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ScienceDirect
Schizophrenia Research 101 (2008) 320–330
SCHIZOPHRENIA RESEARCH
www.elsevier.com/locate/schres

Electrophysiological basis for the ability of olanzapine to improve verbal memory and functional outcome in patients with schizophrenia: A LORETA analysis of P300

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Received 1 October 2007; received in revised form 31 December 2007; accepted 10 January 2008
Available online 5 March 2008

Abstract

Abnormality of P300 waveforms of event-related potentials (ERPs) has been suggested to represent an aspect of the pathophysiology of schizophrenia. Previous work points to the contribution of altered neural function in discrete brain regions in the left hemisphere to psychotic symptoms and cognitive deficits of schizophrenia. In this study, we sought to determine: 1) if patients with schizophrenia elicit a decreased P300 current source density in brain areas, such as the superior temporal gyrus (STG); 2) if decreased P300 generator density in the left STG is recovered by treatment with the most widely-used antipsychotic drug olanzapine; and 3) if the recovery of P300 source density is associated with improvements of cognitive and functional status. P300 in response to an auditory oddball task, as well as verbal learning memory, psychopathology, and quality of life were evaluated in 16 right-handed patients with schizophrenia before and after treatment with olanzapine for 6 months. ERP data were also obtained from 16 right-handed age and gender-matched normal volunteers. Low resolution electromagnetic tomography (LORETA) analysis was used to obtain current density images of P300. Patients with schizophrenia showed significantly smaller LORETA values in several brain regions in the left side, particularly STG, middle frontal gyrus, and precentral gyrus, compared with control subjects. Six-month treatment with olanzapine significantly increased P300 source density only in the left STG. Positive symptoms, negative symptoms, verbal learning memory, and quality of life were also improved during treatment. Significant correlations were found between the increase in LORETA values of left STG vs. improvements of negative symptoms, as measured by Scale for the Assessment of the Negative Symptoms, and verbal learning memory, as measured by the Japanese Verbal Learning Test. Improvement of quality of life, as evaluated by the Quality of Life Scale, were significantly associated with an increase in LORETA values of middle frontal gyrus, and tended to correlate with that of precentral gyrus. The results of this study suggest that changes in cortical activity, as measured by ERPs, are responsible for the ability of some antipsychotic drugs to improve cognition and functional outcome in patients with schizophrenia.

Keywords: Event-related potentials; LORETA; Cognition; Negative symptoms; Quality of Life; Superior temporal gyrus; Atypical antipsychotic drugs; Schizophrenia

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doi:10.1016/j.schres.2008.01.020

1. Introduction

Cognitive function, such as verbal memory, attention, and executive function, is a major determinant of outcome in patients with schizophrenia (Meltzer and Sumiyoshi, 2003; Sumiyoshi and Meltzer, 2003). Treatment with the second generation antipsychotics, or so-called "atypical antipsychotic drugs (AAPDs)", has been found to partially improve cognitive disturbances of schizophrenia (Keefe et al., 2006a,b). There is accumulated evidence for the ability of AAPDs, e.g. clozapine, olanzapine, risperidone, quetiapine, melperone, and ziprasidone to ameliorate cognitive impairments in patients with schizophrenia (Sumiyoshi et al., 2006a; reviewed by Sumiyoshi and Meltzer, 2003), although, their effects have recently been found to be smaller than previously considered (Woodward, 2006; Woodward et al., 2005; Keefe et al., 2007). AAPDs have been shown to possess relatively high serotonin-5-HT_{2A}/dopamine-D_2 affinity ratios compared with those of typical antipsychotic drugs, such as haloperidol (Meltzer et al., 1989; Stockmeier et al., 1993; Sumiyoshi et al., 1995), which is assumed to be related to the ability of these agents to enhance DA and acetylcholine release in the prefrontal cortex and hippocampus (Chung et al., 2004; Huang et al., 2006). For example, 5-HT_{2A} antagonist action of AAPDs inhibits the 5-HT system that regulates activity of DA neurons (Kuroki et al., 1999; Meltzer et al., 2003). These pharmacological properties have been suggested to be critical to the ability of AAPDs to improve negative symptoms and cognitive disturbances of schizophrenia (Farde et al., 1998; Meltzer et al., 1999; Kuroki et al., 1999).

Neurophysiological measurements, such as event-related potentials (ERPs), have been suggested to provide a biological substrate for some aspects of cognitive disturbances of schizophrenia. Particularly, P300 has been shown to provide an electrophysiological measure of attention-dependent information processing (Kawasaki et al., 1997, 2007). Its amplitude, thought to reflect activation of immediate memory, is reduced in subjects with schizophrenia (Kawasaki et al., 1997; Nieman et al., 2002; Umbricht et al., 1998; Sumiyoshi et al., 2006b).

Jeon and Polich (2003) reported that P300 amplitudes are overall smaller in patients with schizophrenia compared to control subjects, and differs in its effect size topography across the midline and temporal electrode sites, with the strongest effect sizes obtained for the Pz and TCP1 lateral electrodes. Bruder et al. (1999) found that normal controls showed greater P300 amplitudes, whereas patients did not. Specifically, Kawasaki et al. (1997) found negative correlations between auditory P300 amplitudes and severity of psychotic symptoms of schizophrenia. Renoult et al. (2007) report a positive correlation between differences in P300 amplitudes at temporal sites (T4–T3) and severity of positive symptoms and worse global functioning, consistent with an association between low P300 amplitudes and verbal memory deficits in schizophrenia (Nagasawa et al., 1999; Nieman et al., 2002).

Efforts have been made to elucidate mechanisms for the ability of AAPDs to ameliorate psychophysiological impairments of schizophrenia. Honey et al. (1999) reported that treatment with risperidone increased blood flow in right prefrontal cortex, as revealed by fMRI. Lieberman et al. (2005) measured the brain volumes of subjects with first episode schizophrenia, and found that patients treated with haloperidol showed a reduced gray matter volume, whereas olanzapine did not have such an effect. Umbricht et al. (1998) found that treatment with clozapine but not haloperidol increased P300 amplitudes in patients with schizophrenia. Specifically, Niznikiewicz et al. (2005) observed an increase in P300 amplitudes in left temporal electrodes during treatment with clozapine, indicating a region-specific response to pharmacological treatment. However, localization of the electrical generator of P300 has been difficult due to limited spatial resolution with traditional ERP methods.

Low Resolution Electromagnetic Tomography (LORETA) provides three-dimensional images of brain electrical activity (Pascual-Marqui et al., 1999). To date, there has been little study on the effect of AAPDs on LORETA images of electrophysiological activity. In a previous study, Sumiyoshi et al. (2006b) reported preliminary results that 6-month treatment with olanzapine restored the left-dominant laterality of the P300 current density in the superior temporal gyrus (STG) in a small sample of subjects with schizophrenia who showed improved performance on a test of verbal learning and memory.

In this study, we sought to test the hypotheses that 1) patients with schizophrenia elicit a decreased P300 current source density in brain regions relevant to the pathophysiology of schizophrenia, such as the left STG; 2) decreased P300 activity is restored by treatment with the most widely-used antipsychotic drug olanzapine; and 3) the recovery of P300 source density is correlated with improvement of cognition and functional status which are relevant to quality of life for patients.

2. Methods

2.1. Subjects

Data were obtained from 16 patients (male/female = 11/5) meeting DSM-IV-R criteria for schizophrenia (APA,