



Research article

Motor point stimulation primarily activates motor nerve

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ABSTRACT

Electrical stimulation for inducing muscle contraction can be divided into peripheral nerve stimulation (PNS) and motor point stimulation (MPS). Although the neural pathways activated by PNS have been well studied, those by MPS are still unclear. Here we investigated whether MPS activates Ia-sensory nerves and induces antidromic firing of motor nerves. Ten able-bodied males and females participated in this study. We confirmed that soleus MPS did not induce the H-reflex while soleus PNS did. Furthermore, MPS of the tibialis anterior muscle did not induce the reciprocal inhibition of soleus muscle while PNS did. For testing the effect of MPS on motor neuron excitability, we examined the H-reflex modulation by soleus MPS. When the conditioning and test interval was under 100-ms and the conditioning stimulus intensity was above 30-mA, soleus MPS induced the H-reflex inhibition. This suggests that soleus MPS produces antidromic firing that can induce after-hyperpolarization. These results suggest that MPS predominantly activates the motor nerve without depolarizing the Ia-sensory nerve. Since MPS is applicable to larger number of muscles compared to PNS, utilizing MPS can lead to more versatile neuromodulation of the spinal cord.

1. Introduction

Electrical stimulation of muscles for inducing muscle contraction can be delivered in two ways: peripheral nerve stimulation (PNS) and motor point stimulation (MPS). PNS is delivered to a superficial nerve trunk at a location that is often distant from the target muscle innervated by the nerve. MPS is applied to the most responsive location over a muscle belly (i.e., motor point).

The neural pathways activated by PNS have been studied extensively. PNS activates both the sensory and motor nerves, thereby, inducing two separate responses. The motor nerve activation induces an early muscle response called the M-wave, which travels from the stimulation location to the muscle, while the activation of the Ia-sensory nerve induces late muscle response called the H-reflex, which travels from the stimulation location to the spinal neural circuit and then to the muscle. Contrarily, only a few studies have investigated the neural pathway activated by MPS [1–3,13] even though MPS has been

regularly used in clinical settings, which is called functional electrical stimulation (FES) [10,15]. The overall objective of this study was to investigate the neural pathway activated by MPS.

Bergquist and colleagues (2011a; 2012) showed that unlike PNS, MPS did not evoke any prominent H-reflex at any stimulus intensities. This implied that MPS did not activate the Ia-sensory nerve. MPS probably activates only superficial nerve terminals at the neuromuscular junctions that are densely distributed at around motor points within a muscle [8,16], but not nerve trunk located in deeper area of the limb. On the other hand, the anatomical distribution of the Ia sensory nerves are not known, while under an assumption that they are evenly distributed within the muscle, MPS may primary activate motor nerves due to the difference in spatial distribution of the motor nerve terminals and Ia-sensory nerves. Therefore, as the first step in investigating how MPS activates the neural circuit, we aimed to (1) test whether MPS induces reciprocal inhibition via Ia-sensory nerve, and (2) examine the effect of MPS on the motor neuron excitability via the

Abbreviations: PNS, peripheral nerve stimulation; MPS, motor point stimulation; FES, functional electrical stimulation; EMG, electromyography; SOL, soleus; TA, tibialis anterior

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antidromic firing on motor nerves.

To test the first aim, we examined the reciprocal inhibition from the tibialis anterior muscle to the soleus muscle. The activation of Ia-sensory nerve induces the inhibition to the antagonist muscle. This is called reciprocal inhibition. If the MPS does not induce reciprocal inhibition, that would indicate that MPS does not activate the Ia-sensory nerves. In the lower leg setting, PNS on the common peroneal nerve, which activate Ia-sensory nerve of the tibialis anterior muscles is often utilized to induce reciprocal inhibition of the soleus muscle [5,9,12,14] because the H-reflex of the tibialis anterior muscle is hardly evoked in the resting condition [5]. To test the second aim, we used MPS as the conditioning stimulation, and examined the H-reflex modulation.

2. Materials and methods

2.1. Participants

Ten able-bodied participants (4 females and 6 males; mean age 26 ± 6 years) with no known history of neurological or musculoskeletal impairments participated. This study consisted of four experiments (Experiment 1, 2, and 3), which were completed by all participants. The experiments were conducted in accordance with the Declaration of Helsinki and were approved by the Research Ethics Board of the University Health Network in Toronto, Canada. All participants gave written informed consent to participate in the study after receiving a detailed explanation about the purposes, benefits, and risks associated with participation in the study.

2.2. Electrical stimulation

Fig. 1 shows the location of stimulation and recording electrodes on the soleus (SOL) and tibialis anterior (TA) muscles. In Experiment 1, a single channel constant current electrical stimulator (DS7A, Digitimer, Welwyn Garden City, UK) was used in a monopolar configuration with a 1-ms pulse duration to deliver MPS and PNS. In Experiment 2 and 3, an additional single channel constant current stimulator (ISO-Flex and Master-8, A.M.P.I., Jerusalem, Israel) was used in a monopolar configuration with a 1-ms pulse duration to deliver conditioning stimulation.

For PNS on the SOL muscle, stimulation was applied on the

posterior tibial nerve. The stimulator was triggered via TTL pulses programmed using a custom script. Surface electrodes (Axelgaard, Fallbrook, USA) were used to deliver the electrical stimulation. The anode was a 5×5 -cm square electrode, and the cathode was a circular electrode with a 3.2-cm diameter. The anode was placed on the anterior aspect of the thigh above of the patella, and the cathode was placed over the posterior tibial nerve in the popliteal fossa where the motor threshold was the lowest.

For PNS on the TA muscle, surface electrodes of the same dimensions as above were used. PNS was delivered to the deep peroneal nerve. The cathode was placed distally and ventrally to the head of the fibula and the anode was placed ~ 2 -cm proximal and ventral to the head of the fibula [14]. The stimulation site was selected to minimize the activation of the peroneus muscles at maximal TA activation. The absence of peroneus muscles activity was confirmed by visual inspection.

For MPS on SOL and TA, circular electrodes with a diameter of 3.2 cm were used (Axelgaard, Fallbrook, USA). For SOL the cathode was placed over the motor point of the lateral side of SOL. The anode was located on the motor point of the medial side of SOL. For TA MPS, the cathode was placed over the motor point at the middle of TA and the anode was placed parallel to the muscle fiber direction with an inter-electrode distance of ~ 1 -cm. Using a hand-made pen-style electrode with approximately 1-cm diameter stimulating ball end, which was fed from Digitimer DS7A, the motor point was identified as the location where the target muscle was activated with the lowest motor threshold for SOL and TA. The motor threshold was defined as the minimum stimulation intensity to produce a muscle twitch that can be observed by visual inspection and palpation.

2.3. Electromyography (EMG)

EMG signals were recorded from the SOL and TA, and the peroneus muscles using adhesive foam circular electrodes (1.89 cm, Covidien, Mansfield, MA, US) in a bipolar configuration. Note that the EMG from peroneus muscle were used only to optimize the location of stimulation electrode. The recording electrodes for SOL were placed on the muscle belly at one third the distance from the lateral malleolus to the head of the fibula. EMG from TA was recorded from the muscle belly at a point 6–10 cm distal and ventral to the head of the fibula. The common reference electrode was placed on the right lateral malleolus. EMG signals were amplified 500-times and band-pass filtered between 10 and 1000-Hz using an EMG amplifier (AMT-8 System, A-Tech Instruments, Toronto, Canada). All EMG and trigger signals were collected using an A/D converter system (Power lab /30 Series, ADInstruments, Colorado Springs, USA) at 40-kHz.

2.4. General protocol

We conducted three experiments over two sessions separated by a minimum of 48-hs. One session lasted no longer than two hours. At Session 1, we conducted Experiment 1 to record the recruitment curve for MPS and PNS [2,3] and Experiment 2 to test reciprocal inhibition between TA and SOL. At Session 2, we conducted Experiment 3 and 4 to examine the effect of MPS on motor neuron excitability by varying stimulation timing (Experiment 3) and stimulus intensity (Experiment 4). The orders of Sessions and Experiments was randomized and counterbalanced among participants. The participants were instructed not to perform vigorous physical activity the day before the first session and in the intervening days between experimental sessions.

In each Experiment, an electrical dynamometer (Biodex System 3, Biodex Medical Systems, Shirley, NY, USA) was used to fix the participant's position and joint angles and hold the leg and foot in place. The participant was seated in the Biodex, with the right leg flexed at the hip (110°), knee (120°), and ankle (plantarflexed at 110°). The right foot was strapped to a foot plate. The participant was instructed to relax and

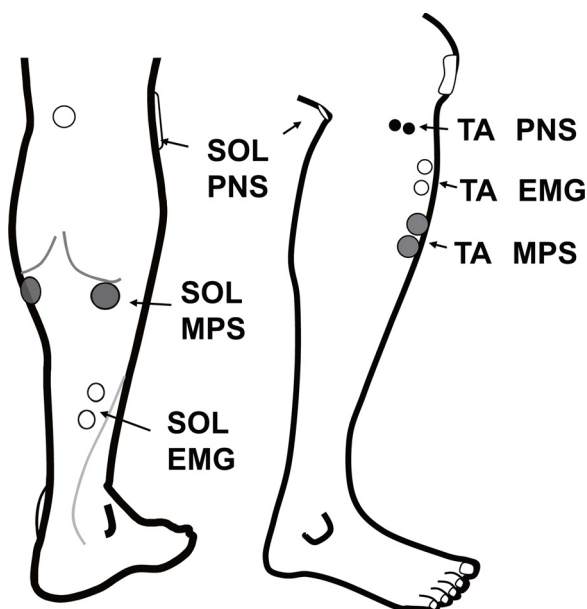


Fig. 1. Stimulation (motor point stimulation: MPS and peripheral nerve stimulation: PNS) and recording electrodes for soleus (TA) and tibialis anterior (SOL) EMG.

not contract the muscles of the right leg.

2.5. Experiment 1: recruitment curve of M-wave and H-reflex of soleus muscle evoked by MPS and PNS

The recruitment patterns of H-reflex and M-wave were recorded separately for MPS and PNS. The stimulus intensity was initially set at a sub-motor threshold level and was gradually increased by increments of 2-mA until the M-wave reached a plateau. Then, stimulus intensity was increased in 10-mA increments up to 100-mA to elicit the supra-maximal M-wave (Mmax).

The main measurements from the recruitment curve were the maximal amplitudes of H-reflex (Hmax) and Mmax. Each of Hmax and Mmax was compared between the MPS and PNS using a paired *t*-test with the significance level of 5%.

2.6. Experiment 2: reciprocal inhibition by MPS and PNS

In order to test reciprocal inhibition, MPS or PNS was applied on TA as the conditioning stimulation and PNS on SOL as the test stimulation (i.e., conditioning-test paradigm). The test stimulus intensity was set to evoke a SOL H-reflex equal to 5% of Mmax amplitude [11]. For both the MPS and PNS, the conditioning stimulus intensity was set to the motor threshold and comprised single rectangular pulses with a 1-ms duration [14].

The conditioned and unconditioned H-reflexes were randomly examined. The inter-stimulus intervals (ISIs) for the conditioned reflexes ranged from -1 to 3-ms, where a positive interval indicates leading conditioning stimulation. For each condition and each ISI, 12 reflexes were evoked and averaged to represent the participant's value. For each participant, the values of the conditioned H-reflexes were normalized to the unconditioned value. Neither the conditioning nor the test stimulation evoked measurable M-waves because of their low intensity.

One sample *t*-tests with Bonferroni correction were used to assess whether the conditioned H-reflexes for MPS and PNS differed from 100 %, which is the normalized unconditioned value.

2.7. Experiment 3: effect of MPS on H-reflex, dependence on inter-stimulus interval

In order to test the effect of MPS on H-reflex and its ISI dependency, the conditioning-test paradigm was applied with MPS on SOL as the conditioning stimulation and PNS on SOL as the test stimulation. Prior to the experiment, recruitment-curves of M-wave and H-reflex were constructed using the same method as Experiment 1 to obtain the Hmax and Mmax on the session day. The H-reflex amplitude for the test stimulation was set to 80 % of Hmax, and the intensity of MPS for the conditioning stimulation was set to 80 % of SOL Mmax. The ISI of the paired pulses increased from 50 to 200-ms with a 50-ms increments, with leading conditioning stimulation. Five test reflexes were recorded at each ISI. Additionally, M-wave amplitudes from the test and conditioning stimulation were calculated.

The conditioned SOL H-reflexes were normalized relative to the unconditioned H-reflexes. One sample *t*-tests with Bonferroni correction were used to test whether the normalized H-reflex amplitudes differ from 100 % or not, at each ISI. M-wave amplitude inform the test stimulation was normalized to Mmax for PNS, and we analyzed the normalized amplitude with a one-way repeated-measures ANOVA for four ISIs: 50, 100, 150, and 200-ms. M-wave amplitude from conditioning stimulation was normalized to Mmax for MPS and, analyzed with a one-way repeated-measures ANOVA for four ISIs: 50, 100, 150, and 200-ms).

2.8. Experiment 4: effect of MPS on H-reflex, dependence on stimulus intensity

Similar to Experiment 3, the conditioning-test paradigm was applied with SOL MPS as the conditioning stimulation and SOL PNS as the test stimulation. The ISI between conditioning and testing stimulation was fixed at 50-ms, with leading conditioning stimulation. The intensity of conditioning stimulation was increased from 10 to 100-mA with an increment of 10-mA. Five H-reflexes were recorded at each intensity. Additionally, M-wave amplitudes from test and conditioning stimulation were also calculated.

The conditioned SOL H-reflexes were normalized to the amplitude of the unconditioned H-reflexes. One sample *t*-tests with Bonferroni correction were used to test whether the normalized H-reflex amplitudes differed from 100 %, at each intensity. M-wave amplitude from test stimulation was normalized to Mmax for PNS. For statistical analysis, we analyzed using a one-way repeated-measures ANOVA for all intensities. M-wave amplitude for conditioning stimulation was normalized to Mmax for MPS, and we analyzed using a one-way repeated-measures ANOVA for all intensities. When a main effect was detected, one sample *t*-tests with Bonferroni correction were used to test whether the normalized M-wave amplitudes differed from 100 % or not, at each intensity.

3. Results

3.1. Experiment 1: recruitment curve of M-wave and H-reflex evoked by MPS and PNS

Fig. 2 shows the recruitment curves of M-wave and H-wave as well as selected waveforms for a representative participant for the SOL PNS (A) and SOL MPS (B). Fig. 2 also shows the group data for the MPS recruitment curves (C) and Mmax and Hmax (D). SOL PNS evoked clear H-reflexes (Fig. 2A), which were observed in all participants (Fig. 2D). On the other hand, SOL MPS did not evoke clear H-reflex although small potentials were observed at a similar onset to that of the H-reflex (Fig. 2B). Hmax was significantly larger for SOL PNS compared to SOL MPS ($p < 0.001$) while there was no significant difference in Mmax between PNS and MPS ($p = 0.13$) (Fig. 2D).

3.2. Experiment 2: reciprocal inhibition by MPS and PNS

The averaged intensities of conditioning stimulation for TA PNS and TA MPS were 6.9 ± 3.6 -mA and 6.8 ± 3.3 -mA, respectively. Fig. 3 shows the averaged waveforms of the conditioning and unconditioned H-reflexes (A) and the normalized amplitude of SOL H-reflex conditioned by TA PNS or TA MPS (B). Only TA PNS at ISI of 0-ms induced significant reciprocal inhibition ($p = 0.01$). With the other ISIs, TA PNS did not induce significant reciprocal inhibition (-1 ms: $p = 0.74$, 1 ms: $p = 0.13$; 2 ms: $p = 0.10$, 3 ms: $p = 0.11$). TA MPS did not induce significant inhibition at any of the ISIs for MPS (-1 ms: $p = 0.46$, 0 ms: $p = 0.34$, 1 ms: $p = 0.62$, 2 ms: $p = 0.73$, 3 ms: $p = 0.42$).

3.3. Experiment 3: effect of MPS on H-reflex, depending on inter-stimulus interval

Fig. 4 represents an example of the changes in waveform for a representative participant (A), the group data of normalized H-reflex amplitude (B), and the group data of normalized M-wave amplitude depending on the ISI. The shorter ISI was, the smaller the H-reflex amplitude became (Fig. 4A). The normalized H-reflex amplitudes were significantly smaller than 100 % (i.e., unconditioned H-reflex amplitude) at the 50-ms ($p < 0.001$) and 100-ms ($p < 0.001$). As for M-wave amplitude of the test stimulation (PNS), one-way ANOVA with repeated measures showed that there was no main effect of ISI ($F_{(3, 24)} = 1.80$, $p = 0.17$). There was also no main effect of ISI on the M-

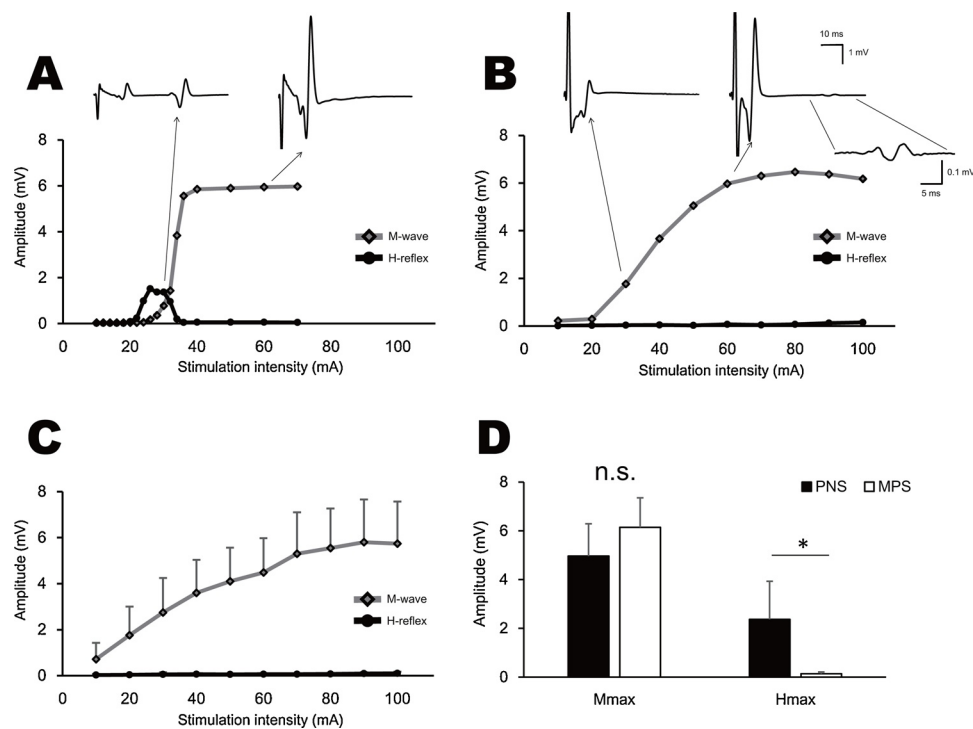


Fig. 2. Recruitment curves and maximum amplitude of H-reflex and M-wave evoked by peripheral nerve stimulation (PNS) and motor point stimulation (MPS) of soleus (SOL) muscle. A and B: recruitment curves for PNS (A) and MPS (B) for a representative participant. Waveforms of electromyography (EMG) at stimulus intensities of 30-mA and 60-mA are shown. C: Group data of the recruitment curves for the MPS. D: Group data of maximum amplitude of H-reflex (Hmax) and M-wave (Mmax) for the PNS and MPS. Asterisk indicates a significant difference between the PNS and MPS ($p < 0.05$). n.s. means the no significant difference between PNS and MPS.

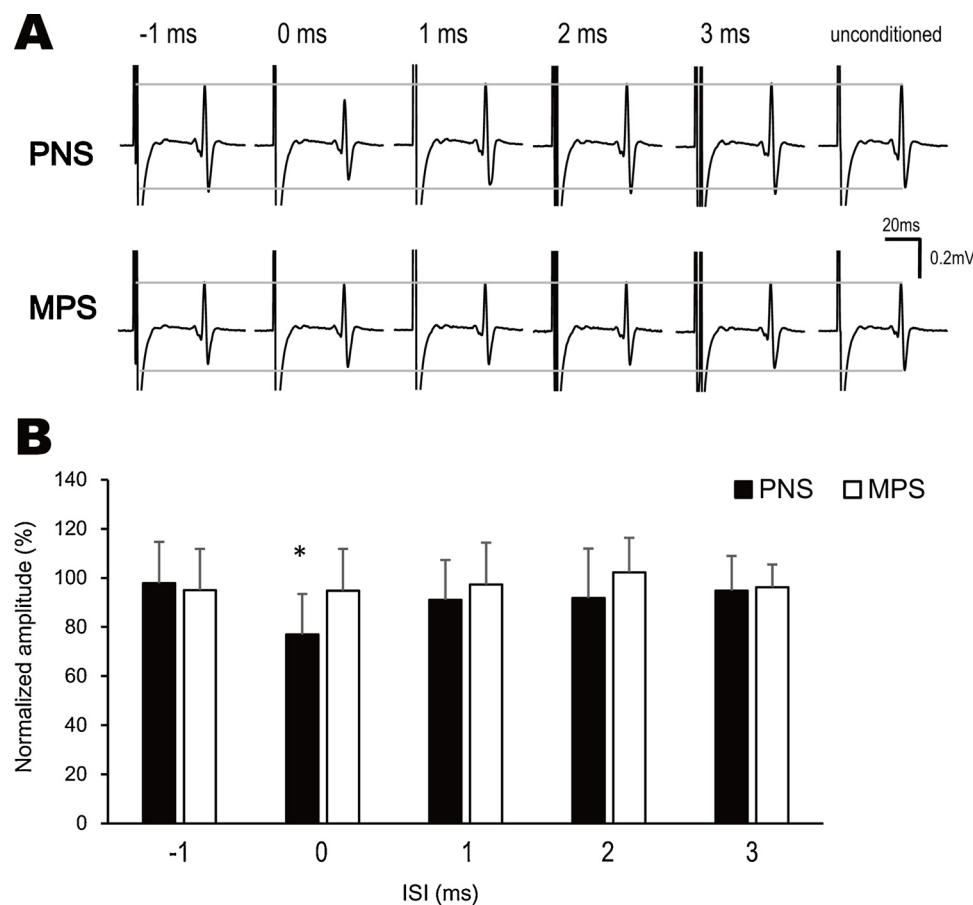


Fig. 3. Reciprocal inhibition of soleus (SOL) H-reflex by conditioning peripheral nerve stimulation (PNS) or motor point stimulation (MPS) of TA with different inter-stimulation intervals (ISI) between conditioning and test stimulation. A: Representative waveforms of the averaged signals from SOL after MPS or PNS in the TA for a single participant. B: Group data in the H-reflex amplitude normalized to the unconditioned value. Asterisk indicates a significant difference from 100 % ($p < 0.05$).

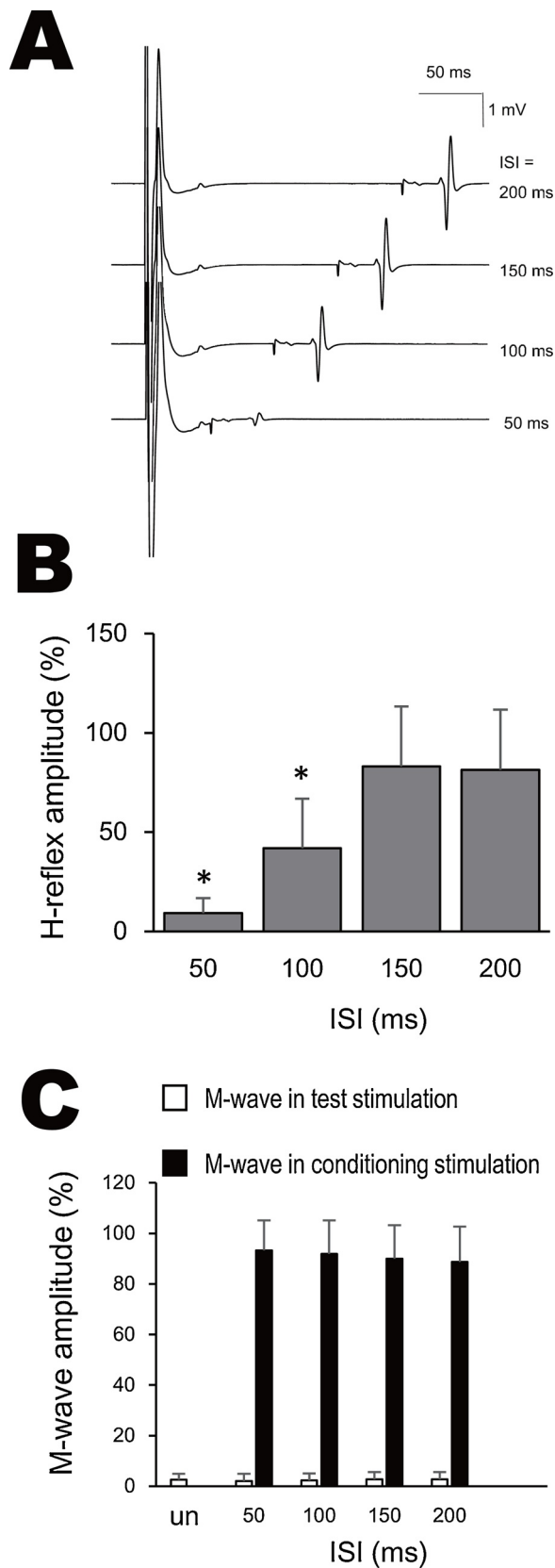


Fig. 4. Effect of MPS conditioning on soleus (SOL) H-reflex with different inter-stimulus intervals (ISI) between conditioning motor point stimulation (MPS) and test stimulation. **A:** Representative waveforms of the averaged signals from SOL for a single participant. **B:** Group data of H-reflex amplitude normalized to unconditioned value. **C:** Group data of M-wave amplitude for test (white bar) and conditioning stimulation (black) normalized to their respective maximum M-wave amplitude. Asterisks indicate the significant differences from 100 % ($p < 0.05$).

wave amplitude of the conditioning stimulation (MPS) ($F_{(3, 24)} = 2.47$, $p = 0.09$).

3.4. Experiment 4: effect of MPS on H-reflex, depending on stimulus intensity

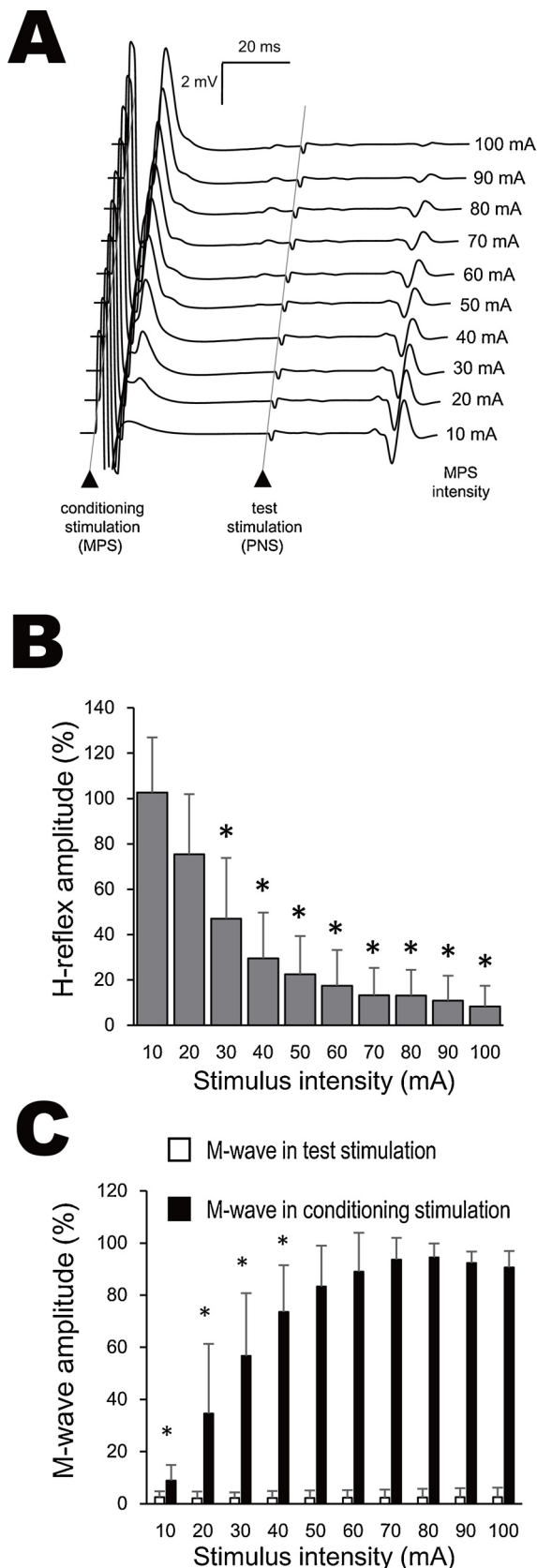
Fig. 5 shows a typical change in waveform for a representative participant (A), the group data of normalized H-reflex amplitude (B) and the group data of normalized M-wave amplitude (C) with different intensities of conditioning SOL MPS. The H-reflex amplitude became smaller with increasing conditioning SOL MPS intensity. Normalized H-reflex amplitudes were significantly smaller than 100 % (i.e., unconditioned H-reflex amplitude) at 30-mA ($p < 0.001$), 40-mA ($p < 0.001$), 50-mA ($p < 0.001$), 60-mA ($p < 0.001$), 70-mA ($p < 0.001$), 80-mA ($p < 0.001$), 90-mA ($p < 0.001$) and 100-mA ($p < 0.001$). The one-way ANOVA revealed no significant main effect of the MPS intensity on the M-wave amplitude for test stimulation ($F_{(9, 54)} = 0.20$, $p = 0.99$). Conversely, the M-wave amplitude for the conditioning stimulation was significantly affected by the MPS intensity ($F_{(9, 54)} = 32.84$, $p < 0.001$). M-wave amplitudes for the conditioning stimulation were significantly smaller than 100 % (Mmax) at the stimulus intensity of 10-mA ($p < 0.001$), 20-mA ($p < 0.001$), 30-mA ($p = 0.007$), and 40-mA ($p = 0.02$).

4. Discussion

First, we confirmed the finding by Bergquist and colleagues [2,3]. Between the MPS and PNS, the recruitment pattern of H-reflex differed (Fig. 2), while the M-wave showed similar pattern of plateauing and comparable values of Mmax (Fig. 2). The H-reflex was not observed prominently with MPS, regardless of stimulus intensity (Fig. 2). Secondly, we demonstrated that TA MPS did not suppress SOL H reflex (Fig. 3), which would indicate that the reciprocal inhibition did not occur with MPS. This suggests that MPS primarily stimulates the motor nerve and induces none or less activation of the Ia-sensory nerve compared to PNS. In addition to lack of H-reflex in MPS, we also observed a small response at a similar onset to that of the H-reflex at higher stimulation intensity (Fig. 2B). This appears to be the typical recruitment curve of the F-wave. The maximum amplitude of the small response was 2.3 % of Mmax in average (range: 0.08–4.3%), which was consistent with the F-wave amplitude previously reported in able-bodied individuals [7]. F-wave is a recurrent discharge of antidromic firing, which is induced by motor nerve stimulation at the spinal neural circuit. Thus, the presence of F-wave itself suggests that MPS induces antidromic firing. Lastly, we demonstrated that SOL MPS induced a long-lasting suppression (up to 100-ms) of SOL H-reflex (Fig. 4 and 5). This also suggests that MPS induced antidromic firing of the motor nerve as well as the subsequent suppression of motor neuron excitability probably due to after-hyperpolarization or the cutaneous inhibition as described below.

4.1. Does MPS activate Ia-sensory nerve?

We observed the lack of H-reflex in MPS. Although one of plausible interpretation of this result is that MPS does not activate Ia-sensory nerve, there might be another possibility that the neural recruitment



order is different between MPS and PNS. That is, threshold of motor nerve might be lower than that of Ia-sensory nerve. In this case, H-reflex would not appear at any stimulus intensity, because MPS-induced

Fig. 5. Effect of MPS conditioning on soleus (SOL) H-reflex induced by peripheral nerve stimulation (PNS) with different intensity of conditioning motor point stimulation (MPS). **A:** Representative waveforms of the averaged signals from SOL of a single participant. **B:** Group data of H-reflex amplitude normalized to the unconditioned value. **C:** Group data of M-wave amplitude for test (white bar) and conditioning stimulation (black) normalized to their respective maximum M-wave amplitude. Asterisks indicate significant differences from 100 % ($p < 0.05$).

antidromic impulse always collides H-reflex. Meanwhile, the reciprocal inhibition was not observed with TA MPS at any ISI while TA PNS induced significant reciprocal inhibition at an ISI of 0-ms (Fig. 3). This result implies that the reciprocal inhibition does not occur with MPS at the conditioning stimulus intensity at which the reciprocal inhibition occurs with PNS. Thus, MPS does not appear to activate Ia-sensory nerves. Since the conditioning stimulus intensity in Experiment 2 was set to the motor threshold with a barely perceptible M-wave or presence of perceived twitch by palpation of the TA tendon in both of PNS and MPS, the magnitude of activation in the antagonist muscle (i.e., the number of activated muscle fibres) should have been similar between PNS and MPS. However, we were unable to confirm this quantitatively as the small M-wave induced by MPS was obscured by a large stimulation artifact. This is a limitation in this study.

Regarding the PNS, the degree of H-reflex suppression at the ISI of 0-ms was more than 20 %, which was similar to those in the previous reports [5,12]. Although there is a report that reciprocal inhibition occurs at the ISI of 0-ms [6], most groups have reported maximum inhibition at ISI of 2 to 3-ms [12,14]. This difference in the ISI might be attributed to the lower testing stimulus intensity (5 % of Mmax) in our study. Most of previous studies used a test stimulus intensity of 15–25 % of Mmax [12,14]. We choose a low intensity compared to the previous study based on our preliminary experiments, in which we were unable to produce reciprocal inhibition at the intensity of 20 % of Mmax but were able to observe the inhibition at 5%. Lower intensity stimulation preferentially activates sensory neural fibers with larger diameters and faster conduction velocities. Therefore, in our study, maximal reciprocal inhibition occurred much earlier compared to previous studies that used stronger stimulation.

In Experiment 2, we did not test SOL MPS but TA MPS, which was dissimilar to the other Experiments in this study. We chose to condition TA, so that the H-reflex could be recorded from the same muscle (SOL) for all four Experiments and TA H-reflex is hardly evoked in the resting condition [5]. However, SOL and TA have different properties. For example, the number of muscle spindles is larger in SOL than TA, and the strength of reciprocal inhibition induced by SOL Ia-sensory fibers is greater compared to TA [17]. Therefore, if SOL is conditioned and TA H-reflex is evaluated, more sensitive Ia-sensory fibers in SOL may be activated and induce reciprocal inhibition on TA even with in MPS.

4.2. Does MPS induce the antidromic firing on motor nerve?

Our results indicate that SOL MPS induced long-lasting (up to 100 ms) (Fig. 4) and intensity dependent (Fig. 5) H-reflex inhibition. This suggests that SOL MPS induces antidromic firing on motor nerves that affects motor neuron excitability. Antidromic firing activates a part of motor neuron, which results in appearance of F-wave as observed in the Experiment 1. Motor neuron activation may induce after-hyperpolarization, which would be one of factors that suppress the H-reflex excitability that was found in this study. Additionally, the strong intensity of the conditioning MPS in this study might induce not only after-hyperpolarization but also the other inhibitory effects such as cutaneous inhibition, which may have caused the uniqueness of long-lasting H-reflex inhibition by SOL MPS [4].

4.3. Conclusion

We demonstrated that 1) SOL MPS does not induce H-reflex while SOL PNS does, and that 2) TA MPS does not induce reciprocal inhibition of SOL while TA PNS does, both of which likely suggests that MPS does not activate Ia-sensory nerves. Further, we demonstrated that 3) SOL MPS induces H-reflex inhibition in the stimulated muscle, suggesting that SOL MPS induces antidromic firing.

CRedit authorship contribution statement

Kento Nakagawa: Conceptualization, Validation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Austin J. Bergquist:** Conceptualization, Methodology, Writing - review & editing, Investigation. **Taro Yamashita:** Conceptualization, Methodology, Software, Investigation, Data curation, Validation. **Takashi Yoshida:** Conceptualization, Investigation, Writing - review & editing, Visualization. **Kei Masani:** Conceptualization, Methodology, Resources, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

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