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Dopamine Reduction in the Substantia Nigra of Parkinson's Disease Patients Confirmed by In Vivo Magnetic Resonance Spectroscopic Imaging

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Abstract

Objectives: Metabolic changes in the substantia nigra of patients with Parkinson's disease were previously investigated in different molecular-pathological examinations. The aim of our study was the in vivo measurement of these alterations using three-dimensional magnetic resonance spectroscopic imaging.

Methods: 21 patients with Parkinson's disease and 24 controls were examined using magnetic resonance spectroscopic imaging at 3 Tesla. The spectra of rostral and caudal substantia nigra regions were analyzed using LCModel. For spectral fitting, an adjusted basis data set with pathology-specific metabolites and macromolecules was used to better reproduce the in vivo spectra. To assess differences between both groups more accurately, especially in metabolites at lower concentrations, group-averaged spectra were evaluated in addition to the analysis of individual data.

Results: We found significantly decreased N-acetylaspartate, choline, creatine, *myo*-inositol, glutathione and dopamine concentrations in patients with Parkinson's disease compared to controls, whereas glutamine+glutamate, γ-aminobutyric acid, and homovanillic acid were slightly increased. According to anatomical features, clear differences in the biochemical profiles were found between rostral and caudal substantia nigra voxels in both groups.

Conclusions: Reduced N-acetylaspartate and dopamine concentrations result from progressive degeneration of dopamine-producing neurons within the substantia nigra pars compacta. Decreased creatine levels can be interpreted as impaired energy metabolism due to mitochondrial dysfunction. Lower glutathione concentrations might be a cause or consequence of oxidative stress. Furthermore, slightly increased glutamine+glutamate and γ-aminobutyric acid levels are expected based on *post mortem* data in Parkinson's disease. To the best of our knowledge, this is the first non-invasive confirmation of these metabolic changes.

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Introduction

Parkinson's disease (PD) is a frequently occurring, age-related, neurodegenerative disorder causing bradykinesia, tremor and motor impairment. It is caused by progressive loss of dopamine-secreting neurons within the substantia nigra (SN) pars compacta [1]. In a post mortem study [2], the neurochemical markers of inhibitory and excitatory neurotransmission were measured within the SN. However, the process of neuron loss is still not well understood. There is strong evidence that mitochondrial dysfunction and oxidative stress play a causal role in PD pathogenesis, and discovering metabolic alterations in the SN would improve early diagnosis and could lead to therapeutic advances.

Magnetic resonance spectroscopic imaging (MRSI) is a widely used non-invasive method that provides information about metabolic composition, especially in MR spectra acquired at high magnetic field strengths and with short echo times, in which various metabolites can be detected. To estimate metabolite concentrations, the LCModel algorithm is most commonly used [3], [4]. However, methodological limitations such as complex multiplet resonance patterns, overlapping metabolites, variations in line shape, and underlying baseline variations make it difficult to quantify metabolites with lower concentrations and to confirm post-mortem results in individual spectra. In particular, it has not yet been possible to identify the dopamine signal in in-vivo spectra of Parkinson patients.

The goal of our study was the non-invasive measurement of metabolic changes within the SN of PD patients using 3D MRSI to confirm molecular-pathological post-mortem results in vivo. For this we used an improved LC-Model analysis and evaluated averaged spectra from groups of patients and controls.

Materials and Methods

Ethics Statement

All subjects gave their written informed consent to the MRSI examination before participating in this study, which was