Reversal of motor-skill transfer impairment by trihexyphenidyl and reduction of dorsolateral striatal cholinergic interneurons in Dyt1 ΔGAG knock-in mice

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Abstract

DYT-TOR1A or DYT1 early-onset generalized dystonia is an inherited movement disorder characterized by sustained muscle contractions causing twisting, repetitive movements, or abnormal postures. The majority of the DYT1 dystonia patients have a trinucleotide GAG deletion in DYT1/TOR1A. Trihexyphenidyl (THP), an antagonist for excitatory muscarinic acetylcholine receptor M1, is commonly used to treat dystonia. Dyt1 heterozygous ΔGAG knock-in (KI) mice, which have the corresponding mutation, exhibit impaired motor-skill transfer. Here, the effect of THP injection during the treadmill training period on the motor-skill transfer to the accelerated rotarod performance was examined. THP treatment reversed the motor-skill transfer impairment in Dyt1 KI mice. Immunohistochemistry showed that Dyt1 KI mice had a significant reduction of the dorsolateral striatal cholinergic interneurons. In contrast, Western blot analysis showed no significant alteration in the expression levels of the striatal enzymes and transporters involved in the acetylcholine metabolism. The results suggest a functional alteration of the cholinergic system underlying the impairment of motor-skill transfer and the pathogenesis of DYT1 dystonia. Training with THP in a motor task may improve another motor skill performance in DYT1 dystonia.

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1. Introduction

Motor-skill learning is broadly viewed to include steps that reflect encoding or consolidation of the memory so that the entire process can be thought to consist of the fast, slow, consolidation, re-consolidation, automatization, and retention phases (Luft and Buitrago, 2005). The phases of motor-skill learning can be divided into two discrete stages, with the initial acquisition stage marked by a rapid improvement in performance, which is then followed by a phase when improvement is more gradual. The efficiency of motor-skill learning is dependent on such factors as the disruption caused by interference and facilitation of sleep during which memory consolidation occurs (Brashers-Krug et al., 1996). Another factor that contributes to the facilitation of motor learning is the ability to transfer a skill acquired during the learning of one task onto the process of more efficiently acquiring a new yet similar task (Kraakauer et al., 2005; Seidler, 2004; Zanone and Kelso, 1997).

DYT1 early-onset generalized torsion dystonia [DYT-TOR1A dystonia; dystonia 1; Online Mendelian Inheritance in Man (OMIM) identifier #128100] is an inherited movement disorder characterized by sustained muscle contractions causing twisting, repetitive movements, or abnormal postures. The majority of the DYT1 dystonia patients have a trinucleotide GAG deletion in DYT1/TOR1A. Trihexyphenidyl (THP), an antagonist for excitatory muscarinic acetylcholine receptor M1, is commonly used to treat dystonia. Dyt1 heterozygous ΔGAG knock-in mice; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase; KO, knockout; LTD, long-term depression; n.s., not significant; PB, phosphate buffer; PBS, phosphate-buffered saline; PET, positron emission tomography; THP, trihexyphenidyl; TrkA, tropomyosin receptor kinase A; VACHT, vesicular acetylcholine transporter; WT, wild-type.

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Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; BSA, bovine serum albumin; ChAT, choline acetyltransferase; ChI, cholinergic interneuron; ChT, choline transporter; CI, confidence interval; DAB, 3,3’-diaminobenzidine; DF, degrees of freedom; Dyt1 KI mice, Dyt1 ΔGAG heterozygous knock-in mice; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase; KO, knockout; LTD, long-term depression; n.s., not significant; PB, phosphate buffer; PBS, phosphate-buffered saline; PET, positron emission tomography; THP, trihexyphenidyl; TrkA, tropomyosin receptor kinase A; VACHT, vesicular acetylcholine transporter; WT, wild-type.
abnormal postures, resulting in motor control and coordination deficits (Albanese et al., 2013; Breakefield et al., 2008). Most patients have a heterozygous in-frame deletion of trinucleotide (ΔGAG) in DYT1/TOR1A, coding for torsinA (Ozelius et al., 1997). About one in three with the ΔGAG mutation develops dystonic symptoms. Non-symptomatic carriers of the DYT1 gene mutation have an impairment in sequence learning (Carbon et al., 2011; Ghiardi et al., 2003). Anticholinergics are a major category of medications used for generalized dystonia (Fahn, 1983; Jankovic, 2006), suggesting a functional alteration in the cholinergic system. Among them, trihexyphenidyl (THP) is an antagonist for excitatory muscarinic acetylcholine receptor M1.

Dyt1 ΔGAG heterozygous knock-in (KI) mice have the corresponding trinucleotide deletion mutation in the endogenous Dyt1/Tor1a. Dyt1 KI mice exhibit the long-term depression (LTD) deficits in the corticostriatal pathway (Dang et al., 2012), sustained contraction and co-contraction of agonist and antagonist muscles of hind limbs (DeAndrade et al., 2016), and motor deficits of the hind limbs in the beam-walking test (Dang et al., 2005). THP ameliorates these deficits. Although the Dyt1 KI mice do not show overt dystonic symptoms, motor deficits in the beam-walking test have been reproduced in distinct batches of this line (Cao et al., 2010; Yokoi et al., 2012) and another KI mouse line (Liu et al., 2021; Song et al., 2012). Similar motor deficits were also reported in other genetic mouse models for DYT1 myoclonus-dystonia (Li et al., 2021; Xiao et al., 2017; Yokoi et al., 2006) and DYT12 rapid-onset dystonia with parkinsonism (DeAndrade et al., 2011; Isaksen et al., 2017; Sugimoto et al., 2014). Motor deficits were also reported in other genetic animal models as previously reviewed (Imbriani et al., 2020; Oleas et al., 2015, 2013; Richter and Richter, 2014). Moreover, Dyt1 KI mice exhibit impaired motor-skill transfer (Yokoi et al., 2015b). In this report, a novel skill transfer task was developed to examine motor-skill learning in Dyt1 KI mice. The motor task involved forcing mice to run on a treadmill with increasing speeds over a training period of 2 weeks. After the training period, they were tested on an accelerated rotarod. WT mice trained on the treadmill improved their rotarod performance in comparison to untrained WT mice with the treadmill belt turned off. On the other hand, treadmill training in Dyt1 KI mice did not affect the overall latency to fall in the rotarod test. This report suggests that trained WT mice had enhanced learning abilities due to their previous training on the treadmill, whereas Dyt1 KI mice were unable to transfer their skills. Although THP ameliorates motor coordination deficits in Dyt1 KI mice (Dang et al., 2012), the effect of THP on motor-skill transfer is not clear.

Acetylcholine (ACh) plays an essential role in striatal function (Eskow Jaanaraja et al., 2015; Lim et al., 2014; Pisani et al., 2007). Choline acetyltransferase (ChAT) catalyzes ACh synthesis from the choline and acetyl group of acetyl-CoA in the cholinergic interneurons (ChIs) (Prado et al., 2013). ACh is transported into the presynaptic vesicle via vesicular acetylcholine transporter (VACHT). The striatal ChIs show spontaneous firing and release ACh. The released ACh binds M1-type muscarinic acetylcholine receptors on the striatal medium spiny neurons and induces a metabotropic cascade to depolarize the membrane potentials (Delmas and Brown, 2005). The mRNAs for muscarinic receptors M1 and M4 are expressed at high levels in the striatal medium spiny neurons (Yan et al., 2001). The activation of dorsomedial striatal M1-type muscarinic cholinergic receptors, but not M4-type muscarinic cholinergic receptors, facilitates the flexible shifting of response patterns by maintaining or learning a new choice pattern (McCool et al., 2008). ACh also inhibits the ChL firing through M2-type inhibitors, maintaining acetylcholine receptors on the Chls as a feedback regulation mechanism. ACh is degraded to choline and acetate by acetylcholinesterase (ACHE). The choline is transported into the Chls by choline transporter (ChT) and recycled to synthesize ACh.

Here, the effect of THP on the impaired motor-skill transfer in Dyt1 KI mice was measured. Furthermore, the striatal cholinergic system in Dyt1 KI mice was characterized by anatomical and biochemical approaches.

2. Experimental procedures

2.1. Animals

All experiments were carried out in compliance with the USPHS Guide for Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committees of the University of Alabama at Birmingham and the University of Florida. Dyt1 KI mice and their littermate wild-type (WT) mice were prepared and genotyped by PCR as described earlier (Dang et al., 2005; Yokoi et al., 2009). Since male Dyt1 KI mice exhibited significant motor deficits in the previous studies, only male mice were used for the present experiments. A total of 119 adult male WT (n = 60) and Dyt1 KI (n = 59) littermates was used [mean, 172 days of age; 95% confidence interval (CI), 159–185]. Mice were housed under a 12 hr light and 12 hr dark cycle with ad libitum access to food and water. The experiments were performed by investigators blind to the treatments and the genotypes.

2.2. THP injection and motor-skill transfer test

Thirty-nine mice were used for a saline-injected control experiment, i.e., 10 WT mice and 10 Dyt1 KI mice were used for no training, and 10 WT mice and 9 Dyt1 KI mice were used for treadmill training. On the other hand, 40 mice were used to examine the effect of THP on the motor-skill transfer, i.e., 10 WT mice and 10 Dyt1 KI mice were used for no training, and 10 WT mice and 10 Dyt1 KI mice were used for treadmill training. Saline or THP (DL-Trihexyphenidyl hydrochloride; Sigma Aldrich, T1516; 0.8 mg/kg in saline) solution was injected intraperitoneally two hours before training onset every other day (total seven injections).

The training group mice were trained for two weeks on the treadmill with daily training on weekdays only. The treadmill apparatus (Weso1) for humans was converted to one for mice with an eight-lane (7 × 20 cm/lane) rectangular wood box divider (Supplementary Fig. 1) suspended 1 cm above the running belt as previously described (Yokoi et al., 2015b). Acrylic beads strung from a thin wire were placed along each lane’s back wall to serve as a non-noxious stimulus for running. The treadmill was started at a running speed of approximately 13 m/min (0.5 mph) for 5 min each day. When more than 90% of the mice could run comfortably at that speed, it was increased by approximately 2.5 m/min (0.1 mph) to a maximum rate of about 18.5 m/min (0.7 mph). The mouse groups with no training were placed on the treadmill for 5 min each day, but the treadmill turned off.

After rest for two days, all mice were tested on an accelerating rotarod (Ugo Basile). It was started at 4 rpm with acceleration at a rate of 0.2 rpm/sec to a final speed of 28 rpm and a cutoff of 2 min as previously described (DeAndrade et al., 2011). Mice were tested with three trials each day for two consecutive days. The latency (seconds; s) to fall off the rotarod was measured for each mouse. Comparisons were made between WT or Dyt1 KI mice with and without treadmill training and in saline- or THP-injected groups.

2.3. Immunohistochemistry

Frozen brain sections were prepared as described earlier to count the striatal Chl numbers (Yokoi et al., 2020b). The mice were anesthetized and perfused with ice-cold 0.1 M phosphate-buffered saline (pH 7.4; PBS) followed by 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4; PB). The brains were dissected and incubated in 4% paraformaldehyde in 0.1 M phosphate buffer at 4 °C overnight. The brains were then incubated in 30% sucrose in 0.1 M PB at 4 °C overnight until the brains sank. The brains were frozen using dry-ice powder and cut into 40 µm thick coronal sections with a Histostile 2000 sliding microtome (Reichert-Jung). The sections were obtained from 6 Dyt1 KI and 8 WT littermates. Every sixth section was stained with goat anti-ChAT antibody (EMD Millipore, AB144P; 1:100 dilution) with
3. Results

3.1. Reversal of motor-skill transfer impairment in Dyt1 KI mice by THP

Dyt1 KI mice show impaired motor-skill transfer (Yokoi et al., 2015b). THP is an antagonist of M1-type muscarinic acetylcholine receptors and is commonly used for dystonia patients. Here, the effect of THP on the impaired motor-skill transfer was examined by injecting either THP or saline every other day during the treadmill training period (Fig. 1A). The training group was forced to run on the treadmill for 5 min each weekday for 2 weeks. The No-training group was put on the static treadmill belt. After 2 days of resting, the motor-skill transfer performance was assayed on accelerated rotarod 3 trials per day for two days.

In the saline-injected group (Fig. 1B), WT mice with treadmill training stayed about 47% longer on the rotarod than WT mice without the training (mean ± standard errors $\mu$; No training: $36.2 ± 4.3$; $n = 10$; Training: $53.3 ± 6.4$; $n = 10$; $Z = 2.51; p = 0.012$). On the other hand, Dyt1 KI mice did not show enhanced performance on rotarod with treadmill training (No training: $54.8 ± 5.2$; $n = 10$; Training: $46.5 ± 5.2$; $n = 9$; $Z = -1.12; p = 0.26$). The results were the same as previously reported without any injection (Yokoi et al., 2015b), suggesting that the vehicle injections do not affect the motor-skill transfer performance in both genotypes. On the other hand, the latency to fall in the accelerated rotarod test without training was not statistically different between WT and Dyt1 KI mice in the saline-injected group ($Z = 1.62; p = 0.11$).

In the THP-injected group (Fig. 1C), WT mice with treadmill training stayed 55% longer on the accelerated rotarod than WT mice without treadmill training (No training: $44.0 ± 4.3$; $n = 10$; Training: $68.3 ± 5.4$; $n = 10$; $Z = 3.47; p = 0.0005$). This result reproduced the corresponding performance in the saline-injected WT mice, suggesting that THP did not affect the motor-skill transfer performance in WT mice. In contrast to the saline-injected Dyt1 KI group, THP-injected Dyt1 KI mice achieved 36% longer latency in accelerated performance after treadmill training than THP-injected Dyt1 KI mice without treadmill training (No training: $53.0 ± 6.1$; $n = 10$; Training: $72.1 ± 6.9$; $n = 10$; $Z = 2.02; p = 0.044$). The results suggest that muscarinic acetylcholine receptor blockade during the treadmill training affected motor learning acquisition and restored the impaired motor-skill transfer in Dyt1 KI mice.

3.2. Reduction of the dorsolateral striatal ChI density in Dyt1 KI mice

To dissect the mechanism of THP on motor skill transfer, we counted the number of the striatal ChIs in the coronal brain sections by ChAT immunohistochemistry in Dyt1 KI mice (Fig. 2A, B). Since the ChIs are not evenly distributed in the striatum, the ChAT-positive neuron density was analyzed in each quadrant area (Pappas et al., 2018) of the striatum. The ChAT-positive neuron density in each quadrant area was obtained from WT (183 areas/8 mice) and Dyt1 KI littermates (142 areas/6 mice). Dyt1 KI mice showed a significant reduction of ChAT-positive neuron density in the dorsolateral striatum (ChI density (ChI numbers per mm²) ± standard errors; WT, $21.4 ± 3.6$; Dyt1 KI, $11.0 ± 4.3$; $z(DF; 77) = -2.02; p = 0.044$; Fig. 2C, DL). On the other hand, there was no significant difference in the ChAT-positive neuron densities between WT and Dyt1 KI mice in the dorsomedial [WT, $30.3 ± 5.1$; Dyt1 KI, $22.5 ± 5.1$; $z(76) = -1.14; p = 0.25$; Fig. 2C, DM] or the ventrolateral striatum [WT, $21.2 ± 5.4$; Dyt1 KI, $13.5 ± 4.8$; $z(77) = -1.43; p = 0.15$; Fig. 2C, VL]. There were trends of reduction of the ChAT-positive neuron density in the ventromedial striatum [WT, $25.0 ± 4.2$; Dyt1 KI, $16.2 ± 2.7$; $z(76) = -1.68; p = 0.093$; Fig. 2C, VM], and when all quadrants were analyzed together [WT, $27.9 ± 4.7$; Dyt1 KI, $19.2 ± 3.8$; $z(320) = -1.73; p = 0.084$; Fig. 2C, Str]. On the other hand, there was no significant difference in the measured area sizes of the quadrants between WT and Dyt1 KI mice (mean ± standard errors (mm²); DL, WT, $0.37 ± 0.01$; Dyt1 KI, $0.35 ± 0.02$; t(11) = −
1.14, p = 0.28; DM, WT, 0.50 ± 0.01; Dyt1 KI, 0.46 ± 0.02; t(11) = −0.61, p = 0.55; VL, WT, 0.60 ± 0.02; Dyt1 KI, 0.58 ± 0.02; t(11) = −0.20, p = 0.84; VM, WT, 0.44 ± 0.02; Dyt1 KI, 0.46 ± 0.02; t(11) = 0.62, p = 0.54; averaged quadrant size, WT, 0.48 ± 0.01; Dyt1 KI, 0.46 ± 0.01; t(11) = −0.49, p = 0.63]. The results suggest a reduction of the striatal ChI density in Dyt1 KI mice, at least in the dorsolateral striatum.

3.3. No significant alteration of the striatal cholinergic enzyme or transporter levels in Dyt1 KI mice

The striatal ACh metabolic enzyme levels were further analyzed by Western blot. The Dyt1 KI mice did not show significant differences in the striatal ChAT [normalized levels ± standard errors; WT: 100 ± 5.5%; Dyt1 KI: 97.0 ± 4.2%; n = 6 each; t(DF: 9) = −0.24, p = 0.81; Fig. 3A], VACht [WT: 100 ± 5.7%; Dyt1 KI: 108.3 ± 6.5%; n = 7 each; t(11) = −0.80, p = 0.44; Fig. 3B], ChT (75 kDa; WT: 100 ± 3.7%; Dyt1 KI: 97.8 ± 2.7%; n = 7 each; t(11) = 0.07, p = 0.95; Fig. 3C).
indicate that complex changes in the striatal cholinergic system might underlie the impaired motor-skill transfer and the pathogenesis of DYT1 dystonia. A limitation in the present study is no direct evidence showing that the reduction of dorsolateral striatal cholinergic interneurons contributes to the impaired motor skill transfer in Dyt1 KI mice. The results shown in Figs. 1 and 2 suggest functional alterations of the cholinergic system or its relating pathways contribute to the impaired motor skill transfer in Dyt1 KI mice. On the other hand, Fig. 3 suggests no significant alteration in the striatal ACh metabolism. One possible mechanism is that the remaining striatal ChIs increased their ACh metabolism to compensate for the low number of ChIs. Therefore the ACh metabolism per ChI may be relatively increased, and this may produce abnormal, hyperactive local ChI circuits.

While the treadmill and rotarod are two separate tests, they are similar in forced running and adaptation to the speed. However, the rotarod has an added challenge of keeping balance on the rotating rod and is different from treadmill running on a flat moving belt. From the neuronal activity perspective, this skill transfer could represent prior priming of the neuronal circuitry involved in learning to facilitate further learning. The present results show that THP injection during the treadmill training period reverses the impaired motor-skill transfer in Dyt1 KI mice, suggesting that THP affects the acquisition phase of motor-skill learning. THP ameliorates the corticostriatal LTD, motor deficits, and abnormal muscle contractions in Dyt1 KI mice (Dang et al., 2012; DeAndrade et al., 2016). Consistent with these findings, striatal levels of ACh are elevated in KI mice (Scarduzio et al., 2017). Moreover, a recent paper suggests that THP stimulates the striatal ChI and increases ACh release. The released ACh stimulates nicotinic receptors on the dopaminergic neurons and increases dopamine release (Downs et al., 2019). One possible cellular mechanism is that THP restores corticostriatal LTD deficits during the treadmill training period and enhances motor-skill learning acquisition.

Most studies suggest that there is no overt neurodegeneration in DYT1 dystonia patients (Breakefield et al., 2008). Consistently, there is no overt neurodegeneration in Dyt1 KI mice (Dang et al., 2005). On the other hand, there is a subtle morphological alteration in the cerebellar Purkinje cells in Dyt1 KI mice (Zhang et al., 2011) and another KI mouse line (Song et al., 2014). The amygdala’s central nucleus’ size is significantly reduced in the KI mice (Yokoi et al., 2009). Moreover, another KI
mouse line of torsinA shows mostly normal density of striatal ChI except an increased ChI density in the dorsolateral striatum (Song et al., 2013). In contrast to the other KI mice, the present study showed a significant reduction of the dorsolateral striatal ChIs in Dyt1 KI mice, consistent with the reduced trkA expression in postmortem tissues from older DYT1 dystonia patients (Pappas et al., 2015). Moreover, a recent study using positron emission tomography (PET) suggests a decrease in VACht expression in the posterior putamen and caudate nucleus of young DYT1 dystonia patients (Mazere et al., 2021). On the other hand, Dyt1 KI mice showed normal levels of striatal cholinergic enzymes and TrkA. Since the detected protein levels from the total spiritual tissues does not reflect the local cholinergic metabolism in each quadrant, the normal Western blot data is mostly consistent with no significant alteration of total ChI density in the combined striatal areas. Moreover, the surviving ChI neurons may upregulate the expression levels to compensate for the partial loss of striatal ChIs. Overall, the results suggest that the anatomical and biochemical properties of the striatal ChIs in Dyt1 KI mice was mostly normal except for the reduction of ChIs in the dorsolateral region. Dorsolateral striatum is known to engage motor skill learning (Vin et al., 2009). The functional alteration of the local striatal cholinergic system may contribute to impairment of the motor skill transfer.

In contrast to the lethality in the complete torsinA loss mouse models (Goodchild et al., 2005; Yokoi et al., 2008), the partial loss of torsinA function models, such as Dyt1 knockdown (Dang et al., 2006) and Dyt1 heterozygous KO mice (Yokoi et al., 2015a), show motor deficits in the beam-walking test. The striatum-specific Dyt1 conditional knockout mice also show motor deficits (Yokoi et al., 2011). Moreover, the cerebral cortex-specific Dyt1 conditional knockout mice show motor deficit without overt developmental alteration in cerebral cortex neurons (Yokoi et al., 2008). On the other hand, dopamine receptor 2-expressing-cells specific Dyt1 conditional KO (Dyt1 d2KO) mice show decreased striatal ChIs and motor deficits (Yokoi et al., 2020b). Moreover, Dlx-CKO mice, which have a combination of the heterozygous KO and Dlx5/6-Cre-derived conditional KO in the forebrain neurons, show a severe reduction of the dorsal striatal ChIs (Pappas et al., 2015). Similarly, the present results showed Dyt1 KI mice had reduced dorsolateral striatal ChIs. Since Dyt1 KI mice express reduced striatal torsinA (Yokoi et al., 2010), these phenotypes may be caused by a partial loss of torsinA function in Dyt1 KI mice. It should be noted that nestin-expressing cell-specific conditional KO mice show complete infant lethality and neurodegeneration in multiple brain regions (Liang et al., 2014). However, overt neurodegeneration and complete lethality seem to be caused by malnutrition due to the failure of the mutant mice competing for food (Yokoi et al., 2020a). These previous studies and the present results support a relationship between the loss of torsinA function and the neurodegeneration, especially the ChIs, in the pathogenesis of DYT1 dystonia.

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Ethical Statement

The authors declare no competing financial interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ibneur.2021.05.003.

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