Increased Basal Ganglia Metabolism by the Dopamine Antagonist Metoclopramide Measured by Perfusion MRI

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Introduction

Metoclopramide is an antiemetic non-specific dopamine antagonist that possesses D1 and D2 receptor selectivity (1) and inhibits dopamine neurotransmission. Parkinson´s disease (PD) is a common neurodegenerative disease whose pathophysiological mechanisms are still unknown. The disease is characterized by a degeneration of dopaminergic neurons in the substantia nigra that results in a loss of brain dopamine, most prominently in the striatum. The clinical manifestations of drug-induced Parkinsonism are often indistinguishable from idiopathic Parkinson's disease. Among the drugs known to produce Parkinsonism are dopamine antagonists prescribed for symptomatic treatment of nausa and vomiting, such as metoclopramide, although this adverse effect is only present after chronic treatment. We used here a standard unique oral dose of metoclopramide to study changes in perfusion associated to the antidopaminergic effect in young healthy subjects.

Materials and Methods

Studies were performed on a 3T Siemens Trio using an 8-channel head array. Fifteen healthy volunteers (8 females) participated in the study after signing informed consent. Eight subjects (age=23±3 years) received an oral dose (10mg) of metoclopramide and seven (age=24±4 years) were given a placebo. The study took place in two sessions: the first prior to taking any medication and the second, one hour after medication intake. During each scanning session resting perfusion was measured using a pseudo-continuous arterial spin labeling (PCASL) technique (2) with EPI readout (TE=20ms, TR=4 sec, resolution=3.44x3.44 mm^2, FOV=220x220 mm^2, 16 slices, slice thickness=6mm, gap=1.5 mm, matrix size=64x64, BW=2365 Hz/pixel). The labeling time was 1.6 sec and post-labeling delay was 1.5 sec. 50 label/control pairs were acquired in a scan time of 6 min. The first pair was discarded because the signal had not reached the steady-state. Each subject's images were realigned and co-registered to the anatomical dataset, acquired using a T_1-MPRAGE sequence, before subtraction of label and control. 49 perfusion images were obtained. A cerebral blood flow (CBF) map was computed from the mean perfusion image using the one-compartment model (3), normalized to the standard template and smoothed with an 8 mm Gaussian kernel. A phase contrast imaging sequence was used to measure blood flow through the carotid arteries. The slice was chosen perpendicular to the carotids, based on an angiogram previously acquired. Imaging parameters were: in-plane resolution = 0.55x0.55 mm^2, slice thickness=5 mm, TE=6.77 ms, TR=21.5 ms, matrix= 256x256, 4 averages, BW=260 Hz/pixel, flip angle=15°, total scan time = 22 s, maximum encoded velocity = 50 cm/s. Mean velocity and area were measured in right and left internal carotid arteries. Voxel-wise statistical analysis of the CBF data was performed using SPM5, without prior normalization by the global mean. In a first step, a flexible factorial design was set up with 3 factors: subject, group (metoclopramide or placebo) and condition (baseline, post-medication). The model included the interaction term group x condition and revealed significant interaction between these two factors. Thus, post-hoc comparisons were realized in the metoclopramide group to assess differences between conditions using a paired t-test. Comparisons in other haemodynamic parameters between the post-medication and baseline measurements were assessed separately in each group (metoclopramide and placebo) using one sample t-tests on the parameter differences.

Results and Discussion

Phase contrast MRI showed that metoclopramide caused a significant reduction in mean blood velocity in the internal carotid arteries that resulted in a decrease in total blood flow through the carotids (Table 1), which is consistent with the hypotensive effect of metoclopramide previously described (4). There were no significant changes in the areas of these blood vessels. Mean whole brain CBF measured using PCASL was also significantly reduced by metoclopramide intake. No significant changes were found in the placebo group. Whole brain voxel-wise statistical analysis on the CBF data showed that metoclopramide intake produced a decrease in CBF distributed throughout the cortex (Figure 1) and an increase in CBF in the striatum (Figure 2), confirmed also by ROI analysis (Table 1). It is worth noting that these are changes in absolute CBF since the data have not been normalized by global values. Basal ganglia hypermetabolism has been found in some studies of PD patients with and without medication, using PET (5), SPECT (6) and DSC-MRI (7). The fact that the same effect is seen in young healthy subjects after the intake of a single oral dose of metoclopramide, would suggest that this metabolic abnormality is due to dopamine reduction in the striatum. We propose the study of striatal hyperperfusion as a very early marker of Parkinson's Disease.

Table 1. Haemodynamic data. All parameters (mean ± standard deviation) are given as differences of measurements taken 1 hour after medication intake minus baseline and expressed as percentage of baseline values. T and one-tailed p values have been obtained using one sample t-tests with the null hypothesis being mean = 0.

	Metoclopramide	T / p	Placebo	T / p
Right internal carotid artery mean blood velocity	-10.00 ± 14.79	1.9142 / **0.0486**	-0.94 ± 9.57	0.2602 / 0.4017
Left internal carotid mean blood velocity	-10.14 ± 13.88	2.0649 / **0.0389**	2.94 ± 8.80	0.8825 / 0.2057
Right internal carotid artery area	-0.10 ± 10.81	0.0272 / 0.4895	-0.65 ± 11.16	0.1535 / 0.4415
Left internal carotid artery area	3.94 ± 8.65	1.2881 / 0.1193	-6.37± 11.81	1.4255 / 0.1020
Total blood flow through the carotids	-9.10 ± 12.91	1.9918 / **0.0433**	-3.07 ± 10.53	0.7719 / 0.2347
Mean CBF	-6.47 ± 7.64	2.3952 / **0.0239**	-1.28 ± 6.98	0.4845 / 0.3226
Right striatum ROI CBF	12.24 ± 13.42	2.5788 / **0.0183**	-2.04 ± 9.74	0.5555 / 0.2993
Left striatum ROI CBF	12.53 ± 12.71	2.7873 / **0.0135**	-3.20 ± 9.58	0.8845 / 0.2052

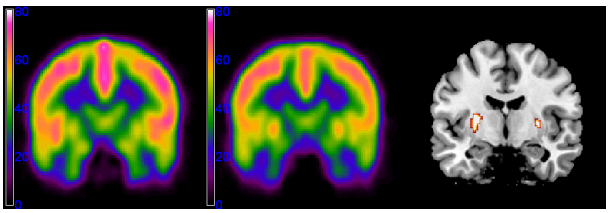

Figure 2. Group mean absolute CBF maps [ml/(min·100g)] in the metoclopramide group: (a) baseline; (b) one-hour after medication intake. (c) SPM{t} map overlaid on an anatomical T_1-weigthed template, showing clusters of significantly higher perfusion in the basal ganglia after metoclopramide intake ($p<0.01$ unc., $k>10$).

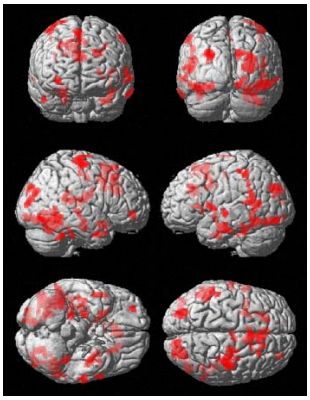

Figure 1. SPM{t} map overlaid on a 3D-rendered brain, showing clusters of significantly lower perfusion after metoclopramide intake ($p<0.01$ unc., $k>50$).

Conclusions

The dopamine antagonist metoclopramide caused a decrease in perfusion distributed throughout the cortex and a perfusion increase localized to the striatum. Striatal hyperperfusion could be a very early marker of PD. ASL perfusion MRI could aid in the early diagnosis of the disease.

Bibliography

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