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INVITED REVIEW

The pathophysiology of primary dystonia

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Summary

Co-contraction and overflow of EMG activity of inappropriate muscles are typical features of all dystonic movements whether voluntary or involuntary. Voluntary movements are slow and more variable than normal, and there is particular difficulty switching between component movements of a complex task. Reduced spinal cord and brainstem inhibition is common to many reflex studies (long-latency reflexes, cranial reflexes and reciprocal inhibition). These reflex abnormalities may contribute to the difficulties in voluntary movements but cannot be causal as they can occur outside the clinically involved territory. Clinical and neurophysiological studies have emphasized the possible role of sensory feedback in the generation of dystonic movements. Abnormalities of cortical and basal ganglia function have been described in functional imaging and neurophysiological studies of patients with dystonia and in animal models of primary dystonia. Studies of cortical function have shown reduced preparatory activity in the EEG before the onset of voluntary movements, whilst magnetic brain stimulation has revealed changes in motor cortical excitability. Functional imaging of the brain in primary dystonia has suggested reduced pallidal inhibition of the thalamus with consequent overactivity of medial and prefrontal cortical areas and underactivity of the primary motor cortex during movements. These findings are supported by preliminary neuronal recordings from the globus pallidus and the thalamus at the time of stereotaxic surgery in patients with dystonia. All this evidence suggests that primary dystonia results from a functional disturbance of the basal ganglia, particularly in the striatal control of the globus pallidus (and substantia nigra pars reticulata). This causes altered thalamic control of cortical motor planning and executive areas, and abnormal regulation of brainstem and spinal cord inhibitory interneuronal mechanisms.

Keywords: dystonia; cortical areas; spinal cord; brainstem

Introduction

The term dystonia is used to describe a syndrome characterized by prolonged muscle contractions causing sustained twisting movements and abnormal postures of the affected body part(s). Despite early clear descriptions of dystonia (Oppenheim, 1911; Herz, 1944), it took more than half a century before physicians accepted that this bizarre condition was due to brain disease (Marsden *et al*., 1976). Dystonia may be classified on clinical examination according to its distribution: focal dystonia, affecting a single body part in isolation; segmental dystonia, affecting adjacent body parts or a segment of the body; hemidystonia, involving one side; and generalized dystonia, affecting two or more body segments of the entire body. Alternatively, dystonia may be classified in four groups according to the underlying cause. (i) Primary dystonia occurs in patients who have no signs of structural abnormality in the CNS. Tremor may or may not be present. When generalized, this disorder is synonymous with idiopathic torsion dystonia. The dystonia can also be focal, as in disorders such as writer's cramp, blepharospasm and spasmodic torticollis. (ii) 'Dystonia-plus' syndromes occur when dystonia is combined with other pathological changes (these include dopa-responsive dystonia and

myoclonic dystonia). (iii) Secondary dystonia is seen when there is a demonstrable exogenous, structural or metabolic cause. (iv) Heredodegenerative dystonia occurs when there is underlying brain degeneration (Fahn *et al.*, 1998). Primary dystonia is the commonest form of dystonia, and recently it has been found to be associated with several different genetic abnormalities. A gene associated with generalized familial primary dystonia codes for an ATP-binding protein (Ozelius *et al*., 1997). A family with spasmodic torticollis had an abnormality in mitochondrial electron transfer complexes (reduced complex I activity) (Benecke *et al.*, 1992).

Most lesions responsible for symptomatic dystonia involve the basal ganglia or thalamus (Marsden *et al.*, 1985; Pettigrew and Jankovic, 1985). In a recent meta-analysis of 240 patients with lesions affecting the basal ganglia and causing movement disorders, 36% exhibited dystonia (Bhatia and Marsden, 1994). The lentiform nucleus (putamen and globus pallidus) was the most frequent site affected in those with dystonia. Dystonia was also observed in 30% of patients with movement disorders associated with lesions of the thalamus and subthalamic region (Lee and Marsden, 1994). Thalamic lesions producing dystonia involved the posterior and midline thalamic nuclei.

No consistent anatomical pathology has been found in primary dystonia. Most MRI has failed to demonstrate consistent basal ganglia abnormalities (Rutledge *et al.*, 1988). However, high field studies by Schneider *et al.* (1994) have revealed some morphological changes in the lentiform nucleus, and it is reasonable to assume that functional abnormalities of the basal ganglia and thalamus will eventually be found to be responsible for the clinical symptoms in many situations. In the last decade neurophysiological and functional imaging studies have provided new insights into the pathophysiology of primary dystonia.

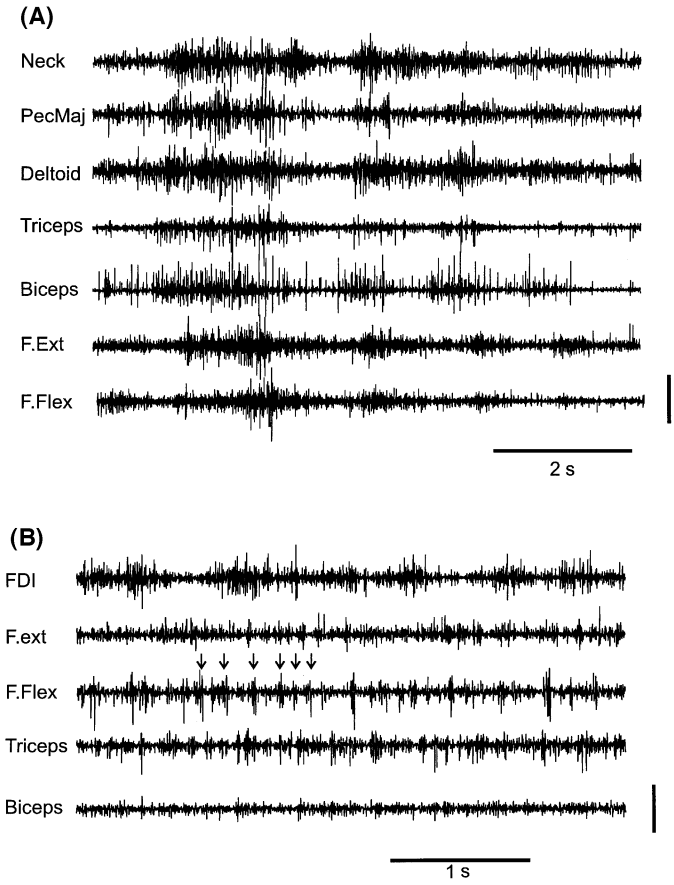

Fig. 1 Electromyographic recordings of dystonic EMG activity in two patients with dystonia. The upper panel shows prolonged EMG bursts in a patient with segmental arm and neck dystonia and the lower panel the presence of tremor activity superimposed (arrows) on the EMG bursts in a patient with writer's cramp. PecMaj = pectoralis major; F.Ext = forearm extensors; F.Flex = forearm flexors.

Involuntary dystonic movements: EMG studies

The abnormal twisting movements of dystonia are characterized by co-contraction of agonist and antagonist muscles. Voluntary movement exacerbates the co-contraction of antagonist muscle pairs. Only in severe cases is muscle activity recorded in subjects at complete rest. In his pioneering observations, Herz (1944) showed that dystonic postures are produced by long periods of continuous EMG activity lasting several seconds. Repeated shorter bursts of EMG activity sometimes occur in addition to the longer spasms. Depending on the duration and regularity of these bursts, they may cause superimposed postural and action tremors (Yanagisawa and Goto, 1971; Jedynack *et al.*, 1991), slow myorhythmia (Herz, 1944) or myoclonus (myoclonic dystonia) (Obeso *et al.*, 1983) (Fig. 1). Such patterns are not specific to any one type of dystonia. They are evident in generalized (Yanagisawa and Goto, 1971; Rothwell *et al.*, 1983) and focal dystonias, including blepharospasm (Berardelli *et al.*, 1985; Aramideh *et al.*, 1994), torticollis (Podivinsky, 1968; Thompson *et al.*, 1990), laryngeal dystonia (Van Pelt *et al.*, 1994) and writer's cramp (Cohen and Hallett, 1988; Marsden and Sheehy, 1990).

Voluntary movement in dystonia: kinematic and EMG studies

In addition to the involuntary movements, a number of other abnormalities interfere with voluntary movement in patients with dystonia (Rothwell *et al.*, 1983; Cohen and Hallett, 1988). There may be a lack of selectivity in attempts to perform discrete independent movements, which results in overflow of activity to remote muscle groups that are not normally activated in the movement (Fig. 2). Occasionally willed activity may fail to occur, as is sometimes seen in patients with rotatory torticollis when they attempt to turn their head against the dystonic contraction.

Simple rapid movements about a single joint in normal subjects are accomplished by a characteristic di- or triphasic pattern of activation of agonist and antagonist muscles (Berardelli *et al.*, 1996). In dystonia the EMG bursts are

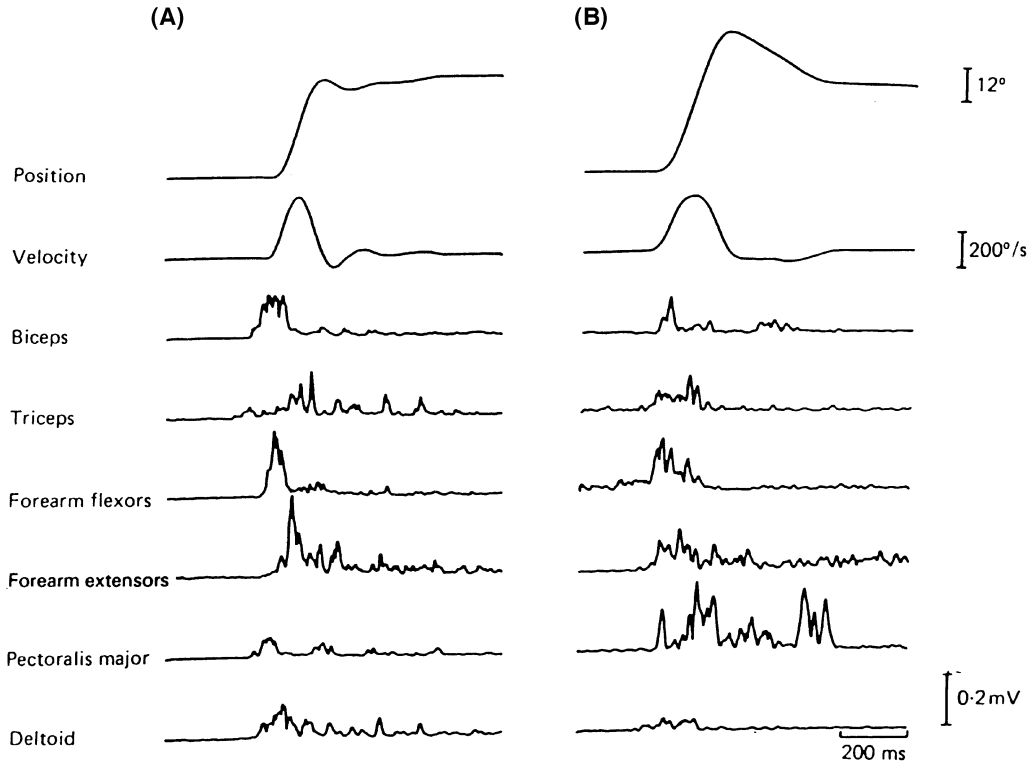

Fig. 2 Rapid flexion arm movements (30°) in a normal subject (**A**) and in a patient with dystonia (**B**). Note the prolonged duration of the first agonist burst (biceps) and the co-contraction and overflow of activity in the other muscles. [From van der Kamp *et al.* (1989), with the authors' permission.]

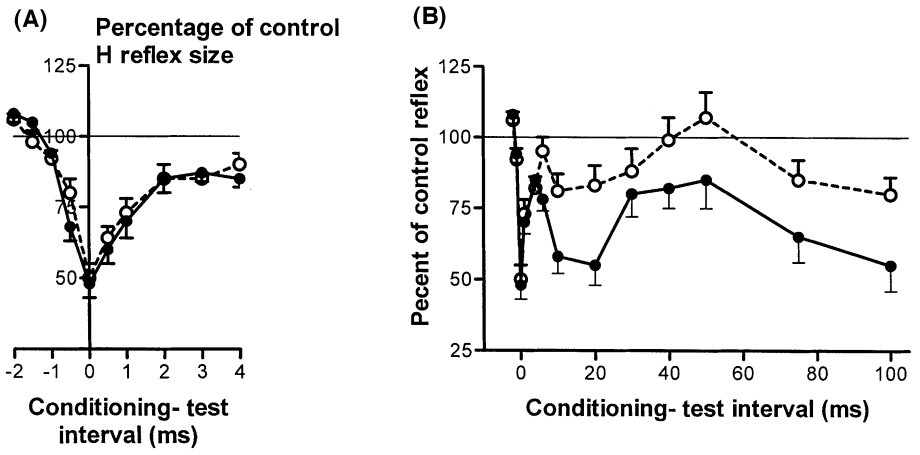

Fig. 3 Reciprocal inhibition in normal subjects (continuous lines) and in patients with dystonia (dashed lines). (**A**) Time course of the first phase of flexor H reflex inhibition produced by radial nerve stimulation; (**B**) Time course of the first, second and third phases of flexor H reflex inhibition produced by radial nerve stimulation. The first phase of inhibition is similar in the two groups of subjects, whereas the second phase is reduced in patients with writer's cramp. [From Nakashima *et al.* (1989*a*), with the authors' permission.]

usually prolonged, and as a consequence the agonist and antagonist activities may overlap in time for a longer period than normal (co-contraction). In addition, simple finger or hand movement may be accompanied by inappropriate activity in remote muscles of the upper limb and trunk (van der Kamp *et al.*, 1989) (Fig. 2). These findings probably contribute to the slowness and increased variability of voluntary movements of dystonic patients.

Additional deficits appear in more complex movements. Agostino *et al.* (1992) recorded subjects making a series of sequential arm movements by outlining a geometric shape on a graphics tablet. When the individual movements were

performed as part of a sequence they were slower than when executed separately. Furthermore, the time taken to switch between one movement and the next at the vertices of the shapes was prolonged. Similar deficits were seen in patients with Parkinson's disease except that movements in the latter also became progressively slower through the sequence ('fatigue'), a finding not seen in dystonia.

Inzelberg *et al.* (1995) have studied the kinematic properties of arm reaching movement in patients with dystonia. As with single-joint tasks, movements were slower and more variable than normal. A novel finding was that the deceleration component was prolonged in these free arm movements, and became even longer when subjects were deprived of visual feedback of limb position.

In summary, simple voluntary movements are slow (bradykinetic) and, like the involuntary dystonic movements, are characterized by excessive and overlapping activity in agonist and antagonist muscles together with overflow of activity to muscles not normally involved in the task. The time taken to switch between components of a complex movement is prolonged.

Spinal cord reflexes in dystonia

Muscle reflexes elicited by stretch or electrical stimulation

Tendon jerks, as tested in the clinic, are normal in primary dystonia. However, electrical testing of the H-reflex recovery cycle suggests that there are subtle changes in spinal reflex pathways (Koelman *et al.*, 1995). Paired shock experiments show that the recovery of the H reflex at intervals of 200 ms is increased in patients with spasmodic torticollis or generalized dystonia (Panizza *et al.*, 1990). The mechanism of this change is unclear. There are alterations also in the long-latency stretch reflex; these reflexes have a longer duration than normal in patients with dystonia and stretch often evokes reflex activity in remote muscles not normally influenced by the displacement, another example of overflow (Rothwell *et al.*, 1983; Tatton *et al.*, 1984).

In contrast with these reports of increased reflex function, Naumann and Reiners (1997) have noted that the LLR2 reflex in thenar muscles is reduced in amplitude in patients with writer's cramp. This response has an onset latency of ~50 ms and can be recorded in active muscles after electrical stimulation of low-threshold afferents in the median nerve. It is thought to be generated by activity in a transcortical reflex pathway (Deuschl and Lücking, 1990). The size of the responses is further decreased by treatment with botulinum toxin. Why naturally elicited stretch reflexes appear to behave differently from these electrically elicited responses is unclear. One reason is that the stretch reflex studies were performed in patients with segmental or generalized dystonia while Naumann and Reiners (1997) studied patients with writer's cramp. Another possibility is that muscle spindles are hypersensitive in dystonia (see section headed The role of sensory feedback in dystonia, below). If so, then natural muscle stretch might evoke a larger than normal input to the reflex pathway which could compensate for its intrinsic insensitivity. The latter would only be revealed by using electrical stimulation of afferents in order to bypass the muscle spindle receptor.

Reciprocal inhibition

The striking co-contraction of agonists and antagonists that is so typical of dystonia suggests a breakdown of the normal pattern of reciprocal innervation between opposing muscles. Reciprocal inhibition of H reflexes in forearm flexor muscles can be demonstrated by stimulation of forearm extensor muscle afferents in the radial nerve. In normal subjects this consists of an initial short-lasting disynaptic Ia inhibitory phase (Day *et al.*, 1984) and a longer-lasting phase which is probably produced by presynaptic inhibition of large proprioceptive afferent fibres (Berardelli *et al.*, 1987). Initial studies in patients with writer's cramp showed that there is a reduction in the amount of inhibition in both the early and late phases of reciprocal inhibition (Panizza *et al.*, 1989; Chen *et al.*, 1995) or only in the later phase of inhibition (Nakashima *et al.*, 1989*a*) (Fig. 3). This abnormality is more pronounced in patients with dystonic rather than simple writer's cramp, and is evident in dystonic arms of patients with symptomatic or primary dystonia. As a possible mechanism, it was suggested that dystonia caused a change in the descending control of spinal interneurons mediating one or both phases of reciprocal inhibition (Nakashima *et al.*, 1989*a*).

This attractive idea that a disorder of reciprocal inhibition could contribute to the co-contraction seen in dystonia was put into question by the results of later studies. Similar changes were seen in the unaffected normal arms of patients with writer's cramp (Chen *et al.*, 1995) and in the unaffected arms of patients with spasmodic torticollis (Deuschl *et al.*, 1992). Thus a disorder of reciprocal inhibition did not cause an obligatory abnormality in the voluntary control of antagonist muscles. A possible explanation is that such tests are always performed at rest, whilst in most cases the dystonia is present only during attempted voluntary movement. It may be that a better correlation between abnormalities or reciprocal inhibition and dystonia would be seen if it were possible to test the system during movement.

Initial investigations on reciprocal inhibition during movement have been made by Valls-Solé and Hallett (1995). They described a sequence of inhibition, excitation and inhibition in active forearm flexor muscles after stimulation of the radial nerve. The first inhibitory period was reduced in patients with simple writer's cramp, consistent with reduced reciprocal inhibition during movement. However, this type of investigation has not yet been applied to a range of patients with different types of dystonia.

In a recent study, botulinum toxin injections into forearm muscles reduced arm dystonia and restored the presynaptic phase of reciprocal inhibition (Priori *et al.*, 1995). This effect

was interpreted as an indirect effect on spinal cord circuitry. Thus, botulinum toxin may have produced a long-term decrease in the amount of muscle spindle input to the spinal cord by causing transmission failure at the intrafusal neuromuscular junction. This may have had the secondary effect of improving transmission in the reciprocal inhibitory pathways, at least when tested at rest.

Brainstem reflexes in dystonia

Blink reflexes

Electrical stimulation of the supraorbital nerve or a light touch of the cornea can produce reflexes in the orbicularis oculi. In primary cranial dystonia, the initial short-latency ipsilateral R1 response is normal, but the later bilateral R2 component of the blink reflex is larger and longer-lasting than normal and its recovery cycle to paired supraorbital nerve stimuli is enhanced (Berardelli *et al.*, 1985; Tolosa *et al.*, 1988) (Fig. 4). This finding has been interpreted as indicating that the neural pathway of the blink reflex is intact in dystonia, but that the excitability of brainstem interneuronal pathways mediating the R2 component of the response is enhanced. Katayama *et al.* (1997) investigated the effects of different types of conditioning stimuli in inhibiting the R2 response and found that patients with blepharospasm had a greater susceptibility to photic conditioning. They suggested that this was related to the enhanced sensitivity to light evident in some patients.

The clearest abnormalities of the blink recovery cycle are evident in patients with cranial dystonia, but similar changes have been observed in cervical and generalized dystonia, even in patients without blepharospasm. Patients with segmental dystonia not affecting cranial or neck muscles have a normal recovery cycle (Nakashima *et al.*, 1990; Pauletti *et al.*, 1993) (Fig. 4). A possible human model of blepharospasm has been proposed in a case report of a patient who developed blepharospasm contralateral to an eyelid weakened by facial nerve palsy (Chuke *et al.*, 1996). Hyperexcitability of the normal eyelid might be a maladaptive consequence of the bilateral increase in gain of eyelid movement due to weakness of the affected lid.

Combined EMG recordings of the orbicularis oculi and levator palpebrae muscles have identified three different patterns of involuntary muscle activity in patients with blepharospasm (Aramideh *et al.*, 1994, 1995) (Fig. 5). In the first, involuntary discharges are confined to the orbicularis oculi. In the second, involuntary activity in the orbicularis oculi is accompanied by either (involuntary) inhibition of the levator palpebrae or disturbed reciprocal innervation between the orbicularis oculi and levator palpebrae. In the third, there is (involuntary) inhibition of the levator palpebrae alone without clinical signs of orbicularis oculi spasm. The correlation that was found between EMG recordings and the blink reflex recovery cycle showed that there was enhanced recovery in patients showing the first pattern, whereas the recovery cycle was normal in 75% of those showing the second pattern and 100% of patients showing the third pattern. These three patterns are reminiscent of the patterns of EMG activity seen in other forms of focal dystonia (see above): (i) excessive muscle activity in the target muscle; (ii) the same as in (i) but also co-contraction of antagonists; (iii) failure to activate a target muscle voluntarily.

Cranial nerve inhibitory reflexes

The masseter inhibitory reflex is characterized by an early (SP1) and a late (SP2) phase of inhibition in ongoing voluntary activity. In patients with primary cranial dystonia, paired-pulse testing showed that the recovery cycle of the late phase of inhibition was enhanced in cranial dystonia (Cruccu *et al.*, 1991), consistent with abnormalities in the excitability of brainstem inhibitory interneurons. Similar to the blink reflex, abnormalities can be observed even in patients who have no overt dystonia of the jaw-closing muscles (Pauletti *et al.*, 1993).

Stimulation of the supraorbital nerve at relatively high intensities can produce a period of suppression in ongoing EMG activity in the sternocleidomastoid muscle. The duration and depth of this inhibition is reduced in patients with torticollis (Nakashima *et al.*, 1989*b*). More recent evidence shows that exteroceptive suppression of EMG activity in the sternocleidomastoid is also reduced in patients with blepharospasm without torticollis (Carella *et al.*, 1994), again suggesting that the abnormality of spinal and brainstem interneuronal function is more widespread than the clinical symptomatology.

The reason for the changes of interneuron function in the brainstem in dystonia is not known. Like the spinal abnormalities identified in reciprocal inhibition, it has been speculated that they are due to changes in the activity of descending inputs from higher centres (e.g. the basal ganglia) to the brainstem and spinal cord rather than to any fundamental defect in the interneuronal circuits themselves.

Vestibular abnormalities

Torticollis is associated with a high incidence of abnormalities in conventional tests of vestibular function (Bronstein and Rudge, 1988; Stell, 1989). Colebatch *et al.* (1995) described an inhibitory reflex that can be evoked in active sternocleidomastoid muscles by brief, but loud clicks played through headphones to the ears. The reflex occurs at very short latency and is thought to be due to acoustic stimulation of otolith receptors in the inner ear. The responses are asymmetrical in torticollis, being smaller in the less affected muscle. Since such responses are only reduced in patients with a long history of torticollis, the authors presumed that they were more likely to be a compensatory rather than a causal effect.

Lekhel *et al.* (1997) have shown that postural responses to vibration of the posterior neck muscles are abnormal in

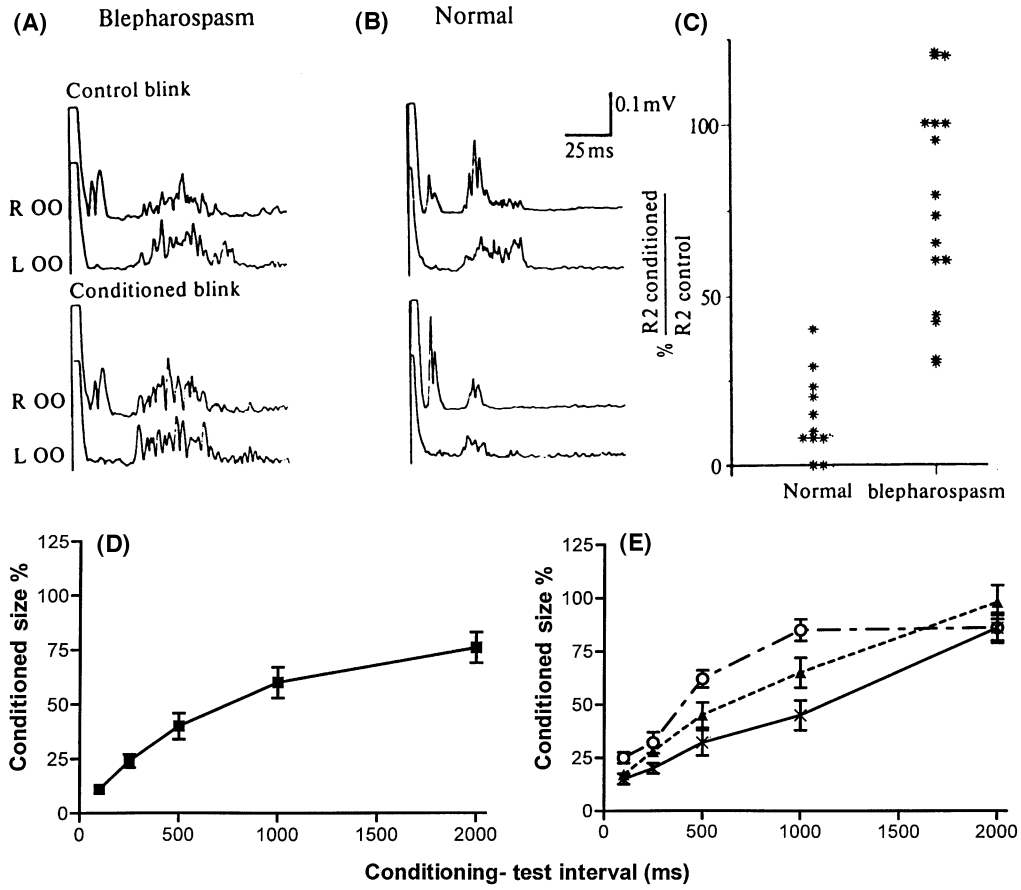

Fig. 4 Recovery cycle of the R2 component of the blink reflex in normal subjects and in patients with dystonia. (**A**–**C**) Recovery cycle of the R2 component of the blink reflex at an interval of 500 ms between test and conditioning stimuli in a patient with blepharospasm and in a normal subject. On the right are shown the amplitudes of the test R2 component when conditioned by a preceding shock at intervals of 500 ms in normal subjects and in patients with blepharospasm. The upper two traces in **A** and **B** are of control blink reflex without a conditioning stimulus; the lower two traces in **A** and **B** are of a conditioned blink reflex. For each response the upper traces are the rectified EMG activity from the right orbicularis oculi (R OO) and the lower traces are from the left orbicularis oculi (L OO) muscles. The stimulus was applied to the right supraorbital nerve. (**D** and **E**) Complete recovery cycles of R2 component at different conditioning test intervals: (**D**) control data; (**E**) data from three groups of patients: crosses indicate patients with arm dystonia; triangles indicate patients with torticollis; circles indicate patients with segmental dystonia. [From Berardelli *et al.* (1985) and Nakashima *et al.* (1990), with the authors' permission.]

torticollis. Vibration increases spindle input from the posterior neck muscles, and this is usually interpreted as being caused by neck flexion. Because there is no change in vestibular input the head position is assumed to be normal with respect to gravity. The net result is that normal subjects behave as if the trunk were leaning backwards with the neck flexed, and they lean forwards to compensate. In contrast, vibration in patients results simply in neck extension, as if the vestibular signal were ignored.

Interpretation of findings of spinal and brainstem studies

Reduced spinal cord and brainstem inhibition is a common finding in dystonia. The fundamental disturbance is most likely to be an abnormal supraspinal command signal rather than a primary disorder of spinal and brainstem circuitry. Since most cases of symptomatic dystonia have structural lesions in the basal ganglia, particularly in the putamen, it is reasonable to suggest that altered basal ganglia motor output destined eventually to control brainstem and spinal cord motor machinery is responsible for primary dystonia. Such distorted basal ganglia output could either engage the motor areas of the cerebral cortex via the thalamus, or descend directly to the brainstem regions that control posture, balance and locomotion.

A fundamental point is that although these changes may contribute to dystonia, they cannot alone be responsible for it. There are two reasons for this. First, abnormalities may be seen outside the clinically involved territory. For example,

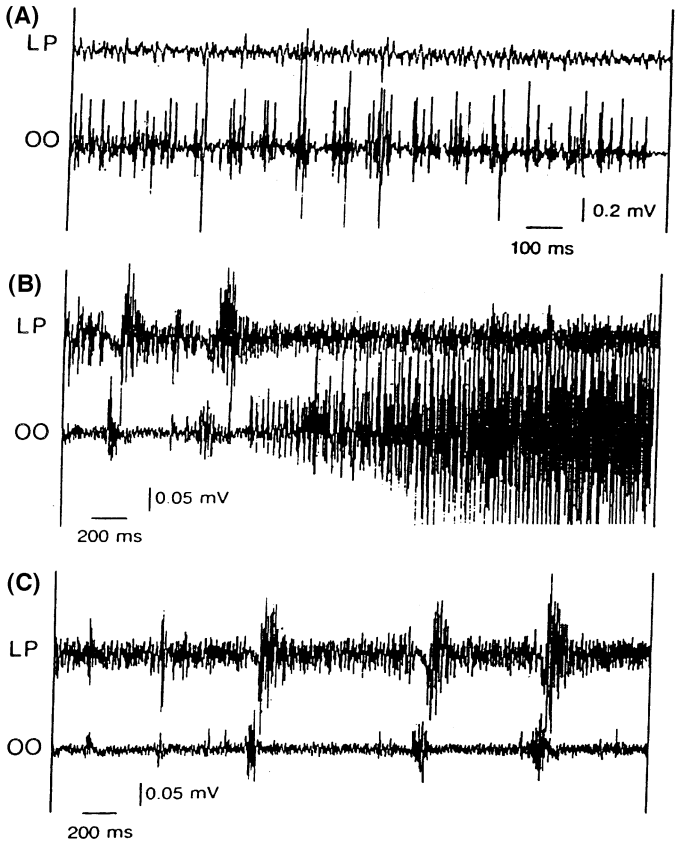

Fig. 5 Different types of dystonic activities of orbicularis oculi (OO) in a patient with blepharospasm. (**A**) Tremulous discharges, while the eyes are kept closed; (**B**) tonic activity causing forceful closing of the eyelids; (**C**) phasic discharges, which are followed by post-inhibition potentiation of levator palpebrae superioris (LP). [From Aramideh *et al.* (1994), with the authors' permission.]

hyperexcitability of blink reflex recovery may be seen in a patient with spasmodic torticollis even without blepharospasm. Secondly, reduced inhibition is not limited to patients with dystonia (Nakashima *et al.*, 1989*a*; Hallett, 1997). Abnormalities of the blink reflex and reciprocal inhibition are also seen in Parkinson's disease (Lelli *et al.*, 1991). Although both have increased tone and bradykinesia, and some patients present with an apparent mild dystonia and later develop Parkinson's disease, their physiology is clearly not identical. For example, there are clear differences in long-latency stretch reflex behaviour, since the amplitude of these reflexes is increased in Parkinson's disease but is normal in dystonia (Tatton *et al.*, 1984).

Studies of cortical function in dystonia

Premovement EEG potentials

A slow rising negative EEG wave, the Bereitschaftspotential, can be recorded from wide areas of scalp before the onset of a self-paced voluntary movement. An initial component (NS1) begins up to 1.5 s before movement onset and is followed by a second, steeper component (NS2 or NS′) beginning some 650 ms before movement onset. Direct recordings from subdural electrodes placed on the cortical surface have shown that NS1 is due to bilateral activity in both the primary and the supplementary motor areas (Ikeda *et al.*, 1992). About half a second before movement onset the activity begins to lateralize to the contralateral primary motor area.

Three recent reports have shown that various components of this EEG activity are reduced in patients with dystonia. In a group of patients with hemi- or generalized dystonia secondary to lesions of the striatum, pallidum or thalamus, both the NS1 and NS2/NS′ components were reduced in size (Feve *et al.*, 1994). A reduction in the peak amplitude of only the NS2/NS′ was found in patients with primary torsion dystonia (van der Kamp *et al.*, 1995) (Fig. 6). A decrease in the NS2/NS′ component localized to the central area contralateral to the moving hand has been described in patients with writer's cramp (Deuschl *et al.*, 1995). Toro *et al.* (1993) found that there was less event-related desynchronization of the EEG prior to movement over the contralateral central region in dystonia.

EEG events prior to movement are sometimes recorded in a slightly different paradigm. The contingent negative variation, like the Bereitschaftspotential, is a slow negative potential recorded from wide areas of scalp, which occurs in the period between a warning and a response signal (an S1–

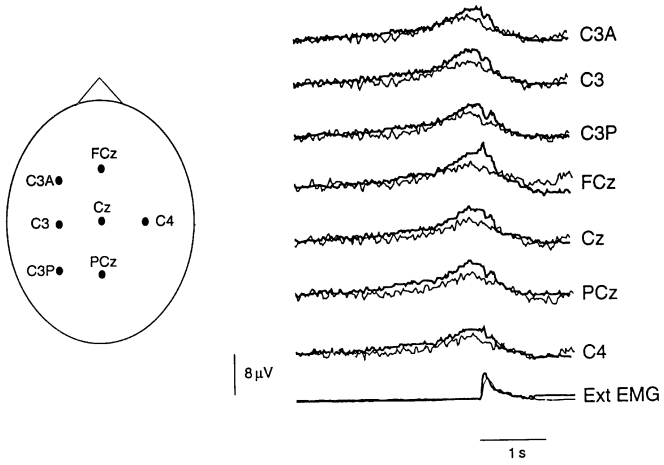

Fig. 6 Movement-related cortical potentials (traces coded to match map on left) in patients with primary dystonia. Grand average of potentials superimposed from patients (thin traces) and normal subjects (thick traces) relative to self-paced finger extension movements. The bottom trace shows the average surface-rectified EMG activity from extensor indicis. [From Van Der Kamp *et al*. (1995), with the authors' permission.]

S2 paradigm). Thus the movement, which comes after S2, is cued, rather than self-paced as in the BP task. Kaji *et al.* (1995*a*) examined the contingent negative variation in a task that required patients with torticollis to rotate their head to the right or the left, depending on the nature of the S2 signal. They showed that the amplitude of the late component of the contingent negative variation was reduced in patients. However, there was no difference between patients and normal subjects when the task was to extend the finger. Patients with focal hand dystonia show a similar abnormality for hand movements (Ikeda *et al.*, 1996).

The general conclusion is that patients with dystonia prepare for movement in a different way from normal subjects, and the implication is that this may contribute to the problems in muscle control that emerge when the patient starts to move. The problem might be either in retrieving movements from memory in response to external cues, or in retaining the movement in memory prior to execution. It is possible that these cortical changes reflect a disorder of basal ganglia outflow (via the thalamus) to the motor areas of the cortex.

Studies with brain stimulation

Transcranial electric and magnetic stimulation has been used for many years to activate the motor cortex in conscious human subjects. In primary dystonia, both the threshold for electrical stimulation and the central conduction time in fast-conducting corticospinal fibres are the same as in normal subjects (Thompson *et al.*, 1986).

Mavroudakis *et al.* (1995) and Ikoma *et al.* (1996) have investigated the input–output relationships of the system in more detail with magnetic stimulation. They found that the size of responses increased more steeply with increasing levels of background contraction in patients with primary dystonia, or with increasing stimulus intensity, than in normal subjects. Effectively the cortical output gain was higher in patients, and this may contribute to the excessive motor output that occurs during voluntary movement in dystonia. Mapping of the cortical sites from which specific muscle responses can be elicited by brain stimulation in patients with writer's cramp also showed an alteration in size and location (Thompson *et al.*, 1996), suggesting some reorganization of cortical excitability in dystonia.

The changes in cortical output gain are most likely to result from changes in the excitability of connections within the motor cortex itself than to changes in the excitability of relay stations in the corticospinal pathway. One method of examining such connections is by giving paired magnetic shocks delivered at varying interstimulus intervals in a conditioning–test design. Kujirai *et al.* (1993) showed that a subthreshold conditioning stimulus could produce inhibition then facilitation of the response evoked in relaxed muscles by a suprathreshold test stimulus given 1–20 ms later. Inhibition predominated at conditioning-test intervals shorter than 6 ms, whereas facilitation predominated at intervals greater than 6 ms. Since a conditioning stimulus of such intensity has no effect on spinal H reflexes, it was proposed that the effects were produced by changes in activity of intracortical circuits. Voluntary movement alters the excitability of these circuits; activation of the target muscle decreases the amount of inhibition and facilitation, but has no effect on the responses evoked in nearby inactive muscles (Ridding *et al.*, 1995*a*).

Ridding *et al.* (1995*b*) found that there was less initial inhibition (conditioning–test interval shorter than 6 ms) in patients with focal, task-specific primary dystonia when tested at rest (Fig. 7). They proposed that under normal circumstances one role of the inhibition was to 'focus' the motor command within the cortex so that the correct muscles were activated by the right amount in any task. Experiments in monkeys by Matsumura *et al.* (1991) supported this hypothesis by showing that application of the GABA antagonist bicuculline to the motor cortex increased the co-contraction of antagonist muscles in a simple wrist movement task. A deficiency in this cortical inhibitory system could therefore contribute to the overflow of activity in dystonia. Indeed, reduced excitability of this inhibitory system could also account for the increased cortical output gain noted above.

A second method of investigating excitability in cortical circuits is by studying the EMG silent period produced by much larger conditioning magnetic scalp shocks applied during active muscle contraction (Priori *et al.*, 1994). The initial part of this silent period is, at least in part, caused by change in spinal inhibitory circuits induced by the scalp stimulus. The later part is thought to be due to a prolonged period of inhibition set up in the cortex by the large shock (Inghilleri *et al.*, 1993; Roick *et al.*, 1993). The mechanism of this later inhibition is presumably different from that of

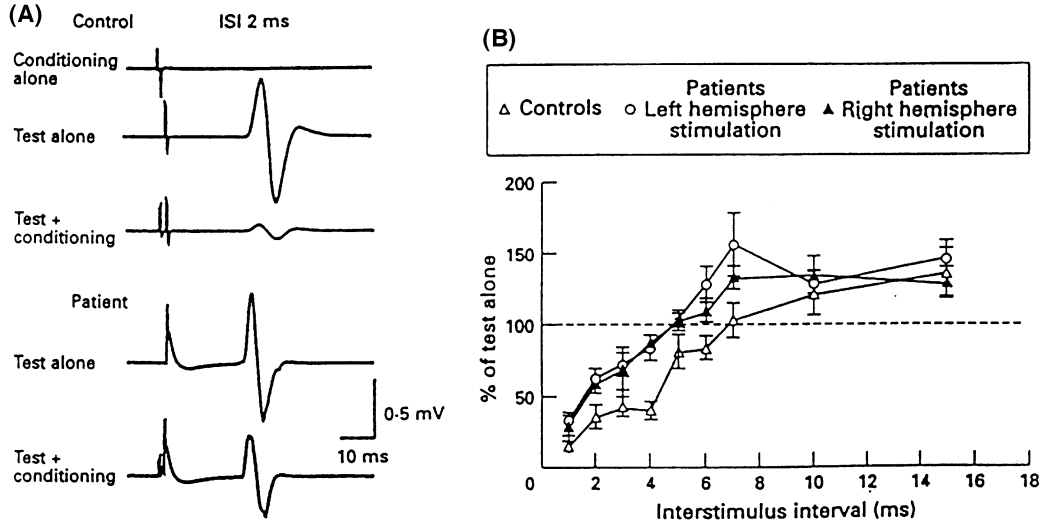

Fig. 7 Corticocortical inhibition in normal subjects and in patients with focal dystonia. (**A**) Data obtained after left hemispheric stimulation and responses recorded in the relaxed right first dorsal interosseous muscle. In the control subject, when the conditioning stimulus was given 2 ms before the test stimulus, there was clear suppression of the response (test + conditioning), whereas in the patient there was less suppression of the test response when conditioned at an interstimulus interval of 2 ms (test + conditioning). (**B**) Data obtained across all interstimulus intervals in controls and patients (stimulation of both left and right hemisphere). [From Ridding *et al.* (1995*b*), with the authors' permission.]

the short-latency effects discussed above since its threshold is so much higher. Several groups (Ikoma *et al.*, 1996; Rona *et al.*, 1998; Filipovic *et al.*, 1997) have now shown that the overall silent period produced by such larger shocks is shorter in dystonia than in normal subjects. In contrast, the duration of the silent period is increased in patients with Huntington's disease (Priori *et al.*, 1994).

Accordingly, the evidence from silent period studies and from double-shock experiments with subthreshold conditioning at short intervals suggests that cortical inhibition is reduced in primary dystonia. It is also consistent with results from a different type of double pulse experiment reported by Chen *et al.* (1997). These authors gave two equal suprathreshold stimuli over the motor cortex at intervals of 20–200 ms and recorded responses from forearm extensor muscles. In normal subjects at rest, the response to the second stimulus was suppressed for >200 ms, whilst during voluntary activity the suppression lasted ~130 ms. Patients with writer's cramp had normal suppression at rest, but reduced suppression (at 60–80 ms) during voluntary activation of the target muscle. However, since Rona *et al.* (1998) obtained opposite results in a very similar experiment, further confirmation is necessary before placing too much weight on this data.

In conclusion, the changes seen with magnetic stimulation suggest that although the resting level of corticospinal excitability is normal, there is an increase in the gain of the input–output relationship of the motor cortex. This is accompanied by changes in the excitability of local cortical inhibitory systems. In the absence of any compensatory changes in the input to the motor cortex, such changes could result in larger and more widespread muscle activation during voluntary movement.

Cortical somatosensory evoked potentials

The late components of the SEPs to median nerve stimulation may be abnormal in dystonia. The N30 component of the median nerve somatosensory evoked potential is a highly variable component with a controversial site of origin, thought by some to be from the supplementary motor area. The N30 is clearly influenced by motor behaviour, and in most studies it is decreased in amplitude in patients with Parkinson's disease.

Some studies have reported that the N30 component is increased in dystonia, whilst others have found it normal or small. Reilly *et al.* (1992) thought that the N30 was enlarged in patients with writer's cramp. However, in spasmodic torticollis Nardone *et al.* (1992) found a normal N30, while Mazzini *et al.* (1994) found it to be smaller than normal (although it must be noted that these patients had no apparent upper limb involvement). Using a very slow rate of stimulation, which produced a marked increase in N30 amplitude, Grissom *et al.* (1995) found a decrease in N30 in patients with focal hand dystonia. It is difficult to draw any conclusions from these somatosensory evoked potential findings at present.

The role of sensory feedback in dystonia

The prominent role of sensory input in influencing some forms of focal dystonia is illustrated by manoeuvres such as the *geste antagoniste* and other 'sensory tricks' that can control the dystonic spasms and postures and return the body part to a more normal position. Vibration of a dystonic limb at rest can induce involuntary co-contractions of muscles that reproduces the dystonic posture of the limb (Tempel and

Perlmutter, 1993; Kaji *et al.*, 1995*b*). On the other hand, it should be noted that vibration can improve spasmodic torticollis (Leis *et al.*, 1992).

Reducing sensory input from the affected limb can sometimes improve dystonia. Sheehy *et al*. (1988) described a patient in whom a local anaesthetic block of large afferent fibres in the hand and forearm, with little effect on muscle strength, produced substantial improvement in writer's cramp. They interpreted this as an effect of cutaneous input on the excitability of reciprocal inhibitory connections between the forearm muscles. In normal subjects, cutaneous input reduces the presynaptic phase of reciprocal inhibition, so that removal of this input by anaesthesia in the dystonic patient may have had the opposite effect of increasing inhibition.

Kaji *et al.* (1995*b*) injected local anaesthetic directly around the motor point of forearm muscles in patients with writer's cramp. The procedure can block muscle afferent function to a greater extent than muscle strength and leaves relatively strong muscles with no tendon reflexes. In patients with writer's cramp, such injections were successful in reducing action-induced dystonia. Since cutaneous afferents are relatively unaffected, the results seem to indicate a possible role for muscle afferents in producing or reinforcing dystonia. The authors suggested that hypersensitivity of muscle spindles (perhaps produced by excessive fusimotor discharge) might be important in producing vibration-induced dystonia. In addition, it may be that abnormal spindle input could be important during the initiation of movement, and might trigger the development of abnormal dystonic contractions. Sensory input might change the level of fusimotor drive and partially account for the phenomenon of the sensory trick. The importance of a tonic sensory inflow is also supported by the demonstration of Priori *et al.* (1995) that intramuscular injection of botulinum toxin modifies reciprocal inhibition between flexor and extensor muscles (see above).

Sensory symptoms may well precede the appearance of dystonia. By examining this issue carefully, Ghika *et al.* (1993) found that sensory symptoms were present in 11 successive patients with cranial dystonia. Symptoms included ill-defined pain, discomfort, distortion of sensation and 'phantom' kinetic or postural sensation. Common examples were a gritty sensation in the eye preceding blepharospasm and irritation of the throat preceding spasmodic dysphonia. In none of the cases, however, could the investigators find an objective substrate. In some cases, their patients said that they made voluntary repetitive movements in order to relieve the sensory symptom, but the movements eventually got out of voluntary control. A recent study has even suggested that there may be elemental sensory deficits in patients with hand dystonia (Byl *et al.*, 1996*a*). Graphaesthesia and stereognosis were abnormal bilaterally even though dystonia was unilateral, although identification and localization of sensory stimuli and kinaesthesia were normal.

This evidence certainly suggests that sensory input can modify dystonia. Whether sensory input can trigger dystonia is another matter, as is the possibility that dystonia itself may be associated with subtle sensory symptoms and signs. These issues deserve further study. It may well be that the sensory signs described by Byl *et al.* (1996*a*) are a consequence of defective sensorimotor integration. It seems unlikely that abnormal sensory input is the drive to dystonia.

Possible animal models of focal dystonia

Occupational cramps are usually regarded as a form of focal dystonia, and occur in parts of the body that are used to produce repeated skilled movement. Byl *et al.* (1996*b*) have recently investigated the changes that can occur in the organization of the monkey somatosensory cortex in two animals trained to produce skilled, repetitive movements of the hand. The animals performed a precise handgrip up to 300 times every day for several weeks. Eventually, both developed problems with their grip which interfered with the accuracy and speed of movement.

Microelectrode exploration of the somatosensory cortex showed that the organization of the hand representation changed over the same period. The receptive fields became enlarged, often covering more than one finger, and the normal segregation in the cortical map between glabrous and hairy skin was lost. It was thought that the task produced regular coincident input from the whole surface of the hand, and that this was the trigger for cortical reorganization. In essence, normal mechanisms of reorganization would be involved in adapting the sensory map in order to improve performance of the monkey in the task. They speculated that similar changes might also occur in the primary motor cortex and produce problems in focusing a motor command onto appropriate groups of muscles in other tasks. If this reorganization remained fixed, it could then become the basis for occupational cramps or focal dystonias.

Focal task-specific dystonias certainly affect the most overtrained skilled movements. Writer's cramp is the commonest, but a whole range of musician's and sportsman's occupational cramps occur. Many of these appear to be focal dystonias, which might be generated by overuse, along the lines suggested by Byl *et al.* (1996*b*), in susceptible individuals.

A second model of focal dystonia has recently been described in the rat. This model of blepharospasm depends, not on over-use, but on the conjunction of an intrinsic biochemical abnormality and extrinsic damage to peripheral nerves. Schicatano *et al.* (1997) report that a mild depletion of striatal dopamine, produced by unilateral 6-OHDA injection, increases the excitability of the blink reflex recovery cycle. If this is coupled with a unilateral lesion of the zygomatic branch of the facial nerve, to weaken the orbicularis oculi, then blink recovery is further enhanced. In addition, the animals show spontaneous spasms of lid closure.

Functional imaging of the brain in dystonia

Results of functional imaging studies are often interpreted using the present anatomical model of information flow in

corticobasal ganglia-cortical loops (see review by Wichmann and De Long, 1996). A recurring finding in human and animal models of dystonia is underactivity of the internal segment of the globus pallidus. Since pallidothalamic projections are inhibitory, this should lead in the model to overactive thalamocortical projections. Some results below fit this model, and others do not. The problem is that we have no adequate physiological model of how disordered pallidal output affects cortical function.

Metabolic studies

Initial studies suggested that at rest there is little difference in regional cerebral blood flow in patients with primary dystonia and normal subjects (Lang *et al.*, 1988; Karbe *et al.*, 1992; Ceballos-Baumann *et al.*, 1995*a*). Early reports of abnormalities in resting glucose metabolism were contradictory [e.g. Chase *et al.* (1988), increased; Karbe *et al.* (1992), decreased; Otsuka *et al.* (1992), unchanged], although recent work in patients with torticollis appears to show increased metabolism of the lentiform nucleus (Galardi *et al.*, 1996; Magyar-Lehmann *et al.*, 1997). Using a principal components method, Eidelberg *et al.* (1995) found some evidence for a relative putamenal hypermetabolism, which has recently been linked to thalamic hypometabolism (Eidelberg *et al.*, 1997). This has been interpreted in terms of increased activity in the direct striatopallidal pathway, inhibiting the internal segment of the globus pallidus. As a result there would be increased inhibitory synaptic activity in the medial globus pallidus (and substantia nigra pars reticulata) and reduced activity in pallidal output to the thalamus.

An intriguing study is that by Eidelberg *et al.* (1998), who investigated fluorodeoxyglucose metabolism in patients with primary dystonia and asymptomatic carriers of the *DYT1* gene. Clear abnormalities of covarying increased metabolism in the lentiform nucleus, cerebellum and supplementary motor area were discovered in both groups. These abnormalities did not express themselves in the form of clinical symptoms in the carriers. The *DYT1* gene is only ~30% penetrant, so it remains to be discovered why carriers do not have symptoms of the disease, and what additional factors trigger expression of the genetic abnormality in those who are affected.

Activation studies

Two features are common to much of this work. First, in accordance with the anatomical scheme outlined above, there is some evidence for overactivity of the prefrontal motor planning areas of the cortex, which could result from decreased pallidal inhibition of thalamic projection nuclei. The second feature, which is perhaps more robust, is reduced activation of the sensorimotor cortex in a number of different tasks. This is not readily explained by the model, and illustrates the need to understand more about the influence of pallidal output on cortical function.

Tempel and Perlmutter (1993) examined the change in cerebral blood flow produced by vibration of the finger-pads. They showed that vibration produced significantly less increase in flow in the sensorimotor cortex of patients with unilateral focal dystonia, whether the affected or unaffected hand was stimulated. This was not the result of the dystonic cramp that was often induced by the stimulation, since it occurred equally in patients in whom no such muscle contractions were seen.

Ceballos-Baumann *et al.* (1995*a*) investigated how paced, freely selected movements of a joystick changed the pattern of cerebral blood flow compared with that seen at rest. Patients with generalized or focal arm primary dystonia showed more activity than normal in the lateral premotor cortex, rostral supplementary motor area, Brodmann area 8, anterior cingulate area 32, ipsilateral dorsolateral prefrontal cortex and bilateral lentiform nuclei. There was underactivation of the caudal supplementary motor area, bilateral sensorimotor cortex, posterior cingulate and mesial parietal cortex (Fig. 8). The same group (Ceballos-Baumann *et al.*, 1997) also examined blood flow changes whilst subjects repeatedly wrote a stereotyped word. The task involved more continuous activity than the joystick task, but did not involve decision-making. Compared with normal subjects, patients with writer's cramp showed underactivation of the contralateral primary motor cortex, caudal supplementary motor area, anterior cingulate, mesial parietal and thalamus. There was overactivation of the ipsilateral premotor, insula, areas of parietal cortex, and cerebellar vermis, and, at a lower level of significance, prefrontal areas similar to those involved in the joystick task. Similar results were reported briefly by Ibanez *et al.* (1996). Treatment with botulinum toxin increased parietal activation still further, possibly because of a change in movement strategy. However, it did not improve the underactivity of the motor cortex, suggesting that this was a direct consequence of dystonia pathology and not a secondary effect of muscular co-contraction (Ceballos-Baumann *et al.*, 1997). These results suggest a relative overactivation of prefrontal motor planning areas (which receive striato-pallido-thalamic cortical projections) and underactivation of sensorimotor executive areas during movement in primary dystonia.

The situation was subtly different in acquired symptomatic hemidystonia caused by lesions in the basal ganglia or thalamus (Ceballos-Baumann *et al.*, 1995*b*). First, these patients had changes in resting blood flow that were not evident in primary dystonia. Resting flow was focally decreased in the ventroanterior thalamus, posterior thalamus, ipsilateral angular gyrus and bilateral frontal-orbital cortex, whilst it was increased in the contralateral lentiform nucleus, hippocampus and insula. Secondly, during movement the same frontal cortical areas showed an increased flow, as in primary dystonia, but there was overactivity rather than underactivity in the sensorimotor cortex. Although the dystonia was slightly more severe in the symptomatic group, this seemed unlikely to account for the differences. The differences may reflect fundamental variation in the way that

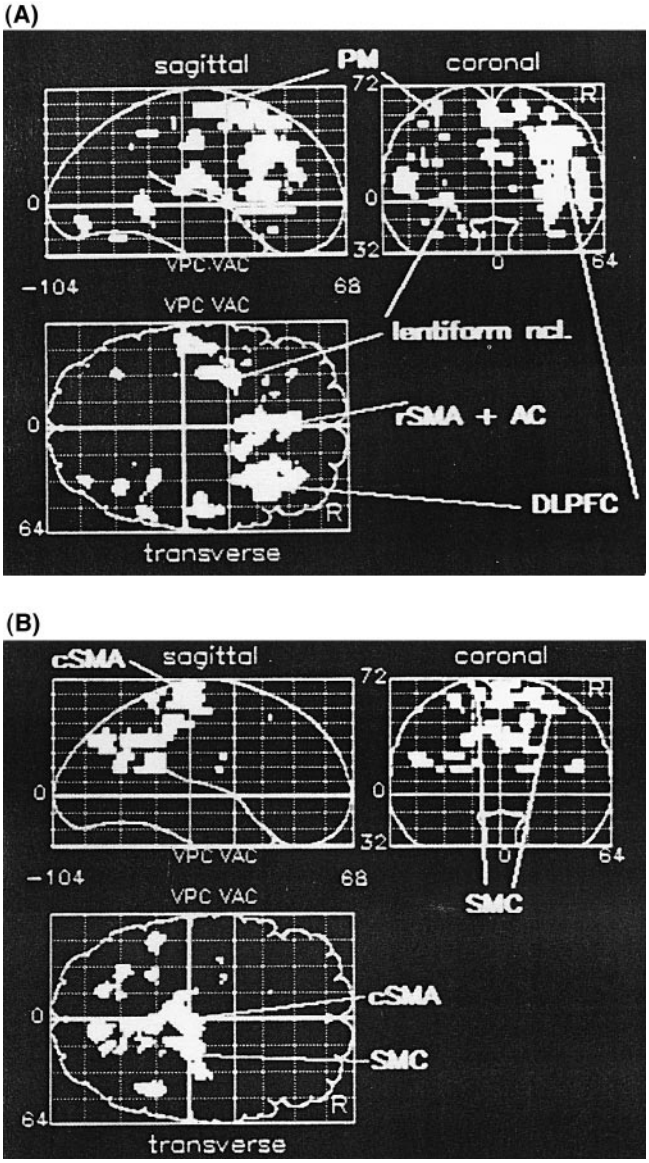

Fig. 8 Differences in activation between patients with primary torsion dystonia and normal subjects during performance of joystick movements. In (**A**) the white areas show all voxels with statistically significant enhanced activation in the patient compared with the control group. PM = premotor cortex; rSMA = rostral SMA; AC = anterior cingulate; DLPFC = dorsolateral prefrontal cortex. In (**B**) the white areas show all voxels with statistically significant impaired activation in the patient compared with the control group. cSMA = caudal SMA; SMC = sensorimotor cortex. [From Ceballos-Bauman *et al.* (1995*a*), with the authors' permission.]

a discrete brain injury produces clinical dystonia, in contrast to mechanisms responsible for primary dystonia.

There remains the problem of why the Bereitschaftspotential is decreased in both primary and symptomatic acquired dystonia, yet the pattern of brain activity revealed by functional imaging is different. There is no definite answer to this paradox except to say that it illustrates a typical problem in marrying data from two such different techniques. Perhaps the increase in flow in the prefrontal motor planning centres in primary dystonia represents an increase in cortical inhibition, which is responsible for the decrease in the Bereitschaftspotential. Alternatively, it may be that because imaging data have no temporal resolution the difference in the pattern of brain activity is the result of processes occurring after, rather than before, movement.

Finally, why should patients with primary dystonia, whose movements are characterized by excess muscular activity, have decreased blood flow in the motor cortex during the performance of movements? As reviewed above in the section on brain stimulation, there is good evidence that the basal ganglia can influence cortical inhibition, and it is therefore possible that metabolic underactivity results from reduced activity in cortical inhibitory interneurons. The consequence of reducing the amount of cortical inhibition might be a loss of selectivity in motor cortex output.

Neuronal activity recorded during neurosurgery in dystonia

Recent recordings have shown that in patients with primary dystonia at rest, the firing rates of neurons in the medial globus pallidus are lower than might be expected from similar studies in primates. They also tend to have large sensory receptive fields, and discharge irregularly in bursts or groups of bursts (Vitek *et al.*, 1998). Abnormal medial globus pallidus activity in humans confirms the data from functional imaging and animal studies (see below). However, two problems arise in trying to fit these data into the model of corticobasal ganglia–cortex loops. The first is that a medial pallidal lesion can improve dystonia, despite the fact that the activity of this zone appears to be reduced by the disease itself. However, it may be best to remove a noisy machine and to do without it! The abnormal pattern of medial globus pallidus neuronal firing in dystonia may be more important than the absolute firing rate.

The second problem is that reduced inhibitory output from medial globus pallidus would be predicted to lead to increased activity in thalamic target regions (V_{oa} and V_{op}). However, direct recording of single cells in V_{op} has not confirmed this prediction (Lenz *et al.*, 1998). V_{op} neurons in dystonic patients appear to have reduced discharge rates, and there are many more sensory cells than normal. It also appears that the discharge in V_{op} is actually linked to dystonic muscle contraction. A similar pattern of reduced activity is found in the cerebellar projection zone in the thalamus, namely nucleus V_{im}. V_{im} projections are distributed predominantly to the motor cortex itself, and it is possible that changes in cerebellar activity underlie some of the abnormalities of motor cortical function described above. The cerebellum has received little attention in metabolic studies, but there is clear evidence for abnormality, at least in the investigations using deoxyglucose (Eidelberg *et al.*, 1998).

Levodopa-induced dystonia in parkinsonian monkeys

Support for the concept of underactive pallidal output in primary dystonia comes from the analysis of levodopa-induced dystonia in MPTP-treated parkinsonian monkeys (Mitchell *et al.*, 1990; Crossman and Brotchie, 1998). Deoxyglucose studies suggest that there is indeed reduced medial globus pallidus activity as a result of excessive drive in the direct (D_1) striatopallidal pathway. Activity in the indirect (D_2) pathway to the lateral globus pallidus and subthalamus is also altered. In particular, there appears to be reduced subthalamic drive to the medial globus pallidus. Abnormal activity in the indirect pathway is probably important because of the demonstration of reduced dopamine D_2 receptor binding in the putamen of patients with dystonia (Horstink *et al.*, 1996; Naumann *et al.*, 1996; Perlmutter *et al.*, 1996, 1998). The net effect of these changes in the direct and indirect striatopallidal pathways appears to be reduced or altered medial globus pallidus inhibition of basal ganglia thalamic targets, with consequent increased thalamic drive to the premotor planning distributed network.

It is by no means clear how the changes in striatopallidal and pallidothalamic activity are different in chorea and dystonia. For diagnostic purposes, chorea and dystonia are considered to be different movement disorders. But the metabolic changes in the basal ganglia of levodopa-treated dyskinetic MPTP-intoxicated parkinsonian monkeys are similar in overall terms, although perhaps different in degree. Furthermore, chorea and dystonia are closely intertwined, often occurring together as 'choreoathetosis'. Indeed, patients with primary dystonia treated with high doses of anticholinergic drugs may be transformed from a dystonic phenotype into a picture of chorea, which returns to dystonia when the dose of anticholinergics is reduced (Nomoto *et al.*, 1987). Much needs to be discovered to explain the differences and similarities between chorea and dystonia.

Another area that deserves attention is the impact of possible changes in descending pathways from the basal ganglia to the brainstem, in particular to the pedunculopontine nucleus and to the other brainstem centres controlling posture and locomotion. These are highly likely to be abnormal in dystonia. Indeed, Eidelberg *et al.* (1998) have shown abnormal deoxyglucose activity in such brainstem regions. No doubt more attention will be paid to these descending pathways in future studies. Interestingly, in the MPTP parkinsonian monkey a thalamic lesion in motor targets from the basal ganglia can abolish levodopa-induced chorea, but does not affect levodopa-induced dystonia (Crossman and Brotchie, 1998). This suggests that the descending projections to the brainstem are critical for the manifestation of this drug-induced dystonia. In contrast, however, thalamic lesions can reduce dystonia in humans. This paradox may be due to the different location of stereotaxic thalamotomy in patients with dystonia, but exactly why this should be so is uncertain.

Dopamine and dystonia

Studies of striatal [^{18}F]dopa uptake in patients with familial primary dystonia have given various results, ranging from low normal (Playford *et al.*, 1993) to increased values (Otsuka *et al.*, 1992; Eidelberg *et al.*, 1995).

One of the most dramatic breakthroughs in the field of dystonia has been the discovery that dopa-responsive dystonia is due to mutations in the gene coding for the enzyme guanosine triphosphate (GTP) cyclohydrolase I (GTP-CH1) on chromosome 14q22.1 (*DYT 5*) (Nygaard, 1998). GTP-CH1 is the first and rate-limiting step in the synthesis of tetrahydrobiopterin from GTP. Lack of tetrahydrobiopterin BH4 in dopa-responsive dystonia leads to failure of synthesis of L-dopa in dopa-responsive dystonia from tyrosine and consequent failure of dopamine formation (Furukawa *et al.*, 1997). It seems clear that the nigrostriatal pathway is anatomically intact in dopa-responsive dystonia, as judged by pathological examination. The nigrostriatal terminal density also appears normal, as indicated by binding of GBR 12935 to the dopamine transporter in the caudate and putamen (Furukawa *et al.*, 1998), and by the binding of the dopamine uptake site ligand (β-CIT on single-photon emission computed tomography scanning in dopa-responsive dystonia patients *in vivo* (Jeon *et al.*, 1998). Treatment of patients with dopa-responsive dystonia with levodopa in small doses causes remarkable relief of symptoms with a stable long-term response.

Why dopamine deficiency causes dystonia along with elements of parkinsonism in dopa-responsive dystonia is a mystery. The role of striatal dopamine in dystonia is complex. In dopa-responsive dystonia severe striatal dopamine depletion, especially in the putamen, produces dystonia which is relieved by levodopa therapy. In Parkinson's disease, levodopa treatment causes dystonic dyskinesias, especially in 'beginning- and end-of-dose' diphasic dyskinesias, which disappear on reduction of the dose. But patients with fluctuating advanced Parkinson's disease also develop 'off-period' dystonia in the mornings or during the day when they become immobile; such 'off-period' dystonias may also disappear after prolonged withdrawal of levodopa. It seems that dystonia may occur in these different conditions with low, high or intermediate brain levels of dopamine, a complex and unexplained relationship.

Conclusions

A remarkable number of physiological changes have been described in patients with primary dystonia. These range from alterations in the excitability of spinal and brainstem reflex pathways to changes in cerebral cortical activity during movement. Despite their widespread nature, the majority of the results point to a common theme of reduced inhibition at many levels of the motor system, and this may account for the excessive muscle activity and overflow seen in dystonia.

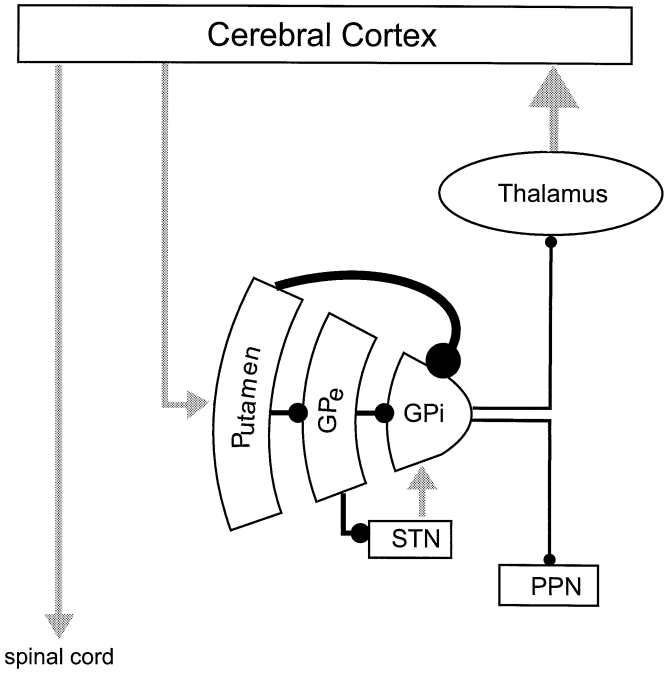

Fig. 9 Highly simplified schematic summary of the basal ganglia circuitry in dystonia. Note the overactivity of the direct putamenopallidal direct pathway leading to reduced output of the medial globus pallidus and increased thalamic input to the cortex. GPi = medial globus pallidus; GPe = lateral globus pallidus; STN = subthalamic nucleus; PPN = pedunculopontine nucleus.

As shown so clearly in many of the reflex studies, each single deficit may be insufficient on its own to lead to dystonia, but together all may contribute to the problem. Thus, increased gain and lack of inhibitory focusing in the motor cortex could lead to excessive activity in the target muscle and overflow to uninvolved muscles. This could be compounded by changes in the excitability of brainstem and spinal reflex pathways, leading to a failure of reciprocal inhibition and prolonged stretch reflexes. Sensory input may influence dystonic contractions by changing the level of excitability in all these pathways so as to alter the motor 'focus'.

One important feature is that patients with dystonia are bradykinetic. Some of this could be caused by co-contraction of antagonist muscles, but in other instances it is the result of inadequate activation of the agonist muscle. This is probably related to disorder of cortical activation, as seen in functional activation and neurophysiological studies.

How might all these changes in the inhibitory control of motor mechanisms arise in primary dystonia? All the evidence from analysis of symptomatic dystonia points to a disorder of the basal ganglia. In primary dystonia this must be a functional as against a structural abnormality. Functional imaging studies lend support to the concept of an abnormality of basal ganglia motor control in primary dystonia, as does the evidence provided by levodopa-induced dystonia in human and subhuman primates with parkinsonism (Fig. 9).

If primary dystonia is indeed a disease of the basal ganglia, then these abnormalities must give some insight into the normal function of those structures. Single-cell recordings from the basal ganglia have shown that neuronal firing usually lags behind the onset of movement, implying that it does not play a central role in initiating voluntary muscle contraction. The present data support this idea and suggest that the basal ganglia have an important role in setting the pattern of excitability in the motor system for both immediate and future movements.

A remaining problem is the task specificity of many types of adult-onset dystonia. In some patients why is it that only certain types of movement produce dystonia, whilst other movements (even if they employ the same muscles) are unaffected? Many of the studies cited above show that subclinical abnormalities can be detected before any overt dystonia is evident. It may be that, in mild cases, other systems can compensate for the deficits, and that dystonia becomes apparent only under conditions where these systems fail. Alternatively it may be that the basal ganglia have a particular role to play in the execution of skilled learned movements. Some indication that this may be the case comes from the work of Brotchie *et al.* (1991), who showed that as a monkey became more familiar with a simple arm movement task, the greater the change in discharge rate of pallidal neurons. If the basal ganglia do have an important role in such tasks, then skilled movements would obviously be the most likely type to be affected. Should this specific role in skilled tasks be to enhance one motor action and inhibit others, then it is clear how a diminution of inhibitory function could lead to overflow of movement and involuntary spasms.

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