Clinical Neurophysiology 129 (2018) 990–1000

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

A reappraisal of the mechanisms of action of ketamine to treat complex regional pain syndrome in the light of cortical excitability changes

Marc Sorel [a,b,c], Naaman Zrek [b], Blanche Locko [b], Catherine Armessen [b], Samar S. Ayache [a,d], Jean-Pascal Lefaucheur [a,d,*]

[a] EA 4391, Faculté de Médecine de Créteil, Université Paris Est Créteil, Créteil, France
[b] Centre d'Etude et Traitement de la Douleur, Centre Hospitalier de Nemours, Nemours, France
[c] Service de Neurologie, Hôpital Henri-Mondor, AP-HP, Créteil, France
[d] Service de Physiologie, Explorations Fonctionnelles, Hôpital Henri-Mondor, AP-HP, Créteil, France

ARTICLE INFO

Article history:
Accepted 14 February 2018
Available online 8 March 2018

Keywords:
Chronic pain
Cortical excitability
Depression
Ketamine
Mechanisms of action
TMS

HIGHLIGHTS

- Ketamine therapy for pain modulates intracortical glutamate/GABA balance.
- The analgesic effects of ketamine appears to be related to an enhanced GABAergic transmission.
- Mechanisms of action of ketamine therapy cannot be resumed to an antiglutamatergic modulation.

ABSTRACT

Objective: To evaluate the changes in glutamate/GABA balance of intracortical excitability produced by ketamine, delivered at subanaesthetic dose to treat patients with complex regional pain syndrome (CRPS).
Methods: In 19 patients with CRPS, we assessed the effect of a 5-day ketamine protocol on various clinical aspects, including pain and depression, and on cortical excitability parameters provided by transcranial magnetic stimulation testing.
Results: The rest motor threshold (RMT) and the amplitude of the motor evoked potentials at 120% of RMT were not modified after ketamine therapy. In contrast, ketamine reduced intracortical facilitation (ICF) in both hemispheres and increased short-interval intracortical inhibition (SICI), which was defective at baseline only in the hemisphere corresponding to the painful side. These changes positively correlated with pain relief.
Conclusion: This study shows for the first time that the remarkable analgesic effects produced by ketamine in CRPS patients is associated with cortical excitability changes in favour of an enhanced GABAergic transmission in the hemisphere corresponding to the painful side and an overall reduction of excitability in the contralateral hemisphere.
Significance: Analgesic effects of ketamine cannot be resumed to its classical antigutamatergic action related to N-methyl-D-aspartate receptor blockade.

1. Introduction

Complex regional pain syndrome (CRPS) is a multi-symptom, multi-system painful syndrome whose pathophysiological mechanisms remain partly unknown. The acronym CRPS refers to a disorder characterized by spontaneous or stimulus-induced pain that is disproportionate to the inciting event and is accompanied by a combination of various autonomic and motor disturbances. The activation of the sympathetic nervous system is likely involved. A neurological injury, when identified, is generally peripheral, leading to the distinction between CRPS type I (without nerve injury) and type II (with nerve injury). The diagnosis of CRPS is a diagnosis of exclusion relying on clinical criteria. The International Association for the Study of Pain (IASP) published a first set of consensus-based diagnostic criteria in 1994 (Merskey and

* Corresponding author at: Service de Physiologie – Explorations Fonctionnelles, Hôpital Henri Mondor, 51 avenue de-Lattre-de-Tassigny, 94010 Creteil, France. Fax: +33 1 4981 4660.
E-mail address: jean-pascal.lefaucheur@hmn.aphp.fr (J.-P. Lefaucheur).

https://doi.org/10.1016/j.clinph.2018.02.124
1388-2457/

Bogduk, 1994), which were refined after an international consensus meeting held in Budapest in 2003 (“Budapest Criteria”) (Harden and Bruehl, 2005). However, this diagnosis remains difficult due to the absence of specific clinical features and the heterogeneity of disease evolution profiles. Many patients spontaneously recover within the first year after onset (Bean et al., 2014; Birklein et al., 2015), but a subset of patients develops chronic pain condition difficult to treat. Early therapeutic management is based on anti-inflammatory agents (steroids), bisphosphonates, or topical application of dimethyl sulfoxide. At a chronic stage, during which many symptoms appear to be related to maladaptive brain plasticity, ketamine infusion was found to be one of the most effective medical treatments (Correll et al., 2004). Ketamine is an anaesthetic agent able to produce analgesia and antidepressant effects at subanaesthetic dose (Schwartzman et al., 2011; De Kock et al., 2013). Infused ketamine rapidly passes through the blood-brain barrier and is primarily thought to act as a non-competitive inhibitor of N-methyl-D-aspartate (NMDA) subtype of glutamate receptor in the central nervous system; various other mechanisms of action, however, may be involved (Strasburger et al., 2017).

The aim of this study was to investigate the pathophysiological processes at the origin of the analgesic effects of ketamine in the treatment of CRPS. To this end, we used a neurophysiological approach, i.e. the study of cortical excitability by means of transcranial magnetic stimulation (TMS) methods based on motor evoked potential (MEP) recording (Chen et al., 2008; Rossini et al., 2015). This approach made it possible to evaluate the intracortical changes in glutamatergic and GABAergic transmission occurring in a series of patients with CRPS treated by ketamine. In addition, sudomotor tests were performed to appraise potentially associated autonomic changes. In particular, the sympathetic skin reflex (SSR) is known to be altered in the CRPS, depending on the severity and phase of the disease (Rommel et al., 1995). This test evaluates the modulation of sympathetic responses by the central nervous system, which may interact with cortical excitability measurements. At least one study has previously assessed the relationship between SSR and MEP parameters (Filippi et al., 2000). In addition, since pain and dysautonomia are closely related in the context of CRPS, the impact of ketamine on autonomic aspects seemed relevant to study.

2. Methods

2.1. Patients

Twenty-one consecutive patients with CRPS type I referred to the Pain Center of Nemours hospital for the indication for ketamine therapy were enrolled. This study was conducted according to the Declaration of Helsinki and approved by the local institutional review board. All the patients fulfilled “Budapest Criteria” for the diagnosis of CRPS type I (with the absence of overt nerve injury). Two patients were excluded because of a motor threshold too high to allow cortical excitability to be studied by techniques of paired-pulse TMS. Therefore, only 19 patients completed the study. They were 15 women and 4 men, aged 20–87 years (mean ± sem: 62.5 ± 4.3). Pain and autonomic symptoms were strictly unilateral in all patients, on the right (n = 9) or left side (n = 10). The knee (n = 13), ankle (n = 3), shoulder (n = 2), or wrist (n = 1) was the articulation concerned by CRPS.

Chronic analgesic drug treatment was maintained stable during the week of ketamine therapy and consisted of paracetamol or nonsteroidal anti-inflammatory drugs (n = 14), serotonin–noradrenaline reuptake inhibitors (n = 4), tricyclic antidepressants (n = 4), cyamemazine (n = 4), nefopam (n = 3), pregabalin/gabapentin (n = 2), oxcarbazepine (n = 1), and baclofen (n = 1). Only four patients were weaned from analgesic medication before ketamine therapy was started.

2.2. Study plan

On Monday morning, the patients underwent clinical examination (including clinical scores, see below) and neurophysiological investigation (including cortical excitability and sudomotor tests, see below). Then, they received intravenous ketamine for 5 days, from Monday afternoon to Friday morning, administered via infusion pump (0.7–1 mg/kg/day with an induction of 1/10th of the total daily dose during the first hour). All patients remained hospitalized during the whole 5-day period of ketamine infusion therapy and they received exactly the same total dose of ketamine according to their weight. Heart rate, blood pressure, and pulse oximetry were monitored throughout ketamine infusion. Neurological, cognitive, and mood status was daily assessed. Finally, on Friday afternoon, at least 3 h after ketamine infusion ending, clinical and neurophysiological assessment was repeated.

2.3. Clinical assessment

Average ongoing pain was scored at rest on a 0–10 visual analogue scale (VAS_{rest}). The pain caused by the active mobilization of the affected joint was also scored on a VAS (VAS_{active}). The symptoms and descriptors of neuropathic pain were evaluated using the Neuropathic Pain Symptom Inventory (NPSI) (Bouhassira et al., 2004). Physical function (including pain stiffness) was assessed using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) (Barr et al., 1994) in patients with lower limb CRPS and the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire (Hudak et al., 1996) for patients with upper limb CRPS. Sleep disturbance was assessed using the Leeds Sleep Evaluation Questionnaire (LSEQ) (Parrott and Hindmarch, 1978). Finally, depression and anxiety were assessed using the Hospital Anxiety and Depression scale (HAD) (Zigmond and Snaith, 1983), the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), and the Beck Depression Inventory (BDI) (short form of 13 items) (Beck et al., 1961).

2.4. Cortical excitability testing

Cortical excitability was tested using TMS methods, as previously described by our group (Lefaucheur et al., 2004, 2006, 2012; Créange et al., 2013; Ayache et al., 2014, 2015). The studied parameters included the rest motor threshold (RMT), the amplitude of the MEPs at 120% of RMT, short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF). The MEPs were recorded bilaterally from the tibialis anterior (TA) muscle in case of lower limb CRPS and the first dorsal interosseous muscle (FDI) in case of upper limb CRPS. Pre-gelled disposable surface electrodes (9013S0242, Natus-Dantec, Skovlunde, Denmark) were used. The electromyographic (EMG) signal was recorded with an EMG machine (Reporter, EsaOte, EB Neuro, Firenze, Italy), amplified (50–500 μV/division), filtered (20–2000 Hz), and digitized for online visual display and later offline analysis. Auditory feedback was provided to ensure complete muscle relaxation during MEP recording. Magnetic stimulation was delivered using monophasic Magstim 200[2] stimulator units combined with a Bistim[2] module (Magstim Co, Carmarthenshire, United Kingdom). A double cone coil (110 mm-double coil type 9902-00, Magstim) was used for lower limb MEPs and a circular coil (90 mm-coil type 3192-00, Magstim) for upper limb MEPs. Patients were seated relaxed in an armchair and the coil was centered over the vertex marked on a cap. When using the double cone coil, its handle was maintained strictly vertical along the craniocaudal axis. When using the