Cerebellar and thalamic metabolic changes visualized by [18]-FDG-PET in olanzapine-induced acute akathisia

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Abstract

OBJECTIVES: Akathisia is a clinical important symptom, frequently induced by neuroleptic treatment. Despite its clinical importance, less is known about its pathophysiology.
METHODS: Using [18]-FDG-PET, imaging patterns of cortical metabolic activity were obtained in a patient during olanzapine-induced akathisia and after recovery.
RESULTS: Akathisia was characterized by a reduced metabolic activity in thalamus and cerebellum. After discontinuing medication akathisia disappeared, reflected by a recovery of metabolic activity in these brain areas.
CONCLUSION: [18]-FDG-PET may be useful to identify cortical regions mediating clinical aspects of drug-induced akathisia, thereby offering a deeper insight into the pathophysiology of this serious side effect.

Introduction

Akathisia is a complex neurobehavioral side effect of neuroleptics characterized by involuntary limb movements and accompanied by a subjective feeling of restlessness, inner tension, and discomfort [8]. Conventional as well as atypical antipsychotics can cause this side effect, emphasizing that akathisia is of utmost importance in the treatment of schizophrenic patients. A variety of clinical symptoms including exacerbation of psychopathology, noncompliance, suicidality and violence underscore the relevance of akathisia for the treatment of schizophrenia. Despite of its clinical significance, the pathophysiology of akathisia remains poorly understood. Focussing on objective features of this side effect, blockade of dopaminergic mesocortical projections has been suggested as one possible underlying mechanism, mainly responsible for movement related manifestations [5]. This hypothesis was confirmed by functional imaging data using [11C]-racloprid-positron-emission-tomography, demonstrating that drug-induced akathisia closely depend on dopamine-D2-receptor blockade in

CASE REPORT

basal ganglia [7]. However, underlying mechanisms generating subjective sensory features of akathisia are still completely unclear. Recently, [18F]-deoxyglucose (FDG) positron emission tomography (PET) was successfully used in detecting thalamic dysfunction associated with a maladaptive integration of sensory information in schizophrenic patients [3]. For this reason, we were interested to know whether FDG-PET-imaging represents a method which is able to gain new insights into the complex pathophysiology of akathisia, especially with regard to subjective sensory features.

Case report

We report the case of a 46-year old man who has been admitted to our hospital with the 6th acute exacerbation of a known chronic schizophrenic disorder, mainly characterized by residual deficits. On admission the patient showed enhanced impulsivity and delusional symptoms together with auditory hallucinations. Careful neurological examination revealed no signs of pre-existing movement disorders. The initial dose of 10 mg olanzapine per day was adjusted up to 20 mg daily as clinically required and led to a rapid disappearance of the florid phase. Under this dosage acute akathisia occurred, including clinical features such as a feeling of inner restlessness paired with pumping legs up and down. Involuntary limb movements were additionally documented by actigraphy. Rating on the global scale of the Barnes Akathisia Rating Scale showed moderate to marked levels of akathisia immediately prior to studying the patient in a PET scanner (ECAT EXACT 47, Siemens, Germany) with [18F]-labelled deoxyglucose. The patient rested 15 minutes in a supine position with eyes closed in a quiet, dimly lit room prior to the intravenous administration of 120–140 MBq – [18F]-fluoro-2-deoxy-D-glucose (FDG). Positron emission computed tomography was performed for 15 minutes beginning 30 minutes after the injection (3-D-acquisition of three frames; 5 minutes/frame). Image reconstruction was done on the frame plane sum by filtered back projection (Shepp-filter with axial filtering and scatter correction, matrix size 256×256 pixel, zoom: 2.5) after automated attenuation correction (threshold: 0.22; tissue attenuation coefficient: 0.095; skull thickness: 0.45 cm; skull attenuation coefficient: 0.151). Six months later a second [18F]-labelled deoxyglucose-PET scan was obtained, when the patient was free of akathisia and completely off medication for 3 weeks due to an intended change of antipsychotic drug treatment. During akathisia, PET imaging showed a reduced glucose-uptake bilaterally both in the thalamus and cerebellum (Figure 1 a,d) as compared to the drug-

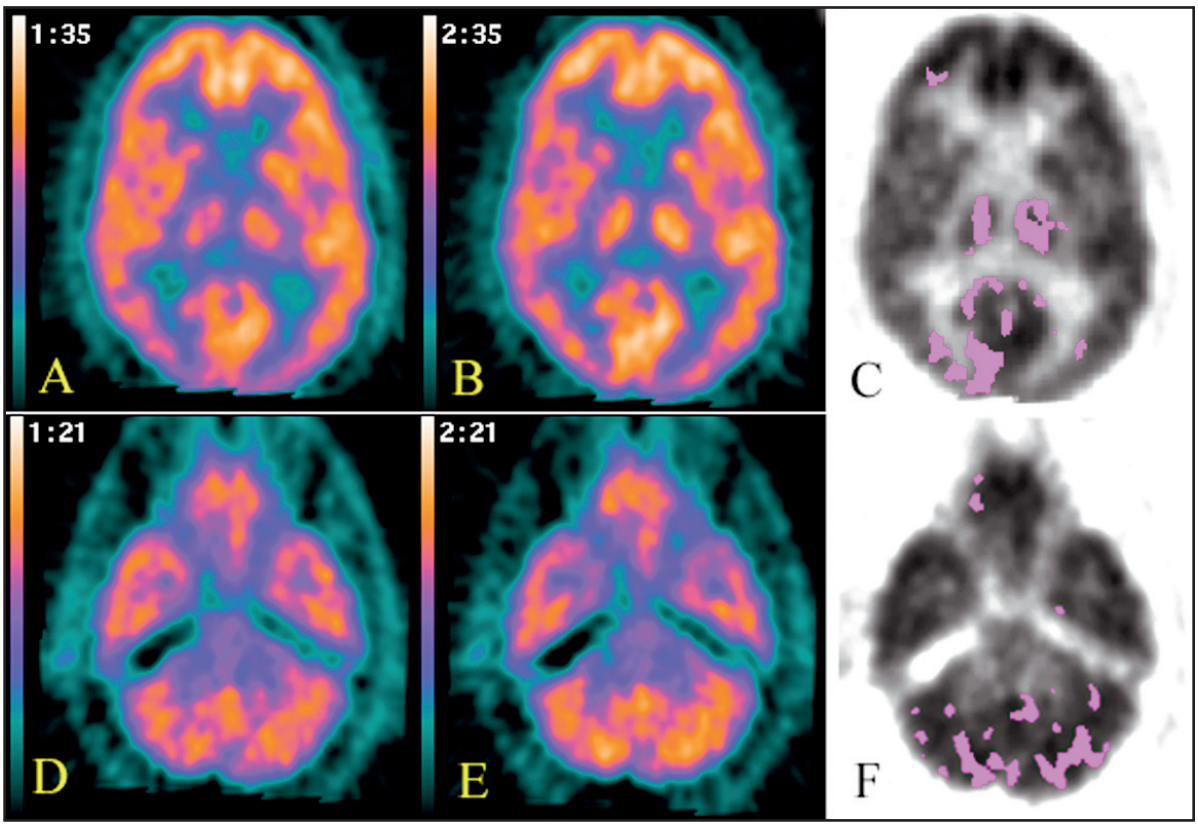

Figure 1: FDG-PET imaging during akathisia induced by 20 mg olanzapine daily (A, D), 6 months later (B, E) and subtraction analysis of both scans (C, F). Note the reduced metabolic activity in bilateral thalamus (A) and cerebellum (D) during olanzapine-induced akathisia compared to 6 months later when the patient was symptom free and off-medication (B and E, respectively). Subtraction analysis shows cortical regions with > 8% difference between both scans (C, F).

free condition, in which the patient was lacking signs of akathisia (Figure 1 b,e). This visual impression was confirmed by substraction analysis of both PET imaging data (Figure 1 c,f; BRASS module on a Hermes work station, Nuclear diagnostics, Sweden). In contrast, during both PET scans a discrete hypometabolism within the right parietooccipital hemisphere remained unchanged.

Discussion

To the best of our knowledge, this is the first use of [18]-FDG-PET imaging in detecting neurobiological processes associated with drug-induced akathisia in schizophrenia. Bilateral reduction of glucose-uptake in the thalamus and cerebellum during akathisia as compared to a drug-free condition without akathisia suggest an essential role of these brain areas in mediating features of this drug-induced side effect. Several lines of evidence support this hypothesis. As has been visualized by [15O] H_2O-PET imaging, schizophrenic patients under drug-free as well as drug-naive conditions are characterized by enhanced blood flow in thalamic and cerebellar regions compared to healthy subjects [4] giving further evidence that schizophrenia can be conceptualized as the result of a disruption within the so-called cortico-cerebellar-thalamic-cortical circuit [1]. In line with this model, atypical antipsychotics such as risperidone [6] and olanzapine [9] have been shown to correct dysfunctional activities within this network, especially by decreasing activity in thalamic and cerebellar regions. Therefore, decrease of hyperactivity in specific brain areas of schizophrenic patients may reflect at least in part the antipsychotic potential of neuroleptic drugs. Based on these data, drug-induced reduction of glucose-uptake in thalamic and cerebellar areas during akathisia as has been observed in our study may be best interpreted as a "forced normalization" or "hyper-correction" of this network. In light of this finding, akathisia may reflect neurobiological alterations induced by neuroleptic agents beyond their intended antipsychotic effect.

Since the thalamus plays a critical role in integrating sensory information, drug-induced dysfunction of this structure as detectable under akathisia may be especially responsible for subjective sensory features of this side effect. Support for this hypothesis comes from functional imaging studies in patients with restless legs syndrome, suggesting that the cerebellum and the thalamus are closely involved in the production of sensory symptoms like sensory leg discomfort [2].

Conclusion

Taken together, [18]-FDG-PET imaging may be especially suitable for studying subjective sensory features of akathisia, whereas [11C]-racloprid-PET imaging may be superior in studying objective, movement-related features of this side effect. Since these data were gained from a single patient, results have to be interpreted with caution and have to be replicated in a larger sample. Nevertheless, this study suggests that drug-induced akathisia may be accompanied by specific metabolic changes in thalamic and cerebellar structures, thereby pointing to possible neurobiological pathways and mechanisms underlying this devastating side effect. Especially, FDG-PET-Imaging seems to be a promising tool to detect these metabolic changes and thereby getting new insights into the pathophysiology of drug-induced akathisia.

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