SHORT REPORT

Intracortical inhibition of the motor cortex is normal in chorea

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Abstract

Intracortical inhibition of the motor cortex was investigated using a paired pulse magnetic stimulation method in 14 patients with chorea caused by various aetiologies (six patients with Huntington's disease, one with chorea acanthocytosis, a patient with systemic lupus erythematosus with a vascular lesion in the caudate, three with senile chorea and three with chorea of unknown aetiology). The time course and amount of inhibition was the same in the patients as in normal subjects, suggesting that the inhibitory mechanisms of the motor cortex studied with this method are intact in chorea. This is in striking contrast with the abnormal inhibition seen in patients with Parkinson's disease or focal hand dystonia, or those with a lesion in the putamen or globus pallidus. It is concluded that the pathophysiological mechanisms responsible for chorea are different from those producing other involuntary movements.

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Diseases of the basal ganglia give rise to various movement disorders ranging from chorea to dystonia or Parkinson's disease; basal ganglia influence movement primarily through their projections to primary and secondary areas of motor cortex. There have been several studies of cortical physiology designed to test whether there is a difference between the pathological mechanisms for hyperkinesia and hypokinesia. Two main approaches have been used: PET and transcranial magnetic stimulation (TMS). Joystick movements in Parkinson's disease are associated with a normal pattern of regional cerebral blood flow (rCBF) in the primary motor cortex, whereas there is decreased rCBF in the supplementary motor area and dorsolateral prefrontal cortex (DLPFC).¹ In idiopathic dystonia, rCBF is reduced in the primary motor cortex (perhaps reflecting lack of inhibitory activity), but the supplementary motor area is overactive.² The results in chorea are inconsistent. Some studies showed a decrease

of cerebral blood flow³ or cerebral metabolic rate of glucose⁴ in the motor cortex and some others showed normal cerebral metabolic rate.^{5,6} As a whole, even in patients with hyperkinesia or hypokinesia, rCBF was decreased or normal in the primary motor cortex. There were no consistent differences in rCBF between hyperkinesia and hypokinesia. By contrast with PET studies, there may be a consistent difference in the intracortical inhibition between patients with chorea and those with other involuntary movements. Intracortical inhibition of the motor cortex has been studied using a paired pulse magnetic stimulation method⁷ in several movement disorders. This inhibition was reduced or absent in focal hand dystonia,⁸ dyskinesia due to a lesion in the putamen or globus pallidus,^{9,10} and in some patients with Parkinson's disease.^{9,11} By contrast, in a few patients with chorea, we found normal intracortical inhibition of the motor cortex.⁹ This may indicate that intracortical inhibition of the primary motor cortex is intact in one type of hyperkinetic basal ganglia disorder, whereas it is disturbed in hypokinetic disorders. To confirm this finding, we studied the intracortical inhibition of the motor cortex using a paired pulse stimulation method in 14 patients with chorea of various aetiologies.

Subjects and methods

SUBJECTS

The subjects were 14 patients (10 men and four women, aged 29-75 years) with chorea due to various aetiologies. Their clinical details are shown in the table. They all had chorea in their upper limbs. All six patients with genetically determined Huntington's disease had moderate chorea, but no or mild dementia. We selected patients with early stage Huntington's disease because our main purpose was to investigate the pathophysiology of chorea itself. In patients with late stage Huntington's disease, chorea is accompanied by other neurological symptoms such as hypertonicity (rigidity or spasticity), parkinsonian features, pyramidal signs, dementia, and psychiatric signs.¹² Because some of these symptoms are known to affect intracortical inhibition, we tried to evaluate a population with relatively pure chorea. The other patients included a 36

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Details of patients

Patient No	Diagnosis	Age (y)	Sex	Disease duration (y)	Medication
1	Huntington's disease	75	F	10	None
2	Huntington's disease	51	M	11	None
3	Huntington's disease	35	M	2	None
4	Huntington's disease	59	M	19	None
5	Huntington's disease	56	F	6	Perphenazine (6 mg)
6	Huntington's disease	47	M	2	Perphenazine (6 mg)
7	Chorea acanthocytosis	36	F	10	Perphenazine (6 mg)
8	Systemic lupus erythematosus	33	F	0	None
9	Senile chorea	81	M	2	None
10	Senile chorea	69	M	6	None
11	Senile chorea	64	M	7	None
12	Unknown	63	M	30	None
13	Unknown	65	M	16	None
14	Unknown	29	M	1	None

year old woman with chorea acanthocytosis (patient 7) had chorea of the face, tongue, and limbs, and distal dominant muscular weakness with decreased deep tendon reflexes due to peripheral neuropathy. Many acanthocytes were found in the blood smear. Brain CT showed caudate atrophy. These were all typical of chorea acanthocytosis. A 33 year old woman with systemic lupus erythematosus (patient 8) developed acute onset hemichorea in the right upper and lower limbs. Brain MRI showed a discrete lesion in the left caudate, which was considered to be caused by an ischaemic accident due to systemic lupus erythematosus. The hemichorea was alleviated by treatment with prednisolone. Three patients with senile chorea (patients 9, 10, and 11) first noticed involuntary movements after the age of 60 and had no other abnormalities in neurological examination or laboratory studies including genetic analyses for Huntington's disease and dentatorubropallidolysian atrophy (DRPLA). The other three patients (12, 13, and 14) also had only chorea. Neither imaging nor laboratory studies showed any abnormalities.

METHODS

Intracortical inhibition of the motor cortex was studied using the same technique as described in a previous report.⁹

Responses on EMG were recorded from the first dorsal interosseous muscle (FDI) on the more affected side with surface cup electrodes. The active electrode was placed over the muscle belly, and the reference electrode over the metacarpophalangeal joint of the index finger. Responses amplified with filters set at 100 Hz and 3 kHz were recorded by a computer (DP-1200, NEC Medical Systems).

For magnetic stimulation, we used Magstim 200 magnetic stimulators (The Magstim Company, UK) with a circular coil (11.5 cm outer diameter) placed over the vertex. The coil current direction was adjusted so that the current in the brain flowed in the posterior-anterior direction at the optimal site for FDI. We used a randomised conditioning test paradigm. Conditioning and test stimuli were given through a same coil by connecting two magnetic stimulators linked with a Bistim module (Magstim company, UK). The intensity of conditioning stimulus was fixed at an intensity 5% below the threshold for active studied muscles. The test stimulus was ad-

justed to evoke a response with an amplitude of approximately 0.3 mV peak to peak in relaxed FDI. In one session of the experiments, several conditioned trials in which a test stimulus was preceded by a conditioning stimulus at various interstimulus intervals were randomly intermixed with control trials in which the test or conditioning stimulus was given alone. Several sessions of trials were performed to investigate the entire time course of the effect. Interstimulus intervals between 1 and 10 ms (1, 2, 3, 4, 5, 6, 7, 8, and 10 ms) were used. Ten responses were collected and averaged for each condition in which both stimuli were given, and 20 responses for the control condition. The amplitudes of every single response under each condition were measured so that we could compare statistically the amplitude of control and conditioned responses in the same session using an unpaired Student's *t* test. We calculated a ratio of the mean amplitude of conditioned response to that of control response for each condition. The time course of the effect of a conditioning shock was plotted with this ratio on the ordinate and the interstimulus interval on the abscissa. The mean time course for all the patients was compared with that for normal controls using a two factor analysis of variance (ANOVA). We also compared the mean time course for patients with Huntington's disease with that for normal controls to investigate the changes in motor cortical excitability in Huntington's disease, because one previous study showed reduced intracortical inhibition of the motor cortex in patients with Huntington's disease.¹³

The intracortical inhibition experiments were done on relaxed subjects. Because muscle relaxation is very important for this experiment, subjects were given audiovisual feedback at high gain to assist in maintaining complete relaxation. If any EMG activity (either voluntary or involuntary) was apparent during data collection, the responses were excluded from the analysis. We did not study inhibition in active muscles (Berardelli *et al*¹⁴) because of the difficulty that patients with chorea have in maintaining a constant level of contraction.

The study protocols were approved by the ethics committee of the University of Tokyo. Written informed consent for the study was obtained from all the subjects. No side effects were noted.

Results

The upper part of the figure shows responses from a normal subject on the left and those from a patient with Huntington's disease on the right. The top traces are control responses and the others are conditioned responses at interstimulus intervals of 2, 3, and 4 ms. All the conditioned responses were significantly smaller than the control responses, which indicates that significant suppression occurred at these intervals in both subjects.

The mean (SEM) time courses for normal subjects, all the patients with chorea, and patients with Huntington's disease are shown in the lower part of the figure. The three time courses showed significant suppression at ISIs

The upper part shows responses from a normal subject (left) and those from a patient with Huntington's disease (right). The top traces are control responses and the others are conditioned responses at interstimulus intervals of 2, 3, and 4 ms. All the conditioned responses were markedly smaller than the control responses. The mean (SEM) time courses of the intracortical inhibition are shown in the lower part. Significant suppression was seen at short intervals in every time courses. At interstimulus intervals of 1–5 ms, the area ratios were significantly less than 1.0 in normal subjects ($p < 0.01$: unpaired Student's *t* test). In patients with chorea and patients with Huntington's disease, they were also significantly less than 1.0 (1, 2, 3, 4 ms; $p < 0.01$; 5 ms; $p < 0.05$). These three time courses did not significantly differ from one another (ANOVA: $p > 0.2$).

of 1–5 ms, and they were not significantly different from one another ($p > 0.2$, ANOVA). The mean (SD) average size ratio over the range of interstimulus intervals of 1–5 ms, which is used as a representative value for the intracortical inhibition, was 0.41 (0.19) for normal subjects, 0.47 (0.11) for all the patients, and 0.48 (0.13) for patients with Huntington's disease.

Discussion

Our present results showed that patients with chorea caused by various conditions including Huntington's disease had normal intracortical inhibition of the motor cortex. This confirms our previous result on a much smaller group of patients with chorea.⁹ The finding that γ aminobutyric acid concentrations are increased in the cortex of patients with Huntington's disease¹⁵ also supports the idea that inhibitory mechanisms of the motor cortex are likely to be relatively intact. Based on these findings, we conclude that patients with Huntington's disease who have chorea but no other symptoms have normal intracortical inhibition.

This finding is in striking contrast with the reduced inhibition in several other movement disorders, such as focal hand dystonia,⁸ dyskinesia due to a discrete cerebrovascular lesion in the putamen or globus pallidus,^{9,10} and some parkinsonian patients.^{9,11} It suggests that the pathophysiology of chorea is different from those of the other involuntary movements. Indeed, the similarity of choreic movements to fractions of normal voluntary movements indicates that the chorea may differ in some way from dyskinesia or dystonia. We suggest, as previously proposed by Kanazawa,¹⁶ that chorea is produced by activation of an intact motor cortex by an abnormal or immature trigger pulse generated in the basal ganglia. The fact that some choreic movements are associated with a complete or a part of movement-related cortical potential,¹⁷ which usually precedes a voluntary movement, supports this hypothesis.

Our results are different from those reported by Abbruzzese *et al.*,¹³ who found reduced intracortical inhibition in patients with Huntington's disease. We think that the differences are due to differences in patient selection.

Huntington's disease, particularly in its late stages, produces widespread changes in the CNS, which can be different from subject to subject. Controversial results from measurement of metabolic rate in the sensorimotor cortex of patients with Huntington's disease³⁻⁶ are presumably due to these individual differences in affected areas. As mentioned above, we studied patients with early stage Huntington's disease who had chorea without any signs of involvement of other systems, such as rigidity, spasticity, pyramidal signs, or parkinsonian features. Because of this, we consider that we could study the pathophysiology of chorea unaffected by other disorders of movement. As there are few clinical details for the patients studied by Abbruzzese *et al*,¹³ we cannot definitely conclude that reduced inhibition of their results are caused by involuntary movements other than chorea. However, it is important to note that they found that patients with high dyskinesia rating scores had less intracortical inhibition. Indeed in two asymptomatic patients with Huntington's disease, intracortical inhibition was normal. As patients with high dyskinesia scores are likely to have had more advanced disease, we suspect that they may have had coexisting dystonia or even parkinsonian signs. These other abnormalities may therefore have contributed to the finding of reduced inhibition in their population data. We cannot completely exclude the possibility that severe chorea might reduce intracortical inhibition or that the sensitivity of the paired stimulation method to detect abnormality of cortical inhibition is not good enough to disclose a slight reduction present even in patients with mild chorea. However, judging from the present as well as our previous results,⁹ we conclude that chorea can occur, even in patients with Huntington's disease, in the presence of normal intracortical inhibition studied by a paired stimulation technique. Similar inconsistent findings of a paired stimulation experiment were also seen in Parkinson's disease. Ridding *et al*¹¹ reported reduced inhibition at interstimulus intervals of 1–5 ms and Berardelli *et al*¹⁴ found normal inhibition at these intervals. This difference may be due to the fact that they studied different types and severity of Parkinson's disease or that one study was done on relaxed muscles¹¹ and the other on active muscles,¹⁴ as suggested by Berardelli *et al*.¹⁴ We have also shown similar variable results for this method in Parkinson's disease, but have not found one clinical feature which determines the amount of intracortical inhibition.⁹

An important point to notice is the dissociation between the inhibitory effect studied by paired stimulation and that studied by measuring the duration of the silent period after magnetic stimulation. The silent period is prolonged in patients with Huntington's disease¹⁸⁻²⁰ whereas intracortical inhibition is

normal. This may be explained by an assumption that different subsets of interneurons are involved in the production of the cortical silent period and the inhibition studied with the paired stimulation method (see also Abbruzzese *et al*).¹³ The same dissociation between the behaviour of the silent period and the results of intracortical inhibition has also been seen in Parkinson's disease.¹⁴

Even though it is difficult to draw definite conclusions at this stage, we propose that intracortical inhibition of the motor cortex is normal in chorea of all aetiologies. The implication is that the pathophysiological mechanisms producing chorea are different from those involved in several other involuntary movements.

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