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Cortical excitability in tramadol dependent patients: A transcranial magnetic stimulation study

Eman M. Khedr (Prof., Dr.)[a,*], Romany H. Gabra[a], Mostafa Noaman[a], Noha Abo Elfetoh[a], Hanan S.M. Farghaly[b]

[a] Neuropsychiatry Department, Assiut University Hospital, Assiut, Egypt
[b] Pharmacology Department, Faculty of Medicine, Assiut University, Assiut, Egypt

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ABSTRACT

Background: Addiction to tramadol, a widely used analgesic, is becoming increasingly common. Tramadol can also induce seizures even after a single clinical dose. We tested whether the epileptogenicity of tramadol was associated with any changes in cortical excitability and inhibitory transmission using transcranial magnetic stimulation (TMS).

Methods: The study included 16 tramadol dependent patients and 15 age and sex matched healthy volunteers. Clinical evaluation was conducted using an addiction severity index. TMS assessment of excitability was conducted on the motor cortex since the response to each TMS pulse at that site is easily measured in terms of the amplitude of the twitches it evokes in contralateral muscles. Measures included resting and active motor threshold (RMT and AMT respectively), motor evoked potential (MEP) amplitude, cortical silent period (CSP) duration, transcallosal inhibition (TCI), and short interval intracortical inhibition and facilitation (SICI and ICF respectively). Urinary level of tramadol was measured immediately before assessing cortical excitability in each patient.

Results: RMT and AMT were significantly lower, the duration of the CSP was shorter and SICI was reduced in patients compared with the control group. These findings are suggestive of increased neural excitability and reduced GABAergic inhibition following exposure to tramadol. Also there were negative correlations between the severity of tramadol dependence and a number of cortical excitability parameters (AMT, RMT, and CSP with P = 0.002, 0.005, and 0.04 respectively).

Conclusions: The results provide evidence for hyperexcitability of the motor cortex coupled with inhibitory deficits in tramadol dependent patients.

1. Introduction

Tramadol is a synthetic, centrally acting and widely used analgesic. It has a dual mechanism of action that includes both inhibition of norepinephrine and serotonin uptake and weak agonistic action on the μ-opioid receptor (Grond and Sablotzki, 2004). It is considered to be a CNS suppressant; however, some studies have indicated an activating effect of tramadol (Fox et al., 2009; Rojas-Corrales et al., 1998; Vaughan et al., 2000). Clinical studies reported tramadol to cause seizures even at recommended analgesic doses, while, experimental studies showed that convulsions only occur after high, toxic doses (Jang et al., 2010; Potschka et al., 2000; Raiger et al., 2012; Ryan and Isbister 2015). Tramadol addiction represents a major social problem and is increasingly reported to be a public health concern, especially among adolescents (Bassiony et al., 2015; Nazarzadeh et al., 2014).The progressive alarming phenomenon of tramadol drug abuse is particularly evident in the Egyptian community (Bassiony et al., 2015; El-Hadidy and Helaly 2015; Shalaby et al., 2015).

Brain stimulation techniques like transcranial magnetic stimulation (TMS) offer an opportunity to explore the physiologic effects of substances such as tramadol in vivo in the human brain. Measurements are carried out on motor cortex because stimulation here produces muscle twitches in contralateral muscles that can easily be measured using standard surface electromyogram techniques. Motor threshold (MT) is defined as the minimum TMS intensity sufficient to produce a predefined motor-evoked potential (MEP) in the contralateral abductor pollicis brevis in at least 50% of trials (Rossini et al., 1994). MT is thought to reflect

* Corresponding author at: Department of Neuropsychiatry, Faculty of Medicine, Assiut University Hospital, Assiut, Egypt.
E-mail address: emankhedr99@yahoo.com (E.M. Khedr).

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sodium and potassium channel conductivity and hence membrane excitability in pyramidal neurons (Ziemann et al., 1996a).The cortical silent period (CSP), a measure of cortical inhibitory processes, is affected by a number of neurotransmitter systems including GABA and dopamine. (Ziemann et al., 1993).Short-interval intracortical inhibition (SICI) between two closely spaced stimuli depends on GABAa-ergic transmission whilst intracortical facilitation (ICF) may involve excitatory glutamatergic transmission (Kujirai et al., 1993; Ziemann et al., 1996b).

In the past studies using these techniques have revealed abnormal cortical excitability and inhibition in cocaine users (Boutros et al., 2005; Hanlon et al., 2015), cocaine dependence (Sundaresan et al., 2007), chronic smokers (Lang et al., 2008), methamphetamine dependence (Li et al., 2013), and chronic cannabis use (Fitzgerald et al., 2009). However, there have been no similar studies tramadol addicts.

The aim of this study was to examine TMS-related evidence that cortical excitability is higher in these patients, since this could potentially contribute to the increased seizure activity. Our hypothesis, based on previous findings in epilepsy (Stafstrom, 2006) was that tramadol would increase measures of neural excitability and reduce activity in GABAergic inhibitory systems. We therefore assessed cortical excitability of tramadol dependent subjects and compared them with healthy non-dependent controls using standard techniques of TMS.

2. Subjects and methods

2.1. Tramadol dependent patients

Sixteen male patients with pure tramadol dependence for at least 6 months [mean age (SD) 26.85 ± 6.6 years, ranging from 20 to 36 years] were recruited from the psychiatry outpatients clinic of AssiutUniversity Hospital, Assiut, Egypt. The mean duration of tramadol abuse (SD) were 19.2 ± 11.5 months ranging from 6 to 60 months. All patients provided fully informed written consent and the local ethical committee of Assiut University had approved the experimental protocol.

Each patient was clinically evaluated using a structured clinical interview DSM IV-TR(SCID-I),as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (First et al., 2002).

According to DSM-V criteria, patients were classified to Mild: Presence of 2–3 symptoms, Moderate: Presence of 4–5 symptoms and Severe: Presence of 6 or more symptoms (American Psychiatric Association, 2013).

Patients with comorbid psychiatric disorder (schizophrenia, bipolar disorders) or other drug abuse (alcohol, cocaine, nicotine), or having implanted metal objects were excluded. Any patient taking neuroleptic or antidepressant medications was also excluded. The causes of tramadol abuse were: Six (37.5%) of the patients started tramadol abuse to improve mood, four (25%) of the patients for sexual purpose, four patients (25%) to get more power for hard work, and two patients (12.5%) for pain relief.

2.2. Control subjects

Fifteen healthy male volunteers, age and education matched were enrolled as a control group for neurophysiological assessment. They had no history of psychiatric disorders which was confirmed during a brief clinical interview with a psychiatrist. The mean age of the controls were 27.47 ± 5.7 years, ranging from 22 to 39 years.

2.3. Study overview

History taking, including duration of drug dependence, time in hours since the last dose of tramadol, history of seizure during the period of dependence was recorded. Endogenous tramadol levels in the urine were measured by Enzyme-multiplied immunoassay technique (EMIT) and analyzed by using the Dade Behring Viva Jr. EMIT Analyzer (300 ng/mLcutoff).

The neurophysiological assessment of cortical excitability was performed in patients and healthy volunteers using TMS, as previously published by our group in other clinical conditions. It includes resting and active motor threshold (RMT, and AMT), motor evoked potential at 130% of resting motor threshold (MEP), cortical silent period (CSP), transcallosal inhibition (TCI), and short-intervalintracortical inhibition and facilitation (SICI and ICF).

2.4. Electrophysiological investigations using TMS

The subjects were seated in a comfortable chair and instructed to be as relaxed as possible. Electromyography (EMG) recordings from right first dorsal interosseous muscle (FDI) were acquired with silver–silver chloride surface electrodes, using a muscle belly-tendon setup, with a 3 cm diameter circular ground placed on the wrist. A Nihon Kohden Machine model 9400 (Japan) was used to collect the signal. EMG parameters included a bandpassof 20–1000 Hz and a recording time window of 200 ms. TMS was performed with a 90 mm figure of eight coil connected to a Magstim200 magnetic stimulator (Magstim, UK).

2.4.1. Determination of resting / active motor threshold. Motor thresholds were determined after localization of the motor "hot spot" for the FDI of left hemisphere as described in previous reports (Khedr et al., 2006). The EMG signals were monitored and recorded for 20 ms before stimulation. RMTwas measured atcomplete rest and AMT, while subjects made a mild contraction of approximately 20% maximum. Both RMT and AMT were expressed as a percentage of the maximal stimulatoroutput (equal to 100%). (details of measuring demonstrated in our previous study Khedr et al., 2015)

2.4.2. Contralateral cortical silent period (CSP). The duration of the CSP was determined for the left hemisphere during isometric 50% maximum voluntary contraction of the contralateral FDI (abduction of the index finger as judged by audio-visual feedback). Audio-visual feedback is a standard technique in clinical neurophysiology in which the operator and subject can hear and see the EMG activity that is being recorded from the muscles. It is available with all commercial clinical machines. Five consecutive stimuli were delivered. The duration of CSP was measured from the end of the MEP until the reappearance of EMG activity. The mean value of the 5 trials was measured (details of methodology in Khedr et al., 2016).

2.4.3. Transcallosal inhibition (TCI). During the testing of a single pulse TCI; stimulation was applied at a frequency of 0.2 Hz. The onset and the offset of TCI were defined as the points where the EMG traces fell persistently below and where it returned persistently above the baseline. The TCI duration was calculated as the time of offset of TCI minus the onset. (details of methodology in Khedr et al., 2016).

2.4.4. Short-interval intracortical inhibition and facilitation (SICI and ICF). In SICI, a subthreshold conditioning stimulus, which was set at 80% of RMT, preceded a suprathreshold test stimulus (TS), which was adjusted to produce an average MEP of 0.5–1.5 mV peak-to-peak amplitude in the contralateral FDI muscle (Kujirai et al., 1993).Conditioning stimuli were applied to the motor cortex before the TS at one of six random inter-stimulus intervals (ISIs): 1, 2 and