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Understanding the mechanisms of neuromuscular fatigue with paired-pulse stimulation

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Transcranial magnetic stimulation (TMS), using both single and paired-pulse techniques, has provided insight in understanding the balance of excitation and inhibition within the corticomotor system during maximal and submaximal exercise. A single pulse of TMS produces a short-latency motor-evoked potential (MEP), indicating the net excitation of the motor pathway which includes the balance within supraspinal (cortical) and spinal sources. The MEP is followed by an interruption of ongoing electromyographic (EMG) activity known as the silent period. Classically, the silent period has been interpreted to represent the inhibition within the motor cortex (i.e. intracortical inhibition) which probably involves γ-aminobutyric acid ($GABA_B$) receptors. Intracortical inhibition is clinically important to understand because chronic pain disorders (migraines) and psychiatric disorders (post-traumatic stress disorder) have demonstrated less cortical inhibition during a voluntary contraction while other disorders such as Parkinson's and Alzheimer's diseases have demonstrated abnormal corticospinal excitatory circuits at rest. Additionally, the fatigue-induced reduction in cortical inhibition may be related to the motor impairments during exercise. The alterations in the MEP and silent period during exercise indicate that the central nervous system (CNS) may necessitate increases in both excitatory and inhibitory activity during fatiguing contractions; however, the mechanisms underlying these effects are yet to be completely understood.

Paired-pulse stimulation, a technique that provides two stimuli at different time intervals (conditioning response–first stimulus and test response–second stimulus), can quantify corticospinal inhibition and facilitation. When the paired-pulse interstimulus interval induced by TMS at the motor cortex is set to ∼50–200 ms, the conditioned MEP in the silent period is smaller than the unconditioned MEP (test stimulus). The suppression of a conditioned MEP response is generally referred to as long-interval intracortical inhibition. Likewise, paired-pulse electrical stimulation applied at the mastoid process elicits a MEP at the cervicomedullary junction (cervicomedullary motor-evoked potential, CMEP). A reduction in the CMEP size demonstrates disfacilitation/inhibition of the motoneurons and an increase in the CMEP size represents an increase in the excitation of the motoneurons.

These techniques were skilfully used in a recently published study in *The Journal of Physiology* (McNeil *et al.* 2011*a*). Their purpose was to understand the effect of fatigue on the conditioned/unconditioned MEPs and CMEPs during a sustained submaximal contraction. This is important because both spinal and supraspinal mechanisms contribute to neuromuscular fatigue. Their protocol included eliciting a motor cortical and cervicomedullary stimulation during a 10 min submaximal contraction with the elbow flexor muscles to assess the fatigue-induced reduction of the conditioned CMEP to the conditioned MEP. Additionally, the authors elicited two different stimulation intensities (15% or 50% maximal compound muscle action potential (M_{max})) to investigate the contribution of low- and high-threshold motoneurons to the submaximal fatiguing task. A constant EMG level was maintained rather than a constant torque level in order to control motoneuronal output. Any fatigue-related loss of torque, therefore, could largely be attributed to fatigue within the muscle fibres. The novel findings from this study were that during a submaximal fatiguing contraction, the conditioned CMEP reduced to a similar magnitude compared with the conditioned MEP (McNeil *et al.* 2011*a*) indicating an absence of motor cortical contribution to the fatigue-related reduction in the conditioned MEP. Consequently, what has been previously known as long-interval intracortical inhibition appears to be attributed to changes in spinal cord excitability and the terminology long-interval inhibition appears more appropriate. McNeil *et al.* (2011*a*) suggests that the silent period therefore may not be a good representation of intracortical inhibition, but may indicate significant inhibition of motoneuronal activity in the spinal cord, which conflicts with previous findings in the literature. Furthermore, when the authors compared a low-intensity (15% M_{max}) and high-intensity (50% M_{max}) cortical stimulus, the low-intensity stimulus resulted in more inhibition for both the conditioned CMEP and MEP during a submaximal contraction. This would be expected as the low-intensity stimulus would stimulate a greater proportion of the low-threshold (Type I) motor units which are predominantly activated during this type of task (25% Maximal Voluntary Contraction (MVC) EMG-based contraction).

The fatigue-induced inhibition in the silent period, which appears to be spinally mediated, may also be demonstrated during maximal fatiguing contractions. For example, McNeil *et al.* (2009) found that the conditioned CMEP reduced to a similar magnitude compared with the conditioned MEP during a maximal fatiguing contraction (McNeil *et al.* 2009). Hence, this dramatic reduction of CMEPs in the silent period during a maximal effort suggests a decline in the excitability of motoneuronal output. Additionally, Iguchi & Shields (2011) evaluated changes to the silent period and H-reflex during several series of intermittent maximal fatiguing contractions of the soleus muscle. Their findings indicated that the H-reflex decreased in amplitude and the silent period increased in duration after the initial series of maximal fatiguing contractions with no further changes for either one throughout the fatiguing task (Iguchi & Shields, 2011). The magnitude of change in the H-reflex and silent period, however, was not the same. Despite the contrasting muscles and contraction type that was used in the McNeil *et al.* (2011*a*) study, if the silent period is due to decreased motoneuron excitability, the results of Iguchi & Shields (2011) provides further evidence that spinal mechanisms may have a large contribution to failure of a motor fatiguing task. Nonetheless, for both the maximal and submaximal fatiguing contraction substantial descending drive is required, which is

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represented by the unchanged or increased unconditioned CMEP and MEP response (McNeil *et al.* 2009, 2011*a*).

When interpreting the fatigue-related suppression of conditioned MEPs and CMEPs a limitation to these techniques should be considered, as acknowledged by McNeil *et al.* (2011*a*). Cervicomedullary stimulation elicits a single volley whereas TMS elicits multiple descending volleys. Therefore, because the output measured at the muscle is reflective of the input–output balance at the motoneuron, the fatigue-induced intracortical inhibition may be lessened by the temporal summation and facilitation of the descending volleys at the motoneuron and thereby underestimate the involvement of the intracortical mechanisms.

Many mechanisms can contribute to the decreased motoneuron excitability during submaximal and maximal fatiguing contractions. The mechanisms could be caused by (a) decrease in excitatory input with reduced muscle spindle firing rates, (b) inhibitory feedback from group III and IV muscle afferents to the motoneuron and/or (c) activity-dependent modulation of the motoneuronal intrinsic properties and the input–output balance of the motoneuron. A fatigue-induced withdrawal of excitatory input to motoneurons from muscle spindle afferents can decrease the motoneuron excitability. To examine the effects of the excitatory input from muscle spindles, McNeil *et al.* (2011*b*) examined the effects of biceps tendon vibration during a maximal voluntary contraction of the elbow flexors. Their findings suggested that the tendon vibration during the sustained maximal effort did not affect the conditioned CMEP size. Importantly, as acknowledged by the authors, the spindle-mediated support to the motoneuron excitability may not be effectively detected by cervicomedullary stimulation. Therefore, the involvement of the muscle spindle feedback to motoneuron excitability may require further investigation.

Group III and IV muscle afferents respond to chemical and mechanical stimuli during maximal and submaximal fatiguing contractions. Although the contribution of the group III and IV afferents to the reduction in the CMEP has demonstrated conflicting results, several studies provide evidence that the afferent activity from group III and IV can increase the presynaptic inhibition of the Ia afferents, thereby reducing muscle spindle discharge rates and input to the α motoneuron. Therefore, it is reasonable to consider that an increase in the firing of the group III and IV afferents would yield inhibition of the motoneurons during a sustained contraction resulting in a reduction of the CMEP size.

Just as the balance of synaptic inhibition and excitation can impact motor output at the cortical level, similar strategies appear to shape spinal motor output and may be relevant to the current paper. Recently, a push–pull organization of synaptic input to motoneurons has been proposed whereby excitatory and inhibitory synaptic inputs act on the motoneuron in a reciprocal fashion (Johnson & Heckman, 2011). With respect to fatigue, if inhibition increases as excitation decreases, the result would be a greater reduction in motoneuron excitability (membrane hyperpolarization). Ultimately, this would result in a decrease in motoneuron firing rate and a reduced ability to generate force.

In conclusion, McNeil *et al.* (2009, 2011*a*,*b*) highlight the contribution of the corticospinal centers during a fatiguing contraction and emphasize the challenges with interpreting the silent period. This work not only questions traditional concepts, but drives the scientific literature forward by attempting to understand the fatigue-induced changes in the central nervous system and the role of spinal-mediated mechanisms. Paired-pulse stimulation may be instrumental in understanding motor control during exercise and recovery in clinical and aging populations. Clinically, this is important because neuromuscular fatigue is the foundation for neuromuscular rehabilitation with implications for training and activities of daily living. Furthermore, mechanisms within the spinal cord appear to be contributing to neuromuscular fatigue and should be addressed in future studies to understand neural mechanisms of fatigability in healthy and clinical populations.

References

Iguchi M & Shields RK (2011). Cortical and segmental excitability during fatiguing contractions of the soleus muscle in humans. *Clin Neurophysiol*; DOI: 10.1016/j.clinph.1006.1031.

Johnson MD & Heckman CJ (2011). Interactions between focused synaptic inputs and diffuse neuromodulation in the spinal cord. *Ann N Y Acad Sci* **1198**, 35–41.

McNeil CJ, Giesebrecht S, Gandevia SC & Taylor JL (2011*a*). Behaviour of the motoneurone pool in a fatiguing submaximal contraction. *J Physiol* **589**, 3533–3544.

McNeil CJ, Giesebrecht S, Khan SI, Gandevia SC & Taylor JL (2011*b*). The reduction in human motoneurone responsiveness during muscle fatigue is not prevented by increased muscle spindle discharge. *J Physiol* **589**, 3731–3738.

McNeil CJ, Martin PG, Gandevia SC & Taylor JL (2009). The response to paired motor cortical stimuli is abolished at a spinal level during human muscle fatigue. *J Physiol* **587**, 5601–5612.

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