Emerging Therapies for Spastic Movement Disorders

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KEYWORDS

• Spasticity • Muscle stiffness • Peripheral mechanism • Stroke • Brain injury
• Hyaluronidase • Hyaluronic acid • Hyaluronan hypothesis

KEY POINTS

- Neural mechanisms of spasticity do not fully explain the motor dysfunction in patients with spastic disorders.
- Peripheral non-neural mechanisms are not fully understood.
- The hyaluronan hypothesis postulates that the accumulation of hyaluronan, which functions as a lubricant in the extracellular matrix of muscle, may lead to the development of muscle stiffness.
- Hydrolysis of the accumulated hyaluronan may be safely achieved using local injections of the enzyme hyaluronidase to reduce muscle stiffness and increase both passive and active motion.
- Hyaluronidase is a potential emerging treatment for the management of patients with spastic movement disorder.

INTRODUCTION

Muscle stiffness and spasticity cause severe disability in approximately 12 million people after neurologic injury of cerebral or spinal origin, such as stroke, cerebral palsy, spinal cord injury, and multiple sclerosis.[1] The prevalence of spasticity increases over weeks and months after the neurologic injury,[2] leading to muscle stiffness that persists for years, contributing to further disability and slowed recovery. Upper limb spasticity and muscle stiffness are associated with reduced functional independence and a fourfold increase in direct care costs during the first year after stroke alone.[3,4] They are challenging to treat, because the underlying mechanisms are not fully understood.[4,5]

Spasticity is classically defined as a velocity-dependent increase in tonic stretch reflexes resulting from hyperexcitability of the stretch reflex[6] because of decreased

Disclosures: New York University has filed a patent on the use of hyaluronidase for muscle stiffness. Dr P. Raghavan is cofounder of MovEase, Incorporated. This article discusses the off-label use of hyaluronidase for muscle stiffness.

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cortical influences on the inhibitory brainstem descending pathways to the spinal cord.[7] The imbalance between inhibitory cortical and brainstem pathways from the ventromedial reticular formation and the excitatory brainstem pathways from the bulbopontine tegmentum and the vestibular nucleus are thought to reduce presynaptic inhibition causing spasticity[8] (Fig. 1). However, hyperreflexia is only one component of the problem in patients with spasticity,[9–11] and the extent of hyperreflexia may not be correlated with the extent of muscle stiffness.[12,13] Nevertheless, central nervous system (CNS) depressants (eg, benzodiazepines, baclofen, and tizanidine) are commonly used to treat muscle stiffness, but they also produce muscle weakness, fatigue, and sleepiness.[14] Botulinum toxin injections are effective in reducing muscle overactivity in patients with spasticity,[15] but it has long been known that muscles can be stiff even in the absence of electromyography (EMG) activation. Thus, although neural mechanisms may initiate spasticity, non-neural peripheral mechanisms clearly play a role in the development and exacerbation of muscle stiffness.[16,17]

Increased resistance to passive stretch can occur because of secondary non-neural changes in muscle fibers, collagen tissue, and tendon properties.[18,19] Early experiments on muscle properties[20] showed that the faster the change in muscle length, the greater is the passive tension generated in the muscle in the absence of muscle activation. This can be quantified with the length-tension curve, which shows a steeper slope in spastic compared with nonspastic muscles at equivalent speeds (Fig. 2). This non-neural, or passive stiffness, is distinct from the increase in EMG activity (neural response) when a muscle is stretched at faster speeds[21]

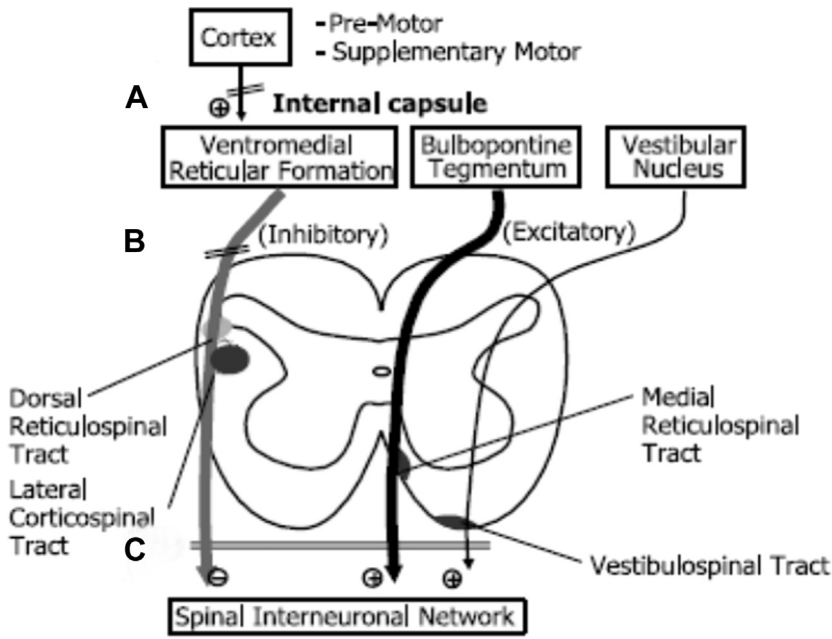

Fig. 1. CNS injury disrupts inhibitory descending pathways controlling spinal stretch reflex excitability. A = corticobulbar fibers; B = dorsal reticulospinal pathway; C = loss of all supraspinal control. (*From* Sheean G. The pathophysiology of spasticity. Eur J Neurol 2002;9(Suppl 1):3–9; with permission.)