The Role of Neuronal Plasticity in Dystonia

Introduction

Herman Oppenheim first coined the term "dystonia" in 1911 to describe a generalised form of the condition with childhood onset, which he called "dystonia musculorum deformans".[1,2] In more recent years, dystonia is now recognised as a spectrum of neurological movement disorders characterised by patterned and sustained muscle contractions, resulting in abnormal postures and involuntary twisting movements.[1] In epidemiological studies, it is estimated that the prevalence of early-onset primary torsion dystonia is as high as 50 per million.[3] In the UK alone, it is estimated over 70,000 people are affected by the condition. However, despite the prevalence of this debilitating disorder, the mechanisms underlying dystonia are poorly understood.

Although dystonia can arise in the context of cerebral damage, patients with primary dystonia show no overt signs of neurological lesions or neurodegeneration.[4] However, imaging studies in these patients have uncovered functional abnormalities in several brain structures and subtle microstructural defects.[5–7] Rather than implicating any particular gene, protein or brain region critical to pathogenesis, these studies suggest that dystonia may result from abnormalities in the motor circuitry. It is hypothesised that aberrant neuroplasticity underlies these functional changes. In this essay I will discuss the experimental evidence surrounding this paradigm and the implications of these findings in the clinical setting. Although there is a myriad of studies implicating numerous genes and molecules, I will limit my discussion to the sensorimotor circuitry itself and the potential mechanisms that may facilitate derangement of these neuronal networks.

Classification of Dystonia

Before I discuss the pathophysiology of dystonia, I must first consider the diversity of this disorder. Indeed, dystonia manifests in a variety of forms and there are three modes of classification: aetiology (i.e. primary dystonia, secondary dystonia, dystonia-plus syndromes and paroxysmal dystonia); age of onset; or anatomical distribution (i.e. generalised, focal, segmental and hemi-dystonia).[1,8] Although

there are numerous methods of classification, these disorders are commonly divided into two rough categories: primary and secondary.[4] Primary dystonias have a strong hereditary component and are not associated with any extrinsic factors. In contrast, secondary dystonias arise due to a variety of causes of known aetiology, including high-profile conditions such as Parkinson's and Huntington's disease.[8,9] From a research perspective, studies of secondary dystonia are complicated by the presence of additional neurological symptoms and potential compensatory changes.[4] Nevertheless, this essay will consider experimental evidence derived from both broad forms of dystonia.

Motor Circuit Abnormalities

The study of secondary dystonia has helped identify several brain structures responsible for the manifestation of dystonic symptoms. These symptoms are typically associated with lesions of the basal ganglia (namely the putamen and globus pallidus), although they are not limited to these structures.[10] Indeed, lesions of the caudate, thalamus and brainstem have also resulted in dystonic symptoms.[11,12] In primary dystonia, functional abnormalities have been observed in almost all brain regions responsible for motor control and sensorimotor integration.[4] Taken together, these findings support the notion that dystonia is caused by aberrant motor circuitry rather than being a disease of an isolated motor brain structure.

Sensorimotor circuitry abnormalities in patients with dystonia were evidenced by brain imaging studies, including functional MRI (fMRI) and positron emission tomography (PET). In patients with idiopathic dystonia, PET imaging revealed an elevation in resting glucose metabolism present in the premotor cortex and lentiform nucleus.[5] Abnormal metabolism in these brain structures was presentin both manifesting and non-manifesting carriers of the DYT1 gene mutation, which is responsible for early-onset primary dystonia.[13] Using fMRI, abnormal activity was reported in the M1 and associated motor regions in patients with both primary and secondary dystonia.[6,14,15] Interestingly, these studies demonstrated conflicting results; activity in these structures was found to be both increased and decreased according to different reports. These changes in motor cortex activity did not correlate with different forms of dystonia, indicating that they may not all arise from the same physiological

abnormalities. Alternatively, these disparities may be explained by methodological differences or changes in neuronal disinhibition (which is discussed later in this essay).[4,16]
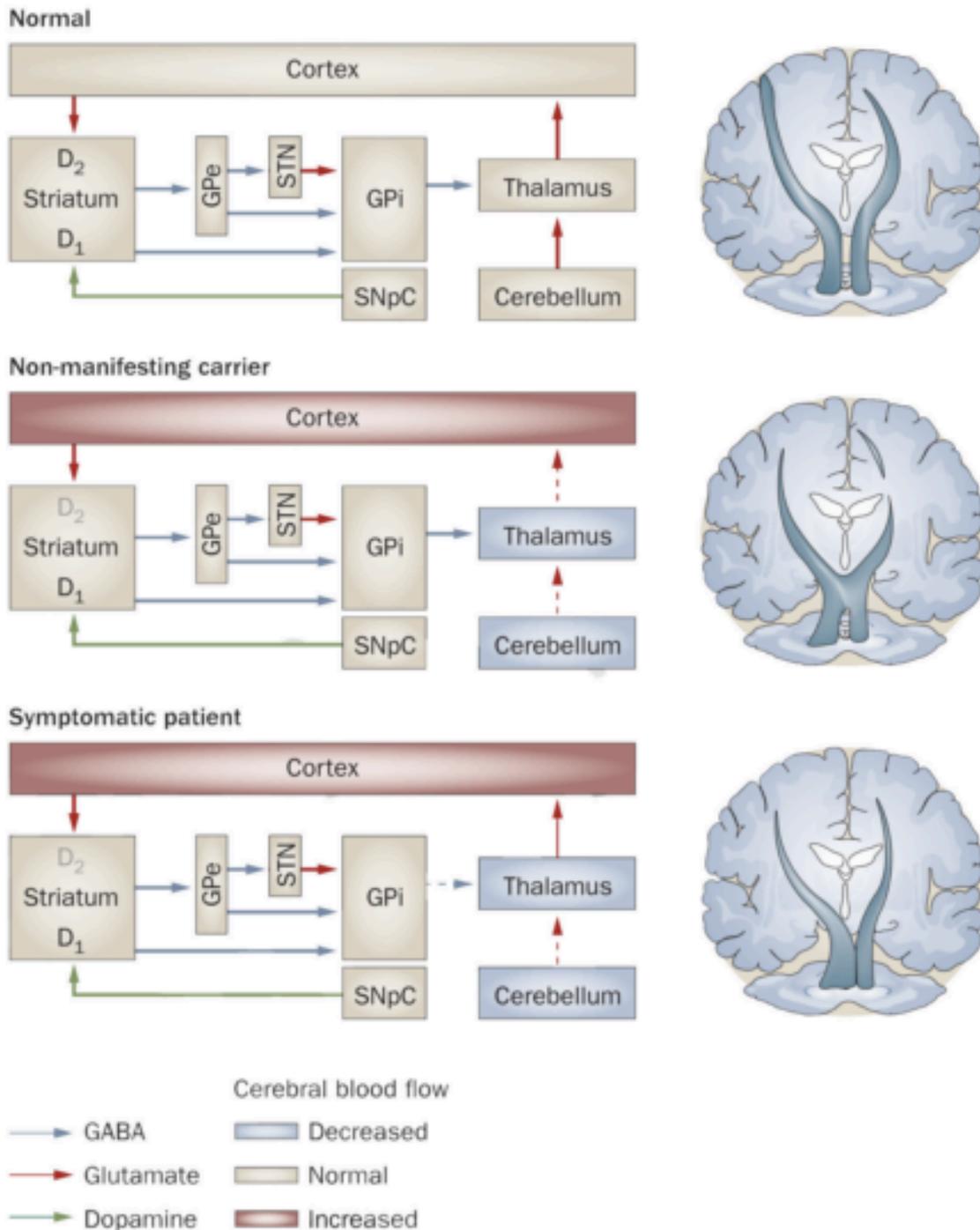

Figure 1| Comparision of the motor circuit abnormalities in manifesting and non-manifesting DYT1 mutation carriers adapted from Tanabe et. al.[4] This updated model was constructed from data derived from studies investigating regional metabolic activity and microstructural defects in dystonia (DYT1) patients.[17,18]

Although multiple brain structures are implicated in the pathophysiology of dystonia, a caveat with regards to the interpretation of these studies is the difficulty in delineating the network abnormalities that cause dystonia from the compensatory changes or internal representations of persistent movement or posture. To circumvent this challenge, hereditary forms of dystonia with reduced penetrance were studied. DYT1 is only ~30% penetrant, therefore the effects of the mutation can be compared in both manifesting and non-manifesting dystonia patients.[19] PET imaging was performed on patients with manifesting dystonic symptoms, while awake and asleep, and in mutation carriers who were asymptomatic.[17] Interestingly, two independent patterns of regional metabolic activity were discovered, which were termed 'movement-related' and 'movement-free' (figure 1). The movement-related pattern was present in patients with manifesting dystonic symptoms and was reduced whilst these patients were asleep. In contrast, the movement-free pattern of activity was present in both sets of patients, both while awake and asleep.[17] Building on these findings, probabilistic tractography based on diffusion tensor imaging (DTI) scans showed more pronounced reduction in the cerebellothalamic tract in non-manifesting dystonia patients compared to manifesting patients, revealing a potential compensatory mechanism by which motor symptoms may be avoided.[18] Collectively, These findings provide further support that abnormal motor circuitry is closely linked with both manifesting and non-manifesting forms of dystonia.

Sensory Influence

Some investigators hypothesise that these abnormalities in the sensorimotor circuitry are mediated by abnormal sensory processing.[20,21] Indeed, it has been a longstanding observation that a sensory trick known as 'geste antagoniste' can ameliorate early dystonic symptoms, indicating that sensory dysfunction may contribute to the pathogenesis of dystonia.[1] Further studies have shown that patients with dystonia exhibit deficient temporal discrimination threshold (TDT), which is a reduction in the ability to differentiate between two close-interval sensory stimuli.[20] Moreover, patients with blepharospasm exhibited deficient TDT when stimuli are administered to their hands and face.[21] These studies implicate the primary somatosensory cortex (S1), a structure responsible for processing temporal discrimination. Indeed, investigation into somesthetic (i.e. somatosensory) temporal

discrimination (STD) of patients with focal hand dystonia (FHD) revealed an STD deficit attributed to dysfunction within S1.[22] However, the mechanisms by which sensory discrimination contributes to dystonia pathogenesis remain unclear.

These findings are also important in the context of therapeutic management. Intramuscular injections of botulinum toxin are administered to dystonia patients to reduce motor symptoms. This toxin acts by blocking vesicular release of the neurotransmitter acetylcholine, thus reducing neuronal activity to the affected muscles. In addition to its peripheral effects, it has been suggested that the toxin may act indirectly on the central nervous system (CNS).[23] Using DTI, hemispherical asymmetry observed in patients with cervical and hand dystonia was reversed with botulinum toxin treatment.[24] The interpretation of these findings was that reorganisation of the motor circuitry is activity-dependent. Moreover, reduction of constant afferent sensory feedback may restore the normal organisation of the motor circuitry, providing a potential avenue for therapeutic intervention.

Animal models have provided valuable insight into the mechanism by which sensory feedback may influence the sensorimotor circuitry. In studies using owl monkeys, investigators trained these primates in a behavioural task that required them to perform highly repetitive, stereotyped hand movements.[25,26] Subsequent electrophysiological mapping of the S1 revealed degradation of the topographical representation of the hand, which was only present in monkeys that developed abnormal, involuntary hand movements.[25] This seminal study provides proof-of-principle that constant afferent sensory feedback can distort the motor circuit organisation, resulting in abnormal motor activity. In dystonia patients, dystonic motor symptoms may drive further motor circuit abnormalities, thus creating a vicious circle of disease progression.

However, an important caveat regarding this study is that only the effects of overstimulation were observed. A key question remained: why do some patients develop dystonia through excessive sensory stimulation, whereas others remain asymptomatic?[27] This issue was addressed in a study of blepharospasm, a focal dystonia that causes involuntary contraction or spasm of the eyelid.[28] In both

rats and humans, weakness of orbicularis oculi, a muscle responsible for eyelid closing, causes an adaptive enhancement in the trigeminal blink reflex. This allows the eyelid to close normally in response to muscle weakness. To investigate this response, a small lesion to the dopaminergic system of the basal ganglia was administered to healthy rats. This challenge alone did not produce dystonic symptoms, but when coupled with weakening of the orbicularis oculi, it initiated maladaptive changes in the reflex circuit resulting in blepharospasm.[28] Based on these findings, it was proposed that excessive sensory feedback might precipitate dystonia in an environment of aberrant neuronal plasticity.

Neuronal Plasticity and Motor Learning

The motor circuitry abnormalities observed in dystonia may be due to maladaptive or aberrant plasticity in response to sensory feedback.[29] As previously mentioned, some forms of dystonia develop in conjunction with excessive sensory stimulation or repetitive motor tasks that elicit adaptive changes to the motor circuitry.[25,28] In the clinical setting, rewiring of the motor circuitry may explain the delayed effects of deep brain stimulation, a therapeutic intervention used to alleviate dystonic motor symptoms.[30] Moreover, imaging studies have shown changes in somatotopy and microstructural abnormalities, which are believed to be at least partially mediated by neuronal plasticity.[5,7,13] Therefore some investigators hypothesise that abnormal plasticity may bridge the gap between sensory processing and motor circuit reorganisation.

Several non-invasive neurophysiological techniques have been developed to allow unprecedented insight into plasticity at a regional level in the human cortex.[27] The role of plasticity in dystonia was investigated directly using paired associative stimulation (PAS). This technique represents a neurophysiological paradigm that combines peripheral nerve stimulation (PNS) with transcranial magnetic stimulation (TMS) of the contralateral motor cortex, enabling simulation of long-term potentiation (LTP) and long-term depression (LDP) during electrophysiological studies.[31] In patients with FHD, the PAS protocol elicited enhanced gain of LTP and LTP-like plasticity.[32]

In corroboration with the plasticity hypothesis is the discovery of motor learning deficits in non-manifesting DYT1 mutation carriers.[33,34] These patients demonstrated a reduction in sequence learning, which correlated with increased activation in the left ventral prefrontal cortex and lateral cerebellum, as measured with PET imaging.[33] It is hypothesised that these increases in activation may normalise the motor output in DYT1 mutation carriers, but may not compensate for these observed abnormalities in motor learning. In another similar study, patients with FHD showed impaired ability when asked to complete tasks involving mental rotation of body parts.[34] Interestingly, these impairments in motor planning appear in both the affected and unaffected hand, indicating that they may exist independent of any overt dystonic symptoms. In both studies, the deficits observed were attributed to abnormalities in neuronal plasticity. However, given the important role of sensory feedback in plasticity, these abnormalities are also likely to arise due to impaired sensory discrimination or abnormal sensorimotor integration.

Impaired Homeostatic Plasticity

The neurons themselves have the capacity to regulate their own excitability relative to the activity of the circuit, which is referred to as homeostatic plasticity.[35] In the context of dystonia, a model of pathogenesis can be devised whereby excessive sensory feedback activates the positive feedback nature of LTP, which may destabilise the circuit and result in abnormal motor output. However, neuronal plasticity is a carefully controlled process: too much plasticity results in the formation of unwanted associations, whereas too little would result in learning difficulties.[35] Although aberrant plasticity may provide an apt explanation as to the mechanism by which motor circuit abnormalities evolve, it remains unclear what causes this abnormal level of neuronal responsiveness.[27] What are the mechanisms that trigger neuronal plasticity to transgress its normal boundaries?

To investigate regional homeostatic plasticity, patients with FHD were assessed with a combination of transcranial direct current stimulation (TDCS) and repetitive TMS (rTMS) in the primary motor hand area (M1).[36] Both techniques can produce bidirectional effects on corticospinal neuron excitability that is dependent on the frequency and polarity of rTMS and TDCS respectively. It was demonstrated that

in normal subjects, preconditioning of the M1 with anodal TDCS (i.e. an excitatory stimulus) enhances the inhibitory effect of subsequent stimulation with rTMS, resulting in decreased corticospinal excitability. Conversely, preconditioning with a cathodal TDCS (i.e. an inhibitory stimulus) reverses the effects of TDCS, leading to increased corticospinal excitability. However, the responses in subjects with dystonia were much different: in dystonic subjects, rTMS after TDCS preconditioning induced no consistent changes in corticospinal excitability. Moreover, preconditioning with cathodal TDCS produced no inhibitory effect.[36] These results suggest that homeostatic mechanisms are responsible for stabilising the level of neuronal excitability, and this response is disrupted in patients with FHD.

Although this study shows clear evidence for the presence of abnormalities in neuronal plasticity in dystonia patients, it does not ascertain whether these abnormalities manifest as the clinical symptoms observed during disease progression.[27] However, in support of this hypothesis, studies have shown that short periods of behavioural motor learning can modulate levels of neuronal plasticity.[37,38] Using the PAS protocol, it was found that motor learning caused increases in inhibitory PAS and parallel decreases in facilitating PAS. These findings are compatible with a key concept of homeostatic plasticity: during a phase of increase neuronal activity, it becomes easier to strengthen inhibitory effects but strengthening excitatory effects becomes more difficult.[35] Given these observations in normal subjects, it is plausible that these homeostatic mechanisms in plasticity become disrupted, resulting in dystonic motor symptoms. However, more direct studies will be required to confirm this hypothesis.

Neuronal Disinhibition

It should be noted that abnormal homeostatic plasticity is not the only mechanism by which elevated neuronal responsiveness to sensory input may occur. A competing theory is that these plastic changes may arise due to a reduction in GABAergic inhibition, resulting in corresponding increases in cortical excitability.[16,39] In support, deficient inhibition in the dystonic brain is widely reported in the literature and has been demonstrated at the level of the cortex, brain stem and spinal cord.[16] Furthermore, the

involuntary movements that are characteristic of dystonia are attributed to loss of reciprocal spinal inhibition between opposing agonist and antagonist muscles.

The role of GABAergic inhibition in neuronal plasticity is perhaps exemplified by a study of the cortico-striatal pathway in a hamster model of paroxysmal dystonia.[40] Using cortico-striatal slices, analysis of the cellular properties of striatal neurons showed no difference between mutant (dt^{sz}) and control hamsters. In contrast, field potential recordings showed an increase in excitability of dt^{sz} cortico-striatal interneurons. In addition, paired-pulse responses and high-frequency stimulation recordings showed a greater shift of dt^{sz} interneurons towards paired-pulse potentiation and LTP respectively.[40] Therefore, it is also plausible that the observed increases in PAS-induced neuronal plasticity are a secondary manifestation of neuronal disinhibition. These findings suggest that modulation of GABAergic disinhibition may provide a useful target for therapeutic intervention. Indeed, it is speculated that the interactions of this mechanism with neuronal plasticity may underlie the beneficial effects of selective GABA-reuptake inhibitors on dystonia in the dt^{sz} hamster.[41]

Conclusion

In recent years, investigators have come to appreciate dystonia as a disorder of the motor circuitry, rather than a disease of a single brain structure or molecule. However, given the diverse aetiology of this disorder, the mechanisms by which these abnormalities arise have been difficult to elucidate. Furthermore, there is a growing appreciation that different forms of dystonia arise due to distinct pathophysiology. Nevertheless, neurophysiological studies and functional imaging have provided valuable insight into their pathogenesis. These major advances have helped us unravel this complex neurological disorder.

Although the mechanisms of pathogenesis remain obscure, aberrant plasticity is believed to play a key role. A model can be proposed whereby biological abnormalities cause impaired homeostatic plasticity or neuronal disinhibition, resulting in abnormal modifiability of the motor circuitry. In other words, mutations can create an environment conducive to the development of dystonia. In this cellular

environment, excessive sensory feedback can reshape the motor circuitry via these maladaptive mechanisms, thus precipitating the motor symptoms characteristic of dystonia.

This model proposes that maladaptive plasticity in the CNS plays a central role in dystonia. Indeed, such a phenomenon is already implicated in other common syndromes, such as phantom limb, tinnitus, central pain and emotional disorders[42–44] Although much of the research in this field has been conducted on patients with FHD, some of the ideas can be generalised to other forms of the disorder. Further work will be necessary to translate the findings from genetic and molecular studies to the systems-level abnormalities discussed in this essay. It is the hope that future advances will aid our understanding of the organisation of the motor circuit and help develop novel therapeutic options to treat this debilitating disorder.

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