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The pathophysiology of focal hand dystonia

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Abstract

Focal hand dystonia is a disabling movement disorder, often task-specific, that leads to impaired hand use. In addition to a genetic predisposition, environmental risk factors including repetitive use and musculoskeletal constraints are contributory. Although the underlying cause is unknown, recent studies have identified several key mechanisms that may play a part in its genesis. Failure of inhibition, abnormal sensorimotor integration, and maladaptive plasticity seem to be important. Understanding the underlying physiology may lead to the design of novel therapies.

Dystonia is a debilitating movement disorder characterized by co-contraction of antagonist muscles and overflow to extraneous muscles, leading to abnormal sustained postures and impaired motor control. Symptoms may be generalized and affect muscle groups throughout the entire body, or be focal and restricted to a specific region such as the face, neck, or a single limb. The exact pathophysiology underlying dystonia is currently unknown, although several thematic principles are emerging.

Most of our current understanding of dystonia comes from the study of focal hand dystonia, an enigmatic form of dystonia that has been an area of intense scientific research over the last two decades. The spectrum of focal hand dystonia includes the task-specific entities of writer's cramp, musician's dystonia, and other occupational hand dystonias. The disorder can also generalize across task and the dystonia may even be present at rest. The restricted symptomatology has made it amenable to study. Its association with skilled manual performance has stimulated interest in its potential as a model disease for understanding basic mechanisms of hand function. A wide body of literature using a variety of sophisticated neuroimaging, electrophysiological, and psychophysical techniques has helped push forward the understanding of its pathogenesis and treatment.[1,2] Studies have identified a wide range of abnormalities throughout the nervous system with the most consistent findings revealing deficient inhibitory mechanisms, aberrant sensation and sensorimotor processing, and maladaptive plasticity.

Lack of inhibition

A common finding in studies of patients with all forms of dystonia is a lack of inhibition, suggesting that this is a fundamental problem in its genesis. Nervous system function requires a balance between excitation and inhibition of neural circuits. The motor system uses a variety of forms of inhibition to control the precision and smoothness of movement. In the hand, this is particularly important as individuated finger movement requires selective and specific

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activation of muscles moving the intended fingers and inhibition of uninvolved ones. In the dystonic hand, wire electromyographic recording identified abnormally prolonged muscle firing, with cocontraction and overflow of activation of inappropriate muscles.[3]

There is evidence for abnormal inhibition at multiple levels of the nervous system in patients with focal hand dystonia. Reciprocal inhibition is one form of inhibition which allows for control of muscles around a single joint. Lack of reciprocal inhibition at the spinal level leads to cocontraction of antagonistic muscles, leading to dystonic posturing in patients with writer's cramp.[4] Abnormal inhibition has also been demonstrated in patients with focal hand dystonia at the cortical level by measuring intracortical inhibition using noninvasive transcranial magnetic stimulation.[5] The abnormal intracortical inhibition exists in both hemispheres despite unilateral symptoms. Another form of inhibition that has been recently identified in the motor system is surround inhibition, a mechanism by which selective control of individual muscles can be achieved by simultaneous inhibition of surrounding muscles. Surround inhibition is abnormal in focal hand dystonia, suggesting a possible mechanism for the clinical manifestation of lack of individuated finger movements and overflow to muscles not intended in the desired movement.[6] Mechanistically speaking, inhibitory interneurons that use GABA as a neurotransmitter seem to be dysfunctional in focal hand dystonia[7,8] and this may mediate the abnormal surround inhibition at the cortical level.

Risk factors: Endophenotype and repetitive use

The current evidence supports both a genetic and an environmental role in the pathogenesis of focal hand dystonia. A fair percentage (30%) of patients with various forms of primary focal dystonia were demonstrated to have at least one first degree relative with dystonia in a recent study, supportive of a genetic contribution.[9] Furthermore, abnormal physiologic measures have been demonstrated in patients with focal hand dystonia in both cerebral hemispheres despite unilateral symptoms, suggesting an underlying predisposition that is likely genetic and known as an endophenotype.[10,11] In patients with sporadic cervical dystonia, unaffected relatives were shown to have abnormal sensory discrimination thresholds detected in the hand, further supporting the concept of an endophenotype underlying dystonia.[12] Whether the abnormal physiological findings identified in various studies are all endophenotypic traits that predispose to developing dystonia instead of reflecting expression of the disease is subject to speculation and may only become clear with further research. The association between highly skilled manual performance and the development of focal hand dystonia is also suggestive of an environmental contribution from repetitive use. However, the observation that the majority of performing artists do not develop focal hand dystonia is further suggestive of an underlying predisposition. A primate model where monkeys who were trained to repetitively perform a complex manual task developed symptoms similar to dystonia supports this learning hypothesis.[13] Sensory mapping of the primate hand representation in the cortex was disorganized, similar to findings from focal hand dystonia patients. Furthermore, a recent study suggests that there may be additional underlying risk factors in the form of musculoskeletal defects that in combination with repetitive use lead to dystonia.[14] Interestingly, patients with psychogenic dystonia also demonstrate abnormal cortical excitability and failure of inhibition,[15] suggesting that there may be a common endophenotypic predisposition to both organic and functional forms of dystonia.

Abnormal motor preparation

A remarkable characteristic of the presentation of many patients with focal hand dystonia is the exquisite task-specificity. Symptoms typically manifest only when patients are writing or playing an instrument and not with other manual tasks. The curious aspect of task specificity led to it being attributed to psychiatric illness in the early 1900's. Musicians with focal hand

dystonia often complain of symptoms that are elicited only while playing specific musical passages and not with others. This suggests that there is a deficiency at the level of the organization of established motor programs and not simply movement. Several studies have demonstrated measures of abnormal movement preparation[16,17] in patients with focal hand dystonia, supporting the hypothesis of defective motor programming. Neuroimaging studies have also shown underactivity of motor areas important for movement preparation during writing compared to normal controls,[18] although the findings are less consistent across other studies likely due to differences in methodology. Studies have also demonstrated that abnormal physiologic measures such as defective intracortical inhibition are present with movement and not at rest,[19] further supporting the concept of defective motor programming.

Sensory abnormalities

Despite the predominance of motor symptoms, there is a great deal of evidence for abnormalities of sensory processing in patients with focal hand dystonia. Patients with various forms of focal dystonia often report symptoms of pain or discomfort in the affected area prior to the development of motor symptoms.[20,21] Somatosensory receptive fields are abnormally enlarged and disorganized in patients with focal hand dystonia in the cortex.[11,22,23] These findings are similar to those in a primate model of focal hand dystonia.[13] The abnormalities are present when testing the affected or unaffected hand. Patients with focal hand dystonia have difficulty discriminating sensory stimuli in both the spatial and temporal domain.[24,25] These perceptual abnormalities are also present in the hands of patients with blepharospasm and cervical dystonia, focal forms of dystonia without hand involvement, suggesting that the findings are a widespread endophenotypic trait rather than simply a result of repetitive use.[26]

In addition, there seems to be a modulatory effect of sensory input on the dystonic movements. Patients may report a sensory trick, where the symptoms may improve upon touching or holding the dystonic hand with the contralateral hand. Tonic vibration leads to worsening of dystonia, whereas anesthetic block can relieve symptoms.[27] Furthermore, sensory retraining in the form of tactile discrimination practice[28] can ameliorate motor symptoms, suggesting that the sensory abnormalities may drive the motor disorder. How the sensory abnormalities lead to the motor manifestations or whether they are solely responsible for the motor disorder is unclear, although they are the subject of debate.[29,30]

Recent evidence for abnormalities in sensorimotor integration, the means by which the sensory system interacts with the motor system, have been demonstrated in focal hand dystonia and may provide a possible explanation for how the sensory findings lead to the motor symptomatology. Modulation of sensory processing in response to movement, known as sensory gating, is abnormal in patients with focal hand dystonia.[31] The somatotopic organization of sensorimotor interactions is also abnormal in patients with focal hand dystonia.[32] The marked sensory deficits may be further translated into abnormal movements by abnormalities in sensorimotor integration, adding another layer of complexity to the pathophysiology.

Maladaptive plasticity

As new motor skills are acquired, nervous system plasticity allows for flexible change in circuits to accommodate adaptation to a dynamic environment and facilitate learning and memory. However, the same mechanisms of plasticity must be bounded in order to regulate for excessive change and destabilization. Homeostatic plasticity is a mechanism that the nervous system utilizes to allow for this regulation. These mechanisms have been demonstrated to be abnormal in focal hand dystonia.[33,34] Using a paradigm where sensory nerve stimulation was paired with motor cortex stimulation with magnetic stimulation to induce plasticity in the motor cortex, patients with focal hand dystonia demonstrated abnormally enhanced plasticity

and an inability to regulate homeostatic mechanisms. This unconstrained plasticity may explain why over time, repetitive hand use leads to uncontrolled reorganization of sensorimotor maps and the eventual development of dystonic symptoms. There may be an enhanced drive to plastic change as well as an inability to downregulate the changes once they occur.[35] Furthermore, a recent study demonstrated abnormal homeostatic plasticity in sensorimotor circuits of the hand in patients with cranial and cervical dystonia, suggesting that deficient homeostatic plasticity may itself be a generalized phenomenon and an endophenotypic trait in focal dystonias.[36]

Therapeutic interventions based on neurophysiology

The identification of predisposing risk factors and putative mechanisms for focal hand dystonia has led to the design of novel behavioral therapies guided by physiological findings. As repetitive hand use seems to be a key factor in the development of focal hand dystonia, training the hand back to a normal state has been studied by several research groups. Sensorimotor retuning, a training paradigm where the uninvolved fingers are immobilized using splints while practicing sequential movements, led to an improvement in dystonic symptoms as well as more ordered sensory somatotopy.[37] Sensory retraining in the form of Braille learning has been shown to improve spatial discrimination deficits as well as symptoms of focal hand dystonia.[28] Motor training in the form of retraining individuated finger movements led to mild improvements in handwriting in patients with writer's cramp.[38,39] However, none of the training based therapies have led to sustained long-term benefit.

Initial benefits from retraining may be impeded by underlying aberrant homeostatic plasticity, which may lead to a return of dystonic symptoms. In the sensory training studies, after patients stopped the exercises, they remanifested symptoms on long term follow-up.[28] Furthermore, intensive training in the presence of impaired regulation may drive the system back into a pathologic state. Effective intervention will require careful restoration of normal physiology in a setting prone to excessive neural adaptation. Markers of normalization that could be followed over time in addition to clinical symptoms include intracortical inhibition, sensory discrimination and sensorimotor organization.

Conclusions

Focal hand dystonia is an intriguing disorder of motor control that is continuing to be better understood. Deficient inhibition, abnormal sensation and sensorimotor processing and maladaptive plasticity are some of the key contributory mechanisms that have been identified in research studies. Which one of these processes is primary in importance is not clear. Further discoveries in neuroimaging, behavioral training and pharmaceuticals will hopefully guide more effective avenues for therapy.

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Figure 1.
Writer's cramp. While writing, the patient's fingers extend involuntarily and he is unable to flex them.

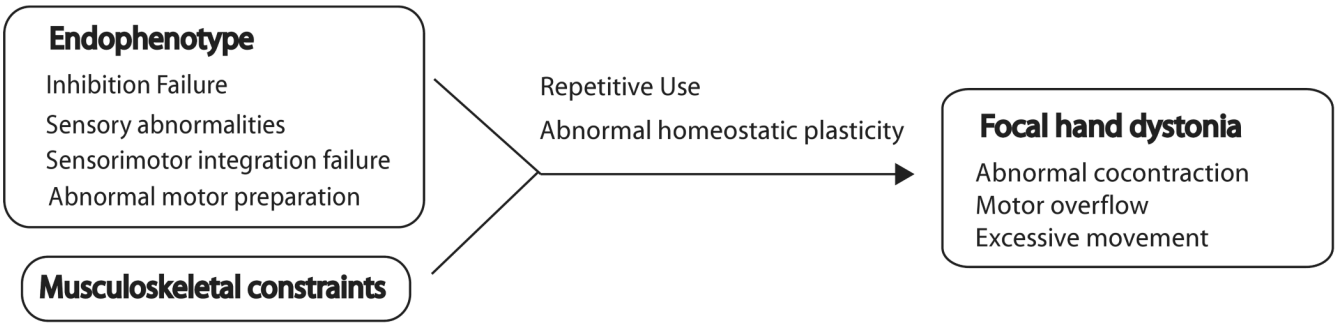

Figure 2.
Summary diagram of pathophysiological mechanisms implicated in the development of focal hand dystonia