



# Update on dystonia

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## Purpose of review

This review considers the recent literature pertaining to the clinical features, genetics, neuropathology and treatment of dystonia syndromes.

## Recent findings

The term dystonia indicates at the same time a clinical phenotype and a collection of neurological syndromes mainly of genetic origin. The physical signs contributing to the phenomenology of dystonia have been recently assembled into a coherent set. The molecular genetics of primary dystonia syndromes (DYT1 and DYT6) have been the object of extensive analysis, providing converging views on their causative mechanisms. The relationship between genotype, phenotype, and endophenotypes has been explored for hereditary and sporadic dystonia syndromes. Neurophysiological studies on DYT1 and DYT6 patients, as well as on nonmanifesting carriers, have demonstrated the presence of altered synaptic plasticity. Several recent data indicate a role of dopamine and acetylcholine (ACh) transmission in the pathophysiology of primary dystonia.

## Summary

Recent findings have led to novel, testable hypotheses on cellular mechanisms and physiopathological abnormalities underlying dystonia. Neurophysiological studies, imaging data and animal models support the view that corticostriatal, cerebellar, and dopaminergic dysfunctions converge to produce the pathophysiological abnormalities of dystonia.

## Keywords

deep brain stimulation, dystonia, genetics, imaging, pathophysiology

## INTRODUCTION

Important advancements have occurred during the last few years on the clinical and preclinical features of dystonia syndromes. The diagnosis of dystonia still remains based on clinical phenomenology, as there is no specific diagnostic test. Recent criteria for recognizing the features of dystonia have been proposed [1]. These entail identification of five physical signs that characterize the phenomenology of dystonia (Table 1). The full-house phenomenology typically occurs in the primary dystonia syndromes, particularly in recognized genetic forms (e.g., DYT1 or DYT6). Clinical recognition becomes straightforward when the phenomenology is complete.

Incomplete phenomenology or mild features (*formes frustes*) hinder the recognition of dystonia and favor misdiagnosis with other hyperkinetic disorders, such as essential tremor, parkinsonian tremor, myoclonus [2]. A remarkable example is the misdiagnosis of Parkinson's disease that has led to the description of dystonia in patients with tremulous phenomenology who had dopamine transporter (DAT) scans without evidence of

dopaminergic deficit (SWEDD) [3]. These observations indicate that features of dystonia should be searched for in patients with a suspicion of Parkinson's disease [4]. A normal DAT scan is a feature of all primary dystonia syndromes: it is also observed in dopa-responsive dystonia [5], as well as in other hyperkinetic disorders, such as essential tremor, psychogenic tremor and myoclonus.

The classification of dystonia syndromes is controversial and has gone through numerous revisions over time [6<sup>¶</sup>]. The most recent classification has been proposed by a European Federation of Neurological Societies task force [7<sup>¶¶</sup>]. A limit of all the available classification schemes is that they only consider the motor phenomenology of

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KEY POINTS

- Significant advances in our understanding of the molecular and genetic changes have provided the basis of possible pathophysiological mechanisms underlying this disorder.
- Current models of the potential neural circuits involved in dystonia highlight the prominent role of dopaminergic, cholinergic and GABAergic signaling.
- A central theme in clinical neurophysiology of dystonia is represented by the theory of the ‘loss of inhibition’.
- Botulinum toxin is the first-line treatment for primary cranial (excluding oromandibular) or cervical dystonia; it is also effective on writing dystonia.
- Pallidal DBS is an efficacious option, particularly for primary generalized or cervical dystonia. DBS is less effective in secondary dystonia.

dystonia, although it has been recently highlighted that, similarly to Parkinson’s disease, dystonia patients also present nonmotor features [8,9]. These accompany the motor symptomatology and may also precede it, akin to what is described in Parkinson’s disease, as is the case for depression [9]. A task force to update the classification of dystonia is currently at work.

In this review, we provide an update on dystonia classification and phenotypes and highlight recent genetic neurophysiological and morphological findings. Finally, we discuss the new available treatments.

GENETIC DYSTONIA SYNDROMES

In the past 12 years, the identification of several new genes causing dystonia syndromes has provided important insights into the nature of this complex disorder (for a review see [10]). The DYT listing encompasses a heterogeneous group of conditions with dystonia (Fig. 1). Research on the function of primary dystonia genes has yielded substantial insights into the molecular and cellular processes involving chaperones, transcription factors, structural proteins and biosynthetic enzymes [11].

Phenotypic expression

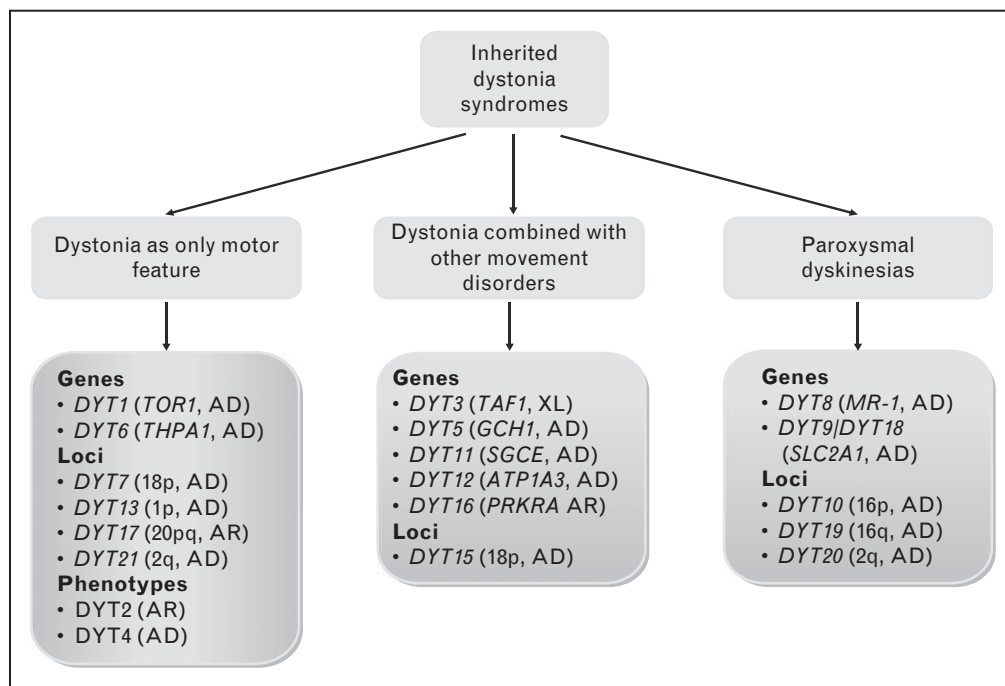
Autosomal dominant forms of dystonia have reduced penetrance (~30% in DYT1 [12], ~60% in DYT6 [13]) and specific phenotypes. The penetrance figures increase if nonmotor and endophenotypic traits are considered beside the motor phenomena of dystonia.

DYT1 dystonia usually starts with action dystonia in one limb and progresses to a segmental or generalized distribution; the cranial and cervical muscles are rarely involved. The DYT6 phenotype typically differs from DYT1 dystonia; even in early-onset forms there is a frequent involvement of the cranial–cervical district. Speech is commonly affected by oromandibular or laryngeal involvement (or both). Myoclonus-dystonia due to  $\epsilon$ -sarcoglycan mutations (*DYT11*) is characterized by early-onset myoclonic jerks, often associated with torsion dystonia. The age of onset is usually in the first decade and second decade, with variability resulting from maternal imprinting [14]. Recently, an autosomal

Table 1. Clinical features of dystonia

| Physical sign                  | Description                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dystonic postures              | A body part is flexed or twisted along its longitudinal axis (not available for blepharospasm or laryngeal dystonia). A sensation of rigidity and traction is present in the affected part                                                                                                                                                                                                                                                  |
| Dystonic movements             | Movement may be fast or slow and may appear as ‘tremor’, ‘tic’, ‘chorea’ or ‘myoclonus’. The dystonic nature is revealed by recognition of: a twisting nature or a pull in a preferred direction, repetitive and patterned attitude (i.e., movements are consistent and predictable), movements are often sustained at their peak to lessen when a given posture (usually opposite to the preferred direction) is identified (‘null point’) |
| Gestes antagonistes (‘tricks’) | Alleviation of dystonia occurs during the geste movement, usually soon after its start. Alleviation may last for as long as the geste or slowly reverses spontaneously before its end. The geste movement is natural and ‘elegant’, never forceful. The geste movement does not push or pull the affected body part, but simply touches it (‘sensory trick’) or accompanies it during alleviation of dystonia                               |
| Mirror dystonia                | Mirror movements are observed in the unaffected (or less affected) body side during repetitive tasks of the most affected body side. Typical tasks include: finger sequence, normal writing, or piano-like movements, performed at low and fast speed                                                                                                                                                                                       |
| Overflow dystonia              | Dystonic movement or dystonic postures extend beyond the commonly involved body region. It is observed at peak of dystonic movements, ipsilaterally or contralaterally, either by inspection or EMG mapping                                                                                                                                                                                                                                 |

For a detailed description see [1]. EMG, electromyography.



**FIGURE 1.** Inherited dystonia syndromes can present with isolated dystonia or a combination of dystonia with other movement disorders. Paroxysmal dyskinesias represent a separate category. Pathogenic genes and known loci are listed. AD, autosomal dominant; AR, autosomal recessive; XL, X-linked recessive.

recessive form of dystonia-parkinsonism (*DYT16*) has been described in two families with a missense mutation in the *PRKRA* gene [15]. The phenotype is characterized by predominant early (2–18 years) limb onset with progression to generalization, prominent bulbar involvement with spasmodic dysphonia, dysarthria, and dysphagia. Four of the affected members in the two families also had parkinsonian features limited to bradykinesia. The *DYT21* locus was recently mapped in a family from Northern Sweden, whose phenotype was characterized by adult onset in the cranial–cervical muscles or in the hands and progression to generalization or multifocal distribution [16].

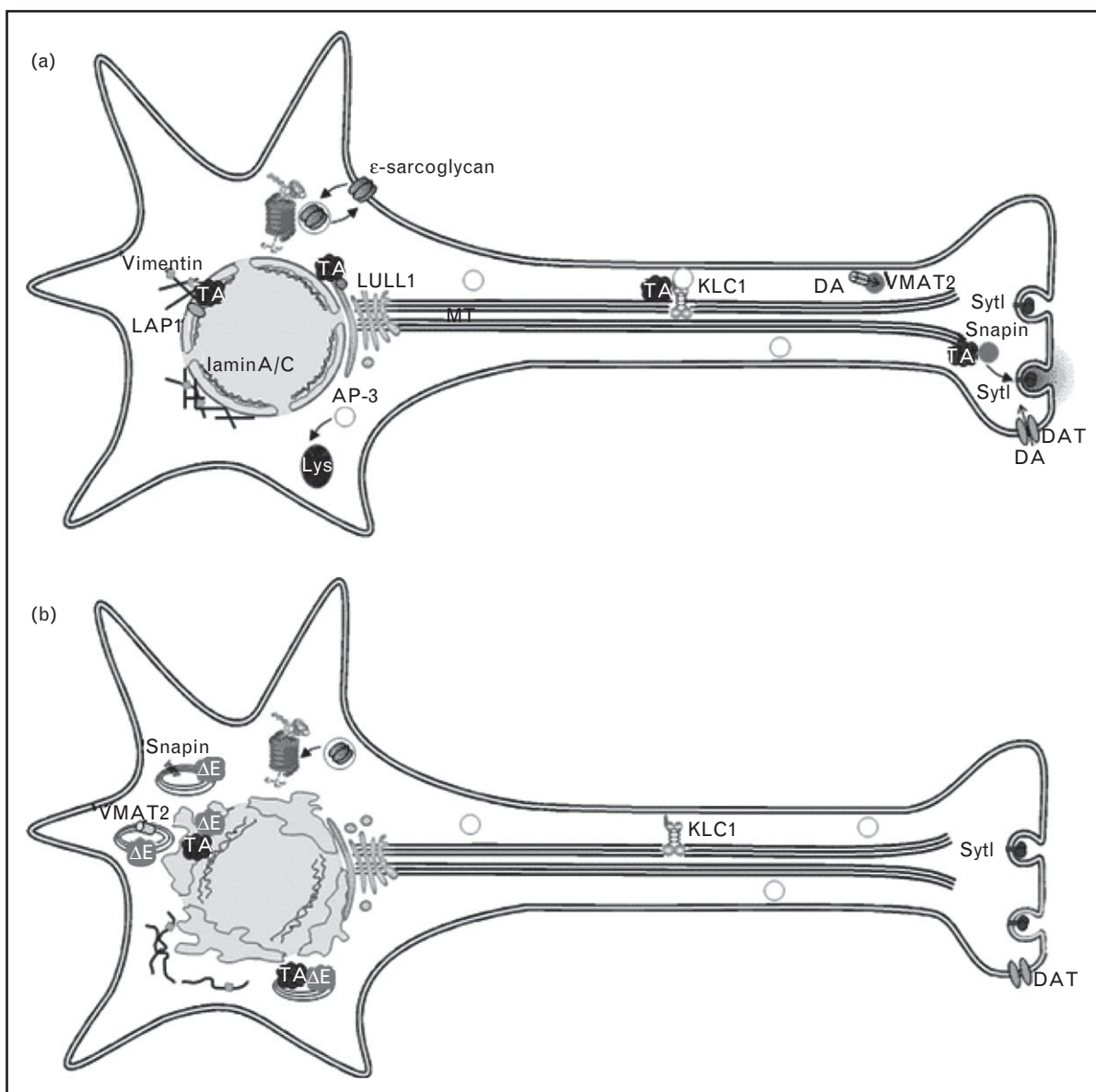
Paroxysmal dyskinesias are a heterogeneous group of disorders with sudden transient attacks of involuntary movements. Their phenotype differs from the typical dystonia presentation due to the addition of chorea and other hyperkinetic features [17]. *DYT18* dystonia is characterized by paroxysmal exercise-induced dyskinesia and autosomal dominant inheritance with reduced penetrance [18,19]. It is caused by mutations in the *SLC2A1/GLUT1* gene, the main glucose transporter in the brain, and has a wide phenotypic expression also including epilepsy, migraine, developmental delay, and hemolytic anemia. Mutations in *SLC2A1* have also been found in sporadic cases [20] and in a family with dystonic tremor as the presenting feature [21].

More recently it has been demonstrated that the *DYT9* dystonia phenotype is also caused by mutations in the same gene [22], highlighting the ample phenotypic expression of GLUT1-related dyskinesias [23], which are caused by insufficient glucose transport into the brain, particularly when energy demand is high after prolonged exercise.

### Molecular genetics

The discovery of genetic mutations underlying inherited forms of dystonia holds great promise for contributing to our understanding of the pathogenesis of primary dystonia. Most of this progress derives from experimental models of *DYT1* dystonia, focusing on the endocellular role of mutant TorsinA.

The wide distribution of TorsinA in the central nervous system is remarkable considering that the only neurological manifestation of dysfunctional TorsinA is dystonia [24]. TorsinA is located in several subcellular compartments of neurons, such as the endoplasmic reticulum, the nuclear envelope, the cytoskeleton, the cytoplasm and the synaptic vesicles (Fig. 2), wherein it is thought to contribute to multiple functions, including vesicle fusion, membrane trafficking, protein folding, and cytoskeletal dynamics [25]. Normal TorsinA serves



**FIGURE 2.** Schematic model of TorsinA and  $\Delta$ -TorsinA subcellular localization and potential cellular roles. (a) TA is seen in the endoplasmic reticulum (ER) and nuclear envelope (NE), where its interacting proteins are shown. TA is also associated with kinesin light chain 1 (KLC1) and is present at the synapse where it binds snapin. TA appears involved in the degradation of  $\epsilon$ -sarcoglycan (SGCE), in the traffic of AP-3, the localisation of dopamine transporter (DAT), the recycling of synaptotagmin I (Syt1) and the correct function of vesicular monoamine transporter 2 (VMAT2). (b) Cellular alterations consequent to TA mutation are shown. TA and other factors controlling synaptic vesicle (SV) dynamics and composition, including snapin and VMAT2, are 'sequestered' in the perinuclear inclusion. The NE structure is abnormal and SGCE appears to be degraded. Also KLC1 function and the recycling of Syt1 may be affected. DA, dopamine; TA, TorsinA. Adapted with permission from [25].

a protective function to maintain a homeostatic threshold against endoplasmic reticulum stress [26,27]. When it is mutated, TorsinA buffering capacity is greatly diminished, its translocation to the endoplasmic reticulum is prevented, its ATPase activity is reduced and the protein levels in the nuclear envelope increase compared with those in the endoplasmic reticulum. Although hypoactive,

mutated TorsinA concentrates in the nuclear envelope, suggesting that it can also interact with a nuclear envelope-localized binding partner [28]. Mutated TorsinA increases its binding capabilities to endocellular partners, thus causing a gain-of-function condition [29].

Homozygous *THAP1* mutations may be associated with a less severe dysfunction of the encoded

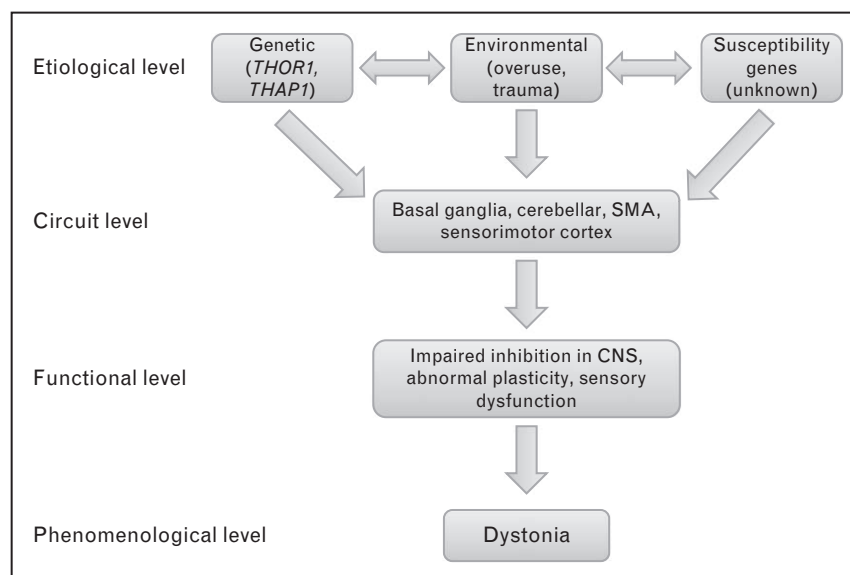
protein compared with heterozygous disease-causing mutations [30]. *THAP1* was recently found mutated also in sporadic cases with focal or segmental late-onset dystonia involving the cervical or laryngeal district, suggesting that this gene may also play a role in the pathogenesis of apparently sporadic adult-onset cases [31,32]. Although the mechanism underlying dysfunction of the *THAP1* protein in *DYT6* dystonia is not known in the same detail as that of *TorsinA*, these two genetic disorders are capable of producing comparable motor abnormalities that likely underlie a similar disruption of communication within the basal ganglia. It has been recently demonstrated that a physical interaction occurs between *THAP1* and the *TOR1A* promoter, which is abolished by pathogenic mutations [33]. This link is probably not just a simple *THAP1*–*TOR1A* promoter interaction, but is likely to involve other genes as well. In addition, *THAP1* also binds to the promoter region of a *TAF1* transcript that is implicated in *DYT3* dystonia [34].

TATA-binding protein-associated factor (N-TAF1), whose activity is reduced in *DYT3* dystonia, labels nuclei of medium spiny neurons in the rat brain [35]. This topography is strikingly similar to the patterns of neuronal loss observed in the striatum of *DYT3* patients, suggesting that the distribution of N-TAF1 protein could represent a key molecular feature contributing to the peculiar pattern of striatal degeneration in *DYT3* dystonia. Interestingly, experimental data on *DYT1*, *DYT6*, and *DYT3* dystonias provide converging views on their causative mechanisms.

## PATHOPHYSIOLOGY

Primary dystonia is traditionally regarded as a basal ganglia disorder without overt structural abnormalities (hence the name ‘primary’). More recent views indicate that primary dystonia can be regarded as a neurodevelopmental circuit disorder, involving the cortico–striato–pallido–thalamo–cortical and cerebello–thalamo–cortical pathways [36<sup>■</sup>]. Anatomical disruption of the cerebellar outflow is found in nonmanifesting and manifesting *DYT1/DYT6* mutation carriers, and a second downstream disruption in thalamo–cortical projections appears clinically protective in nonmanifesting carriers [37]. *DYT1* and *DYT6* patients with dystonia show relative metabolic increases in the presupplementary motor area and parietal association regions [38], whereas nonmanifesting *DYT6* gene carriers have a different pattern of abnormalities compared with *DYT1* carriers with regional hypometabolism in the putamen, cerebellum, and upper brainstem and hypermetabolism in the temporal cortex [38]. Similarly to human gene carriers, *DYT1*-mutant mice exhibit cerebello–thalamo–cortical tract changes, as well as abnormalities in the brainstem regions linking cerebellar and basal ganglia motor circuits [39]. The relative role of basal ganglia and cerebellar dysfunction could be related to age at onset and other interfering variables (Fig. 3). Learning of motor skills is altered in primary dystonia patients [40] and *DYT1* manifesting and nonmanifesting mutation carriers, but not in *DYT6* carriers [41<sup>■</sup>].

Deficient inhibition is a key feature occurring in the cerebral cortex, brainstem and spinal cord



**FIGURE 3.** Pathogenic mechanisms in primary dystonia. SMA, supplementary motor area.

of patients with primary dystonia [42,43<sup>¶</sup>]. Three interrelated neurophysiologic abnormalities have been identified: impaired inhibition, including surround inhibition, increased plasticity, and sensory processing dysfunction [44]. Neurophysiology has recently tried to detect abnormalities beyond the visibly affected territories, suggesting a potential future diagnostic use. Transcranial magnetic stimulation (TMS) studies using the paired associative stimulation (PAS) protocol showed abnormal cortical plasticity also in unaffected body regions [45]. A recent study showed that sensory abnormalities are present on both sides of patients with unilateral focal hand dystonia and even in unaffected body regions of patients with cervical dystonia and blepharospasm [46]. The same abnormalities were also found in a number of relatives of patients with dystonia, suggesting that they could contribute to identify nonmanifesting carriers [47].

Abnormal plasticity has been demonstrated for several different primary dystonia types. In primary focal dystonia, PAS produced enhanced effects consistent with increased cortical excitability associated with loss of spatial specificity [48,49]. Changes in excitability induced by facilitatory PAS may share features of long-term potentiation (LTP) of synaptic efficacy, providing converging evidence for abnormal enhancement of LTP-like plasticity in focal dystonia. A combination of MRI with TMS in patients with writer's cramp showed that a prolonged suppression (i.e., immobilization) or enhancement (i.e., training) of manual activity induced opposing MRI changes in the contralateral motor cortex [50]; immobilization decreased cortical excitability and subsequent training reversed these effects, causing an increased cortical excitability. In DYT1 patients, discontinuation of deep brain stimulation (DBS) for 2 days caused the relapse of clinical symptoms [51]; the greater the response to PAS with active DBS, the better clinical benefit was maintained with DBS turned off. This indicates that the degree of abnormal cortical plasticity correlates with the time required for the re-emerging of neurophysiological features.

Several recent data indicate a role of dopamine and acetylcholine (ACh) transmission in the pathophysiology of primary dystonia. Cholinergic interneurons are autonomous pacemakers, and their spiking activity, and consequently ACh release, are under the inhibitory control of both muscarinic M2/M4 autoreceptors and D2 dopamine receptors [52]. In *DYT1*-mutated mice the M2/M4 muscarinic response is preserved, whereas D2 receptor-mediated inhibition is shifted toward excitation, suggesting that dysfunctions in dopamine signaling are associated to the occurrence of

dystonia. In keeping, a reduction of D2 receptor availability has been found in the caudate and putamen of manifesting and nonmanifesting *DYT1* mutation carriers [53]. Mice overexpressing mutant TorsinA also display an increased dopamine turnover and altered dopamine transporter function [54]. A study examining D2 receptor transmission demonstrated a link with the occurrence of *TOR1A* mutation [55]; furthermore, pharmacological blockade of adenosine A2A receptors rescues physiological striatal synaptic plasticity. In mice overexpressing mutant TorsinA, abnormal D2 receptor signaling may have relevant functional consequences on striatal circuitry by elevating the levels of ambient ACh, enhancing ACh turnover and reducing corticostriatal long-term depression and synaptic depotentiation of striatal medium spiny neurons [56]. Striatal cholinergic terminal density is known to be decreased in cervical dystonia [57], coherently with the clinical observation that anticholinergic drugs, such as trihexyphenidyl, are efficacious in primary dystonias, including DYT1 [58].

A D2 receptor trafficking defect is further supported in DYT1 by recent PET imaging studies [53]: significant reductions in radioligand binding were detected in DYT1 caudate, putamen, and ventrolateral thalamus irrespective of the clinical manifestation, suggesting a carrier trait of DYT1 dystonia [59]. In keeping, reduced D2 receptor availability has been recently identified in *DYT1* and *DYT6* mutation carriers regardless of whether they manifested dystonia [53]. Compared with controls, reduction in D2 receptor availability was greater in DYT6 patients than in DYT1 and was independent of disease severity. These data provide an intriguing link between DYT6 and dopamine function.

Recent evidence also points to a deficient inhibition by GABA, the primary central inhibitory neurotransmitter, at the level of corticobasal ganglia circuitry [52]. A PET study recently evidenced central GABA-A receptor dysfunction in the sensorimotor systems of patients with DYT1 and non-DYT1 primary dystonia [60<sup>¶</sup>]. Understanding of disruption of neurotransmitter communication involving striatal dopaminergic and cholinergic neurotransmitter systems, as well as an overall loss of GABA-mediated inhibition, will help not only in the creation of therapies for this disorder, but also in the elucidation of the homeostatic neural mechanisms involved.

## TREATMENT

Although botulinum toxin (BoNT) treatment continues to be the first choice approach for most

focal dystonia types [7<sup>•</sup>,61], DBS of the globus pallidus internus is a new management procedure for both adults and children with dystonia [62]. A thematic issue has recently been dedicated to the diverse aspects of DBS treatment, ranging from inclusion criteria to preoperative, intraoperative and postoperative management, neuropsychology, and quality of life [63]. Better results are obtained from DBS in patients with DYT1 dystonia, shorter duration of symptoms and lower baseline severity score [64]. The few DYT6 patients studied initially responded to DBS much like the DYT1 patients, but later regressed, requiring repeated adjustments of stimulation parameters [65<sup>•</sup>]. Reported levels of improvement with DBS in secondary dystonia vary widely [66,67]. Satisfactory results have so far been obtained in patients with tardive dystonias [68,69]. In other dystonia types, such as dystonia-plus, posttraumatic, postanoxic or postencephalitic, small cohorts and single cases report variable outcomes [66,70]. Dystonia in neurodegeneration with brain iron accumulation improves after bilateral DBS, although the benefit is not comparable to that observed in patients with primary generalized forms [71].

Recently, epidural premotor stimulation has been attempted in patients with focal dystonia [72]. Cervical dystonia improved on average by 20%, whereas prevalently fixed cervical dystonia had a reduced benefit.

## CONCLUSION

Dystonia is a set of syndromes, whose hallmark clinical feature is now being increasingly recognised under a unique clinical and pathophysiological mechanism. The study of genetic forms, mostly focusing on the role of mutant TorsinA, sheds light on the molecular causes and has allowed development of animal models. The pathophysiology of dystonia can be imagined as a multistep pathway that begins with a 'trigger' event or susceptibility factor, leading to fallout of consequences ultimately altering synaptic circuitry in the motor system (Fig. 3).

A central theme in the pathophysiology of dystonia is centered on the concept of 'loss of inhibition' that has been intensely investigated in both affected and unaffected gene carriers.

Although the last 10 years have seen dramatic advances in treatment options for dystonia, there have been no significant advances in oral medications for primary dystonias: all existing treatments, including BoNT and DBS, are symptomatic. Treatments aimed at correcting the etiologic causes of dystonia may derive from animal models.

## Acknowledgements

None.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 517).

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