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

Hongmei Cao^{a,b}, Johanna Thompson-Westra^b, Mark Hallett^b, and Dietrich Haubenberger^{b,*}

^aDepartment of Neurology, The First Affiliated Hospital of Medical College, Xi'an Jiaotong University, 277 Yanta Western Road, Xi'an 710061, China

^bNational Institute of Neurological Disorders and Stroke, National Institutes of Health, 9000 Rockville Pike, Building 10, Bethesda, MD 20892, USA

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 crossover 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.

Keywords

Essential tremor; Electromyography; Physiological tremor; Octanoic acid

*Corresponding author at: NINDS Intramural Research Program, Office of the Clinical Director, Clinical Trials Unit, National Institutes of Health, 9000 Rockville Pike, B10, Rm 2A23J, Bethesda, MD 20892, USA. Tel.: +1 301 496 7563; fax: +1 301 496 3528., dietrich.haubenberger@nih.gov (D. Haubenberger).

Declaration of interest

Hongmei Cao, Johanna Thompson-Westra, Mark Hallett, Dietrich Haubenberger declare no conflict of interest.

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 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 (± 1 Hz) 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.

3.2. Correlation of central and peripheral component of tremor

In order to determine the sensitivity of both components to OA, we compared the normalized power of the central and peripheral tremor components (Fig. 2). This analysis revealed a similar pattern in both components, indicating similar effects on both the central and peripheral tremor components.

Given this similar behavior between the two components, an exploratory correlation analysis was performed to assess the strength of this relationship. To determine whether this correlation was due to a specific effect of OA on the two components, we also performed the same correlation analysis on tremor power for the placebo visit, which showed a similarly strong correlation between the central and the peripheral tremor component. The correlation coefficients (Spearman's rho, ρ) are shown below (Table 2). Spearman's rho was 0.861 ± 0.101 on the OA administration day and 0.840 ± 0.102 on the placebo day.

To further explore the role of physiological tremor in ET in our limited sample, we compared the baseline properties of these four subjects to the remaining fourteen subjects. Although the power of the central tremor component was relatively lower in those four patients with peripheral tremor components than the other fourteen subjects, likely given the

great variation across subjects, this difference did not reach statistical significance ($t = -0.618$, $p = 0.545$). The four subjects with a peripheral component demonstrated a relatively higher peak central tremor frequency compared to those in the fourteen-subject group without detectable peripheral tremor components (6.79 ± 1.10 Hz vs. 5.88 ± 0.88 Hz).

4. Discussion

Tremor in ET consists of both a mechanical/peripheral as well as a central tremor component, and these two components may be demonstrated in accelerometric recordings with the addition of weights. In our study, four out of 18 subjects had these two components of tremor clearly present and were therefore included in our analysis. While physiological tremor is present in every human, it is typically difficult to see, unless tremor is enhanced by endogenous or exogenous factors. Given that the peripheral peak frequency decreases with weight, it may overlap with the central peak during weighting if the central peak frequency is too low, thus making it difficult to distinguish between them. Thus, it may be more likely to identify the peripheral component of tremor when there is a higher central peak frequency. Secondly, a relatively weaker central tremor component may lead to a more easily detectable peripheral component of tremor in power spectrum, while at the presence of stronger central tremor peaks the peripheral component may separate less prominently from the downslope of the spectral tremor peak. Therefore, increasing the weighted condition to more than 1 lbs. per limb may allow for greater separation between these two components by further driving down the peripheral peak frequency. These methods may help to uncover the peripheral component of tremor on accelerometric recordings in more patients in future studies.

In our analysis, a strong correlation was found between the central and peripheral component of tremor at each time point of the four subjects on OA administration day, which was also shown after placebo. Moreover, coefficients for these correlations between the different two visits suggest a strong positive correlation. Given that this correlation was also present during the placebo visit, we speculate that this correlation is not due to the effects of OA, but due to an intrinsic property of tremor in ET.

Previous studies (Zeuner et al., 2003; Bushara et al., 2004; Shill et al., 2004; Nahab et al., 2011) investigating the ethanol effect in ET have focused on the central component of tremor, but, knowledge is limited about the response of the peripheral component of tremor. ET is a central movement disorder driven by a presumed central oscillator, though the site or networks of this oscillator is largely unknown. Nevertheless, a peripheral component of tremor will always have some contribution to tremor ET. Weighting changes the frequency of the peripheral tremor component, and thus provides a method of separating it from the central tremor component. While the ballistocardiac impulse maybe an important source of mechanical tremor in healthy subjects, we hypothesize that this is insignificant compared to that of the central oscillator in ET. One can therefore expect that the magnitude of the peripheral component is determined at least in some part by the energy produced by the central component. The strong correlation between central and peripheral tremor components in our study supports this concept.

Another possible explanation of the positive correlation between the two components could be that OA may directly affect both components to a similar degree. Our previous paper demonstrated that OA decreases the power of the central tremor component. In this present analysis, we found that OA also reduced the peripheral tremor power as well. However, this finding could well be an indirect effect of OA acting exclusively on the central component, with any peripheral changes resulting from downstream effects of the dominant central tremor.

The primary limitation of our study was the aforementioned small sample size and the fact that this analysis represents a secondary outcome of the protocol. Another limitation arose from the possibility of overlap between the central and peripheral peak frequencies, which would affect our tremor analysis. We descriptively analyzed the half-widths frequency intervals around the spectral peaks (see Table 1) (Timmer et al., 1996), and demonstrated that peripheral peaks were located outside the half-widths of the central peaks, although there is some overlap of the half-widths between central and peripheral peaks. To account an overlap, we narrowed the range of spectral analysis from ± 1 Hz to ± 0.5 Hz around each peak, ensuring the comparison of distinct peaks. Due to the small sample size and exploratory nature of the study, any inferences about the potential origin of these correlations will need to be studied in a prospective manner.

5. Conclusion

Our data suggest that the magnitude of the mechanical component may primarily be driven by the power of the central component.

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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.

Fig. 1.

The columns show normalized (baseline = 1) tremor power after OA administration minus normalized tremor power after placebo at each time point, given in minutes after administration. Panel A shows the power of the peripheral tremor component of both hands, B shows the power of the central tremor component of both hands. Values below zero indicate benefit of OA in tremor reduction compared to placebo. Values are shown as mean $\pm$ SE.

Fig. 2.

Central and peripheral tremor components show similar fluctuations in tremor power on the day of OA administration. Values are normalized to baseline (baseline = 1).

Central and peripheral tremor peak frequencies, as well as ranges of the half-power frequency width around the individual peaks (“half-width”; HW) of both left and right upper limbs after placebo and OA (means across 11 time-points each).

Table 1

Subj ID	OA (Hz)		PL/ACEBO (Hz)											
	Central component tremor		Peripheral component tremor				Central component tremor				Peripheral component tremor			
	R		L		R		L		R		L		R	
	Peak	HW	Peak	HW	Peak	HW	Peak	HW	Peak	HW	Peak	HW	Peak	HW
S04	6.5	1.2	6.0	1.7	5.1	1.3	5.0	1.2	6.4	1.3	6.1	1.9	5.3	1.3
S08	5.4	0.7	5.9	0.9	3.7	1.1	4.5	3.3	5.3	0.6	5.8	0.8	3.8	1.7
S14	9.2	3.6	7.0	0.8	7.2	2.1	5.2	1.2	9.3	2.3	6.9	0.9	6.6	1.6
S17	7.1	2.1	6.9	2.2	4.3	1.0	5.2	2.7	6.8	2.9	6.7	1.8	5.2	1.6
													5.5	0.9

Table 2

Correlation between central and peripheral components of tremor power after OA and placebo.

TIMEPOINTS (min)	Spearman correlation coefficient (ρ)	
	OA (central vs. peripheral)	PLACEBO (central vs. peripheral)
BASELINE	0.905	0.810
20	0.905	0.714
40	0.571	0.952
60	0.893	0.990
80	0.960	0.974
100	0.881	0.762
120	0.881	0.881
150	0.905	0.786
180	0.786	0.690
210	0.833	0.857
240	0.929	0.905
300	0.881	0.762