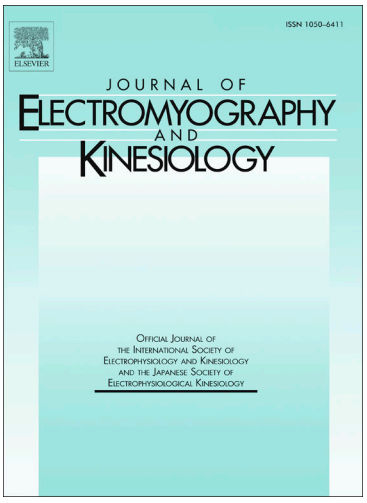

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Comparison of the temporal properties of medium latency responses induced by cortical and peripheral stimulation

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Abstract

Sudden foot dorsiflexion lengthens soleus muscle and activates stretch-based spinal reflexes. Dorsiflexion can be triggered by activating tibialis anterior (TA) muscle through peroneal nerve stimulation or transcranial magnetic stimulation (TMS) which evokes a response in the soleus muscle referred to as Medium Latency Reflex (MLR) or motor-evoked potential-80 (Soleus MEP80), respectively. This study aimed to examine the relationship between these responses in humans. Therefore, latency characteristics and correlation of responses between soleus MEP80 and MLR were investigated. We have also calculated the latencies from the onset of tibialis activity, i.e., subtracting of TA-MEP from MEP80 and TA direct motor response from MLR. We referred to these calculations as Stretch Loop Latency Central (SLLc) for MEP80 and Stretch Loop Latency Peripheral (SLLp) for MLR. The latency of SLLc was found to be 61.4 ± 5.6 ms which was significantly shorter (P = 0.0259) than SLLp (64.0 ± 4.2 ms) and these latencies were correlated (P = 0.0045, r = 0.689). The latency of both responses was also found to be inversely related to the response amplitude (P = 0.0121, r = 0.451) probably due to the activation of large motor units. When amplitude differences were corrected, i.e. investigating the responses with similar amplitudes, SLLp, and SLLc latencies found to be similar (P = 0.1317). Due to the identical features of the soleus MEP80 and MLR, we propose that they may both have spinal origins.

Keywords: transcranial magnetic stimulation, medium latency reflex, motor evoked potential, spinal circuits, reflexes

Introduction

Stretch reflexes are muscle contractions that are triggered by rapid elongation of muscles to keep the skeletal muscle length stable. When a muscle's length increases, muscle spindles are activated, in turn, primary afferents convey information to certain inhibitory and excitatory neurons in the spinal cord (Edin and Vallbo 1990; Matthews 1984; Yavuz et al, 2014). Activation of the primary afferents excites the agonists and inhibits the antagonists; therefore, muscle contraction occurs in the agonist muscle/s to bring the length of the muscle back to its pre-stretched value.

Another spindle afferent, the secondary group, also cause the agonist muscle to contract to maintain the muscle length (Avela et al, 1999; Matthews 1984). Various methodologies have been put forward to test this reflex and its central neuronal mechanisms (Boes 2014; Calota and Levin 2009; Taube et al, 2012; Yavuz et al, 2014). Stretch reflex in a muscle can be evoked directly via stretching the muscle or indirectly via inducing a contraction in its antagonist muscle (referred to as indirect stretch reflex or mid-latency reflex (MLR)) (Uysal et al, 2012; Uysal et al, 2009). For instance, the stretch reflex can be evoked in the soleus muscle by activating its antagonist, tibialis anterior (TA), via peroneal nerve stimulation or sudden dorsiflexion (Corna et al, 1995; Grey et al, 2002; Marque et al, 2001). Similarly, an indirect stretch reflex can be achieved from the finger flexor muscles via sudden contraction of the wrist extensor muscles by radial nerve stimulation (Uysal et al, 2012). The indirect approach allows electrophysiological determination of the stretch reflex and can be easily used towards clinical examination for muscle spindle function in health and disease (Calota and Levin 2009; Matsumoto and Ugawa 2008; Mullick et al, 2013; Yates et al, 2011). However, some deficiencies for using indirect stretch reflex, including the lack of information on prestimulus activation level, should be overcome to make this method as the primary tool to be used to test the functionality of muscle spindles (Uysal et al, 2012; Uysal et al, 2009; Uysal et al, 2019).

A similar late response from the soleus muscle can be obtained after transcranial magnetic stimulation (TMS) (Ertekin et al, 1995; Sammut et al, 1995; Suga et al, 2001). TMS-induced long-lasting motor evoked potential (MEP) (Haavik et al, 2018; Ozyurt et al, 2019) can cause dorsiflexion of the foot due to TA contraction that leads the Achilles tendon to stretch. The latency of the EMG response following TMS is approximately 80 ms, therefore, this response was named as the soleus Motor Evoked Potential 80 (soleus-MEP80) (Ertekin et al, 1995; Suga et al, 2001). However, soleus MEP80 and indirect stretch reflex (MLR) have not been directly compared in terms of latency properties to date. Therefore, this study aims to compare the temporal characteristics of these responses. We hypothesize that soleus MEP80 and MLR have identical origins.

Materials and Methods

Subjects

The study was approved by the Local Ethics Committee (Issue: 70904504/310, No: 492). Informed consent was obtained in accordance with the principles of the Helsinki Convention. Subjects with chronic back pain, history of neuromuscular diseases, and neuromuscular medication users were excluded from the study. Bipolar surface electromyography (SEMG) in 15 healthy volunteers (11 Male, 4 Female, Age: 20.7±1.4 years, Height: 174.1±10 cm, Weight: 68.5±14.9 kg), and intramuscular EMG in 6 healthy volunteers (3 Male, 3 Female, Age: 22.8±4.1 years, Height: 175±12.8 cm, Weight: 72.6±14.4 kg) were recorded.

Setup and recording configuration

For recording and analysis; software Synergy (Synergy Healthcare Solutions, Maryville, USA), for data acquisition; Nicolet EDX (Natus Neurology, Middleton, USA), for electrical

stimulation; Nicolet EDX system and for the TMS; Magstim 200 (Magstim Co., Whitland, UK) were used. Both SEMG and intramuscular EMG were sampled at 48 kHz. Bandpass filter for SEMG and intramuscular EMG was 20 Hz-1 kHz and 200 Hz – 5 kHz, respectively.

General procedure

The subjects lied on a bed in a prone position and their leg muscles were relaxed. Optimum recording locations for TA and soleus muscles were determined by palpating the muscles while subjects were asked to perform dorsiflexion and plantar flexion, respectively. For TA muscle, the recording locations were on the anterolateral side of the leg, and for the soleus, it was the dorsolateral side of the leg, distal to the gastrocnemius muscle. One SEMG electrode (10 mm diameter Ag/AgCl disc electrode) was placed on the muscle belly and the other electrode was placed on the distal tendon, after rubbing the skin and application of conductance gel to reduce its impedance. Besides, concentric needle electrode was placed around the muscle belly, close to the SEMG electrodes. Ground electrodes for both muscles were placed on the malleolus.

Experimental protocols

Three experimental configurations were followed in the recordings: I) neutral foot position at rest, ii) ankle dorsiflexion and iii) ankle plantar flexion.

Soleus H-reflex: The tibial nerve was stimulated with a cathode placed on the midpoint of the popliteal fossa and anode just above the patella using 1-ms pulse width (Hugon 1973; Özyurt et al, 2018). Stimulus intensity ranged between zero and a level to induce supra-maximal direct motor response (M-response) with an interstimulus interval of around 5 seconds. Within these steps, the highest amplitude H-reflex was found, and its latency, as well as amplitude, were recorded for 10 stimuli.

Soleus-MLR: To stimulate the common peroneal nerve, we employed the same configuration as we have used earlier in Uysal et al., 2019. The peroneal nerve was stimulated using a bipolar stimulation configuration where the anode and cathode were placed with an elastic bandage just under the head of the fibula. (Uysal et al, 2019). After the motor threshold of TA muscle was determined, stimuli with an intensity of 1.5x motor threshold were delivered to the peroneal nerve while recording from the TA and soleus muscles, simultaneously. The M-response was detected in TA muscle and the late responses were recorded at the soleus muscle.

Soleus-MEP80: TMS was delivered to the midline circumference starting from Cz according to the 10/10 EEG cap system (Seeck et al, 2017). The stimulation area which induces a large MEP from the TA muscle but little to no response in the soleus muscle was defined as the optimal location of stimulation. A 90 mm diameter round coil was used to deliver 10 magnetic pulses with around 5 seconds of interval between each stimulus and having 1.5x resting motor threshold intensity during mild dorsiflexion.

Analysis

Latencies were defined as the onsets of responses and amplitudes were defined as amplitudes between the positive peak and negative peaks (peak-to-peak amplitude). Maximum amplitudes and shortest latency responses were selected for each individual and these values were used for calculation in each subject. Therefore, we neither took the averages of traces nor built cumulative sum algorithm as they would have given a somewhat longer than actual latency due to a large variability in SEMG recordings. Instead, we superimposed all the traces and observed the fastest response (shortest latency) for that subject. Since the fastest response would be the first response arrives at the muscle, we calculated the latency of the particular response for each subject as the first deflection from the isoelectric level.

Latency and amplitude values for all subjects were averaged and results were shown as mean ± standard deviation (SD). Plantar flexion and dorsiflexion levels were determined in SEMG after rectifying and smoothing (0.2 s time constant) the traces. Plantar flexion level was normalized to subjects' soleus MVC whereas the dorsiflexion level was normalized to TA MVC.

To compare the latencies of soleus MEP80 and MLR, we used evoked responses (MEP and M-response, respectively) as trigger points after which dorsiflexion occurs following an electromechanical delay (EMD). Therefore, we defined the latency as Stretch Loop Latency Central (SLLc = Soleus MEP80 – TA MEP) and Stretch Loop Latency Peripheral (SLLp = Soleus MLR – TA M-response). Before performing any statistical analysis, the distribution of the data was analyzed using the Shapiro-Wilk test. A paired t-test was used to analyze the latency between SLLc and SLLp, and the Wilcoxon matched-pairs signed-rank test was used to analyze the amplitude difference between MEP80 and MLR. Also, linear regression was performed for SLLc vs SLLp, latency vs amplitude of SLL as well as between Soleus MEP80 and MLR. The level of significance was selected as $P < 0.05$. All tests were two-tailed.

To exclude the effect of the amplitude on the latency, we used ROUT as an outlier identification method in GraphPad Prism v8 (San Diego, CA, USA) where we used Q value as 0.1% which identifies definite outliers.

Results

The latencies of soleus H-reflex, TA M-response, soleus MLR, TA MEP, and soleus MEP80 whose details are provided in **Table 1**.

Table 1. Latency values for TA M-response, soleus MLR, TA MEP, soleus MEP80, and soleus H-reflex were shown in Table 1. We also report the amplitudes of MLR and MEP80 responses in soleus muscle during voluntary dorsiflexion.

n=15	Latency (ms)					Amplitude (mV)	
	TA M-response	Soleus MLR	TA MEP	Soleus MEP80	Soleus H-reflex	Soleus MLR	Soleus MEP80
Mean±SD	4.0±0.5	68.4±4.4	27.3±2.6	88.7±6.3	29.1±2.1	1.3±0.8	2.4±1.5

Ankle dorsiflexion facilitates MEP80 and MLR

Upon stimulation of the motor cortex with TMS and peroneal nerve with electrical stimulation, we recorded responses in both TA and soleus muscles at rest, ankle dorsiflexion, and plantar flexion positions. In addition to MEP which was observed in both muscles at around 27 ms, we detected soleus MEP80 response at 88.7 ± 6.3 ms which was prominent during the dorsiflexion but weak at the rest position (**Figure 1**). On the other hand, upon peroneal nerve stimulation, we detected M-response in TA muscle at 4 ms latency and soleus MLR during dorsiflexion at a latency of 68.4 ± 4.4 ms (**Figure 1**). Both MLR and MEP80 had a slightly longer latency at rest compared to the dorsiflexion possibly due to tendon stiffness. Dorsiflexion at 10.6 ± 3.3 % MVC was sufficient to evoke MLR whereas 24.4 ± 9.4 % MVC of plantar flexion did not result in any MLR response. Therefore, all calculations to compare the latency of responses were performed during dorsiflexion.

(FIGURE 1)

We have also investigated a possible crosstalk between soleus and TA. We recorded EMG activity by intramuscular and surface electrodes simultaneously. We detected MLR only in the soleus muscle by intramuscular EMG even if SEMG showed activity in both muscles (**Figure 2**). Therefore, cross talk may be the reason for detecting similar SEMG signals in TA muscle.

(FIGURE 2)

Latencies of MEP80 and MLR are correlated, and the loop latencies are identical for similar response amplitudes

Since TA contraction evokes a late response in the soleus muscle, we compared the latencies of soleus MEP80 and MLR in terms of loop latencies, where conduction delays (i.e. corticospinal conduction and TA motor axon conduction) were subtracted from their original latencies (**Figure 3**). The latency of SLLc (61.4 ± 5.6 ms) was shorter than SLLp (64.0 ± 4.2 ms) significantly (P = 0.0259) (**Figure 3A**). Moreover, we also found positive correlation for the latencies of MEP80 and MLR (P = 0.0165, r = 0.607) as well as for the latencies of SLLc and SLLp (P = 0.0045, r = 0.689) (**Figure 3B**). Regarding the amplitude, MEP80 was significantly larger than MLR (P = 0.0007) (**Figure 3C**). For both circuitries, the amplitude was inversely correlated with the SLL (**Figure 3D**), showing that higher the amplitude shorter the latency probably due to the recruitment of faster-conducting motor units (P = 0.0121, r = 0.451). After deletion of the outliers to minimize the amplitude effect on latency (Q=0.1%, the definitive outliers; 3 maximum values identified; linear regression P = 0.0983, r = 0.325), the latencies of SLLc and SLLp were found to be similar (P = 0.1317) (**Figure 3E**).

(FIGURE 3)

Discussion

In this study, the identity of MLR obtained from soleus muscle as a result of stimulation of peroneal nerve and MEP80 response from soleus muscle as a result of TMS were investigated. We found a slight but significant difference between SLLc and SLLp, however, the changes within participants were correlated providing insight about their mechanism. Shorter latency in SLLc compared to SLLp and an inverse correlation with latency and SLL amplitude might be

because of the activation of larger/faster-conducting motor units (Dietz and Sinkjaer 2007; Mrachacz-Kersting et al, 2006; Suresh et al, 2005) which was minimized when latencies were compared at similar amplitudes.

Earlier studies of the late response from the soleus muscle by transcranial stimulation showed that a similar response could be produced in soleus by electrical stimulation of the peroneal nerve at the fibular neck. This response was first described by Sammut et al, (1995) who reported the soleus late response latency as 77.3 ± 5.5 ms by electrical stimulation of the peroneal nerve. They also suggested that the soleus late response elicited by TMS is a soleus stretch reflex resulting from the dorsiflexion of the foot due to activation of the TA following cortical stimulation. The equivalent of these responses in our study were SLLp and SLLc, whose latency values were close to each other, especially when MLR and MEP80 amplitudes were similar in size.

The late responses due to ankle dorsiflexion evoked by cortical and peripheral stimulation have been described and their mechanisms were discussed. Ertekin et al, (1995) described the soleus late response by TMS. They concluded that soleus late response is a polysynaptic extensor response related to postural mechanisms and originating through the convergence of descending motor commands and peripheral sensory feedback (Ertekin et al, 1995). Moreover, Suga et al, (2001) described the same soleus late response elicited by TMS. But they did not obtain soleus late response by electrical peroneal nerve stimulation and since they did not find any correlation between the soleus primary response and late response, they suggested that the soleus late response does not originate from the corticospinal tract. The soleus late responses may thus be a polysynaptic response related to the postural control of the agonist and antagonist organization between the TA and soleus (Suga et al, 2001). Moreover, Kurokawa-Kuroda et al, (2007) described soleus late response latency changes in pure cerebellar ataxic patients. Latency prolongation and frequency abnormalities suggest that “pure cerebellar” degeneration affects

the mechanism responsible for soleus MLR which is related to the control of posture. Hence, they suggested that MLR may be related to/modulated by the supraspinal mechanisms (Kurokawa-Kuroda et al, 2007). However, the correlation of these responses evoked by peripheral or cortical stimulation has not been examined systematically previously in the same participants. Therefore, investigating both responses, that have similar latencies and mechanisms, in the same participants would allow us to explore the correlation of these responses as presented in this study.

Several possible mechanisms about soleus MEP80 have been discussed previously. It has been suggested that the origin of MEP80 could be due to the activation of proprioceptive inputs on spinal motoneurons through the transcortical or polysynaptic pathway (Holmgren et al, 1990). Moreover, descending motor pathways that have slow conduction velocity (Dimitrijević et al, 1992; Holmgren et al, 1990) and startle reflex-like circuits (Holmgren et al, 1990) have been proposed as other candidate mechanisms. On contrary, Sammut et al, (1995) argue that since MEP in TA was significantly larger than soleus in line with the findings of Brouwer and Ashby (1990), Holmgren et al, (1990), and Dimitrijević et al, (1992), soleus late response is a product of foot dorsiflexion rather than startle reflex or due to slowly conducting descending pathways. Additionally, the latency of this late response may not be consistent with long loop reflex which should have the latency of summation of twice the MEP latency and electromechanical delay between MEP onset and tendon stretch (Sammut et al, 1995). In addition to this, Ertekin et al, (1995) showed that this response is affected by ankle position and therefore suggested MEP80 have a spinal origin with the contribution of cortical mechanisms, inhibited in the sitting position but more pronounced during standing or walking. Our findings supported that both MLR, which has a spinal origin, and MEP80 have related mechanisms due to similarities in their temporal properties.

Soleus late responses evoked by the TMS and peroneal nerve stimulation resemble and differ from each other in several perspectives. TMS resulted in significantly larger soleus muscle activation compared to MLR in this study. This larger response would be due to the recruitment of the higher threshold motor units (i.e. faster-contracting motor units) which reduces the conduction time/latency. Therefore, although the significance of the latency difference between the responses may indicate some differences in neuronal circuitry, variations in the motor pool activation (i.e. faster motor units activated by TMS compared to peroneal nerve stimulation) might cause this latency difference. This issue is also supported by the correction of the amplitudes (i.e. using the latencies with similar amplitudes), after which the latencies of SLLc and SLLp were found to be similar. Lastly, another similarity of the responses could be that the dorsiflexion of the foot by stimulation activates similar stretch-related afferents which would include both group Ia and II spindle afferents. For instance, the variations in late responses as a result of cold and ischemia maneuvers support that the group II afferents are involved in these late responses (Uysal et al, 2011; Uysal et al, 2012; Uysal et al, 2009).

When the amplitudes of MEP80 and MLR were similar, their latencies were found to be identical proving that both responses are affected by influences that alter the excitability of the motor pool. Also, both responses were affected by the stiffness of the tendon as active dorsiflexion slightly reduces the onset of the responses. Although these effects could have a central and peripheral origin, the latter would be the main mechanism for MLR, as it can still be obtained in patients with central lesions (Uysal et al, 2011). Moreover, just before obtaining the MLR, TA-induced reciprocal inhibition of soleus motoneurons was observed as the first event in the circuitry possibly also includes recurrent inhibition (Özyurt et al, 2019; Uysal et al, 2019). Following this early inhibition, the activation of the group II fibers along with Ia fibers due to soleus muscle tension can activate the soleus motor pool eliciting the late responses

(**Figure 4**). These findings support the origin of the late responses to be in the peripheral-dominant mechanisms.

(FIGURE 4)

Conclusions

The soleus late responses obtained either by motor cortex or peripheral nerve stimulation can be regarded as medium latency responses. When investigating the responses with comparable amplitudes, the similarity of the latencies, as well as other evidence such as the effect of ankle position on both responses and correlation between the responses, support the hypothesis that both MEP80 and MLR might have analogous neuronal circuitries possible in the spinal cord.

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Figure Legends

Figure 1. *Latency and amplitude characteristics of soleus MEP80 and MLR. The traces on the left shows the recording of TA and soleus SEMG at rest, dorsiflexion (DF), and plantar flexion (PF) upon TMS to characterize MEP80 response. The traces on the right demonstrates SEMG*

recordings in both muscles at rest, DF and PF following peroneal nerve stimulation to evoke soleus MLR. Red arrows show the onset of the responses at rest and DF.

Figure 2. *Detection of crosstalk between soleus and TA. The upper two traces show the intramuscular EMG response to peroneal nerve stimulation where clear MLR in soleus and M-response in TA was observed. On the other hand, SEMG shows both responses in both muscles revealing possible crosstalk.*

Figure 3. *The comparisons and correlations of the responses. A) The latency of soleus MLR and MEP80 as well as SLLp and SLLc. B) Correlation between soleus MLR and MEP80 and between SLLp and SLLc. C) Amplitude comparison of MLR and MEP80 responses. D) Correlation between SLL latency and response amplitudes. E) Correlation between SLL and response amplitudes after deletion of the outliers and comparison between SLLp and SLLc without outliers.* $^{ns}p>0.05$, $*p<0.05$, $***p<0.001$.

Figure 4*. Possible mechanisms responsible for MEP80 and MLR. The figure on the left is the suggested mechanism for MEP80 whereas the figure on the right is for MLR. Both responses originate from the activation of TA muscle by TMS or peroneal nerve stimulation during voluntary dorsiflexion and result in soleus muscle to stretch and activate group I and II fibers that evoke these late reflexes. TMS resulted in a clearer contraction in TA compared to soleus. Therefore, we have shown the upper motoneuron axons on TA thicker than the one on the soleus, in the figure on the left.*