Clinical neurophysiology of dystonia

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Abstract

It took decades to accept that dystonia, a bizarre condition which often produces abnormal movements exclusively during specific activities like writing, was due to brain disease. Clinical neurophysiology certainly added to this evolution of thinking. Recent neurophysiological observations demonstrate that dystonia is not only due to an isolated brain motor dysfunction, but also to sensory and sensorimotor integration disturbances.

We hope that new treatment strategies will arise thanks to our better understanding of dystonia pathophysiology.

Key words : Pathophysiology ; dystonia ; magnetic stimulation.

Introduction

Dystonia is a syndrome characterized by involuntary movements due to sustained involuntary muscle contractions and co-contractions leading to abnormal postures or movements, generally occurring during a motor task (Hughes and McLellan, 1985, Cohen and Hallett, 1988). In patients with focal dystonia the dystonic features tend to be present only with specific activities and disappear most often at rest. Idiopathic focal dystonia is probably the consequence of abnormal regulation of cortical and subcortical circuits involved in preparing and executing motor tasks (Alexander and Crutcher, 1990, Chevalier and Deniau, 1990, Ryan and Sanders, 1994). Patients with secondary dystonia frequently show lesions in the putamen (Burton *et al.*, 1984, Marsden *et al.,* 1985, Pettigrew and Jankovic, 1985). The basal ganglia provide a strong input to motor areas of the cortex and it is thought that abnormal function in focal dystonia occurs mainly at the level of the striatum (Marsden *et al.,* 1985, Pettigrew and Jankovic, 1985, DeLong, 1990).

The electrophysiological studies, which will be described below, suggest the existence in dystonic patients of a generalized disorder characterized by lack of inhibition or hyperactivity of brain structures concerned with motor activity. Only studies performed in humans will be discussed in this article.

Neurophysiological studies

Spinal cord and brainstem reflexes

The co-contraction phenomenon observed in dystonic patients rapidly leaded clinical neurophysiologists to focus their attention on reciprocal inhibition (Cohen and Hallett, 1988, Nakashima *et al.*, 1989, Panizza *et al.*, 1990 Deuschl *et al.*, 1992, Chen *et al.*, 1995). In the spinal cord reciprocal innervation of agonist – antagonist muscles around a joint produces inhibition of antagonist motoneurons through spinal inhibitory interneurons activation mediated by Ia afferents of the agonist muscle. Patients with generalized dystonia, spasmodic torticollis, blepharospasm or writer's cramp exhibit reduction of reciprocal inhibition even in asymptomatic arms (Nakashima *et al.*, 1989 , Panizza *et al.*, 1990). A decrease of presynaptic (10 msec interstimulus intervals) and disynaptic inhibition is demonstrated. These abnormalities probably reflect a change in the descending control of spinal interneurons at rest or during movement (Nakashima *et al.*, 1989).

The use of paired pulse stimulations allows the study of spinal H reflex recovery curves over flexor carpi radialis muscle in the forearm or soleus muscle in the leg (Panizza *et al.*, 1990, Koelman *et al.*, 1995). At interstimulus intervals of 200 msec the relative potentiation of H reflex response which is thought to be mediated by cutaneous afferents is more pronounced in dystonic patients when compared to normal.

The brainstem blink reflex is also disturbed in dystonia. The study of recovery curves through paired pulse stimuli allows the demonstration of a defect of inhibition of the bilateral R2 component of the blink reflex (Berardelli *et al.*, 1985, Cohen *et al.*, 1989, Nakashima *et al.*, 1990, Pauletti *et al.*, 1993). The abnormality is obvious in patients with blepharospasm with or without torticollis but

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absent in patient with arm dystonia (Nakashima *et al.*, 1990).

Exteroceptive reflexes are elicited through electric stimulation of supraorbital or infraorbital nerve when subjects try to maintain a sustained contraction of masseter or sternocleidomastoid muscles respectively. A period of inhibition can be elicited in normal subjects. The degree of inhibition is reduced in patients with cranial dystonia (Pauletti *et al.*, 1993).

These electrophysiological observations suggest a lack of inhibition or hyperexcitability of brainstem and spinal cord structures in dystonic patients. It is agreed that disturbed supraspinal and brainstem influences are probably responsible for these abnormalities. Lesions of cerebral structures like the basal ganglia, which are frequently involved in symptomatic dystonia, probably lead to altered basal ganglia output and consequently to disturbed control of brainstem and spinal cord structures (Berardelli, 1998).

CORTICAL FUNCTION

Recently the introduction of transcranial magnetic stimulation allowed the non invasive study of the excitability of motor pathways (Barker *et al.*, 1985, 1986). The injection of a current varying in time in a coil produces a magnetic field varying in time which in turn will produce a current in conductive tissues. Motor evoked responses (MEPs) can be measured with the target muscle at rest or when the subject performs a contraction. With facilitation the amplitude of MEPs increases and the onset latency shortens (Day *et al.*, 1989, Mills *et al.*, 1987, Rothwell *et al.*, 1987, Thompson *et al.*, 1991). A silence of the background electromyographic signal follows the MEPs recorded with facilitation when the subject tries to maintain a steady tonic contraction after stimulus delivery (Inghilleri *et al.*, 1993 , Wilson *et al.*, 1993). This inhibitory motor response is called the silent period. The duration of the silent period increases with the increase of stimulus intensity (Inghilleri *et al.*, 1993). It can be concluded from these observations that magnetic stimulation allows the study of excitatory and inhibitory motor pathways (Cracco *et al.*, 1990, Triggs *et al.*, 1992, Berardelli, 1999).

Our group applied this technique to study patients with focal hand dystonia (Mavroudakis *et al.*, 1995). We postulated that magnetic stimulation would help us to understand to what extent dystonia results from disturbed excitatory or inhibitory motor mechanisms.

We demonstrated an abnormal relationship between the amplitude of MEPs evoked at rest and MEPs obtained with facilitation during tonic contraction. In patients with dystonia the amplitude of MEPs obtained tended to be lower at rest but tended to be increased with facilitation. This abnormal behavior can be expressed through calculation of the ratio between amplitudes of MEPs obtained with facilitation and at rest. The median of the calculated ratio is significantly higher in the dystonic group (15.1) when compared to controls (5.4) (p < 0.04). Expressed in a simple way, the amplitude increase observed with facilitation is higher in dystonic patients. This result was observed with low magnetic stimulus intensity. We confirmed these findings for higher magnetic stimulus intensities in a more extensive study of 21 dystonic patients compared to 22 controls (personal data).

Most of these findings were rapidly confirmed by Ikoma *et al.* in 1996 in patients with hand dystonia and by Amadio *et al.* in 2000 in patients with torticollis. It is interesting to note that in Parkinson's disease (PD) MEPs behave in the opposite way : amplitude of MEPs obtained at rest is higher and lower with facilitation when compared to normal (Valls-Sole *et al.*, 1994).

For inhibitory motor responses we showed that the duration of the silent period tends to be shorter (Mavroudakis *et al.*, 1995). In addition the recruitment of the silent period with increasing stimulus intensities is disturbed in dystonia : patients with dystonia reach the maximal duration of the silent period more rapidly when compared to normal. Many studies published since 1995 confirmed that silent period duration is or tends to be shorter in patients with dystonia (Ikoma *et al.*, 1996, Chen *et al.*, 1997, Filipovic *et al.*, 1997, Curra *et al.*, 2000). The shortening of silent period observed in facial muscles of patients with oromandibular dystonia or blepharospasm suggests that this phenomenon is not due to spinal abnormalities but indeed to disturbed cortical inhibitory mechanisms (Curra *et al.*, 2000). The disturbance of cortical inhibitory mechanisms is convincingly demonstrated with the use of a more complex experimental paradigm developed by Kujirai *et al.* in 1993. Paired magnetic shocks are delivered through a magnetic coil. The first conditioning shock is delivered with a stimulus intensity lower than facilitation motor threshold. The experiment consists to analyze the effect of the conditioning shock on the amplitude of a supra threshold test stimulus shock given at short interstimuli intervals ranging from 2 to 15 msec. With short intervals (< 7 msec) an inhibition of the test shock is observed in normal subjects. The inhibition observed in this type of paradigm must be strictly produced by cortical mechanisms as the conditioning shock does not produce any descending volley to the spinal cord. Patients with hand dystonia present a decrease in the amount of inhibition evoked with interstimulus intervals ranging from 2 to 6 msec suggesting decreased excitability of cortical inhibitory structures (Ridding *et al.*, 1995).

Trains of repetitive 1 Hz transcranial magnetic stimulation applied to patients with writer's cramp

produce an increase of corticomotor output of the affected hand instead of the decrease of corticomotor output observed in normal subjects (Siebner *et al.*, 1999).

Magnetic stimulation over multiple sites of the scalp allows the determination of motor maps representation of various hand muscles (Wilson *et al.*, 1993). In patients with writer's cramp Byrnes *et al.* in 1998 demonstrate distortion of the motor maps with loss of symmetry of the centers of the maps across the midline. Treatment with botulinum toxin allows a transient reversal of the distortion. The motor map distortion is greater in patients with long standing hand dystonia.

Bara Jimenez *et al.* in 1998 demonstrated a distortion of the primary somatosensory representation of first (D1) and fifth (D5) digits over the scalp. In normal subjects finger sensory cortical representation of D1 is located lateral and inferior to D5. The distance separating D1-D5 center fields representations in the coronal plane is 12.7 ± 5.7 mm. In writer's cramp there is a collapse of primary cortical somatosensory D1-D5 finger representations with a measured distance in the coronal plane of 6.5 ± 3 mm ($p = 0.016$). The degree of distortion correlates with the severity of dystonia.

Before the onset of a self paced movement it is possible to record a slow rising negative electroencephalographic wave called "bereitschaft potential" (Deuschl *et al.*, 1995, Van der Kamp *et al.*, 1995). The first negative component of this slope called NS1 begins approximately 1500 msec before movement onset and is bilaterally distributed over motor primary motor cortex and supplementary motor area (SMA). The second part of the slope called NS2 begins approximately 650 msec before movement onset and rises steeper. NS2 wave is lateralized contralaterally to the hand used to perform the task. Decreased amplitude of NS1 and / or NS2 has been described in patients with primary or secondary dystonia (Deuschl *et al.*, 1995, Van der Kamp *et al.*, 1995). A recent study analyses preparatory movement cortical potentials generated with motor tasks producing a flexion of the wrist either by activation of the wrist flexor or relaxation of wrist extensor muscles (Yazawa *et al.*, 1999). With relaxation of extensor muscles a "bereitschaft potential" is generated during movement preparation with maximal amplitude over the contralateral central area. In dystonic patients the preparatory premovement potential is abnormally distributed demonstrating disturbed processing of voluntary muscle relaxation.

With somatosensory evoked potentials a negative frontal waveform can be recorded approximately 30 msec after electric stimulation of the median nerve at the wrist (Hallett, 2000, Murase *et al.*, 2000). The N30 potential reflects probably early cortical sensory processing (Hallett, 2000). Movement or thinking of movement before stimulus delivery produces a decrease in amplitude of the N30 frontal potential in normal subjects, the so called gating phenomenon. Abnormal premovement gating of somatosensory input is clearly demonstrated in patients with writer's cramp (Murase *et al.*, 2000).

Cortical magnetic stimulation study of patients with writer's cramp after a conditioning shock of the median nerve given 200 msec before motor cortex activation demonstrates different motor responses in normal controls and patients with cervical dystonia. In patients with hand dystonia facilitation of the test MEP size is observed in contrast to the amplitude reduction observed in both controls and patients with torticollis (Murase *et al.*, 2000).

These observations demonstrate the abnormal central processing of sensory input in patients with hand dystonia.

NEURONAL ACTIVITY RECORDED DURING SURGERY

Basal ganglia-thalamocortical motor circuitry in primates can be summarized as follows : the inputs to the basal ganglia are essentially focused on the putamen (Alexander and Crutcher, 1990, Wichmann and Delong, 1998). Inputs originate from primary motor and somatosensory cortex, from premotor areas including SMA. The putamen modulates the activity of globus pallidus interna (GPi)/Substantia Nigra pars reticulata (SNr) through the activity of 2 separate pathways. The direct pathway projects directly to GPi/SNr. The indirect pathway projects to globus pallidus externa (GPe), from GPe to the Subthalamic Nucleus (STN) and from STN to GPi/SNr. The 2 pathways produce opposite effects upon GPI/SNr : direct pathway inputs are GABA-ergic, indirect pathway inputs are glutamatergic. The GPi/SNr GABA-ergic efferents, the main basal ganglia output pathway for the motor circuit, project mainly to the ventrolateral thalamus pars oralis (VLo) and the centromedian (CM) nuclei. Glutamatergic efferents from VLo and CM nuclei project essentially to the SMA, premotor areas and motor cortex.

Recently the development of deep brain stimulation techniques for the treatment of Parkinson's disease and severe dystonia gave the opportunity to record basal ganglia neuronal activity in anesthetized or awakened subjects (Sanghera *et al.*, 2003). These techniques allow to challenge the theories derived from the Alexander and Crutcher model to clinical observations. Sanghera found that the discharge rate of putamen neurons is low in dystonia and PD. The discharge rates of GPe neurons is lower than in the GPi in PD but similar in dystonia. The discharge rate of GPe and GPi neurons is lower in dystonia when compared to PD. A low discharge rate in the putamen will produce in the indirect pathway an increase in GPe discharges

which will in turn produce a decrease in the activity of GPi neurons (Wichmann and Delong, 1998). Consequently increased thalamocortical activity will occur as expected in dystonia. It must be noted that not all the observations fit adequately with the theoretical responses derived from the currently admitted models.

Discussion

Dystonia is an example of a hyperkinetic movement disorder characterized by twisting movements, abnormally prolonged muscle contractions during the execution of tasks like writing (Hallett, 1993, Cohen and Hallett, 1988). Patients with secondary dystonia frequently show lesions in the putamen (Marsden et al., 1985, Pettigrew and Jankovic, 1985). One of the basic roles of basal ganglia is to modify cortical excitability so that movement is executed efficiently (Hallett, 1993, Cohen and Hallett, 1988, Perlmutter et al., 1997).

Idiopathic dystonia shares some abnormal pathophysiologic features with PD, a well known model of striatal dysfunction. Movement-related cortical potentials (Dick et al., 1989, Botzel et al., 1995, Deuschl et al., 1995, Van der kamp et al., 1995) and the contingent negative variation potentials (Oishi et al., 1995, Kaji et al., 1995) are abnormal in both disorders. This is in agreement with the view that both PD and idiopathic dystonia are related to dysfunction of basal ganglia.

Positron emission tomography (PET) studies added further evidence that both disorders are due to dysfunction at the levels of the striatum and striato-cortical projections to premotor cortices (Eidelberg et al., 1994, 1995, Jahanshahi et al., 1995, Ceballos-Baumann et al., 1995). Interestingly, the metabolic abnormalities of premotor areas appear to be opposite in these disorders. In PD, at rest, a decreased metabolic activity in the lateral premotor cortex and the SMA is demonstrated (Eidelberg et al., 1994). The same areas show a relative increase in resting metabolism in patients with focal dystonia (Eidelberg et al., 1995). Similarly, PET studies with motor activation show decreased blood flow in the premotor cortex and SMA in PD (Jahanshahi et al., 1995) in contrast to increased blood flow in these areas in patients with idiopathic dystonia (Ceballos-Baumann et al., 1995). Thus, opposite metabolic changes occur at premotor cortices, presumably related to abnormal excitability of motor circuits.

Abnormally low metabolic reactivity of primary sensorimotor cortex and SMA to external stimuli like hand vibration is shown in idiopathic dystonia by Tempel and Perlmutter in 1990. This lower response is attributed to decreased activity in neurons that project to sensory motor cortex or decreased activity of local interneurons. Furthermore, decreased blood flow reactivity in the primary sensory

motor cortex and caudal SMA during voluntary joystick movements occurs in idiopathic dystonia (Ceballos-Baumann et al., 1995). Karbe et al. in 1992 demonstrated decreased frontal cortex metabolism in areas known to receive major input from mediodorsal thalamic nucleus. Obviously the main problem with interpretation of glucose metabolism investigations by PET is related to the uncertain significance of hypometabolism reported in sensorimotor cortex in dystonia : can we relate reduction in synaptic activity to changes in excitatory or inhibitory pathways, or both ? The combination of PET and neurophysiological studies is crucial to solve some of these questions. In our study the lower amplitude of MEPs at rest may be the neurophysiological correlate of low sensorimotor cortex reactivity demonstrated by PET studies and indicate a lower excitability of neuronal systems involved in motor control in patients with focal dystonia (Mavroudakis et al., 1995, Tempel and Perlmutter, 1990). With magnetic stimulation most studies demonstrate, often with high intensity stimulation, shortening of the silent period in dystonia and PD (Mavroudakis et al., 1995, Priori et al., 1994, Ridding et al., 1995, Ikoma et al., 1996, Filipovic et al., 1997). Hallett suggested that clinical and neurophysiological abnormalities shared by dystonia and PD may be related to overactivity of the indirect pathway (Hallett, 1993). The latter hypothesis may suggest that duration of the silent period which is decreased in the two disorders is modulated by the indirect pathway activity.

The clear disturbance of inhibitory processes in dystonia points to the importance of cortical inhibitory control of basal ganglia structures during preparation of movement (Mink, 1996). To produce an adequate movement not only excitation of the adequate motor structures directly involved with the selected movement is necessary but also inhibition of the activity of motor structures which may interfere with the realization of the desired movement (Perlmutter et al., 1997).

The corticospinal motor output measured as the ratio of the MEPs amplitude with facilitation and at rest is modulated in the opposite direction in patients with PD and patients with hand dystonia : the output is increased in dystonia and decreased in PD (Valls-Sole et al., 1994, Mavroudakis et al., 1995). These findings suggest that the amplitude increase of MEPs with facilitation depends on the activity of the direct pathway. The amplitude increase with facilitation is reduced in hypokinetic movement disorders like PD and increased in dystonia. These neurophysiologic abnormalities may be related to the opposite metabolic changes occurring in premotor cortices observed in Dystonia and PD (Eidelberg et al., 1994, 1995, Jahanshahi et al., 1995, Ceballos-Baumann et al., 1995).

The recent studies demonstrating the importance of sensory processing alterations in patients with

dystonia will certainly improve our clinical approach of the disease and the development of new treatment strategies (Hallett, 1995, Priori *et al.*, 2001, Zeuner *et al.*, 2002).

Conclusion

During the last decades clinical neurophysiologic studies of dystonic patients allowed the demonstration of abnormal activity of inhibitory circuitry in central nervous system, excessive gain in motor outflow, abnormal movement preparation, distortion of cortical somatosensory and motor maps and abnormal processing of sensory inputs. These observations improve our understanding of dystonia pathophysiology. Our views concerning abnormalities leading to dystonia evolved from a pure motor condition to a condition where abnormal inhibitory control and abnormal processing of sensory inputs play certainly a key role.

These observations lead to the development of original treatment strategies like limb immobilization or learning to read braille in order to decrease disability in patients with focal hand dystonia (Priori *et al.*, 2001, Zeuner *et al.*, 2002).

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