Advances in the Management of Multiple Sclerosis Spasticity: Multiple Sclerosis Spasticity Nervous Pathways

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Key Words

Cannabinoid receptors · Corticospinal tract injury · Glutamatergic pathways · Motor cortex plasticity · Stretch reflex · THC:CBD oromucosal spray

Abstract

Background: Spasticity arises from hyperexcitability of the neural stretch reflex arc secondary to injury of the corticospinal tract. In response to injury, the density of glutamatergic inputs from afferent 1A fibers to motor neurons increases dramatically and adaptive changes occur in the morphology of microglia cells in the spinal cord. **Summary:** Involvement of the endocannabinoid system in pathophysiological mechanisms responsible for spasticity has been demonstrated in animal models of MS. Stimulation of cannabinoid (CB)₁ receptors reduces the hyperglutamatergic drive from sensory afferents to spinal cord motor neurons and blocks the synaptic effects of activated microglia and pro-inflammatory mediators (e.g. TNF- α) on glutamatergic transmission. Enhancing corticospinal tract excitability through intermittent theta burst stimulation inhibits the stretch reflex and spasticity by promoting long-term potentiation, a form of synaptic plasticity that requires stimulation of CB₁ receptors. Evidence indicates that the antispasticity effects of THC:CBD oromucosal spray (Sativex[®]) are associated with enhanced

cortical long-term potentiation. **Key Messages:** Glutamatergic and GABAergic pathways are involved in the regulation of muscle tone. CB₁ receptors, which are associated with movement, postural control, and pain and sensory perception, influence glutamatergic pathways. THC:CBD oromucosal spray was shown to reverse motor cortex plasticity from long-term depression through long-term potentiation of synaptic transmission, thereby restoring, at least in part, effective corticospinal inputs to spinal circuits.

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Pathophysiology of Muscle Tone Control and Spasticity Generation

The most plausible mechanism at the basis of spasticity is hyperexcitability of the neural stretch reflex arc secondary to injury of the corticospinal tract [1]. The stretch reflex arc is composed mainly of afferent 1A fibers activated by muscle stretch and detected at the level of muscle spindle; these fibers activate alpha motor neurons directed to the same muscle. Activation of secondary motor neurons counteracts muscle elongation by causing contraction. It is generally accepted that the corticospinal tract has inhibitory control of this mechanism.

The pathophysiological mechanism of stretch reflex arc hyperexcitability induced by selective injury has been investigated at the level of single neuron morphology. In response to corticospinal tract injury, the density of glutamatergic inputs from afferent 1A fibers to motor neurons increases dramatically and adaptive changes occur in the morphology of microglia cells in the spinal cord [2].

Given the relevance of reactive microgliosis in the pathophysiology of MS, its possible role in the regulation of excitatory synaptic inputs to central neurons was addressed. In the presence of microglial cells derived from primary cultures of immortalized cell lines, the shape and duration of spontaneous excitatory postsynaptic currents (sEPSCs), a neurophysiological measure of glutamatergic inputs to motor neurons, was increased [3]. Inhibition of this effect by etanercept, a tumour necrosis factor (TNF)- α antagonist, indicated that microgliosis modulates glutamatergic transmission contributing to hyper-excitability of corticospinal reflexes through the release of pro-inflammatory mediators.

Role of the Endocannabinoid System in Control of MS Spasticity

The role of the endocannabinoid system in controlling spasticity has been demonstrated in various animal models of MS.

In mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), modulating the endogenous tone of endocannabinoids through various pharmacological manipulations that inhibited the synthesis, transport or degradation of anandamine reduced the resistance to flexion; this effect was inhibited in the presence of CB₁ and CB₂ receptor antagonists [4]. In this same mouse model of MS, THC + CBD at a 1:1 ratio (equivalent to Sativex[®]) reduced spasticity in a dose dependent manner; the effect at a dose of 10 mg/kg was similar to that of baclofen 5 mg/kg [5].

In chick embryo spinal cords, stimulation of CB₁ receptors with the specific cannabinoid agonist WIN inhibited the frequency of sEPSCs by reducing glutamatergic inputs to alpha motor neurons, but had no effect on GABAergic inputs, indicating that cannabinoids ameliorate spasticity by selectively reducing the hyperglutamatergic drive from sensory afferents to spinal cord motor neurons [6]. Elsewhere, Rossi and colleagues demonstrated in CREAE mice that stimulation of CB₁ receptors with the cannabinoid agonist HU201 attenuated alteration in the shape and duration of striatal glutamate-mediated sEPSCs by TNF- α [7].

Collectively, the results of these studies confirm the role of the endocannabinoid system in pathophysiological mechanisms responsible for the generation of spasticity.

Another interesting means of controlling spasticity involves modulation of plasticity at the level of the motor cortex. Repetitive transcranial magnetic stimulation (rTMS) induces adaptations in cortical neuronal circuitries. Application of rTMS over the leg motor cortical area in 10 human volunteers reduced activation of the stretch reflex by increasing corticospinal drive to the spinal cord in specific spinal circuitries [8]. A refinement of this technique known as theta burst stimulation (TBS) induces long-term potentiation of synaptic transmission in the motor cortex after only a short application period (90–120 seconds) [9]. In a study involving 20 MS patients with lower limb spasticity, the group who received 5 sessions of rTMS in the form of intermittent TBS showed a significant and persisting reduction in the stretch reflex (measured by H/M amplitude ratio) and improvement in modified Ashworth Scale scores compared with the group who received sham stimulation [10]. To explore the potential involvement of the cannabinoid system on TBS-induced synaptic plasticity in humans, the effects of THC:CBD oromucosal spray on continuous TBS and intermittent TBS protocols were tested in patients with MS [11]. Whereas continuous TBS induced inhibition of motor-evoked potentials (MEP) before exposure to THC:CBD oromucosal spray, it caused persisting enhancement of MEP amplitude at 4 weeks after exposure, implicating the cannabinoid system in the modulation of synaptic plasticity.

Confirmation that cannabinoids are involved in ameliorating spasticity, not only by regulating spinal cord circuits, but by regulating the excitability of the motor cortex, has come from a recent observation in a group of MS patients who had genetic variants associated with reduced expression of cannabinoid receptors [12]. Individuals with a long number of repeats in the promoter region of cannabinoid receptors had reduced CB₁ receptor protein expression in peripheral tissues, possibly indicative of a defective cannabinoid receptor mechanism. A particularly intriguing study result was the association between a 'long AAT' phenotype and poor clinical response to rehabilitation. Whereas a classical rehabilitation protocol produced some improvement in Expanded Disability Status Scale and spasticity 0–10 Numerical Rating Scale scores in patients with a preserved genetic cannabinoid signal, there was no effect in those with altered cannabinoid regulation mechanisms [manuscript submitted].

Disclosures/Conflict of Interest

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