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Characterizing cannabis-induced psychosis: A study with prepulse inhibition of the startle reflex

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ABSTRACT

Cannabis-induced psychotic disorder (CIPD) refers to psychotic symptoms that arise in the context of cannabis intoxication. Prepulse inhibition (PPI) deficits have been extensively identified in schizophrenia and in cannabis abusers. We aimed to characterize PPI in CIPD patients. We used a sample of 48 CIPD patients, 54 schizophrenia patients and cannabis abuse (SCHZ), 44 cannabis dependents (CD), and 44 controls. CIPD, SCHZ and CD were abstinent of cannabis consumption for 9 months. Participants were assessed with PPI at 30, 60, and 120 ms. At 30 ms, CIPD showed lower PPI levels than controls, and SCHZ obtained worse functioning than controls and CD. At 60 ms, only SCHZ exhibited worse PPI percentages (of object) than controls. Finally, at 120 ms, CIPD showed higher PPI levels than SCHZ, and SCHZ obtained lower percentages than controls. We found that CIPD and SCHZ patients showed deficits at the most pre-attentional levels, whereas CIPD patients performed better than SCHZ at higher attentional levels. These results suggest that CIPD constitutes a different group of patients than that of SCHZ. Deficits in PPI functioning at 30 ms could be a useful psychophysiological measure to detect CIPD patients, who are frequently confused with cannabis abusers whose symptoms may mimic that of schizophrenia.

1. Introduction

Cannabis-induced psychotic disorder (CIPD) is characterized by several psychotic symptoms that arise in the context of cannabis intoxication but persist beyond elimination of the drug (APA, 1994). However, there is little research regarding the potential differences between CIPD and patients with schizophrenia, let alone the prevalence and etiopathogenesis of this disorder. These studies have included patients with cannabis–psychosis mainly focus on examining symptoms that could distinguish them from subjects with schizophrenia (Nuñez and Gurpegui, 2002; Caton et al., 2005). Our group carried out a follow-up study with patients admitted to the hospital, and that showed psychotic symptomatology in the context of cannabis abuse. This study showed the existence of clinical differences between patients with CIPD and patients with schizophrenia and cannabis abuse, during their first weeks of admission. The CIPD group obtained a profile of psychophathological symptoms that was similar to a neurotic profile. Subjects who develop CIPD are those who have personality traits similar to subjects with predominance of interpersonal sensitivity and social phobic anxiety and that, after consuming large quantities of cannabis, they develop induced psychosis, that is, psychosis due to a substance–personality trait interaction (Rubio et al., 2012). However, all of these studies are still cross-sectional studies, and they have been limited to the severe phase of the clinical stage. This is considered one of the main limitations of these studies (Caton et al., 2005). Moreover, those few follow-up studies have only focused on detecting which clinical variables may predict which patients will finally develop schizophrenia. The scarce interest for this specific clinical disorder can be explained by the controversy that still persists regarding the diagnosis of CIPD. Some authors consider this disorder an induced disorder that is time-limited (Nuñez and Gurpegui, 2002; Dawe et al., 2011), whereas other authors would conclude this disorder to be directly caused by the intoxication of cannabis consumption (Imade and Ebie, 1991; D'Souza, 2007). More

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interestingly, for both theories, CIPD can be characterized as a controversial disorder. Little attention has been paid as not all subjects exposed to cannabis consumption develop psychotic symptoms (Sewell et al., 2009).

One way to increase our understanding of the nature of psychotic symptoms would be to assess the potential endophenotypes that characterize subjects with psychosis, such as the prepulse inhibition (PPI) of the startle reflex. PPI is the reduction of the startle reflex by the presence of a weaker stimulus, and is an operational measure of sensorimotor gating (Braff and Geyer, 1990). PPI is modulated by a number of cortical and subcortical brain areas such as the hippocampus, prefrontal cortex, thalamus and limbic regions (Braff et al., 1978, 1992; Swerdlow et al., 2001; Mayer et al., 2009), many of which are implicated in the pathophysiology of schizophrenia. The PPI paradigm has been extensively used in patients with schizophrenia, and several authors have demonstrated PPI deficits in this population (Grillon et al., 1992; Dawson et al., 1993). These impairments are also found in the first stages of the disease (Swerdlow et al., 1995), as well an in their relatives (Cadenhead et al., 2000). These PPI impairments have been hypothesized to be caused by the existence of a dysfunction of the sensorimotor gating (Braff et al., 2007). However, our group found that these impairments may also be related to stress response (Martinez-Gras et al., 2009).

Interestingly, PPI is impaired in subjects with a history of cannabis abuse. A study by Kedzior and Martin-Iverson (2006) regarding active PPI paradigms aimed to determine whether healthy subjects using cannabis exhibited attention-modulated deficits of PPI. They found that cannabis abusers showed significantly lower PPI functioning compared to non-cannabis abusers, and that this decrease correlated with the duration of cannabis abuse. This data supports the hypothesis that cannabis abuse plays a role in mediating deficits in PPI. These previous results were confirmed by subsequent studies that found that cannabis users showed an attention-dependant alteration in PPI, which appeared to reflect a deficit in sustain attention (Scholes and Martin-Iverson, 2009). Further research has been performed within animal models to study the effects of some cannabinoid components of PPI, and PPI impairments in rats due to the effects of cannabinoid receptor agonists have been reported (Martin et al., 2003). Some data suggests that chronic stimulation of the cannabinoid receptor in rodents leads to persistent PPI disruption. The existence of PPI deficits in rats stimulated with cannabinoid agonists is a valid animal model of sensorimotor gating deficits in patients with schizophrenia (Swerdlow et al., 1994). D2 receptors are important for the regulation of PPI in rats, and there also exists a synergistic interaction between D1 and D2 substrates in the regulation of PPI (Wan et al., 1996). Following the bibliography regarding PPI impairments in subjects with schizophrenia and their relatives, and in cannabis abusers, this paradigm may be a valid marker to determine the vulnerability to psychosis in patients with CIPD. These subjects may have had these impairments previously, but they would be asymptomatic until cannabis consumption. Thus, PPI would appear impaired. Another possible explanation might be that these patients would not show initial PPI deficit, but after a continuous consumption of cannabis, these PPI deficits may appear and eventually these patients may show a major vulnerability to psychotic symptoms. Impairments in sensory gating processes as a result of chronic exposure to cannabis may be related to disruption of the regulatory role of the endocannabinoid system on synaptic neurotransmission (Broyd et al., 2013).

In order to show the relevance of PPI in subjects with CIPD, we carried out a study with a sample of CIPD patients that were free of psychotic symptoms for 9 months and were not taking any psychiatric medication. These patients came from a previous study (Rubio et al., 2012), in which patients attending emergency services with psychotic symptoms and cannabis abuse were recruited. To the best of our knowledge, there is to date no data focused on PPI deficits in CIPD patients. Examining PPI functioning in patients with CIPD might allow for greater understanding of the processes underlying PPI, as well as help in understanding the clinical and psychophysiological manifestations of the psychotic symptoms.

2. Methods

2.1. Participants

A total sample of 190 subjects were recruited for this study, and the sample consisted of 48 CIPD patients, 54 patients with schizophrenia and cannabis abuse (SCHZ), 44 subjects with cannabis dependence (CD) and 44 healthy controls.

From January 2005 to January 2008, consecutive patients who were admitted to the psychiatry inpatient units of three university general hospitals in Madrid (Spain) for psychotic symptoms and cannabis use were screened for entry into the study. The majority of subjects were identified during their first admission. They were recruited to the study when they were able to give voluntary informed consent. The patients were treated at their respective hospitals, but after hospital discharge, CIPD patients were exclusively followed in one center. After 9 months of follow-up, contact was established again with the patients with schizophrenia and CIPD, and they were referred to another clinical assessment that included a PPI task. The clinical diagnosis that they received in the hospital was again confirmed (i.e. SCHZ or CIPD), which accomplished the different psychological scales.

Both groups of patients displayed a history of cannabis abuse, and they started this abuse at similar ages. Both groups stopped using cannabis, but SCHZ patients still showed psychotic symptomatology, whereas in CIPD patients, these psychotic symptoms disappeared and they were not under any antipsychotic medication. CIPD or SCHZ with cannabis abuse diagnoses were confirmed 9 months after patients were discharged from the hospital. Regarding CIPD patients, they were required to be free from psychotic symptoms for 9 months and they were not under any psychiatric medication. SCHZ patients were stable after 9 months since the onset of the disease, and were with maintenance treatment. Both groups of patients were abstinent of cannabis use for a period of 9 months.

Subjects with CD were selected from the Addiction Disorders Program in our hospital. From the subjects that attended the program from 2005 to 2008 ($n=146$), only those patients with similar sociodemographic characteristics to CIPD patients were selected. These subjects were under therapeutic treatment for 6–9 months and were abstinent of cannabis use for 9 months.

Control subjects were psychiatrically, medically, and neurologically healthy volunteers who were not receiving any psychiatric medication, had no first- or second-degree relatives with psychosis, and did not show history of any substance abuse disorder. The sample was selected in terms of the sociodemographic variables of CIPD group (age, gender and years of education).

The research protocol was approved by the institutional ethics committee of the hospitals from which study subjects were recruited and informed consent was obtained from all the participants.

2.2. Instruments

Schizophrenia symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1992) at the time of inclusion. This instrument assesses psychotic symptoms experienced in the week before the assessment. The subscales provide data on the positive and negative symptoms of psychosis, as well as on overall general psychopathology.

Research diagnoses were made using the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (Hasin et al., 1996), which was developed to assess psychiatric and substance use comorbidity based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (APA, 1994). For this study, we used the Spanish version validated in our country (Torrens et al., 2004).

2.3. Procedure

After 9 months of follow-up, the SCHZ and CIPD patients from a previous study by our group (Rubio et al., 2012) were assessed again with the same clinical scales and psychophysiological tasks. For this current study, two more subgroups of CD patients and control subjects were recruited. SCHZ and CIPD patients were assessed in two different sessions for both the PRISM clinical interview and the psychiatric scales, and for PPI, respectively. CD patients and controls only required one assessment for PPI.

Urine analyses were performed on all subjects to exclude the presence of cannabis or other recreational drugs—hallucinogens, amphetamines, cocaine, opiates, barbiturates, benzodiazepines, and alcohol. These toxicological analyses