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Prepulse inhibition of acoustic startle in subjects with schizophrenia treated with olanzapine or haloperidol

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Abstract

Studies of the acoustic startle response and of its inhibition by the presentation of a non-startling preliminary stimulus (prepulse inhibition, PPI) have revealed deficits in PPI in schizophrenic subjects compared to healthy controls. Animal studies indicate that atypical antipsychotics improve PPI deficits induced by NMDA antagonists more consistently than typical antipsychotics. The effect of medication status on PPI in schizophrenia is unresolved in the literature. In the current study the effects on PPI of the atypical antipsychotic olanzapine and the typical antipsychotic haloperidol were compared to the unmedicated state in subjects with schizophrenia. In a between-group design, 11 schizophrenic subjects on olanzapine, 16 subjects on haloperidol, and 14 subjects who were on no medication received acoustic startle testing with PPI determination. ANOVAs revealed no significant differences in startle to pulse alone stimuli, habituation of startle, or PPI between the olanzapine, haloperidol and unmedicated groups. These 41 subjects with schizophrenia were compared to a group of 21 historical healthy controls and found to have reduced PPI. These data do not indicate a preferential effect of olanzapine compared to haloperidol on sensorimotor gating in schizophrenia. The results are consistent with the hypothesis that PPI impairments are relatively stable across treatment conditions.

Keywords: Sensorimotor gating; Prepulse inhibition; Antipsychotic; Olanzapine; Haloperidol

1. Introduction

The acoustic startle response (ASR) is a reflex contraction of the skeletal muscle that occurs in all mammals as a response to a sudden, intense acoustic stimulus. It is mediated by a simple pontine based neural circuit that has been well defined (Davis et al., 1982; Davis, 1997; Koch, 1999; Fendt et al., 2001). In humans, the eye-blink component of the startle response elicited by

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a strong, abrupt acoustic signal is measured by electromyographic (EMG) assessment of the orbicularis oculi facial muscle response (Graham, 1975). The ASR demonstrates several forms of behavioral plasticity, one of which is prepulse inhibition (PPI).

Prepulse inhibition of the startle response represents a normal attenuation of the startle reflex following the presentation of a weak prestimulus (prepulse) at brief intervals (i.e. between 30 and 500 ms) prior to the startle-eliciting stimulus (pulse). PPI has been observed in animals (Hoffman, 1997; Hoffman and Searle, 1968; Hoffman and Ison, 1992) and humans (Graham, 1975). The measured changes reflected in amplitude inhibition, latency of blink onset, and latency to peak amplitude reduction are indicators of inhibition of startle response. It is hypothesized that PPI reflects the functioning of a preattentive filtering system whereby the prepulse exerts an inhibitory influence until the processing of the prepulse is complete, thus protecting the organism against information overload and cognitive disruption (Braff et al., 1978).

In patients with schizophrenia, the ability to filter irrelevant exteroceptive or enteroceptive stimuli and discriminate important information from the environment is impaired, resulting in information overflow (Venables, 1964). Sensorimotor gating deficits may allow irrelevant thoughts and sensory stimuli into conscious awareness and contribute to the hallucinations, delusions and cognitive disintegration seen in schizophrenic patients (McGhie and Chapman, 1961).

Patients with schizophrenia display a fully normal initial startle response, but have impaired habituation of startle (Geyer and Braff, 1982, 1987; Bolino et al., 1992; Parwani et al., 2000), and fail to display normal PPI. A number of studies have demonstrated such an impairment in PPI in subjects with schizophrenia (Braff et al., 1978, 1992, 1999, 2001; Braff and Geyer, 1990; Grillon et al., 1992; Bolino et al., 1994; Schall et al., 1996; Cadenhead et al., 2000; Weike et al., 2000; Parwani et al., 2000).

Deficient PPI has been proposed as a biologic marker of schizophrenia (Braff, 1993; Swerdlow and Geyer, 1998). However, the literature to date is inconclusive regarding the effect of treatment status on PPI. The studies demonstrating abnormal PPI have been conducted on patients who were on neuroleptics at the time of testing (Braff et al., 1978, 1992; Grillon et al., 1992; Bolino et al., 1994; Schall et al., 1996), indicating that treatment does not completely normalize PPI deficits. Several studies have reported results indicating a differential effect of medication status on PPI. Kumari et al. (1998) initially reported a trend level difference in PPI between subjects with schizophrenia treated with typical and atypical antipsychotics. A larger series from this group (Kumari et al., 2000) did not confirm this difference, but showed that only subjects on typical antipsychotics but not atypicals had less PPI than healthy controls. Weike et al. (2000) found PPI impairment only in five unmedicated subjects with schizophrenia compared to healthy controls, but no impairment in 20 medicated subjects with schizophrenia. Similarly, several recent between-group studies found that schizophrenic subjects treated with typical antipsychotics had reduced PPI compared to healthy controls (particularly at low to medium intervals between prepulse and pulse stimuli), whereas the atypical-treated subjects had normal PPI (Kumari et al., 1999, 2002; Kumari and Sharma, 2002; Oranje et al., 2002b). Leumann et al. (2002) reported a similar finding, and additionally found a significant difference in PPI between subjects on typicals and atypicals.

On the other hand, several other studies report findings of no difference between subject groups differing in medication status. The study of Parwani et al. (2000) did not detect differences in PPI between unmedicated schizophrenic subjects and those on neuroleptics. Perry et al. (2002) found equivalent PPI deficits in acutely hospitalized subjects with schizophrenia whether they were on medication (including both atypicals and typicals) or unmedicated for the week prior to testing. In the first study using a within-subjects test–retest design, Mackeprang et al. (2002) found no increase in PPI when a group of first break schizophrenic patients were treated with either atypical or typical antipsychotic drugs. Finally, Duncan et al. (2003) used both a between-group and a within-subjects test–retest design, and