

Pathophysiology of Idiopathic Focal Dystonia



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Acknowledgements:

I am very grateful to Dr Mark Baker and Dr Anais Thouin for their helpful comments on the manuscript.

The term dystonia refers to a group of conditions in which sustained muscular contractions lead to abnormal posturing and repetitive movements.¹ The primary or idiopathic dystonias are non-degenerative conditions where dystonia (with the possible exception of a co-existent tremor) is the only clinical abnormality. Within this group are the focal dystonias in which dystonic movements of the eyelids (blepharospasm), neck (cervical dystonia), mouth and jaw (oro-mandibular dystonia), vocal cords (laryngeal dystonia) or hand (focal hand dystonia) develop in adulthood. Focal hand dystonia is often task specific, affecting fine, repetitive hand movements. The commonest forms are writer's cramp and musician's dystonia. This article will give a brief overview of the aetiology of idiopathic focal dystonia, concentrating on insights gained from neurophysiological abnormalities detected in patient studies.

Genetics

To date, no causative genetic mutations have been identified in late onset idiopathic focal dystonia. In those patients with a positive family history, inheritance is mostly complex and non-mendelian, although a small number of families with autosomal dominant inheritance have been reported. DYT4 has been described in a single family, with the majority of affected members presenting with laryngeal dystonia, which eventually becomes generalised.² No chromosomal locus has been identified. DYT7 was identified in a family with affected members displaying either cervical or focal hand dystonia.³ Linkage analysis has mapped this condition to chromosome 18. The same locus has been implicated in a separate family with three brothers affected by writer's cramp.⁴ DYT13 has been reported in a family with dystonia presenting in the head and neck or in the arms⁵ and has been mapped to chromosome 22.⁶

A mutation within the DYT1 gene (torsin A) is the commonest identifiable cause of primary generalised dystonia. It most commonly presents in childhood with focal lower limb dystonia followed by generalisation, with a tendency to spare the head and neck.⁷ However, there is a degree of phenotypic variability and mutations have been identified in patients with multifocal or segmental dystonia presenting as writer's cramp in both childhood and adulthood.⁸ DYT6 is a more recently recognised form of generalised dystonia caused by mutations in the THAP1 gene on chromosome 8.⁹ It typically presents in childhood or adolescence with focal

onset dystonia of the head, neck or limbs and there is often generalisation. Frequent involvement of the cervical, laryngeal and cranial muscles differentiates this condition from DYT1. Again, there is wide phenotypic variability and it can present with late onset focal or segmental dystonia.¹⁰

The above points clearly demonstrate that a particular gene can be associated with a variety of forms of dystonia. This suggests that different forms of late onset focal dystonia share a common genetic background, and that the expression of a particular dystonic phenotype rests on the interplay between other genetic and environmental factors.¹¹

Cortical reorganisation

Monkeys trained to carry out repetitive hand movements over many months can develop abnormal posturing reminiscent of focal hand dystonia.¹² Subsequent recordings from individual neurones in sensory cortex of these monkeys revealed enlarged receptive fields and overlapping representations of individual digits. This change in cortical representation is presumed to be because the maintenance of precise somatotopy depends upon the temporal and spatial separation of afferent inputs, which breaks down during unnaturally repetitive fine motor tasks.¹³ Such movements are comparable with those required for hand writing or playing a musical instrument and similar abnormalities of cortical reorganisation have been demonstrated in patients with musician's dystonia.¹⁴ It has been hypothesised that these enlarged receptive fields map inappropriately onto networks of neurones in the motor system and in doing so produce dystonic movements.¹³

Sensory overload from repetitive hand movements may well contribute to the development of focal hand dystonia. Given that painful stimuli¹⁵ and peripheral nerve injury¹⁶ are also known to produce abnormal cortical reorganisation, such forms of sensory overload could contribute to other types of focal dystonia. In keeping with this idea, case control studies have revealed an association between blepharospasm and ocular disease,¹⁷ cervical dystonia and blunt neck trauma¹⁸ and laryngeal dystonia and sore throat.¹⁹ There are also a number of reported cases of oro-mandibular dystonia occurring shortly after facial injury or surgery.²⁰

Similar abnormalities of cortical organisation have been found in the motor system. A study using transcranial magnetic stimulation (TMS) has demonstrated displacement of upper limb

corticomotor maps in patients with writer's cramp,²¹ a finding that was later extended to patients with cervical dystonia.²² These abnormalities were temporarily reversed following the injection of botulinum toxin into the affected muscles, leading the authors to speculate that the observed change in cortical topography was caused by altered afferent feedback from the dystonic muscles. At the same time, the presence of neurophysiological abnormalities in clinically unaffected body parts suggests that this may occur against a background of a more generalised disturbance of sensorimotor control.

Sensory abnormalities

While dystonic patients do not have clinically apparent sensory loss they are impaired in measures of both temporal and spatial tactile discrimination.²³ These impairments are not just limited to body parts affected by dystonia; they have been found bilaterally in the hands of patients with unilateral focal hand dystonia,²⁴ cervical dystonia and blepharospasm.²⁵ They have also been found in unaffected relatives of patients with dystonia, suggesting that they may be carrying a genetic risk factor for the future development of the condition.²⁶ In addition to these behavioural findings, a study using magnetoencephalography in patients with unilateral focal hand dystonia showed abnormalities in the somatotopic organisation of the sensory cortex.²⁷ Similar to the results detailed above, these abnormalities were bilateral in patients with unilateral symptoms.

These findings may result from a failure to adequately focus sensory afferent inputs. When somatosensory evoked potentials (SEPs) are produced simultaneously from both the ulnar and median nerves, the combined SEP is smaller than the sum of the individual SEPs. Similarly, when two SEPs are evoked in quick succession from the same site, the first SEP inhibits various components of the second. These inhibitory interactions are either impaired or absent in patients with focal hand dystonia and it has been suggested that this may be secondary to a generalised defect in lateral inhibition.²⁸

Impaired motor inhibition

Abnormalities in motor inhibitory circuits are seen at all levels of the central nervous system in patients with dystonia. For example, patients with writer's cramp have reduced lev-

els of reciprocal inhibition in forearm muscles²⁹ and TMS protocols have revealed under-activity of cortical inhibitory circuits.³⁰ These changes are not, however, sufficient to generate dystonic movements as they can be seen bilaterally in patients with unilateral symptoms.

There is evidence to suggest that the output of the motor system is controlled by a process of surround inhibition.³¹ It has been shown that at the onset of a voluntary contraction of a hand muscle, both neighbouring and contralateral hand muscles are less readily stimulated with TMS. In this way the motor system can focus muscle activity and facilitate precise, individuated movements. In patients with focal hand dystonia this mechanism is impaired³² and this could help to explain the co-contraction and overflow of muscle activity that typifies this condition.

Excessive neuroplasticity

Neuroplasticity refers to the ability of neuronal circuits to undergo structural and functional changes in connectivity and underlies the process of learning and memory. Paired associative stimulation (PAS) is a paradigm used to measure plasticity in the human brain.³³ Repeated afferent impulses generated by electrical stimulation of the median nerve are timed to reach the cerebral cortex just before the delivery of a TMS pulse sufficient to activate muscles of the thumb supplied by the same nerve. Depending on the exact inter-stimulus interval used, subsequent TMS pulses can lead to either enhanced or depressed motor evoked potentials, and this change is restricted to those muscles supplied by the median nerve. These alterations outlast the conditioning protocol by around thirty minutes and are thought to represent long-term potentiation and long-term depression. When applied to patients with writer's cramp this facilitation is exaggerated and the spatial specificity is lost.³⁴ Such changes are unlikely to be secondary to dystonic movements as they are also present in the asymptomatic hands of patients with blepharospasm and cervical dystonia.³⁵ Excessive neuroplasticity could drive the maladaptive reorganisation of cortical sensorimotor maps thought to underlie the generation of dystonic movements.

Basal ganglia involvement

Secondary dystonia is the term used to describe dystonia that is the result of an iden-

tifiable metabolic insult or structural lesion. The majority of such lesions are found to affect the basal ganglia, thalamus or their connections³⁶ and it is likely that abnormal activity in basal ganglia–thalamo–cortical loops plays a large part in the aetiology of all forms of dystonia. Indeed, neurophysiological studies on patients undergoing deep brain stimulation (DBS) for generalised dystonia have found patterns of neuronal activity in the globus pallidus internus (GPi) and motor thalamus that correlate with dystonic EMG activity.³⁷ Imaging studies in dystonia have yielded many conflicting results, likely due to variation in methodology and patient selection, but a relatively consistent finding is the presence of both increased functional activity and increased grey matter volume in the basal ganglia.³⁸ Perhaps the strongest evidence for the role of abnormal basal ganglia output in the pathogenesis of dystonia is the simple fact that modulation of the GPi and motor thalamus with DBS is an effective treatment for both generalised³⁹ and focal dystonias.⁴⁰

Cerebellar involvement

While the basal ganglia undoubtedly play a key role in the genesis of dystonic movements there is mounting evidence to suggest that the cerebellum may also be involved.⁴¹ Recent work looking at eye blink classical conditioning, a process that is dependent on cerebellar function,⁴² has been particularly informative. Within this experimental paradigm an auditory tone is played immediately prior to the delivery of an electrical stimulus to the supra-orbital nerve. After repeated stimulus pairings normal subjects produce conditioned responses consisting of eye blinks that begin after the onset of the tone but prior to the onset of the electrical stimulus. Data from stroke patients have localised this process to the territory of the superior cerebellar artery.⁴³ This area includes lobules V and VI of the cerebellar cortex, which have been shown to be structurally abnormal in patients with focal hand⁴⁴ and cervical dystonia.⁴⁵ The finding that patients with focal dystonia have impaired eye blink conditioning provides physiological evidence for cerebellar dysfunction in this group of conditions.⁴⁶

Putting it all together

Research into focal dystonia has revealed abnormalities in basal ganglia function, cerebellar function, sensory processing, motor

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inhibition, neuroplasticity and somatotopic cortical organisation. How these separate strands interact to explain the development of dystonia is uncertain and a perennial difficulty is establishing which elements are causative and which are simply epiphenomena. Despite this, some necessarily speculative suggestions can be made.

The diffuse abnormalities of sensory processing and motor inhibition may be secondary to a fundamental problem with lateral inhibition, which could in turn reflect a general functional disturbance of cortical GABAergic interneurons.²⁸ Such a mechanism could account for reorganisation of the sensory and motor cortices, as pharmacological blockade of cortical inhibitory neurones with the GABA antagonist bicuculline has been shown to expand cortical representations in rat brain,⁴⁷ presumably by unmasking preexisting lateral excitatory connections. A generalised reduction in inhibitory activity could also fail to adequately gate synaptic inputs and so lead to circuits that more readily undergo long-term potentiation and depression. In this way enhanced neuroplasticity could be a direct consequence of impaired inhibition.²⁸ However, in patients with psychogenic "fixed" dystonia, cortical inhibition is reduced⁴⁸ while measures of neuroplasticity remain normal.⁴⁹ Similarly, measures of cortical inhibition have been found to be abnormal in both manifesting and non-manifesting carriers of the DYT1⁵⁰ mutation while levels of neuroplasticity were found to be enhanced only in manifesting carriers.⁵¹ Furthermore, non-manifesting carriers were found to have reduced levels of plasticity when compared to normal subjects, suggesting that underactivity of this mechanism confers protection to individuals who are otherwise at risk of becoming symptomatic. These findings would place abnormalities in the control of neuroplasticity as a primary force behind the development of dystonic symptoms, with impaired surround inhibition resulting from an increased tendency of the brain to form new excitatory connections.

The basal ganglia are generally accepted to be involved in both the activation of appropriate motor programmes and the concurrent inhibition of competing patterns of motor activity⁵² and so are well placed to control surround inhibition in the sensory and motor cortices. On this basis it has been proposed that abnormal basal ganglia activity could drive the aforementioned impairment of inhibitory interneurone function.²⁸ In dystonic patients the basal ganglia generate abnormal patterns of oscillatory activity and neuronal synchrony. Given that neuronal oscillations have been shown to enhance cortical plasticity,⁵³ it has also been suggested that abnormal basal ganglia oscillations could directly underlie the aberrant levels of plasticity seen in dystonia.⁵⁴

The relevance of abnormal cerebellar function in the aetiology of dystonia remains

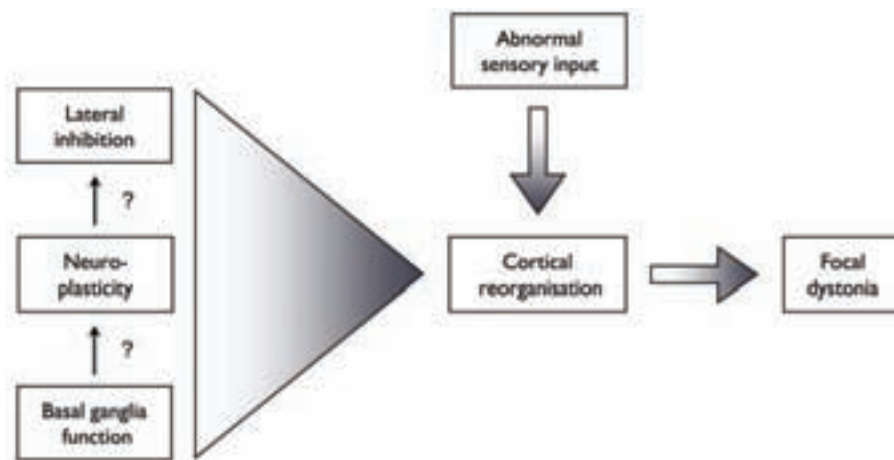


Figure 1: A possible model for the development of focal dystonias

Abnormalities of neuronal inhibition, neuroplasticity and basal ganglia function appear to promote a state of cortical reorganisation. The relative importance of each factor and the interactions between them remain unclear, but a number of findings point to enhanced neuroplasticity as having a central role (see main text). In combination with particular patterns of sensory input, further focal cortical reorganisation presumably occurs, with dystonic movements appearing when this reaches a threshold.

unclear. One possibility is that the cerebellum represents simply one node within a complex motor network that also includes the dopaminergic system, the basal ganglia and cerebral cortex.⁵⁵ Dysfunctional activity at any of these sites could disrupt the activity of the network as a whole and contribute to the neurophysiological abnormalities detailed in this review.

Abnormalities of sensory processing, somatotopic organisation, motor inhibition and neuroplasticity have been found repeatedly in areas not displaying dystonic movements. These changes may represent genetically mediated risk factors for the future development of focal dystonias and are often referred to as endophenotypic traits.²⁷ Against this background of generalised disturbed sensorimotor function and enhanced neuroplasticity, an external drive to further plastic change (repetitive hand movements, excessive blinking, peripheral injury etc) could then lead to further, localised somatotopic reorganisation. Once this reaches a level where the sensorimotor feedback loop is sufficiently compromised, motor control is disturbed and dystonic movements ensue.⁵⁶

Evidence to support this general schema comes from studies that demonstrate a normalisation of various neurophysiological parameters in response to treatment. Sensorimotor retuning is one of a number of rehabilitative strategies found to be partially effective in the treatment of musician's dystonia. This strategy involves splinting the unaffected digits and exposing individual affected digits to systematic training with the relevant musical instrument. It has been shown that clinical improvement is associated with a normalisation of somatotopic organisation as assessed by magnetoencephalography.⁵⁷ In

general, such rehabilitative approaches produce only temporary clinical improvements,⁵⁸ a finding that is to be expected if there is an underlying defect in sensorimotor processing and plasticity that is continually driving further aberrant cortical reorganisation.

DBS of the GPI is an effective treatment for generalised dystonia, although its precise mechanism of action is unknown. In contrast to the immediate response of parkinsonian symptoms to DBS in patients with Parkinson's disease, the clinical response in patients with dystonia is progressive, taking place over a number of months. Serial measures of brainstem⁵⁹ and spinal cord⁶⁰ inhibition taken pre-operatively and over a period of six months post-operatively have been shown to normalise in line with this clinical improvement. Furthermore, measures of PAS in patients treated with DBS for six months show levels of neuroplasticity comparable to those seen in normal controls.⁶¹ These findings suggest that modulating the oscillatory output of the basal ganglia may normalise levels of inhibition and neuroplasticity, allowing for the gradual replacement of aberrant sensorimotor networks with more physiological patterns of activity.⁵⁴

Conclusion

A number of consistent physiological abnormalities have been identified in various forms of idiopathic dystonia. How these elements interact to produce dystonia remains uncertain but the emerging model is that genetically mediated abnormalities of basal ganglia function, sensorimotor inhibition and neuroplasticity culminate in a brain state that, when exposed to particular patterns of sensory stimulation, facilitates a process of maladaptive cortical reorganisation that ultimately leads to dystonic movements (Figure 1). ♦

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