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Relationship between dopamine D_2 receptor occupancy, clinical response and drug and monoamine metabolites levels in plasma and cerebrospinal fluid. A pilot study in patients suffering from first-episode schizophrenia treated with quetiapine

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ABSTRACT

Combining measurements of the monoamine metabolites in the cerebrospinal fluid (CSF) and neuroimaging could increase efficiency of drug discovery for treatment of brain disorders. To address this question, we examined five drug-naïve patients suffering from schizophrenic disorder. Patients were assessed clinically using the Positive and Negative Syndrome Scale (PANSS): at baseline and then at weekly intervals. Plasma and CSF levels of quetiapine and norquetiapine as well CSF 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxyindole-acetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) were obtained at baseline and again after at least a 4 week medication trail with 600 mg/day quetiapine. CSF monoamine metabolites levels were compared with dopamine D_2 receptor occupancy (DA-D_2) using [^{18}F]fallypride and positron emission tomography (PET). Quetiapine produced preferential occupancy of parietal cortex *vs.* putamenal DA-D_2, 41.4% ($p < 0.05$, corrected for multiple comparisons). DA-D_2 receptor occupancies in the occipital and parietal cortex were correlated with CSF quetiapine and norquetiapine levels ($p < 0.01$ and $p < 0.05$, respectively). CSF monoamine metabolites were significantly increased after treatment and correlated with regional receptor occupancies in the putamen [DOPAC: ($p < 0.01$) and HVA: ($p < 0.05$)], caudate nucleus [HVA: ($p < 0.01$)], thalamus [MHPG: ($p < 0.05$)] and in the temporal cortex [HVA: ($p < 0.05$) and 5-HIAA: ($p < 0.05$)]. This suggests that CSF monoamine metabolites levels reflect the effects of quetiapine treatment on neurotransmitters *in vivo* and indicates that monitoring plasma and CSF quetiapine and norquetiapine levels may be of clinical relevance.

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1. Introduction

Quetiapine is a dibenzothiazepine that exhibits properties of a second generation antipsychotics (Goldstein, 1995). The prediction of atypicality is based on the pharmacological profile of the compound, which seems to be similar to that of clozapine (Chiodo and Bunney, 1983; Goldstein et al., 1993; Meltzer, 1992). The atypicality of quetiapine is mainly a consequence of antagonism of the serotonergic 5-HT_{2A} receptors, which leads to disinhibition of dopamine and noradrenaline release, that is dopaminergic and noradrenergic signaling in the mesocortical pathway (Shayegan and Stahl, 2004).

Chronic treatment with quetiapine produces depolarization inactivation of ventral tegmental DA neurons, sparing those in the substantia nigra, whereas haloperidol inactivates both (Chiodo and Bunney, 1983; Goldstein et al., 1993). Although quetiapine binds to multiple CNS neurotransmitter receptors (Schotte et al., 1996), the above studies suggest that its atypical profile may be mediated, at least in part, by preferential effects on dopamine (DA) D_2 receptor-mediated neurotransmission in cortex and limbic regions, compared to the dorsal striatum.

Quetiapine is rapidly absorbed after oral administration (t_{max}: 1–1.5 h; C_{max} after 25 mg quetiapine: 53–117 ng/ml) but also rapidly eliminated ($t_{1/2}$: 3.1–5.5 h) (DeVane and Nemeroff, 2001). Among its metabolites, norquetiapine displays high affinity for 5-HT_{2A} receptors and therefore, it may contribute to the antipsychotic activity of quetiapine. In addition, norquetiapine is probably an antidepressant, by its high affinity for the norepinephrine reuptake site and for the 5-HT_{1A} receptor (Jensen et al., 2008). Dose corrected steady-state trough concentrations of quetiapine in p[illegible] are highly variable (Gerlach et al., 2007; Hasselstrøm and L[illegible]net, 2004; DeVane and Nemeroff, 2001). Very little is known about the pharmacokinetic properties of norquetiapine. In steady-state conditions, its peak (2 h) levels are considerably lower than those of its parent compound, after administration of 600 mg/day quetiapine (Winter et al., 2008). It is generally considered that drug CSF better than plasma concentrations reflect its fate in the brain (Bianchine and McConnell, 1994; D[illegible]ange and [illegible]anhof, 2002). Therefore, in this study, both quetiapine and norquetiapine levels in plasma and CSF were compared with D_2-occupancy in brain and with their clinical activity.

One way to examine the DA, serotonin (5-HT) and noradrenaline (NA) systems in the brain is through measurement of their metabolites homovanillic acid (HVA), 5-hydroxyindolacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylglycol (MHPG), in cerebrospinal fluid (CSF). Several studies with typical antipsychotics (Garelis and Sourkes, 1974; Potter and Manji, 1993; Weir et al., 1973) have demonstrated that levels of HVA, 5-HIAA and MHPG in CSF reliably reflect their levels in the brain, implying that they actually reflect central DA, 5-HT and NA turnover and thus can be used to examine the effects of antipsychotic drugs *in vivo* (Agnati et al., 1995; Silver et al., 1996). However, studies examining the effects of the second generation antipsychotics on CSF monoamine metabolites in schizophrenia are lacking (Scheepers et al., 2004).

To evaluate quetiapine binding to DA-D_2 receptor in extrastriatal regions, we used PET with [^{18}F]fallypride (Kessler et al., 2000; Mukherjee et al., 2002) to measure the levels of DA-D_2 receptor occupancy in putamen, caudate nucleus, thalamus, temporal cortex, parietal cortex and occipital cortex in schizophrenic patients who were treated with quetiapine for 4 weeks. [^{18}F]fallypride is a high-affinity radioligand for DA-D_2 and D_3 receptors that can be used to quantitate levels of DA-$D_{2/3}$ receptors in man in both striatal and extrastriatal regions with a single tracer injection (Siessmeier et al., 2005; Stark et al., 2007).

Previously, two groups of authors already demonstrated in their PET studies occupation of DA-D_2 receptors by quetiapine, using either [C^{11}]raclopride or [^{18}F]fallypride as ligands (Kessler et al., 2006; Kapur et al., 2000), but quetiapine was only measured in plasma. In the present study, the relationship between DA-D_2 receptor occupancy, and the quetiapine and norquetiapine and monoamine metabolites levels in plasma and CSF was investigated immediately before injection of the radiotracer [^{18}F]fallypride.

2. Patients and methods

The study was approved by the local ethics committee in Frankfurt a.M., Germany, and the German radiation safety authorities. During the study all patients were patients at the Klinikum Fulda gAG, Department of Psychiatry and Psychotherapy, Fulda. All PET investigations were performed at the Department of Nuclear Medicine, Klinikum Fulda gAG, Fulda, Germany.

2.1. Patients

Five drug-naive male schizophrenic patients in their first episode who fulfilled the criteria for schizophrenia according to the DSM-IV (APA, 2004) were included after giving written informed consent. The mean ± SD age was 34.4 ± 4.4 years (age range; 25–46 years). To determine clinical outcome, each patient was rated on the Positive and Negative Syndrome Scale (PANSS) for severity of illness and for improvement with treatment (Kay et al., 1987). All patients were treated with quetiapine 600 mg/day for 4 weeks.

2.2. Radiochemistry

The [^{18}F]fallypride was synthesized by a novel high-yield modification of the method for the synthesis of [^{18}F]desmethoxyfallypride (Gründer et al., 2003). In brief, the tosylated precursor ((S)-*N*-[(1-allyl)-2-pyrrolidinyl)-methyl]-5-(3-toluenesulfonyloxy-propyl)-2,3-methoxybenzamide (5 mg, 10 μmol) was dissolved in 1 mL acetonitrile, treated for 5 min at 65 °C with potassium carbonate (5 mg, 36 μmol), and subsequently transferred into a 5 mL vial containing [^{18}F]fluoride using the method of Hamacher et al. (1986). The reaction mixture was heated for 20 min at 85 °C, diluted with 1 mL phosphoric acid (10%), and separated using high-performance liquid chromatography (HPLC) (250 × 10 mm, RP8; CH_3CN: 0.25 mol/L ammonium acetate buffer + 5 mL acetic acid/L, 30:70; 5 mL/min). The fraction containing [^{18}F]fallypride was isolated, diluted with 0.15 mol/L disodium hydrogen phosphate buffer, and adsorbed on a C_{18} cartridge to remove the HPLC solvent. The column was washed with 2 mL water and the product was eluted with 1 mL ethanol. The eluant was diluted with 9 mL of an isotonic sodium chloride solution and sterilized by filtration (0.22 μm). Quality control before injection included determination of the chemical and radiochemical purity, specific activity, pH, and absence of pyrogens.

2.3. Data acquisition and analysis

Images were acquired on a GE Advance whole body PET scanner. Data acquisition comprised of a series of 38 time frames [5 min transmission scan followed by injection of [^{18}F]fallypride; 10 × 1 min, 6 × 5, (15 min pause), repositioning, 8 × 5, (15 min pause) and a final 8 × 5 min] with total scan duration of 165 min. A mean of 327 ± 94 MBq (mean ± SD) [^{18}F]fallypride was injected intravenously as a bolus. Measured binding potentials (BP) were calculated on a voxelwise basis using the Lammertsma Simplified Reference Tissue Model, which is based on a two-tissue compart-