Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Effects of varenicline on motor cortical plasticity in non-smokers with schizophrenia

Alanna C. Bridgman [a,b], Mera S. Barr [a,b,c], Michelle S. Goodman [b,c], Reza Zomorrodi [c], Tarek Rajji [b,c,d], Bernard Le Foll [b,g,h], Robert Chen [b,f], Zafiris J. Daskalakis [b,c,e], Tony P. George [a,b,c,*]

[a] Schizophrenia Division, Centre for Addiction and Mental Health, Canada
[b] Institute of Medical Science, Faculty of Medicine, University of Toronto, Canada
[c] Division of Brain and Therapeutics, Department of Psychiatry, University of Toronto, Canada
[d] Division of Geriatric Psychiatry, Centre for Addiction and Mental Health, Canada
[e] Mood and Anxiety Division, Centre for Addiction and Mental Health, Canada
[f] Division of Neurology, Faculty of Medicine, University of Toronto, Canada
[g] Department of Family and Community Medicine, Faculty of Medicine, University of Toronto, Canada
[h] Department of Pharmacology and Toxicology, University of Toronto, Canada

ARTICLE INFO

Article history:
Received 4 July 2016
Received in revised form 29 August 2016
Accepted 31 August 2016
Available online xxxx

Keywords:
Transcranial magnetic stimulation
Neuroplasticity
Nicotinic acetylcholine receptors
Long-term potentiation

ABSTRACT

Background: Nicotinic acetylcholine receptors (nAChR) have been implicated in the pathophysiology of schizophrenia, and deficits in this system may contribute to high rates of cigarette smoking in this population. nAChR stimulation may modulate neuroplasticity, or long-term potentiation (LTP), which is a key mediator of cognitive performance. Varenicline is a nAChR partial agonist that may improve cognitive deficits in both smokers and non-smokers with schizophrenia; however, the mechanism by which varenicline alters cognition in schizophrenia remains unclear. Thus, the aim of this randomized, double-blind, placebo-controlled, crossover study was to determine the effects of varenicline on LTP-like plasticity indexed through transcranial magnetic stimulation (TMS) in non-smokers with schizophrenia.
Methods: Varenicline (0.5 mg BID × 5 doses) or placebo was administered to 9 non-smokers with schizophrenia and 10 non-smoker healthy subjects. LTP-like plasticity was induced by TMS and paired associative stimulation (PAS) at 0.1 Hz to the left motor cortex and measured every 15 min for two hours post-PAS.
Results: There was a significant diagnosis × medication interaction on peak potentiation ($F(3, 34) = 6.04$, $p < 0.02$) and post-hoc analyses indicated that varenicline significantly increased LTP in schizophrenia and decreased LTP in healthy subjects.
Conclusions: These preliminary findings suggest that varenicline may produce differential effects in non-smoking schizophrenia compared to control subjects. Given the role of LTP in learning and memory, these observations may suggest the potential for varenicline in the treatment of cognitive deficits in patients with schizophrenia.

1. Introduction

Schizophrenia is a severe neuropsychiatric illness affecting approximately 1% of individuals worldwide (Saha et al., 2005), and is characterized by positive, negative, and cognitive symptoms. Cognitive deficits remain one of the most important predictors of poor functional outcome in schizophrenia (Green, 2006), yet there are currently no effective treatments. Nicotine alters cognitive performance via nicotinic acetylcholine receptors (nAChRs). Interestingly, cigarette smoking prevalence in schizophrenia is very high (de Leon and Diaz, 2005; Mackowick et al., 2012; McClave et al., 2010), and nAChR density and number are reduced in post-mortem brains of patients with schizophrenia compared to non-psychiatric subjects (Guan et al., 1999; Severance and Yolken, 2008). Smokers with schizophrenia may perform better than non-smokers on some cognitive tasks (Harris et al., 2004; Morisano et al., 2013; Smith et al., 2006; Wing et al., 2011). Mechanisms that underlie nicotine's procognitive effects in schizophrenia are, however, poorly understood.

nAChRs are widely dispersed throughout the brain and likely contribute to a variety of downstream processes involved in learning, memory, and cognition (Becker et al., 2013; Jones et al., 1999), that are, in turn, reliant on functional neuroplasticity (Martin et al., 2000). Long-term potentiation (LTP) is one form of Hebbian neuroplasticity (Hebb, 1949) that occurs when synaptic strength increases in response to coincident activation of neighboring cells. Associative LTP occurs when presynaptic inputs from different regions converge onto the same post-

* Corresponding author at: 100 Stokes Street, Bell Gateway Building, Room 3288, Toronto, ON M6J 1H4, Canada.
E-mail address: tony.george@camh.ca (T.P. George).

http://dx.doi.org/10.1016/j.schres.2016.08.031
0920-9964/

synaptic cell (Levy and Steward, 1983), providing a temporal framework for how brain regions communicate and form lasting connections. Nicotine, by activating nAChRs, can alter LTP at the pre-synaptic or post-synaptic level by altering Ca^{2+} flux into the cell and increasing the likelihood of response (Ji et al., 2001), and by modifying the density of glutamatergic receptors on the cell surface (Levy and Aoki, 2002). LTP can be measured in vivo using a non-invasive brain stimulation technique called paired associative stimulation (PAS).

The PAS paradigm pairs right peripheral nerve stimulation (PNS) at 0.1 Hz 25 ms before delivery of a transcranial magnetic stimulation (TMS) pulse to the contralateral motor cortex (Stefan et al., 2000). These paired stimulations are administered for 30 min, and the motor-evoked potential (MEP) amplitude is assessed before and after PAS to determine the extent of potentiation (Stefan et al., 2000). Studies have shown reliable and long-lasting potentiation induced in the motor cortex using the PAS paradigm (Classen et al., 2004; Rajji et al., 2011; Stefan et al., 2000), reflective of the properties of LTP. Subjects with schizophrenia demonstrate deficits in motor cortical plasticity compared to non-psychiatric subjects using the PAS paradigm, evaluated at 0, 15, 30, and 60 min post-PAS (Frantseva et al., 2008). Patients in this study also showed a relationship between LTP and motor skill learning during a rotary pursuit task, suggesting that the PAS protocol may be a neurophysiological measure of LTP in humans (Frantseva et al., 2008).

Varenicline is a nAChR partial agonist at the $\alpha4\beta2$ receptor and a full agonist at the $\alpha7$ receptor (Coe et al., 2005). It is one of the most effective smoking cessation medications available, and appears to be safe and tolerable in smokers with schizophrenia (Shim et al., 2012; Williams et al., 2012). In addition to improving cessation outcomes in patients with schizophrenia (Evins et al., 2014; Williams et al., 2012), varenicline has been shown to enhance cognition (Hong et al., 2011; Roh et al., 2014; Shim et al., 2012; Smith et al., 2009) and blunt abstinence-induced deficits in cognition in smokers (Liu et al., 2011; Wing et al., 2013). Only one study has evaluated the effects of varenicline on PAS-induced LTP, and found that varenicline had no effect on LTP in healthy non-smokers (Batsikadze et al., 2015), perhaps due to a ceiling effect of nAChR function or to single dose methodology. In contrast, non-smokers with schizophrenia may selectively benefit from varenicline due to pre-existing deficits in nAChR density and function (Breese et al., 2000; Leonard et al., 2000).

As patients with schizophrenia show impaired nAChR function as well as cognitive deficits, the aim of this study was to use varenicline to determine whether nAChRs are involved in mediating LTP-like plasticity in schizophrenia. To eliminate the potential confounds of cigarette smoking and withdrawal, we studied biochemically-verified non-smokers. Using a randomized, placebo-controlled, double blind cross-over design, our objective was to examine whether varenicline given at 0.5 mg bid for 5 doses affects LTP-like plasticity in schizophrenia versus healthy subjects. We hypothesized that PAS-induced LTP would be impaired in non-smokers with schizophrenia, and that varenicline would selectively improve these deficits relative to non-smoking healthy subjects.

2. Materials and methods

2.1. Subjects

A total of 9 non-smokers with a diagnosis of schizophrenia or schizoaffective disorder (confirmed by Structured Clinical Interview for the DSM-IV (First et al., 2002)) and 10 non-smoker non-psychiatric healthy subjects completed this study. Inclusion criteria for both non-smokers with schizophrenia and healthy subjects were: 1) age between 18 and 55 years, 2) biochemically verified current non-smoking status, 3) IQ score ≥90 as determined by the Wechsler Test of Adult Reading (Wechsler, 2001), and 4) right handedness. Exclusion criteria were: 1) illicit drug use currently or in the past month, 2) history of neurological disorders, 3) co-morbid medical illness, 4) a diagnosis of bipolar disorder or current major depressive episode, 5) personal or family history of epilepsy, or 6) history of past concussion lasting more than one hour. Chlorpromazine (CPZ) equivalents were calculated according to the method described by Woods and colleagues (Woods, 2003). All healthy subjects were also free from any current psychiatric diagnoses and were not taking any psychiatric or psychotropic medications. All subjects were recruited from the Centre for Addiction and Mental Health (CAMH), associated clinics, local primary care clinics, and online advertisement sites in Toronto, Canada. The study was approved by the CAMH Research Ethics Board (Protocol #214-2012), and written consent was obtained from all subjects by study staff.

2.2. Study design

This study was conducted in a randomized, placebo-controlled, double blind, crossover fashion. After an initial screening assessment, subjects were randomized to receive either 0.5 mg of varenicline twice per day and one dose before the commencement of testing for a total of 5 doses, or placebo over a 3-day period. Subjects then returned a minimum of two weeks later to participate in the other treatment arm (Fig. 1). Subjects received the first dose of medication at 9 a.m. two days before testing and were supervised by study staff. Subjects were instructed to take the remaining 3 doses at 6 p.m. the same day, and at 9 a.m. and 6 p.m. the following day. Study staff administered the fifth and final dose the morning of the testing day. All testing sessions started at approximately 12 p.m., as afternoon testing has been shown to produce the most reliable and robust effects of PAS-induced LTP (Sale et al., 2007). Sessions lasted for approximately 3 h.

2.3. Electromyography recording

Surface electromyography (EMG) was recorded using previously published methods (Bridgman et al., 2016; Daskalakis et al., 2002) from the right abductor pollicis brevis (APB) muscle.

2.4. Transcranial magnetic stimulation

Monophasic TMS pulses were administered according to previously published methods (Bridgman et al., 2016; Daskalakis et al., 2002). The resting motor threshold (RMT) was defined as the output intensity that produced a MEP of at least 50 μV in 5 of 10 trials conducted in the relaxed APB muscle, and reflects cortical excitability (Rossini et al., 1994). The 1 mV peak to peak was evaluated as the output intensity that elicits a running MEP average between 0.4 and 0.55 mV in the relaxed APB muscle, and was the intensity used for the PAS paradigm (Rossini et al., 1994).

2.5. Peripheral nerve stimulation

Peripheral nerve stimulation (PNS) to the median nerve of the wrist was conducted using a bar electrode with constant current square wave pulses with the cathode positioned proximally. The sensory threshold was defined as the lowest possible stimulator intensity that the participant could detect, and three times sensory threshold was used for testing (Stefan et al., 2000).

2.6. Paired associative stimulation

Baseline MEP amplitude was measured before the PAS paradigm was administered, and according to our previously published protocol (Rajji et al., 2011) (Fig. 2). Baseline and post-PAS intervals were calculated as the average of twenty pulses delivered to the left motor cortex at the 1 mV peak-to-peak intensity. To account for the effects of attention on plasticity (Stefan et al., 2000), subjects were asked to count the number of paired pulses they felt for use as a covariate if necessary. Post-PAS measurements were conducted at 0, 15, 30, 45, 60, 75, 90, 105,

Please cite this article as: Bridgman, A.C., et al., Effects of varenicline on motor cortical plasticity in non-smokers with schizophrenia, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.08.031