HIGH LIGHT

Influence of alcohol on gait in patients with essential tremor

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Abstract—*Objective:* To study the effect of ethanol on gait in patients with essential tremor (ET). *Methods:* Using a three-dimensional opto-electronic gait analysis system, the authors analyzed gait at free-speed walking, at a given velocity, and during tandem gait. Patients with ET with advanced disease were examined before and after a small oral dose of ethanol. The results of the patients with ET were compared with those from age-matched healthy controls (HCs). The primary outcome criteria were the number of missteps and the ataxia score during tandem gait. *Results:* Before alcohol, patients with ET had more missteps and an abnormal ataxia score compared with HCs. The ingestion of alcohol with a mean blood level of 0.45‰ led to a significant improvement of the ataxia score and the number of missteps. HCs showed a worsening of the ataxia score and an increase of the number of missteps after alcohol, which failed to reach significance. *Conclusions:* Orally administered ethanol improved gait ataxia in patients with essential tremor (ET). This may reflect a reversible effect of ethanol on receptors being involved in the pathology of ET. Ethanol may act via an influence of the inferior olive or directly on alcohol-sensitive γ-aminobutyric acid receptors within the cerebellum.

NEUROLOGY 2005;65:96–101

Essential tremor (ET) presents with postural and action tremor of the upper extremities.[1] The pathophysiology of this often-inherited disease is still unclear. An abnormal olivocerebellar oscillation of the Guillain–Mollaret triangle was assumed.[2] This hypothesis was derived from animal studies with the harmaline model of tremor,[3] PET studies,[4,5] and recent electrophysiologic studies of goal-directed arm movements[6,7] and eye movements.[8] The latter studies found a subgroup of patients with advanced ET indistinguishable from patients with a cerebellar malfunction.

The pathophysiologic concept of a cerebellar involvement was further supported by studies of the lower extremity demonstrating a gait disorder with an abnormal tandem gait performance in patients with ET,[9-11] confirmed with an objective quantitative study.[11] The latter showed that the gait disorder in ET could not be distinguished from the cerebellar gait disorder in cerebellar degenerations.[11-13]

The tremor-suppressing potential of ethanol on ET for the upper extremity was first reported in 1975[14] and later confirmed by several studies.[15,16] The effect of low blood levels of ethanol on ET seems to be stronger than that of two of the most prescribed drugs, propranolol and primidone, especially when administered orally.[17] Ethanol most likely acts centrally via a reduction of cerebellar overactivity, which results in a reduced tremor amplitude, whereas the frequency remains unaffected.[15,18,19]

This study was designed to clarify if not only tremor but also the cerebellar disturbances seen in ET can be influenced by alcohol ingestion. Gait analysis has proven to be the most reliable examination of the cerebellar disturbance according to our earlier studies.[11] Therefore, we have chosen gait analysis using a three-dimensional opto-electronic gait analysis system to study normal gait either at a self-chosen speed or at a given velocity and tandem gait of advanced patients with ET before and after a small oral dose of ethanol. The results of the patients with ET were compared with those of age-matched healthy controls (HCs).

Methods. Patients with ET were randomly selected from the patient database of the Department of Neurology if they had ET and intention tremor according to the following criteria: Patients with ET were included only if they fulfilled the diagnostic criteria of classic ET as defined by the consensus statement of the Movement Disorders Society[1] and had substantial intention tremor on the finger-to-nose test, as proposed elsewhere,[1] or a clinical gait disturbance during tandem gait examination. The examination was performed by movement disorder specialists at the department.

All 16 patients (4 women, 12 men) were included between 2002 and 2003. Their ages ranged from 23 to 78 years (mean 59.31 ± 14 years). Disease duration ranged from 4 to 50 years (mean 20.5 ± 13.9 years). Nine patients reported a positive family history for ET in first-degree relatives. Eleven patients spontaneously reported a positive effect after ingestion of small doses of ethanol on ET. Three reported no significant effect, and two patients never tested the effect of ethanol.

Eleven age-matched individuals of both sexes (seven women, four men) ages 50 to 80 (mean 63 ± 10 years) served as HCs. The subjects were excluded if either the history or the neurologic examination showed a hindrance that interfered with an unrestrained gait.

None of the patients with ET or HCs had a history of ethanol abuse. The patients were currently not treated with medication.

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Supported by the German Research Council (DFG).

Received December 16, 2004. Accepted in final form March 18, 2005.

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All patients with ET and HC gave their informed consent to participate in the study, which was approved by the local ethical committee.

The clinical assessments were performed by movement disorders specialists. Tremor was rated according to the Clinical Tremor Rating Scale[20] on a 5-point scale (0 to 4) for each side of the upper and lower extremities and the head. Intention tremor was defined as described elsewhere.[1] Intention tremor was rated in the terminal period of the finger-to-nose test and the heel-to-shin test. Subscales for the upper (Items 5 and 6 of Part A) and lower (Items 8 and 9 of Part A) extremities were constructed.

Additionally, the missteps during tandem gait were counted (see below). The clinical scores were performed at baseline and 30 minutes after oral ingestion of ethanol. Therefore, patients with ET and HC received 0.25 mL of 10% ethanol. Thirty minutes after ethanol ingestion, venous blood samples were taken, and the ethanol blood level was measured in each patient.

The effect of ethanol on gait was assessed by use of a three-dimensional gait analysis system in patients with ET and HC before (baseline) and 30 minutes after ethanol ingestion. The natural walking speed of each subject was measured during overground locomotion twice, before baseline gait analysis and after ethanol ingestion. For this purpose, the subjects were instructed to walk a distance of 13 m at their own selected comfortable speed on a walkway. In the central part of the 13-m walkway, two infrared light barriers were installed 5 m apart. The gait velocity was calculated by measuring the time each subject needed to cover the 5-m distance (mean of four runs), and the mean gait velocity was selected for further analysis.

Subsequently, a complete gait analysis was carried out barefoot on a motor-driven treadmill (Woodway; length 2.2 m, width 0.7 m) in three different conditions: First, the treadmill speed was adjusted exactly to the subject's individual gait velocity measured during normal gait. Second, a standard gait velocity of 2 km/h was chosen that every patient could perform to compare the ethanol effect at the same velocity in all patients and HCs. Third, tandem gait was analyzed at a velocity of 1 km/h, which was used in our earlier study.[11] Subjects were trained to walk with their hands folded over their necks (if possible) to avoid different strategies of balance control, for example, walking with horizontally outstretched arms. If necessary, the patients were additionally secured with a safety belt suspended from the ceiling of the laboratory (without weight support). Further missteps during tandem gait, defined as those steps taken with the whole foot outside the bounds of a red tape, were counted over 60 seconds. The red tape had a diameter of 1.5 cm and was placed in the middle of the treadmill. During normal locomotion on the treadmill, the subjects were instructed to let their arms swing freely.

Before recording, the subjects were given 5 minutes to familiarize themselves with treadmill locomotion and again 2 minutes before the recording of tandem gait.

The quantitative off-line analysis was performed using an infrared movement analysis system (Qualisys, Sandvälen, Sweden), which has been described elsewhere.[21]

The following standard variables were calculated: gait velocity, stride length, cadence, step width, foot angle (outward rotation denoted as positive), step height, gait cycle time, stance, swing, and double-limb support phase duration. The ataxia ratio measuring the regularity of the strides was calculated as a ratio of the standard deviation of foot placement in all three room directions ([SD of step length + SD of step width + SD of step height]/3).[11] The coefficients of variation were calculated for stride length and step width to quantify the intraindividual variability.

Using the Kolmogorov–Smirnov test of normality, we found normal distribution for all experimental data. Therefore, we used the Student paired sample t test to analyze clinical scores and gait analysis between baseline and after ethanol ingestion. The ataxia ratio and the number of missteps were determined as the primary variables of this study. The difference between ET and HC subjects was analyzed using the Student independent sample t test. Correlation coefficients between gait analysis data and clinical scores were analyzed by using Pearson r. The level of significance was set at $p < 0.05$.

Results. *Clinical data.* The demographic data and clinical results are summarized in tables 1 and 2.

Both populations were matched by frequency matching for age, sex, weight, and leg length. In addition, mean serum ethanol levels 30 minutes after ingestion of ethanol were 0.47% in the patients and 0.45‰ in the HCs and were statistically not different. However, there was a large interindividual variability between 0.2 and 1.2‰.

Tremor was scored before and 30 minutes after ethanol ingestion. At baseline, the total tremor score was 32.6 ± 19.7 (mean ± SD; range 14 to 81) in patients with ET. After ethanol ingestion, the tremor score improved significantly to 21.8 ± 14.2 (range 1.5 to 57). Both upper extremity ($p = 0.01$) and lower extremity ($p = 0.031$) tremor subscores showed a reduction.

Gait analysis. We investigated tandem gait at 1 km/h. In addition, normal bipedal gait was studied on a treadmill at the natural walking speed or at a defined velocity of 2 km/h. The results of gait analysis are summarized in table 3 and in figures 1 and 2.

The ataxia score was significantly larger in the patients compared with control subjects before ethanol (ET: mean 24.7 ± 10.9; HC: mean 12.6 ± 4.7). After ethanol ingestion, the patients improved significantly (ET: mean 18.2 ± 10.4). The score worsened slightly but not significantly for the HCs (mean 15.1 ± 8.9). At baseline, the patients exhibited 8.8 ± 12.6 missteps/min (mean ± SD; range 0 to 50 missteps/min) compared with 0.4 ± 0.7 missteps/min in HCs (range 0 to 2 missteps/min). This difference was significant ($p < 0.005$). After ethanol ingestion, the number of missteps decreased in patients with ET to 5.6 ± 8.4 (range 0 to 30 missteps/min) and increased in the HCs to 0.7 ± 1.3 (range 0 to 4 missteps/min). Within each group, the changes before and after ethanol showed the decrease of the number of missteps were significant in patients with ET ($p < 0.05$), but the increase in HCs failed significance.

Step length and width are not completely independent from the ataxia score and are reported here for further illustration. Both for the step width and for the step length, the variability was increased in the patients. For the step length, the difference between patients and HCs was significant before ethanol ($p < 0.01$) but failed to reach significance after ethanol ($p > 0.464$).

Normal bipedal gait at the subjects' own comfortable velocity and forced gait at a standard velocity of 2 km/h showed only small abnormalities in patients with ET. As in the tandem gait condition, the variability of step length was larger for the forced speed condition in the patients than in the HCs but not significantly different at normal walking speed.

During both normal gait conditions, the step width was reduced by alcohol ingestion both in the patients and in the subjects at normal walking speed and in the forced speed condition.

Correlations between gait analysis and clinical scores. Correlations for the patients with ET were found only between the ataxia score during tandem gait and the missteps after ethanol ingestion ($p = 0.038$), and there was a meaningful trend before ethanol ($p = 0.053$).

No correlation occurred between the Clinical Tremor Scale and the ataxia score during the natural walking speed, the forced velocity, or the tandem gait condition.

Further, no significant correlation could be found between the Clinical Tremor Scale and the subscores or between the demographic data (age, duration) or serum

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Table 1 *Characteristics of patients with ET and HC*

Subject no.	Sex	Age, y	Weight, kg	Size, cm	Leg length, cm
ET1	M	60	81	172	87
ET2	M	68	80	176	90
ET3	M	71	83	182	102
ET4	M	78	72	174	84
ET5	M	23	98	190	109
ET6	M	57	100	193	104
ET7	M	64	85	182	104
ET8	M	65	92	183	97
ET9	F	71	54	172	91
ET10	M	71	80	170	98
ET11	F	43	62	164	89
ET12	M	66	98	170	90
ET13	F	65	60	158	82
ET14	F	44	54	163	94
ET15	M	44	71	176	102
ET16	M	59	83	185	106
Mean ET		59.31 ± 14	78.3 ± 15.1*†	175.6 ± 9.8*‡	95.6 ± 8.3*‡
HC1	F	61	73	172	97
HC2	F	50	68	164	93
HC3	M	58	80	183	102
HC4	M	69	75	165	88
HC5	F	60	72	172	96
HC6	F	77	65	161	91
HC7	M	59	97	185	102
HC8	M	57	86	178	97
HC9	F	70	54	150	89
HC10	F	53	61	168	100
HC11	F	80	60	162	97
Mean HC		63 ± 10	71.9 ± 12.4*	169.1 ± 10.3*‡	95.6 ± 4.9*
Total		60.9 ± 12.5	75.7 ± 14.2*†	172.9 ± 10.3*‡	95.6 ± 7*‡

Correlations between the variables are calculated using the Pearson rank correlation. Correlation is significant at the 0.01 level (two tailed).

* Correlation with leg length.
† Correlation with size.
‡ Correlation with weight.

ET = essential tremor; HC = healthy control.

ethanol levels with clinical scores or gait analysis data. Correlations between weight, size, and leg length are indicated in table 1.

Discussion. We sought to assess the effect of orally administered ethanol on lower extremity functions and gait in advanced patients with ET. We could confirm the earlier observation that patients with advanced ET have an ataxic gait pattern.[10,11,22] The disturbance is best visible with tandem gait and consists of an abnormal ataxia score and an increased number of missteps.[11] The surprising result of this study is the modulation of this abnormality by the ingestion of ethanol.

Recent studies favor an abnormality of the cerebellum in ET. The cerebellum is considered to be organized in different subsystems, which are labeled as the vestibulocerebellum (vestibular and oculomotor functions), the spinocerebellum (adjusting of stance and gait), and the neocerebellum (differential hand functions).[11,23,24] In ET, all three subsystems of

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Table 2 *Mean ± SD values for Clinical Tremor Rating Scale and missteps at baseline and after ethanol of patients with ET*

ET	Baseline	Ethanol
Total	32 ± 19.7	21.8 ± 14.2†
Subscore arm	5.7 ± 4.5	3.4 ± 3.4*
Subscore leg	2.1 ± 1.7	1.5 ± 1.7*
Missteps/min	8.8 ± 12.6	5.6 ± 8.4*

Significance after ethanol ingestion:

* $p < 0.05$.
† $p < 0.005$.

ET = essential tremor.

the cerebellum seem to function abnormally, but to a different amount. Patients have severe abnormalities of the neocerebellar system with an overshoot of goal-directed movements, slowness of voluntary movements,[7] and a disturbance of the agonist–antagonist coupling of voluntary arm movements.[6,25,26] More subtle abnormalities were found for stance and gait functions with an increased amount of missteps[10,22] and an abnormal ataxia score.[11] Only the impaired tandem gait is clinically visible. The most subtle abnormalities were found for oculomotor functions with an impaired smooth pursuit initiation and a pathologic suppression of the vestibulo-ocular reflex time constant by head tilts.[8] The oculomotor abnormalities cannot be observed clinically. A simple but convincing clinical argument for a critical role of the cerebellum in ET is the disappearance of tremor after an ipsilateral cerebellar stroke.[27]

The cause for these cerebellar abnormalities is unknown. It could indicate either a receptor-mediated or a morphologic abnormality. fMRT and PET studies have shown functional abnormalities of the cerebellum and the brainstem in patients with ET.[4,5,19,28-30] Recently, two MR spectroscopic studies have demonstrated an abnormal relation of choline and *N*-acetylaspartate in ET,[31,32] which might indicate a morphologic abnormality despite the fact that earlier pathologic studies were not able to show a consistent abnormality on pathologic examination of patients.[33] One of the important questions emerging from these studies therefore concerns if the cerebellar abnormality in ET is indicating a "neurodegenerative" process of the cerebellum.

To our knowledge, this is the first study investigating the effect of ethanol on lower extremity functions and gait in patients with advanced ET. Ethanol has a pronounced effect on ET[14] and is considered

Table 3 *Mean ± SD values for comparison of gait analysis data and missteps between patients with ET and HC and within groups using Student independent sample t test at given velocity (2 km/h), normal walking speed, and tandem gait condition*

			Normal gait (walking speed)			
	Tandem gait		2 km/h standard		Individually preferred	
	ET	HC	ET	HC	ET	HC
Ataxia score						
Baseline	24.7 ± 10.9	12.6 ± 4.7***	13.8 ± 6.1	8.6 ± 2.2**	13.4 ± 4.7	12.1 ± 4.8
Alk.	18.2 ± 10.4†	15.1 ± 8.9	12.1 ± 3.3	10 ± 2.2	12.8 ± 4.9	11 ± 2.2
Missteps						
Baseline	8.8 ± 12.6	0.4 ± 0.7***	NA	NA	NA	NA
Alk.	5.6 ± 8.4†	0.7 ± 1.3	NA	NA	NA	NA
Step width, cm						
Baseline	57.6 ± 45.8	34.3 ± 20.5	156.9 ± 116.1	157.7 ± 67.3	156.7 ± 101.1	154.1 ± 62.7
Alk.	48.8 ± 45.5	35.8 ± 32.5	127.2 ± 120.4†††	133.9 ± 68.8	131.9 ± 106.4†††	131.8 ± 70.5
CV Step width						
Baseline	64.3 ± 46.1	40.5 ± 24.1	8.9 ± 4.4	9 ± 6.6	12.3 ± 5.4	14.3 ± 10.1
Alk.	73.3 ± 77.2	53.3 ± 34.9	12.5 ± 5.3†	16.1 ± 11.2	13.8 ± 5.8	17.8 ± 11.4
Velocity m/s						
Baseline	NA	NA	NA	NA	1.1 ± 0.2	1.2 ± 0.2
Alk.	NA	NA	NA	NA	1.1 ± 0.2	1.2 ± 0.2
CV Step length						
Baseline	17.6 ± 17.2	4.6 ± 1.4**	9.1 ± 8.9	4 ± 1.8*	3.8 ± 1.6	3 ± 1.3
Alk.	12.7 ± 14.4	8.8 ± 10.1	5.8 ± 2.5	4.9 ± 1.7	4 ± 3	2.7 ± 1.2

* Level of significance between ET and HC. † level of significance within the patients with ET (*/† = $p < 0.05$; **/†† = $p < 0.01$; ***/††† = $p < 0.005$).

ET = essential tremor; HC = healthy control; Alk. = after ethanol.

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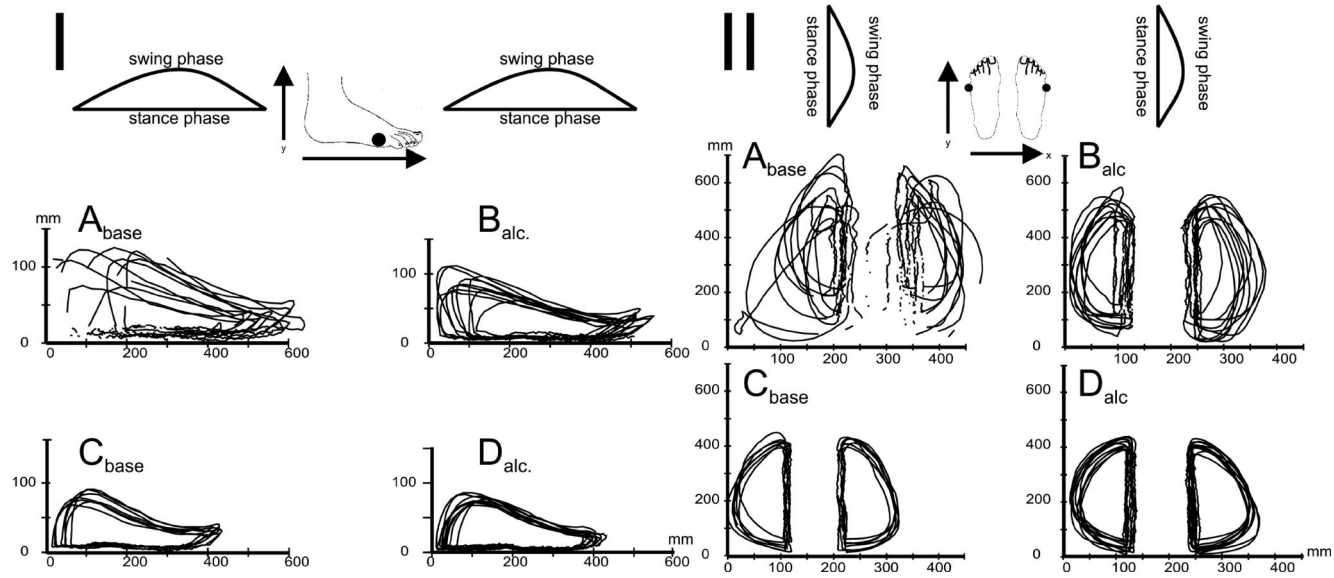

Figure 1. Traces of markers attached to the forefoot in a view from lateral (I) and above (II) (see schematic drawing at the top) for patients with essential tremor (A, B) and healthy control subjects (C, D) at baseline and after ethanol. Recordings were made during walking with natural walking speed on the treadmill over 20 seconds of continuous measurement.

the most potent drug for the treatment of ET.[15] On the other hand, it is common experience that ethanol at higher dosages induces a specific disturbance of gait, which is considered a model of cerebellar gait abnormalities.[34] Therefore, the dosage of ethanol is critical for such effects. We have chosen an oral application and dosage that are able to produce effects on ET without clinically visible gait disturbances in normal humans. Profound effects on tremor and gait were found for the patients but not much of an effect on the gait of normal subjects despite a wide variation of blood ethanol levels. Of course, a more individual titration of alcohol might have led to more pronounced effects, but this was practically impossible in the setting of our study. We have further chosen to test the effect of ethanol on gait functions, as the abnormality of gait in ET is clinically visible but does not correlate with the scoring of tremor of the leg and thus seems to represent an abnormality that is independent of leg tremor. This finding confirms our earlier study.[11] We want to stress the argument that the cerebellar disturbance of ET is independent of the severity of tremor: First, subgroup analysis of the Clinical Tremor Rating Scale revealed no influence of ethanol on the postural and intention tremor of the leg. Second, even patients without cerebellar abnormalities of the lower extremities are known to develop an ataxic gait pattern. Finally, no correlation was found between clinical and instrumental measures of ataxia and the severity of tremor of the legs. This is important for our argument that the positive effect of ethanol on gait might otherwise be simply due to an improvement of the postural and intention tremor of the lower extremities.

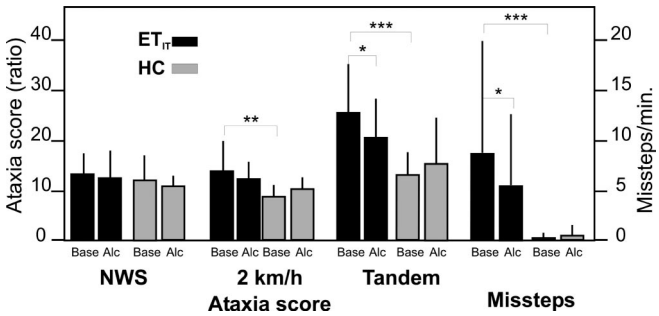

*Figure 2. Ataxia score for patients with essential tremor and healthy control subjects calculated as a ratio of the standard deviation of foot placement in all three room directions ([SD of step length + SD of step width + SD of step height]/3) during gait analysis (left) and number of missteps during tandem gait at baseline and after ethanol (right). Base = baseline; alc = after ethanol; NWS = normal walking speed. *p < 0.05, **p < 0.0, ***p < 0.005.*

Thus, we conclude that the cerebellar malfunction in ET is reversible by a potent drug, in this case ethanol. With respect to the "neurodegeneration hypothesis" of ET, the current data allow only limited conclusions. If the ataxia had not been reversible following medication, our results would have favored a permanent lesion of cerebellar functions (e.g., neurodegeneration). But as this is not the case, our findings indicate either that the degenerated functions can be compensated by a system activated by alcohol or that the alcohol effect is a purely pharmacologic one in a morphologically intact system.

Ethanol has many different actions, which could explain the observed effects. One of them has been elaborated with the harmaline model of tremor in rats sharing some features with human ET.[35] Purkinje cells are the principal output cells of the cerebellum. The spontaneous discharge pattern of cerebellar Purkinje cells consists of randomly distributed simple and complex spikes. The inferior olive neurons are responsible for complex spikes. Harma-

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line activates rhythmic complex spikes and eliminates simple spike activity.[36,37] Ethanol administration decreases complex spikes and increases single-spike activity generated in the inferior olive and might thereby antagonize the action of harmaline[38] at the level of the inferior olive. A similar mechanism may also work for octanolol,[39,40] another alcohol with excellent therapeutic effect on rat harmaline tremor. Two recent studies have demonstrated a therapeutic effect of octanolol in patients with ET.[41,42] Following this line of reasoning, the rhythmic activity of complex spikes in the cerebellum in patients with ET may interfere with the function of the cerebellum, providing feed-forward function, which is necessary for the execution of smooth and regular movements.[43] The result is an ataxic gait being specifically activated during tandem gait. Ethanol may inhibit or desynchronize inferior olive cell activity. Such normalization of the discharge pattern may be the mechanism for the normalization of gait after ingestion of ethanol. A second option would be a direct action of alcohol on cerebellar receptors. It is known that the *N*-methyl-D-aspartate subtype of glutamate receptor is sensitive to ethanol,[44] and this receptor seems to be specifically expressed in the cerebellum. It may be hypothesized on the basis of these results that this receptor could function abnormally in ET. Further studies are necessary to clarify the existing hypothesis.

References

1. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord 1998;13(suppl 3):2–23.
2. Deuschl G, Bergman H. Pathophysiology of nonparkinsonian tremors. Mov Disord. 2002;17(suppl 3):S41–S48.
3. Llinas R. Rebound excitation as the physiological basis for tremor: a biophysical study of the oscillatory properties of mammalian central neurons in vitro. In: Capildeo R, ed. Movement disorders: tremor. London: Macmillan, 1984:339–351.
4. Hallett M, Dubinsky RM. Glucose metabolism in the brain of essential tremor patients. J Neurol Sci 1993;114:45–48.
5. Wills AJ, Jenkins IH, Thompson PD, Findley LJ, Brooks DJ. A positron emission tomography study of cerebral activation associated with essential and writing tremor. Arch Neurol 1995;52:299–305.
6. Koster B, Deuschl G, Lauk M, Timmer J, Guschlbauer B, Lucking CH. Essential tremor and cerebellar dysfunction: abnormal ballistic movements. J Neurol Neurosurg Psychiatry 2002;73:400–405.
7. Deuschl G, Wenzelburger R, Loffler K, Raethjen J, Stolze H. Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. Brain 2000;123:1568–1580.
8. Helmchen C, Hagenow A, Miesner J. et al. Eye movement abnormalities in essential tremor may indicate cerebellar dysfunction. Brain 2003;126:1319–1332.
9. Hornabrook RW, Nagurney JT. Essential tremor in Papua, New Guinea. Brain 1976;99:659–672.
10. Singer C, Sanchez-Ramos J, Weiner WJ. Gait abnormality in essential tremor. Mov Disord 1994;9:193–196.
11. Stolze H, Petersen G, Raethjen J, Wenzelburger R, Deuschl G. The gait disorder of advanced essential tremor. Brain 2001;124:2278–2286.
12. Palliyath S, Hallett M, Thomas SL, Lebiedowska MK. Gait in patients with cerebellar ataxia. Mov Disord 1998;13:958–964.
13. Stolze H, Klebe S, Petersen G, et al. Typical features of cerebellar ataxic gait. J Neurol Neurosurg Psychiatry 2002;73:310–312.
14. Growdon JH, Shahani BT, Young RR. The effect of alcohol on essential tremor. Neurology 1975;25:259–262.
15. Koller WC, Biary N. Effect of alcohol on tremors: comparison with propranolol. Neurology 1984;34:221–222.
16. Koller WC, Busenbark K, Miner K. The relationship of essential tremor to other movement disorders: report on 678 patients. Essential Tremor Study Group. Ann Neurol 1994;35:717–723.
17. Koller WC. A new drug for treatment of essential tremor? Time will tell. Mayo Clin Proc 1991;66:1085–1087.
18. Lakie M, Frymann K, Villagra F, Jakeman P. The effect of alcohol on physiological tremor. Exp Physiol 1994;79:273–276.
19. Boecker H, Wills AJ, Ceballos-Baumann A, Samuel M, Thompson PD, et al. The effect of ethanol on alcohol-responsive essential tremor: a positron emission tomography study. Ann Neurol 1996;39:650–658.
20. Fahn S, Tolosa E, Marin C. Clinical Rating Scale for Tremor. In: Tolosa E, ed. Parkinson's disease and movement disorders. 2nd ed. Baltimore: Williams & Wilkins, 1993:271–280.
21. Stolze H, Kuhtz-Buschbeck JP, Mondwurf C, et al. Gait analysis during treadmill and overground locomotion in children and adults. Electroencephalogr Clin Neurophysiol. 1997;105:490–497.
22. Hubble JP, Busenbark KL, Pahwa R, Lyons K, Koller WC. Clinical expression of essential tremor: effects of gender and age. *Mov Disord* 1997;12:969–972.
23. Ito M. Controller-regulator model of the central nervous system. J Integr Neurosci 2002;1:129–143.
24. Brodal A. Neurological anatomy in relation to clinical medicine. 3rd ed. New York: Oxford University Press, 1981.
25. Britton TC, Thompson PD, Day BL, Rothwell JC, Findley LJ, Marsden CD. Rapid wrist movements in essential tremor patients. The critical role of the second agonist burst. Brain 1994;117:39–47.
26. Zackowski KM, Bastian AJ, Hakimian S. et al. Thalamic stimulation reduces essential tremor but not the delayed antagonist muscle timing. Neurology 2002;58:402–410.
27. Dupuis MJ, Delwaide PJ, Boucquey D, Gonsette RE. Homolateral disappearance of essential tremor after cerebellar stroke. Mov Disord 1989;4:183–187.
28. Colebatch JG, Findley LJ, Frackowiak RS, Marsden CD, Brooks DJ. Preliminary report: activation of the cerebellum in essential tremor. Lancet 1990;336:1028–1030.
29. Jenkins IH, Bain PG, Colebatch JG, et al. A positron emission tomography study of essential tremor: evidence for overactivity of cerebellar connections. Ann Neurol 1993;34:82–90.
30. Wills AJ, Jenkins IH, Thompson PD, Findley LJ, Brooks DJ. Red nuclear and cerebellar but no olivary activation associated with essential tremor: a positron emission tomographic study. Ann Neurol 1994;36:636–642.
31. Pagan FL, Butman JA, Dambrosia JM, Hallett M. Evaluation of essential tremor with multi-voxel magnetic resonance spectroscopy. Neurology 2003;60:1344–1347.
32. Louis ED, Shungu DC, Chan S, Mao X, Jurewicz EC, Watner D. Metabolic abnormality in the cerebellum in essential tremor patients: a proton magnetic resonance spectroscopic imaging study. Neurosci Lett 2002;333:17–20.
33. Rajput AH, Rozdilsky B, Ang L, Rajput A. Clinicopathologic observations in essential tremor: report of six cases. Neurology 1991;41:1422–1424.
34. Nieschalk M, Ortmann C, West A, Schmal F, Stoll W, Fechner G. Effects of alcohol on body-sway patterns in human subjects. Int J Legal Med 1999;112:253–260.
35. Wilms H, Sievers J, Deuschl G. Animal models of tremor. Mov Disord 1999;14:557–571.
36. Llinas R, Volkind RA. The olivo-cerebellar system: functional properties as revealed by harmaline-induced tremor. Exp Brain Res 1973;18:69–87.
37. De Montigny C, Lamarre Y. Effects produced by local applications of harmaline in the inferior olive. Can J Physiol Pharmacol 1975;53:845–849.
38. Sinclair JG, Lo GF, Harris DP. Ethanol effects on the olivocerebellar system. Can J Physiol Pharmacol 1982;60:610–614.
39. Sinton CM, Krosser BI, Walton KD, Llinas RR. The effectiveness of different isomers of octanol as blockers of harmaline-induced tremor. Pflugers Arch 1989;414:31–36.
40. Rappaport MS, Gentry RT, Schneider DR, Dole VP. Ethanol effects on harmaline-induced tremor and increase of cerebellar cyclic GMP. Life Sci 1984;34:49–56.
41. Shill HA, Bushara KO, Mari Z, Reich M, Hallett M. Open-label dose-escalation study of oral 1-octanol in essential tremor patients. Neurology 2004;62:2320–2322.
42. Bushara KO, Goldstein SR, Grimes GJ Jr, Burstein AH, Hallett M. Pilot trial of 1-octanol in essential tremor. Neurology 2004;62:122–124.
43. Allen GI, Tsukahara N. Cerebrocerebellar communication systems. Physiol Rev 1974;54:957–1006.
44. Sultana R, Babu PP. Ethanol-induced alteration in *N*-methyl-D-aspartate receptor 2A C-terminus and protein kinase C activity in rat brain. Neurosci Lett 2003;349:45–48.

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