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Dystonia and Muscle Spindles: The Link in Idiopathic Focal Dystonias

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1. Introduction

Idiopathic focal dystonia (IFD) is the commonest type of dystonia, characterised by more or less fixed abnormalities of posture, involuntary movements and muscular spasm. Published estimates of prevalence vary ¹⁻⁴. The condition appears to run in families ⁵. As certain groups, such as musicians, seem to be at much higher risk ^{6, 7}, it would seem that one or more common genes with low penetrance may be responsible, but such genes interact with physical factors, overuse being one. Damage to several different brain areas, including the basal ganglia, has been associated with secondary dystonia ⁸. This, and the lack of demonstrable neurodegeneration, has contributed to the idea that the pathophysiology of IFD relates to subtle abnormalities of the circuits between cerebral cortex and basal ganglia ⁹, perhaps involving defective sensory processing, abnormal central nervous system excitability or loss of inhibition of motor control. Some authors have hypothesized a deficiency in a specific class of brain interneurons ¹⁰.

Experiments based on research that has been undertaken at the University of Sheffield over the last 14 years ¹¹⁻¹⁴ have demonstrated that there is a predisposing proprioceptive sensory abnormality in subjects with dystonia. Fatigue-induced distortion of the proprioceptive feedback subserved by muscle spindles appears to characterise the condition. The primary abnormality in IFD is likely to be a physical property of muscle spindles, specialised stretch receptors present in skeletal muscle, which are responsible for signalling to the brain proprioceptive information about body position, velocity, muscle load, fatigue and muscular effort. Our experiments do not suggest a primary abnormality of sensory processing in the neural networks of the brain. Instead the experiments imply that the abnormality is in the genetically determined, elastic property of muscle spindles that produces distortion of feedback when the muscle spindles are over-stretched. It is plausible that this endophenotype interacts with other predispositions, such as other genes which predispose to generalised dystonia (for example DYT1), the effects of drugs such as those which block dopamine receptors in the brain, or disorders of the basal ganglia, such as idiopathic parkinson's disease, to produce the dystonic phenotype. The evidence, its interpretation and the resulting hypothetical pathophysiological basis for IFD are discussed below.

2. Clinical features and what they tell us about dystonia

IFD (e.g. torticollis, blepharospasm, writer's cramp and other dystonias affecting localised areas of the body) involves abnormality of posture or positioning of part of the body. A hypothesis to account for the underlying mechanisms of IFD must account for the clinical features of the condition:

1. The commonest form, neck dystonia, is "task-independent", but many dystonias may be apparent only with particular learned movements (so-called task-specific dystonia). For example, a patient may develop dystonic posturing of the hand whilst typing but not whilst playing the piano, despite the same muscles being involved (although there may be a tendency for the dystonia gradually to evolve and interfere with more tasks). This implies that the condition involves corruption of sensorimotor programming specific to particular learned activities, rather than an abnormality of the motor control of specific muscle groups.
2. After treatment of neck dystonia with botulinum toxin, patients may return to the clinic with weakness of head rotation in one direction as an effect of the treatment. Despite the imbalance in the strength of the muscles of the neck, the postural abnormal posture at rest may persist, though it may be easier for the patient to correct voluntarily. Another feature of idiopathic focal dystonia that has to be accounted for in models of the disorder, is the phenomenon of the '*geste antagonistique*', the relief of the abnormal posture, typically in patients with cervical dystonia, by touching, or approximating, the affected part with the patient's own hand. The *geste antagonistique* does not involve physical force to oppose muscle spasm. These observations imply that dystonia involves a problem with proprioceptive feedback, and the pathophysiology is likely to involve the way the brain senses body posture, i.e. to involve proprioception.
3. Contrary to some assertions in the literature, IFD does not necessarily involve co-contraction of agonist and antagonist muscles (though this is usual when the patient tries to achieve function with the affected body part). With hand dystonias, especially in early stages, a single muscle, such as the extensor of the index finger, may be over-active during the dystonic movement. Hand and arm dystonia is often highly task-specific initially, though there is a tendency for the dystonia gradually to evolve to affect other skilled movements, at least to some extent. These features imply a role of abnormal motor learning in the pathophysiology of IFD.

We can conclude that the essential clinical features imply that IFD is a disorder of the way posture and learned movement is programmed by the central nervous system, rather than spasm, inadequate inhibition or overactivity of a muscle or group of muscles.

3. A disorder of the basal ganglia?

A common concept is that dystonia is primarily a disorder of the basal ganglia and its connections. This is based partly on the observation that pathology in the basal ganglia, such as vascular insult, neurodegenerative disorders and kernicterus, can sometimes lead to types of dystonia. This type of dystonia differs from IFD in that it is constant, "task-independent", and affects large contiguous areas of the body. In contrast, no structural or biochemical abnormality has been demonstrated in association with IFD, and the subjects with the condition generally retain high skill levels in the dystonic limb when undertaking

tasks which do not trigger the dystonia (for example, musicians with IFD can often write without difficulty or play another musical instrument without dystonia). There is therefore little reason to postulate that structural abnormalities of the basal ganglia are the prime cause of IFD. However, the observation of improvement of IFD after neurosurgical implantation and stimulation of electrodes in the corpus striatum suggest that basal ganglia may have an important role in the generation of dystonia.

Physiological abnormalities of the brain and spinal cord have been documented in subjects with IFD. Interpretation of such abnormalities is problematic – some may represent adaptive changes in response to the presence of dystonic muscle contractions rather than being related to processes that predispose to, and antedate, the development of dystonia. Physiological abnormalities that are found bilaterally in subjects with unilateral dystonia and in areas of the nervous system that serve parts of the body remote from the site of dystonia are less likely to be adaptive and more likely to reflect predisposing factors. Such predisposing abnormalities include reduced short latency intracortical inhibition¹⁵. Increased excitability of the motor cortex during voluntary muscle contraction¹⁶, and excessive excitability of primary motor cortex upon magnetic stimulation¹⁷ are not invariably found in dystonic subjects. Abnormalities in the ‘silent period’ of electromyographic activity following transcranial magnetic stimulation (TMS) and of long interval intracortical inhibition assessed by paired suprathreshold transcranial magnetic stimulation pulses have been documented, but are restricted to the symptomatic hand^{18,19} as are inhibitory effects in TMS threshold on peripheral nerve stimulation²⁰. In the spinal cord there is also abnormal excitability, demonstrable by reduced reciprocal inhibition of forearm H reflexes²¹⁻²³. The importance of such abnormalities in the pathophysiology of IFD is undermined by the demonstration of similar abnormalities in psychogenic dystonia²⁴. Such phenomena remain difficult to interpret and translate into a coherent theory of IFD pathophysiology.

Subtle sensory abnormalities have also been demonstrated in IFD and in asymptomatic relatives, including reduced tactile spatial discrimination²⁵. The sensory pathways involved in such perception are complex and such observations, whilst of undoubted importance, do not in themselves clarify the understanding of the pathophysiology of the condition.

4. Muscle spindles, proprioception and basal ganglia in movement control

It has been known since the 1970's that stretch receptors within skeletal muscle, the muscle spindles, subserve proprioceptive sensation²⁶, and since it is apparent that IFD involves a proprioceptive problem it makes sense to examine muscle spindle responses in IFD. A review of the role of muscle spindles in dystonia has been published²⁷.

The function of muscle spindles is complex²⁸. In a situation of maintained posture, muscle spindle stretch reflects muscle load, and signals to the brain how to vary drive to the skeletal muscle to maintain the posture. If the muscle is contracted voluntarily, this shortens the muscle spindle stretch receptor, ‘unloading’ it. The resulting loss of proprioceptive information would be catastrophic for maintenance of posture. To circumvent this, each muscle spindle has its own muscle and nerve supply (fig 3). When a muscle contracts voluntarily, the intrafusal muscle of the muscle spindle simultaneously contracts (so-called alpha gamma co-activation) to maintain muscle spindle stretch, thus maintaining sensitivity to changes in applied load.

In order to undertake willed movement the brain has to appreciate body position, posture, centre of gravity and velocity so as to maintain balance during movement. This relies mainly on proprioceptive information with some contribution from visual or vestibular feedback. To determine hand position relative to the body, activity from muscle spindles of the forearm and hand must be interpreted in the context of in the context of proprioceptive proprioceptive information from muscle spindles situated more proximally, in the upper arm, shoulder and neck. All this information has to be integrated with that from the legs and trunk, interpreted in the context of the afferent volleys to the intrafusal fibres, for the body to maintain posture and balance during a hand movement. Muscle spindles also encode information about muscle fatigue ^{29, 30}.

It is likely that a major function of the basal ganglia is to interpret muscle spindle feedback to facilitate maintenance of posture and balance in the face of superimposed willed movements. This is consistent with the observation that most neurones of the globus pallidus interna are sensitive to passive movement ³¹. In broad conceptual terms, extrapyramidal systems may dominate control of posture and balance, are inhibited focally during superimposed voluntary movement, and re-established when the movement is completed.

5. What is the evidence that muscle spindles are involved in dystonia?

Muscle or muscle tendon vibration at a rate of 50-100 cycles a second produces a tendency for that muscle to contract (known as the 'tonic vibration reflex' ²⁹). It also produces a sensation of movement of the vibrated limb that is not dependent on physical movement of the limb, known as the vibration-induced illusion of movement. This is likely to be caused by stimulation of the muscle spindle afferents near the vibrator ³². This phenomenon enables quantitative study of muscle spindle function in human subjects.

Our experimental protocol involved a subject sitting with elbows resting on a table and with one arm resting relaxed in a splint to stop it moving. The splint maintained the elbow joint at approximately a right angle. The subject was blindfolded to remove visual feedback of arm position and the biceps tendon was vibrated at 50 to 100 cycles a second. This produced a feeling of slow extension of the arm around the elbow joint, the 'vibration induced illusion of movement', despite the arm being fixed in a splint. This sensation results from the brain interpreting the vibration-induced muscle spindle afferent volleys from the biceps muscle as the biceps being stretched. Since the arm is relaxed, the brain infers that the muscle spindle afferent discharge from the biceps implies that the arm is extending at the elbow (if the arm were actively maintaining a posture the vibration induced muscle spindle afferent activity would be interpreted as an increased load on the muscle, the basis of the tonic vibration reflex).

We quantified this illusion by asking the experimental subject to match the movement felt in the vibrated arm using the opposite arm which was free to move. Movement of the 'tracking' arm in 45 seconds was recorded using a digital camera. These simple experiments demonstrated that in subjects with IFD, the vibration-induced illusion of movement is reliably *subnormal* ¹², figure 1. This abnormal perception occurs all over the body, in parts unaffected by IFD as well as parts that are ¹¹. It is found in patients who have received treatment with botulinum toxin and those who have not, implying that it is not a phenomenon associated with treatment or spread of botulinum toxin. It thus appears to

represent a factor that predisposes to IFD ¹⁴. Initially we interpreted this as an abnormality of interpretation of the sensory information from the muscle spindles somewhere in the central nervous sensory pathways to the cerebral cortex. However, a second series of experiments made us revise this view.

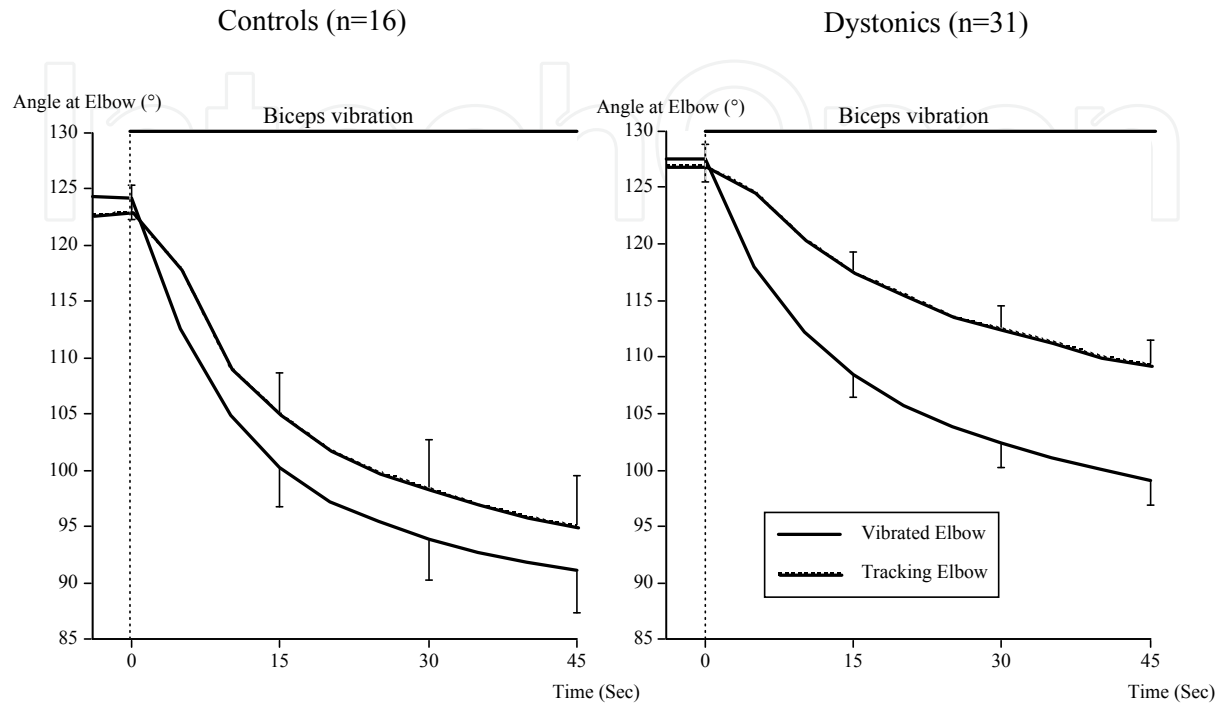


Fig. 1. The tonic vibration reflex differs in dystonic subjects and controls. Mean angular displacement of the elbow vibrated arm and tracking arm in the groups of healthy control subjects and dystonic subjects on stimulation of the biceps brachii tendon. The tonic vibration reflex is similar in both groups, but the tracking movements are smaller in the dystonic patients.

6. The vibration-induced illusion of movement and fatigue

Subjects with and without IFD were required repeatedly to lift a dumbbell with the arm we were going to vibrate until they could lift it no longer, and then immediately slip the arm back into the splint ¹³. We then immediately retested the vibration-induced illusion of movement, vibrating the fatigued biceps tendon.

Immediately after fatigue the vibration-induced illusion of movement in the subjects with IFD *increased* so that it was now similar to normal subjects. This was temporary – the effect only lasted as long as the biceps remained fatigued. In contrast, the healthy control subjects *showed no change* in the vibration-induced illusion of movement with muscle fatigue (figure 2).

It is difficult to imagine how the manoeuvre of lifting a dumbbell a dozen or so times could have any effect on the way in which the central nervous system processes sensory information. It is easier to imagine a direct effect on peripheral muscle. Lifting a dumbbell until the muscle fails physically stretches the muscle spindles to their physiological limit. We were attracted by the idea that we were likely to be looking at an effect of lifting the dumbbell on the elastic properties of the muscle spindles themselves. Muscle spindles

thixotropic properties are critical to their function as stretch receptors ³². A simple explanation is that the muscle spindles in dystonic subjects are stiffer than those in normal subjects, but become more elastic after they are over-stretched, rather like an elastic band when warmed by stretching.

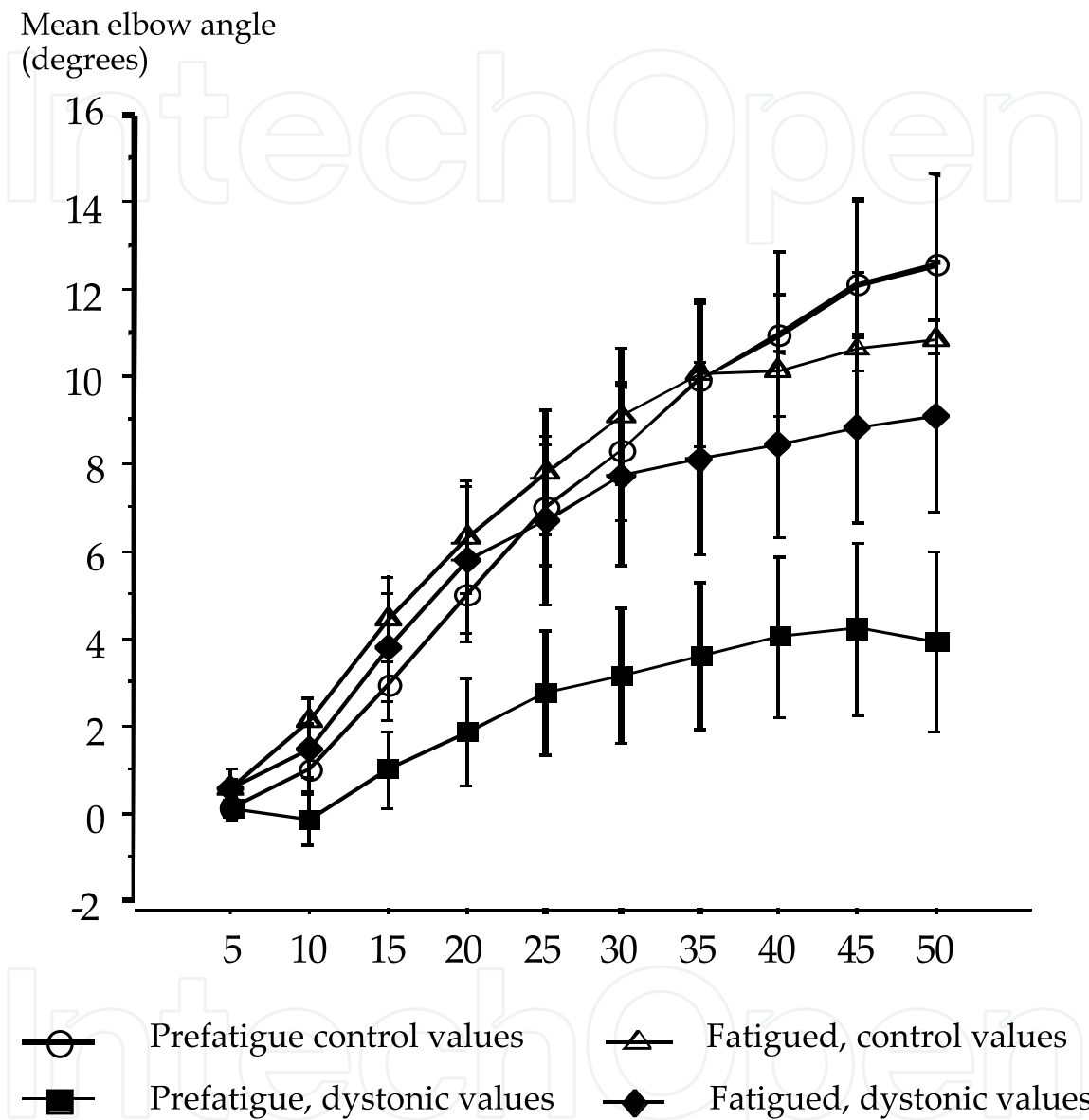


Fig. 2. Assessment of the vibration-induced illusion of movement in dystonic and healthy control subjects. Extension of the tracking arm in response to 50Hz vibration of opposite biceps tendon over 50s in ten dystonic and 10 healthy control subjects. Dystonic subjects (black squares) show significantly less extension of the tracking arm than healthy subjects (white circles), implying subnormal vibration-induced illusion of movement. When the vibrated arm is fatigued after lifting a dumbbell (black diamonds), the vibration-induced illusion of movement improves to become indistinguishable from control subjects. In contrast, fatigue does not affect the vibration-induced illusion of movement in control subjects (white diamonds).

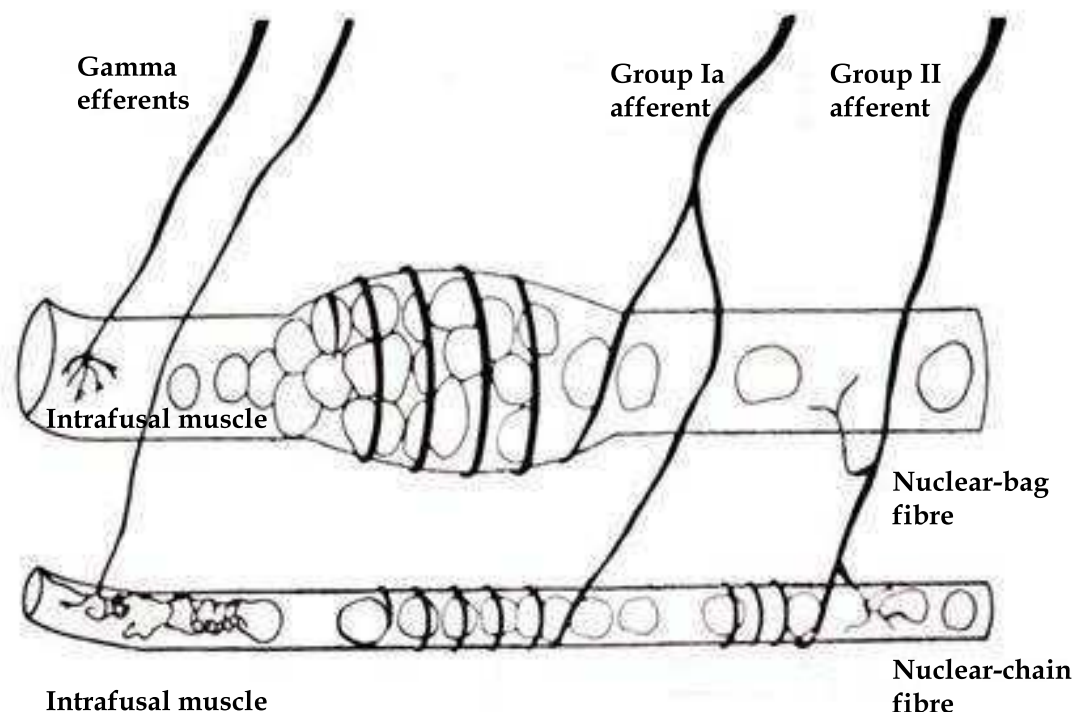


Fig. 3. Diagram of a muscle spindle (after Matthews, 1972). Muscle spindle afferents provide information on position, load, fatigue and effort that are integrated by the nervous system to ensure the maintenance of posture and balance during a willed movement. Interpretation of this afferent activity has to be undertaken in the context of gamma efferent discharge, which contracts intrafusal muscle fibres of the spindle and increases the afferent discharge frequency. This is necessary in order to maintain the sensitivity of the spindles to applied load when the surrounding skeletal muscle contracts.

The idea that a peripheral muscular abnormality such as the mechanical properties of muscles spindles predispose to the development of IFD, and represents a significant change in the way we think about dystonia, hitherto considered a disorder of higher central nervous system functioning. The observation that limb cooling improves IFD is also consistent with the suggestion that it is a disorder generated in the periphery ³³.

An implication of this experiment is that IFD develops when the brain attempts to use information from muscle spindles that changes disproportionately as muscles fatigue. Writer's cramp, musician's cramp, and other occupational dystonias such as those which effect sports players, occur in muscle groups which are used repeatedly when practising a particular skill so that the subject will be learning the movement sequence whilst the muscle is fatigued. In contrast to normal subjects, the relationship between body position and muscle spindle afferent information in dystonic subjects differs in the fatigued state from the unfatigued state (figure 4). This provides insight into why dystonic subjects may develop involuntary muscle spasm with learned movements ³⁵.

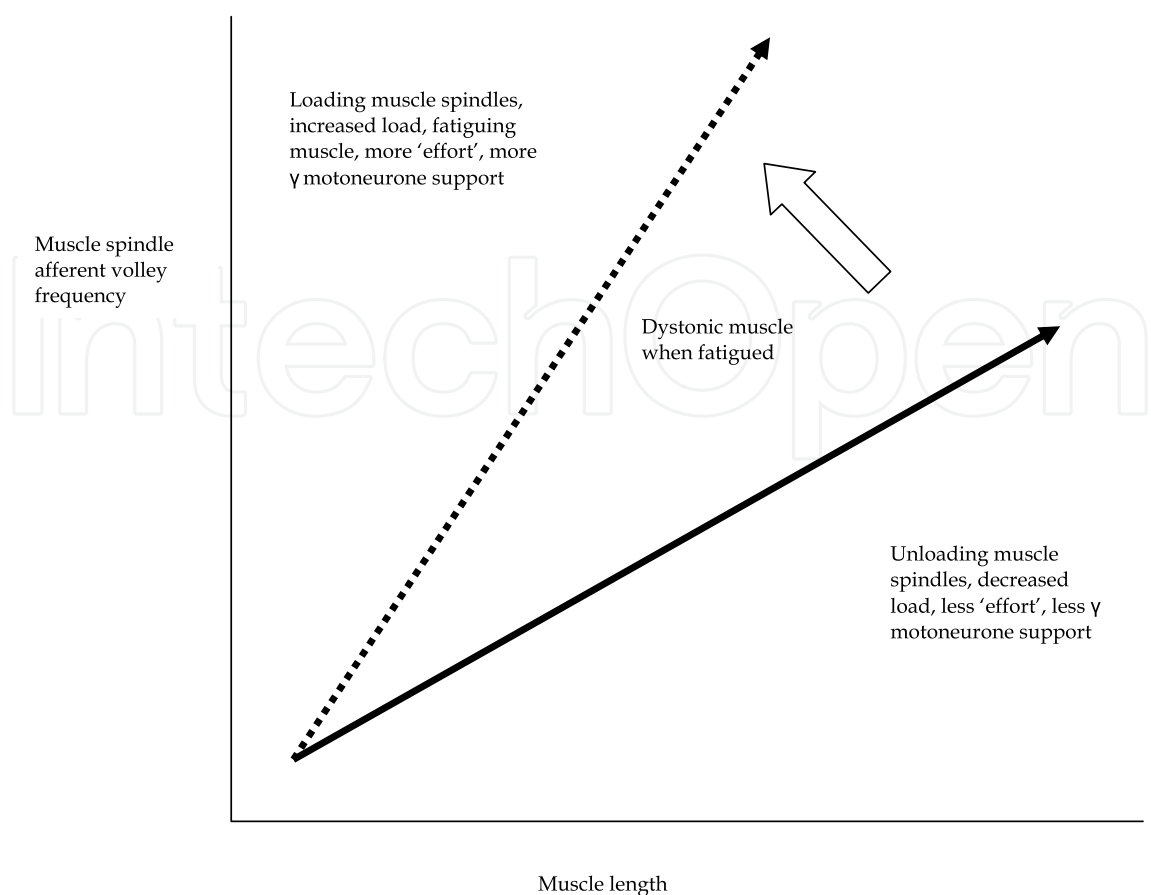


Fig. 4. Factors which influence muscle spindle afferent activity. In healthy subjects the nervous system can interpret changes in muscle spindle afferent activity in terms of load and position. In dystonic subjects the relationship between muscle spindle stretch and afferent discharge becomes steeper after fatigue. In such circumstances the increase in muscle spindle afferent activity is interpreted as weakening of the surrounding muscle. This corrupts the motor program for overlearned movements of the limb, causing muscles to be driven excessively (i.e. dystonic spasm).

7. Role of muscle spindles in motor learning and the evolution of symptoms

Writing is a motor skill which is commonly affected in IFD. The skill of writing is sophisticated. We can write using a variety of materials on surfaces of variable texture, and our signature will usually remain recognisable throughout. Writing can be undertaken without visual feedback and scaled as required. The movements of the hand whilst writing have to be able to adapt to different resistance to the movement of the pen and the size of the letters required. This implies that the motor subroutines of writing involve proprioceptive feedback. If affected by writer’s cramp, the grip of the pen becomes abnormal soon after writing starts and the effort required to control writing increases. Pain in the hand or arm results as muscles contract to control the hand as writing posture becomes distorted.

The patterns of movements required to write seem likely to be stored in motor memory as a pattern of proprioceptive feedback (possibly in frontostriatal circuits) from arm and

hand during the neuronal activity driving the muscles involved in writing. In order to control the pen, the brain must continuously compare proprioceptive feedback with efferent volleys in order to adapt to resistance to movement of the pen and the fatigue of the muscles involved in writing. The relationships between the effort to drive muscles and the feedback from muscle spindles is continuously over-learned as motor skills are repeated or practiced.

In dystonic subjects, afferent muscle spindle activity increases disproportionately as writing occurs whilst muscles fatigue. Increased muscle spindle afferent discharge is interpreted by the brain as meaning either increased load or weakening muscle, i.e. an increase in effort or drive to the muscle is required (figure 4). Since increased muscle spindle afferent activity for a particular muscle position implies to the brain that the muscle is disproportionately fatiguing, the motor 'subroutine' for that movement adapts to one appropriate for an excessively weakened or fatigued muscle. This results in the corrupted motor subroutine for that movement over-driving the affected muscle group when the motor subroutine is activated. The dystonic subject sees this as spasm or over-activity of particular muscles involved in the learned movement.

Thus, the abnormalities of the vibration induce illusion of movement suggest a mechanism whereby motor subroutines become corrupted when movements are over-learned in the fatigued state. This provides an explanation for why IFD symptoms tend to affect skilled and heavily practiced movements. It also may explain why sometimes dystonic symptoms evolve with time^{35,36}. For example dystonia may affect writing, then perhaps involve typing or holding a cup. When learning a manual motor skill, abnormally enhanced fatigue resulting from attempts to counter the dystonic muscle spasm places extra stress on the other muscles of the hand involved in the movement. Other muscles, therefore, fatigue more rapidly when the motor subroutines for writing are activated (which is felt as the 'cramp' of writer's cramp). As writing continues, other muscles of the hand fatigue faster than normal, and as with continued motor learning in this state the motor subroutines of other muscles become corrupted and dystonia evolves. This may explain why injuries, myasthenia and spinal scoliosis may occasionally precipitate IFD. The phenomenon may also explain the tendency of the geste antagonistique to disappear with time. As a greater proportion of neck muscles provide corrupted proprioceptive information to the basal ganglia as the dystonia evolves, the contribution of 'correct' proprioceptive input obtained by touching the affected part with the hand may become relatively less influential.

8. Why is cervical dystonia the commonest IFD?

Although this is a plausible explanation for the development of writer's cramp or occupational dystonias where motor activity is practiced in the fatigued state, it provides no explanation for the most common dystonia, that of the neck (torticollis).

Assuming that the same principal of fatigue-induced distortion of muscle spindle feedback leads to abnormal motor programming in cervical dystonia, a plausible explanation of the development of torticollis is that a twisted posture and poorly supported neck during sleep might result in asymmetric patterns of fatigue, and corruption of the motor program to position the head straight.

9. What is the physical substrate of abnormal muscle spindle function in IFD?

A plausible explanation is that in individuals with a predisposition to IFD the muscle spindles have abnormal elastic, or more precisely 'thixotropic', properties (see reference 31 for a review of the topic). In order to reflect optimally how the surrounding muscle is moving, the elastic properties of muscle spindles must match the surrounding muscle. The simplest explanation of the abnormal vibration-induced illusion of movement in dystonic subjects is that the muscle spindles are too stiff, and are therefore relatively insensitive to any change in muscle load.

For the most part the elastic properties of the muscle spindles are not critical to motor control, as the neural networks learn the relationship between movement and the feedback from muscle spindles with practice as motor skills develop. Indeed the learning of the relationship between proprioceptive feedback and movement occurs as we practice movement from birth onwards. Subjects with IFD are therefore not generally clumsy before the onset of dystonia. In IFD it is not only that the muscle spindles too stiff, but rather that their elastic properties change as they are stretched, as demonstrated by the change in perception of the vibration-induced illusion of movement with muscle fatigue, which poses problems for motor learning. It is the inconstancy of elastic properties of the dystonic muscle spindle that leads to the corruption of the motor subroutine.

10. Inheritance of the trait and the endophenotype

We examined the vibration-induced illusion of movement in both patients with IFD, members of their family and in unrelated healthy subjects ¹⁴. First degree relatives of those with dystonia had a higher rate of abnormal vibration-induced illusion of movement than control subjects. This implied that the vibration induced illusion of movement was a true endophenotype.

Thus, abnormal thixotropy of the muscle spindles is likely to be determined genetically. It may be, for example, that the elastic properties of the muscle spindles are determined by genetically determined structural properties of the muscle spindles.

Our experiments revealed that many people who inherit the abnormal vibration-induced illusion of movement do not develop dystonia. Of the other genes which are involved in dystonia, the best defined, DYT1, has low penetrance, with only about one third of those with the gene abnormality developing the disorder. It is likely that this gene interacts with others to producing dystonia, and it is plausible that patients with DYT1 only develop symptoms if they happen also to inherit abnormal vibration-induced illusion of movement as well. Whilst consistent with our own observations, we have not systematically studied asymptomatic families with DYT1 to confirm this observation. How genes other than those which are involved in the vibration induced illusion of movement influence the pathophysiology of dystonia is unclear. Some genes involved in the dystonic phenotype may act peripherally, at the level of the muscle spindle, whereas others may act centrally to influence, say, flexibility of motor learning.

11. What about tremor?

Many people with dystonia have an associated tremor, and tremor may be commoner in first degree family members ^{37,38}. For this reason we looked at whether other people with

tremor had abnormal vibration-induced illusion of movement³⁹. About half of people with apparently 'essential' tremor and no family history of dystonia showed the same abnormality of the vibration-induced illusion of movement as those with IFD.

The maintenance of posture is an active process involving feedback from muscle spindles to the brain. If the muscle spindle thixotropic properties are abnormal this may be expected distort the phase of their feedback response to perturbation of the posture. If phase of the feedback is so delayed as to reinforce rather than damp the perturbation, tremor may result. We have suggested that the increased prevalence of tremor with age might be related to age-related changes in elastic properties of muscle spindles. That essential tremor is suppressed by limb cooling supports the notion that peripheral factors are involved in its generation⁴⁰.

12. Why do only some subjects with the endophenotype develop symptoms?

The relationship between afferent feedback and efferent drive changes as limbs grow and muscle strength changes, so some flexibility in motor learning is essential. On the other hand, to develop exquisitely refined skills, such as those of a musician or athlete, such learning must result in precise, reliable and stable motor subroutines. The nervous system therefore has to provide both for plasticity and consistency. It may be that abnormal plasticity demonstrated in dystonic subjects by the abnormalities of cortical and spinal neural inhibition facilitate corruption of established motor programmes by distorted muscle spindle feedback, but represent no more than an extreme of a continuum of normal motor plasticity of the nervous system.

I propose that the development of IFD requires both an abnormality of muscle spindle thixotropy and an abnormality of neural inhibition or plasticity of the cortical and spinal pathways involved in motor learning to produce the phenotype^{41,42}. If the former only is present, the endophenotype may be asymptomatic or result in tremor only, but if there are abnormalities of cortical plasticity the motor subroutines are more readily corrupted by overlearning of motor subroutines in the fatigued state using distorted muscle spindle feedback.

13. Conclusions

The hypothesis within this paper is based on the premise that there is an underlying proprioceptive disorder in subjects predisposed to IFD caused by abnormal thixotropic properties of the muscle spindles. Testable predictions which follow from this hypothesis include:

1. that a gene contributing to the phenotype will code for a structural muscle spindle protein,
2. that adequate head support in sleep might prevent cervical dystonia in predisposed individuals or reduce its progression,
3. that abnormalities of sensorimotor integration in IFD will be interpretable mainly in terms of abnormal proprioception, and
4. that despite symptomatic improvement, deep brain stimulation treatment of dystonia will have little effect on the abnormal vibration-induced illusion of movement of patients with IFD.

The interaction between this endophenotype and the other genes identified as associated with dystonia is intriguing as are the insights that these processes provide into the functioning of the motor systems in health and disease. The substantial literature on abnormal sensorimotor integration in dystonia is difficult to interpret in this context, as physiological abnormalities such as reduced tactile discrimination are complex perceptions involving many different sensory modalities, but these observations should trigger a re-interpretation of some of the experimental evidence which has accumulated concerning this intriguing disorder.

14. Acknowledgements

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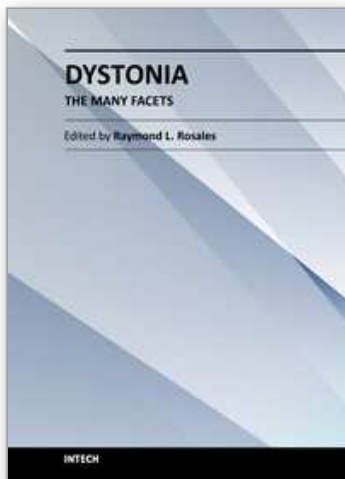
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Dystonia has many facets, and among those, this book commences with the increasingly associated genes identified, including a construct on how biology interacts with the dystonia genesis. The clinical phenomenology of dystonia as approached in the book is interesting because, not only were the cervical, oromandibular/lingual/laryngeal, task-specific and secondary dystonias dealt with individually, but that the associated features such as parkinsonism, tremors and spasticity were also separately presented. Advances in dystonia management followed, and they ranged from dopaminergic therapy, chemodenervation, surgical approaches and rehabilitation, effectively complementing the approach in dystonia at the clinics. A timely critical pathophysiologic review, including the muscle spindle involvement in dystonia, is highlighted at the book's end.

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