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The response of the central and peripheral tremor component to octanoic acid in patients with essential tremor

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HIGHLIGHTS

- Octanoic acid (OA) reduced both central and peripheral components of postural tremor.
- The central and peripheral tremor components were positively correlated, both after placebo and OA.
- It is likely that the mechanical tremor component is driven by the magnitude of the central tremor.

ABSTRACT

Objective: To investigate the effect of octanoic acid (OA) on the peripheral component of tremor, as well as OA's differential effects on the central and peripheral tremor component in essential tremor (ET) patients.
Methods: We analyzed postural tremor accelerometry data from a double-blind placebo-controlled cross-over study evaluating the effect of 4 mg/kg OA in ET. The weighted condition was used to identify tremor power for both the central and peripheral tremor components. Exploratory non-parametric statistical analyses were used to describe the relation between the central and peripheral component of tremor power.
Results: A peripheral tremor component was identified in 4 out of 18 subjects. Tremor power was reduced after OA administration in both the central and the peripheral tremor component. There was a positive correlation of tremor power between the central and peripheral component, both after placebo and OA.
Conclusions: When present, the peripheral component was closely related to the central tremor component. We hypothesize that the magnitude of the peripheral mechanical component of tremor is determined by that of the central component.
Significance: Both central and peripheral component of tremor are reduced after OA, with the central component providing the energy driving the peripheral component.
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1. Introduction

Essential tremor (ET) is one of the most common neurological movement disorders with a prevalence of 3.06% among individuals aged 50 or older (Wenning et al., 2005). In general, tremor in ET is progressive, eventually producing disabilities with basic daily activities such as eating, writing, body care, and driving. However, there is currently no curative therapy, and medical agents such as propranolol and primidone are only symptomatic therapeutic options. Only about half of ET patients respond to these two first-line drugs, and this response is modest. Elderly patients are particularly susceptible to side effects of these drugs, and fewer than 20% of ET patients can tolerate the side effects (Deuschl et al., 2011).

Up to 74% of subjects with ET report a significant reduction in tremor intensity after ingesting small amounts of ethanol (Koller et al., 1994). However, ethanol is not a reasonable therapeutic option due to its narrow therapeutic window and risk of excessive alcohol use. The long chain alcohol 1-octanol has been explored for potentially achieving similar beneficial effects in alcohol-responsive ET without the risk of intoxication. Octanoic acid (OA), the product of rapid metabolism of 1-octanol, is well tolerated in ET up to a dose of 128 mg/kg (Voller et al., 2016). Our

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previous study (Haubenberger et al., 2013) using a crossover design showed that OA was safe and potentially effective in reducing postural tremor in ET. In this first double-blind placebo-controlled, single-dose study of 4 mg/kg OA, the study drug and a placebo were administered to subjects in a randomized sequence on subsequent days. During each visit, postural tremor was measured using accelerometry and surface electromyography (EMG) of bilateral wrist extensors and flexors. Tremor was recorded in two conditions: one with 1lbs. weights on each hand of the patient ("weighted" condition), and one without weights, aiming at investigating the effect of OA on the central component of tremor (Haubenberger et al., 2013).

Given that any body part operates as a physical object with mechanical properties, ET may also exhibit a mechanical or peripheral component (Hallett, 1998) of tremor as well. For the central component of tremor, spectral analysis of ET shows a similar frequency peak in accelerometric and surface EMG recordings, and this peak is not affected by weighting of the limbs. However, weighting the limbs lowers the frequency of the accelerometric peak of the peripheral component of tremor, also referred to as mechanical reflex component, which is part of what constitutes physiological tremor (Hallett, 2014). Therefore, adding weight may reveal two peaks in the tremor spectra of patients with ET: a peripheral peak shifting downwards in frequency, and the central peak maintaining the same frequency with EMG recording compared to the non-weighted condition. This approach allows the separation of these two components of tremor. Inertial loading leads to a reduction tremor amplitudes in ET (Heroux et al., 2009). Therefore, we presumed that the peripheral tremor component contributes to disability of ET, in addition to the central component. Given this consideration, we aimed to assess the peripheral component of tremor in previously collected clinical trial data. The aim of our analysis was first to investigate the effect of OA on the peripheral component of tremor, as well as the relationship between the central and peripheral tremor components.

2. Methods

2.1. Procedures and data analysis

Patient demographics, and tremor measurement were described previously in detail (Haubenberger et al., 2013). Patients with the diagnosis of classic ET according to the MDS consensus criteria, aged 21 years or older were eligible to participate in the double-blind, placebo-controlled, cross-over, single-dose clinical trial to assess the safety and effect of a single oral dose of OA (4 mg/kg). The protocol was approved the NIH CNS IRB, and subjects consented to the protocol before participation. 19 Patients were randomized 1:1 to a treatment sequence of OA/placebo or placebo/OA, with study drugs being administered on subsequent study days. Postural tremor was recorded using a 4 g triaxial piezo-sensitive accelerometer and surface EMG. Tremor and EMG were recorded simultaneously for 2 min at 30 and 15 min before administration, as well as at 11 time-points up to 300 min post-dose. Power spectra were calculated by Fast Fourier Transformation of each time-series collected at a sampling rate of 1000 Hz, segmented in epoch-lengths of 8192 data-points, allowing a frequency resolution of <0.5 Hz. For this analysis, the weighted condition of the accelerometry measurements was used to analyze tremor power for both the central and peripheral tremor components. The central tremor peak was defined as the spectral accelerometric peak with a corresponding EMG peak that remained unchanged in frequency compared to the non-weighted condition. The peak peripheral frequency during weighting was expected to separate from that of the central component on accelerometric recordings (Deuschl et al., 2001). Peak selection was performed using a Matlab-based selection algorithm taking into account the relative power and frequency of the two largest spectral peaks, correspondence to spectral EMG peak, and spectral location of peaks in preceding recordings on the same study day and hand.

As described before, the area under the curve of the central component peak frequency (±1Hz) was extracted for tremor power analysis using self-developed Matlab® scripts. For this analysis, we reduced the frequency window from ±1 Hz to ±0.5 Hz to avoid any cross-contamination of the derived measures from both components. Thus, the area under the curve across the central and peripheral peak (±0.5 Hz) was calculated for tremor power analysis separately. We furthermore compared the results from the algorithm-based peak-selection process to the spectral graphs of the corresponding accelerometry traces to visually verify the central and peripheral component peak frequencies ensuring reliability within our data and resolve any discrepancies.

2.2. Statistics

Descriptive statistics were applied given the small sample size. Non-parametric correlation analyses were used to analyze the correlation between the central and peripheral component of tremor power, and a log transformation was performed before analysis to account for tremor power that was not parametrically distributed. The analysis was planned in an exploratory and descriptive fashion, with the goal to inform future prospective studies on the differential contributions of peripheral and central tremor components to overall tremor in ET.

3. Results

3.1. Description of subjects with peripheral component of tremor

Of the 18 subjects who completed the trial (1 subject dropped out after the administration of OA and was not included in this analysis due to the missing placebo data), we identified 4 subjects in which an unequivocal peripheral component could be detected in addition to a central component on accelerometric recording. After log- and square root-transforming the tremor power spectra to magnify smaller spectral peaks in relation to the central peak, no additional subjects were identified with detectable peripheral components. Therefore, 4 subjects with peripheral components were further analyzed. We demonstrate data on a subject-level as well as using descriptive statistics to visualize any trends in the data.

The peak tremor frequencies, including half-widths around the spectral peaks of the 4 subjects during the weighted condition are shown in Table 1. Across visits, the frequency of the central and peripheral peak was similar. The spectral distance of the frequencies between the two components was more than 1 Hz both on placebo and OA administration days (see Table 1).

To account for baseline variations, we averaged data taken at 30 and 15 min prior to OA or placebo administration as well as at the time of administration. Tremor power was also normalized to baseline (baseline = 1) to account for variation within and between subjects. Next, normalized tremor power of each time point during OA was subtracted separately from those of the placebo day. Negative values indicate reduced tremor after OA administration, compared to placebo (Fig. 1).

The comparison of the effect of OA and placebo suggested that the tremor power was reduced after OA administration in both the central and the peripheral tremor components.

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