Brain Stimulation 10 (2017) 275–282

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Differential effects of cannabis dependence on cortical inhibition in patients with schizophrenia and non-psychiatric controls

Michelle S. Goodman [a, c, d, 1], Alanna C. Bridgman [a, c, d, 1], Rachel A. Rabin [a, d], Daniel M. Blumberger [b, c, d, e], Tarek K. Rajji [b, c, d, e], Zafiris J. Daskalakis [b, c, d], Tony P. George [a, b, d], Mera S. Barr [a, b, c, d, *]

[a] Schizophrenia Division, Centre for Addiction and Mental Health (CAMH), 250 College Street, Toronto M5T 1R8, ON, Canada
[b] Division of Brain and Therapeutics, Department of Psychiatry, University of Toronto, 250 College Street, Toronto M5T 1R8, ON, Canada
[c] Temerty Centre for Therapeutic Brain Intervention, CAMH, 1001 Queen Street West, Toronto M6J 1H4 ON, Canada
[d] Institute of Medical Science, Faculty of Medicine, University of Toronto, 1 King's College Circle Room 2374, Toronto M5S 1A8, ON, Canada
[e] Division of Geriatric Psychiatry, CAMH and Department of Psychiatry, University of Toronto, 80 Workman Way, Toronto M6J 1H4, ON, Canada

ARTICLE INFO

Article history:
Received 1 June 2016
Received in revised form
4 November 2016
Accepted 10 November 2016
Available online 14 November 2016

Keywords:
Transcranial magnetic stimulation
GABA
Cortical inhibition
Schizophrenia
Cannabis

ABSTRACT

Background: Cannabis is the most commonly used illicit substance among patients with schizophrenia. Cannabis exacerbates psychotic symptoms and leads to poor functional outcomes. Dysfunctional cortical inhibition has been implicated in the pathophysiology of schizophrenia; however, the effects of cannabis on this mechanism have been relatively unexamined. The goal of this study was to index cortical inhibition from the motor cortex among 4 groups: schizophrenia patients and non-psychiatric controls dependent on cannabis as well as cannabis-free schizophrenia patients and non-psychiatric controls.
Methods: In this cross-sectional study, GABA-mediated cortical inhibition was index with single- and paired-pulse transcranial magnetic stimulation (TMS) paradigms to the left motor cortex in 12 cannabis dependent and 11 cannabis-free schizophrenia patients, and in 10 cannabis dependent and 13 cannabis-free controls.
Results: Cannabis-dependent patients with schizophrenia displayed greater short-interval cortical inhibition (SICI) compared to cannabis-free schizophrenia patients ($p = 0.029$), while cannabis-dependent controls displayed reduced SICI compared to cannabis-free controls ($p = 0.004$). SICI did not differ between cannabis dependent patients and cannabis-free controls, or between dependent schizophrenia patients compared to dependent controls. No significant differences were found for long-interval cortical inhibition (LICI) or intra-cortical facilitation (ICF) receptor function, suggesting a selective effect on SICI.
Conclusion: These findings suggest that cannabis dependence may have selective and differing effects on SICI in schizophrenia patients compared to controls, which may provide insight into the pathophysiology of co-morbid cannabis dependence in schizophrenia.

1. Introduction

Schizophrenia is one of the most severe and debilitating brain disorders [1]. High rates of co-morbid substance use disorders [2] further complicate our understanding of the etiology and treatment for this illness. Recent research has focused on cannabis use comorbidities, due in part, to the fact that it is one of the most commonly used illicit substance in both the general population [3] and in schizophrenia [4]. Approximately one-third of patients with schizophrenia and other psychoses report daily use [5] and one-quarter meet criteria for a cannabis use disorder [6]. Co-morbid cannabis use in schizophrenia is associated with symptom exacerbation, higher rates of relapse, reduced treatment compliance and worse functional outcomes [7–10].

In spite of its high prevalence, many questions still exist regarding the neurophysiological impact of cannabis use among patients with schizophrenia. Evidence suggests that the neurophysiological and neurocognitive effects of cannabis on the brain lie

* Corresponding author. Department of Psychiatry, University of Toronto Schizophrenia Division, Centre for Addiction and Mental Health, 33 Russell Street, Toronto M5S 2S1, ON, Canada.
E-mail address: mera.barr@camh.ca (M.S. Barr).
[1] Michelle S. Goodman and Alanna C. Bridgman contributed equally to this work.

http://dx.doi.org/10.1016/j.brs.2016.11.004
1935-861X/

within the complex interaction between the endocannabinoid system and inhibitory neuronal networks [11]. More specifically, cannabinoids both exogenous and endogenous, act through cannabinoid type 1 receptors (CB1Rs) to inhibit the release of GABA [12–14] and enhance mesolimbic dopamine levels [15–17]. Interestingly, dysfunctional GABAergic [18–21] and dopaminergic neurotransmission [22,23] have been implicated in the pathophysiology of schizophrenia. This finding has been reliably observed through post-mortem studies and more recently through technological advancements utilizing non-invasive brain stimulation techniques [19,21,24] and neuroimaging [25]. Thus, it follows that aberrant GABA functioning in schizophrenia may be further exacerbated by the inhibitory influence of cannabis on GABA.

One technique used to index GABA mediated cortical inhibition is through transcranial magnetic stimulation (TMS) combined with electromyography (EMG). $GABA_A$ receptor function can be examined using the short-interval cortical inhibition (SICI) paradigm [26,27], while $GABA_B$ receptor function can be assessed through the long-interval cortical inhibition (LICI) [28–30] and cortical silent period (CSP) paradigms [31,32]. N-methyl-D-aspartate (NMDA) receptor function can be assessed using the intra-cortical facilitation (ICF) paradigm [33,34]. Previous studies utilizing non-invasive brain stimulation techniques have demonstrated specific $GABA_A$ and $GABA_B$ receptor deficits in individuals with schizophrenia [19,24]. For example, a recent meta-analysis reported significantly reduced SICI, and thus $GABA_A$ deficits in patients with schizophrenia after controlling for age and medication. Importantly, this finding showed specificity as a characteristic of schizophrenia when compared to patients with major depression and obsessive-compulsive disorder [35].

To date, two studies have investigated the effects of cannabis on cortical inhibition using TMS. The first study revealed that cannabis impaired $GABA_A$ function, through reduced SICI, in heavy and light cannabis-using controls compared to cannabis-free controls [36]. Similarly, Wobrock and colleagues found $GABA_A$ deficits in cannabis using first-episode patients with schizophrenia in comparison to cannabis-free patients [37]. Both studies revealed alterations in cortical inhibition selective to $GABA_A$ among cannabis using/dependent populations. Interestingly, Wobrock also found enhanced ICF in fist-episode patients with schizophrenia and co-morbid cannabis use [37].

However, beyond these two studies, little is known about the effect of cannabis in patients with chronic schizophrenia, and this has not yet been explored across diagnosis and cannabis use status in a 2×2 factorial design (e.g., cannabis-dependent schizophrenia patients vs. cannabis-free schizophrenia patients, and cannabis-dependent controls vs. cannabis-free controls) within a single study. Accordingly, the aim of the current study was to assess motor cortical inhibition and facilitation in individuals with and without cannabis dependence and in those with and without co-morbid schizophrenia. This study, unlike previous studies, utilized single- and paired-pulse TMS measuring SICI, ICF, LICI, and CSP across all four groups.

2. Material and methods

2.1. Subjects

Four groups were recruited for this study: 12 cannabis-dependent (mean age = 29.4, SD = 8.4) and 11 cannabis-free (mean age = 38.5, SD = 8.9) patients with a diagnosis of schizophrenia or schizoaffective disorder and 10 cannabis-dependent (mean age = 30.4, SD = 7.4) and 13 cannabis-free (mean age = 35.5, SD = 10.5) non-psychiatric controls. All cannabis-free schizophrenia patients were taking atypical antipsychotics: 37% olanzapine, 18% clozapine, 18% quetiapine, 18% risperidone, and 9% paliperidone. Cannabis-dependent patients were taking a mix of atypical and typical antipsychotics: 33% risperidone, 25% quetiapine, 8% olanzapine, 8% clozapine, 8% paliperidone, 8% flupentixol, and 8% fluphenazine. It is important to note that the controls and patients in the cannabis groups were also daily nicotine users. Participants in the cannabis-free groups were both cannabis and nicotine free, and were secondarily analyzed from the study of Bridgman et al (2016) [38]. General exclusion criteria for this study were: 1). current or past history of seizures, syncope or neurological disorders, 2) co-morbid medical illness or current pregnancy, 3) a diagnosis of bipolar disorder or current major depressive episode, 4) full scale IQ < 80 as determined by the Wechsler Test of Adult Reading (WTAR), 5) personal or family history of epilepsy, and 6) past concussion or serious head injury.

Cannabis dependence, substance use patterns and severity of use were assessed by the Structured Clinical Interview for DSM-IV diagnostic criteria (SCID) [39]. Participants in the cannabis dependent groups (i.e., patients and controls) were daily cannabis users, with at least one year of regular use and could not be seeking treatment for such dependence. Given the prevalence of co-morbid nicotine and cannabis use [40], participants also had to be daily cigarette smokers, using at least 5 cigarettes per day. MEDTOX urine toxicology was used to verify the presence of cannabis metabolites for those in the cannabis dependent groups as well as to rule out the presence of any additional substance among all study participants. Participants were excluded if they met criteria for abuse or dependence of alcohol or illicit substances within the past 6 months. Demographic and cannabis information for all participants is presented in Table 1.

A diagnosis of schizophrenia or schizoaffective disorder was confirmed using the Structured Clinical Interview for DSM-IV (SCID-IV) [39]. The SCID was also used to rule out any current or past Axis I psychiatric disorders in non-psychiatric controls, with the exception of cannabis dependence and past major depression. Patients were in stable remission from positive symptoms of psychosis as judged by psychiatric evaluation (SCID) and a Positive and Negative Symptom Scale (PANSS) [41] total score <70) [41]and could not have experienced hospitalization within the past three months prior to study enrollment. All patients were treated with first or second-generation antipsychotic medications and had to be on a stable dose for at least one month. Chlorpromazine (CPZ) equivalents were calculated to assess daily doses of the different antipsychotics (Table 1).

2.2. Procedure

Schizophrenia patients were recruited through the Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada, via flyers and referrals, and controls were recruited through various online advertisements. Data was analyzed form two different studies. All the experiments were conducted using identical protocols and equipment set-up at the Temerty Centre for Therapeutic Brain Intervention at CAMH. All participants gave their written informed consent. The study was approved by the CAMH in accordance with the Declaration of Helsinki. An in-person screening assessment evaluated demographics, psychopathology in the patient groups and an in-depth cannabis use history in the cannabis dependent groups. Following enrollment, cortical inhibition was assessed using TMS. Cannabis dependent participants were instructed to abstain from cannabis 12 h prior to the TMS session to avoid both acute cannabis intoxication and withdrawal; however, ad libitum cigarette use was allowed throughout the test session.