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Prepulse inhibition deficits in schizophrenia are modified by smoking status

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ABSTRACT

Background: Schizophrenia is associated with high rates of cigarette smoking and deficits in sensorimotor gating, as measured by prepulse inhibition (PPI) of the startle response. However, the relationship between PPI deficits and smoking status is unclear. We examined whether smoking status modifies PPI deficits in schizophrenia.

Methods: We studied PPI as a function of smoking status and schizophrenia diagnosis in four groups using a cross-sectional design: Smokers with schizophrenia (SS; $n=14$), non-smokers with schizophrenia (SNS; $n=15$), control smokers (CS; $n=11$), and control non-smokers (CNS; $n=10$). PPI in smokers was recorded under conditions of smoking satiation, and smoking status was verified biochemically.

Results: The Diagnosis × Smoking Status × Prepulse Interval interaction was significant ($F_{11,140}=5.01$, $p<0.001$). At all prepulse to pulse intervals (PPTPIs; 30, 60 and 120 ms), we found that SNS had reductions (~50%; $p<0.01$) in PPI compared to CNS. However, when SS were compared to CS under conditions of smoking satiation, SS had comparable levels of PPI to CS, and significantly higher levels of PPI than SNS.

Conclusions: Our findings suggest that PPI deficits are present in nonsmokers with schizophrenia, and may be modified by smoking status. Acute smoking in schizophrenia is associated with an elevation of PPI to the levels in non-psychiatric control smokers. These findings have significant implications for understanding vulnerability to tobacco dependence in schizophrenia, which may lead to the development of more effective treatments for PPI deficits and tobacco dependence in this population.

1. Introduction

Schizophrenia is associated with a number of psychophysiological abnormalities, including deficits in sensorimotor gating, as operationalized by prepulse inhibition (PPI) of the startle (e.g. acoustic, tactile) response (Braff et al., 1992, 2001). PPI deficits appear to be a stable trait associated with schizophrenia and are not modified by clinical state. In addition, PPI deficits meet criteria for being an endophenotype of schizophrenia as they are also present in first-degree relatives of patients with schizophrenia (Braff and Freedman, 2002; Gottesman and Gould, 2003). Cigarette smoking is also very common in patients with this disorder, and the prevalence in clinical populations is in the 70–90% range (Kalman et al., 2005; Morisano et al., 2009). Several recent studies (Kumari et al., 2001; George et al., 2006; Postma et al., 2006) have suggested that nicotine and cigarette smoking may improve PPI, while acute nicotine withdrawal may impair PPI in smokers with schizophrenia, but not in non-psychiatric control smokers. The effects of cigarette smoking on PPI appear to be dependent on nicotinic receptor stimulation (George et al., 2006). Accordingly, it has been suggested that nicotine intake may selectively ameliorate PPI

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deficits in smokers with schizophrenia, and that such deficits may constitute a vulnerability factor to tobacco dependence in these patients, similar to deficits in spatial working memory and sustained attention (George et al., 2002; Smith et al., 2002; Sacco et al., 2005).

However, little is known about the PPI deficits in schizophrenia as a function of smoking status (e.g. smokers versus nonsmokers). Only one study has reported on the effects of smoking status in schizophrenia and control subjects and found that PPI was higher in smoking versus non-smoking patients, but this study did not control for time of last cigarette in smoking subjects (Swerdlow et al., 2006). Accordingly, the purpose of the current study was to characterize the interactive effects of smoking status (after carefully controlling for time of last cigarette smoked) and schizophrenia diagnosis on PPI by studying the four possible groups using a cross-sectional design: 1) smokers with schizophrenia; 2) nonsmokers with schizophrenia; 3) control smokers; 4) control nonsmokers. Our data suggest that while PPI deficits are present in non-smokers with schizophrenia, acute smoking ameliorates PPI deficits in schizophrenia patients.

2. Methods

2.1. Subjects

Seventy-five subjects were screened for study participation. Schizophrenia smokers (SS; $n=23$) and schizophrenia non-smokers (SNS; $n=19$) were recruited from the outpatient clinics of the Connecticut Mental Health Center (CMHC). Non-psychiatric control smokers (CS; $n=19$) and control non-smokers (CNS; $n=14$) were recruited by newspaper and radio advertisements in the Greater New Haven (Conn.) area. Informed consent was obtained from all subjects and the study protocol was approved by the Human Investigation Committee (HIC) at Yale University School of Medicine.

Subjects were evaluated using the Structured Clinical Interview for the DSM-IV (SCID-IV) Axis I Disorders (First, 1994). Subjects with schizophrenia were clinically stable outpatients and were prescribed stable doses of antipsychotic medication (first or second generation agents) for at least three months prior to the study entry. Controls demonstrated no current Axis I disorder and were not prescribed psychotropic medications; those with a past history of major depression ($n=3$; CS group) or drug and alcohol abuse in remission for at least 1 year ($n=5$; CS group) were included if they satisfied other study criteria. Patients and controls were required to have an estimated IQ$\geq$80 using the Shipley IQ scale (Shipley and Burlington, 1941).

Smokers met DSM-IV criteria for nicotine dependence, had a score of $\geq$5 on the Fagerstrom Test for Nicotine Dependence (Heatherton et al., 1991), smoked $\geq$15 cigarettes per day, and had expired breath carbon monoxide (CO) levels of $\geq$10 ppm and plasma cotinine levels of $\geq$150 ng/ml. Nonsmokers did not report tobacco use in the past six months prior to study participation, and at the time of study participation had expired CO levels $<$10 ppm and a plasma cotinine $<$15 ng/ml. Psychotic and depressive symptoms were assessed using the Positive and Negative Symptoms Scale for Schizophrenia [PANSS; (Kay et al., 1987)], and the Beck Depression Inventory (BDI-II) (Beck et al., 1996).

2.2. Study procedures

The procedures for assessment of prepulse inihibition (PPI) of the acoustic startle response have been described previously (George et al., 2006), and are an adaptation of the procedures of Braff et al. (1992). PPI was recorded at the end of a series of cognitive testing procedures which included assessments of psychotic and affective symptoms and neuropsychological tests of working and verbal memory, attention, executive function, and intellectual function (Sacco et al., 2005). In smokers, PPI was recorded under satiated conditions, such that smokers received a 15 minute ad lib smoking break just prior to the recording of PPI and acoustic startle response during a 20 minute session.

2.3. Prepulse inhibition (PPI) of the acoustic startle response

All subjects underwent audiometry to ensure intact auditory thresholds to tones $<$35 dB at 250, 500, 750, 1000, 1500, 2000, 3000, 4000, and 6000 Hz. Subjects were classified as acoustic startlers if they had acoustic startle responses which displayed $\geq$20 machine unit ($\geq$25 μV, where 1 machine unit = 1.221 μV) increases in the first block of startle stimuli over baseline amplitudes (Braff et al., 1992). Of the $N=75$ subjects screened for the PPI testing procedures (George et al., 2006), a total of 14/23 (60.9%) SS, 11/19 (57.9%) CS, 15/19 (78.9%) SNS and 10/14 (71.4%) CNS were classified as acoustic startlers.

The eyeblink component of the acoustic startle reflex was measured using electromyography of the obicularis oculi muscle. Acoustic stimuli were produced on a computerized startle response system (Windows-based SR-LAB; San Diego Instruments, San Diego, CA) and presented binaurally through headphones. The system was programmed to record for 250 ms after the onset of the startle stimulus. EMG data were collected and stored for off-line analysis.

Test sessions began with a 1-minute acclimation period of 70-dB white noise that continued during the testing session. The test paradigm consisted of 9 blocks of 4 acoustic startle trials per block (36 trials per session). In each block the 0 ms (pulse alone) condition was presented first, followed by the three prepulse intervals (30, 60 and 120 ms) presented in a random order. Startle stimuli consisted of 40 ms, 115.5-dB bursts of white noise with near instantaneous rise time. Prepulse trials consisted of a 20-millisecond, 85-dB burst of white noise that was presented 30, 60 or 120 ms before the startle pulse. Inter-trial intervals ranged from 14–17 s (Mean = 15.7 ± 1.3). PPI sessions lasted 10 min, 40 s.

Criteria for inclusion of startle trials were described previously (Braff et al., 1992). Using these parameters, 11.3% of trials in schizophrenia subjects and 14.7% of trials in controls were discarded (from 36 trials per session). PPI was defined as the percentage difference in startle magnitude with and without prepulse [1-(pre-pulse to pulse interval startle magnitude/pulse alone startle magnitude) × 100%] (Braff et al., 1992; George et al., 2006).