for regional measurements (Powers et al. 2008).

The 12 participants (6 men/6 women) with PD were 44–77 years old (mean 60). Symptoms had been present for 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). Twelve normal control subjects from a cohort of 23 were matched by age to the 12 participants with PD without reference to any PET data. Their ages were 45–71 (mean 61) years. There were 6 men and 6 women.

There was a statistically significant 24% increase in hemispheric $CMRO_2$ in PD (p=.037) (Table 1). This change was in the opposite direction of the decrease that occurs with defects in mitochondrial electron transport. Hemispheric CMRglc also was increased by 15% and $CMRO_2$/CMRglc was increased by 10%. Both of these changes are also in the opposite direction that occurs 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 $CMRO_2$/CMRglc is reduced by 10% or more.

Similar results, albeit with more measurement imprecision as expected for regional data, were found in the substantia nigra, putamen and globus pallidus (Tables 1 and 2). Analysis of regional/hemispheric ratios for putamen and globus pallidus showed no difference between controls and participants with PD indicating that the increases in regional metabolism were primarily a reflection of overall brain changes.

Previous PET studies of cerebral metabolism in PD

Previous PET studies of cerebral metabolism 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, 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 (Berding et al. 2001). Berding et al. (2001) have suggested that hypometabolism parallels disease duration.

Table 2 Bilateral basal ganglia metabolism in early Parkinson Disease (from Powers et al. 2008)

	Number	$CMRO_2$	Regional/Hemispheric $CMRO_2$ 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

$CMRO_2$—cerebral metabolic rate of oxygen (micromoles 100 g^{-1} min^{-1}), CMRglc—cerebral metabolic rate of glucose (micromoles 100 g^{-1} min^{-1}), Values are mean ± SD

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.

Regional basal ganglia metabolism in PD measured with PET 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, 1994, 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, 1995; Piert et al. 1996). The validity of analysis methods that use normalization based on whole brain values for assessing relative basal ganglia metabolism has recently been challenged (Borghammer et al. 2009). We found no evidence for relative increases or decreases in basal ganglia $CMRO_2$ or CMRglc in early PD using either absolute values or normalization based on whole brain values.

Increased cerebral oxidative metabolism in early PD

The pathophysiological basis for the increase in cerebral oxidative metabolism in early PD is not known. Based on the classic study by Wooten and Collins (1981) who described transient glucose hypermetabolism focally restricted to ipsilateral globus pallidus following unilateral 6-hydroxydopamine lesions of the substantia nigra in rats, 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). A generalized loss of inhibitory dopaminergic input throughout the brain is a possible cause for the general increase in metabolism. Alternatively, this general increase in $CMRO_2$ 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 $CMRO_2$ 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.

Summary and conclusions

In summary, we found a generalized increase in cerebral oxygen metabolism in never-medicated patients with early PD. Since PD symptoms were already manifest, we can exclude reduced oxidative 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 defects in cerebral oxidative metabolism in these12 patients with early PD indicates that dysfunction of ETS-mediated oxidation cannot be essential to the pathogenesis of neuronal death in early PD.

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