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Short- and long-latency afferent inhibition; uses, mechanisms and influencing factors

Claudia V. Turco, Jenin El-Sayes, Mitchell J. Savoie, Hunter J. Fassett, Mitchell B. Locke, Aimee J. Nelson*

Department of Kinesiology, McMaster University, Canada

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ABSTRACT

Transcranial magnetic stimulation (TMS) is an ideal technique for non-invasively stimulating the brain and assessing intracortical processes. By delivering electrical stimuli to a peripheral nerve prior to a TMS pulse directed to the motor cortex, the excitability and integrity of the sensorimotor system can be probed at short and long time intervals (short latency afferent inhibition, long latency afferent inhibition). The goal of this review is to detail the experimental factors that influence the magnitude and timing of afferent inhibition in the upper limb and these include the intensity of nerve and TMS delivery, and the nerve composition. Second, the neural mechanisms of SAI are discussed highlighting the lack of existing knowledge pertaining to LAI. Third, the usage of SAI and LAI as a tool to probe cognition and sensorimotor function is explored with suggestions for future avenues of research.

Introduction

Afferent inhibition is the phenomena by which a sensory afferent volley inhibits the motor response in a given muscle and is typically studied by combining non-invasive electrical nerve stimulation with TMS over M1. Specifically, TMS delivers a magnetic pulse to M1 that *trans*-synaptically depolarizes corticospinal neurons to elicit a MEP recorded over the target muscle. Non-invasive peripheral nerve stimulation delivered prior to the TMS pulse may inhibit or facilitate the MEP depending on the ISI between the nerve stimulus and TMS pulse. Two time-dependent phases of afferent inhibition occur called SAI and LAI owing to the short and long intervals between the nerve and TMS inputs [1,2]. Fig. 1 illustrates the general methodology for SAI and LAI.

Over the past two decades, afferent inhibition has been studied extensively to identify the experimental factors that impact the magnitude of this phenomenon, and to determine the underlying neural mechanisms. Sensory and motor paths are required to generate afferent inhibition. As such, SAI and LAI have been used as tools to probe changes in sensorimotor function in disease and following neurological injury to advance our understanding of sensorimotor control. The goal of this review is to provide a comprehensive profile of the factors influencing the magnitude of afferent inhibition, the neural mechanisms responsible for

Abbreviations: ACh, acetylcholine; AD, Alzheimer's disease; ADM, abductor digiti minimi; AP, anterior-posterior; APB, abductor pollicis brevis; BB, biceps brachii; cTBS, continuous theta burst stimulation; DEL, deltoid; DLPFC, dorsolateral prefrontal cortex; DN, digital nerve; D1, digit 1; D2, digit 2; D5, digit 5; EDC, extensor digitorum communis; FCR, flexor carpi radialis; FDI, first dorsal interosseous; FHD, Focal Hand Dystonia; FPD, flexor digitorum profundus; GABA, gamma-amino butyric acid; IPSP, inhibitory post-synaptic potential; ISI, interstimulus interval; iTBS, intermittent theta burst stimulation; LAI, long latency afferent inhibition; LICI, long interval intracortical inhibition; LIHI, long-latency interhemispheric inhibition; LTD, long-term depression; LTP, long-term potentiation; MCI, mild cognitive impairment; MEP, motor evoked potential; MMSE, Mini Mental State Examination; MN, median nerve; MoCA, Montreal Cognitive Assessment; MRS, magnetic resonance spectroscopy; MT, motor threshold; M1, primary motor cortex; nAChR, nicotinic acetylcholine receptor; PA, posterior-anterior; PAS, paired associative stimulation; PD, Parkinson's disease; PPC, posterior parietal cortex; rPAS, repetitive paired associative stimulation; SAI, short latency afferent inhibition; SCI, spinal cord injury; SEP, somatosensory evoked potential; SICI, short interval intracortical inhibition; SIHI, short-latency interhemispheric inhibition; ST, sensory threshold; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; TE, thenar eminence; TMS, transcranial magnetic stimulation; UN, ulnar nerve.

* Corresponding author. Department of Kinesiology, McMaster University, 1280 Main Street, West Hamilton, ON L8S 4K1 Canada.

E-mail addresses: turcocv@mcmaster.ca (C.V. Turco), elsayej@mcmaster.ca (J. El-Sayes), savoiemj@mcmaster.ca (M.J. Savoie), fassethj@mcmaster.ca (H.J. Fassett), lockemb@mcmaster.ca (M.B. Locke), nelsonaj@mcmaster.ca (A.J. Nelson).

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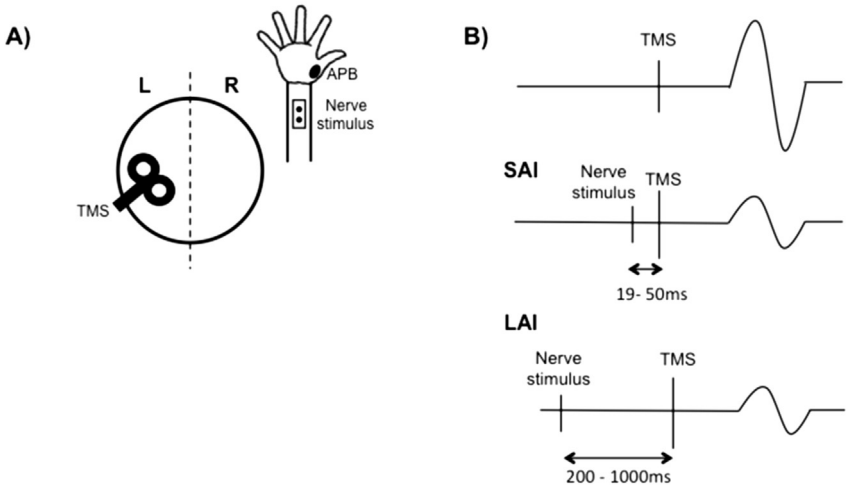

Fig. 1. Schematic of SAI and LAI.
A) SAI and LAI are evoked by delivering nerve stimulation (shown as MN over wrist) contralateral to the M1 receiving the TMS pulse. SAI/LAI are recorded via surface EMG from the TMS targeted muscle of interest (APB shown). **B)** Top Panel: Unconditioned MEP produced by a single TMS pulse. Middle Panel: SAI is induced by a nerve stimulus delivered 19–50 ms before the TMS pulse depending on nerve composition (see text) resulting in inhibition of the MEP. Bottom Panel: LAI is induced by a nerve stimulus delivered 200–1000ms before the TMS pulse [2], resulting in inhibition of the MEP.

generating and modifying this process, and the relation of SAI/LAI to human cognition and behavior. However, our current understanding of SAI/LAI is far from sufficient. LAI is significantly understudied compared to SAI and the neural circuitries underlying these phenomena are unclear. Therefore, we aim to identify the existing gaps in knowledge that, if filled, will yield significant advance in the use of SAI and LAI as reliable tools to better understand human nervous system function. The tables in this review provide exhaustive accounts of SAI/LAI in the literature.

Factors that influence the presence and magnitude of SAI/LAI

Nerve composition influences the interstimulus range at which SAI is evoked. Mixed nerves include afferents originating from joint, muscle and cutaneous mechanoreceptors while cutaneous nerves include only the latter. DN stimulation of D2 evokes SAI from 20 to 50ms in APB and FDI [3,4] and for D5 evokes SAI from 20 to 45ms in ADM [4,5]. In contrast, following stimulation of the mixed MN at the wrist, SAI is observed over a smaller ISI range extending from 18 to 28ms in FDI [6] and APB [1]. Although both nerve types contain cutaneous afferents that span a wide range of conduction velocities, only mixed nerves contain the largest and fastest conducting muscle/joint afferents that may truncate the temporal window in which SAI occurs. A possible mechanism for this action is such that S1 neurons receiving fast-conducting proprioceptive input experience post-excitation inhibition therefore the arrival of subsequent slower conducting afferents terminate on hyperpolarized neurons. In macaques, post-excitation inhibition persists for ~10–20ms following the period of excitation [7]. Despite the differences in the ISI range to evoke SAI, both cutaneous and mixed nerves appear to yield similar SAI magnitude (Table 1**)** [3,8].

Following mixed MN stimulation, LAI is evoked at ISIs from 200 to 1000ms in FDI. Following D3 stimulation, LAI occurs at ISIs from 200 to 600ms in FDI [2]. The difference in ISI range between nerves may relate to the specific cortical areas targeted by proprioceptive (i.e. areas 3a/2 [9]) versus cutaneous afferents (area 1/3b [9]) including S2 and PPC [10–18]. The magnitude of LAI is similar between mixed and cutaneous nerves [2,19,20].

SAI increases with greater nerve stimulation intensity. For mixed MN and UN, increasing nerve stimulation intensity from ST (minimum intensity for perception) to MT (minimum intensity for muscle twitch) increases SAI [21]. Similarly, MN-evoked SAI increases up to 3xST and plateaus at greater stimulation intensities [6,22]. Recently, the relationship between SAI and the amplitude of the SNAP recorded at the elbow was assessed [8]. These data indicate that SAI increases with greater contribution of the sensory volley (i.e. as SNAP increases) and plateaus when presumably all sensory afferents are recruited. For MN, both sensory afferents and motor efferents contribute to the SNAP. Growth in SNAP amplitude beyond ~50% of the maximum SNAP for MN is contributed by antidromic efferents and not sensory afferents as determined by the relationship with concomitantly recorded SEPs [8]. Therefore, for MN, SAI magnitude recorded from the FCR increases until all sensory afferents are recruited (i.e. ~50% of maximum SNAP), which corresponds to ~1.2xMT for a muscle twitch in APB [8]. For DN, SAI recorded from FDI and FCR increases until the SNAP is near maximum (i.e. 84–100% SNAP) which corresponds to ~3xST [8]. Therefore, for both nerve types, maximum SAI is achieved at the intensity expected to recruit all available sensory afferents (i.e. 3xST for DN, 1.2xMT for MN). A follow-up study shows that LAI is also sensitive to nerve stimulation intensity. MN-evoked LAI from FDI increases with the added recruitment of sensory afferent fibers, peaking at 50% of the maximum SNAP [19]. However, in contrast to SAI, LAI from D2 stimulation only emerges, and is maximal, at 50% of the maximum SNAP [19]. Therefore, the stimulation intensity to achieve maximum LAI is at ~50% of the maximum SNAP (i.e. 2 × ST for DN, MT for MN) [19].

In consideration of nerve stimulation intensity, it is important to avoid painful sensation. SAI is reduced immediately following the removal of pain-inducing hypertonic saline infusion into the FDI muscle, while the reduction in LAI is delayed by 15 min [23]. As suggested by the authors, pain-induced reduction of afferent inhibition may be a protective response, as less inhibition to the muscle may allow the restoration of motor function [23]. LAI is also reduced in complex regional pain syndrome [24], suggesting an association with the sensory feature of pain processing. Therefore, delivery of high stimulation intensities that elicit pain may decrease SAI and LAI.

The depth of afferent inhibition depends on the proximity of the nerve stimulated to the muscle from which SAI/LAI is recorded.