Neuroprotective effects of modafinil in a nonhuman primate Parkinson model

S. A. van Vliet[1,2], E. L. Blezer[3], M. Jongsma[1], R. A. van Wersch[1], and I. H. Philippens[1]

[1]Diagnostics and Therapy, TNO Defense, security and safety, Rijswijk, Netherlands, [2]Psychopharmacology, Institute of Pharmaceutical Sciences and Rudolf Magnus Institute of Neurosciences, Utrecht, Netherlands, [3]Image Sciences Institute, University Medical Center Utrecht, Utrecht, Netherlands

Introduction

Parkinson's disease (PD) is caused by progressive neuronal loss in the substantia nigra pars compacta (SNc) resulting in bradykinesia, tremor and muscle rigidity. PD is incurable, since present medications do not counteract progression of the disease and chronic therapy is associated with declined efficacy and increased side effects. Therefore, a better strategy would be to prevent neuronal loss. Modafinil, a vigilance-stimulating compound, has shown to be effective in protecting SNc neurons from various kinds of damage. In this study the protective effects of modafinil are tested with MRI/MRS in a nonhuman primate model of PD and results are compared with recently published neurological outcomes (1).

Material and Methods

Study protocol: Marmosets (n=12) were intoxicated with 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP, sc). MPTP selective destroys dopaminergic cells in the SNc. Intoxication was over 9 days (day 0: 2 mg/kg and days 1, 2, 5 and 8: 1 mg/kg). Animals orally received daily vehicle (control: n=6, 10% sucrose solution) or modafinil (n=6, 100 mg/kg).

Behavioral tests: Tests included 1) a clinical scoring list (appetite; inadequacy of fur grooming; apathy; immobility; rigidity and presence of tremors) and 2) the abnormal involuntary movement scale (AIMS) which records in detail the occurrence of involuntary movements. Scores start from 0 (no abnormalities) and increase with increasing deficits.

MRI experiments: Experiments were performed before, 6 (experimental day 15) and 26 days (experimental day 34) after MPTP intoxication. During MRI (4.7T, Varian) animals were mechanically ventilated with isofluorane (1-1.5%) in N2O/O2 (70/30). Transversal slices (11x0.75mm) were defined including the SNc. Quantitative T2 relaxation time images were obtained (TR=2000ms; TE=17.5+7*17.5ms; FOV 4x4cm; matrix 128x128). Single voxel 1H MRS was performed using a PRESS sequence (TR=4000 ms; TE=30 and 144ms, NEX=64). CHESS pulses and dephasing gradients were used to suppress the water signal. The VOI (3x9x3mm) included both left and right SNc. Brains were collected for quantitative histological analyses one day after the last MR-session.

MRI evaluation: The SNc and a reference area in the cortex were outlined from which a T2 relaxation time ratio was calculated. Spectra (TE=30ms) were analyzed using jMRUI (version 2.1). Pre-processing included: removal of the first two data points, apodization (Gaussian, 5Hz) and residual water signal filtering. Spectra were fitted in the time-domain using AMARES. An a priori knowledge database was constructed including peak position and maximal metabolite line-widths. NAA/tCr, Cho/tCr and Ino/tCr ratios were calculated. The presence of lactate was qualitatively examined in spectra (TE=144ms).

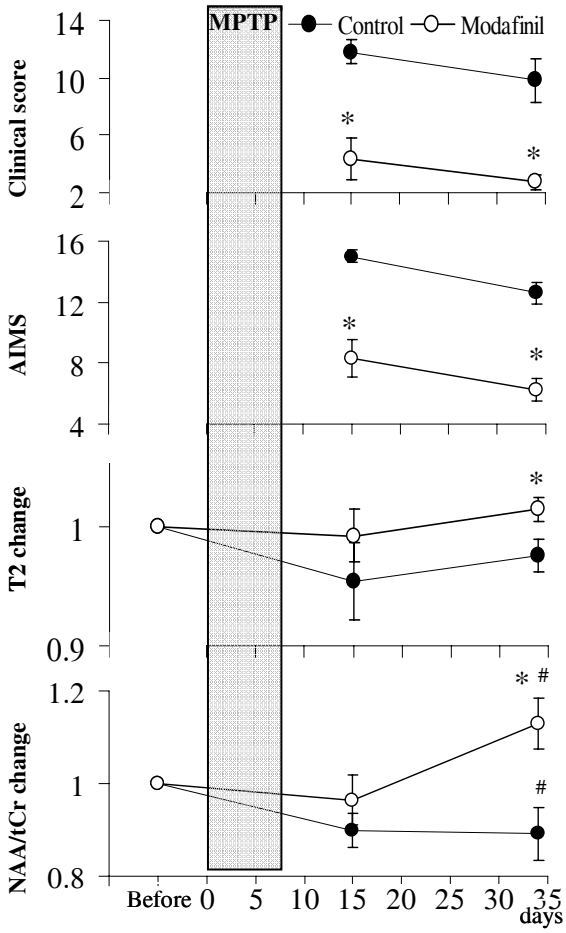
Data evaluation: MRI-data are shown as relative changes compared to before MPTP intoxication. Data (mean±sem) were evaluated by one-way ANOVA followed by a multiple comparison procedure (LSD-Method). $P<0.05$ was considered statistically significant.

Results

The figure shows the results of MPTP intoxication/modafinil treatment on all observed parameters. Neurological symptoms were clearly reduced after initiation of modafinil treatment. Control animals showed a reduction in the T2-relaxation time of the SNc which was absent in treated animals Eventually, T2 relaxation times were significant different at the last MR experiment. NAA/tCr ratios of controls were lower after MPTP intoxication becoming significant at the last MR experiment. Modafinil treated animals showed initially no changes. However values were significantly increased during the last MR experiment and were different from controls. None of the other ratios changed significantly and no lactate peaks were observed throughout the experiment. Histological analyses showed that the reduction of dopaminergic neurons in the SNc was lower in the modafinil treated animals (data not shown)

Discussion

MPTP intoxication resulted in worsening of neurological symptoms as has been reported before in this (1) and other species (2-4). T2 relaxation times decreased which is not in agreement with results obtained after MPTP intoxication in cats (4) and other nonhuman primates (2,3). However a decrease in T2 has been reported in the SNc of PD patients (5) and is associated to the presence of iron (6). Iron deposition has been shown in MPTP intoxicated nonhuman primates (7). Decrease in NAA/tCr has been reported in patients (8) and in MPTP intoxicated nonhuman primates (4), and is most likely the result of neuronal damage. Modafinil treatment has a clear ameliorating effect in all observed parameters. Interestingly, we see a clear increase in the NAA/tCr in the modafinil treated animals for which we have currently no clear explanation. In conclusion modafinil protects neurons from damage induced by MPTP making it a promising therapy for PD.



Changes in the neurological symptoms and MR-characteristics of the SNc as a result of MPTP intoxication/modafinil treatment. $P<0.05$, * versus control, # versus before

Literature

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