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Neuroleptic effects on P50 sensory gating in patients with first-episode never-medicated schizophrenia

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ABSTRACT

Sensory gating deficit, as reflected by P50 suppression, has been demonstrated in schizophrenia. Despite extensive evidence of the irreversible effects of typical neuroleptics on this deficit, recent studies of atypical neuroleptics have produced inconsistent findings on the reversibility of P50 suppression in schizophrenia. As the majority of these studies were limited by either their cross-sectional design or the recruitment of patients on multiple medications, the current study was designed to examine the effects of different neuroleptic medications on the P50 sensory gating index in patients with first-episode, never-medicated schizophrenia. P50-evoked potential recordings were obtained from 62 normal controls when they entered the study and from 65 patients with first-episode, never-medicated schizophrenia at baseline and after six weeks of different neuroleptic treatments (sulpiride [n=24], risperidone [n=24] and clozapine [n=17]). The first-episode, never-medicated schizophrenia patients had impaired sensory gating relative to the normal controls (mean=94.19% [SD=61.31%] versus mean=41.22% [SD=33.82%]). The test amplitude S2 was significantly higher in the schizophrenia patients than in the normal controls. The conditioning amplitude S1 and the positive symptom scores were related to the P50 gating ratios in schizophrenia at baseline. There was no change in P50 sensory gating (P>0.10) and a significant improvement in the clinical ratings (P>0.10) after six-week neuroleptic treatment for schizophrenia. P50 sensory gating was not significant for the patients who received sulpiride, risperidone or clozapine at baseline (F=1.074, df=2, 62, P=0.348) or at endpoint (F=0.441, df=2, 62, p=0.646). Our findings indicate that there is P50 sensory gating impairment in first-episode, never-medicated schizophrenia and that treatment with typical and atypical antipsychotics has no significant impact on such gating in this illness.

1. Introduction

The inhibitory properties of the central nervous system have long been examined using conditioning-testing paradigms, under which the amount of attenuation in the neural response to the second of two identical stimuli indexes the strength of the inhibitory pathway. This paradigm has been adapted in psychophysiological research as a test of "sensory gating," and it has provided basic support for theories that postulate that individuals with schizophrenia demonstrate less effective regulation over the influx of sensory information to the brain (Adler et al., 1982; Braff et al., 1995). More specifically, the decrement in the amplitude of the P50 event-related potential (ERP) evoked by the second S2 relative to the first S1 of two auditory "clicks," which is commonly expressed

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as the suppression ratio S2/S1, is smaller in schizophrenia and is thought to reflect weak inhibition or the gating of the repeated stimulus (Freedman et al., 1987).

This deficient P50 suppression in schizophrenia patients has been confirmed repeatedly and is, according to two meta-analytic studies, one of the strongest and most reliable findings in the schizophrenia literature (Heinrichs, 2004; Bramon et al., 2004). It has prompted further studies to clarify the clinical and neural substrates of the earlier findings. Poor P50 suppression also occurs among the non-psychotic family members of patients with schizophrenia, which indicates that these deficits are not sufficient to produce the syndrome of schizophrenia, but may reflect an intermediate phenotypic marker (Adler et al., 1999; Freedman et al., 2000; Myles-Worsley, 2002). In this context, a linkage between P50 gating and the α_7 nicotinic receptor has been reported (Freedman et al., 1997).

The effects of medication on P50 suppression were initially studied to assess the dopaminergic involvement in deficient P50 suppression among schizophrenia patients. This initial study compared unmedicated patients with those taking typical antipsychotics and with normal subjects. P50 suppression was lower in the schizophrenia patients than it was in the normal subjects, and, in addition, there were no significant differences in this suppression between the medicated and unmedicated patients (Freedman et al., 1983). Myles-Worsley (2002) also found that patients who had been free of typical antipsychotic medication for at least 10 weeks were just as likely to exhibit the P50 sensory gating deficit as were patients who were receiving therapeutic doses of these medications. Furthermore, in the medicated patient group, the P50 sensory gating ratio was uncorrelated with the medication dose (Myles-Worsley, 2002). A recent study failed to find any relationship between a conventional antipsychotic dose and the P50 ratio (Louchart-de la Chapelle et al., 2005). These results suggest that impaired P50 sensory gating occurs independently of the effects of typical antipsychotics in a variety of patients at different stages of the illness.

Typical neuroleptic treatment fails to ameliorate this deficit. However, recent studies of atypical antipsychotic medications suggest that they do have an effect on P50 gating. Clozapine treatment improved P50 gating in the patients who responded to it, although this gating had been abnormal during previous treatment with typical neuroleptics (Nagamoto et al., 1996). Clozapine's amelioration of the P50 auditory gating deficit was stable in a subsequent follow-up over a 5- to 27-month period of observation (Nagamoto et al., 1999). In a cross-sectional study, Becker et al. (2004) compared patients treated with clozapine and those treated with conventional antipsychotics and found that the former had significantly lower sensory gating ratios than did the latter. Significantly reduced sensory gating ratios have been found in patients treated with clozapine, risperidone and olanzapine compared with those treated with conventional antipsychotics (Light et al., 2000). Adopting a double-blind, placebo-controlled trial design, Arango et al. (2003) found no significant differential effects in sensory gating ratios between inpatients with schizophrenia who received haloperidol and olanzapine. A recent meta-regression analysis of the relationship between medication and P50 ratios, which reviewed study reports from January 1994 to August 2003, found no significant effect of antipsychotics on the P50 sensory gating ratio, but the researchers did not divide these antipsychotics into typical and atypical medicines (Bramon et al., 2004).

Atypical medications differ from one another in their occupancy of various catecholaminergic and serotonergic receptors at therapeutic doses (Kinon and Lieberman, 1996; Kasper et al., 1999), and there are significant differences in their effects on behavioral outcome measures such as negative symptoms, cognitive dysfunction and mood stabilization (Ichikawa and Meltzer, 1999). A post hoc division of subjects treated with atypical antipsychotics by Light et al. (2000) suggested that the improvement appeared to be mainly based on the effects of clozapine and, to a lesser degree, olanzapine, as the subjects who received risperidone continued to have sensory gating in the range seen in patients who received typical neuroleptics (Light et al., 2000). By adopting a Bonferroni adjustment for pair-wise comparisons, it was found that the patients treated with clozapine had significantly better sensory gating ratios than did those who received any other atypical medication. Sixty-two percent of the patients treated with clozapine had P50 ratios within the normal range, compared with 24% of the patients who received risperidone, 14% of those who received olanzapine and 0.0% of those who received quetiapine (Adler et al., 2004). As the majority of these studies was limited, either by their cross-sectional design or because the subjects observed had been treated with multiple medications or had a medicated history, the current study was designed to observe the effects of different neuroleptic medications, both typical and atypical, on the P50 sensory gating index of patients with never-medicated, first-episode schizophrenia.

2. Methods

2.1. Subjects

All of the participants were recruited from the Mental Health Center of Shantou University. These patients had been admitted to the Mental Health Center by family members or by themselves after experiencing some type of psychotic symptom. None of them had previously contacted psychiatric services or been medicated with any antipsychotics. The patients were administered the Structured Clinical Interview for DSM-IV by trained psychiatrists, and all of them met the DSM-IV criteria for schizophrenia or schizophreniform disorder. Those with the latter diagnosis were followed up for at least six months to confirm a diagnosis of schizophrenia. The exclusion criteria included cardiovascular or neurological disease, a history of a head injury that resulted in a loss of consciousness, meeting the DSM-IV criteria for substance dependence or meeting the diagnostic criteria for current DSM-IV Axis I mood or anxiety disorder. All of the patients began to receive antipsychotic medication once their diagnoses had been confirmed. They were treated with different antipsychotics based on a discussion with their clinical psychiatrist and family members. The psychiatrist did not know the results of the electrophysiological recordings. The normal controls were recruited from the staff of Shantou University. None of them had any personal or family history of an Axis II psychotic disorder or was taking any kind of medication. All of the subjects had normal hearing acuity and signed informed consent. The sensory gating measures for the