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The coenzyme Q_{10} status of the brain regions of Parkinson's disease patients

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ABSTRACT

There is increasing evidence that impairment of mitochondrial function and oxidative damage are contributing factors to the pathophysiology of Parkinson's disease (PD). Studies have reported decreased levels of the mitochondrial electron transport chain carrier, coenzyme Q_{10} (CoQ_{10}) in plasma and platelets from PD patients. Although a deficit in peripheral CoQ_{10} has been reported no studies have assessed the CoQ_{10} status of the PD brain. In this study we investigated the CoQ_{10} status of the substantia nigra, cerebellum, cortex and striatum brain regions of both PD patients and age-matched controls. The results of this study indicate a significant reduction ($p = 0.007$) in CoQ_{10} concentration in the cortex region of the brain. In conclusion, the results of this study indicate evidence of a deficit in brain CoQ_{10} status may be involved in the pathophysiology of PD.

Parkinson's disease (PD) is a multisystem neurodegenerative disorder that is pathologically characterised by proteinaceous intraneuronal Lewy bodies and widespread neuronal degeneration. Whilst the majority of PD cases are sporadic (~85% [6]), to date, most of our knowledge of the disease's aetiology has come from the five genes which when mutated result in Mendelian forms of the disease [21,14,4,30,29]. One of the first insights into the pathogenesis of sporadic PD, later corroborated by genetic evidence, was the involvement of both mitochondrial dysfunction and oxidative stress in the aetiology of PD [9]. Initial evidence for the involvement of mitochondrial electron transport chain (ETC) dysfunction in PD resulted from the studies with *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which was found to induce a Parkinsonian-like syndrome by the inhibition of ETC complex I (NADH coenzyme Q_{10} reductase) activity [16]. In a subsequent study evidence of decreased ETC complex I activity was reported in postmortem brain tissue of PD patients [24]. Evidence of extracerebral ETC dysfunction has also been noted in PD with decreased activities of complex I and complexes I–II (succinate coenzyme Q_{10} reductase) and complex I, II–III and IV (cytochrome oxidase) being detected in platelets [11] and skeletal muscle [26], respectively of PD patients. The origins to this ETC dysfunction remain unknown, despite numerous studies no genetic links have been established. One contributory factor may be the oxidative stress which has been associated with PD [10]. Loss of ETC function may result from oxidative damage to the mitochondrial membrane phospholipids and mitochondrial DNA [15,13]. Evidence of a deficiency in the ETC electron carrier and cellular antioxidant, coenzyme Q_{10} (CoQ_{10} [3,17]) has also been reported in both plasma [19] and platelet mitochondria from PD patients [27]. Supplementation with CoQ_{10} has been reported to reduce the loss of dopaminergic neurons in aged mice treated with MPTP indicating a possible therapeutic role of CoQ_{10} in the treatment of PD [2]. Whilst clinical studies have demonstrated the ability of CoQ_{10} supplementation to slow the progressive deterioration of function in early stage PD [28] a symptomatic efficacy of CoQ_{10} in the treatment of this disease has yet to be demonstrated.

At present it is uncertain whether the purported therapeutic potential of CoQ_{10} in the treatment of PD is the result of its antioxidant potential or the replenishment of an underlying deficiency. Although studies in peripheral tissue have indicated evidence of a potential CoQ_{10} deficiency, CoQ_{10} status of PD brain remains unknown.

In this study we have examined CoQ_{10} levels in the, striatum, cerebellum, substantia nigra and cortex of postmortem PD and age-matched control brain samples.

This study was approved by the Joint Research and Ethics Committee of the Institute of Neurology and the National Hospital for

Abbreviations: CoQ_{10}, coenzyme Q10; ETC, electron transport chain; MPTP, *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease.

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Neurology and Neurosurgery. Informed consent was obtained from all patients.

Pathological confirmation of the PD samples was obtained from the Queen Square Brain Bank for Neurological Disorders (QSBBND), UK. All cases showed severe depletion of pigmented neurons in the substantia nigra and locus coeruleus and the presence of Lewy bodies. There were no glial inclusions or other pathology that could account for their Parkinsonism. Mean age of disease onset was 61 ± 4 years; mean age at death was 75 ± 3 years. Age- and sex-matched control samples were obtained from the QSBBND, none showed any pathological signs of neurological disease at post-mortem examination.

All reagents were of analytical grade and obtained from BDH Ltd. (Dagenham, UK) or Sigma Chemical Company (Poole, UK). HPLC grade orthophosphoric acid was supplied by Fisher Scientific (Loughborough, UK). A Techsphere ODS 5-μm HPLC column was purchased from HPLC technology (Macclesfield, UK).

Flash-frozen brain tissue homogenates were prepared as described by Heales et al. [12]. Brain biopsies (10–40 mg) were homogenised 1:9 (w/v) in media: 320 mmol/L, 1 mmol/L ethylenediamine tetra acetic acid dipotassium salt, 10 mmol/L Trizma-base. The homogenates were stored at −70 °C prior to CoQ_{10} determination.

Coenzyme Q_{10} was determined in human brain homogenates by HPLC and UV detection at 275 nm by the method of Duncan et al. [7].

Protein amounts were determined by the method of Lowry et al. [18] using bovine serum albumin as a standard.

To determine the most appropriate statistic, intragroup variances were first compared by the *F*-test. Having demonstrated no significant differences in the variances of any of the four groups, significance was assessed using the Wilcoxon rank sum test with continuity correction which assumes a common continuous distribution under the null but does not require sampling from a normal population.

Endogenous CoQ_{10} levels were determined in multiple PD and age-matched controls. All four regions were analysed, substantia nigra, striatum, cerebellum and cortex. However, only the cortex showed a significant decrease in CoQ_{10} levels in PD brain compared to controls (Fig. 1), with a mean difference of 87.3 CoQ_{10} pmol/mg protein.

In this study we investigated CoQ_{10} status directly in PD brain tissue. Our results indicate evidence of a CoQ_{10} deficit in the cortex region of the brain ($p = 0.007$). CoQ_{10} is an electron carrier and proton translocator that forms an essential component of the ETC

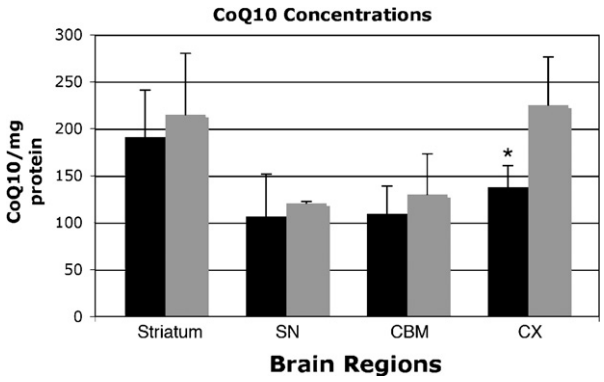

Fig. 1. CoQ_{10} concentrations per milligram of protein plotted in four brain regions; striatum $n = 20$, substantia nigra (SN) $n = 8$, cerebellum (CBM) $n = 25$ and cortex (CX) $n = 13$. Mean values for each group and associated standard errors are depicted; black bars PD and the controls are in grey. *Indicates a statistically significant difference in mean CoQ_{10} concentrations in the cortex ($p = 0.007$).

[17], as well as an electron carrier CoQ_{10} also acts as a lipid soluble antioxidant [3]. A CoQ_{10} deficiency may therefore either impair oxidative energy metabolism resulting in increased free radical production and oxidative stress through deregulation of the ETC or increase oxidative stress in its capacity as an antioxidant. Studies have reported reduced CoQ_{10} concentrations in plasma [19] and platelet mitochondria from PD patients [27]. However, this is the first study as far as the authors are aware to examine the CoQ_{10} status directly in PD brain tissue. The cause of the deficit in brain cortical CoQ_{10} status observed in this study is as yet unknown and remains to be elucidated. However, the putative increase in brain cortex oxidative stress as indicated in PD patients by both an increase lipoxidative damage [5] and up-regulated superoxide dismutase activity [22] may be a contributory factor to the decrease in cortical CoQ_{10} status.

Deficiency in ETC complex I activity of the substantia nigra has long been suspected as the origin of PD-associated mitochondrial dysfunction in the brain [24]. However, in this study we demonstrate a deficit in the CoQ_{10} status of the cortex region of the brain that may also be involved in the pathophysiology of PD either through failure in energy metabolism or a decrease in cellular antioxidant capacity. Whilst the exact functional consequences of the diminution in CoQ_{10} are unclear, it has been shown that ETC activity remains unaffected even after a 60–70% decrease in cellular CoQ_{10} [1]. Indeed, assessment of ETC complex II–III activity, an enzyme that is dependent upon endogenous CoQ_{10} [23] in the remaining brain material from the PD ($n = 2$ for each region; striatum, cerebellum, substantia nigra and cortex) and control brain regions ($n = 5$) revealed no decrease in the activity of this enzyme between PD or control brain samples (results not shown). Therefore, this may suggest that the antioxidant function of CoQ_{10} may be more pertinent to the pathogenesis of PD. *In vitro* studies using fibroblasts from PD patients have indicated that the ability of exogenously administered CoQ_{10} to restore ETC activity in these cells was due to its antioxidant property rather than its ETC electron carrier/proton transporter function [31].

The cause of this diminution in brain CoQ_{10} status in PD is as yet unknown. However, since this decrease in CoQ_{10} is not as profound as that reported in inborn errors of CoQ_{10} biosynthesis [20] it may suggest that secondary factors such as oxidative stress which is associated with PD [9] may be responsible for this diminution in CoQ_{10} status. In the present study, citrate synthase activity (a mitochondrial marker enzyme) [25] was found to be comparable between the PD brain regions ($n = 2$ for each PD brain region) and their respective controls ($n = 5$; results not shown), This may suggest that the decrease in CoQ_{10} level detected in this study may not have resulted from a loss of mitochondrial volume/enrichment since 45% of cellular CoQ_{10} is intramitochondrial [8].

In conclusion, the evidence of decreased brain CoQ_{10} status identified in this study is therefore consistent with the reported efficacy of CoQ_{10} supplementation in the retardation of functional deterioration in early stage PD [28]. However, at present it is uncertain as to what extent this deficit in brain CoQ_{10} status may contribute to the pathophysiology of PD.

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