Neuropharmacology 123 (2017) 455–464

Contents lists available at ScienceDirect

Neuropharmacology

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

The effects of analgesics on central processing of tonic pain: A cross-over placebo controlled study

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ARTICLE INFO

Article history:
Received 10 November 2016
Received in revised form
2 June 2017
Accepted 20 June 2017
Available online 22 June 2017

Keywords:
SNRI
Opioid
EEG
Brain source localization
LORETA

ABSTRACT

Introduction: Opioids and antidepressants that inhibit serotonin and norepinephrine reuptake (SNRI) are recognized as analgesics to treat moderate to severe pain, but the central mechanisms underlying their analgesia remain unclear. This study investigated how brain activity at rest and exposed to tonic pain is modified by oxycodone (opioid) and venlafaxine (SNRI).

Methods: Twenty healthy males were included in this randomized, cross-over, double-blinded study. 61-channel electroencephalogram (EEG) was recorded before and after five days of treatment with placebo, oxycodone (10 mg extended release b.i.d) or venlafaxine (37.5 mg extended release b.i.d) at rest and during tonic pain (hand immersed in 2 °C water for 80 s). Subjective pain and unpleasantness scores of tonic pain were recorded. Spectral analysis and sLORETA source localization were done in delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta1 (12–18 Hz) and beta2 (18–32 Hz) frequency bands.

Results: Oxycodone decreased pain and unpleasantness scores ($P < 0.05$), whereas venlafaxine decreased the pain scores ($P < 0.05$). None of the treatments changed the spectral indices or brain sources underlying resting EEG. Venlafaxine decreased spectral indices in alpha band of the EEG to tonic pain, whereas oxycodone decreased the spectral indices and brain source activity in delta and theta frequency bands (all $P < 0.05$). The brain source activity predominantly decreased in the insula and inferior frontal gyrus.

Conclusion: The decrease of activity within insula and inferior frontal gyrus is likely involved in pain inhibition due to oxycodone treatment, whereas the decrease in alpha activity is likely involved in pain inhibition due to venlafaxine treatment.

1. Introduction

Opioids are often used to treat severe pain. Opioids act by binding to opioid receptors, which can be found in the periphery, spinal cord and the brain. Antidepressants that inhibit serotonin and norepinephrine reuptake (SNRI) have also shown a pain relieving effect as serotonin and norepinephrine have been implicated as principal mediators of e.g., endogenous analgesic mechanisms in the descending pain pathways (Millan, 2002). Central opioid effects have been widely investigated in the recent years and these imaging studies have pointed to structures such as medial thalamus, anterior cingulate cortex and insula being involved in opioid analgesia (Brooks and Tracey, 2005; Lelic et al., 2014; Leppa et al., 2006; Petrovic, 2005; Wise et al., 2002). The analgesic effect of SNRIs has not yet been clarified in humans and it is likely that the mechanisms underlying its analgesic effects differ from the mechanisms underlying its antidepressant effect (Gallagher et al., 2015). It furthermore remains debatable whether the analgesic effect of SNRIs is opioid dependent.

In this placebo-controlled study, we wanted to investigate effects of an opioid, oxycodone, on the brain activity recorded via electroencephalogram (EEG) during pain and how these effects differed from those of an SNRI, venlafaxine. Quantitative EEG has

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http://dx.doi.org/10.1016/j.neuropharm.2017.06.022
0028-3908/

excellent temporal resolution on millisecond time scale and has previously shed some light on alterations in resting brain activity due to opioids (Bromm et al., 1986a, 1987; Egan et al., 1996; Graversen et al., 2015; Noh et al., 2006). The most consistent changes occurred in low frequency bands, pointing to importance of the low EEG frequency in opioid analgesia. Spatial resolution of EEG is poor, but brain source localization of EEG signals can provide estimates of the brain generators (i.e. center of gravity) underlying the EEG. Low Resolution Electromagnetic Tomography (LORETA) (Pascual-Marqui et al., 2011) is a brain source localization method that gives accurate estimates of cortical activity and has successfully been used in a number of resting pharmaco-EEG studies, mainly involving psychotropic drugs (Alonso et al., 2015; Romero et al., 2009; Saletu et al., 2002, 2006) but also involving opioids such as remifentanil (Khodayari-Rostamabad et al., 2015). Although the previous resting state EEG studies have explained some of the mechanisms in altered cortical processing due to opioids, understanding of opioid effects on spectral EEG activity during pain is still in its infancy and the brain areas contributing to these spectral changes are largely unknown. It has been demonstrated that tonic pain models are superior to short-lasting phasic pain models to mimic clinical pain and are more sensitive to study analgesic response (Olesen et al., 2012, 2014; Staahl et al., 2009). The cold-pressor test (immersion of the hand in cold water) has been shown to be a reliable test to evoke tonic pain and has given reproducible within-subject pain ratings (Gram et al., 2015; Lewis et al., 2012). In this study, we hypothesized that EEG spectral indices and LORETA would reveal changes in cortical processing of tonic pain (cold-pressor test) due to oxycodone as compared to baseline. We furthermore hypothesized that these changes would be different from the ones occurring due to placebo or venlafaxine treatment and hence showing the opioid central effect is different from that of an SNRI. We used vigilance controlled resting-EEG as a control in order to assess whether the changes seen are due to the tonic pain stimulus or they show general effect on the brain activity. Therefore, in this double-blinded, placebo-controlled, cross over study, the aims were: 1) to assess the potential changes induced by venlafaxine and oxycodone on: a) cold-pressor pain and unpleasantness scores; b) spectral indices of vigilance-controlled resting EEG and cold-pressor EEG; c) brain activity (sLORETA solution) underlying vigilance-controlled resting EEG and cold-pressor EEG and 2) to assess whether the changes in spectral indices and sLORETA solution correlate to changes in pain and unpleasantness ratings.

2. Methods

The trial was registered with the European Clinical Trials Database (Eudra-CT, 2013-000170-30, registration date: 2013-03-04). The local Ethics Committee (N-20130011) and the Danish Medicines Agency (201300017030) approved the study. The study was conducted in the laboratories at Mech-Sense, the Department of Gastroenterology & Hepatology, Aalborg University Hospital according to the rules of Good Clinical Practice and monitored by the Good Clinical Practice unit, Aalborg and Aarhus University Hospitals, Denmark. The study volunteers were treated over a five-day period. Side effects (nausea, vomiting, headache, dizziness, sedation, mouth dryness, rapid heart rate, constipation, itching, low appetite, increased sweating, general discomfort) were recorded on a 5-point Likert scale (i.e. 0 = no side effect, 1 = minimum, 2 = moderate, 3 = high and 4 = very high) each day. Pain and neurophysiological assessments were done on days one and five of each treatment arm.

2.1. Study volunteers

Twenty male volunteers (mean age 24.6 ± 2.5) participated in this study. Before inclusion, a medical doctor conducted a routine health screening for each participant, ruling out any pain related conditions and history of abuse (participant and closest family). Moreover, before enrolment, the volunteers gave written informed consent acknowledging that all methods and procedures used in the experiment were understood and that they were free to withdraw from the experiment at any time. Inclusion criteria for the study were: 1) normal medical examination; 2) age between 20 and 35 years; 3) male; 4) able to read and understand Danish; and 5) Scandinavian origin.

2.2. Drug and placebo administration

This was a randomized, double blind, three-way cross over study, with minimum 1 week “wash-out” intervals. Oxycodone (10 mg extended release, “Accord”), venlafaxine (37.5 mg extended release, “Stada”) and placebo (8 mm tablets) were orally administered. Tablets were over-encapsulated in DBcaps®, Swed.orange, size AA, “Capsugel®”. All drugs followed the same administration: once on day 1 and day 5, and twice on day 2–4 in total 8 doses. Medication was handled, packed and delivered by Hospital Pharmacy, Central Denmark Region, Denmark who also performed the randomization of the study. The randomization list was generated by www.randomization.com, where all subjects were randomized to receive placebo, oxycodone and venlafaxine in period 1, 2 and 3. Mirror randomization was employed in case of participant drop-outs. The staff at the Hospital Pharmacy packed and labeled the medication to ensure that all participants received correct medication for specific periods. Thus, the experimenters and the participants were fully blinded for randomization.

2.3. Tonic pain stimulation/cold-pressor test

The cold-pressor test was performed using circulated water bath with a temperature of 2 °C (Grant, Fischer Scientific, Slangerup, Denmark). The subjects immersed their left hand to the wrist for 80 s. The volunteers were asked to rate the sensation on pain and unpleasantness scales. Each scale ranged from 0 to 10, 0 meaning no pain/unpleasantness and 10 meaning maximum imaginable pain/unpleasantness.

2.4. EEG recordings

A 61-channel prewired cylindrical Ag/AgCl surface electrode EEG cap (MEQNordic A/S, Jyllinge, Denmark) was used for cortical evoked potentials. The reference electrode was between AFz and Fz. Electrode gel was applied to keep the electrode impedance below 10 kΩ. Vigilance-controlled resting state EEG (Jobert et al., 2012) was recorded for five minutes. To control for vigilance, the volunteers were continuously asked to do simple arithmetic as follows: computerized random number generator (Random Number Generator Pro v2.17. ©2000–2012, Segobit Software) was used to generate two random numbers between 1 and 10 and the experimenter read the two numbers to the volunteer every few seconds and the volunteer reported the sum out loud. The simple arithmetic task should not require much mental capacity but was enough to prevent the volunteer from drowsing off. Moreover, the arithmetic task assured that the attention, arousal and vigilance are consistent and similar between subjects (Dowman et al., 2008). The vigilance controlled resting-EEG served as a control in order to assess whether any potential drug effects on the EEG during tonic pain are related to the pain stimulus or if what we are observing is a general