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Low baseline serotonin-2A receptors predict clinical response to olanzapine in first-episode schizophrenia patients

Belén Arranz [a], Pilar Rosel [b], Luis San [a,*], Nicolás Ramírez [a], Rosa María Dueñas [c], Josep Salavert [a], Meritxell Centeno [c], Enrique del Moral [a]

[a] *Department of Psychiatry, Hospital San Rafael, Barcelona, Spain*
[b] *Department of Clinical Chemistry, Ciutat Sanitaria i Universitaria de Bellvitge, Barcelona, Spain*
[c] *Benito Menni, Mental Health Care Institute, Barcelona, Spain*

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Abstract

The purpose of this study was to determine whether platelet serotonin-2A (5-HT_{2A}) binding sites and inositol 1,4,5 trisphosphate (IP3) concentrations before treatment can identify olanzapine-responsive patients. The study included 21 never medicated, first-episode schizophrenia patients (antipsychotic-naïve) and 21 patients with a DSM-IV-TR diagnosis of paranoid schizophrenia who had not received depot antipsychotic treatment in the previous 6 months or oral antipsychotic or antidepressant treatment in the previous 2 months (antipsychotic-free). In the antipsychotic-naïve group, olanzapine responders had a significantly lower number of 5-HT_{2A} receptors and lower IP3 concentrations at baseline than non-responders. The combination of baseline 5-HT_{2A} and IP3 values significantly predicted an improvement in negative symptomatology after 6 weeks of treatment with olanzapine. In the antipsychotic-free group, responders had significantly higher positive and lower negative symptomatology at baseline, together with a reduced number of 5-HT_{2A} receptors. However, basal 5-HT_{2A} receptors or IP3 concentrations did not significantly predict positive, negative or general clinical response. The reported results suggest that platelet 5-HT_{2A} binding might be a trait marker that could help to identify those patients likely to show greater improvement in negative symptomatology after olanzapine treatment.

Keywords: 5-HT2A receptor; Second messenger; Inositol trisphosphate; Platelet; First episode; Schizophrenia; Olanzapine

1. Introduction

Despite general agreement that the *in vitro* binding affinity of antipsychotics for both dopamine D_2 and serotonin-2A (5-HT_{2A}) receptors predicts clinical efficacy, the neurobiological correlates of clinical response to antipsychotic administration have not been systematically investigated. Significant relationships between plasma homovanillic acid (HVA), 3-methoxy-4-hydroxy-phenylglycol (MHPG) concentrations and clinical symptoms have been noted, with increased levels associated with a positive clinical response to haloperidol (Bowers et al., 1984; Davila et al., 1988; Amin et al., 1995; Nagaoka et al., 1997). The serotonergic system has been the focus of attention in recent years, with high plasma 5-hydroxyindoleacetic acid (5HIAAA) concentrations being related to sulpiride

* Corresponding author. Department of Psychiatry, Hospital San Rafael, Passeig Vall d'Hebron 107–117, Barcelona, Spain.
E-mail address: 12636LSM@comb.es (L. San).

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response (Alfredsson and Wiesel, 1990), and increased platelet 5-HT_{2A} binding sites during antipsychotic treatment being associated with a low degree of clinical improvement (Arora and Meltzer, 1994). The 5-HT_{2A} T102C and 5-HT_{1A} receptor gene polymorphisms have also been linked to clozapine responsiveness (Arranz et al., 1995) and to negative symptom response (Reynolds et al., 2006). The relevance of post-receptor mechanisms in antipsychotic drug treatment has been assessed in one animal model (Ashizawa et al., 1996) and in two human studies (Memo et al., 1983; Nishino et al., 1993), in which chronic antipsychotic treatment has been shown to cause an up-regulation of G protein-stimulated adenylyl cyclase activity in both striatum and cortex.

In vitro binding studies in both rodent and human brain have shown a binding profile of the atypical antipsychotic olanzapine similar to that of clozapine, with affinity for dopamine D_1, D_2, D_4, α-adrenergic, histamine H_1 and five muscarinic receptor subtypes (Bymaster et al., 1999a). With regard to the serotonergic system, olanzapine has been shown to possess significant affinity for the 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C} and 5-HT_6 receptor subtypes, lower affinity for the 5-HT_3 and 5-HT_7 subtypes, and negligible affinity for the 5-HT_1 and 5-HT_4 subtypes (Bymaster et al., 1997), also a potent antagonist of the 5-HT-stimulated increases in inositol 1,4,5 trisphosphate (IP3) in cell lines transfected with 5-HT_{2A} or 5-HT_{2B} receptors (Bymaster et al., 1999b). So far, alterations in the phosphoinositide signalling system have been proposed as a possible biological marker of schizophrenia (Strunecka and Ripova, 1999).

To our knowledge there have been no reports on the predictive value of the serotonergic system in relation to the clinical response to olanzapine in schizophrenic patients. Therefore, it was the purpose of this study to determine whether the number of 5-HT_{2A} binding sites and IP3 concentrations before treatment can identify olanzapine-responsive patients. As a 5-HT_{2A} receptor with similar pharmacological properties to that of human brain has been identified in human blood platelets (Elliot and Kent, 1989; Cook et al., 1994), platelet measures were used as a peripheral index of cortex 5-HT_{2A} receptors.

2. Methods

2.1. Subjects

Forty-two patients (mean age 29±8 years) were recruited over a period of 2 years (2004–2005) and admitted to a psychiatric unit due to psychotic symptomatology. The following two groups of patients were included: (1) Never medicated patients with a first episode of schizophrenia (*antipsychotic-naïve*), in whom diagnosis was confirmed with the Structured Clinical Interview for DSM-IV after 1-year follow-up ($n=21$, 14 men and 7 women), and (2) patients with a DSM-IV-TR diagnosis of paranoid schizophrenia ($n=21$), 14 men and 7 women who had not received depot antipsychotic in the previous 6 months, or oral antipsychotic or antidepressant treatment in the previous 2 months (*antipsychotic-free*).

At study entry, none of the patients had any confounding major medical or neurological illness, suicidal ideation or suicide attempt in the last 6 months, thus ruling out 5-HT_{2A} or IP3 changes being linked to suicidality (Rosel et al., 2004). None of the patients had previously received olanzapine, with the first-episode patients not having received any antipsychotic treatment, and the antipsychotic-free patients being excluded if they had previously been exposed to olanzapine. With this procedure it was our aim to rule out the possibility of antipsychotic-free schizophrenic patients with a history of lack of response to olanzapine.

Blood samples were collected on admission to the study and before onset of olanzapine treatment (*baseline values*). The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was administered to each patient both at baseline and after 6 weeks of olanzapine treatment at fixed doses (15–20 mg/day), and data from the Positive (PANSS-P), Negative (PANSS-N) and General Psychopathology (PANSS-GP) subscales were recorded. All patients were hospitalised during the 6-week study, hence ensuring medication compliance. Clinical response was defined as a reduction ≥40% in the Positive, Negative and General Psychopathology PANSS subscale scores after 6 weeks of treatment with olanzapine.

Patients were included in the study after receiving detailed written information about the study procedures and providing written informed consent. The study procedure was in accord with the ethical standards of the Local Committee on Human Experimentation and received its approval.

2.2. Materials

[^{3}H]Ketanserine was purchased from New England Nuclear, mianserine chlorhydrate was generously given by Organon, and the Inositol IP3 RIA assay was acquired from Amersham (TRK 1000).