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RAPID COMMUNICATION

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Dopamine transporter density in patients with tardive dyskinesia: a single photon emission computed tomography study

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Abstract *Rationale:* Tardive dyskinesia occurs frequently in schizophrenic patients chronically treated with classical antipsychotic medication. It may be caused by loss of dopaminergic cells, due to free radicals as a product of high synaptic dopamine levels. *Objective:* To evaluate dopamine transporter density in the striatum in patients with tardive dyskinesia. *Methods:* Striatal [^{123}I]FP-CIT binding was measured with SPECT in seven schizophrenic patients with tardive dyskinesia and eight healthy controls. *Results:* No significant difference was found between striatal [^{123}I]FP-CIT binding ratios in patients with tardive dyskinesia and controls. *Conclusions:* This preliminary study indicates no change in striatal dopamine transporter density in schizophrenic patients with tardive dyskinesia. This finding does not support the hypothesis that tardive dyskinesia is caused by dopaminergic cell loss.

Keywords Tardive dyskinesia · Dopamine transporter · Schizophrenia · Antipsychotic treatment · Single photon emission computed tomography

Introduction

Chronic treatment with classical antipsychotic medication can induce tardive dyskinesia, a chronic choreoathetoid movement disorder. One theory on the pathophysiology of tardive dyskinesia supposes a supersensitivity of dopamine receptors from prolonged receptor blockade or upregulation of these receptors.

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An alternative hypothesis is the free radical hypothesis. According to this theory tardive dyskinesia is a neurodegenerative process, with neuronal damage in the basal ganglia. Prolonged treatment with antipsychotic medication increases the dopamine metabolism and turnover. In this process free radicals are generated. This excessive production of free radicals could lead to neuronal membrane instability and dopaminergic cell death (Lohr et al. 1988). Treatment with the free radical scavenger vitamin E is based on this theory (Soares and McGrath 1999). However, to date it has to be established whether there is loss of dopaminergic cells in patients with tardive dyskinesia. Furthermore, the role of a typical antipsychotic in inducing tardive dyskinesia is still unclear. Clozapine hardly induces tardive dyskinesia, and both olanzapine and risperidone seem to induce less tardive dyskinesia than classical antipsychotics.

Dopamine transporter density can be used as a marker for the integrity of the dopaminergic neurons. Single photon emission computed tomography (SPECT) with *N*-ω-fluoropropyl-2β-carbomethoxy-3β[4-iodophenyl]tropane ([^{123}I]FP-CIT, ioflupane) makes it possible to visualize dopamine transporters in the striatum (Booij et al. 1999) and has proved to be a sensitive tool to demonstrate even a small loss of nigrostriatal dopaminergic neurons.

Materials and methods

Imaging was performed in seven patients (three males and four females) with schizophrenia according to DSM IV, with a mean age of 50.6 years (range 42–60 years, SD 5.94). Mean duration of illness was 24 (14–36) years, with a mean duration of antipsychotic medication of 20 (14–24) years. Five patients were treated with classical antipsychotic medication at the time of imaging. Two were treated with olanzapine, with a history of chronic treatment with classical antipsychotics of 14 and 20 years. Five patients were co-medicated with benzodiazepines and with paroxetine, which were withheld on the day of assessment.

Eight healthy volunteers, four males and four females (mean age 48.5 years, range 39–59 years, SD 7.8) were included. The difference in age between patients and controls was not significant. Volunteers were free from any neurological or psychiatric

disease and were not taking any drugs, as assessed by a clinical interview. After complete description of the study to the subjects, written informed consent was obtained. The research protocol was approved by the medical ethics committee of the Academic Medical Center in Amsterdam.

For SPECT imaging a brain-dedicated camera was used (Strichman Medical Equipment, Medfield, Mass., USA). All subjects received potassium iodide orally to block thyroid uptake of free radioactive iodide. An approximate dose of 110 MBq [^{123}I]FP-CIT was injected intravenously and SPECT acquisition was performed 3 h later, as previously described (Booij et al. 1999). Assessment of [^{123}I]FP-CIT binding in the whole striatum, caudate nucleus, putamen, and occipital cortex (as a reference region) was performed with a recently developed fully automated three-dimensional technique (Habraken et al. 1999). This method automatically places volumes of interest (VOI) over the brain areas. Specific to non-specific [^{123}I]FP-CIT binding was calculated as (VOI–OCC)/OCC, in which VOI represents the mean radioactivity in the VOI (striatum, caudate nucleus, or putamen) and OCC the occipital binding. Image analysis was performed blind to clinical data.

Tardive dyskinesia was rated with the Abnormal Involuntary Movement Scale (AIMS). All assessments were made in the week of imaging by two of the investigators (J.L. and A.S.). Interviews were recorded on video and movement disorders were rated by a senior psychiatrist. All patients were diagnosed as having moderate to severe tardive dyskinesia by all three raters. While AIMS scores were not significantly different between raters a consensus score was used in the analysis.

Differences in [^{123}I]FP-CIT binding ratios between groups were calculated with a Student's *t*-test. A significance level of $P<0.05$ was used.

Results

No significant difference in specific to non-specific striatal [^{123}I]FP-CIT binding ratios in patients with tardive dyskinesia (mean ± SD: 2.62±0.27) and controls (2.48± 0.26) was found (t=1.05, df=13, P=0.31; Fig. 1). This was also true for binding ratios in the caudate nucleus (2.60±0.34 in patients, 2.51±0.32 in controls; t=0.54, df=13, P=0.60) and in the putamen (2.64±0.25 in patients, 2.46±0.23 in controls; t=1.43, df=13, P=0.18).

The mean total AIMS score was 8.4 (range 4–13, SD 3.1). [^{123}I]FP-CIT binding ratios were not significantly correlated with AIMS ratings.

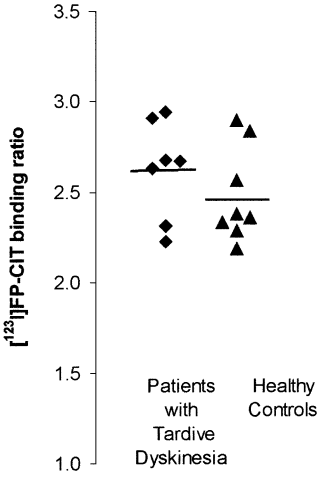

Fig. 1 Individual ratios of specific striatal to non-specific [^{123}I]FP-CIT binding in patients with tardive dyskinesia (n=7) and controls (n=8)

Discussion

This study showed no significant difference in striatal [^{123}I]FP-CIT binding ratios between patients with tardive dyskinesia and controls. The number of subjects was limited, and therefore no definite conclusions can be drawn from this study. The power of this study, particularly because of the negative finding, should be taken into account. However, it was shown that [^{123}I]FP-CIT SPECT is a sensitive tool in assessing even small changes in dopamine transporter density.

It should be kept in mind, however, that the extent to which the density of striatal dopamine transporters reflects that of nigrostriatal neurons is uncertain. However, in patients with nigrostriatal degeneration, dopamine transporter imaging with [^{123}I]FP-CIT SPECT was able to detect this degeneration (Booij et al. 1999). Moreover, the decrease of striatal [^{123}I]FP-CIT binding was related to progression of degeneration. Therefore, [^{123}I]FP-CIT-binding ratios most likely reflect the density of nigrostriatal neurons.

If replicated, however, our present finding does not support the free radical hypothesis of tardive dyskinesia, which suggests loss of dopaminergic neurons. Our observation is in line with a recent large study, which reported no evidence for efficacy of vitamin E in the treatment of tardive dyskinesia (Adler et al. 1999).

In SPECT (Lavalaye et al. 2001) and PET studies (Laakso et al. 2000), patients with schizophrenia, but without tardive dyskinesia, were shown to have no change in dopamine transporter density. Therefore, in this study, patients were compared with healthy controls. This study did match patients and controls for age and gender, since both age and gender have shown a clear effect on dopamine transporter density (Lavalaye et al. 2000b).

All patients were on antipsychotic medication at the moment of imaging. However, this medication was shown not to influence striatal [^{123}I]FP-CIT binding (Lavalaye et al. 2000c, 2001). No co-medication was used with a known influence on [^{123}I]FP-CIT binding. However, it can not be completely excluded that this medication has an effect on [^{123}I]FP-CIT binding, therefore, benzodiazepine and paroxetine treatment were withheld on the day of assessment.

In conclusion, our preliminary study did not show loss of dopamine transporters in patients with tardive dyskinesia and is therefore not in support of the free radical hypothesis of tardive dyskinesia. Interestingly, the dopamine receptor hypersensitivity hypothesis received recent support by the finding of upregulation of dopamine D_2 receptor in patients with tardive dyskinesia (Silvestri et al. 2000).

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