S-phase, high mitotic index, pleomorphic nuclei with prominent nucleoli, and severe necrosis). The distinct appearance of a proto-oncogene activation in a certain histopathological tumour type also shows the importance of using histologically well defined materials when investigating new markers of tumour behaviour.

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MITOCHONDRIAL COMPLEX I DEFICIENCY IN PARKINSON'S DISEASE

SIR,—The cause of dopaminergic cell death in the substantia nigra of patients with Parkinson's disease is unknown. The meperidine analogue, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), is selectively toxic for dopamine-containing cells of the substantia nigra and produces parkinsonism. 1-methyl-4-phenylpyridinium (MPP+), a metabolite of MPTP, is a specific inhibitor of nicotinamide adenine dinucleotide (reduced) (NADH) ubiquinone (CoQ) reductase (complex I), the first enzyme of the respiratory chain, within mitochondria. Complex I inhibition, and the consequent reduction of ATP synthesis, has been proposed as a possible cause for nigrostriatal cell death in MPTP models of parkinsonism.[1] We have studied the activity of mitochondrial respiratory chain in the substantia nigra of nine patients who died with Parkinson's disease.

Substantia nigra were obtained at necropsy from the nine patients and from nine controls matched for age and time of death to refrigeration and brain dissection. Parkinson's disease was confirmed pathologically. All patients had been receiving L-dopa up to the time of death. Controls had no evidence of neurological or psychiatric disease and no pathological abnormalities in the substantia nigra. Mitochondrial respiratory chain enzyme analyses and protein concentrations were measured by standard techniques (details from A. H. V. S.).

There was no difference in the total protein content of the control and Parkinson's disease nigral tissue homogenates (table). Citrate synthase activity was also similar in the two groups, which indicates that there was no difference in the substantia nigra mitochondrial concentrations. Rotenone sensitive NADH cytochrome c reductase activity, which measures complexes I and III of the respiratory chain, was significantly reduced in the Parkinson's disease patients. Antimycin A sensitive succinate cytochrome c reductase activity, which reflects the activity of complexes II and III, was normal. The ratio of these enzyme activities provides an internal standard for complex I activity. This ratio was significantly reduced in the patients with Parkinson's disease. The activity of NADH CoQ reductase, an enzyme specific to complex I, was also significantly reduced in these patients.

We found a significant and specific reduction of mitochondrial complex I activity in Parkinson's disease patients. It is not possible to distinguish between the contributions of the astrocytic and neuronal components of substantia nigra. Dopamine containing neurons are especially susceptible to MPP+ because of its accumulation by the dopaminergic re-uptake system.[2] Therefore a more severe reduction of substantia nigra neuronal complex I activity than shown in these experiments may be masked by normal or only moderately reduced activity in the surrounding astrocytes. However, inhibition of astrocytic complex I activity cannot be excluded. The similarity of the findings in Parkinson's disease described here and the effects of MPP+ suggest that complex I deficiency in Parkinson's disease may be related to the primary

MEAN (SD) RESPIRATORY CHAIN ENZYME ACTIVITIES IN SUBSTANTIA NIGRA

—	Control (n = 9)	Parkinson's disease (n = 9)
Age (yr)	66·1 (23·0)	64·3 (21·3)
Death to refrigeration (min)	107·4 (52·2)	128·9 (72·5)
Death to brain removal (h)	19·0 (5·9)	17·7 (11·1)
Substantia nigra protein concentration (mg/g wet weight)	109·0 (8·9)	109·7 (17·8)
Citrate synthase	110·4 (42·1)	105·8 (50·0)
NADH cytochrome c reductase (rotenone sensitive) (=A)	4·36 (1·41)	2·68 (1·01)‡
Succinate cytochrome c reductase (=B)	9·46 (3·01)	9·59 (3·15)
A/B ratio	0·48 (0·16)	0·30 (0·11)†
NADH CoQ reductase (rotenone sensitive)	3·36 (0·44)§	2·34 (0·76)*§

Unpaired t test: *p < 0·05; †p < 0·02, ‡p < 0·01. §n = 5. Enzyme activities in nmol/min mg total protein.

disease process. A toxin could be taken up into nigral mitochondria, in much the same way as MPP+, and induce complex I deficiency. The mechanism by which MPP+ produces complex I deficiency is not known but could be through direct binding or the induction of oxidative stress and the generation of free radicals.

Rotenone, another inhibitor of complex I, has similar effects to MPP+ on the nigrostriatal pathway in rats.[3] Rotenone binds to a polypeptide of molecular mass 33 kDa, one of the polypeptides of complex I encoded by mitochondrial DNA (mt DNA).[4] The generation of free radicals within mitochondria might chronically damage mt DNA. mt DNA is more vulnerable to the destructive and mutagenic effects of free radicals than is nuclear DNA.[5] This probably reflects the absence of a histone coat on mt DNA and the lack of nucleotide excision repair and recombinational DNA repair.[6] As mt DNA encodes 7 of the 25 polypeptides of complex I,[7] extensive damage to mt DNA would result in reduced complex I activity. The effects of L-dopa on brain mitochondrial respiratory chain function needs to be studied to exclude this is a possible cause for the complex I defect.

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