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Stress induced by the socially evaluated cold-pressor test cause equivalent deficiencies of sensory gating in male subjects with schizophrenia and healthy controls

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ABSTRACT

It is known that patients with schizophrenia show a deficiency in the prepulse inhibition reflex (PPI). These patients display abnormalities in autonomic nervous system and hypothalamic–pituitary–adrenal function and may have an altered sensitivity to stress. To date, no studies have been carried out to determine the effect of acute stress on the PPI. We investigated whether there was a differential response in reactivity to acute stress caused by the socially evaluated cold-pressor test (SECPT) in a sample of 58 chronic male patients with schizophrenia and 28 healthy control subjects. PPI, salivary cortisol and heart rate (HR) were measured. The patients were evaluated in two sessions (with and without the SECPT) 72 h apart and basal measurements were carried out and 30 min post-startle probe. We found an increase in salivary cortisol levels and the HR with SECPT condition in both groups and a significantly lower PPI% in patients with schizophrenia. The most relevant findings of this study are that the impairment of the PPI is increased by stress. Stress-induced increase in cortisol in both groups, mainly in healthy control group which allows us to hypothesize that at least such deterioration may be due to the hypercortisolemia caused by the SECPT.

1. Introduction

The pathophysiology of schizophrenia is not totally known. In the last few decades there has been a particular focus on the malfunctioning of the sensory–motor system gating mechanisms that rely on the prefrontal cortex of those patients. The gating of information flow within the limbic system and the pathophysiology of schizophrenia has been assumed (Grace, 2000) and social deficits of schizophrenia (emotional processing, social perception, emotion recognition, etc.) could be linked to it. Thus, higher stress levels could affect sensory input. It has come to be considered that these deficiencies could be an endophenotype of schizophrenia (Braff, 2010). This deficit has been linked with weak dopamine regulation by the frontal cortex (Arnsten, 2013). Although several paradigms of startle reflex have been used (Hasenkamp et al., 2011; Dominelli et al., 2014), one of the most classic for studying this deficient sensory gating in schizophrenia is the prepulse inhibition of the startle reflex (PPI) (Hasenkamp et al., 2010).

The PPI is the inability to effectively attenuate the startle

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response when it is preceded by a weak prepulse stimulus (Braff and Geyer, 1990). In a recent review on PPI in patients with schizophrenia, the existence of impaired inhibition of the PPI was confirmed in those patients (García-Sánchez et al., 2011). These alterations may be modulated by drug use; improve due to treatment with antipsychotics, especially atypical antipsychotics; be present in the initial stages of the illness; seem to be stable throughout the evolution of the disorder; and have been linked with positive or negative symptoms, or with the general psychopathology (Martínez-Gras et al., 2009; Jurado-Barba et al., 2011). Together with that the loss of sensory gating seems independent from a psychotic state, it may be suggested that it reflects a trait rather than a state phenomenon (Baker et al., 1987). Thus, in schizophrenia, a loss of sensory gating may result in an overflow in the brain of irrelevant stimuli and may therefore alter perception of the environment (see Mazza et al., 2013; Ebisch et al., 2014). This may have repercussions on the way that a stress stimulus could be interpreted.

Another area of investigation connected to schizophrenia is its relationship with stress. According to the vulnerability-stress model, schizophrenia is described as the result of a complex interaction between biological and psychosocial factors, the former being genetically determined, the latter being predominantly developed during life, which both contribute to the individual's vulnerability to develop a psychosis under stressful circumstances (Nuechterlein et al., 1994).

Although data on the impairment of the PPI in schizophrenia and the model of vulnerability to stress date back to the end of the 70s (Zubin and Spring, 1977; Braff et al., 1978), no studies have been carried out to determine the impact of acute stress on the PPI. For this reason, we conducted this study, which aimed to investigate whether there was a differential response in reactivity to acute stress caused by the socially evaluated cold-pressor test (SECPT) among a sample of subjects with schizophrenia and healthy controls. Our main hypothesis was that the subjects with schizophrenia, after being exposed to the SECPT would have a worse inhibition response in the PPI than the healthy controls. Bearing in mind the results of previous studies (Brenner et al., 2009), we also hypothesized that cortisol response would be blunted, while that of heart rate would be increased.

2. Methods and materials

2.1. Subjects

Fifty-eight male patients (age range: 25–56 years; mean age: 36.3 years, SD: 6.4) with schizophrenia diagnosed using the structured clinical interview for DSM-IV (SCID-P) (First et al., 1995) were recruited through the Brief Hospitalization Unit at the Mental Health Services of 12 de Octubre University Hospital (Madrid, Spain). The study sample was limited to male subjects because of previous reports of gender differences in PPI (Kumari et al., 2004). Subjects were excluded if they had any other Axis I psychiatric disorder, significant active medical illness, mental retardation, history of any neurological condition, head trauma or loss of consciousness, substance abuse within the past year, or any history of substance dependence (excluding nicotine and caffeine). Subjects who regularly used caffeine or smoked cigarettes maintained their usual pattern on the days of testing. No first-episode patients were included. All patients had been treated with haloperidol (mean dose 7.9 ± 0.9 mg) for 5–8 days, being hospitalised.

Twenty-eight healthy subjects (all males, age range: 29–53 years; mean age: 36.6 years, SD: 6.2) were recruited from the community and among the staff of the Mental Health Services. Before being included as participants, they were screened using a semi-structured interview for exclusion criteria: thyroid dysfunction, heart disease, hypo- or hypertension, regular medical prescriptions, a history of mental illness, rapid mood changes, drug (ascertained by urine toxicology screen) and alcohol abuse, and psychosis in first-degree relatives. All subjects included in the study were also screened to ensure intact auditory abilities (using an AudioScope 3, Welch Allyn WA® audiometer) and to exclude those who could not detect 40 dB tones at 1000 Hz.

2.2. Saliva sampling, cortisol analysis and cardiovascular data

Saliva was collected by the subjects themselves using standard Eppendorf tubes (1.5 ml, Eppendorf, Hamburg, Germany), stored at room temperature until completion of the session, and then kept at −20 °C until analysis. After thawing for biochemical analysis, the fraction of free cortisol in saliva (salivary cortisol) was determined using a RIA with *Salivettes* (Sarstedt Inc., Texas). Inter- and intra-assay coefficients of variance were below 9%. Heart rate (HR) was measured with a wrist cuff monitor (beats/minute).

2.3. Measurement of PPI

A commercial human startle response monitoring system (CIBERTEC, S.A.) was used to generate and deliver the startle stimuli and to record and score electromyographic (EMG) activity (STARTLEH software, a WNS 220 electronic module, an ADInstrument Bio Amp, and a PowerLab data unit). Startle stimuli were presented to subjects binaurally through headphones. EMG recordings were taken with subjects sitting comfortably in a moderately lit, soundproof room. The eye blink component of the startle response was indexed by recording EMG activity of the orbicularis oculi muscle directly beneath the right eye, with two, miniature silver/silver chloride electrodes filled with Dracard electrolyte paste. The startle system recorded EMG activity for 250 ms (sample interval 1 ms) from the onset of the startle stimulus. Recorded EMG activity was band-pass filtered, as recommended by the SR-LAB™ Startle Response System. A 50 Hz filter was used to eliminate 50 Hz interference. EMG data were scored off-line by the system's analytic program for response amplitude (in arbitrary analogue-to-digital units), and latencies to response onset and peak (in ms).

The methodology used in the startle session was consistent with previous studies (Braff et al., 1992; Martínez-Gras et al., 2009), starting with a 5min acclimatisation period of 70 dB white noise, followed by four blocks. The first and last blocks consisted of five pulse-alone trials of 40 ms, 115 dB startle stimuli. Blocks two and three consisted of pulse-alone and prepulse–pulse trials presented in pseudorandom order. The 20 prepulse stimuli preceded the startle stimulus by 30, 60 or 120 ms, and were 15 dB above the 70 db background noise.

The inter-trial interval averaged 15 s (range: 8–22 s). Settings were adjusted so that the program excluded spontaneous and voluntary eye blinks. Criteria for excluding a stimulus were a difference between the onset and peak latencies greater than 95 ms, or a baseline shift exceeding 90 digital units.

Subjects were regarded as PPI non-responders if the mean pulse-alone magnitude in the first block was less than 10 digital units. Data from subjects who showed extreme inconsistency in PPI within the same session (mean PPI change from block 2 to block $3 \geq 1.5$ standard deviations in at least one interstimulus interval) were also excluded from the analyses (see Martínez-Gras et al., 2009). Three control subjects and 8 patients were excluded based on this criterion. Thus the final sample consisted of 50 patients with schizophrenia and 25 healthy control subjects.

The prepulse inhibition was calculated as the percentage decrement in startle amplitude in the presence vs. in the absence of the prepulse, i.e. $100 - [\text{prepulse amplitude}/\text{pulse amplitude}] \times 100$ (Braff et al., 1992; Martínez-Gras et al., 2009).

2.4. The socially evaluated cold-pressor test (SECPT)

We followed this procedure as a stressor stimulus (Schwabe et al., 2008). Subjects were informed that they would be videotaped and that these video recordings would be analysed for facial expression. After participants provided written consent for the video recordings to be used for scientific purposes, they were asked to immerse their right hand up to and including the wrist into ice water (0–2C). Subjects were instructed to look into the camera and keep their hand in the water for as long as possible. Those participants who kept their hand in the water for 4 min were instructed at that point to remove their hand. Then, they responded to a questionnaire (Likert visual analogue scale 0–10) on the stimulus aversiveness through three subscales (unpleasant/painful/unexpected).

The research protocol for this study was approved by the Research Ethics Board of the 12 de Octubre University Hospital and all participants signed an informed consent form on the day of their participation. All experimentation sessions began at 13:00 h and were completed by 15:30 h, to capitalize on the slow descent in cortisol levels at this time of day (Smyth et al., 1997), permitting changes in salivary cortisol following the SECPT to be observed without extensive correction. The experimentation sessions were 72 h apart (the first part on Monday or Tuesday and the second on Thursday or Friday).The procedure used in this protocol is presented graphically in Fig. 1.

Upon arrival at the psychophysiology lab room, participants were asked to refrain from drinking beverages, eating, smoking, exercising and brushing their teeth for the duration of the 2 h protocol. Water was available for all participants to drink.

2.4.1. Experimentation session without the SECPT

First, participants completed the various questionnaires. A trained research assistant was present to help complete them as needed. Participants were then

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