Neocortical serotonin2A receptor binding predicts quetiapine associated weight gain in antipsychotic-naive first-episode schizophrenia patients

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Abstract

Antipsychotic-induced weight gain is of major clinical importance since it is associated with severe metabolic complications and increased mortality. The serotonin2A receptor system has been suggested to be implicated in weight gain and obesity. However, no previous in vivo imaging data have related serotonin2A receptor binding to weight gain before and after antipsychotic monotherapy. Fifteen antipsychotic-naive first-episode schizophrenia patients were included and investigated before and after six months of quetiapine treatment. We examined the relationship between serotonin2A receptor binding as measured with positron emission tomography (PET) and [18F]altanserin and change in body mass index (BMI). Quetiapine was chosen because it is characterized by a moderately high affinity for the serotonin2A receptor and a fast dissociation rate from the dopamine D2 receptor. At baseline the mean BMI was 24.2 kg/m², range 18–36 kg/m². After six months of quetiapine treatment (mean dose: 383 mg/day) the BMI had, on average, increased by 6.7%, corresponding to an average weight gain of 5.0 kg. We found a significant positive correlation both between neocortical serotonin2A receptor binding prior to treatment and subsequent increase in BMI (rho=0.59, p=0.022). At follow-up, the serotonin2A receptor occupancy was positively correlated with BMI increase (rho=0.54, p=0.038). To our knowledge, these are the first in vivo receptor imaging data in initially antipsychotic-naive first-episode schizophrenia patients to show that the cerebral serotonin2A receptor is associated with antipsychotic-induced weight gain.

Introduction

Weight gain is a common side effect of antipsychotic drug treatment, and is among the main reasons for a patient to discontinue medical treatment (Allison et al., 1999). Weight gain induced by antipsychotics is commonly associated with metabolic side effects and contributes to a substantial increase in mortality (Roerig et al., 2011). Being overweight is an important risk factor for developing a variety of disorders, including type-2 diabetes, cardiovascular diseases and some cancer types (Eyre et al., 2004). It has been estimated that patients with schizophrenia may lose up to 20 years of life expectancy, with the majority of this excess in premature deaths being attributed to overweight- and obesity-related cardiovascular disease and not to suicide (Newcomer and Hennekens, 2007; Laursen et al., 2013). This ‘mortality gap’ between patients with schizophrenia and the general population has potentially been accentuated by the introduction of second-generation antipsychotics (SGAs) (Saha et al., 2007).

Previous data have implicated a role of the serotonin2A receptor (5HT2A) in weight gain: SGAs with a high affinity for the 5HT2A (Ebdrup et al., 2011) are more liable to induce weight gain than first-generation antipsychotics (FGA’s) (Newcomer, 2005). Furthermore, clozapine and olanzapine, which are the SGAs that are most liable to induce the highest
weight gain, have a very high 5HT2A affinity (Correll, 2008).

Reduction in cerebral serotonin levels has been shown to induce hyperphagia and weight gain (Breisch et al., 1976). In rodents stimulation of the 5HT2A results in satiety and reduced feeding (Roerig et al., 2011). Furthermore, mice that became obese by exposure to a high-fat diet showed increased serotonin2A receptor density in comparison to obese-resistant mice fed on the same diet (Huang et al., 2004). A specific role of 5HT2A in the regulation of body weight has also been suggested in other studies. For example, G/G carriers of the A (~1438)G promoter polymorphism of the 5HT2A gene have increased body mass and predominantly abdominal distribution of body fat (Rosmond et al., 2002). Some studies argue that carriers of the same polymorphism are at higher risk of developing anorexia nervosa but the results are mixed (Ricca et al., 2002). In further support of a relationship between serotonin2A receptor binding (5HT2A-BPp) and regulation of eating and body weight, PET and SPECT studies have suggested that both anorexia nervosa patients and patients who have recovered from regular anorexia nervosa and bulimia-type anorexia nervosa display decreased cerebral 5HT2A-BPp (Kaye et al., 2005).

Finally, in a PET study of 52 healthy, largely normal weight subjects, we have previously identified a positive correlation between BMI and 5HT2A-BPp in the cortical regions (Adams et al., 2004), which we have confirmed later in a larger independent sample (Erritzoe et al., 2009).

In the present study we investigated the relationship between in vivo 5HT2A-BPp as measured with PET and BMI changes in first-episode, antipsychotic-naïve schizophrenia patients before and after six months ofquetiapine treatment. Quetiapine (immediate-release preparation used in the present study) is an SGA characterized by a high affinity for the serotonin2A receptor (Ki=0.13 nm) combined with a fast koff and a low affinity for dopamine D2 receptors (Kessler et al., 2006).

Here we explore possible associations between 5HT2A-BPp in the antipsychotic-naïve state, 5HT2A occupancy (5HT2A-O) of the same receptors following treatment and BMI change. Based on the literature above we expected 5HT2A-BPp to be positively associated with change in BMI.

Method

The study was approved by the Ethics Committee of Copenhagen and Frederiksberg ((KF)11-061/03, (KF) 12-291906 and (KF) 11-323091). After complete description of the study to the subjects, written informed consent was obtained.

Participants

Initially, 30 antipsychotic-naïve patients (23 males) diagnosed with schizophrenia according to both ICD-10 and DSM-IV were included after voluntary first-time referral to a psychiatric unit at one of several university-affiliated hospitals in the Capital Region of Copenhagen. Data from this cohort regarding 5HT2A-BPP and psychopathology has previously been published (Rasmussen et al., 2010). The present cohort was identical to that included in our previously published PET study on 5HT2A-O and clinical effect after treatment for six months with quetiapine (Rasmussen et al., 2011). In short, the diagnosis was verified by means of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1) interview. In the six-month period between baseline and follow-up the dropout rate was 50%. Reasons for dropout were: refusal to participate at follow-up (n=7), side effects (n=4), clinically inadequate effect (n=2) and pregnancy (n=2). The patients who dropped out were not significantly different from those who completed the study with regards to age, gender, BMI, 5HT2A-BPp and symptom severity.

As a result fifteen initially antipsychotic-naïve first-episode schizophrenia patients completed the study (10 males, mean age: 28.9 years, S.D.=5.4) see Table 1 for demographics, clinical and PET related data.

A Grubb’s outlier test (Grubb, 1969) did not show any outliers in the weight/BMI distribution of the patients at baseline. This has been added to the participants’ section.

Two patients were treated with the selective serotonin reuptake inhibitors (SSRIs) fluoxetine (n=1) and citalopram (n=1) in stable doses (40 mg/day for both compounds) throughout the investigation period. Four patients had some form of previous substance abuse. During the treatment period, none of the 15 patients had any substance abuse as determined by regular clinical contacts, and all patients had a negative urine screening for substance intake prior to the PET scans. Thirteen patients had no lifetime history of antidepressant exposure. For more details see (Rasmussen et al., 2011). None of the patients were treated with benzodiazepines or anticholinergic agents during the study. Urine screening for drugs of abuse was performed prior to the PET scan.

None of the patients had a history of significant head injury or non-psychiatric disorder. All patients had normal neurological and physical examinations, and structural magnetic resonance imaging (MRI) brain scans were without abnormalities, as reported in a separate MRI study done in the same cohort (Ebdrup et al., 2010).

Imaging

PET receptor imaging was performed with a bolus infusion steady state design using the selective 5HT2A ligand [18F]altanserin, as previously described (Rasmussen et al., 2010). In short, 5HT2A-BPp (Rasmussen et al., 2010) and 5HT2A-O were calculated as described below:

\[ BPp = \frac{C_{VOL} - C_{Reference}}{C_{Plasma}} = f_p \cdot \frac{B_{max}}{K_d} (ml/ml) \] (1)
Table 1. Demographics, clinical and PET-related data for baseline, follow-up patients and dropouts modified from (Rasmussen et al., 2011)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>S.D.</th>
<th>Follow-up</th>
<th>S.D.</th>
<th>Drop-out</th>
<th>S.D.</th>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>26.9</td>
<td>5.5</td>
<td>27.6</td>
<td>5.4</td>
<td>25.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>10/5</td>
<td></td>
<td>10/5</td>
<td></td>
<td>13/2</td>
<td></td>
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<tr>
<td>PANSS</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Positive</td>
<td>19.5</td>
<td>5.4</td>
<td>15.7</td>
<td>6.6</td>
<td>19.4</td>
<td>5.0</td>
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<tr>
<td>Negative</td>
<td>20.3</td>
<td>6.1</td>
<td>18.4</td>
<td>6.5</td>
<td>23.5</td>
<td>6.6</td>
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<tr>
<td>General</td>
<td>38.0</td>
<td>8.7</td>
<td>33.0</td>
<td>11.1</td>
<td>40.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Total</td>
<td>77.8</td>
<td>17.1</td>
<td>67.0</td>
<td>22.8</td>
<td>83.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Quetiapine dose (mg)</td>
<td>–</td>
<td>–</td>
<td>383.0</td>
<td>144.7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Plasma quetiapine (ng/ml)</td>
<td>–</td>
<td>–</td>
<td>352.0</td>
<td>201.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5-HT2A receptor binding</td>
<td>2.30</td>
<td>0.43</td>
<td>1.72</td>
<td>0.20</td>
<td>2.20</td>
<td>0.30</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>24.2</td>
<td>4.5</td>
<td>25.8</td>
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<td>24.8</td>
<td>3.5</td>
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<td>Body weight (kg)</td>
<td>75.5</td>
<td>16.2</td>
<td>80.5</td>
<td>20.4</td>
<td>78.2</td>
<td>17.2</td>
</tr>
</tbody>
</table>

C_{VOI} and C_{Reference} are the steady state mean count density in the VOI and in the reference region, respectively; C_{Plasma} is the steady-state activity of non-metabolized tracer in plasma; f_P is the free fraction of radiotracer; B_{max} is the density of receptor sites available for tracer binding; and K_d is the affinity constant of the radiotracer to the receptor. The cerebellum was used as a reference region, since it represents non-specific binding only (Rasmussen et al., 2010).

A global neocortical region was defined for each subject and served as the primary region of interest. This region consisted of a volume-weighted average of eight cortical regions (orbitofrontal cortex, medial inferior frontal cortex, superior frontal cortex, superior temporal cortex, medial inferior temporal cortex, sensory motor cortex, parietal cortex and occipital cortex).

\[ V_T = C_T/P \]

The distribution volume (V_T) of a radioligand is defined as the ratio of the radioligand concentration in tissue target region (C_T, kBq/cm³) to that in plasma (C_P, kBq/ml) at equilibrium (Innis et al., 2007). C_P represents the concentration of parent radioligand in plasma.

\[ 0 = 1 - \frac{V_{T,b} - V_{ND}}{V_T - V_{ND}} \]

A measure of 5HT2A-O was calculated from the distribution volume in the unblocked (V_T) and in the partially blocked condition (V_{T,b}) where V_{ND} is the distribution volume of the non-displaceable tracer, i.e. the free and non-specifically bound tracer. Rearrangement of equation 3 leads to:

\[ V_{T,b} = (1 - O) V_T + O V_{ND} \]

By inserting corresponding values for each measured brain region in the unblocked and partially blocked condition, an occupancy plot can be made for each individual, and hence, an estimate of the occupancy can be determined in each individual using linear regression analysis (Rasmussen et al., 2011).

PET images and 3D T1 weighted MRI scans were co-registered using a Matlab (Mathworks Inc., USA)-based program, where PET images and MRIs are fitted through manual translation and rotation of the PET image with subsequent visual inspection in three planes (Rasmussen et al., 2010).

\[ {^{18}F}\text{altanserin} \]

As compared to the radioligands \[ {^{18}F}\text{setoperone} \] and \[ {^{11}C}\text{N-methylspiperone} \] used in previous studies e.g. \( \text{(Gefvert et al., 1998, 2001; Kapur et al., 2000)} \) \[ {^{18}F}\text{altanserin} \] is not limited by relatively poor selectivity for the 5HT2A. In conjunction with the poor selectivity of these tracers, a lower ratio of 5HT2A to D2 receptors in subcortical areas compared to cortical areas makes these ligands inadequate to measure subcortical binding \( {^{18}F}\text{altanserin} \) has a 200 to 500-fold 5HT2A/D2 selectivity measured as 1/(5HT2A Ki/D2)=1/(0.13–0.3/62 nM)=1/(0.002–0.005) (Tan et al., 1999; Kristiansen et al., 2005) making it between eight and fifty times more selective for 5HT2A than \[ {^{18}F}\text{setoperone} \] ((1/(1/10–25 nM)=1/(0.1–0.04)=10–25-fold 5HT2A/D2 selectivity (Lewis et al., 1999). In addition, the affinity of \[ {^{18}F}\text{altanserin} \] for 5HT2A is at least 20-fold higher than for other 5-HT subtypes (Tan et al., 1999). We have previously demonstrated that \[ {^{18}F}\text{altanserin PET} \] with a bolus infusion design is a highly reproducible method for reliable quantification of 5HT2A (Haugbol et al., 2007).

Currently another ligand \[ {^{11}C}\text{MDL 100907} \] is available for imaging 5HT2A. This tracer is highly comparable with \[ {^{18}F}\text{altanserin} \] (Kristiansen et al., 2005). Both \textit{in vitro} and \textit{in vivo} experiments reveal that both ligands have high affinity, selectivity and a satisfactory ratio of specific to non-specific binding for 5HT2A (Kristiansen et al., 2005;
However, the selectivity of $[^{13}C]$MDL 100907 for the 5HT2A as compared to $[^{18}F]$altanserin is slightly higher and metabolites of $[^{13}C]$MDL 100907 do not enter the brain to any significant extent. Notwithstanding, a major advantage of $[^{18}F]$altanserin over $[^{13}C]$MDL 100907 is the possibility to perform steady state scanning lasting several hours based on the 110 min half-life of $^{18}$F-fluorine (Herth et al., 2009). However, for both radioligands, the binding seen in PET studies is not directly influenced by changes in endogenous 5-HT levels.

One of the general requirements of a radiotracer is that it should preferably not yield any radiolabelled metabolites crossing the blood–brain barrier (Lammertsma and Hume, 1996). However, after systemic injection, $[^{18}F]$altanserin gives yield to radiolabelled metabolites of which primarily radiolabelled altanserinol crosses the blood–brain barrier (Price et al., 2001) and with a bolus-infusion protocol, the lipophilic metabolites accumulate and increase the signal from non-specific binding over time (Pinborg et al., 2003; Adams et al., 2004). This can however be compensated for in the steady state approach as in the current study where the contribution from radiolabelled lipophilic metabolites can be subtracted directly from the reference region void of receptors i.e. the cerebellum.

Since $[^{18}F]$altanserin has second highest affinity for the 5HT2C subtype (after the 5HT2A) it could be argued that cortical $[^{18}F]$altanserin binding potential could reflect a combined measure of both the 5HT2A and 5HT2C receptor (Tan et al., 1999). However, this seems unlikely since $[^{18}F]$altanserin has a 5HT2A and 5HT2C selectivity ratio of 20 (Tan et al., 1999) and since the expression of the cortical is 5HT2A much higher than the 5HT2C receptor (Nichols and Nichols, 2008). In addition brain homogenate binding studies have shown that blockade with the serotonin2B/2C selective compound SB 206553 does not alter $[^{18}F]$altanserin binding (Kristiansen et al., 2005). Although our radioligand altanserin is a highly selective 5HT2C receptor radioligand suitable for measurement in both cortical and subcortical areas the subcortical areas are 5HT2A receptor poor and noisy and the risk that a potential interregional difference reflects noise instead of a genuine biological difference is present. Therefore we chose the global cortical neocortex as region of interest – also avoiding statistical multiple comparison issues. It was also in this region we previously found decreased 5HT2A-BPP binding in 30 antipsychotically-naïve, first-episode schizophrenia patients as compared to matched healthy controls and a relation to degree of positive symptomatology (Rasmussen et al., 2010).

**Statistics**

BMI is used as a measure for nutritional state and generally correlates well with other anthropometric measures such as weight and waist circumference. Generally, a BMI $>25$ kg/m$^2$ is defined as overweight, and a BMI over 30 kg/m$^2$ as obese. All data analyses were performed using the Statistical Package for the Social Sciences (SPSS © Inc., USA).

Since Probit diagrams of the data did not confirm a normal distribution of data, non-parametric tests were used to analyse the data. Accordingly, we used the Spearman’s rank correlation coefficient (rho) to test associations between 5HT2A-BPP as well as 5HT2A-O and BMI change and weight before and after quetiapine treatment.

Given that we had identical dependent variables (change in BMI before and after quetiapine treatment) on the Y-axis on both of our two plots we tested the potential effect of statistical multicollinearity using a multidimensional regression analysis with the dependent variable (change in BMI before and after quetiapine treatment) and 5HT2A-BPP and 5HT2A-O as independent variables. The analysis reflected tolerance and variance inflation factor on acceptable numerical values and therefore no risk of statistical multicollinearity was present. Two-tailed analyses were performed for all tests and the significance level was set to $p < 0.05$.

**Results**

At baseline the patients had BMI’s ranging from 18–36 kg/m$^2$, mean 24.2 kg/m$^2$, and a mean BMI increase after the quetiapine treatment period of 6.7% (corresponding to a weight gain of 5.0 kg, see also Table 1). There was a significant positive correlation between the global 5HT2A-BPp at baseline and change in BMI (rho=0.59, $p=0.022$, see Fig. 1a). Also, there was a significant positive correlation between 5HT2A-BPP after treatment and change in BMI (rho=0.54, $p=0.038$, see Fig. 1b). A trend level correlation was detected between quetiapine dose and BMI increase (rho=0.49, $p=0.064$). In addition there was a significant non-linear relationship between dose, quetiapine plasma concentration and 5HT2A-O (Rasmussen et al., 2011)

5HT2A-O can be considered as a relative measure of the level of neurotransmission that has been pharmacologically removed by quetiapine treatment. If we multiply our 5HT2A-O with the baseline 5HT2A-O we get a measure of the absolute measure of the neurotransmission that has been removed. This last measure gives rise to a more tight association to quetiapine-induced increase in BMI difference (rho=0.54, $p=0.038$ vs. rho=0.63, $p=0.013$).

Previously, we have reported a significant reduction in PANSS-positive symptoms together with significant non-linear relationships between 5HT2A-O, quetiapine dose and plasma concentration, see Table 1 and (Rasmussen et al., 2011). Controlling for the potential effect of gender, age, SSRI use, previous substance abuse, PANSS negative symptoms and baseline weight in the analyses did not alter the results of the present study.

We did not replicate the correlation between serotonin2A binding and baseline weight, as reported in our two other papers on healthy normal-weight and
obese individuals (Adams et al., 2004; Erritzoe et al., 2009).

Discussion

We found that 5HT2A-BPP in antipsychotic-naïve first-episode schizophrenia patients predicted their subsequent increase in BMI following six months of antipsychotic monotherapy with quetiapine. Our finding suggests that patients, who, prior to antipsychotic treatment have a high 5HT2A-BPP, are at an increased risk of gaining weight during the course of quetiapine treatment. Based on that observation alone we cannot establish whether the 5HT2A receptors are directly involved in the regulation of eating behaviour, or whether the higher 5HT2A-BPP is secondary to other differences in the serotonergic transmitter system, such as low cerebral baseline serotonin levels. In any instance, our data suggest that 5HT2A-BPP potential in antipsychotic-naïve schizophrenia patients can be seen as a biomarker for risk of weight gain associated with antipsychotic treatment. We did not replicate the correlation between 5HT2A-BPP and baseline weight, as reported in our two other papers on healthy normal-weight and obese individuals (Adams et al., 2004; Erritzoe et al., 2009). However, interestingly the investigated cohort in this study was antipsychotic-naïve, first-episode schizophrenia patients (and not normal control and obese subjects) where such a relationship might in fact not be present maybe because of a fundamental biological difference in the 5HT2A receptor system exclusive for schizophrenia and therefore not just an epiphenomenon. This is supported by our earlier finding of decreased cortical 5HT2A-BPP in 30 antipsychotic-naïve, first-episode schizophrenia patients as compared to matched healthy controls (Rasmussen et al., 2010).

We also, however, observed a significant positive correlation between change in BMI and 5HT2A-O, i.e. higher blockade of the 5HT2A receptor was associated with a larger increase in BMI. As discussed above our baseline finding could mean that 5HT2A receptor availability is compensatory to a low level of endogenous serotonin meaning that low endogenous serotonin levels correlate to BMI increase. From this interpretation high 5HT2A-O means that there is a lower possibility that endogenous serotonin will bind to the 5HT2A receptors during quetiapine treatment and generate a lower serotonin neurotransmission. The observation that low cerebrospinal fluid levels of serotonin metabolites has been found in women with primarily abdominal obesity could support this notion (Bjorntorp, 1995). Our calculation of the absolute measure of neurotransmission in the results section could support the interpretation that it is the level of quetiapine-induced decrease in 5HT2A neurotransmission that gives rise to increase in BMI difference.

Weight gain seems to vary with the length of treatment and across different antipsychotic agents (Nasrallah, 2008). Long-term studies indicate that quetiapine induced weight gain is approximately 2–3 kg over the first year of treatment (Haupt, 2006). Our finding of a nearly double that increase in weight gain (on average 5.0 kg) in only six months, suggests that young, previously non-medicated first-episode schizophrenia patients might be at particularly high risk for developing antipsychotic-induced weight gain as suggested by (De Hert et al., 2012).

A limitation of the study is that we only measured one specific receptor since quetiapine is characterized by a complex pharmacology and has affinity to multiple receptor systems (in vitro $K_i$: $D_2=700$; $5HT2A=96$; $5HT1A=320$; $5HT2C=1.184$; $\alpha_1=3.63$; $\alpha_2=22$: $H_i=2.2$; $M_i=1.94$) (Horacek et al., 2006)). The 5HT2C receptor to which quetiapine has a high affinity has also been implicated in weight gain (Roerig et al., 2011). For example 5HT2C receptor knockout mice have been shown to become obese.

Fig. 1. (a) Positive correlation (rho=0.59, $p=0.022$), between neocortical 5HT2A-BPP and change in BMI (in %) between baseline and follow-up (b) Positive correlation (rho=0.54, $p=0.038$) between 5HT2A-O and change in BMI (in %) between baseline and follow-up.
and hyperphagic (Tecott et al., 1995). Other evidence is also conflicting. The mRNA receptor expression for the serotonin2C receptor has been reported to be unaffected by olanzapine treatment, which is a strong antagonist on the 5HT2C (Ki=14) (Huang et al., 2006). On the other hand, aripiprazole, which has a high affinity for the serotonin2C receptor as a partial agonist, has a low weight gain liability.

The possibility of 5HT2A as the primary site of regulation should also be considered. Stimulation of this receptor causes a decrease in the firing of raphe nuclei serotonin neurons (Boothman et al., 2003) through negative feedback possibly mediated by glutamatergic projections from cortex to raphe GABA interneurons (Sharp et al., 2007). A high level of 5HT2A receptor activity could therefore potentially decrease serotonin neuron firing from raphe nuclei and thus, through decreased serotonin release, lower subcortical and cortical serotonin transporter levels.

In a recent report, however, we reviewed the most selective 5HT2A antagonists in the pipeline and their potential in the treatment of schizophrenic symptoms (Ebdrup et al., 2011). The selective 5HT2A antagonists are not weight neutral (Ebdrup et al., 2011) indicating a specific role of the 5HT2A in weight gain.

An important strength of the present study was that all included patients were antipsychotic-naïve at the baseline investigations and they were suffering from their first episode of schizophrenia. Therefore, the patients were not affected by repeated relapses, social deprivation or previous antipsychotic medication. Moreover, the patients were treated with antipsychotic monotherapy in a long-term longitudinal design.

Some limitations in the current study should be mentioned. The number of subjects might seem low however we do, in fact, consider 15 initially antipsychotic-naïve, first-episode schizophrenia patients examined twice in a rather invasive, long and extensive bolus-infusion PET set up before and after six months of quetiapine monotherapy as a rather high number.

Regarding attrition we consider it very important to underline the reasons for dropout. Seven patients had, at baseline, explicitly stated that they refused to participate at follow-up and undergo medical treatment, two patients got pregnant during the course of the study, four had side effects and finally two had clinically inadequate effect. Importantly the patients who dropped out were also not significantly different from those who completed the study with regards to age, gender, BMI, 5HT2A-BPP and symptom severity.

It should be noted, that there is a large variability in weight gain across different SGAs, which, as a group, are quite different in their receptor affinities (Leucht et al., 2009). Together with inter-individual variability in patients treated with the same SGA point towards a multifactorial phenomenon and may involve, for example, genetic polymorphisms and several different peptide, neurotransmitter systems in the appetite and reward systems in the brain (Roerig et al., 2011). Consequently, an obvious limitation of the current study is that we, due to logistical reasons and radioactivity concerns, did not simultaneously assess the other receptors on which quetiapine has a modifying effect and which may contribute to weight gain. For example, dopamine is also an important neurotransmitter in the control of feeding behaviour and reward mechanisms (Berridge, 2007). Another example is the selective D2/D3 receptor antagonist amisulpride, which in animal models has been associated with weight gain and fat accumulation (Roerig et al., 2011).

Furthermore, at follow-up, because of the same reasons, we only obtained a binding measure in the medicated state. Therefore, we cannot make direct inferences regarding a potential paradoxical down-regulation of 5HT2A-BPP caused by the quetiapine treatment as suggested by (Gray and Roth, 2001; Dean, 2003). Hence, it cannot be excluded that the volume of distribution in the blocked state (V_{T,bb}) at follow-up might have been reduced by the six months quetiapine treatment. If indeed true, then this would have resulted in an overestimation of our reported 5HT2A-O.

In summary, the present data in first-episode initially antipsychotic-naïve schizophrenia patients point to a role of the 5HT2A in antipsychotic-induced weight gain. To our knowledge this is the first longitudinal in vivo imaging data to demonstrate an association between 5HT2A activity and weight gain in first-episode schizophrenia patients following six months of antipsychotic monotherapy. We consider these findings of high clinical importance since antipsychotic weight gain and obesity is considered to be the single most important risk factor for dysmetabolism and ultimately premature death in schizophrenia.

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Statement of Interest

Dr Ebdrup has received lecture fees from Bristol-Myers Squibb, Otsuka Pharma Scandinavia AB, and Eli Lilly and is part of the Advisory Board of Eli Lilly Danmark A/S and Takeda Pharmaceutical Company Ltd. The other authors report no biomedical financial interests and potential conflicts of interest.
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