Double-Pulse Magnetic Brain Stem Stimulation: Mimicking Successive Descending Volleys

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OBJECTIVE—We previously developed a technique using double-pulse BST to elicit MEPs in patients with corticospinal tract lesions by magnetic BST, and even in some normal subjects (Ugawa et al. 1994). For that reason, a powerful method is needed to obtain MEPs to BST even in patients in whom no MEP is elicited by single-pulse magnetic BST.

Herein, we report a novel powerful technique to elicit MEPs by activating the corticospinal tract at the brain stem level using a double-pulse magnetic BST.

METHODS

Subjects

For this study, we recruited 11 right-handed healthy volunteers (8 men and 3 women). The mean ± SD of age and body height of these subjects were, respectively, 37.9 ± 8.4 (28–54) yr and 167.3 ± 5.9 (155–174) cm. We also recruited 12 patients in whom no discernible MEP was evoked by single-pulse magnetic BST, either in the active or relaxed condition, even at the intensity of maximal stimulator output. Of those 12 patients, 3 had amyotrophic lateral sclerosis, 3 had adrenomyeloneuropathy, one had adrenoleukodystrophy, one had cerebrotendinous xanthomatosis, one had familial and one had sporadic spastic paraplegia of unknown etiology, one had multiple sclerosis, and one had cerebral infarction having right hemiplegia. One patient with adrenoleukodystrophy showed progressive ataxia and dementia without defined pyramidal signs. Diagnoses of adrenoleukodystrophy, adrenomyeloneuropathy, and cerebrotendinous xanthomatosis were based on genetic analyses. The diagnoses and clinical features of the patients are presented in Table 1.

Informed consent to participate in this study was obtained from all subjects. The protocol was approved by the Ethics Committee of The University of Tokyo and carried out in accordance with the ethical standards of the Declaration of Helsinki.

Stimulation and recording

HEALTHY SUBJECTS. Subjects were seated comfortably on a reclining chair. Surface electromyographic activities were recorded from the right first dorsal interosseous muscle (FDI) with pairs of Ag/AgCl surface cup electrodes placed in a belly tendon montage. Signals were fed to an amplifier (Biotop GE Marquette Medical System, Tokyo, Japan), with filters set at 100 Hz and 3 kHz, and recorded using computer software (TMS stimulate tester; Medical Systems, Tokyo, Japan) for later off-line analyses.

We performed single-pulse magnetic BST (single BST) as reported previously (Ugawa et al. 1994). Double-pulse magnetic (MEPs) in patients with corticospinal tract lesions by magnetic BST, and even in some normal subjects (Ugawa et al. 1994). For that reason, a powerful method is needed to obtain MEPs to BST even in patients in whom no MEP is elicited by single-pulse magnetic BST.

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Herein, we report a novel powerful technique to elicit MEPs by activating the corticospinal tract at the brain stem level using a double-pulse magnetic BST.
BST (double BST) was given by connecting two magnetic stimulators (Magstim 200; Magstim, Dyfed, UK) linked with a Bistim module (Magstim). A double-cone-coil (type 9902; Magstim) was placed with center of the junction region over the inion. The coil current flowed downward at the junction of the coil so that the maximal current induced in the head flowed upward because this

**TABLE 1. Clinical features of 12 patients**

<table>
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<th>Case</th>
<th>Age/Sex</th>
<th>Disease</th>
<th>Gene Mutation</th>
<th>Duration of Illness, yr</th>
<th>Main Symptom(s)</th>
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<th>FDI</th>
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ALS, amyotrophic lateral sclerosis; ALD, adrenoleukodystrophy; AMN, adrenomyeloneuropathy; CTX, cerebrotendinous xanthomatosis; SP, spastic paraplegia; MS, multiple sclerosis; CI, cerebral infarction; MMT, manual muscle test; FDI, first dorsal interosseous muscle; FFR, finger flexor reflex; N, normal; ↑, exaggerated.

BST (double BST) was given by connecting two magnetic stimulators (Magstim 200; Magstim, Dyfed, UK) linked with a Bistim module (Magstim). A double-cone-coil (type 9902; Magstim) was placed with center of the junction region over the inion. The coil current flowed downward at the junction of the coil so that the maximal current induced in the head flowed upward because this.

**Single-BST**

Control

**ISI=3 ms**

**Double-BST**

**ISI=1.5 ms**

**ISI=5 ms**

**ISI=2 ms**

**ISI=10 ms**

**0.5 mV**

**10 ms**

**FIG. 1.** Representative motor-evoked potential (MEP) waveforms elicited by single brain stem stimulation (BST) and double BST from the first dorsal interosseous muscle in one healthy subject in the relaxed condition. The MEP at an interstimulus interval (ISI) of 2 ms was the largest; those at ISIs of 1.5, 3, and 5 ms were smaller, but still larger than the control MEP.
current direction has the lowest threshold for evoking MEPs (Ugawa et al. 1995). We measured MEPs to double BST in both relaxed (11 subjects) and active (20% of maximum contraction; 8 subjects) conditions. The intensities of single BST and double BST were fixed at the resting motor threshold (RMT) in relaxed condition experiments and at the active motor threshold (AMT) in active condition experiments. For this study, RMT was defined as the lowest intensity that evoked a response of >50 μV in more than half of the trials. Similarly, AMT was defined as the lowest intensity that evoked a smaller response (<200 μV) than the prestimulus background activity in more than half of the trials. The interstimulus intervals (ISIs) were 1.5, 2, 3, 5, and 10 ms. In one session, trials in which double stimuli were given at various ISIs were intermixed randomly with control trials in which a single stimulus was given. Several sessions of trials were performed to construct the time course of MEP size. Eight trials were recorded for the double BST condition at each ISI and 10 trials in the control condition. For each trial, we measured the mean peak-to-peak amplitude of MEP. At each ISI, we calculated the ratio of the mean amplitude of MEP elicited by double BST to that of control MEP (single BST). The time course was shown with the mean ratio on the ordinate and the ISI on the abscissa.

The latencies were measured from MEPs having a stable latency. Then, the onset latency of MEP to double BST at the most effective ISI in relaxed muscles was compared with that of single BST MEP in active muscles (the intensity of 120–150% AMT was used in single BST for comparison of latency). The onset latency of MEP to double BST was measured from the time of second pulse in double BST experiments.

PATIENTS. Surface electromyographic activities were recorded from the FDI on the more affected side. We performed double BST using an ISI of 2 ms in the relaxed condition in the patients because in this condition an ISI of 2 ms is best for enhancing MEPs in healthy subjects (see RESULTS). We collected four to six MEPs to double BST at the intensity of maximal stimulator output for each patient. We also measured the central motor conduction time (CMCT) in each patient. For this purpose, we measured the onset latency of MEP elicited by transcranial magnetic stimulation (TMS) over the contralateral hand motor area using a round coil (10-cm diameter) placed over the cervical spinal enlargement (Ugawa et al. 1985; Rossini et al. 1994). The onset latency of MEP to magnetic spinal motor root stimulation (Root) was also measured by activating cervical spinal nerves with a round coil (10-cm diameter) placed over the cervical spinal enlargement (Ugawa et al. 1989). In addition, CMCT was calculated by subtracting the spinal latency from the cortical latency (Rossini et al. 1994). The cortical–brain stem and brain stem–spinal conduction times were obtained by subtracting the brain stem latency from the cortical latency and the spinal latency from the brain stem latency. We compared present results with the normal values described in a previous study (Iwata et al. 2008). We correlated these conduction times with clinical features or the pyramidal tract lesion sites demonstrated by MRIs.

Statistical analyses

In healthy subjects, the time course of MEP enhancement was analyzed using one-way ANOVA with the factor of ISI (1.5, 2, 3, 5, 10 ms, and control). Post hoc analyses were carried out using Dunnett’s t-test. The latencies of MEPs elicited by double BST at an ISI of 2 ms in a relaxed condition and single BST in an active condition were compared using paired t-test: P values <0.05 were inferred as significant.

RESULTS

Healthy subjects

In the relaxed condition, MEPs were elicited by single BST at RMT level in 10 subjects. However, in one subject, stimulation even at the maximal stimulator output failed to evoke discernible MEPs. This subject was excluded from analysis of the MEP amplitude ratio of double BST to single BST. In the active condition, MEPs were elicited by single BST at the AMT level in all eight subjects studied. The RMT was 97.3 ± 5.2% (mean ± SD) of the maximal stimulator output; AMT was 68.3 ± 10.6% in single BST. Figure 1 portrays the waveforms of double BST elicited at an intensity of 100% in a single representative healthy subject in the relaxed condition. The MEP to double BST was greatest at an ISI of 2 ms; those at ISIs of 1.5, 3, and 5 ms were smaller than those at 2 ms but still larger than the control MEP. Similar effects were obtained in other subjects. Figure 2A depicts the individual amplitudes of MEPs evoked by single BST and double BST in the relaxed condition. Figure 2B shows the mean size of MEP to double
BST normalized to that to single BST against the ISI for all healthy subjects. The amplitude of MEP to single BST at the intensity of RMT (control MEP) was 20 ± 20 μV (mean ± SD). The ratio of amplitudes at an ISI of 2 ms was 15.7 ± 6.1 (mean ± SE). Subsequently, ANOVA showed that the ISI had a significant effect on the MEP size in the relaxed condition \(F(5,47) = 4.798, P = 0.001\). Post hoc analysis revealed the MEP size was significantly enlarged at an ISI of 2 ms \(P < 0.001\).

On the other hand, in the active condition, the MEP size was almost identical to that of control MEP across all ISIs (Figs. 3 and 4). No significant facilitation was observed at any interval; ANOVA failed to show any significant effect of the interval on the MEP size \(F(5,37) = 0.264, P = 0.930\).

In each healthy subject, the onset latency of MEP to double BST at an ISI of 2 ms in the relaxed condition was identical to that to single BST in the active condition (Fig. 5). The mean \((± SD)\) onset latencies of MEPs to both double BST in relaxed muscles and single BST in active muscles were 17.3 ± 0.9 ms. Paired \(t\)-test showed no significant difference \((P = 0.809)\).

**Patients**

Table 2 presents results of double BST in 12 patients. The CMCT was prolonged in 10 patients and within normal range in cases 2 and 3. Double BST at an ISI of 2 ms in the relaxed condition elicited MEPs in 8 of the 12 patients (cases 1, 2, 4, 5, 8, 9, 10, and 12) who had no MEPs to single BST with maximal stimulator output in active muscles.

The corticospinal tract involvement was revealed by our method in some patients in whom such lesions were not detected by MRI in structure. The cortical–brain stem conduction time was prolonged in cases 1, 4, and 8, even though no structural abnormality was detected using brain MRI. The brain stem–spinal conduction time was prolonged in cases 1, 5, and 8 in spite of normal cervical MRI.

**Case report: case 5**

To demonstrate the clinical utility of double BST, we present case 5, from which double BST provided us with clinical useful information that would have been otherwise unobtainable using conventional stimulation methods.

The patient noticed dysesthesia and weakness in both legs at age 25. Symptoms worsened progressively; he was unable to run and showed urinary incontinence at the age of 27. Three years later, at age 30, he was admitted to our hospital. Neurological findings showed spastic paraplegia with hyperreflexia and positive Babinski signs, diminished superficial and deep sensation, and urinary incontinence. Conventional TMS studies showed delayed cortical latency with normal cervical latency, i.e., prolonged CMCT (13.0 ms, upper limit of normal values 8.0 ms) (Fig. 6). Single BST elicited no MEPs in active or relaxed conditions. Double BST at an interval of 2 ms elicited clearly defined MEPs (17.6 ms). Both the cortical–brain stem (7.8 ms, upper limit of normal values 4.1 ms) and brain stem–spinal conduction times (5.2 ms, upper limit of normal values 5.0 ms) were prolonged, suggesting the corticospinal tract involvement both at intracranial and extracranial segments. Subsequently, MRI yielded longitudinal high-intensity lesions along the pyramidal tract on T2-weighted images of the brain, but no abnormal findings in the spinal cord. The patient was diagnosed as having adrenoleukodystrophy (adrenomyeloneuropathy type) based on the remarkably increased serum very long chain fatty acids and the mutation of the ABCD1 gene. Physiological examination revealed not only a severe intracranial involvement of the corticospinal tract, compatible with the notable findings on brain MRI, but also an extracranial involvement despite the lack of cervical MRI abnormalities.

**Single-BST**

Control

**ISI=3 ms**

**Double-BST**

**ISI=1.5 ms**

**ISI=5 ms**

**ISI=2 ms**

**ISI=10 ms**

\(0.5 \text{ mV}\)

\(10 \text{ ms}\)

**FIG. 3.** Representative waveforms in an active condition. The top left trace portrays the MEP waveform in control trials (single BST). The other traces give MEP waveforms to double BST at ISIs indicated on the left. No significant enlargement of MEP is apparent at any ISI.
DISCUSSION

Using the technique of double BST, we obtained maximal enlargement of MEPs at an ISI of 2 ms in the relaxed condition, which reached ~15-fold as large as that to single BST. The enlargement gradually decreased with increasing ISI and returned to the baseline level (MEP size to single BST) at an ISI of 10 ms. The onset latency was the same for single BST and double BST. Double BST in the relaxed condition is a powerful new method to elicit MEPs in patients with corticospinal tract involvement. We propose that this new method is useful to evaluate the corticospinal tract involvement, even in patients from whom single BST cannot elicit discernible MEPs.

Mechanism of MEP enlargement

In this study, MEPs in the relaxed condition were maximally enhanced at an ISI of 2 ms. Previous reports of animal and human studies using cortical and spinal stimulation have described that double or repetitive stimuli at an ISI of 2 ms are suitable for enhancing motor responses (Bannister and Porter 1967; Calancie et al. 1998; Muir and Porter 1973; Taniguchi et al. 1993; Taylor BA et al. 1993). The studies of animals and humans described earlier revealed that the temporal summation of EPSP at the spinal cord level might be maximal at an interval of 2 ms because facilitation within the cortex does not contribute in the anesthetized condition. Taylor JL et al. (2002) performed double-pulse electrical BST in three awake healthy subjects. They recorded MEPs from biceps brachii muscle and observed MEP facilitation at ISIs of 2 and 3 ms (Taylor JL et al. 2002). Although all these studies used electrical and not magnetic stimulation, the physiological mechanisms of electrical and magnetic BSTs are fundamentally identical (Ugawa 1999). We interpreted our present results based on those previous findings. Our present finding—that the 2-ms interval led to maximal MEP enhancement—is consistent with results of these previous studies. The BST produces a single descending volley in the corticospinal tract axons (Ugawa et al. 1994). Then no intervening synapse is present until the volley reaches the spinal MNs. The MEP facilitation at the 2-ms interval is expected to be produced by EPSP summation at this synapse. Based on these arguments, we conclude that the MEP enhancement in double BST is produced by the temporal EPSP summation at the spinal cord level. One conspicuous point is that 2 ms is almost identical to the interval between successive descending volleys produced by cortical stimulation either using electrical or magnetic stimulation. That is, double BST at an interval of 2 ms might mimic successive descending volleys elicited by single pulse cortical stimulation (artificial successive descending volleys).

Innovative Methodology

DOUBLE-PULSE MAGNETIC BRAIN STEM STIMULATION

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FIG. 4. Effects of the interval of double BST on the MEP size in an active condition. Conventions are as described for Fig. 2. The MEPs to double BST do not significantly differ in size from those to single BST at any ISI.

B MEP size ratio (double-BST/single-BST)

FIG. 5. Correlation of MEP latency between single BST and double BST. The abscissa gives the MEP latency to single BST in the active condition. The ordinate shows the MEP latency to double BST at an ISI of 2 ms in the relaxed condition. The plots approximately fall on the slanted line of unison, which shows that the latency was equal for the 2 stimulation methods.
Several issues related to temporal summation of spinal EPSP

Why does MEP enlargement last for 10 ms? The single descending volley produced by the first BST is considered to depolarize a part of the spinal MN pool subliminally along with activation of a considerable number of neurons. The temporal EPSP summation at such subliminally depolarized spinal MNs by the following descending volley produced by the second BST would induce activation of MNs. The duration of MEP facilitation is expected to indicate the duration of EPSP at the spinal MNs if

<table>
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<td></td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>7</td>
<td>11.3 †</td>
<td>Not detected</td>
<td></td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>8</td>
<td>10.9 †</td>
<td>4.6 †</td>
<td>6.3 †</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>9</td>
<td>17.1 †</td>
<td>7.9 †</td>
<td>9.2 †</td>
<td>(±); subcortical abnormal intensity</td>
<td>(++); spinal cord atrophy</td>
</tr>
<tr>
<td>10</td>
<td>8.1 †</td>
<td>3.7</td>
<td>4.4</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>11</td>
<td>13.0 †</td>
<td>Not detected</td>
<td></td>
<td>(+); multiple plaques</td>
<td>(++); multiple lesions</td>
</tr>
<tr>
<td>12</td>
<td>12.5 †</td>
<td>8.6 †</td>
<td>3.9</td>
<td>MCA area</td>
<td>(−)</td>
</tr>
<tr>
<td></td>
<td>Mean ± 2.5SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.0 ± 0.4</td>
<td>3.3 ± 0.3</td>
<td>3.7 ± 0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CMCT, central motor conduction time; BST, brain stem; Root, spinal nerve root; MCA, middle cerebral artery.

Several issues related to temporal summation of spinal EPSP

Why does MEP enlargement last for 10 ms? The single descending volley produced by the first BST is considered to depolarize a part of the spinal MN pool subliminally along with activation of a considerable number of neurons. The temporal EPSP summation at such subliminally depolarized spinal MNs by the following descending volley produced by the second BST would induce activation of MNs. The duration of MEP facilitation is expected to indicate the duration of EPSP at the spinal MNs if

![Graphical representation of MEPs in case 5 with adrenomyeloneuropathy. The top trace shows an average MEP elicited by transcranial magnetic stimulation (TMS) over the hand motor area. The cortical latency was 25.4 ms. The bottom trace shows MEP to magnetic spinal motor root stimulation (Root). The cervical latency was 12.4 ms. Therefore the central motor conduction time 13.0 ms (upper limit of normal values 8.0 ms) was abnormally prolonged. Single BST evoked no MEPs in active or relaxed conditions. Nevertheless, double BST at an ISI of 2 ms elicits MEPs (the 4th trace) (BST 17.6 ms). Both the cortical-brain stem and brain stem–spinal conduction times were prolonged. The findings suggest corticospinal tract involvement at both the intracranial and spinal cord levels.](http://jn.physiology.org/)

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DOUBLE-PULSE MAGNETIC BRAIN STEM STIMULATION

Innovative Methodology

Discomforts associated with double BST

The discomfort produced by double stimulation is one problem of this method. Some subjects described that the double stimulation gave a more uncomfortable feeling than single stimulation at the same intensity, but it was tolerable. Some others felt similar discomfort in both stimulations and single stimulation at the same intensity, but it was tolerable. Although we did not use a rating scale for formal assessment, double BST was considerably less painful than electrical stimulation and was tolerable by the participants.

Clinical advantages and issues of double BST

Based on the results of healthy subjects, we applied double BST at an ISI of 2 ms to patients whose MEPs were unobtainable using single BST. In 8 of the 12 patients, we were able to obtain MEPs using the new method presented herein.

In patients with corticospinal tract involvement, single BST sometimes fails to elicit any MEP. Both the abnormally high threshold for corticospinal tract activation and the difficulty in maintaining voluntary contraction of the involved muscles might explain the lack of MEPs to BST. Double BST is useful because it enables us to obtain MEPs to BST in the relaxed condition, as shown here.

The greatest merit of obtaining MEPs to BST is to localize a corticospinal tract lesion by detecting conduction delays. In cases 9 and 12, the localization was compatible with the lesion sites demonstrated by imaging techniques. In several cases of degenerative disorders (cases 1, 4, 5, and 8), this technique can localize lesions that could not otherwise be localized by imaging methods.

In fact, MEP enhancement with double BST was largest at an ISI of 2 ms in healthy subjects. However, it is unknown whether the interval of 2 ms is also optimal for patients with corticospinal tract involvement. Further investigation is necessary to determine the best ISI for patients with cortical spinal tract involvement.

In conclusion, double BST at an ISI of 2 ms in the relaxed condition enhances MEPs both in healthy subjects and in many patients with no MEPs to single BST. By virtue of the improved localization obtained using this method, we can expand the usefulness of BST in patients with neurological disorders.

GRANTS

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REFERENCES


This mechanism is the main reason for MEP facilitation. Then, the time course of MEP enlargement suggests that EPSP at the MNs lasts nearly 10 ms. This estimation is compatible with the EPSPs recorded from the spinal MNs after activation of the pyramidal tract in the baboon (Landgren et al. 1962).

Why is the MEP latency to double BST in relaxed muscles the same as that to single BST in active muscles? We also showed that the latency of MEP to the second pulse of double BST is the same as that to single BST in each healthy subject. Previous studies (Ugawa et al. 1991, 1994) reported that the MEP latency to single BST was the same in both the active and the relaxed conditions because BST induces a single descending volley, irrespective of the state of muscle activation. For double BST, the MEP latency from the time of second BST is identical to the MEP latency to single BST. The identical latencies are explainable by a single descending volley induced by either type of BST (Ugawa et al. 1994). Therefore double BSTs in the relaxed condition are applicable to clinical practice by comparing them with normal values of MEP latency to single BSTs.

Why is MEP enlargement not observed in the active condition? One possible explanation for the lack of MEP enhancement in the active condition is that some part of spinal MNs has already been activated subliminally by voluntary contraction. Therefore subliminal depolarization by the first BST cannot add more depolarization that is sufficiently effective to engender firing. Another possibility is that antidromic volleys induced by the first BST might collide with some descending impulses conveying voluntary command from the cortex to the brain stem. This collision might eliminate some part of the subliminal activation induced by voluntary contraction of the target muscle. The already present subliminal depolarization of some MNs before the first BST and the collision between voluntary command descending volleys and ascending antidromic volleys by the first BST might reduce the effectiveness of the first BST for subliminally activating the MN pool.

However, we cannot deny the possibility that BST activates fewer descending fibers because of the lower intensity in the active condition or the variance of the MEP size leads to difficulty in maintaining muscle contraction might mask the expected facilitation. Therefore an experiment using the stimulation at higher stimulus intensities in the active condition or the experiment investigating MEP size at various levels of muscle contraction might be useful for explaining the lack of MEP enhancement.


