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Unraveling dystonia circuitry in rodent models using novel neuromodulation techniques

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Dystonia is a network disorder presumed to result from abnormalities in multiple brain regions and in multiple cell populations. The specific pathomechanisms affecting the motor circuits in dystonia are, however, still largely unclear. Animal models for dystonia have long been used to advance our understanding on how specific brain regions and cell populations are involved in dystonia symptomatogenesis. Lesioning, pharmacological modulation and electrical stimulation paradigms were able to highlight that both the basal ganglia and the cerebellum are pathologically altered in these animal models for dystonia. Techniques such as optogenetics and chemogenetics now offer the opportunity for targeted modulation of brain regions and most importantly cell populations and circuits. This could not only allow for a better understanding of the dystonic brain, but potentially improve and expand treatment options. In hopes that the insights from these neuromodulation techniques will eventually translate into therapies, we aim to summarize and critically discuss the findings from different *in vivo* approaches used to dissect the network dysfunctions underlying dystonia.

KEYWORDS

dystonia, network disorder, deep brain stimulation, optogenetics, basal ganglia, cerebellum, chemogenetics

Introduction

Dystonia encompasses a heterogeneous group of hyperkinetic movement disorders assumed to be caused by a dysfunctional motor network. The entire cortico-basal ganglia-thalamo-cortical network, the brainstem with regions such as the pedunculopontine nucleus (PPN) as well as cerebellar regions have been implicated in the development of dystonia. The degree to which these brain structures are involved is, however, still unresolved [1, 2].

Further studies are needed to clarify the specific cell populations within these structures causing dystonia. This need is especially pressing since deep brain stimulation (DBS) of the globus pallidus internus (GPi) and the subthalamic nucleus (STN) represent the best therapeutic options for most forms of dystonia. However, the response rate is variable and can be compromised by side effects as well as a secondary failure of DBS [3]. Especially some monogenic forms of dystonia do not respond to GPi or STN DBS. Elucidating the motor circuit changes involved in dystonia development and understanding the mechanisms of action of DBS in dystonia could allow for better neuromodulation protocols and alternative targets.

Over the past decades, different approaches have been utilized in order to study the network pathologies in rodent models for dystonia. Within this review, we will summarize the findings from brain structure lesions in animal models. We will further present the advances in the field of *in vivo*, region- and cell-specific neuromodulation. Lesioning of brain structures is a common approach in animal models to understand the role of specific brain regions in dystonia symptomatogenesis [4, 5]. DBS in animal models is another method allowing for the modulation of brain nuclei and circuits, albeit with lack of specificity and an underlying mechanistic unclarity [6–9]. Allowing for a more cell-specific intervention of the motor circuit are now optogenetic and chemogenetic tools [10]. For optogenetics, a light-sensitive ion channel is expressed in a specific cell population via targeted injection of a viral vector [10–12]. Light pulses are then applied via an implanted optical fiber, allowing for neuronal depolarization or hyperpolarization of cells. Chemogenetic tools modulate distinct cell populations via engineered receptors or channels, which are selective for specific ligands [13]. This allows for reversible modulation of the cells expressing these receptors or channels. Viral vectors are used in order to express the receptors or channels in the confined neural population. Cell population-specific neuromodulation techniques have not yet been used widely in dystonia basic research. In contrast, for Parkinson's disease, an optogenetic approach was recently applied to specifically excite parvalbumin-expressing neurons and inhibit lim-homeobox-6–expressing neurons of the globus pallidus externus (GPe) simultaneously in a 6-hydroxydopamine (6-OHDA) mouse model [14]. The authors were able to show a long-lasting effect of stimulation even after DBS was turned off, which could not be seen with conventional DBS. This publication highlights how population-specific neuromodulation can advance our understanding of the circuit defects underlying movement disorders and advance DBS to more targeted stimulation potentially allowing for a better response and less side effects.

Within this review, we will discuss neuromodulation approaches in animal models for dystonia and in some cases for levodopa-induced dyskinesias. It can be assumed that dystonia and levodopa-induced dyskinesias share some common pathomechanisms [15, 16]. This review only touches upon methods of pharmacological modulation, however, does not discuss them at length. Many studies have been performed studying the response of brain regions or cell populations to different drugs [17–19]. We would like to refer to other comprehensive reviews discussing the contributions of these studies [20, 21].

Lesioning of brain regions in dystonia rodent models

Multiple studies have been able to show that dystonia can be elicited in wildtype, non-predisposed animals via lesioning of different brain regions. In wildtype rodents, the injection of 3-nitropropionic acid causes striatal damage and the emergence of a dystonia-like phenotype [22, 23]. Mechanistically, 3-nitropropionic acid primarily leads to a loss of GABAergic striatal projection neurons [24]. In previously healthy baboons, the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces transient dystonia-like manifestations [25, 26]. MPTP induces apoptosis in dopaminergic neurons within the substantia nigra. Development of transient dystonia in this model has been reported to be associated with a striatal decrease of dopamine and a transient reduction in D2 dopamine receptors, however, the pathomechanisms have not been clearly elucidated. It has been speculated that abnormal cortico-striatal plasticity might underlie the phenomenon [27]. Both the targeted, pharmacological inactivation as well as activation of the GPi with a GABA agonist or antagonist, respectively, caused dystonic movements of the upper limbs in wildtype monkeys [28, 29]. Contrasting findings such as these have led to the hypothesis that the firing pattern of the GPi might be more relevant in dystonia pathophysiology than the firing rate [16, 30]. Studies in wildtype animals have also identified the cerebellum as a potentially important player in dystonia development. Stimulation of the cerebellum of wildtype mice using injections of the excitatory glutamate agonist kainate led to a dystonia-like phenotype [5, 31, 32]. A hypothesized explanation for this phenomenon is an aberrant firing of Purkinje cells, as dystonia was notably absent in mice without these cells when exposed to kainate [31]. Beyond basal ganglia and cerebellum, pharmacological lesioning of the PPN in wildtype mice triggered dystonia-like behavior in a tail suspension test [33]. In case of bilateral lesions, decreased *c-FOS* activity, a marker for neuronal activity, was found in the dorsolateral striatum, in the GPi, the STN and the substantia nigra. The PPN is an important interface between the basal ganglia and the cerebellum. Altogether, these studies in non-mutated animal models have highlighted the role of the basal ganglia, the cerebellum and the PPN in dystonia development.

Further underlining these findings are studies in tottering mice, which have a mutation in the *Cacna1a* gene impairing calcium channel activity and resulting in paroxysmal episodes of stress-induced dystonia-like movements. An aggravation of the dystonia-like phenotype was achieved in tottering mice through lesioning of the striatum by administration of substances such as 6-OHDA or quinolinic acid [5]. It is hypothesized that the manifestation of dystonia in this model predominantly originates from a secondary increased expression of calcium channels within the cerebellum. Indeed, removal of the cerebellum in these mice led to a complete remittance of dystonic attacks [5]. Cerebellectomies were also effective in eliminating dystonic attacks in genetically dystonic rats with a suspected deficiency in the protein caytaxin, which was proposed to be imperative for cerebellar cortex development and function [34, 35]. The cerebellum was also found to underlie development

of dystonia in a pharmacological mouse model for DYT/PARK-ATP1A3 dystonia [36]. Blocking the α3-subunit of the sodium-potassium channel with ouabain in the cerebellum led to the development of generalized dystonia-like movements in wildtype mice. The sodium pump dysfunction was shown to be associated with erratic cerebellar activity. In this model, electrical lesions bilaterally ablating the centrolateral thalamus were employed, thus targeting the di-synaptic connection between the cerebellum and the basal ganglia. These lesions yielded a significant reduction in dystonia-like movements. Neurotoxic silencing of the centrolateral thalamus achieved a similar result in the same DYT/PARK-ATP1A3 mouse model, corroborating the findings [37]. Interestingly, bilateral silencing of the motor cortex using the sodium channel blocker tetrodotoxin reduced dystonia only slightly, leading the authors to conclude that the role of the cortex is less essential in DYT/PARK-ATP1A3 pathophysiology than that of the cerebellum [36].

Overall, lesioning of various brain regions has allowed for important strides in understanding whether specific brain structures influence the development of dystonia. Focusing primarily on the basal ganglia and the cerebellum, these lesions have provided insights on the overall importance of these structures in the dystonic network. However, it is important to note that this approach, although valuable, is somewhat imprecise in terms of anatomy and lacks specificity for distinct cell populations. Moreover, it often results in unwanted additional symptoms, such as hypokinesia in case of nigrostriatal damage induced by MPTP or 6-OHDA.

Neuromodulation with DBS in dystonia rodent models

Exploring various animal models of dystonia, researchers have employed DBS targeting the entopeduncular nucleus (EP), which serves as the rodent equivalent of the human GPi. The classical DBS approaches in rodent dystonia models have undergone extensive scrutiny in previous reviews [7, 8]. One study utilized a genetically susceptible DYT-TOR1A rat model and induced dystonia-like movements in the hindlimbs through a peripheral nerve injury [38]. The underlying hypothesis here is the second-hit hypothesis, suggesting the necessity of extragenetic factors to trigger the development of dystonic symptoms in a mutation carrier for dystonia [39, 40]. The authors demonstrated that 3 weeks of high-frequency stimulation effectively alleviated the dystonia-like phenotype and reduced the pathologically enhanced theta power observed in the EP of dystonic animals. An abundance of data has been gathered from DBS of the EP in the dt^{sz} mutant hamster [41–46]. Summarizing the key discoveries, a study revealed circuit plasticity effects following 10 h of unilateral EP-DBS. Both dt^{sz} mutant hamsters and control animals exhibited increased *c-Fos* expression in the ipsilateral striatum, while dt^{sz} hamsters showed reduced *c-Fos* expression in the thalamus, distinguishing them from the control group [42]. *In vitro* measurement of field excitatory postsynaptic potentials from the striatum immediately after 3 h-long high-frequency stimulation in the dt^{sz} mutant hamster revealed effects on cortico-striatal synaptic communication and an increase of the inhibitory tone in the striatal tissue of dystonic animals when compared to non-dystonic hamsters [44].

A study reporting on DBS of the deep cerebellar nuclei and the centrolateral thalamus in dystonia focused on a mouse model targeting the olivocerebellar pathway [47]. A genetic approach was used to specifically silence glutamatergic signaling at the olivocerebellar synapses. The authors conditionally deleted the vesicular glutamate transporter 2 from *Ptf1a*-expressing excitatory neurons in the inferior olive, thus blocking the fast neuronal communication from climbing fibers to Purkinje cells. Mice with this targeted genetic silencing exhibited a strong dystonia-like phenotype. The loss of climbing fiber neurotransmission was found to cause highly irregular firing of downstream neurons in the cerebellar nuclei. Interestingly, dystonia was alleviated by either silencing the cerebellar nuclei output with lidocaine or by DBS of the interposed nuclei of the cerebellum as well as by DBS of the centrolateral thalamus.

In summary, DBS studies in dystonia animal models have been used to validate the model used, to understand the acute or chronic effects of DBS on different networks and to explore new DBS targets. However, the lack of understanding of the mechanisms of actions of DBS as well as the simultaneous stimulation of more than one cell population can make it difficult to draw conclusions about the underlying neuronal dysfunction. Furthermore, DBS is primarily applied in already symptomatic rodent models, where the network effect of stimulation as well as the effect on the phenotype can be evaluated. However, the most widely used animal model for DBS studies in dystonia is the dystonic hamster dt^{sz}, which is not without its limitations, featuring only transient dystonia and an unidentified genetic mutation [48].

Cell-specific neuromodulation in dystonia rodent models

Only a handful of studies have looked at the cell populations of the striatum in dystonia using optogenetics (Figure 1). Using DYT-TOR1A knock-in mice expressing channelrhodopsin-2 in cholinergic interneurons, Richter et al. applied bilateral optogenetic stimulation to the dorsolateral striatum with the aim of provoking a dystonia-like phenotype [49]. The striatal cholinergic system has long been suspected to play a major role in dystonia. Aside from anticholinergic drugs effectively alleviating symptoms in some dystonia patients, DYT-TOR1A mouse models have shown an abnormal excitation of cholinergic interneurons and increased striatal acetylcholine [50]. By

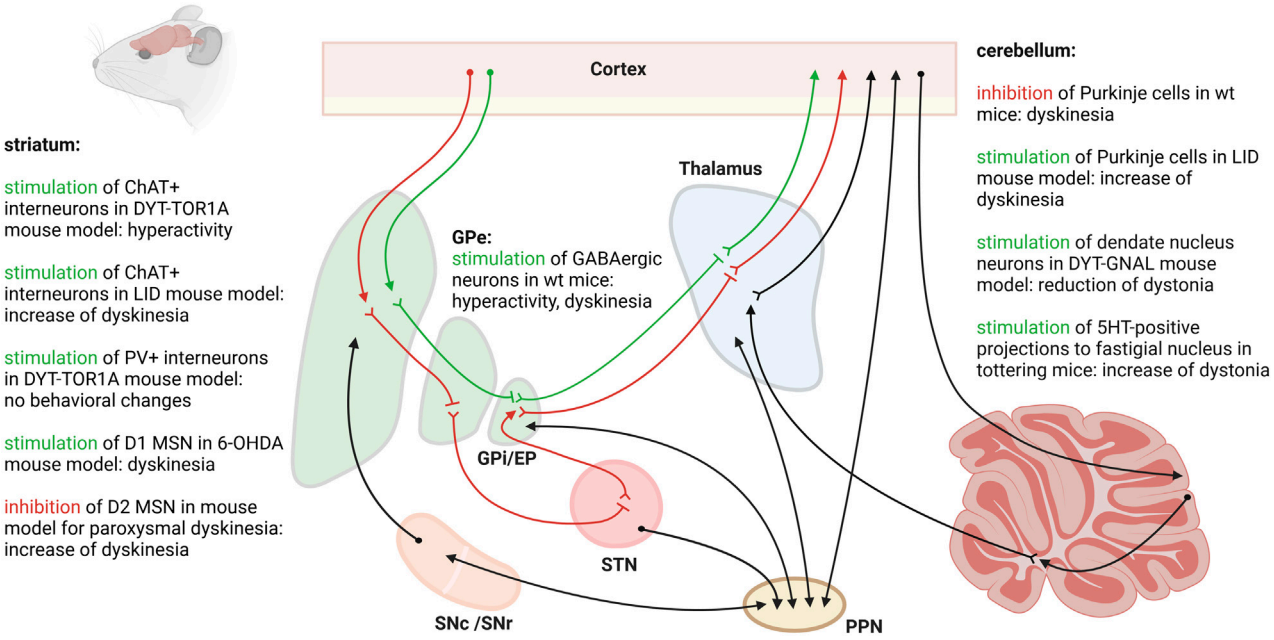

FIGURE 1
Different cell populations and regions of the central motor circuit have been targeted with optogenetics in rodent models for dystonia or levodopa-induced dyskinesias (LID). The figure was created with biorender.com.

optogenetically stimulating the striatal cholinergic interneurons, the authors aimed to increase the activity of these neurons as well as the acetylcholine levels, thus studying whether this could directly cause dystonia in genetically-predisposed mice. Burst firing with increased release of acetylcholine was optogenetically induced. DYT-TOR1A knock-in mice responded with transient hyperactivity, while wildtype animals did not. On the other hand, in a transgenic mouse model expressing cre-recombinase under the control of the choline acetyltransferase promoter (ChAT-Cre), channelrhodopsin-2 was selectively expressed in cholinergic neurons in order to study the contributions of the cholinergic system to levodopa-induced dyskinesias [51]. Intriguingly, following a unilateral 6-OHDA lesion, the researchers demonstrated that optical pulses targeted at the dorsolateral striatum increased the frequency of levodopa-induced dyskinesias. These observations underline the contribution of cholinergic interneurons to the development of abnormal movement output, but reveal that a disturbance of this population alone is insufficient for dystonia development. Another group of striatal interneurons presumed to play an important role in hyperkinetic movement disorders are parvalbumin-positive, fast-spiking interneurons, which exert a strong feedforward inhibition on medium spiny neurons. In the dt^{sz} hamster model of paroxysmal dystonia, a delayed maturation of parvalbumin-positive interneurons coincides with an age-dependent development of a dystonia-like phenotype and abnormal basal ganglia output [52]. However, although selectively inhibiting striatal parvalbumin-positive interneurons led to a hyperactivation of cholinergic interneurons in DYT-TOR1A knock-in mice compared to wildtype controls, this manipulation failed to induce any behavioral changes, particularly dystonia [53]. Interestingly, optogenetic activation of the striatal D1 medium spiny neurons triggered dyskinesias in 6-OHDA mice [54]. Conversely, the chemogenetic inhibition of D2 medium spiny neurons triggered dyskinesia attacks in a mouse model for paroxysmal non-kinesigenic dyskinesia [55]. So far, the direct and indirect pathways have not been optogenetically targeted in rodent models for dystonia.

Optogenetic stimulation of the right GPe with targeted expression of ChR2 in the GABAergic neurons led to hyperactivity and dyskinesias with torsion of the neck and of the left forelimb in mice [56]. The authors found that stimulation of the GABAergic neurons of the GPe reduced *c-Fos* expression in the EP and increased *c-Fos* expression in the motor cortex and the striatum.

Optogenetic stimulation of the cerebellar cortex in a mouse model expressing ChR2 in molecular layer interneurons was used to locally suppress the activity of Purkinje cells. This inhibition of Purkinje cell activity was shown to induce involuntary movements in mice [57]. Using single-unit extracellular activity recordings, the authors determined that suppression of

Purkinje cell activity leads to increased firing, i.e., a disinhibition, of the downstream neurons of the deep cerebellar nuclei of the cerebellum. Conversely, chronic optogenetic stimulation at theta frequency of Purkinje cells expressing ChR2-YFP led to a significant improvement of dyskinesias in a mouse model for levodopa-induced dyskinesias [58]. The effect even outlasted the end of cerebellar stimulation by 2 weeks. The authors found that chronic Purkinje cell stimulation specifically influenced the aberrant firing patterns recorded in the interposed nuclei of the cerebellum, in the motor cortex and in the parafascicular thalamus in mice with levodopa-induced dyskinesias. Specific chemogenetic inactivation of projections from the deep cerebellar nuclei to the parafascicular thalamus prevented the beneficial effect from chronic Purkinje cell stimulation highlighting the importance of the cerebello-thalamic pathway in hyperkinetic movement disorders. Indeed, optogenetic activation of the parafascicular thalamus induced abnormal involuntary movements in wildtype rats [59].

The three nuclei making up the deep cerebellar nuclei are the fastigial nucleus, the interposed nucleus and the dentate nucleus. The neurons of the dentate nucleus were targeted with optogenetic stimulation in an asymptomatic and a symptomatic state in a DYT-GNAL knock-out mouse model [60]. In their asymptomatic state, DYT-GNAL mice revealed increased excitability of the cerebello-thalamic pathway upon low-frequency stimulation of the dentate nucleus compared to wildtype controls. Dystonia-like movements were transiently induced by a nonselective cholinergic agonist, which led to a long-lasting further increase in cerebello-thalamic excitability when stimulation was applied 2 days post drug exposure in DYT-GNAL mice. Theta-burst stimulations of the dentate nucleus were able to reduce cerebello-thalamic excitability and the dystonia-like phenotype in symptomatic DYT-GNAL mice. In tottering mice with stress-induced attacks of dystonia, optogenetic stimulation of the serotonin (5HT)-positive dorse raphei nuclei inputs to the fastigial nucleus led to an increase in the frequency of dystonic attacks [61]. Single-unit recordings revealed an enhanced firing rate of the neurons of the fastigial nucleus upon photostimulation. On the other hand, bilateral photoinhibition of the 5HT-positive inputs to the fastigial nucleus reduced dystonic attacks. Bilateral knockdown of 5HT-2A receptor genes in the fastigial nucleus using short hairpin RNA reduced the frequency of dystonia attacks. The authors conclude that stress increases the excitability of the deep cerebellar nuclei via 5HT, which was directly correlated with the development of transient dystonia.

Taken together, cell population-targeted studies have led to compelling findings such as the involvement of the cerebello-thalamo-striatal pathway in dystonia development and the 5-HT positive projections to the deep cerebellar nuclei as possible targets for DBS [60, 61]. The challenge in targeting single cell populations in dystonia might be the final interpretation of the findings, since dystonia is assumed to be a network disorder with a possible malfunction of multiple structures and multiple cell populations [62].

Discussion

The advent of cell-specific stimulation and inhibition techniques holds great promise in unraveling the intricate involvement of specific neuron populations in dystonia. These techniques hold the potential to pave the way for the exploration of optimized stimulation techniques for DBS in human patients. As exemplified by the study of Spix et al. for Parkinson's disease, showing advantages of a cell-population specific stimulation in the GPe compared to conventional DBS, the answer to better stimulation paradigms might not necessarily be a different target, but a more specific stimulation technique [14]. On the other hand, in the field of dystonia, there are first encouraging studies exploring new targets such as the optogenetic theta-burst stimulation of dentate nucleus neurons in a symptomatic mouse model for DYT-GNAL [64]. DYT-GNAL is a form of monogenic dystonia known to have a very variable response to GPi DBS in humans [63]. Of course, both optogenetic- and chemogenetic-mediated neuromodulation do have limitations, such as, for example, the need for an invasive application of a viral vector into the target brain structure. Additionally, interpreting the findings in animal studies in dystonia remains an overall challenge due to the difficulties in clearly defining a dystonic phenotype. The scientific community still has not defined a common set of parameters for dystonia manifestation in animal models [4]. However, embracing these advancements is key to moving our understanding and treatment of dystonia forward. Aside from the insights cell specific neuromodulation techniques may give into dystonia pathophysiology in animal models, it has even been proposed that these techniques may eventually be applicable in patients [64, 65].

Author contributions

Conceptualization: CI and LR. Writing of the original draft: LR. Review, editing and supervision: CI. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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