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Dystonia Pathophysiology: A Critical Review

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1. Introduction

During the past years, dramatic progress have been achieved in our knowledge of the pathophysiology of dystonia on the basis of imaging and electrophysiological data collected in human patients. Converging arguments now support the role of combined corticostriatal and cerebellar dysfunctions in the genesis of this movement disorder (1). Several excellent reviews have been recently proposed on this topic (2-8). Moreover, animals models of dystonia can help us to investigate the pathogenesis since they provide the opportunity to dissect more precisely the abnormal neuronal networks leading to primary dystonia and its genetic background (9-12).

However, many points remain to be clarified. Here, we discuss some of the findings previously reviewed but will detail more specifically less recognized aspects of the pathophysiology of dystonia, such as the link between phenomenology and physiology and the lessons that we can get from animal models.

2. Phenomenological considerations

Dystonia is defined as a syndrom of sustained muscular contractions leading to repetitive movements and abnormal postures. However, a rapid overview of the litterature reveals that this term is broadly used in very different contexts and can be associated with various pathological conditions. Thus, there is a need for clarification, not only for highlightening the concept of dystonia, but above all because of the pathophysiological and therapeutical consequences. In dystonia, abnormal posture is linked to repetitive muscular spasms triggered or worsened by voluntary movement (13). The overspreading of muscular activity to muscles usually not involved in the movement corresponds to a loss of inhibition during movement execution (3, 14). However, dystonia can be observed in different conditions such as spasticity, primary dystonia, secondary dystonia, levodopa-induced dystonia and off-dystonia in parkinsonian patients, among others.

Initially, several types of dystonia have been proposed depending on the age of onset, topography of clinical signs, and primary or secondary origin of dystonia (13). Focal dystonia is the most frequent form with a categorization depending on localization in the facial musculature (blepharospasm, oromandibular dystonia), cervical region (spasmodic

torticolis), limb (occupational dystonia e.g. writer'scramp or musician's cramp) or the larynx (laryngeal dystonia). Segmental dystonia involves two or more contiguous regions e.g. the cervical region and one limb, and corresponds to the diffusion of the dystonic process to close anatomic regions. This point suggests a spreading of abnormal motor command in a somatotopic manner. Although multifocal dystonia encompasses non-adjacent body part, it is less frequent in clinical practice. Hemidystonia is limited to one hemibody and frequently associated with lesions of the controlateral hemisphere. However, as for most of secondary dystonia, it is characterized by permanent tonic postures very different from the clinical pattern seen in primary dystonia. General dystonia have a broader distribution than focal dystonia but also frequently encompasses adjacent parts of the body e.g lower limb and trunks and/or upper limbs. Dystonia is primary when no lesions of the central nervous system or metabolic abnormalities are found (15) whereas it is associated with other neurological troubles in dystonia-plus syndroms (2). In secondary dystonia, lesions generally concern the basal ganglia and more particularly the putamen although lesions in other regions have been reported (16).

It is critical to be precise as to which type of dystonia we are dealing with. The fixed focal dystonia frequently observed in untreated Parkinson's disease (off-dystonia) or in various neurological disorders encompassing dystonia and parkinsonism is likely to correspond to a form of focal akineto-rigid syndrome There are clinical and experimental arguments supporting this view. For instance, off-dystonia in Parkinsonian patients is observed in a state of low dopaminergic plasma levels either before treatment (off-state) or as a end-of-dose effect. A fixed focal dystonia, generally in the lower limb, is frequently noticed in MPTP-treated monkey at the onset of intoxication and before the development of a full akinetic-rigid syndrome in a situation where dopaminergic neurons are only partially destroyed (17). In dopa-sensitive dystonia (DRD), tonic postures are frequently encountered, sometimes in association with a parkinsonian syndrome ; the use of dopaminergic treatment is effective because there is a decrease in the production and consequently the availability of dopamine at the nigro-striatal synapsis. In secondary dystonia where most of the lesions involve the putamen, a fixed dystonia with a somatotopic organisation is most frequently observed. In this case, lesions seriously disrupt the organisation of motor patterns at the striatal level, the support of procedural memory. This point explains the inability of patients to control accurately the spatio-temporal pattern of agonist and antagonist muscles necessary to achieve a smooth and goal-directed movement.

Primary dystonia is clearly an hyperkinetic movement provoked or accentuated by voluntary movement. Fixed posture at rest are observed only in the most evoluated forms of the disease such as long-lasting DYT1 dystonia or spasmodic torticollis. A critical feature of mobile dystonia is that each patient exhibits his own abnormal motor pattern, repetitive in time and space. For instance, a patient with cervical dystonia will have a specific pattern of neck posture, a patient with generalized dystonia the same kind of back-arching movements and lower limb movements. Similar remarks could be made for levodopa-induced dyskinesia (LID) and/or dystonia: each patient exhibits his own pattern of LID. In addition, we must point out the fact that by many aspects, LID are more dystonic in nature than choreic: they frequently associate repetitive myoclonic jerks and mobile abnormal postures but are rarely eratic as the choreic movements observed in Huntington's disease. One interpretation of the phenomenon could be that in primary dystonia the disorganization of networks controlling movement occurs in patch within the striatum (18, 19).

3. Lessons form primate models of dystonia: The physiological approach

Primate models of dystonia are informative, first because of the tight phylogenetic link between monkeys and humans, but also because they provide the possibility to obtain phenotypes of dystonia in the monkey using a more invasive physiological approach than in humans.

It was found initially that brain regions involved in the regulation of muscular tone, such as the red nucleus or dorsomedial mesencephalic tegmentum, provoked the appearance of a spasmodic torticollis (20). The head was turning to the side of the tegmental lesion. Moreover, electrical stimulations or pharmacological inactivation of the interstitial nucleus of Cajal (NIC) induced neck dystonia, a result which can be explained by the role of NIC in the control of head posture (21). The cervical dystonia observed in this condition is characterized by lateral flexion of the head to the shoulder opposite to the site of the lesion and intermittent co-contraction of neck muscles resulting in spasmodic head movements. Muscimol (22) or histamine (23) injections within the red nucleus also induced a cervical dystonia as well as pharmacological manipulations of vestibular nucleii (24).

In monkeys, as in humans, systematic treatments acting on the dopaminergic system induce dystonia. These models could provide some lights on two aspects of the pathophysiology of primary dystonia : 1) the putative role of dopaminergic receptors, 2) the implication of the direct and indirect striato-pallidal pathways. Acute dystonia was first reported in the primate after haloperidol injections (25) with a response to anti-cholinergic drugs (26, 27) and reserpine (28). On the other hand, clozapine (a second generation antipsychotic agent) compared to classical neuroleptics (first generation antipsychotic agents) did not provoke acute dystonia possibly due to its particular post-synaptic receptor affinity to D1 receptors (29). Conversely, injections of D1 agonists induced less frequently acute dystonia than D2 receptor antagonists (30, 31). Thus, it seems that acute dystonia, frequently hypertonic in its clinical expression, is mainly trigerred by the blockade of D2 receptors. Tardive dystonia can be induced by a chronic treatment with neuroleptics (32-35). As for acute dystonia, drugs that prevent dopamine storage (reserpine), synthesis (α-methyl-p-tyrosine) or block dopamine receptors decrease tardive dyskinesias (36). However, there is some pharmacologic evidences for a peculiar implication of D1 dopaminergic receptors in orofacial dystonia (37). The substitution of a D2 antagonist by a D1 antagonist decreases the clinical expression of dystonia (38). Thus, in tardive dystonia which is frequently mobile, the overactivity of the direct pathways could play a preponderant role.

When Bicuculline (Bic), a potent antagonist of $GABA_A$ receptors, is injected directly within the GPi or SNr, it induces at high volumes (10µl) a severe parkinsonian syndrome similar to that observed in MPTP-treated monkeys. However, when lower volumes (2µl) are used, abnormal focal postures in the lower limbs close to off-dystonia are observed (39). Severe hypertonic postures in controlateral limbs are noticed after GPi injections whereas SNr injections generally induce more axial symptoms, particularly in the neck. Thus, this type of dystonia characterized by hypertonia and bradykinesia corresponds to a form of focal akinetic-rigid syndrome, the somatotopy of which depending on the targeted basal ganglia. In MPTP monkeys, chronic treatment with levodopa or apomorphine induces dyskinesia (40-42). Metabolic studies relying on 2-Desoxyglucose (2-DG) show an increase of GABAergic inhibition of the subthalamic nucleus, suggesting a diminished subthalamo-

pallidal activity (40-42). This data would suggest an increased activity within the thalamo-cortical network although thalamotomy did not improve dystonia in MPTP-treated monkeys (43, 44). During peak-dose dystonia, an increase in the expression of D1 dopaminergic receptors was observed and interpreted as an overactivity of the direct striato-pallidal pathway. On the other hand, D1 agonists induce less dyskinesias than D2 agonists (45, 46).

Bic injection into the STN blocks GABAergic inputs, increases activity and leads to a tonic dystonia (42). Conversely, the injection of muscimol, a GABAergic agonist, within the basal ganglia output structures, namely the internal pallidum (GPi), and pars reticulata of the substantia nigra (SNr) induces a mobile dyskinesias encompassing mixed choreic and dystonic features mimicking the hyperkinetic movements observed in idiopathic dystonias (39). The mechanism could be related to an inhibition of neuronal activity in these regions (47).

A line of evidence also suggest that manipulations of the striatum might induce dystonia. Bicuculline injections within the putamen in the cat provoked neck dystonic movements directed towards the controlateral side, associated with an increased activity within the striatum and concomitent inhibition in the substantia nigra pars reticulata (SNr) (48). Injection of the same drug within the putamen also induced contralateral dyskinesia in the monkey (49). The blockade of striatal $GABA_A$-receptors in the striatum increases GPI neuronal activity and induces EEG spikes in the primary motor cortex (50). Direct electric stimulation of the putamen in the monkey using various duration of stimulation trains induces movement disorders the nature of which depending on the duration of the stimulation train (51). With short duration (100ms), myoclonic jerks of the contralateral hemibody are observed whereas dystonic and stereotyped movements are noticed with longer duration trains (>500ms). These data suggest that the difference between myoclonus and dystonia relies on the duration of the abnormal neuronal activity generated within the putamen.

An increased activity in the direct striato-pallidal pathway is likely to induce changes in the motor thalamus. Lesion studies in humans indicate that dystonia is mainly observed after lesions of the caudal motor thalamus (Vc, VIM) but not of the rostral pallidal segment (Vop) (52, 53). In monkey, the motor thalamus is a complex structure encompassing several regions (54). Its rostral part, corresponding to the ventrolateral pars oralis (VLo) and ventral anterior (VA) nucleii, receives inputs from basal ganglia output structures and send projections to the supplementary motor area (55). The caudal part corresponding to the ventroposterolateral, pars oralis (VPLo) and ventrolateral, pars caudalis (VLc) nucleii mainly receive cerebellar inputs. The projections are directed to the primary motor cortex (54). Several lines of evidence suggest that the thalamus plays a role in the synchronization of cortical activity in time and space (56). Thus, its dysfunction could potentially inducea loss of selectivity in the implementation of cortical modules during motor planning. Injection of bicuculline within the rostral part (VLo and VA) provoked a mobile contralateral dystonia whereas a myoclonic dystonia was observed after injections into the caudal region (VPLo, VLc) (57, 58). These bicuculline injections increased the discharge frequency of thalamic neurons and decreased the threshold of current necessary to evoke motor responses after intrathalamic microstimulation (58). Moreover, a bursty pattern correlating with myoclonic jerks was observed for most neurons in the caudal region. These results suggest that the tonic and myoclonic components frequently associated in dystonic patients could be the result of a dysfunction in both the rostral (pallidal) and caudal

(cerebellar) parts of the motor thalamus. These notions are also in congruity with the view that an hyperexcitability of thalamo-cortical pathway induces dystonia as proposed by Berardelli et al. (59). Interestingly, a greater number of thalamic neurons responded to passive joint manipulations after bicuculline injection (58). The data obtained in an acute experimental situation reveal the drastic and immediate modifications of somesthesic receptive fields that thalamic neurons may exhibit, highlighting the role of the motor thalamus in sensori-motor processing.

Taken as a whole, the results of pharmacological studies in monkeys suggest that in primary dystonia there would be an overactivity in the direct striato-palidal pathway, potentially associated with a decreased activity in the indirect striato-palidal pathway leading to a disrupted activation of the thalamo-cortical projections.

So far, the only phenotypic model of primary dystonia in the primate was that obtained in monkeys trained to perform repetitive movements (60-62). The animals performed the same movement of grasping 2 hours a day 5 days a week for 12 to 25 weeks and experienced difficulties removing their hands from the handpiece after 5-8 weeks of training, associated with a reduction in the number of trials correctly performed (60). The animals also exhibited difficulties in hand motor control during feeding, a loss of digital dexterity, evoking dystonia. In parallel, a disorganization of hand somatotopy was observed in area 3b of the primary somaesthetic cortex (S1). Receptive fields of recorded neurons became larger, encompassing more than one digit and segregation between glabrous and hairy skin was altered. Moreover, it was found that hand-face border in S1 normally sharp became patchy and spread over 1 mm of cortex (60). Thus focal dystonia induced by repetitive behaviors generates aberrant sensory representations which interfere with motor control (63). Abnormal motor control strengthens sensory abnormalities and the positive feed-back loop reinforces the dystonic condition.

4. Lessons from rodent models of dystonia: The genetic approach

Models of dystonia in the rodent provide valuable tools for exploring the contribution of genetic factors in the pathophysiology of dystonia. They can be divided into those that mimic the dystonic phenotype and those that duplicate the genetic abnormalities (2). In genotypic models, the mutations that produce dystonia in humans have been introduced into mice. Several models have been developed (11). Mouse models of DYT1 include both transgenic mice expressing human mutant torsin A (hMT) (64, 65), and heterozygous knock-in mice in which the GAG mutation has been introduced in the mouse torsin A gene (Dyt1) (66, 67). These mice do not have obvious dystonic features (65, 66) but exhibit some learning motor deficit (64). In striatal explant slices from transgenic hMT mice, cholinergic interneurons manifest an abnormal physiology: they respond to dopamine receptor (D2) activation with an increase in spiking, rather than an inhibition as observed in normal mice (68). Genotypic mouse models have also been generated for DYT5, DYT11 and DYT12 (2).

The role of dopaminergic dysfunction in dystonia is supported by several studies in the rodent (1). In a transgenic model of dopa-responsive dystonia, a depletion of tyrosine hydroxylase was found in the striatum (69). There was a marked posterior to anterior gradient with a predominant loss of striosome tyrosine hydroxylase expression in the remaining tyrosine hydroxylase staining areas at an early stage of the postnatal

development. A DYT1 mouse model had a decreased amphetamine-induced dopamine release and evidence for an increased dopamine turnover was found (70).

In phenotypic models, mutations that produce dystonic movements occur naturally (12). The dt/dt rat has an autosomal, recessive condition with dystonic posturing appearing 10 days after birth encompassing twisting movements of the neck, padding motions of the limbs and postural instability of increasing severity (71). Purkinje cell soma are smaller (10) and the defective protein, caytaxin, is a lipophilic binding protein that is expressed at high levels in cerebellar neurons during development (11, 72). This protein might be involved in signalling pathways that use calcium and phosphatidyl-inositol, and in regulating the synthesis of glutamate. Cerebellectomy eliminates the motor syndrome and rescues animals from juvenile lethality. In the df/dt mouse model, neuronal degeneration results from loss of a cytolinker protein (dystonin), which is expressed in the central and peripheral nervous systems and resembles the proposed function of torsinA (73). The tottering mice carry a homozygous mutation in a P/Q-type calcium channel expressed abundantly within Purkinje cells (10). The animals exhibit episodic dyskinetic attacks reminiscent of the attacks experienced by patients with paroxysmal non-kinesigenic dyskinesia (2). At the most advanced stages of attacks, tottering mice assume prolonged twisting postures involving the whole body and a mild ataxia. Lethargic mice also exhibit paroxysmal dyskinesia triggered by procedures that promote motor activity (12). In these animals, cytochrome oxydase histochemistry revealed increased activity in the red nucleus. Surgical removal of the cerebellum worsens ataxia but improved dyskinesias.

Thus, lesions of the cerebellum in rodents models of dystonia abolish the motor disorder suggesting that the cerebellum is necessary for the expression of dystonia (12). Morevover, it was shown in the dt rat that abnormal signaling in cerebellar cortex can lead to abnormal cerebellar output (11, 74). Moreover, microinjections of low doses of kainic acid into the cerebellar vermis of the mice elicited reliable and reproductible dystonic postures of the trunk and limbs (75). Peripheral administration of 3-nitropropionic acid to rodents, as in the primate, induced a dystonic phenotype associated to striatal lesions (76). In comparison with controls, hMT1 mice show increased glucose utilization (GU) in the inferior olive (IO) medial nucleus (IOM), IO dorsal accessory nucleus and substantia nigra compacta, and decreased GU in the medial globus pallidus (MGP) and lateral globus pallidus (77). They also showed increased CO activity in the IOM and Purkinje cell layer of cerebellar cortex, and decreased CO activity in the caudal caudate-putamen, substantia nigra reticulata and MGP. These findings suggest that the DYT1 carrier state increases energy demand in the olivocerebellar network and the IO may be a pivotal node for abnormal basal ganglia-cerebellar interactions in dystonia (77).

The dtSZ/dtSZ hamster, which manifests as an autosomal recessive condition with episodes of generalized dystonia induced by stress is a robust model of paroxysmal non-kinesigenic dyskinesias (78, 79). Attacks can last for hours and appear to be age-dependent (10). A line of evidence suggests a GABA-mediated neurotransmission defect and drugs that target these molecules are able to relieve the dystonic symptoms (80). The dtSZ hamster also exhibit highly irregular pattern of electrical activity within the striatum and globus pallidus (81).

The interaction between the basal ganglia and cerebellum in the expression of dystonic movement has been studies in two rodent models of dystonia (82). One of the model

involved tottering mice, the other one was obtained by local application of kainic acid into the cerebellar cortex. Subthreshold lesions of the striatum exaggerated dystonic attacks in both models. In tottering mice, microdyalisis of the striatum revealed that dystonic attacks were associated with a significant reduction in extracellular dopamine. This interesting result demonstrates the functional interactions between cerebellar and basal ganglia circuits in dystonia.

However, some forms of focal dystonia could be related to different mechanisms. Blepharospasm corresponds to involuntary spasms of bilateral eyelid closure. The increased spontaneous blink rate may result from the increased excitability of the trigeminal system which is dependent on the basal ganglia (83, 84). It seems that reduction in dopamine induces a reduction in nucleus raphe magnus activity via the subtantia nigra pars reticulata and superior colliculus (85, 86). Schicatano and collegues created a two component model of benign blepharospasm based on the combination of a permissive condition (dopamine depletion) and a precipitating event (corneal irritation and dry eye caused by partial lesion of the zygomatic branch of the facial nerve). They considered that spasms of eye lid closure was an exaggeration of the normally compensatory process evoked by eye irritation (87). In this situation, there was a dysfunctional sensorimotor integration in which the central nervous system either misinterpret sensory signals or misrepresents the desired movement.

Taken as a whole most of these rodent models reveal that dysfunctional cerebellar output is sufficient for the expression of generalized dystonia. However, it is important to be aware that the organization and physiology of the central nervous system is quite different between rodents and primates. For instance, the main basal ganglia output structure is represented by the subtantia nigra pars reticulata (SNr) in the rodent, a region involved in the control of the axial musculature, whereas it is the internal pallidum (GPi) in the primate, a region associated with the development of sophisticated hand dexterity. It is likely that the respective roles of the basal ganglia and cerebellum in motor control are different between rodents and primates.

5. Loss of inhibitory control

Electrophysiological studies are easier to perform in humans than in animals but must be based on non invasive techniques that limits exploration to a specific brain region. Two main techniques have been used : 1) Transcranial magnetic stimulation (TMS) of the cerebral cortex, 2) neuronal recordings in the basal ganglia during surgery.

Concerning the TMS, an excellent review has been recently proposed (Hallett, 2011) and here we we will only focus on specific segments. A line of evidence suggests that inhibition processes are defective during movement execution in dystonia. The loss of selectivity and overflow of muscular activity to muscles not usually involved in the on-going movement is clearly increased by voluntary action (3, 14, 88, 89). TMS allowed to show a decrease in both intra-cortical inhibition and silent period (3, 4). The coupling of a peripheral stimulation delivered prior to TMS shocks (PAS) at different intervals between the two stimuli also revealed an abnormal inhibition in dystonia (3, 8, 90, 91). As mentionned by Hallett (3), the results obtained with TMS are valuable, but they remain at a phenomenological level and focused the primary cortex whereas there have been only few data reporting stimulation of the premotor cortex (92) or cerebellum (93).

While dystonia is mainly a motor problem, mild sensory abnormalities have been reported in patients with hand dystonia both in the spatial (94-97) and temporal (98-100) domains. Kinesthesia is also impaired (101-103) and abnormal somatotopy was demonstrated by somatosensory evoked potential mapping based on EEG (94), MEG (94, 104, 105) and fMRI (106-108). As for motor control, a loss of lateral inhibition in sensory processing in space and time was reported (109-111). Moreover, the existence of bilateral abnormalities in the dystonic and non dystonic sides, suggests that this phenomenon is an endophenotypic trait (104) leading to changes in sensorimotor integration (3, 105).

Single unit recording of pallidal or thalamic nucleii have been performed in dystonic patients candidate to deep brain stimulation (DBS). They revealed interesting but contradictory data. A trend for low firing rate with a bursty pattern and oscillations was reported in the internal pallidum (112-116) and subthalamic nucleus (117). However, the role of anaesthesia was debated because some authors found no difference between dystonic and PD patients (118, 119). The current pathophysiological model of dystonia was also questioned by data showing that pallidal DBS was able to inihibit a subpopulation of motor thalamic neurons (120) and the abscence of difference between GPe and GPi firing rate (119). However, clear correlation between abnormal neuronal activitiy and EMG activity was reported in the basal ganglia and thalamus of patients with dystonia (116, 121-123). Moreover, single unit recording performed in cerebellar relays of the thalamus revealed abnormal firing pattern and increased response to peripheral inputs in dystonic patients (123-125). The technique of local field potentials (LFPs) allows to study local populations of neurons within a given brain region. Low oscillatory activity was recorded in the GPi of dystonic patients (126). This activity was found to be correlated with dystonic EMG (112, 114, 127) and single unit neuronal activity (112, 128). The conclusion was that the frequency of synchronization in the basal ganglia is a critical problem in dystonia, as in other movement disorders (129).

Thus, electrophysiological data revealed an impaired surround inhibition in several régions including the cerebral cortex, thalamus and basal ganglia with a trend for low and bursty firing rate in the GPi in line with the current models of dystonia (18, 19, 59). It is noteworthy that an abnormal pattern in the thalamus was observed in relays receiving cerebellar inputs (124).

6. Neuronal networks (imaging data)

Most of structural MRIs studies failed to show robust evidence of neural degeneration in patients with primary dystonia (130) although subtle grey and white matter micro-structural alterations were reported (131). Contradictory results have been found with voxel-based morphometry. Some studies noticed increased volumes in the sensorimotor cortex (132), putamen (133), globus pallidus (134) and cerebellum (135), but other decreased volumes in the putamen (136) sensorimotor cortex (137), cerebellum and thalamus (136, 137). These results must be interpreted in a phenomenological perspective since dfferent types of dystonia may yield different results.

Diffusion-weighted imaging (DWI) is sensitive to the random motion of water molecules and provide an estimate of the micro-structural integrity of the brain parenchyma and the directionality of molecular diffusion. The last parameter, also called anisotropy, is measured

using indices such as fractional anisotropy (FA). Changes in FA are interpreted as "micro-structural" changes in axonal amounts, axonal integrity, myelination, and has also been used to trace specific fiber tracts and to quantify abnormalities along them (4). DTI tractography is interesting in primary dystonia because this neurodevelopment disorder might disrupt cortico-striatal and/or cerebello-thalamic pathways. Indeed, abnormalities have been reported in the cortex (138-140), basal ganglia (141, 142), internal capsule (143), or thalamocortical pathways (144).

Initial PET studies with $^{[O15]}H2O$ revealed an overactivity in the cerebral cortex (particularly the rostral supplementary motor area i.e. pre-SMA), basal ganglia, cerebellum, and thalamus. The role of the caudal supplementary motor area (SMAp) and primary sensory-motor cortex was debated. Metabolism was deceased during execution of a learned movement (145-147) but increased when primary dystonia occurs at rest or in secondary dystonia (148). These abnormalities were also found in non-symptomatic patients carrying the DYT1 gene (149). In line with electrophysiological studies, abnormal sensory processing was reported in focal hand dystonia (150), blepharospasm (151), and cervical dystonia (152). Similar results were also obtained in non-manifesting DYT1 carriers (153, 154). The loss of inhibition in motor control was supported by the finding that an impaired GABA was observed in the striatum of dystonic patients (155).

The involvement of the dopaminergic system in primary dystonia was also demontrated with imaging techniques. Indeed, reduced D2 receptor availability in the striatum was reported in DYT1 (156-160) as well as in DYT6 patients (158). This data is compatible with dysfunction or loss of D2-bearing neurons, increased synaptic dopamine levels, or both. These changes, which may be present to different degrees in the DYT1 and DYT6 genotypes, are likely to represent susceptibility factors for the development of clinical manifestations. Moreover, abnormalities in motor sequence learning associated with increased cerebellar activation during task performance was observed in non-manifesting carriers of the DYT1 and DYT6 mutation but did not correlate with striatal D2 receptor binding (161). In a recent study, sequence learning deficits and concomitant increases in cerebellar activation were found to be specific features of the DYT1 genotype versus DYT6 carriers (162).

Disruption in information processing within the cortico-striato-pallido-thalamo-cortical and cerebello-thalamo-cortical pathways at rest was analyzed using sophisticated statistical tools (5). FDG-PET studies revealed abnormal functional connectivity with a specific pattern characterized by relative increase of metabolic activity in the posterior putamen/globus pallidus, cerebellum and SMA in DYT1 patients. In DYT6 patients, slight different results were obtained since opposite patterns of tracer uptake in the putamen were observed (154, 163, 164). In blepharospasm, there was a predominent role of the thalamus and midbrain/brainstem rather than basal ganglia and cortex. Thus, it appears clearly that different types of dystonia may be associated with different metabolic patterns (5).

Among a larger number of fMRI studies, the most commonly affected regions included various portions of the cerebral cortex, basal ganglia, and cerebellum (4, 5). Most studies reported either normal or increased basal ganglia activation during motor or sensory tasks. In the cortex, activation level was variably altered, depending on the task, the type of dystonia, and whether patients expressed dystonia during task performance or not. The primary sensory cortex was activated frequently (165-167) but not always (107, 166, 168).

Dystonic movements were commonly associated with overactivation in the sensorimotor cortex (166, 167, 169, 170), whereas activation levels may be normal (171) or decreased (168) during non-dystonic movements. However, reduced sensorimotor activation also may occur during dystonic movements (165, 166). The abnormal fMRI signals for representation of digits in the primary sensory cortex (107, 108) or other body parts in the basal ganglia (171) have been interpreted as a loss of neuronal selectivity. It is noteworthy that although fMRI presumably monitors neuronal activation, results only partially correlate with PET studies of blood flow.

Thus, imaging studies point to the role of combined corticostriatal and cerebellar pathways in the pathophysiology of dystonia. Anatomical disruption of the cerebellar outflow was found in non manifesting carriers and manifesting mutation carriers, and a second downstream disruption in thalamo-cortical projections appeared clinically protective in non-manifestationg carriers (5).

7. Plasticity in dystonia: A central mechanism

Dystonia seems to be a motor circuit disorder rather than an abnormality of a specific brain region (7). There are lines of evidences showing that dytonia is associated with abnormal plasticity (6, 172-174). On a phenomenological point of view, primary dystonia, appears in the young age when procedural motor learning and plasticity are optimal (6, 172-174). Even in secondary dystonia, the delayed appearence of symptoms after brain lesion suggests some form of plasticity (175) as well as the delayed therapeutic effect of pallidal stimulation in primary dystonia (176, 177). Long term potentiation (LTP) and long term depression (LTD) are the most widely recognized physiological models of plasticity. In humans, the physiological basis of LTP and LTD is limited to TMS and transcranial direct current stimulation (TDCS) of the cerebral cortex (7). Two main techiques have been used to study plasticity at the cortical level: repetitive TMS (rTMS) with variable frequencies inducing either LTP or LTD (172, 178) and paired-associative stimulation (PAS) combining electrical stimulation of a peripheral nerve and cortical TMS (172, 179, 180). It was shown that the sensorimotor cortex (SM) exhibited an exaggerated responsiveness to rTMS responding protocols (90, 181-184). Associative plasticity (LTP, LTD, PAS) is enhanced with a loss of spatial specificity explained by a failure of surround inhibition (3, 7). Morever, somatosensory evoked response in SM was more enhanced by PAS in dystonic patients than in normal controls (182) revealing an increased susceptibility to peripheral events. Another way to test cortical plasiticity is to use theta burst stimulation (TBS) which relies on short trains of pulses (5Hz) with an high intra-burst frequency (50Hz). TBS after-effect was enhanced in dystonic patients but not in their symptomatic relatives (185). Moreover, in dystonic patients, cortical responses to 1Hz rTMS is unaffected by pre-conditionning with anodal TDCS contrarily to normal controls (179, 181). In dystonia, there would be an increased tendency to form associations between sensory inputs and motor inputs which may lead to de-differentiation of motor representations in accordance with the theory of synaptic homeostatis (7, 186, 187).

The question remains to whether the loss of surround inhibition and synaptic homeostasis is a trait of the whole sensorimotor system or the result of dysfuntionning of specific regions such as the striatum and the cerebellum. The processing of sensory inputs is for instance altered either in the basal ganglia (187), the thalamus (124) and cerebral cortex (3).

Moreover, pharmacological manipulations of the thalamus induce immediate changes in the receptive fields of thalamic neurons (58) probably mimicking the effect of plasticity occuring in dystonic patients. Thus, abnormal plasticity seems to be an endophenotypic trait of dystonia (6, 7, 179).

Several lines of evidence suggest that dystonic symptoms are generated by an abnormal functionning of the putamen, a basal ganglia region involved in motor control (188). The striatofugal medium spiny cells (MSC) receive strong cortical glutamatergic inputs and represent the main projection neurons of the striatum. They are modulated by a complex interneuronal network in which local cholinergic interneurons (Ach-I), GABAergic interneurons and mesencephalic dopaminergic inputs play critical roles. In the current accepted model of dystonia, there is an imbalance between the direct and indirect striato-pallidal output pathways (189). Use-dependent long lasting changes in synaptic efficacy at cortico-striatal synpases has been proposed as a model of motor learning and memory (7). As in humans, LTP and LTD can be obtained by high frequency stimulation of cortico-striatal afferents. Moreover, LTP can be reversed by low frequency afferent stimulation (synaptic depotentiation). These phenomena are modulated by striatal interneurons. A series of elegant experiments performed in a rodent genetic model of DYT1 dystonia recently revealed the close interaction between cholinergic and dopaminergic transmission (68, 190, 191). In trangenic mice expression of the mutant form of the torsinA, increased long-term potentiation (LTP) but decreased long-term depression (LTD) and depotentiation (SD). Hence, these phenomena were reversed by lowering endogenous Ach level or by antagonizing muscarinic M1 receptors (191). On the other hand, no difference was found in electrophysiological and morphological characteristics of MSC and Ach-I between mutant and non-mutant mice (190, 191). These results may provide an explanation for the efficacy of anticholinergic drugs in dystonia. Thus, long-term modifications of synaptic strength at the cortico-striatal synapse exhibit a highly dynamic organization ensuring the maintenance of a synaptic homeostasis within basal ganglia circuitry (7).

As we saw previously, strong evidences have recently emerged suggesting that the cerebellum also actively contributes to the pathophysiology of dystonia. Indeed, dystonia can be associated with cerebellar dysfunction in different forms of genetic ataxia and the neuronal network involved in primary dystonia consistently encompasses the cerebellum (4, 5). Conversely, the cerebellum has the ability to inhibit cortical activity, control sensori-motor integration and play a part in maladaptative neural plasticity (4). The fundamental mechanism may be the ability of the cerebellum to control cortico-striatal long-term depression, a mechanism thought to underlie neural plasticity. As previously noticed, the paradox is that most of genetic rodent model of dystonia associated with cerebellar dysfunctionning do not exhibit a clear phenotype of dystonia (2).

8. Conclusion and perspectives

Primary dystonia is a developement disorder with a strong genetic basis but the phenotype is likely to be triggered by risk factors such as environment insults, increased sensory inputs or physiological stress (2). Several lines of evidence suggest that dystonia corresponds to a disruption in the homeostatic regulation of neural plasticity within the sensorimotor circuitry (1, 3). However, the term dystonia encompasses a broad spectrum of disease and it is important to take up its pathophysiology on the basis of clear phenomenological

considerations. In addition, different pathophysiological mechanisms may underlie similar phenotypes whereas different genotypes (e.g. DT6 and DYT1) may share similar functional abnormalities (1).

Imaging data support the hypotheses of the respective roles of basal ganglia and cerebellum by showing that dystonia disrupts the whole motor circuits involved in motor learning (5). Disruption in surround inhibition and aberrant plasticity are critical features of dystonia but we do not know whether this phenomenon occurs in a critical region (striatum, cerebellum) or is a feature of the whole sensorimotor network. How and where cerebellar circuits interact with basal ganglia circuits still remains a partially unsolved question. The thalamus which receive inputs from both systems in anatomically close nucleii could potentially play a critical rôle in the intégration of pallidal and cerbellar inputs. Indeed, disruption in sensory information and increased activity were reported in this region either in dystonic patients and in a primate model of the disease.

We began to have an idea of the disrupted networks within the striatum based on experimental models of dystonia showing that plasticity is impaired by an abnormal functionning of acetylcholine interneurones and their paradoxical response to D2 dopaminergic stimulation (7). The net result is a disequilibrium between LTP and LTD, the bases of plasticity at the cortico-striatal synapsis. The impairment of surround inhibition could also be related to decreased GABA transmission within the striatum as suggested by data obtained in human patients (3, 155) but also by the loss of parvalbumin-reactive GABArgic interneurones in a hamster model of paroxysmal dystonia (192). The cellular mechanisms leading to a dysfunctionning of the cerebellum remains less clear but some observations in rodent models suggest a possible dysfunctionning of Purkinje cells potentially related to some forms of channelopathy (11). Thus, animal models are promising although none of them can perfectly mimic the complexity of the clinical features observed in humans (1, 12). A problem in the genotypic rodent models is that they do not induce a phenotypic of dystonia. As stated above, it is possible that this discrepancy is due to the different organization of the subcortico-cortical networks between rodents and primates. However, the rodent models may be particularly challenging to make the gap between genes and the functional brain abnormalitites associated with primary dystonia (2). They can also be useful to develop experimental therapeutics. In primates, most models have focused on basal ganglia dysfunction. However, the elegant model proposed by Mink several years ago on this basis (18, 189) still lacks a direct experimental demonstration in the monkey. It will be probably necessary in the near future to develop more sophisticated models of dystonia in the sub-human primate to test directly some pathophysiological hypotheses concerning the disruption of information processing within the striato-pallidal and/or cerebello-cortical pathways.

Finally, a great challenge will be to understand how the ubiquitous cellular mechanisms disrupted by genetic mutations might explain the focal phenotypic expression of dystonia. As recently pointed by Pisani and collegues, dystonia would represent a high priority for medical reseach in the field of movement disorders for several reasons (193). First, this pathological model is unique because it represents a window to study the role of plasticity in the development of the central nervous system. Second, it provides the opportunity to explore the subtle interactions between the basal ganglia and cerebellum networks in motor control. Third, there is a fascinating challenge to undestand how the genetic defects will be

translated into phenotypic effects. Finally, the development of new therapeutics may necessitate novel strategies based on original technologies. There is no doubt that a large collaboration of scientists with different expertises will be necessary to achieve this goal.

9. References

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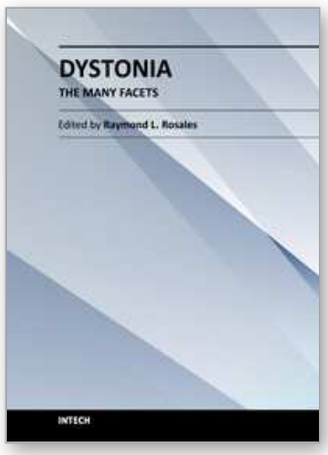

Dystonia - The Many Facets

Edited by Prof. Raymond Rosales

ISBN 978-953-51-0329-5
Hard cover, 220 pages
Publisher InTech
Published online 14, March, 2012
Published in print edition March, 2012

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Pierre Burbaud (2012). Dystonia Pathophysiology: A Critical Review, Dystonia - The Many Facets, Prof. Raymond Rosales (Ed.), ISBN: 978-953-51-0329-5, InTech, Available from: http://www.intechopen.com/books/dystonia-the-many-facets/dystonia-pathophysiology-a-critical-review

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