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Effect of a single dose of retigabine in cortical excitability parameters: A cross-over, double-blind placebo-controlled TMS study

Michel Ossemann[a,b,*], Katalin de Fays[a,b], Benoit Bihin[c], Yves Vandermeeren[a,b]

[a] Université catholique de Louvain (UCL), CHU UCL Namur, Department of Neurology, Avenue Dr G. Thérasse, B5530 Yvoir, Belgium
[b] Université catholique de Louvain (UCL), Institute of NeuroSciences (IoNS), Avenue Hippocrate, 54 Bte 54.10, 1200 Brussels, Belgium
[c] Université catholique de Louvain (UCL), CHU UCL Namur, Scientific Support Unit Avenue Dr G. Thérasse, 5530 Yvoir, Belgium

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ABSTRACT

Background: Antiepileptic drugs (AEDs) decrease the occurrence of epileptic seizures and modulate cortical excitability through several mechanisms that likely interact. The modulation of brain excitability by AEDs is believed to reflect their antiepileptic action(s) and could be used as a surrogate marker of their efficacy. Transcranial magnetic stimulation (TMS) is one of the best noninvasive methods to study cortical excitability in human subjects. Specific TMS parameters can be used to quantify the various mechanisms of action of AEDs. A new AED called retigabine increases potassium efflux by changing the conformation of KCNQ 2–5 potassium channels, which leads to neuronal hyperpolarisation and a decrease in excitability.
Hypothesis: The purpose of this study is to investigate the effect of retigabine on cortical excitability. Based on the known mechanisms of action of retigabine, we hypothesized that the oral intake of retigabine would increase the resting motor threshold (RMT).
Methods: Fifteen healthy individuals participated in a placebo-controlled, double-blind, randomised, clinical trial (RCT). The primary outcome measure was the RMT quantified before and after oral intake of retigabine. Several secondary TMS outcome measures were acquired.
Results: The mean RMT, active motor threshold (AMT) and intensity to obtain a 1 mV peak-to-peak amplitude potential (SI1 mV) were significantly increased after retigabine intake compared to placebo (RMT: $P = 0.039$; AMT: $P = 0.014$; SI1 mV: $P = 0.019$). No significant differences were found for short-interval intracortical inhibition/intracortical facilitation (SICI/ICF), long-interval intracortical inhibition (LICI) or short-interval intracortical facilitation (SICF).
Conclusion: A single dose of retigabine increased the RMT, AMT and S1 mV in healthy individuals. No modulating intracortical facilitation or inhibition was observed. This study provides the first *in vivo* demonstration of the modulating effects of retigabine on the excitability of the human brain, and the results are consistent with the data showing that retigabine hyperpolarizes neurons mainly by increasing potassium conductance

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1. Introduction

Epilepsy is a devastating medical condition with many psychosocial implications. According to the World Health Organization (WHO), it affects more than 50 million people worldwide (WHO Epilepsy, 2016). The annual cost of epilepsy in Europe was estimated as €15.5 billion in 2004 (Pugliatti et al., 2007).

Despite advances in epilepsy surgery, vagus nerve stimulation and other innovative approaches, the current management of epilepsy relies overwhelmingly on pharmacologic neuromodulation, i.e., the adequate use of antiepileptic drugs (AEDs) (French et al., 2004; Glauser et al., 2006; Panayiotopoulos et al., 2005). Approximately 30% of epilepsy patient continue to suffer from recurrent seizures despite taking a combination of potent AEDs (Perucca et al., 2007). As the pathophysiology of epilepsy is being unveiled, new AEDs targeting specific neuronal mechanisms have been developed (Rogawski and Löscher, 2004).

AEDs decrease seizure frequency by multiple – and likely interacting – mechanisms of action (Brodie et al., 2011). Among these mechanisms, the regulation of cortical excitability is particularly important. Indeed, epilepsy is mostly a disorder of brain excitatory/inhibitory balance. Thus, controlling brain excitability and/or maintaining cortical excitability within a certain range (i.e., below

* Corresponding author at: CHU UCL Namur, Department of Neurology, Avenue Dr G. Thérasse, B5530 Yvoir, Belgium.
E-mail address: michel.ossemann@uclouvain.be (M. Ossemann).

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the threshold needed to trigger a seizure) is a major challenge in the therapeutic management of chronic epilepsy. Furthermore, researchers have suggested that monitoring cortical excitability might serve as a surrogate marker of the efficiency of AED therapy (Badawy et al., 2010).

To diagnose and follow chronic/resistant epilepsy, clinicians use the electroencephalogram (EEG) as the reference neurophysiology method. However, current EEG methods do not allow for quantification of adequate brain excitability. Consequently, researchers have developed other, complementary methods for quantifying brain activity/excitability, such as positron emission tomography, functional magnetic resonance imaging, magnetoencephalograpy, electrocorticography with implanted electrodes, and transcranial magnetic stimulation (TMS).

In general, drugs that block voltage-gated sodium or calcium channels, such as carbamazepine (Lang et al., 2013; Ziemann et al., 1996a,b), diphenylhydandoin (Mavroudakis et al., 1994), lamotrigine (Boroojerdi et al., 2001; Ziemann et al., 1996a,b) and lacosamide (Lang et al., 2013) increase the motor threshold (MT) and do not influence other TMS measures. In contrast, drugs acting as $GABA_A$ agonists, such as benzodiazepines (Ziemann et al., 1996a,b), barbiturates (Inghilleri et al., 1996), vigabatrin (Pierantozzi et al., 2004) and tiagabine (Werhahn et al., 1999), may lead to an increase in the cortical silent period (CSP), short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI) and/or a decrease in intracortical facilitation (ICF), motor evoked potential (MEP) amplitude and SICI. Others AEDs, with multiple or unknown mechanisms of action, modulate the cortical excitability parameters in various patterns. For example, levetiracetam increases MT and decreases the MEP amplitude (Epstein et al., 2008; Solinas et al., 2008), topiramate increases SICI (Reis et al., 2002) and pregabalin decreases SICI (Lang et al., 2006). The subtle effects of AEDs on cortical excitability can be studied using TMS, which is a potent, versatile, noninvasive method that allows for these observations. Beyond exploring the neurophysiology of AEDs, TMS may be used as a surrogate marker of AED efficiency in epilepsy monitoring.

Because only 70% of patients are seizure-free despite top-quality AED management, new AEDs are continuously being developed. One example is retigabine (RTG), which is a drug with and unique profile. *In vitro* experiments have shown that RTG increases potassium efflux by changing the conformation of KCNQ2-5 potassium channels, leading to neuronal hyperpolarisation and a decrease in excitability (Gunthorpe et al., 2012). Therefore, based on RTG's known mechanism of action, we hypothesize that the oral intake of 400 mg of RTG will increase the resting motor threshold (RMT) in healthy individuals.

2. Material and methods

2.1. Study design

This study is a cross-over, double-blind, placebo-controlled, randomised clinical trial (RCT) (Fig. 1). The study conformed to the Declaration of Helsinki, and approval of the Ethics Committee of the CHU UCL Namur was obtained. Written informed consent was obtained at enrolment. This study is registered on ClinicalTrial.gov (ID: NCT01823159).

All subjects participated in two experimental sessions, separated by at least four days, once with RTG and once with a placebo, in a randomised and balanced order. TMS recordings were performed before (Baseline) and two hours after (Post) the oral intake of a single 400 mg oral dose of RTG or placebo. This two-hour interval has been chosen because, in young adults, a single dose of RTG reached its maximum concentration within this period (Hermann et al., 2003). The sessions were performed at the same time of day to avoid nycthemeral fluctuations. The subjects fasted for at least two hours before the session, and they were instructed to avoid alcohol or caffeine consumption for $\geq$24 h before the experimental sessions. The RTG and placebo pills were furnished by GSK (Research & Development Department, UK). The placebo pills were undistinguishable from the RTG pills.

2.2. Subjects

Fifteen healthy individuals (10 males, 5 females; mean age 25 ± 8 years) participated in this study, after answering a detailed

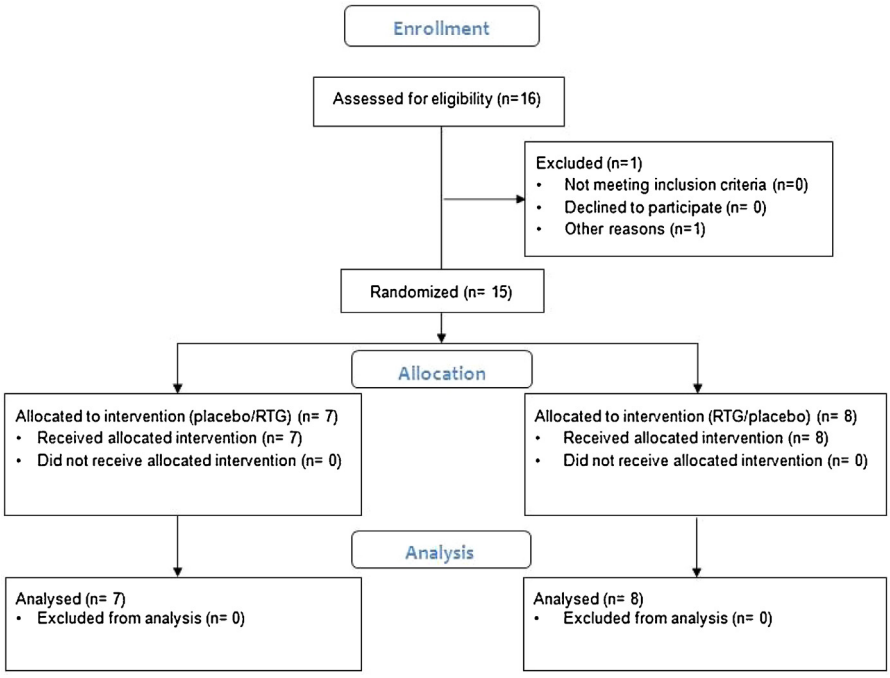

Fig. 1. CONSORT 2010 Flow Diagram.

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