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Symptomatic animal models for dystonia

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Abstract

Symptomatic animal models have clinical features consistent with human disorders and are often used to identify the anatomical and physiological processes involved in the expression of symptoms and to experimentally demonstrate causality where it would be infeasible in the patient population. Rodent and primate models of dystonia have identified basal ganglia abnormalities, including alterations in striatal GABAergic and dopaminergic transmission. Symptomatic animal models have also established the critical role of the cerebellum in dystonia, particularly abnormal glutamate signaling and aberrant Purkinje cell activity. Further, experiments suggest that the basal ganglia and cerebellum are nodes in an integrated network that is dysfunctional in dystonia. The knowledge gained from experiments in symptomatic animal models may serve as the foundation for the development of novel therapeutic interventions to treat dystonia.

Keywords

mouse model; primate model; cerebellum; basal ganglia

There has been an explosion of animal models for dystonia in the past decade. In general, animal models of neurologic disorders are used to test hypotheses suggested by human studies because it is often impossible to examine the molecular, cellular and physiologic abnormalities underlying the problem in humans. Animal models can be used to determine mechanisms of pathogenesis or pathophysiology and are used to develop novel therapeutics. Because few animal models of dystonia reproduce every aspect of the human disorder from inciting event to dystonic movements, animal models of dystonia are generally divided into two categories: etiologic or symptomatic. Etiologic models, which are addressed in detail elsewhere in this issue, recapitulate the inciting event or genetic predisposition and are useful for understanding the ensuing molecular, biochemical and cellular derangements, but often lack overt motor manifestations typical of dystonia. Symptomatic animal models have clinical features consistent with human dystonia and are often used to identify the anatomical and physiological processes involved in the expression of the motor syndrome, although the inciting event may not perfectly align with the etiology of dystonic disorders. Symptomatic models occur in several different species including mice, rats, hamsters, and monkeys. Some models arose as spontaneous mutations in breeding colonies; others were induced through pharmacological manipulations or after targeted gene alterations (Table 1).

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Symptomatic animal models have been used extensively to better understand the anatomy of dystonia. Dystonia generally results from neuronal dysfunction, rather than overt degeneration or detectable insult. Therefore, it has been difficult to localize brain defects in dystonia. The basal ganglia were initially implicated because early and influential studies demonstrated neuropathological defects in the basal ganglia of some, but not all, individuals with acquired dystonia.¹⁻⁴ However, modern functional imaging studies suggest that the anatomy of dystonia is more complex. Abnormalities are frequently detected in several motor regions, including basal ganglia, thalamus, cortex and cerebellum in many different forms of dystonia, as summarized in recent reviews.^{5, 6} Indeed, the most recent data from human imaging studies suggesting that dystonia is a network disorder involving cortico-striato-pallido-thalamo-cortical and cerebello-thalamo-cortical pathways.^{7, 8} Although functional imaging studies in humans are invaluable for providing direct evidence of abnormalities in patients, it is difficult to distinguish cause from consequence. Therefore, symptomatic animal models have been exploited to provide a deeper understanding of the brain regions and networks involved. Because striatum and cerebellum are consistently implicated across imaging studies, experiments in animals have focused on these regions.

Basal ganglia dysfunction in animal models of dystonia

PET imaging studies have revealed changes in basal ganglia metabolic activity (most frequently increases in the putamen) in multiple forms of dystonia, including cervical dystonia,^{9, 10} DOPA-responsive dystonia,¹¹ DYT1 dystonia,¹¹⁻¹³ DYT6 dystonia,¹¹ and hemidystonia.¹⁴ Deep brain stimulation of the internal globus pallidus is an effective treatment for dystonia in some patients, providing strong support for the association of dystonia with abnormal basal ganglia function.¹⁵⁻¹⁷ Histopathological studies in tissue from patients also implicate the basal ganglia. Lesions were found in the putamen, globus pallidus, caudate, or closely related structures,^{1-4, 18} although brain lesions are apparent in only a small number of patients with dystonia. The basal ganglia are also implicated in the acquired dystonia that occurred in response to ingestion of moldy sugarcane, which contains the mitochondrial toxin 3-nitropropionic acid (3-NPA).¹⁹ Affected patients developed segmental or generalized dystonia that was consistently associated with striatal and pallidal lesions.^{20, 21}

Lesion studies in humans have provided information used to guide more extensive experimentation in animals to examine the role of the basal ganglia in dystonia. Similar to 3-NPA intoxicated patients, 3-NPA causes striatal lesions that result in dystonic movements in rodents^{19, 22, 23} and primates.²⁴⁻²⁶ In animals, the size of the striatal lesion corresponds with the severity of the dystonic movements.^{25, 27} Further, histological studies in both rodents and primates treated with 3-NPA demonstrate a major loss of GABAergic striatal projection neurons.^{28, 29} Animal models have been used to investigate the putative role of GABAergic signaling in greater depth. Results suggest that alterations in GABA transmission within the basal ganglia can play a causal role in dystonia. In the *dt^{sz}* hamster, which exhibits paroxysmal generalized dystonia, there is a reduction in striatal GABAergic interneurons. This GABAergic abnormality may mediate the dystonia as systemic or striatal administration of GABA receptor agonists decreases dystonia,³⁰⁻³² while systemic or striatal administration of GABA receptor antagonists increases dystonia.³⁰⁻³² This response accurately predicts the efficacy of benzodiazepine treatment for paroxysmal dystonia in humans.³³ Similarly, in primates, injections of GABA receptor antagonists into the globus pallidus,³⁴ substantia nigra,³⁴ and thalamus (VLo/VA)^{35, 36} provoke dystonic movements. Studies in primates suggest that the type of dystonia may be determined by the location of the insult within the basal ganglia. Muscimol inactivation of the substantia nigra pars reticulata causes cervical dystonia,³⁷ whereas inactivation of the globus pallidus pars interna causes dystonic movements in the upper limbs.^{38, 39} Similarly, bicuculline injection of the

globus pallidus pars interna causes upper and lower limb dystonia.³⁷ It is not yet clear why injection of either GABA receptor agonists or antagonists into the basal ganglia provoke dystonic movements, but these results suggest that the absolute firing rate may be less important than changes to the firing patterns within the basal ganglia.

In addition to GABAergic defects, abnormal striatal dopaminergic neurotransmission is also associated with dystonia in humans. Mutations in genes critical to the synthesis of dopamine, including GTP-cyclohydrolase (*GCHI*) and tyrosine hydroxylase (*TH*) cause L-DOPA-responsive dystonia.^{40–48} Dystonia is a prominent feature of several other inherited disorders in which dopamine transmission is disrupted including dopamine transporter deficiency syndrome,⁴⁹ amino acid decarboxylase deficiency^{50, 51} and Lesch-Nyhan disease.^{52, 53} Dystonia can also occur in Parkinson's disease, where there is frank loss of dopaminergic innervation.^{54, 55} Indirect evidence based on measurements of dopamine metabolites in postmortem striatum suggests that dopamine transmission is reduced in early onset torsion dystonia (DYT1 dystonia).^{56, 57} Abnormal dopamine transmission is also suggested by PET imaging studies whereby reduced striatal D2 dopamine receptor availability is observed in several different forms of dystonia, including blepharospasm,⁵⁸ rotational torticollis,⁵⁹ cervical dystonia⁶⁰ and DYT1 carriers.⁶¹ Thus, dystonia appears to be associated with a chronic reduction in dopamine transmission.

Toxin-induced animal models support the association between a reduction in dopaminergic transmission and dystonia. Dystonia is an early feature in MPTP-induced primate models of Parkinsonism. Unilateral intracarotid injection of MPTP destroys dopaminergic neurons in the substantia nigra and causes contralateral dystonia, which is associated with decreased striatal dopamine and a transient decrease in D2 dopamine receptors.^{62, 63} In contrast, in both primates and rodents with dopaminergic neuronal lesions, dystonia can also occur in response to chronic L-DOPA administration, similar to the dystonia observed in patients with Parkinson's disease after long-term L-DOPA treatment.^{64, 65} Together, these results suggest that both acute and long-term changes in dopamine signaling contribute to dystonia.

Animal models have also been used to assess the relationship between striatal dopamine release and dystonia. In the *tottering* mouse model of generalized dystonia, striatal extracellular dopamine is reduced during dystonic attacks. Striatal extracellular dopamine is also reduced after pharmacologic induction of generalized dystonia in normal mice by applying glutamate agonists to the cerebellum.⁶⁶ In a mouse model of paroxysmal nonkinesogenic dyskinesia, a movement disorder characterized by both dystonia and chorea, extracellular dopamine is reduced by ~40%.⁶⁷ Likewise, though not symptomatic, in mice carrying the DYT1 mutation, striatal extracellular dopamine concentrations are also reduced to ~40% of normal.⁶⁸ In both models, total tissue dopamine concentrations in the striatum are normal suggesting that the deficit is downstream of catecholamine synthesis, perhaps disrupting the release of dopamine.⁶⁷ That extracellular dopamine concentrations were ~40% of normal concentrations in both models suggests the intriguing possibility that extracellular dopamine deficits of this magnitude may be a critical determinant. Overall, a reduction in dopamine release, not a complete abolition of dopamine release, is observed in a variety of mouse models of dystonia.

Although dopamine replacement therapy is highly effective for treating DOPA-responsive dystonia, most other types of dystonia do not respond to L-DOPA treatment.^{69, 70} Other drugs that enhance or inhibit dopamine signaling are ineffective for most dystonias.^{70–72} Similarly, drugs that act at GABA receptors, such as benzodiazepines, are not satisfactory for the treatment of most dystonias. Further, directly altering the physiological properties of the basal ganglia with deep brain stimulation is effective in some, but not all patients.

Because interventions targeting the basal ganglia are not effective in all patients with dystonia, it is likely that other factors contribute to the pathogenesis of dystonia.

Cerebellar dysfunction in animal models of dystonia

The cerebellum is also implicated in dystonia. Dystonia occurs as a secondary feature of cerebellar disorders, such as ataxia, and can accompany cerebellar stroke and posterior fossa tumors that primarily affect the cerebellum and brainstem.^{73–75} Both structural and histological studies demonstrate cerebellar abnormalities in patients with cervical dystonia.^{76, 77} Further, lesions of the deep cerebellar nuclei,^{78–80} cerebellar stimulation,⁸¹ or posterior fossa tumor removal^{73, 82} have been effective for ameliorating dystonia in some patients. Imaging studies in patients with dystonia also frequently reveal cerebellar involvement.^{5, 6} Diffusion tensor imaging implicates abnormal cerebellothalamic connectivity.⁸³ Abnormal cerebellar signaling is observed with PET and fMRI in multiple forms of dystonia, including focal dystonias (e.g. blepharospasm,⁸⁴ cervical dystonia,⁹ and writer's cramp^{85, 86}), inherited forms of generalized dystonias (e.g. DOPA-responsive,¹¹ DYT1,⁸⁷ and DYT6¹¹ dystonia), and acquired dystonias (e.g. post-stroke⁸⁸ and tardive dystonia⁸⁹). In fact, functional imaging studies in dystonic patients generally reveal *increases* in cerebellar perfusion or metabolism in both focal and generalized dystonias.

The studies in humans have guided experiments in animals examining the mechanisms underlying the role of the cerebellum in dystonia. Similar to humans, abnormal cerebellar activation is observed in several different genetic mouse models of dystonia, including both symptomatic (dystonic (*dt*) rats and *tottering* mice) and nonsymptomatic models (transgenic and knockin DYT1 mice).^{90–93} Aberrant cerebellar firing patterns may contribute to this abnormal activation. In *dt* rats, which exhibit generalized dystonic movements caused by a mutation in the caytaxin gene, Purkinje cell firing patterns are abnormal with a reduction in complex spike frequency accompanied by abnormal simple spike firing patterns.⁹⁴ Cells of the deep cerebellar nuclei in *dt* rats also exhibit abnormal firing patterns and the extent of this abnormality correlates with the severity of the abnormal movements.^{95, 96} In *tottering* mice, which exhibit episodic generalized dystonic movements caused by a mutation in the gene encoding the alpha subunit of the Ca_v2.1 calcium channel, Purkinje cell activity is abnormal and the aberrant cerebellar activity is tightly coupled to the abnormal EMG activity observed in affected muscles.^{97, 98} Finally, abnormal cerebellar activity is observed in a pharmacologically-induced mouse model of Rapid-onset Dystonia Parkinsonism (RDP), whereby an increase in cerebellar EEG amplitude correlates with dystonic postures.⁹⁹ Overall, in these models, the cerebellar firing patterns reflect the abnormal movements.

Cerebellar lesions have been used to demonstrate that the cerebellum is a critical link in the pathway leading to dystonia in these models. Surgical removal of the cerebellum prevents the development of dystonia in young *dt* rats and eliminates the episodes of generalized dystonia in *tottering* mice.^{66, 100} Lesioning the deep cerebellar nuclei, which eliminates cerebellar efferents, is similarly effective in both *dt* rats and RDP mice.⁹⁹ Pharmacological inactivation of the cerebellum with GABA also reduces the dystonic movements in RDP mice.⁹⁹ Further, eliminating Purkinje cells, the only efferents of cerebellar cortex, through the use of specifically expressed toxic transgenes or mutations also abolishes dystonia in the *tottering* mutant, suggesting that a single cell type may mediate the abnormal movements.^{101, 102} However, while these experiments suggest that cerebellar signaling is necessary for the expression of dystonia, it is not possible to discern whether the cerebellum actually causes the dystonia based on lesion experiments.

Because it is neither feasible nor ethical to perform experiments testing causation in humans, animals have been used to establish a causal relationship between abnormal cerebellar

signaling and dystonia by inducing cerebellar dysfunction in an otherwise normal cerebellum. Pharmacologic disruption of cerebellar signaling by delivery of the excitatory glutamate agonist kainic acid directly into the cerebellum elicits generalized dystonia in both mice and rats.^{103, 104} These results are consistent with observations in human imaging studies that consistently reveal an increase in cerebellar activity in patients with dystonia. To determine if a simple increase in overall cerebellar activity is sufficient to induce dystonia or if specific signaling pathways are involved, mice were used to probe the underlying mechanism.¹⁰⁵ These experiments demonstrated that a nonspecific increase in cerebellar excitability, such as that produced by GABA receptor antagonists, potassium channel blockers or sodium channel activators, is not sufficient to induce dystonia. Instead, experiments revealed that AMPA receptor activation was sufficient to evoke dystonia but activation of other glutamate receptors subtypes such as kainate or NMDA receptors did not provoke dystonia. In addition, these studies also demonstrated that AMPA receptor desensitization mediated the severity of the dystonia. Thus, studies in animals suggest that the cerebellar overactivity observed in neuroimaging studies of patients with dystonia may be associated with abnormal glutamate signaling.

The pharmacological challenges implicate specific cerebellar signaling pathways in dystonia but are not useful to identify cell types involved. Therefore, conditional genetic manipulations in mice have been used to implicate a single cell type. Studies in several different models suggested that abnormal Purkinje cell activity may be involved. To address this question, the dystonia-causing *tottering* gene defect was isolated to Purkinje cells by permanently altering the genome of only Purkinje cells using cre-lox recombination technology, while leaving neurons elsewhere in the brain intact.¹⁰² Mice with defects restricted to Purkinje cells exhibited dystonic movements demonstrating that abnormal Purkinje cells alone are sufficient to generate dystonic movements. Thus, work in animals has extended the functional imaging studies in humans by demonstrating that the cerebellum, specifically cerebellar Purkinje cells, has the capacity to instigate dystonic movements.

Functional imaging in humans demonstrates that cerebellar dysfunction is a common feature of focal and generalized dystonias, suggesting that different forms of dystonia share similar pathological processes differing only by the region or amount of cerebellum affected. While it is challenging to determine the relationship between focal and generalized dystonias from functional imaging in patients, animals were used to examine this relationship. Dysfunction of the entire cerebellum, as occurs with the *tottering* mouse mutation, the *dt* mutation or kainic acid delivery to the cerebellum, to name a few, causes abnormal postures of many body parts that resemble generalized dystonia. Small areas of cerebellar dysfunction created by electrical stimulation or conditional genetic manipulations of the *tottering* mutation produced abnormal movements in an isolated body part that resembled focal dystonia.¹⁰² Thus, the extent of cerebellar dysfunction determines the extent of abnormal movements. Overall, it appears that focal and generalized dystonias can arise through similar mechanisms and therefore may be approached with similar therapeutic strategies.

Animal models and brain networks

Strong evidence from human studies and experiments in animals implicates both the basal ganglia and cerebellum in dystonia. Detailed anatomical tract-tracing experiments in rodents and primates suggest that these two regions probably do not act independently. Di-synaptic connections (with thalamic relay) exist between the cerebellum and the basal ganglia.^{106, 107} These connections are functional: changes in cerebellar output alter neuronal firing and extracellular dopamine concentrations in the basal ganglia.^{108–110} Reciprocal di-synaptic connections between the basal ganglia and the cerebellum have also been identified.¹¹¹

Further, animal models have been used to demonstrate that basal ganglia and cerebellar pathology interact to mediate dystonia. Pharmacological manipulation of either pallidal or cerebellar inputs to the thalamus elicits dystonic symptoms in primates.^{35, 36} Basal ganglia insult exacerbates cerebellar dystonia in the *tottering*, kainic acid and RDP mouse models of dystonia.^{66, 99} Severing the cerebellar-basal ganglia connection by thalamic lesion of the centrolateral nucleus also ameliorates dystonic symptoms in RDP mice.⁹⁹ Therefore, it is possible that the basal ganglia and cerebellum form an integrated functional network that is dysfunctional in dystonia.

The most recent data from human imaging studies suggest that dystonia is even more complex and involves a network that may include cortico-striato-pallido-thalamo-cortical and cerebello-thalamo-cortical pathways.^{7, 8, 66, 91, 92, 99, 112} In a network model of dystonia, dystonic symptoms could result from a single site of dysfunction, multiple sites of dysfunction, or aberrant communication between sites. For example, blepharospasm can be induced in rats through mild striatal dopamine depletion combined with abnormal cortical input from a weakened eyelid muscle, but neither intervention alone is sufficient to cause dystonia.¹¹³ A genetic, pharmacological, or physical insult could cause dystonia directly, or dystonia may be an indirect result caused by maladaptive changes in other members of the network; this may explain why dystonia sometimes occurs as a delayed reaction to insult.

Neither basal ganglia nor cerebellar activity alone or in combination is sufficient to cause dystonic movements; the abnormal signal must be relayed to the lower motor neurons and muscles, but the descending pathways are unknown. Identifying the complete network is critical because any member of the network could be a substrate for maladaptive compensatory response, or be vulnerable to insult in a “second-hit” scenario of pathogenesis and therefore is a potential target for therapeutics. Canonically, both basal ganglia and cerebellum signals are relayed through separate thalamic nuclei to the cortex, and then to lower motor neurons and muscles. Although the cortex serves as the final common pathway for organizing motor output, it may not be the common substrate for dystonic efferents since movement features altered in dystonia (including posture and reflexes) may not require cortical input. As such, midbrain or brainstem relays may be key substrates in the network model of dystonia. Animal models support the importance of these regions. In primates, midbrain lesions^{114–116} or pharmacological manipulation of the red nucleus causes dystonia.¹¹⁷ In rodents, red nucleus lesions have been observed in the dystonia musculorum *Dst^{dt-J}* mutant mouse and injection of sigma receptor agonists into the red nucleus in rats causes cervical dystonia.^{118, 119} Although midbrain or brainstem lesions are seen infrequently in patients with dystonia, this could be because small specific lesions are difficult to detect, and large lesions in these regions are catastrophic. Further, changes in neuronal activity in these regions, rather than destructive lesions, may be critical as suggested by PET studies that reveal altered midbrain activity in patients with dystonia.^{12, 120}

The use of symptomatic models of dystonia has further elucidated the role of the basal ganglia in dystonia, provided a growing body of evidence for extensive cerebellar involvement and demonstrated possible mechanisms underlying a network model of dystonia. Experiments in symptomatic animal models have suggested new directions for therapeutics, such as modifying neurotransmission rather than complete activation or blockade of signaling. For example, dopaminergic transmission in animal models is reduced, but not abolished, suggesting that subtle interventions may be needed. Likewise, desensitization of AMPA receptors in Purkinje cells reduces the severity of dystonia in mice suggesting that fine-tuning Purkinje cell firing patterns may be effective. Ultimately, the goal of experiments in animal models is to provide a platform for the development of novel therapeutics or the prevention of dystonia by suggesting new directions for clinical research.

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Table 1

Symptomatic Animal Models of Dystonia

Model	Species	Cause	Motor Phenotype	References
Genetic Models				
<i>Dst^{dt-J}</i>	Mouse	<i>Bpag1</i> mutation	Generalized dystonia	Duchen (1976) ¹²¹
<i>dt</i>	Rat	<i>Atcay</i> mutation	Generalized dystonia	Lorden et al. (1992) ⁹⁵ ; Xiao and Ledoux (2005) ¹²²
<i>dt^{sz}</i>	Hamster	Unknown recessive mutation	Paroxysmal generalized dystonia	Loscher et al. (1989) ³⁰
<i>Pnkd</i>	Mice	<i>Pnkd</i> mutation	Paroxysmal non-kinesogenic dyskinesia	Lee et al. (2012) ⁶⁷
<i>Tottering</i>	Mouse	<i>Cacna1a</i> mutation	Paroxysmal generalized dystonia	Campbell and Hess (1999) ¹⁰¹
Purkinje cell specific <i>Tottering</i>	Mouse	<i>Cacna1a</i> pathology limited to cerebellar Purkinje cells	Paroxysmal generalized dystonia	Raike et al. (2013) ¹²³
<i>Tottering</i> Flox + Cre lentiviral injections into cerebellum	Mouse	<i>Cacna1a</i> pathology limited to small cerebellar region	Focal hindlimb dystonia	Raike et al. (2012) ¹⁰²
Induced Models				
Bicuculline injection into globus pallidus	Primate	GABA receptor antagonist	Upper and lower limb dystonia	Burbaud et al. (1998) ³⁷
Bicuculline injection into substantia nigra	Primate	GABA receptor antagonist	Torticollis and lower limb dystonia	Burbaud et al. (1998) ³⁷
Bicuculline injection into thalamic relay of pallidal inputs	Primate	GABA receptor antagonist	Tonic hemidystonia	Guehl et al. (2000) ³⁵ ; Macia et al. (2002) ³⁶
Bicuculline injection into thalamic relay of cerebellar inputs	Primate	GABA receptor antagonist	Myoclonic dystonia	Guehl et al. (2000) ³⁵ ; Macia et al. (2002) ³⁶
Muscimol injection into globus pallidus	Primate	GABA receptor agonist	Upper limb dystonia	Burbaud et al. (1998) ³⁴
Muscimol injection into substantia nigra	Primate	GABA receptor agonist	Cervical dystonia	Burbaud et al. (1998) ³⁴
3-nitropropionic acid	Mouse, rat, or primate	Striatal lesion by mitochondrial toxin	Trunk and limb dystonia	Fernagut et al. (2005) ²³ ; Ouary et al. (2000) ¹²⁴ ; Palfi et al. (1996) ²⁵
Unilateral intracarotid MPTP injection	Primate	Striatal lesion by mitochondrial toxin	Transient contralateral dystonia	Perlmutter et al. (1997) ⁶²
Unilateral intracarotid MPTP injection + chronic L-DOPA	Primate	Striatal lesion by mitochondrial toxin + dopamine replacement	Contralateral dystonia	Clarke et al. (1989) ⁶⁴
6-hydroxydopamine injection into substantia nigra + chronic L-DOPA	Rat	Striatal lesion by dopaminergic toxin + dopamine replacement	Trunk and limb dystonia	Pearce et al. (1995) ⁶⁵
Partial facial nerve lesion + Injection of 6-hydroxydopamine into substantia nigra	Rat	Facial nerve dysfunction + nigrostriatal toxin	Blepharospasm	Schicatano et al. (1997) ¹¹³
Injection of kainic acid into cerebellum	Mouse or rat	AMPA receptor agonist	Generalized dystonia	Pizoli et al. (2002) ¹⁰³

Model	Species	Cause	Motor Phenotype	References
Oubain perfusion into basal ganglia + cerebellum	Mouse	Sodium pump blockade	Dystonia Parkinsonism	Calderon et al. (2001) ⁹⁹
Electrical stimulation of the cerebellum	Mouse	Regional cerebellar dysfunction	Focal dystonia	Raike et al. (2012) ¹⁰²
Midbrain lesion	Primate	Electrolytic lesion	Torticollis	Foltz et al. (1959) ¹¹⁵
Red nucleus lesion	Primate	Electrolytic lesion	Torticollis	Carpenter et al. (1956) ¹¹⁴
Sigma receptor ligand injection into red nucleus	Rat	Binding to sigma receptors	Generalized dystonia	Matsumoto et al. (1990) ¹²⁵