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Task-dependent intracortical inhibition is impaired in focal hand dystonia

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Abstract

We tested whether task-dependent modulation of inhibition within the motor cortex is impaired in patients with dystonia. Paired-pulse transcranial magnetic stimulation (TMS) at an interstimulus interval of 2 ms was used to measure the effect of two different tasks on cortical inhibition (SICI) in dystonic and normal subjects. In two experiments, SICI of the fourth dorsal interosseus (4DIO) and abductor pollicis brevis (APB) muscles were measured prior to and at the end of the training task. In the first experiment, subjects performed a nonselective task consisting of abducting the thumb, where the APB acted as agonist and the 4DIO as synergist. In the second experiment, the function of the 4DIO was changed as the subjects were asked to consciously inhibit this muscle while abducting the thumb (selective task). Therefore, while the APB was activated in both tasks, the 4DIO was activated in the nonselective task but was in the inhibitory surround in the selective task. We found that performance of the selective but not the nonselective task resulted in increased SICI in the 4DIO of normal but not in dystonic subjects. We conclude that task-dependent SICI is disturbed in patients with dystonia.

Keywords

Dystonia; Transcranial magnetic stimulation; Intracortical inhibition

Abbrevations

APB = abductor pollicis brevis muscle; 4DIO = fourth dorsal interosseus muscle; MEP_{APB} = motor evoked potential of the abductor pollicis muscle; MEP_{4DIO} = motor evoked potential of the fourth dorsal interosseus muscle; MT = motor threshold; ISI = interstimulus interval; SICI= short ISI intracortical inhibition

INTRODUCTION

Dystonic movements are characterized by abnormal muscle activity with co-contraction of agonist and antagonist muscles [1,2] and overflow into extraneous muscles [3]. Although the pathophysiology remains unclear, there is considerable evidence from secondary dystonias

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suggesting that the primary abnormality is located in the basal ganglia circuitry [4,5]. In the motor cortex, the activity of intracortical inhibitory neurons may be one mechanism by which the influence of the basal ganglia is manifested because cortical inhibition is abnormal in basal ganglia disorders, like Parkinson's disease [6,7] and Huntington's disease [8]. In dystonic patients, deficient cortical[9–11], spinal cord and brainstem inhibition has been demonstrated[12–17]. Reduced GABAergic inhibition within the primary motor cortex causes abnormal spread of neuronal activity in slice preparations of neocortex [18], co-contraction of antagonist muscles[19] and is thought to be involved in functional linking of cortical representations such as for recruitment of synergist muscles [20]. Correspondingly, reduced intracortical inhibition was demonstrated in muscles acting as agonist and synergist in a motor task [21]. Undesired recruitment of synergistic muscles can be prevented by increasing intracortical GABAergic inhibition [20]. Similarly, consciously inhibiting the recruitment of synergistic muscles results in increased intracortical inhibition of the synergist [21]. These results are supportive of a concept where the selectivity of a motor task is achieved by increasing the intracortical inhibition of the area surrounding the cortical representation of muscles that act as agonist or synergist in the selective task (concept of surround inhibition). Thus, reduced inhibition with a lack of focusing recruitment of the desired muscles may be an important mechanism in dystonia (for review [22,23]).

Intracortical inhibition can be evaluated by paired-pulse transcranial magnetic stimulation (TMS). In this protocol, a weak subthreshold conditioning stimulus is followed by a stronger suprathreshold test stimulus [24]. The conditioning pulse inhibits the responses to the test pulse at short interstimulus intervals (ISI) of 1–6 ms. This is referred to as short intracortical inhibition (SICI). One paradigm to study the role of intracortical inhibition in performance of hand movements in humans exploits the fact that in normal subjects SICI is modulated by the function of the target muscle. In a nonselective task such as abducting the thumb, the abductor pollicis brevis (APB) acts as agonist while the fourth dorsal interosseus muscle (4DIO) acts as synergist. Following this nonselective task, SICI was reduced in both muscles. When subjects were ask to inhibit the 4DIO consciously (with the help of EMG-feedback of that muscle) while abducting the thumb, the function of the former synergist 4DIO was changed to a "surround muscle" as this muscle was now in the inhibitory surround [21]. SICI was increased in the 4DIO ("surround muscle") while decreased in the APB (agonist) following this selective task. In the present study, we used this paradigm to test the hypothesis that in dystonic patients the increase in SICI is impaired when the function of the 4DIO is changed from a synergist to a "surround muscle". Our endpoint measure was task-dependent changes in SICI in the 4DIO and APB. We hypothesized that the selective but not the nonselective task would elicit increased SICI in 4DIO of normal but not in dystonic subjects. SICI in APB served as control.

METHODS

Subjects

All patients with task-specific dystonia referred to the Human Motor Control Section of NINDS, National Institutes of Health, Bethesda, MD, USA were assessed for inclusion in the study. Seven patients with task-specific focal dystonia (one female, age 50.9 ± 3.8; for patient characteristics, Table 1) fulfilled the following inclusion criteria and were included in the study: task-specific dystonia strictly confined to one hand since the onset of symptoms, no dystonic movements at rest, normal MRI scan of the brain, no botulinum toxin injections for at least three months prior to the study, no intake of CNS active drugs, no contraindication for TMS, and ability to perform the selective task. The dystonia affected the right hand in six subjects and the left hand in one, always corresponding to the dominant hand. Consequently, the left hemisphere was studied in six dystonic subjects and the right hemisphere in one. This was compared with the results from the left hemisphere in seven age-matched right handed healthy

controls (four females, age 43 ± 9 years). All studied subjects gave their written informed consent and the protocol was approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke, Maryland, USA and Ethikcommittee of the University Hospital of Duesseldorf, Germany.

Study design

The effect of a nonselective and selective task on SICI was tested in each subject in two separate experiments separated from each other by at least 2 hours (Fig. 1). In the non-selective task, subjects abducted the thumb freely. In this task, the APB, a hand muscle mediating thumb movements in an abduction direction, acted as agonist while the 4DIO, a hand muscle usually co-activated during thumb abduction, could be considered a synergist. In the selective task, subjects abducted the thumb but were asked to consciously inhibit the 4DIO with the help of EMG feedback. In this task, the APB acted as agonist, but the function of the 4DIO was changed to a surround muscle as it was now functionally moved into the inhibitory surround. The order of the two tasks was randomly assigned and balanced across dystonic and normal subjects. Recording electrodes and stimulation sites remained constant throughout the two experiments. MT and intensity of test pulse for each muscle were determined at the beginning of each experiment and the conditioning pulse adjusted accordingly.

Transcranial magnetic stimulation

TMS was delivered from two Magstim 200 stimulators connected via a Bistim module (Magstim Company, UK) through a figure-of-eight-shaped magnetic coil (wing diameter 7.0 cm). The coil was placed tangentially to the scalp and rotated 45° away from the midline. The current induced in the brain was, therefore, directed approximately perpendicular to the central sulcus, which is the optimal condition for transsynaptically activating the corticospinal tract [25,26]. Stimuli were delivered to the optimal scalp position for eliciting MEP in either the APB or 4DIO[21]. Both positions were marked with a soft tip pen directly on the scalp. The MT of each target muscle was determined to the nearest 1% of the maximum stimulator output and defined as the minimum stimulus intensity that evoked an MEP of >50 μV in at least 5 of 10 trials[27].

SICI was tested using paired pulse TMS at an ISI of 2 ms [24]. Ten pairs of stimuli were delivered and interspersed with single stimuli. The sequence of timing of stimuli was controlled by customized software. Conditioning stimulus intensity was 80% of resting MT [24]. The intensity of the test stimulus was set to produce an average MEP of 1 mV [21] that in practice varied from 0.4 – 1.5 mV. EMG was monitored at a gain of 50 μV per division to ensure complete muscle relaxation.

Surface electromyographic (EMG) (bandpass 1 Hz – 1 kHz) activity was recorded from the 4DIO and APB muscles of the dominant hand, using surface electrodes (11 mm diameter) in a belly-tendon montage and a Counterpoint Electromyograph (Dantec Electronics, Denmark) or a preamplifier (Toennis) and data acquisition program (LabVIEW ™, National Instruments Corp., USA).

Training task

Motor training consisted of a brisk abduction of the thumb paced by a metronome at 1 Hz (Fig. 1). For the selective task, auditory and visual feedback of the EMG activity of the 4DIO was explained prior to the experiment and given to the subject at a sensitivity of 50 μV/division during the training. The subject was then asked to abduct the thumb briskly in such a way that the EMG recording of the 4DIO showed no bursts of EMG activity in that muscle during the abduction of the thumb. In the nonselective task, EMG activity of 4DIO was monitored by the investigator to verify that there was synergistic co-activation, but no feedback was given to the

subject. For this intervention, the subject was asked to abduct the thumb briskly. If EMG activity of 4DIO was evident in the selective task, or abduction of the thumb was too slow, the subject was asked to perform better.

Experimental set-up

SICI AT BASELINE—SICI was measured in each subject prior to performing the different tasks (baseline). The 4DIO and APB were tested in two separate sessions. The order of the two testing sessions was randomly assigned and balanced across dystonic and normal subjects. For each muscle the measurements consisted of 10 TMS test pulses alone and 10 conditioned TMS pulses at ISI of 2 ms delivered in random order.

TASK-DEPENDENT CHANGES IN SICI—Following the baseline measurements each subject underwent a 15-min training. After completion of the training the 4DIO and APB were tested again in two separate sessions. The order of the two testing sessions was randomly assigned and balanced across dystonic and normal subjects. For each muscle, the measurements consisted of 10 TMS test pulses alone and 10 conditioned TMS pulses at ISI of 2 ms delivered in random order.

Data analysis and statistical methods

MEP amplitudes were measured off-line. Recordings with EMG background activity were discarded from further analysis. For each recording block, MEP amplitudes evoked at ISI of 2 ms were calculated as the percentage of the mean MEP amplitude evoked by single TMS in that block. Correction for multiple comparisons was done by adjusting the alpha level for the number of comparisons. All data were expressed as mean ± SE.

BASELINE MEASUREMENTS—Separate one-way factorial ANOVAs were used to test the effect of "subject type" (dystonic vs. healthy subject) on age and measures of corticomotoneuron excitability of 4DIO and APB such as MT and intensity of the test stimulus to produce a MEP amplitude of 1 mV. For each muscle, a two-way factorial ANOVA with "conditioned MEP" (MEP amplitude evoked at ISI of 2 ms) as dependent variable and "subject type" (dystonic vs. normal subject) and "Training task" (selective vs. nonselective task) as independent variable was calculated to test whether SICI was different in normal and dystonic subjects prior to the training of the different tasks (baseline).

TASK-DEPENDENT CHANGES IN SICI—The effect of the two different training tasks on SICI of 4DIO and APB was expressed by calculating the ratio between the conditioned MEP amplitudes at baseline (baseline) and at the end of the training (post-training) for 4DIO and APB (Fig 1). The following formula was used: (conditioned MEP_{4DIO} post-training − conditioned MEP_{4DIO} baseline)/(conditioned MEP_{4DIO} post-training + conditioned MEP_{4DIO} baseline); APB: (conditioned MEP_{APB} post-training − conditioned MEP_{APB} baseline)/(conditioned MEP_{APB} post-training + conditioned MEP_{APB} baseline). Therefore, a negative contrast ratio indicates that training increased paired pulse inhibition whereas a positive contrast ratio indicates that training decreased paired pulse inhibition. For hypothesis testing, a repeated measures ANOVA with "Training task" as within group variables and "subject type" as the between group variable was calculated for 4DIO. For post-hoc analysis, two paired (comparison between the two different tasks in normal and dystonic subjects) and two unpaired t-tests (comparison between normal and dystonic groups in each task) were calculated. As a control, similar testing was done for APB (repeated measures ANOVA with "Training task" as within group variables and "subject type" as the between group variable).

RESULTS

Subjects

All patients had their dystonia strictly confined to the hand since the onset of symptoms (duration of symptoms prior to study: 8.4 ± 1.6 months). None of the patients had symptoms at rest or during the experimental tasks. All but one patient had previously been treated with botulinum toxin injections, and all patients were studied at least 3 months after their last injection. The age of the dystonic (50 ± 9 years) and normal (43 ± 9 years) subjects was similar (one way factorial ANOVA:ns).

Training

In the dystonic subjects, no involuntary movements were seen at rest. EMG recording of the APB and 4DIO muscles revealed no EMG activity at rest in the dystonic and normal subjects. In the selective task, all subjects completely relaxed their 4DIO within the first five minutes of training as indicated by the disappearance of EMG bursts in the 4DIO during thumb abduction. No EMG bursts of 4DIO were seen thereafter. For the nonselective task, bursts of 4DIO EMG activity during the thumb abduction were seen throughout the training in all subjects.

Corticomotoneuron excitability and SICI at baseline

At baseline, corticomotoneuron excitability of 4DIO and APB as measured by MT and intensity of the test stimulus to produce a MEP amplitude of about 1 mV (separate one way factorial ANOVAs: ns, Table 2) and SICI of both muscles (two separate two-way factorial ANOVAs: ns) were similar in normal and dystonic subjects.

Task-dependent changes in SICI

For 4DIO, the repeated measures ANOVA with “Training task” as within group variable and “subject type” as the between group variable revealed an effect for “Training task” ($F=12.33$, $p= .005$) but not for “subject type”. The interactions of “subject type” and “Training task” was significant ($F=6.58$, $p= .02$). The interactions of “subject type” and “Training task” indicate that the selective and nonselective task had different effects in dystonic and normal subjects. Following the selective task (Fig. 2A, right panel), but not the nonselective task (Fig. 2A, left panel), the inhibitory effect of the conditioning pulse increased in normal (open bars, paired t-test: $t= 4.09$, $p= .01$) but not in dystonic subjects (filled bars, paired t-test ns). Following the selective task, but not the nonselective task, SICI was significantly greater in normal when compared to dystonic subjects (unpaired t-test: $t = -2.65$, $p= .04$).

In the APB contrast ratios of normal and dystonic subjects were above zero (Fig. 2B) indicating that neither task resulted in an increase in SICI in this muscle. The repeated measures ANOVA with “Training task” as within group variable and “subject type” as the between group variable revealed no effect of either variable in this muscle.

DISCUSSION

The main finding of this study was that in patients with task-specific dystonia performing a highly selective task, cortical GABAergic interneurons in areas representing muscles in the inhibitory surround are disturbed. Because measures of corticomotoneuronal excitability such as MT and intensity of test-stimulus were comparable at baseline the findings cannot be explained by differences in the overall corticomotoneuronal excitability in the two groups. Further, because inhibition was expressed as the percentage of the mean test-amplitude evoked by a single pulse which was kept at a range of 0.4–1.5 mV throughout the experiment, any training induced change in test-MEP was accounted for by adjusting the stimulus intensity of

the test pulse. Cross-talk from adjacent muscles may have reduced the task related effect on cortical inhibition but would not explain the differences between the two groups as the cross-talk from adjacent muscles would likely be similar in the two groups.

The cortical site of the disturbed inhibition in dystonic subjects is supported by the smaller inhibitory effect of the conditioning pulse in dystonic when compared to healthy subjects despite the similarity of corticomotoneuronal excitability in the two groups at baseline. Because there is evidence that the inhibitory effect of the conditioning pulse at short ISIs occurs at a cortical level[28,29] and arises from GABAergic interneurons [30,31] of small areas close to the tested corticospinal neurons[32], our finding at baseline is consistent with the idea that the abnormality in dystonia is in the inhibitory circuits. This role of GABAergic inhibition is supported by primate studies demonstrating co-contraction of antagonist muscles following the injection of bicuculline in the primary motor cortex [19] and by in vitro experiments suggesting that inhibitory circuits are crucial for focusing normal neural activity within the motor cortex [18].

Inhibition within the motor cortex is modulated to maintain or adjust cortical motor representation[21,33]. In replication of previous results in normal subjects,[21] the inhibition in motor cortex as measured with paired pulse technique at short ISIs, decreased when a muscle was co-activated and increased when the function of the same muscle was changed to a surround muscle by consciously suppressing it in a selective task. In the present study, we found that this increased inhibition after training of the selective task is absent in dystonic subjects as indicated by the lack of change in MEP_{4DIO} ratio in the selective task. Thus, although the task was done correctly, the excitability of the motor system was not affected as it was in normal subjects. The lack of change is, therefore, not related to lack of suppression of overt overflow, but shows the abnormality of dystonia.

The absence of an increased inhibitory effect of the conditioning pulse on the conditioned MEP_{4DIO} in dystonic subjects performing the selective task likely reflects disturbance of cortical GABAergic interneurons in areas representing muscles in the inhibitory surround when performing a highly selective task. We hypothesize that this disturbance could result in a failure to focus the desired motor action within the motor cortex (disturbed center- surround inhibition) and may predispose for co-contraction of antagonist muscles and overflow into extraneous muscles in dystonic patients.

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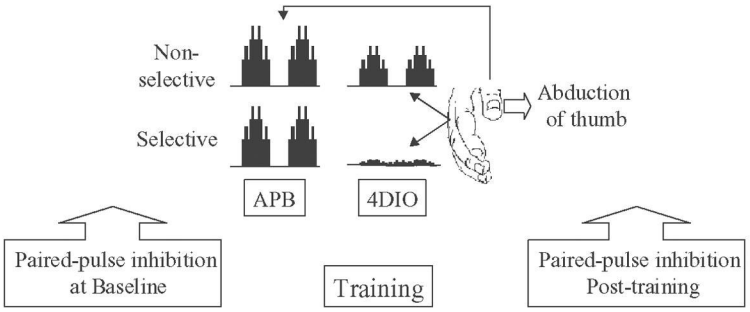

Figure 1.

Experimental set-up: The effect of two different training tasks on paired pulse inhibition in the abductor pollicis brevis muscle (APB) and fourth dorsal interosseus muscle (4DIO) was measured. Paired pulse inhibition was measured prior to and at the end of each training task (large open arrows). In the nonselective task, APB, a hand muscle mediating thumb movements in an abduction direction (small open arrow) acted as agonist while the 4DIO, a hand muscle usually co-activated during the abduction of the thumb acted as synergist (indicated by the schematic drawing of EMG bursts with each movement in APB and 4DIO). In the selective task, subjects abducted the thumb (small open arrow) but were asked to consciously inhibit the 4DIO via EMG feedback (indicated the lack of EMG bursts in 4DIO).

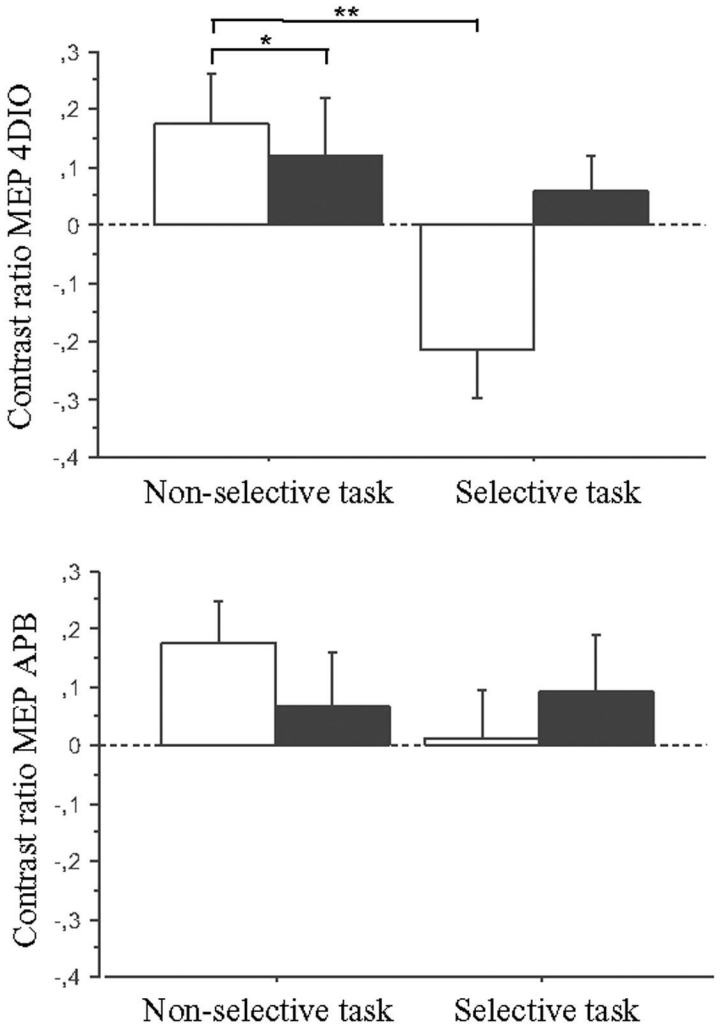

Figure 2.

Effect of training task on SICI of 4DIO and APB in dystonic and normal subjects. **A** Contrast ratios of conditioned MEP_{4DIO} following the selective (right panel) and the non-selective task (left panel). In normal subjects (open bars) training of the selective task, but not the non-selective task resulted in an increase in SICI as indicated by the negative MEP_{4DIO} contrast ratio (right panel, open bar). This effect was not seen in dystonic subjects as indicated by their positive contrast ratio (right panel, filled bar). **B** Contrast ratios of the $MEP_{APB.}$ Training of either the selective task (right panel) or nonselective task (left panel) resulted in a decreased SICI in both groups as indicated by the positive contrast ratios. Mean ± SE, ** p = .01, * p= . 04.

Table 1

Patient characteristics.

Age	Sex	Handedness	Affected side	Task	Dystonic movement	Duration of sympt. (years)	Side of Testing
50	m	right	right	writing	finger extension	9	right
44	m	right	right	playing piano	finger flexion	6	right
51	m	right	right	writing	wrist flexion	11	right
67	m	right	right	playing piano	index finger flex	15	right
57	f	left	left	writing	finger flex	9	left
52	m	right	right	writing	wrist flex	1	right
35	m	right	right	playing guitar	digit 2 and 3 flex	8	right

Abbreviations: f=female, m=male.

Table 2

MT measured at the beginning of each experiment (nonselective and selective task) and intensities of TMS test pulses used in normal and dystonic subjects for measurement of SICI.

	Non-selective task		Selective task	
	normal	**dystonic**	**normal**	**dystonic**
MT (APB)	53.6 ± 10.6	47.9 ± 9.3	53.7 ± 9.9	46.9 ± 8.8
Stimulus intensity (APB)	63.7 ± 11.4	59.7 ± 13.7	62.1 ± 11.9	59.3 ± 12.1
MT (4DIO)	51.2 ± 11.6	45.3 ± 8.8	53.0 ± 10.1	45.9 ± 9.2
Stimulus intensity (4DIO)	61.7 ± 11.1	58.6 ± 10.8	62.4 ± 11.5	61.0 ± 11.9

Stimulus intensities of test pulses and motor thresholds are expressed as percentage of maximal stimulator output (mean ± SD). MT (APB) and MT (4DIO) are the motor thresholds of abductor pollicis brevis and fourth dorsal interosseus muscle.