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Effects of afferent stimulation rate on inhibitory spinal pathways in hemiplegic spastic patients

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HIGHLIGHTS

- The major finding of this study was that, contrary to that observed at the Ia fibre-α motoneurone synapse, increasing the conditioning stimulus rate in hemiplegic patients leads to an increase in the synaptic efficacy of inhibitory spinal circuits.
- For the first time, a significant correlation was found between the severity of flexor carpi radialis muscle spasticity and the decrease of disynaptic inhibition.
- Reinforcement of inhibitory spinal networks by repetitive stimulation of afferent fibres opens new vistas for novel spasticity therapies based on non-invasive plasticity techniques.

ABSTRACT

Objective: It has recently been demonstrated in the cat and in healthy subjects that the effects of repetitive afferent fibre stimulation depends on the target spinal neurones. The purpose of this series of experiments was therefore to determine whether central nervous system lesions modify the behaviour of the inhibitory spinal pathways in response to repetitive activation of afferent fibres.
Methods: The H-reflex technique was used to study the effect of increasing the conditioning stimulus rate from 0.16 to 1 Hz on disynaptic inhibition and on presynaptic Ia inhibition on the affected side of 36 hemiplegic patients.
Results: The major finding was that, similar to results previously obtained in healthy subjects, increasing the conditioning stimulus rate in hemiplegic patients leads to an increase in the synaptic efficiency of inhibitory spinal circuits. Furthermore, a significant correlation was found between the severity of flexor carpi radialis muscle spasticity and the amount of disynaptic inhibition.
Conclusions: The reinforcement of inhibitory spinal networks induced by repetitive stimulation of afferent fibres is preserved in spastic patients, whereas the mechanisms underlying this phenomena might be altered.
Significance: The results of these experiments open up a number of possibilities for novel spasticity therapies based on non-invasive techniques.

1. Introduction

Ia afferent fibres from muscle spindle primary endings have monosynaptic excitatory projections to the α-motoneurones innervating the muscle from which they originate (the monosynaptic arc reflex). Transcutaneous electrical stimulation of these Ia afferent fibres produces a synchronous response in the corresponding muscle known as the H-reflex (Hoffmann 1918, 1922; Magladery and McDougal, 1950; Eccles and Rall, 1951). It has long been known that repetitive activation of Ia afferent fibres, achieved by increasing the electrical stimulation rate, reduces the H-reflex amplitude (Magladery and McDougal, 1950) (Fig. 1A and B). This depressive effect of stimulus rate on H-reflex amplitude has been termed post-activation depression (Crone and Nielsen, 1989) and probably involves changes in the readily releasable transmitter

Abbreviations: CNS, central nervous system; ECR, extensor carpi radialis; FCR, flexor carpi radialis; H_{max}, maximum H-reflex response; ISI, conditioning test interstimulus interval; M_{max}, maximum M response; SOL, soleus.

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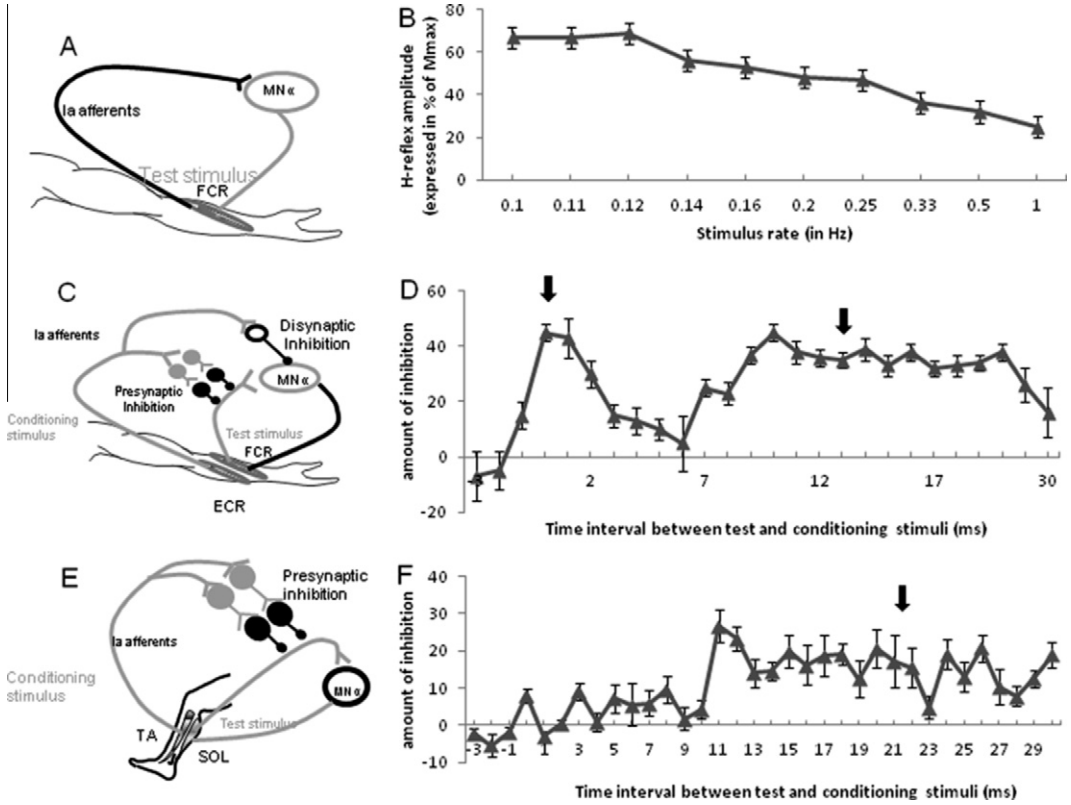

Fig. 1. Diagram and time course of the variations of post-activation depression, disynaptic inhibition directed from ECR to FCR, presynaptic inhibition of FCR and SOL Ia terminals. A: diagram of monosynaptic FCR arc reflex. B: modification of FCR H-reflex amplitude induced by modifying the stimulation rate in one representative healthy subject. *Abscissa*: stimulus rate in Hz. *Ordinate*: amplitude of the FCR H-reflex (expressed in% of M_{max}), each point represents the mean value of 10 H-reflexes, vertical bars represent the standard error of the mean (±1 SEM). C: diagram of disynaptic inhibition directed from ECR to FCR and presynaptic inhibition on FCR Ia terminals. D: time course of the variations of the FCR H-reflex induced by a stimulation of the radial nerve in one healthy representative subject. *Abscissa*: time interval between the conditioning (radial) and test (median) nerve stimulation in milliseconds, progressively varied from −3 to 30 ms. Left arrow indicates the conditioning-test interval corresponding to the maximum value of disynaptic inhibition at which the experiments with different stimulus rates were performed. The right arrow (conditioning test interval 13 ms) indicates the time interval at which the experiments studying the effects of varying the stimulus rate on presynaptic inhibition of FCR Ia terminals were performed. *Ordinate*: Amount of inhibition. The amount of inhibition was defined as: ((mean unconditioned *H* value − mean conditioned *H* value)/mean unconditioned *H* value) × 100. Twenty reflexes (10 unconditioned and 10 conditioned reflexes) were evoked for each time interval. Vertical bars represent the standard error of the mean (±1 SEM). E: diagram of presynaptic inhibition on SOL Ia terminals. F: time course of the variation of the SOL H-reflex induced by the stimulation of the posterior tibial nerve in one representative healthy subject. *Abscissa*: time interval between the conditioning (common peroneal nerve) and test (posterior tibial nerve) nerve stimulation in milliseconds, progressively varied from −3 to 30 ms. The arrow (conditioning-test interval 21 ms) indicates the time interval at which the experiments studying the effects of varying the stimulus rate on presynaptic inhibition of SOL Ia terminals were performed. *Ordinate*: Amount of presynaptic Ia inhibition. The amount of presynaptic Ia inhibition was defined as: ((mean unconditioned *H* value − mean conditioned *H* value)/mean unconditioned *H* value) × 100. Twenty reflexes (10 unconditioned and 10 conditioned reflexes) were evoked for each time interval. Vertical bars represent the standard error of the mean (±1 SEM).

pool within the presynaptic terminals (Lev-Tov and Pinco, 1992). Moreover, it has been generally assumed that post-activation depression does not occur exclusively at Ia fibre-α motoneurone synapse but probably at all synapses (i.e., afferent fibre-interneurone synapses, interneurone-α motoneurone synapses, etc.), and that, in the spinal cord, this mechanism depresses synaptic transmission at all synapses. Hammar et al. (2002) demonstrated in the cat that this is not the case since they revealed that the degree of post-activation depression differs depending on the type of afferent fibre and, for the collaterals of a given afferent fibre, on the type of the target neuron. This unexpected finding has since been confirmed in humans. Lamy et al. (2005) assessed the effects of varying the group I afferents activating various intermediate synapses within spinal inhibitory pathways in healthy humans, including disynaptic inhibition between extensor carpi radialis (ECR) and flexor carpi radialis (FCR) muscles and presynaptic inhibition of both FCR and soleus (SOL) Ia terminals. They showed that increasing the stimulation rate of the conditioning volley results in an increase in the amount of both disynaptic inhibition and presynaptic Ia inhibition regardless of the motor nucleus involved. In other words, whereas increasing group I afferent stimulation rate depresses transmission at the Ia fibre-α motoneurone synapse, increasing conditioning group I afferent fibre stimulation rate enhances transmission in inhibitory spinal circuits. This study confirmed the results obtained in the cat and demonstrated that in healthy humans, whereas increasing Ia afferent stimulation rate from 0.1 to 1 Hz (Fig. 1B) always results in a depression of Ia fibre-α motoneurone synaptic efficiency, it results in an increase of transmission efficiency through some spinal pathways, including disynaptic inhibition and presynaptic Ia inhibition.

Decreased post-activation depression at the Ia fibre-α motoneurone synapse in patients with central nervous system (CNS) lesions has been extensively reported (Nielsen et al., 1995; Aymard et al., 2000; Schindler-Ivens and Shields, 2000; Masakado et al., 2005; Lamy et al., 2009) and is one of the few changes in transmission in spinal pathways consistently associated with severity of spasticity (Schindler-Ivens and Shields, 2000; Grey et al., 2008; Lamy et al., 2009; Achache et al., 2010). To the best of our knowledge, impaired responses to repetitive afferent fibre stimulation have only ever been studied at the Ia fibre-α motoneurone synapse in patients with CNS lesions. The purpose of the present study was thus to investigate if in these patients similar impairments occur in oligosynaptic pathways mediating disynaptic and presynaptic inhibition. To this end, we explored the effects of increasing the