Positron emission tomography with (18F)methylspiperone demonstrates D2 dopamine receptor binding differences of clozapine and haloperidol

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Summary. Four schizophrenic patients were investigated with dynamic positron emission tomography (PET) using (18F)fluorodeoxyglucose (FDG) and (18F)methylspiperone (MSP) as tracers. Two schizophrenics were on haloperidol therapy at the time of MSP PET. The other two schizophrenics were treated with clozapine, in one of them MSP PET was carried out twice with different daily doses (100mg and 450mg respectively). Neuroleptic serum levels were measured in all patients. Results were compared with MSP PET of two drug-free male control subjects and with a previous fluoroethylspiperone (FESP) study of normals. Three hours after tracer injection specific binding of MSP was observed in the striatum in all cases. The striatum to cerebellum ratio was used to estimate the degree of neuroleptic-caused striatal D2 dopamine receptor occupancy. In the haloperidol treated patients MSP binding was significantly decreased, whereas in the clozapine treated patients striatum to cerebellum ratio was normal. Even the increase of clozapine dose in the same patient had no influence on this ratio. Despite the smaller number of patients the study shows for the first time in humans that striatal MSP binding reflects the different D2 dopamine receptor affinities of clozapine and haloperidol.

Keywords: Positron emission tomography, (18F)methylspiperone, clozapine, haloperidol, D2 dopamine receptors, schizophrenia.

Introduction

The extrapyramidal Parkinson-like side effects caused by neuroleptics suggested that the beneficial effect of these drugs is due to the disruption of dopaminergic transmission. Even a direct relation has been demonstrated between the anti-
psychotic potencies of neuroleptics and the blocking of dopamine D₂ receptors (which inhibit adenylate cyclase) (Seeman, 1987). However, the blocking of dopamine transmission caused by typical neuroleptics became also the limiting factor in their application. After chronic neuroleptic treatment dyskinetic, sometimes permanent movement disorders occurred, known as tardive dyskinesia. A typical neuroleptic agent with high antipsychotic potency but also with a high incidence of extrapyramidal side effects is the butyrophenone haloperidol (Stahl and Wets, 1988).

Especially because of these unwanted extrapyramidal side effects great efforts were made in order to find other “atypical” antipsychotic agents which do not alter the extrapyramidal system. The dibenzodiazepine derivate clozapine was one of the first agents of this class of atypical neuroleptics. Clozapine proved efficacy in the treatment of acute and chronic schizophrenics with a strong antipsychotic effect but without extrapyramidal side effects like tardive dyskinesias (Matz et al., 1974; Simpson and Varga, 1974). Recent studies even demonstrated a significant greater improvement of schizophrenic symptoms in clozapine treated patients in comparison to haloperidol treatment (Kane et al., 1988).

The most striking difference between clozapine and typical neuroleptics like haloperidol is its relatively low affinity for the dopamine D₂ receptor but high affinity for other receptors, e.g., the serotonine 5-HT2 receptor (Meltzer et al., 1989). Animal studies with positron emission tomography (PET) and with radiolabelled clozapine as tracer showed that this low D₂ receptor affinity is mostly due to a very high dissociation rate in comparison with the D₂ dopamine receptor antagonists N-methylspiperone and raclopride (Hartvig et al., 1988). In humans PET demonstrated ¹¹C-clozapine binding in striatum and in frontal cortex; but striatal much more than frontal cortex binding was reduced after haloperidol administration, which indicated different receptor affinities of haloperidol and clozapine especially in the frontal cortex (Lundberg et al., 1989). Post mortem studies of human brains with radioligand binding assays of receptors confirmed the low affinities of clozapine, unlike spiperone and haloperidol, for D₂ dopamine receptors (Richelson, 1984).

PET with radiolabelled ligands allowed to study noninvasive dopamine receptors in humans. Previous studies showed that the derivates of spiperone, e.g. ¹¹C-N-methylspiperone (Wagner et al., 1983), MSP (Smith et al., 1988) or FESP (Coenen et al., 1987; Barrio et al., 1989; Wienard et al., 1990) are able to image D₂ dopamine receptors. The present study with PET and MSP explores D₂ dopamine receptors in schizophrenics treated with clozapine or haloperidol respectively. It compares the influence of these two drugs on striatal D₂ receptor occupancy.

Patients and methods

Four patients (two men, two women, aged 21 to 51 years) who satisfied DSM-III-R criteria (American Psychiatric Association, 1987) for schizophrenic disorder and two male normal