length, step width, single support time) for gait disturbance or symmetrical gait. He maintained a static posture for 30 seconds and gait five times and the mean values were calculated. All gait data were normalized by the gait cycle.

RESULTS

1. Posture

1-1) Foot pressure and COM

Skelton models confirmed the external differences in static posture (Fig. 2). The patient's model before DBS inclined to the left side with poor position of his neck and trunk. His right foot pressure was distributed to his toe and heel (forefoot 51% and hindfoot 49%, average 415 g/cm^2) and the left was deviated to his heel (forefoot 19% and hindfoot 81%, average 543 g/cm^2). The LNG, which showed postural instability, was 923.2 mm. After DBS, distribution of foot pressure was on the right side (forefoot 65% and hindfoot 35%, average 361 g/cm^2) and on the left (forefoot 18% and hindfoot 82%, average 510 g/cm^2), and the LNG decreased to 502.9 mm. The balance of weight bearing and right-left ratio of foot pressure showed no difference between before and after DBS. LNG revealed clear shortening of 54.5% and shifted to the middle of his feet after DBS.

1-2) Neck and spine angle

His spine had extended to the left side, bent and rotated to the left before, and was slightly bent and rotated to the left after DBS (Fig. 3). His neck, however, had extended to the right side, bent and rotated to the right before, and was slightly bent and rotated to the left after DBS. His postural alignment

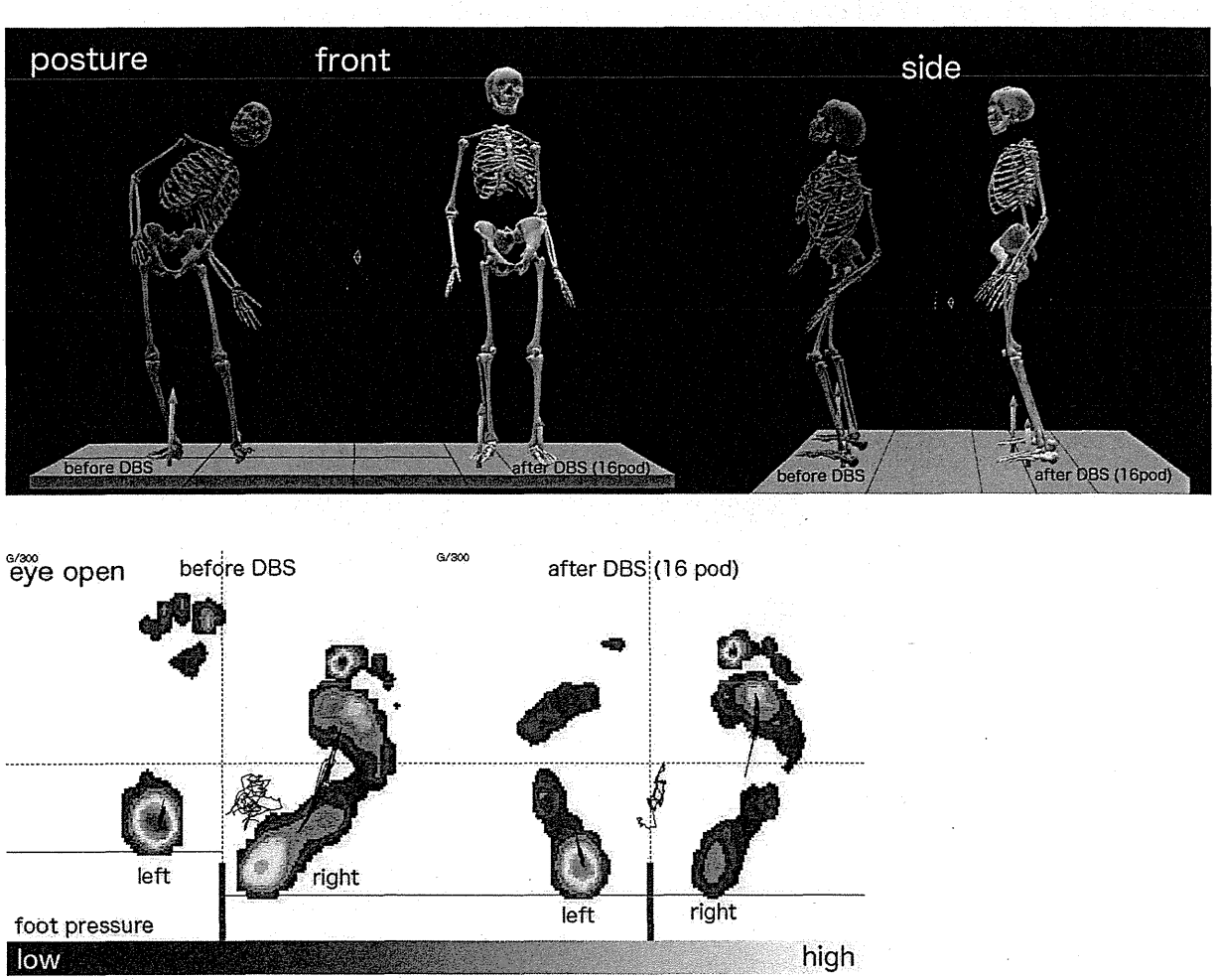

Figure 2. Static posture and foot pressure
Skelton models from Polygon 3.1 simulated and visualized the postural alignments in frontal and sagittal planes. The patient stood on force plates with the eyes open and relaxed. Abnormality before DBS (left) especially showed spinal torsion with left postural deviation. The lines of the center of pressure showing postural instability improved on middle of the foot images after DBS.

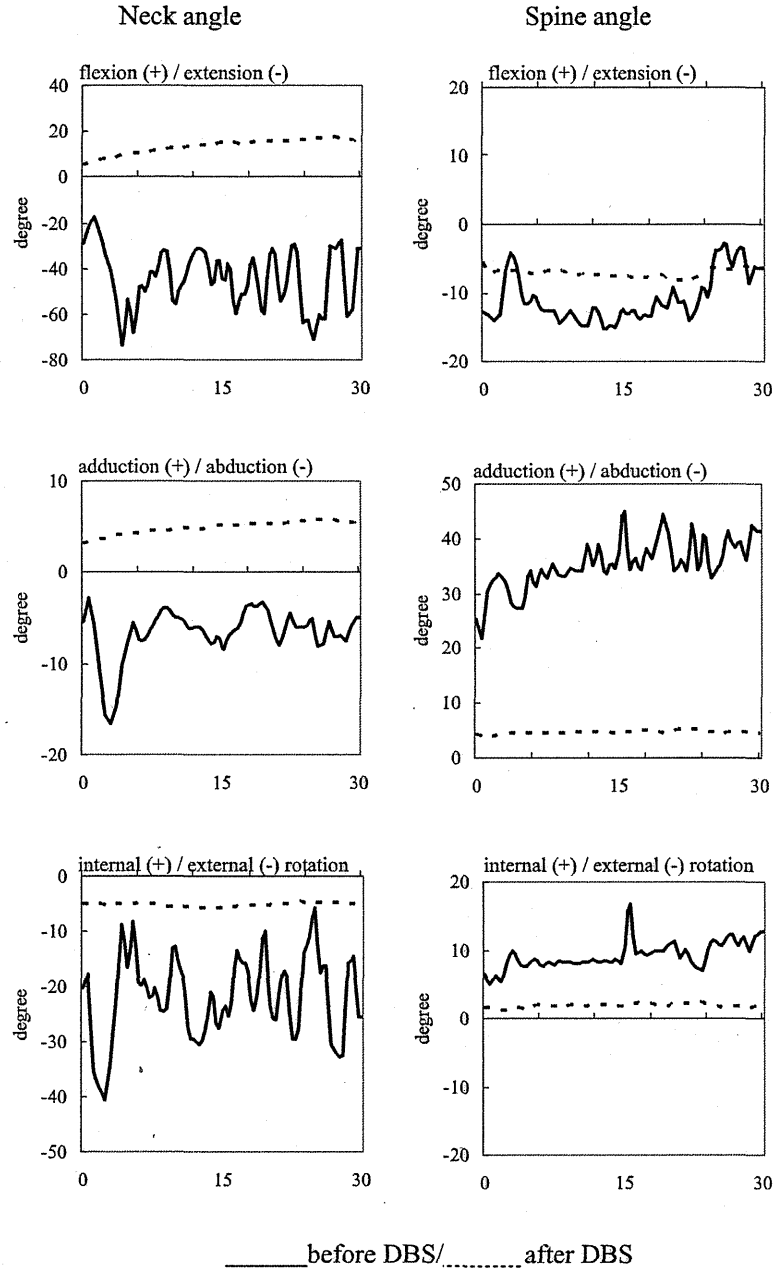

Figure 3. Neck and spine angle in static posture
The degree of neck and spine angles with static standing for thirty seconds improved to maintain a stable position after DBS in three dimensions. Neck movements before DBS were antagonists of those of the spine in lateral bend and vertical directions ; these symptoms decreased after DBS.

remained almost straight (offset) from the center of his body (0 degrees) after DBS (neck offset : flexion 13.5±3.4 degrees, left bending 4.9±0.8 degrees, right rotation 5.1± 0.7 degrees, spine offset : flexion 13.3± 2.8 degrees, left bending 4.7± 0.3 degrees, left rotation 1.8± 0.8 degrees).

2. Gait

2-1) Gait parameters

The changes in gait parameters are shown in Table 1. The following parameters were also compared with normal data (normal values) (10-12). All values after DBS were better than before but could not reach normal values for increasing cadence (110-120 steps/min), faster walking speed (1.36 m/sec), longer step length (0.65 m), shorter step width and single support time.

2-2) Neck and spine angle

The alignments of his spine before, which extended, bent and rotated to the left, changed to a

Table 1. Gait parameters

	Before DBS		After DBS	
	Left	Right	Left	Right
Cadence (steps/min)	93.8± 13.0	91.3± 18.3	100.0± 8.79	92.7± 5.83
Walking speed (m/sec)	0.65± 0.09	0.62± 0.20	0.86± 0.15	0.86± 0.05
Step lengths (m)	0.26± 0.10	0.54± 0.14	0.45± 0.18	0.58± 0.05
Step width (m)	0.30± 0.04	0.28± 0.02	0.20± 0.05	0.21± 0.03
Single support (sec)	0.56± 0.11	0.45± 0.05	0.48± 0.07	0.49± 0.08

Values are expressed gait parameters (mean± SD) for five times walking. The parameters became more symmetry after DBS.

lower degree of spinal deviation close to a straight position on gait after DBS (Fig. 4). His neck angles after DBS were still abnormal (flexion, left bending and right rotation) even after DBS. The standard deviations of each angle stayed in the lower ranges, showing stability during a gait cycle.

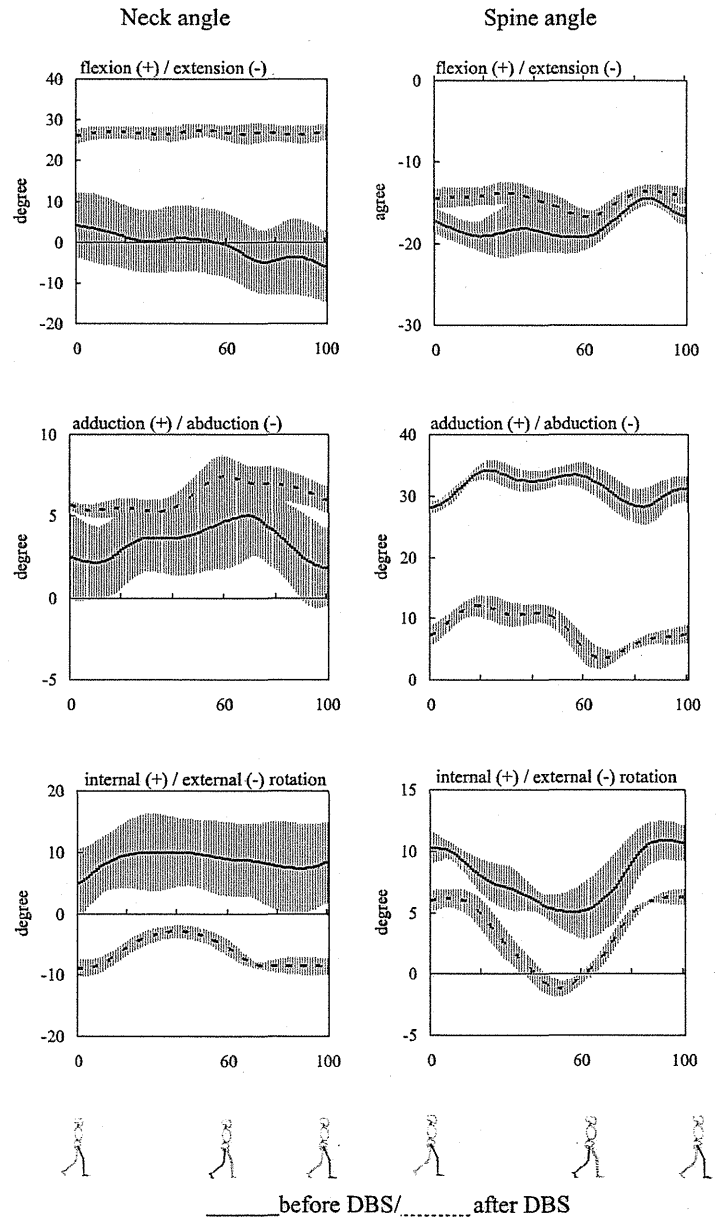

Figure 4. Neck and spine angles during a gait cycle
Angles (mean± SD, degree) of the patient with five times gait. After DBS, the spine angle became close to the median line of the body with moderate standard deviation in all planes (sagittal, frontal and coronal planes). Neck position remained inclined to the left.

2-3) Ground reaction force (GRF)

The asymmetry of GRF patterns (Fig. 5) before DBS became close to symmetrical after DBS (lateral shear and vertical forces), except for a progressive pattern. Each lower limb had a respective role in braking force for the left and driving force for the

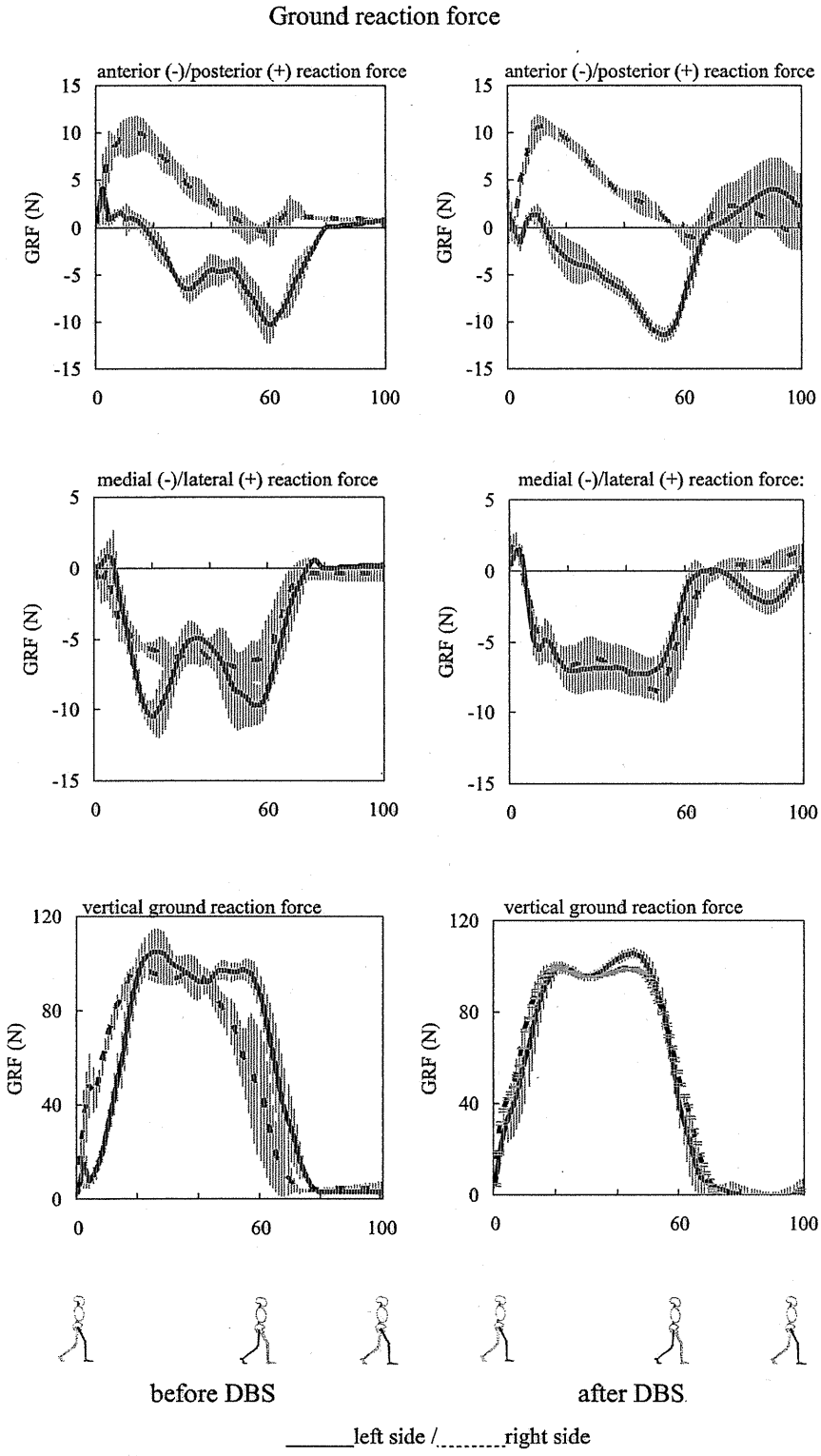

Figure 5. Ground reaction force during a gait cycle
GRF (mean± SD, Newton) from force plates with five times gait showed close to symmetrical bilateral gait patterns after DBS, except progressive shear forces. Dystonia side (left) reversed normal side (right).

right in progressive shear force.

2-4) Center of mass (COM)

The ranges (distance) of COM were, before DBS : 173.4± 26.7 mm (lateral : L), 66.5± 22.4 mm (vertical : V) and after : 70.5± 17.2 mm (L), 22.5± 4.8 mm (V). The normal values were 58.0± 20.0 mm (L) and 48.0± 11.0mm (V) (10). The deviation of COM revealed stability in both lateral and vertical directions during a gait cycle (Fig. 6).

DISCUSSION

The mechanism of the DBS effect was associated with the disruption of pathological network activity in the cortico-basal ganglia-thalamic circuits by affecting the firing rates and bursting patterns of neurons and synchronized oscillatory activity of neuronal networks (13). There is a consensus that idiopathic generalized, cervical and segmental dystonia

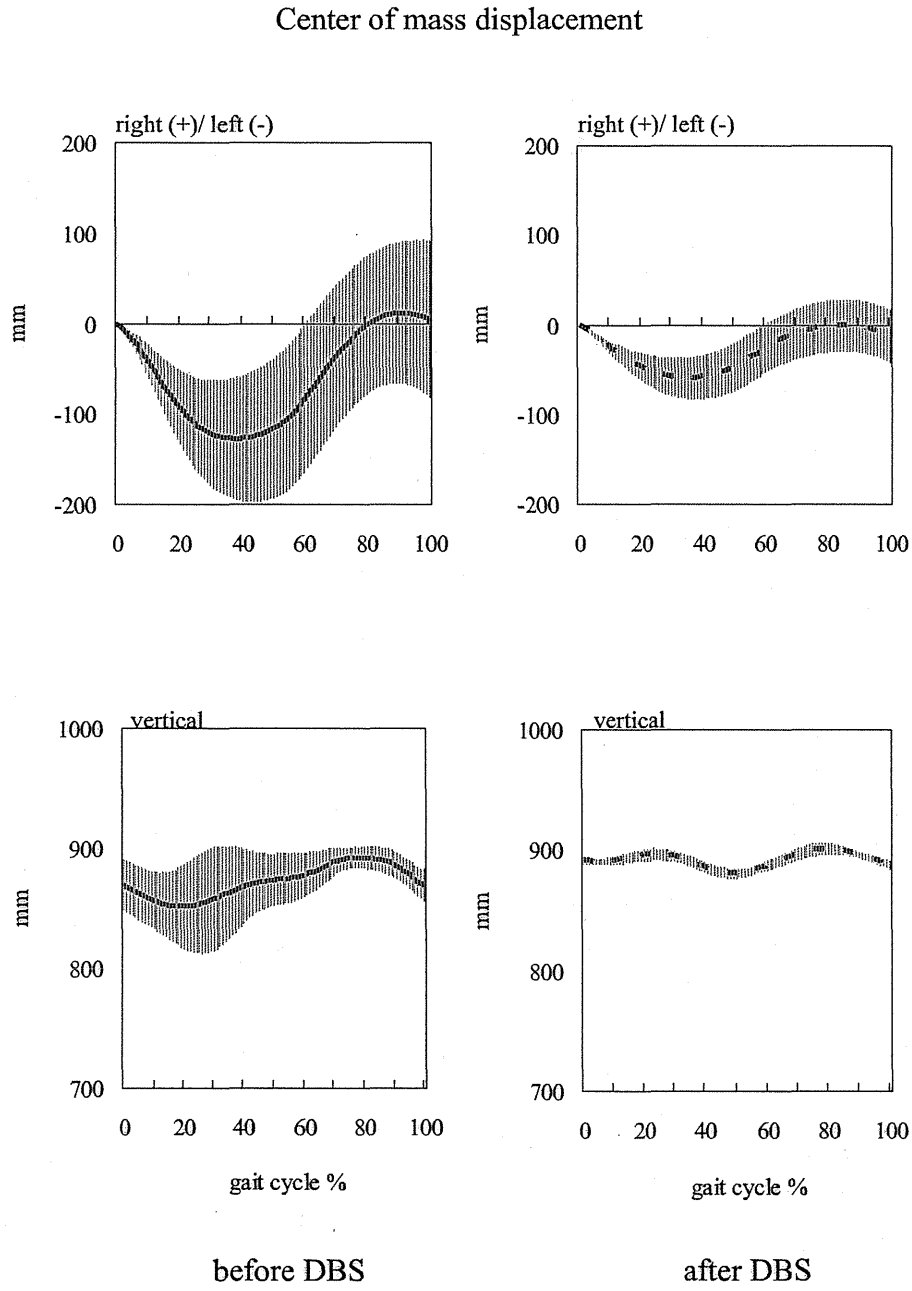

Figure 6. COM patterns during a gait cycle
Displacement of center of mass (mean± SD, mm) with five times gait in lateral and vertical directions for gait instability ; wide ranges of standard deviations before DBS revealed less stability than after DBS during the gait cycle.

are good indications of DBS and efficacy is maintained long term. Although pallidal DBS has been shown to be cognitively safe, non-dystonic extremities have not received much attention (14). We clarified which involuntary movements were related to postural instability and gait disturbance by DBS in a dystonic patient using three-dimensional motion analysis in this study. His posture and gait were asymmetrical and unstable before DBS ; therefore, he quickly became exhausted easily and fell down frequently (15), but they improved close to symmetrical after DBS. Functional body balance was controlled by changes of symptoms (with partial corrections of neck and spinal alignments in a static posture) and maintained the stability of COM and COP. His neck angles remained abnormal with specific motions during gait compared to the spine, which was not disturbed in walking. Functional improvements of gait, such as gait parameters including increasing of cadence (step rate) and walking speed, increased step length, reduction of a wide base, extension of single support time and symmetrical GRF patterns in lateral and vertical shear force close to normal patterns in consecutive gait showed dynamic stability simultaneously. Gait needs the neuromuscular function of the whole body and involves involuntary as well as voluntary motor elements (11). DBS facilitated the possible relations of gait asymmetry to postural instability in dystonia as well as Parkinson's disease (16). These improvements of gait parameters also explained that of neuromuscular function, which well responded to DBS. Not all symptoms could be treated with DBS (2-4). Our patient improved 80% by BFMS with slightly abnormal movement in his posture and gait. Some dependence on the right side remained for weight bearing to substitute the symptomatically dominant side during gait even after DBS. Other symptoms, including slightly better vocalization, swallowing and keeping his eyes open could help the patient to be independent and active during hospitalization. These remaining symptoms will necessitate a rehabilitation program, using training to establish new movement patterns, to preserve an appropriate activity level, and to treat the specific disability, which resulted from secondary changes of the musculoskeletal system during pathological muscle tension in dystonia (17) after DBS.

The results of this study revealed that three-dimensional motion analysis could inclusively assess the level of improvement in a patient with movement disorders and could assist in diagnosis or effect measurement. We also need to collect more data from patients with movement disorders and clarify their specific characteristics in future studies.

REFERENCES

1. Sako W : Gait disturbance and deep brain stimulation. Brain Nerve 62(11) : 1221-1225, 2010 (in Japanese)
2. Evidente VG, Lyons MK, Wheeler M, Hillman R, Helepolelei L, Beynen F, Nolte D, Müller U, Starr PA : First case of X-linked dystonia-parkinsonism ("Lubag") to demonstrate a response to bilateral pallidal stimulation. Mov Disord 22(12) : 1790-1793, 2007
3. Martinez-Torres I, Limousin P, Tisch S, Page R, Pinto A, Foltynie T, Bhatia KP, Hariz MI, Zrinzo L : Early and marked benefit with GPi DBS for Lubag syndrome presenting with rapidly progressive life-threatening dystonia. Mov Disord 24(11) : 1710-1712, 2009
4. Wadia PM, Lim SY, Lozano AM, Poon YY, Diaz CT, Moro E : Bilateral pallidal stimulation for X-linked dystonia parkinsonism. Arch Neurol 67(8) : 1012-1015, 2010
5. Oyama G, Fernandez HH, Foote KD, Zeilman P, Hwynn N, Jacobson CE 4th, Malaty IA, Rodriquez RL, Okun MS : Differential response of dystonia and parkinsonism following globus pallidus internus deep brain stimulation in X-linked dystonia parkinsonism (Lubag). Stereotact Funct Neurosurg 88 : 329-333, 2010
6. Blanc Y, Merio A, Landis T, Burkhard PR : Kinesiologic analysis of gait and abnormal movements. Rev Med Suisse Romande 123 : 327-33, 2003
7. Müllar U : The monogenic primary dystonias. Brain 132(8) : 2005-2025, 2009
8. Evidente VG, Nolte D, Niemann S, Advincula J, Mayo MC, Natividad FF, Müller U : Phenotypic and molecular analyses of X-linked dystonia-parkinsonism ("lubag") in women. Arch Neurol 61(12) : 1956-1959, 2004
9. Comella CL, Leurgans S, Wuu J, Stebbins GT, Chmura T : Rating scales for dystonia : A Multicenter Assessment. Mov Disord 18 : 303-312, 2003
10. Oberg T, Karasznia A, Oberg K : Basic gait parameters : Reference data for normal subjects, 10-79 years of age. J Rehabil Res Develop 30 : 210-223, 1993

11. Nakamura R, Saitoh H : Fundamental Kinesiology fifth edition, chapter 8, Ishiyaku Publishers, Inc. Tokyo, 2000, pp.333-353 (in Japanese)
12. Perry J, Judith M Burnfield : Gait analysis. Normal and pathological function. 2nd ed, chapter 24, SLACK Incorporated, Thorofare, 2010, pp.483-518
13. UcEY, Follett KA : Deep brain stimulation in movement disorders. Semin Neurol 22(2) : 170-182, 2007
14. Krauss JK : Surgical treatment of dystonia. Eur J Neurol 17(1) : 97-101, 2010
15. Botzel K, Kraft E : Strategies for treatment of gait and posture associated deficits in movement disorders : the impact of deep brain stimulation. Restor Neurol Neurosci 28(1) : 115-122, 2010
16. Johnsen EL, Mogensen PH, Sunde NA, Ostegaar K : Improved asymmetry of gait in Parkinson's disease with DBS : Gait and postural instability in Parkinson's disease treated with bilateral deep brain stimulation in the subthalamic nucleus. Mov Disord 22(4) : 590-597, 2009
17. Page D, Butler A, Jahanshahi M : Quality of life in focal, segmental, and generalized dystonia. Mov Disord 22(3) : 341-347, 2007

Neuroscience 170 (2010) 497–502

OLFACTORY TYPE G-PROTEIN α SUBUNIT IN STRIOSOME-MATRIX DOPAMINE SYSTEMS IN ADULT MICE

W. SAKO,[a,b] R. MORIGAKI,[a,c] S. NAGAHIRO,[a,c] R. KAJI[a,b] AND S. GOTO[a,b,c*]

[a]*Parkinson's Disease and Dystonia Research Center, Tokushima University Hospital, Tokushima 770–8503, Japan*

[b]*Department of Clinical Neuroscience, Institute of Health Biosciences, Graduate School of Medical Sciences, University of Tokushima, Tokushima 770–8503, Japan*

[c]*Department of Neurosurgery, Institute of Health Biosciences, Graduate School of Medical Sciences, University of Tokushima, Tokushima 770–8503, Japan*

Abstract—There is a growing body of evidence that striosome-matrix dopamine systems are tightly linked with motor and behavioral brain functions and disorders. In this study, we used an immunohistochemical method to show differential expression of the olfactory type G-protein α subunit (Gαolf) that involves in the coupling of dopamine D1 receptor with adenylyl cyclase in the striatal compartments of adult mice, and observed heightened density of Gαolf labeling in the striosomes relative to the matrix compartment. Our findings suggest that Gαolf could be one of the key molecules for controlling differential responses of the striosome and matrix compartments to dopamine D1 receptor signaling in the striatum of adult mice.

Key words: striatum, compartmentalization, dopamine D1 receptor, DARPP-32, c-Fos, G-protein.

The mammalian striatum comprises a unique mosaic organization composed of two functional subdivisions: the striosome and matrix compartments (Graybiel and Ragsdale, 1978). These compartments are defined according to the intensity of histochemical staining for a wide variety of neurotransmitter-related substances including the dopamine-signaling molecules (Graybiel, 1990; Gerfen, 1992). Accumulating evidence has suggested that differential involvement of the striosome-matrix dopamine systems is associated with movement and behavioral disorders (for recent reviews, see Graybiel, 2008; Goto et al., 2010), and psychostimulant addiction (Capper-Loup et al., 2002; Granado et al., 2008).

*Correspondence to: S. Goto, Department of Clinical Neuroscience, Institute of Health Biosciences, Graduate School of Medicine, University of Tokushima, Tokushima 770-8503, Japan. Tel: +81-88-633-7206; fax: +81-88-633-7208.
E-mail address: sgoto@clin.med.tokushima-u.ac.jp (S. Goto).

Abbreviations: DAB, diaminobenzidine; DARPP-32, the dopamine and cAMP-regulated phosphoprotein of 32 kDa; Gαolf, the olfactory type G-protein α subunit; Gαs, the isoform of stimulatory G-protein α subunit; IgG, immunoglobulin G; MOR, μ-opiate receptor; PB, phosphate buffer; PBS, phosphate buffered saline; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; TH, tyrosine hydroxylase.

Dopamine receptor signaling plays a key role in motor and behavioral control of brain function. Among five known subtypes of dopamine receptors, the dopamine D1 receptor (D1R) that stimulates cAMP production is most abundant and widespread in the brain. It is known that in the rodent striatum, D1R couples to adenylyl cyclase via the olfactory type G-protein α subunit (Gαolf), and not via the isoform of stimulatory G-protein α subunit (Gαs; Zhuang et al., 2000; Corvol et al., 2001). By using an immunohistochemical technique, we here show a striking pattern of Gαolf distribution in the striatum of adult mice, and heightened expression of the protein in the striosomes relative to the matrix compartment. Our results suggest that in the adult mouse striatum, striosomal enrichment of the Gαolf protein is attributable to the predominant responsiveness of the striosomes to D1R signaling.

EXPERIMENTAL PROCEDURES

All procedures involving the use of animals and analysis of brain anatomy were approved by the Institutional Care and Use Committees of Tokushima University.

Animals and tissue preparation

The adult mice were administered an i.p. injection of a lethal dose of pentobarbital and were perfused transcardially with 0.9% saline in 0.01 M phosphate buffered saline (PBS; pH 7.4) and cold 0.1 M phosphate buffer (PB; pH 7.4) containing 4% paraformaldehyde. The brains were removed, post-fixed overnight in the same fixative at 4 °C, and stored in 0.1 M PB containing gradient (10–30%) sucrose at 4 °C for cryoprotection. Sections with 30 μm-thickness were cut on a cryostat and stored in PBS/0.05% NaN_3 until use. In a c-Fos induction experiment, adult mice were given an i.p. injection of apomorphine (10 mg/kg) 2 h prior to perfusion.

Western blot analysis

The brains from deeply anesthetized adult mice were homogenized in 0.05 M Tris–HCl (pH 7.2) containing 0.025 M KCl, 0.005 M $MgCl_2$, and 0.32 M sucrose. The protein lysates were subjected to 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and separated proteins were then transferred onto a polyvinylidene difluoride membrane. The membranes were incubated with an antibody to Gαolf (Santa Cruz Biotechnology, Santa Cruz, CA, USA; 1:5000) and Can Get Signal (Toyobo Inc., Osaka, Japan), and then with horseradish peroxidase-conjugated anti-rabbit IgG. Bound antibodies were detected by chemiluminescence staining (ECL plus kit, GE Healthcare, Buckingham, UK).

Immunohistochemistry and digital imaging

Immunohistochemical staining was performed on free-floating sections as described in a previous report (Sato et al., 2008). Rabbit polyclonal antibody to tyrosine hydroxylase (TH; 1:100,000) (Sato et al., 2008), rat monoclonal antibody to D1R (Sigma-Aldrich, St

0306-4522/10 $ - see front matter
doi:10.1016/j.neuroscience.2010.06.072

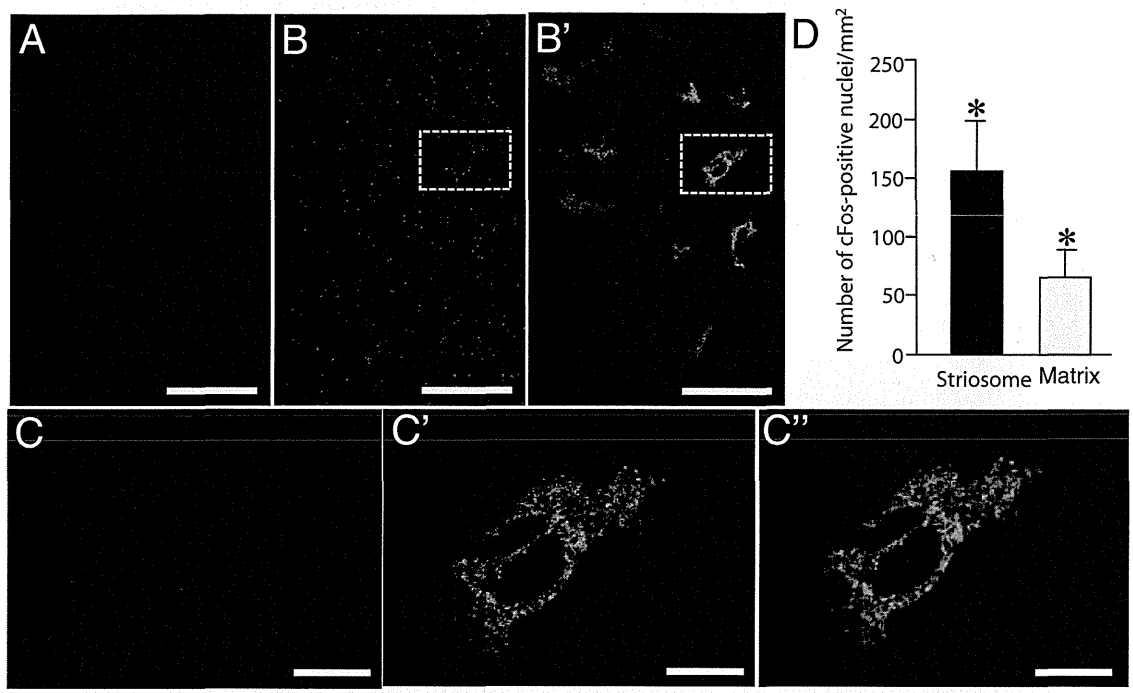

Fig. 1. Striosome-predominant expression of c-Fos protein with apomorphine treatment in adult mice. (A) Immunofluorescence staining for c-Fos in the striatal section from a mouse with no treatment of apomorphine. (B, B′) Dual antigen immunofluorescence staining for c-Fos (B) and MOR (B′) in the striatal section from a mouse with apomorphine treatment. Region shown in dashed open boxes in (B, B′) is illustrated at higher magnification in (C, c-Fos), (C′, MOR) and (C′′, merged). Apomorphine induces patchy striosome-predominant expression of c-Fos in the caudoputamen. (D) Density measurements of c-Fos-labeled nuclei in the striosome and matrix compartments. Data are represented as the mean (SEM) (bars) values (n=25). * indicates P=0.01 striosome vs. matrix. MOR, μ-opioid receptor. Scale bars: (A, B) 500 μm; (C) 100 μm.

Louis, MO, USA), rabbit polyclonal antibody to μ-opiate receptor (MOR; Millipore, Billerica, MA, USA; 1:10,000), rabbit polyclonal antibody to the dopamine and cAMP-regulated phosphoprotein of 32 kDa (the dopamine and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32); Cell Signaling, Danver, MA, USA; 1:1000), rabbit polyclonal antibody to phospho-[Thr34]-DARPP-32 (Cell Signaling; 1:1000), rabbit polyclonal antibody to phospho-[Thr75]-DARPP-32 (Cell Signaling; 1:1000), rabbit polyclonal antibody to c-Fos (Oncogene Science, Cambridge, MA, USA; 1:2000), and rabbit polyclonal antibody to Gαolf (Santa Cruz Biotechnology; 1:500) were used as primary antibodies. For detection of the bound antibodies, we used the Histofine Simple Stain kit (Nichirei Company, Tokyo, Japan) with diaminobenzidine (DAB) as a chromogen. Dual antigen immunofluorescence staining for c-Fos and MOR was performed as previously described (Sato et al., 2008). The digital microscopic images from the immunostained sections were acquired with Meta-Morph software (Molecular Devices, Tokyo, Japan), imported into Adobe Photoshop CS4, and processed digitally.

Densitometry and statistics

To estimate the density of Gαolf labeling, we immunostained the striatal sections in parallel at the same time with the same protocols. The optical densities of DAB products were measured as gray levels. For each animal, measurements were made in five striatal fields from five sections. Measurements of the density of c-Fos-labeled nuclei in the striatal compartments were made on the sections doubly-stained for c-Fos and MOR. We counted the number of c-Fos-positive nuclei within the striosomes (n=25) and in the matrix areas (n=25) from five striatal fields of each rat (n=5), and calculated the density of c-Fos-positive nuclei/mm^2 in each compartment. For statistical analysis we used Student's two tailed t-test and P-values less than 0.05 were considered as statistically significant.

RESULTS

To test whether the striosome and matrix compartments differentially respond to dopaminergic stimulation in the adult mice used in the present study, we performed an assay for c-Fos expression after treatment with apomorphine (Fig. 1). Because the induction of immediate early gene reflects acute elevation of cAMP-dependent signaling caused by the activation of postsynaptic D1Rs within striatal neurons, c-Fos induction can be considered as an indicator of D1R-mediated signal transduction in the striatum (Moratalla et al., 1996; Kim et al., 2002). With the dual-antigen detection for c-Fos and MOR, a marker for striosomes (Canales and Graybiel, 2000; Sato et al., 2008), we confirmed preferential localization of the nuclei labeled for c-Fos in the striosomes relative to the matrix compartment in adult mice that were administered a high dose (10 mg/kg) of apomorphine (Fig. 1).

Next, to identify a molecular candidate responsible for the differential responses of the two striatal compartments to the D1R signaling, we reappraised the distributional profile of TH and D1R (Fig. 2) in the striatum of adult mice. Immunohistochemistry for TH, a marker for striatal dopaminergic afferent fibers, showed a nearly homogeneous staining (Fig. 2A). No obvious compartmentalization of D1R-labeling (Fig. 2B) was also found. On the other hand,

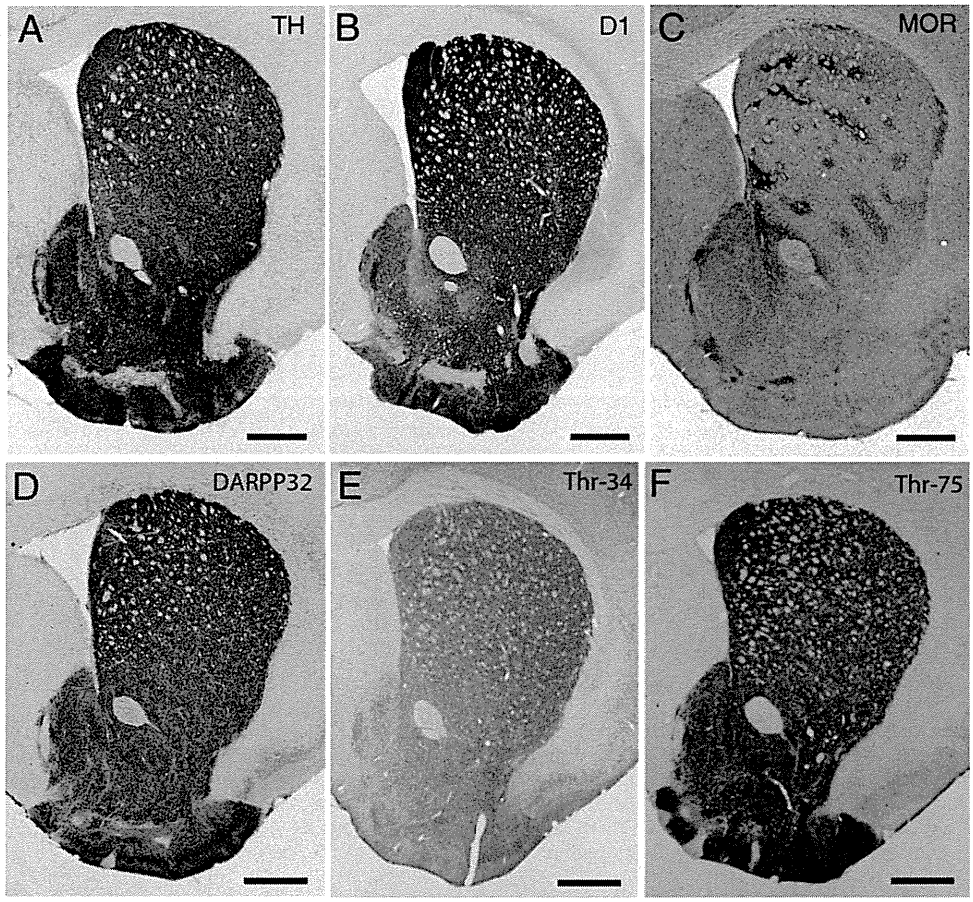

Fig. 2. Striatal localization of D1 dopamine signal-related molecules in adult mice. Striatal sections stained for TH (A), D1R (B), MOR (C), DARPP-32 (D), phospho-[Thr34]-DARPP-32 (E), and phospho-[Thr75]-DARPP-32 (F). TH, tyrosine hydroxylase; D1R, dopamine D1 receptor; MOR, μ-opioid receptor, DARPP-32, the dopamine and cAMP-regulated phosphoprotein of 32 kDa. Scale bars=500 μm.

the striosome and matrix compartments were clearly identified on staining for MOR (Fig. 2C). Hence, it is likely that dopaminergic afferents and D1Rs are almost homogeneously distributed in the striosome-matrix system. In addition, DARPP-32, a major component of the D1R-signaling cascade (Greengard, 2001), also showed no obvious compartmentalized distribution in the striatum (Fig. 2D), as did its site-specific phosphorylated forms such as phospho-[Thr34]-DARPP-32 (Fig. 2E) and phospho-[Thr75]-DARPP-32 (Fig. 2F).

Lastly, we examined the localization pattern of Gαolf in the striosome-matrix systems of adult mice (Fig. 3). For this purpose, we used a rabbit polyclonal antibody to the Gαolf protein. On immunoblots of rat brain extracts, a protein band with an approximate molecular mass of 42 kDa, corresponding to the predicted size of the native Gαolf protein, was selectively detected with the antibody (Fig. 3A). From the anterior to posterior levels of the striatum (Fig. 3B–D), immunoreactivity for Gαolf was highly concentrated in the striatum that consists of the caudoputamen, nucleus accumbens, and olfactory tubercle. Under high-power magnifications, Gαolf labeling was strongly expressed in numerous neuronal fibers but less intensely in neuronal perikarya in the striatum (Fig. 3E). Of particular interest was the finding that within the caudoputamen, there were focal zones of particularly high Gαolf immunostaining. These zones of heightened Gαolf labeling corresponded to the striosomes identified in the adjacent sections stained for MOR (Fig. 3F, G). Serial section analysis on negative images (Fig. 3H, I) also illustrates this higher expression of Gαolf in the striosomes relative to the nearby matrix area. Densitometric measurements confirmed this visual impression (Fig. 3J). A quantitative study revealed a significant difference in the Gαolf staining density between the striosome and matrix compartments (P=0.001). Hence, we inferred that the striosome compartment is enriched with the Gαolf protein in adult mice.

DISCUSSION

Given that c-Fos induction by apomorphine is significantly high in the striosomes relative to the matrix compartment, our results indicate that there exists a predominant responsiveness of the striosome compartment to D1R signaling in the adult mouse striatum. However, according to our data, no apparent compartmentalization was found in adult mice with respect to the distribution of D1R or TH. This finding is consistent with the known expression pattern of D1R and

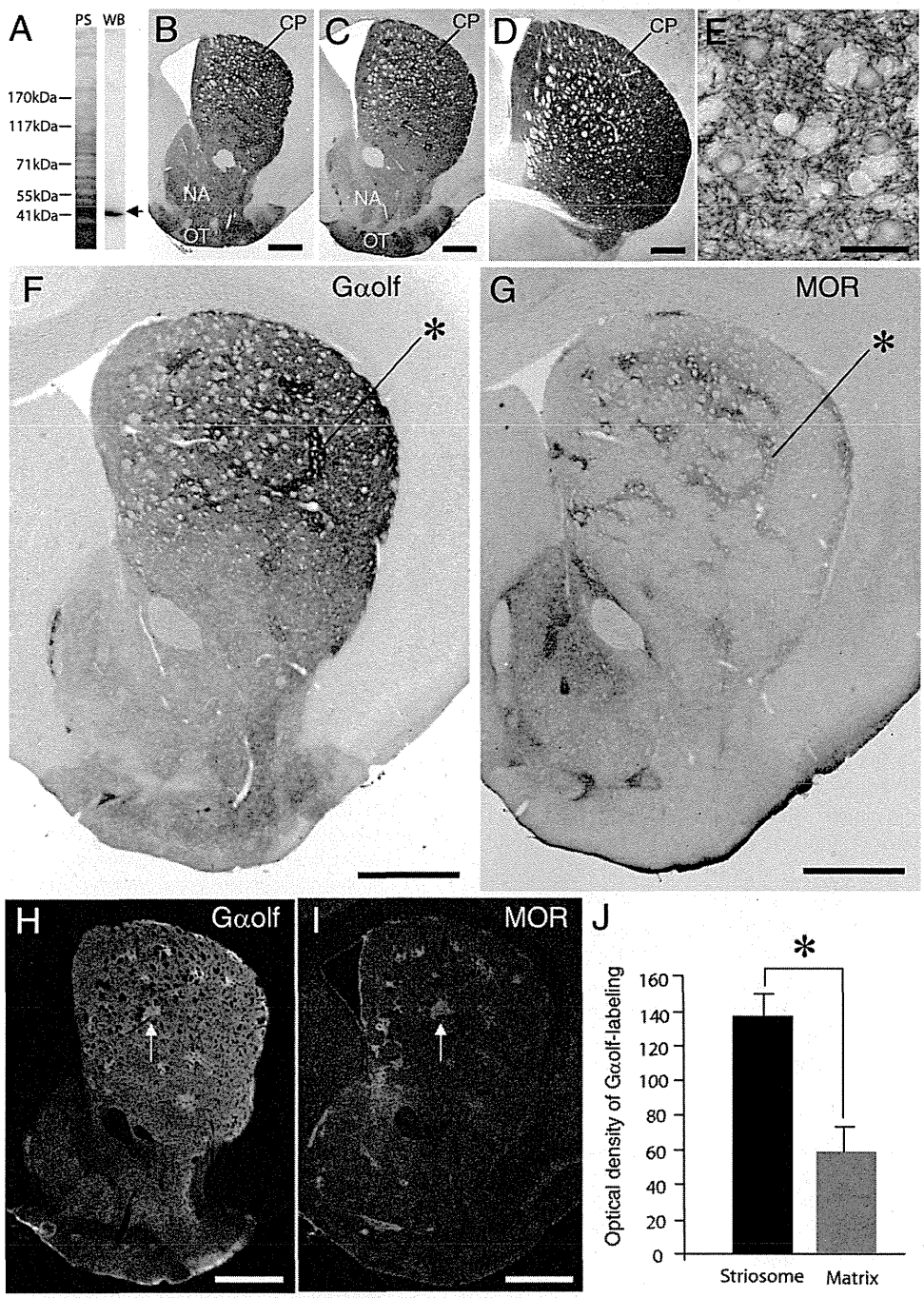

Fig. 3. Striatal localization of Gαolf in adult mice. (A) Western-blot assay. Rat brain extracts (50 μg of protein) were loaded onto 10% SDS-PAGE and then processed for the transimmunoblot technique using anti-Gαolf antibody. Note that a protein band (arrowhead) with an approximate molecular mass of 42 kDa, corresponding to the predicted size of the native Gαolf protein was selectively detected. PS, protein staining; IB, immunoblot. (B–D) Gαolf-immunostaining at the anterior (B), middle (C), and posterior (D) levels of the striatum. (E) High-power photomicrograph of the striatal area stained for Gαolf. (F, G) Serial sections stained for Gαolf (F) and MOR (G). Asterisks indicate a corresponding striosome. MOR, μ-opioid receptor. (H, I) Negative prints of serial sections stained for Gαolf (H) and MOR (I). Arrows indicate a corresponding striosome. (J) Density measurements of Gαolf-labeling in the striosome and matrix compartments. Data are represented as the mean (SEM) (bars) values (n=25). * indicates P=0.01 striosome vs. matrix. Scale bars: (B–D), (F–I), 500 μm; (E) 50 μm.

TH in the mouse striatum (Kim et al., 2002; Granado et al., 2008; Sato et al., 2008). Immunostaining of D1R and TH first appears in discrete "dopamine islands" that correspond to developing striosomes (Graybiel, 1984) at the early postnatal period. With development, the level of D1R- and TH-staining intensity in the matrix compartment is increased to the level found in striosomes, and hence their compartmentalization becomes obscure during adulthood (Kim et al., 2002). Therefore, it is likely that in adult mice, the striosome and matrix compartments differentially re-

spond to D1R signaling, despite no obvious difference in the distribution of D1Rs and dopaminergic inputs as determined by TH-staining between the two striatal compartments. This notion could raise the possibility that certain molecules that play a role in the intracellular dopamine D1 signaling cascade are differentially expressed in the striosome-matrix systems in adult mice. Although a previous study showed a homogeneous pattern of Golf mRNA expression throughout striatal development in rats (Sakagami et al., 1995), in the present study, we have shown that the Gαolf protein is differentially expressed in the striatal compartments of adult mice. The present study first showed compartmentalized distribution of the Gαolf protein in the adult mouse striatum, with a heightened density of Gαolf-staining in the striosomes relative to the matrix compartment. Because activation of D1R increases cAMP production via Gαolf-mediated stimulation of adenylyl cyclase in rodents (Zhuang et al., 2000; Corvol et al., 2001), we suggest that Gαolf could be one of the key molecules for controlling differential response of striosome-matrix systems to D1R signaling in adult mice.

Accumulating evidence has shown that differential involvement of the striosome-matrix dopamine systems could be critical to identifying mechanisms underlying the genesis of movement disorders such as Parkinson's disease (Wilson et al., 1987; Moratalla et al., 1992; Graybiel et al., 2000; Iravani et al., 2005; Crittenden et al., 2009) and dystonias (Sato et al., 2008). It has also been suggested that a significant change in striatal Gαolf expression is strongly linked with the induction of the hypokinetic or hyperkinetic state in models of striatal dopamine deficiency in both animals (Herve et al., 1993, 2001; Marcotte et al., 2001; Cai et al., 2002) and humans (Corvol et al., 2004). Moreover, an important finding indicates that the striatal level of Gαolf serves as a key regulator for acute responses to psychomotor stimulants (Corvol et al., 2007). Taken together, we suggest that striosomal enrichment of the Gαolf protein may give new insights in the compartment pathology of striatal dopamine systems in movement and behavioral disorders.

Acknowledgments—This work was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan (grant-in-aid for Scientific Research, 20591025). We express our sincere appreciation to Professor Ann M Graybiel, Massachusetts Institute of Technology, for her helpful comments on this work.

REFERENCES

Cai G, Wang HY, Friedman E (2002) Increased dopamine receptor signaling and dopamine receptor-G protein coupling in denervated striatum. J Pharmacol Exp Ther 302:1105–1112.

Canales JJ, Graybiel AM (2000) A measure of striatal function predicts motor stereotypy. Nat Neurosci 3:377–383.

Capper-Loup C, Canales JJ, Kadaba N, Graybiel AM (2002) Concurrent activation of dopamine D1 and D2 receptors is required to evoke neural and behavioral phenotypes of cocaine sensitization. J Neurosci 22:6218–6227.

Corvol JC, Muriel MP, Valjent E, Feger J, Hanoun N, Girault JA, Hirsch EC, Herve D (2004) Persistent increase in olfactory type G-protein α subunit levels may underlie D1 receptor functional hypersensitivity in Parkinson's disease. J Neurosci 24:7007–7014.

Corvol JC, Stundler JM, Schonn JS, Girault JA, Herve D (2001) Galpha(olf) is necessary for coupling D1 and A2a receptors to adenylyl cyclase in the striatum. J Neurochem 76:1585–1588.

Corvol JC, Valjent E, Pascoli V, Robin A, Stipanovich A, Luedtke RR, Belluscio L, Girault JA, Herve D (2007) Quantitative changes in Gαolf protein levels, but not D1 receptor, alter specifically acute responses to psychostimulants. Neuropsychopharmacology 32: 1109–1121.

Crittenden JR, Cantuti-Castvetri I, Saka E, Keller-McGandy CE, Hernandez LF, Kett LR, Young AB, Standaert DG, Graybiel AM (2009) Dysregulation of CalDAG-GEFI and CalDAG-GEFII predicts the severity of motor side-effects induced by anti-parkinsonian therapy. Proc Natl Acad Sci U S A 106:2892–2896.

Gerfen CR (1992) The neostriatal mosaic: multiple levels of compartmental organization. Annu Rev Neurosci 15:285–320.

Goto S, Nagahiro S, Kaji R (2010) Striosome-matrix pathology of dystonias: a new hypothesis for dystonia genesis. In: Dystonia: causes, symptoms and treatment, (Kurstot J, Forsstrom M, eds), pp 1–22. New York, NY: Nova Science Publishers.

Granado N, Escobedo I, O'shea E, Colado MI, Moratalla R (2008) Early loss of dopaminergic terminals in striosomes after MDMA administration to mice. Synapse 62:80–84.

Graybiel AM (1984) Correspondence between the dopamine islands and striosomes of the mammalian striatum. Neuroscience 13:1157–1187.

Graybiel AM (1990) Neurotransmitters and neuromodulators in the basal ganglia. Trends Neurosci 13:244–254.

Graybiel AM (2008) Habits, rituals, and the evaluative brain. Annu Rev Neurosci 31:359–387.

Graybiel AM, Canales JJ, Capper-Loup C (2000) Levodopa-induced dyskinesias and dopamine-dependent stereotypies: a new hypothesis. Trends Neurosci 23(Suppl 10):S71–S77.

Graybiel AM, Ragsdale CW Jr (1978) Histochemically distinct compartments in the striatum of human, monkey and cat demonstrated by acetylthiocholinesterase staining. Proc Natl Acad Sci U S A 75:5723–5726.

Greengard P (2001) The neurobiology of slow synaptic transmission. Science 294:1024–1030.

Herve D, Levi-Strauss M, Marey-Semper I, Verney C, Tassin JP, Glowinski J, Girault JA (1993) G(olf) and Gs in rat basal ganglia: possible involvement of G(olf) in the coupling of dopamine D1 receptor with adenylyl cyclase. J Neurosci 13:2237–2248.

Herve D, Moine CL, Corvol JC, Belluscio L, Ledent C, Fienberg AA, Jaber M, Studler JM, Girault JA (2001) Gαolf levels are regulated by receptor usage and control dopamine and adenosine action in the striatum. J Neurosci 21:4390–4399.

Iravani MM, Syed E, Jackson MJ, Johnston LC, Smith LA, Jenner P (2005) A modified MPTP treatment regime produces reproducible partial nigrostriatal lesions in common marmosets. Eur J Neurosci 21:841–854.

Kim DS, Froelick GJ, Palmiter RD (2002) Dopamine-dependent desensitization of dopaminergic signaling in the developing mouse striatum. J Neurosci 22:9841–9849.

Marcotte ER, Chugh A, Barlas C, Mishra RK (2001) Differential regulation of striatal G protein levels following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine administration in C57 BL/6 mice. Neurosci Lett 306:21–24.

Moratalla R, Quinn B, DeLanney LE, Irwin I, Langston JW, Graybiel AM (1992) Differential vulnerability of primate caudate-putamen and striosome-matrix dopamine systems to the neurotoxic effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proc Natl Acad Sci U S A 89:3859–3863.

Moratalla R, Xu M, Tonegawa S, Graybiel AM (1996) Cellular response to psychomotor stimulant and neuroleptic drugs are abnormal in mice lacking the D1 dopamine receptor. Proc Natl Acad Sci U S A 93:14928–14933.

Sakagami H, Sawamura Y, Kondo H (1995) Synchronous patchy pattern of gene expression for adenylyl cyclase and phosphodiesterase but discrete expression for G-protein in developing rat striatum. Brain Res Mol Brain Res 33:185–191.

Sato K, Sumi-Ichinose C, Kaji R, Ikemoto K, Nomura T, Nagatsu I, Ichinose H, Ito M, Sako W, Nagahiro S, Graybiel AM, Goto S (2008) Differential involvement of striosome and matrix dopamine systems in a transgenic model of dopa-responsive dystonia. Proc Natl Acad Sci U S A 105:12551–12556.

Wilson JS, Turner BH, Morrow GD, Hartman PJ (1987) MPTP produces a mosaic-like pattern of terminal degeneration in the caudate nucleus of dog. Brain Res 423:329–332.

Zhuang X, Belluscio L, Hen R (2000) G(olf)α mediates dopamine D1 receptor signaling. J Neurosci 20:RC91.

(Accepted 25 June 2010)
(Available online 15 July 2010)

frontiers in NEUROLOGY

ORIGINAL RESEARCH ARTICLE
published: 17 April 2012
doi: 10.3389/fneur.2012.00058

Efficacy of zolpidem for dystonia: a study among different subtypes

Yoshimichi Miyazaki[1,2], Wataru Sako[1,3], Kotaro Asanuma[1], Yuishin Izumi[1], Tetsuro Miki[2] and Ryuji Kaji[1,3]*

[1] Department of Clinical Neuroscience, Institute of Health Biosciences, Graduate School of Medicine, University of Tokushima, Tokushima, Japan
[2] Department of Geriatric Medicine and Neurosurgery, Graduate School of Medicine, Ehime University, Ehime, Japan
[3] Parkinson's Disease and Dystonia Research Center, Tokushima University Hospital, Tokushima, Japan

Edited by:
Jaime Kulisevsky, Sant Pau Hospital – Sant Pau Institute of Biomedical Research, Spain

Reviewed by:
Miguel Coelho, University of Lisbon, Portugal
Pedro Chana, Universidad de Santiago de Chile, Chile

***Correspondence:**
Ryuji Kaji, Department of Clinical Neuroscience, Institute of Health Biosciences, Graduate School of Medicine, University of Tokushima, 2-50-1 Kuramoto, Tokushima 770-8503, Japan.
e-mail: kajkyoto@mbox.kyoto-inet.or.jp

Although there are some newly developed options to treat dystonia, its medical treatment is not always satisfactory. Zolpidem, an imidazopyridine agonist with a high affinity on benzodiazepine subtype receptor BZ1 (ω1), was found to improve clinical symptoms of dystonia in a limited number of case reports. To investigate what subtype of dystonia is responsive to the therapy, we conducted an open label study to assess the efficacy of zolpidem (5–20 mg) in 34 patients suffering from miscellaneous types of dystonia using the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS). Patients were entered into the study if they had been refractory to other medications as evaluated by BFMDRS (no change in the previous two successive visits). After zolpidem therapy, the scores in the patients as a whole were decreased from 7.2 ± 7.9 to 5.5 ± 5.0 ($P = 0.042$). Patients with generalized dystonia, Meige syndrome/blepharospasm, and hand dystonia improved in the scale by 27.8, 17.8, and 31.0%, respectively, whereas no improvement was found in cervical dystonia patients. Overall response rate among patients were comparable to that of trihexyphenidyl. Zolpidem may be a therapeutic option for generalized dystonia, Meige syndrome, and hand dystonia including musician's. Drowsiness was the dose-limiting factor.

Keywords: generalized dystonia, Meige syndrome, hand dystonia, zolpidem

INTRODUCTION

Dystonia is a syndrome of sustained muscle contractions causing twisting and repetitive movements or abnormal postures (Fahn et al., 1998). Although there are several options to treat dystonia, its medical treatment is notoriously difficult and often unsuccessful. Zolpidem, an imidazopyridine agonist with a high affinity to benzodiazepine subtype receptor BZ1 (ω1; Holm and Goa, 2000), is reported to improve basal ganglia disease including Parkinson's disease (Daniele et al., 1997) and various types of dystonia (Evidente, 2002; Garretto et al., 2004; An et al., 2008; Park et al., 2009) Despite these case reports, zolpidem has not been tested in a large number of patients with various subtypes of dystonia. Here we report two dystonia patients who improved remarkably by oral zolpidem therapy, and assessed treatment outcome of zolpidem in 34 medically intractable patients suffering from miscellaneous types of dystonia, in order to determine what subtypes of dystonia are good candidates for zolpidem trial.

MATERIALS AND METHODS

PATIENTS

Dystonia patients were selected, not in randomized, nor controlled design, from those seen at Tokushima University Hospital and Takeda General Hospital, Japan. The diagnosis of primary dystonia was made according to standard criteria (Albanese et al., 2006): Major exclusion criteria were the presence of brain lesion in basal ganglia detected by 1.5 T magnetic resonance image and the past history of antipsychotics administration. We enrolled 34 patients with dystonia, who were treated with trihexyphenidyl (4–12 mg/day), clonazepam (0.5–3 mg/day), baclofen (15–60 mg/day), and others (9 generalized dystonia; 10 Meige syndrome/blepharospasm; 7 cervical dystonia; 8 hand dystonia). All patients were refractory to further dose increases of oral medications other than zolpidem. Their doses were unchanged if continued in the zolpidem trial. Of all, 23 patients were resistant to botulinum toxin type A (OnabotulinumtoxinA: 50–200 IU, 0.5–8 ml) injections. The refractoriness was evidenced by the lack of improvement in the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) in the last two visits. All focal dystonia patients (Meige syndrome/blepharospasm, cervical dystonia, and hand dystonia) did not spread to multiple body parts during 1 year follow up. One patient underwent palidal stimulation before entry. Their clinical characteristics are summarized in **Table 1**. Their mean age was 48.8 ± 15.8 years; mean disease duration was 5.2 ± 5.1 years. Zolpidem was started at 10 mg/day (once a day in the evening), later increased or decreased in dosage (5–20 mg/day: once or twice a day in the morning and evening) depending on the tolerability and the benefit. The mean dosage of zolpidem was 11.2 ± 5.12 mg.

ASSESSMENTS

All patients were assessed before and 1 month after zolpidem administration using BFMDRS, including the Dystonia Movement Scale (Part I) and Disability Scale (Part II; Burke et al., 1985).

We defined the global improvement as follows; more than 40% improvement in BFMDRS as "remarkable improvement," less than 40% improvement as "mild improvement," and no change in the scale as " no improvement."

Table 1 | Patients' summary.

	Generalized dystonia ($n=9$)	Meige/blepharospasm ($n=10$)	Cervical dystonia ($n=7$)	Hand dystonia ($n=8$)	Total ($n=34$)
Gender (male/female)	3M/6F	6M/4F	7M/0F	5M/3F	21M/13F
Age	38.3 ± 19.4	60.6 ± 9.6	45.7 ± 14.4	48.4 ± 10.1	48.8 ± 15.8
Duration (years)	4.6 ± 6.8	3.6 ± 3.2	6.0 ± 4.9	7.4 ± 5.2	5.2 ± 5.1
BFMDRS: before	15.8 ± 10.0	6.2 ± 5.4	2.4 ± 1.1	2.9 ± 2.0	7.2 ± 7.9
BFMDRS: after	11.4 ± 5.7	5.1 ± 3.0	2.4 ± 1.1	2.0 ± 0.9	*5.5 ± 5.0
Zolpidem (mg/day)	12.2 ± 6.2	12.0 ± 4.8	10 ± 0	8.8 ± 5.1	10.9 ± 4.8
BTX	6	10	6	1	26

$P = 0.041$ vs before administration (t-test).

Standard protocol approvals, registrations, and patient consents

This study was approved by JSPS Grants-in-Aid for Scientific Research (No. 21390269), and informed consent was obtained from all patients.

Data analysis

Statistical analyses were made using t-test, results were considered significant at a level of $P < 0.05$.

RESULTS

CASE REPORTS

Case 1

A 36-years-old man, who was a clarinet player, had 1-year history of cramps during the performance. His physical condition and mental condition was normal, and there were no neurologic abnormalities. At the age 35, he noticed an abnormal cramp on the left little finger during clarinet performance. The symptoms gradually worsened over time, finally he became no longer able to play the clarinet in the concert. He had been on medications with trihexyphenidyl up to 12 mg/day and clonazepam (1–3 mg/day) with no benefits.

At the age of 36-years-old, we tried zolpidem on him, which improved his symptoms dramatically to the extent that he had no problems in the performance. He took 10 mg of zolpidem before playing the clarinet, and found the beneficial effect within 30 min, its durations of action being about 3 h. One year later, he was still using zolpidem 10 mg once or twice a day for occasional concert.

Case 2

A-20-years-old woman, who was a softball player, had 1-year history for lower limbs dystonia. Her physical condition and mental condition was normal, and there were no neurologic abnormalities except for dystonic symptoms on the bilateral lower limbs. At the age 19, she noticed an abnormal inversion of the left ankle during walking. The symptoms gradually worsened, and she developed difficulty in walking because of her lower limbs muscle hyperactivity. Her dystonic symptoms did not change with or without shoes. She was tried medication with trihexyphenidyl (up to 12 mg/day), baclofen (up to 30 mg/day), and gabapentin, with no effect. At age 20, she became unable to walk, or to bend her knees and ankles. She was referred to us with a diagnosis of lower limb dystonia (**Figure 1**).

We treated her with zolpidem oral monotherapy with a dose up to 20 mg/day. Three days after the therapy, she found it easy to bend her right knee and could stand without any help. She could walk on day 7, and finally she could climb up and down stairs on day 14. One year later, she was still on zolpidem, with continued benefit.

Effects of zolpidem in miscellaneous types of dystonia

Table 1 depicts summary of the patients. BFMDRS in total dystonia patients were significantly decreased from 7.2 ± 7.9 to 5.5 ± 5.0 ($P = 0.041$).

As for subtypes of dystonia, the scale decreased on the average in generalized, Meige syndrome/blepharospasm, and hand dystonia (**Table 1**). After zolpidem, 3 of 9 generalized dystonia (33%), 2 of 10 Meige syndrome/blepharospasm (20%), and 3 of 8 hand dystonia patients (38%) improved in the motor subscale of BFMDRS (generalized dystonia; 29–75% improvement, Meige syndrome/blepharospasm; 33–39% improvement, hand dystonia; 33–67% improvement), whereas cervical dystonia patients did not. Overall, the present study showed that 8 of 34 dystonia patients (24%) responded to zolpidem.

Adverse effects associated with zolpidem were drowsiness, amnesia, and abnormal behavior (somnambulism). Moderate or severe drowsiness occurred in eight patients (three cases of responders and five non-responders), and transient amnesia occurred in four patients (two responders and two non-responders).

DISCUSSION

Here we described the outcome of zolpidem trial in patients with miscellaneous types of dystonia, whose symptoms had been refractory to other medications. In all dystonia patients, 24% of the patients responded to zolpidem, and remarkable improvements were found particularly in generalized and hand dystonias. No improvement was found in cervical dystonia. Despite the different outcome measures and clinical protocols, the present data are comparable to the efficacy of trihexyphenidyl in a previous study reporting improvements in 44% for generalized dystonia patients, 63% for Meige syndrome/blepharospasm, and 28% for focal dystonia patients (Jabbari et al., 1989).

Our result has a limitation that the design was not a randomized controlled trial. Indeed this is a pivotal study so that the conclusion regarding efficacy of zolpidem should be cautious and other studies are needed to replicate our results, It is

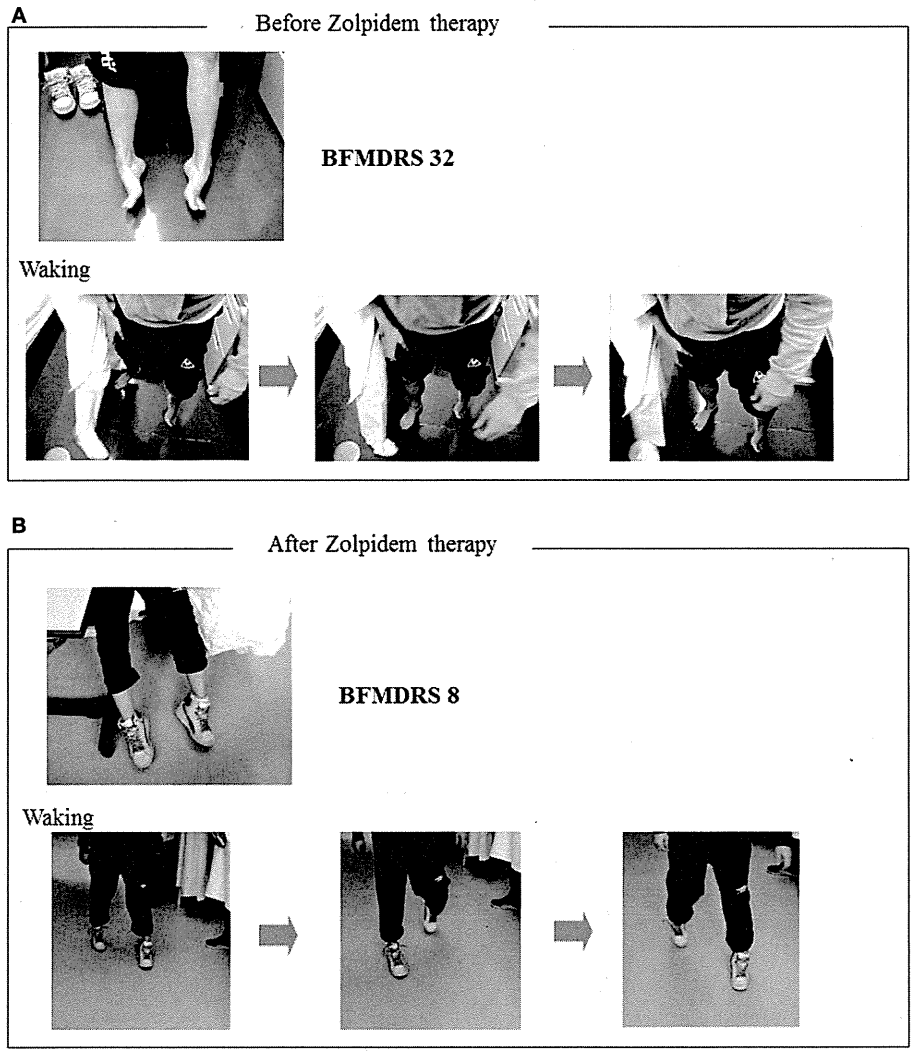

FIGURE 1 | (A) It is before treatment. She could not walk without help because of left dominant lower limbs dystonic spasm. **(B)** We started zolpidem 20 mg/day monotherapy, and at the day 14, she could walk without any support, despite the persisting inversion of the left ankle.

however unlikely that the beneficial effects are entirely placebo-based, because the patients had been equally tried on other medications with no benefit before enrollment. Moreover, improvement in the scale of the whole patients was significant. We therefore consider that zolpidem is a useful option for treating dystonia.

It was reported that some of adult onset primary focal dystonia patients spread proximally or contralaterally or become generalized within several years of symptom onset (Weiss et al., 2006). For that reason, we assessed all patients using BFMDRS, one of the major clinical dystonia scales for generalized dystonia, in this study. It would be desirable to evaluate on the scale suitable for each types of dystonia in future trials, with divided subtypes, being randomized, blinded, and placebo-controlled.

For the patients with generalized dystonia, Meige syndrome/blepharospasm, and hand dystonia, mild to remarkable improvements (29–75% improvement in BFMDRS) were observed, whereas no significant changes were found for cervical dystonia after zolpidem (**Figure 2**). Despite the small number of cases, blepharospasm was also refractory. Even within the same subtype, responsiveness to zolpidem considerably varied among patients.

We used zolpidem 5–20 mg/day for the patients with dystonia, and drowsiness was tolerated for most of the subjects. Eight out of 34 subjects complained relatively persistent drowsiness (3 cases of responders and 5 of non-responders). No correlation between drowsiness and effects to dystonia syndrome was found. It is however possible that doses used in this study may not be large enough to obtain the maximal benefit, because the previous studies used the doses up to 50–70 mg/day (Garretto et al., 2004; Young et al., 2008).

Focal hand dystonia (writer's cramp and other occupational cramps) is a primary dystonia produced by the excessive co-contraction of antagonistic muscles of the hand and forearm

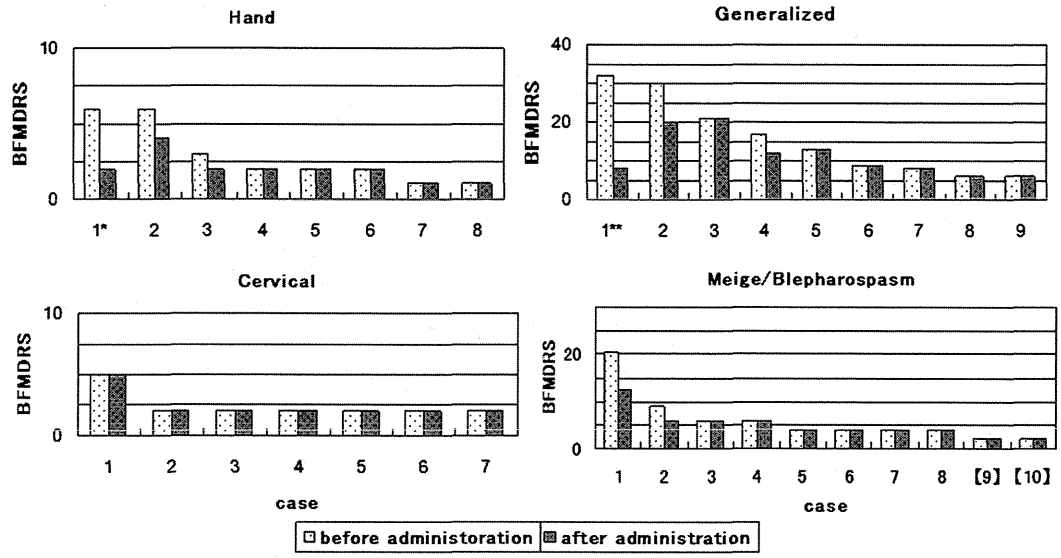

FIGURE 2 | Before and 1 month after zolpidem administration, patients with patients with generalized dystonia, Meige syndrome/ blepharospasm, cervical dystonia, and hand dystonia experienced improvement in the motor subscale of Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS). *Case 1; **Case 2; [9][10], blepharospasm.

(Sheehy and Marsden, 1982). In our study, 38% of the hand dystonia patients improved after zolpidem. In past study, botulinum toxin treatment of hand dystonia showed less favorable benefits than cervical dystonia or blepharospasm (Karp et al., 1994). Musicians' cramp or dystonia of other highly skilled performance are even more difficult to obtain the satisfactory outcome. Zolpidem is worth being tried on such patients as Case 1 in our study.

Zolpidem is an imidazopyridine agonist with a high affinity on the benzodiazepine site of $GABA_A$ receptors containing $\alpha 1$ subunit in combination with $\beta 2$ and $\gamma 2$ subunits (McKernan and Whiting, 1996; Sanna et al., 2002), equivalent to $\omega 1$ subtypes, present in interneurons in all brain areas including the hippocampus, the cortex, and the cerebellar Purkinje cells (McKernan and Whiting, 1996). Recently a high density of zolpidem binding sites was found in the thalamus (Licata et al., 2009) and the subthalamic nucleus (Chen et al., 2007), and possibly the globus pallidus (Duncan et al., 1995; Chen et al., 2004). After binding to these sites, zolpidem could enhance inhibitory pathways in the basal ganglia motor loop, accounting for the clinical improvement in dystonia.

Lack of responsiveness in cervical dystonia is unexplained in the present study. Intriguingly, the clinical improvement in cervical dystonia after globus pallidus internus deep brain stimulation (GPi-DBS) was reported to be less satisfactory than other subtypes (Starr et al., 2006; Lee et al., 2007). It might be possible that GPi-DBS and zolpidem could have similar mechanisms of action.

In conclusion, zolpidem may be a useful option for treating generalized/hand dystonias, and Meige syndrome who do not respond to botulinum toxin or oral medications.

ACKNOWLEDGMENTS

This study was supported by JSPS Grants-in-Aid for Scientific Research (No. 21390269). We thank the patients and their families for participating in this study.

SUPPLEMENTARY MATERIAL

The Movies S1–S5 for this article can be found online at http://www.frontiersin.org/Movement_Disorders/10.3389/fneur.2012.00058/abstract

REFERENCES

Albanese, A., Barnes, M. P., Bhatia, K. P., Fernandez-Alvarez, E., Filippini, G., Gasser, T., Krauss, J. K., Newton, A., Rektor, I., Savoiardo, M., and Valls-Solè, J. (2006). A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES task force. *Eur. J. Neurol.* 13, 433–444.

An, J. Y., Kim, J. S., Kim, Y. I., and Lee, K. S. (2008). Successful treatment of the Meige syndrome with oral zolpidem monotherapy. *Mov. Disord.* 23, 1619–1621.

Burke, R. E., Fahn, S., Marsden, C. D., Bressman, S. B., Moskowitz, C., and Friedman, J. (1985). Validity and reliability of a rating scale for the primary torsion dystonias. *Neurology* 35, 73–77.

Chen, L., Savio, C. C., and Yung, W. H. (2004). Electrophysiological and behavioral effects of zolpidem in rat globus pallidus. *Exp. Neurol.* 186, 212–220.

Chen, L., Xie, J. X., Fung, K. S., and Yung, W. H. (2007). Zolpidem modulates GABA(A) receptor function in subthalamic nucleus. *Neurosci. Res.* 58, 77–85.

Daniele, A., Albanese, A., Gainotti, G., Gregori, B., and Bartolomeo, P. (1997). Zolpidem in Parkinson's disease. *Lancet* 349, 1222–1223.

Duncan, G. E., Breese, G. R., Criswell, H. E., McCown, T. J., Herbert, J. S., Devaud, L. L., and Morrow, A. L. (1995). Distribution of [3H] zolpidem binding sites in relation to messenger RNA encoding the $\alpha 1$, $\beta 2$ and $\gamma 2$ subunits of GABAA receptors in rat brain. *Neuroscience* 64, 1113–1128.

Evidente, V. G. (2002). Zolpidem improves dystonia in Lubag or X-linked dystonia-parkinsonism syndrome. *Neurology* 26, 662–663.

Fahn, S., Bressman, S. B., and Marsden, C. D. (1998). Classification of dystonia. *Adv. Neurol.* 78, 1–10.

Garretto, N. S., Bueri, J. A., Rey, R. D., Arakaki, T., Nano, G. V., and Mancuso, M. (2004). Improvement of

blepharospasm with zolpidem. *Mov. Disord.* 19, 967–968.

Holm, K. J., and Goa, K. L. (2000). Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs* 59, 865–889.

Jabbari, B., Scherokaman, B., Gunderson, C. H., Rosenberg, M. L., and Miller, J. (1989). Treatment of movement disorders with trihexyphenidyle. *Mov. Disord.* 4, 202–212.

Karp, B. I., Cole, R. A., Cohen, L. G., Grill, S., Lou, J. S., and Hallett, M. (1994). Long-term botulinum toxin treatment of focal hand dystonia. *Neurology* 44, 70–76.

Lee, J. Y., Deogankar, M., and Rezai, A. (2007). Deep brain stimulation of globus pallidus internus for dystonia. *Parkinsonism Relat. Disord.* 13, 261–265.

Licata, S. C., Jensen, J. E., Penetar, D. M., Prescot, A. P., Lukas, S. E., and Renshaw, P. F. (2009). A therapeutic dose of zolpidem reduces thalamic GABA in healthy volunteers: a proton MRS study at 4 T. *Psychopharmacology (Berl.)* 203, 819–829.

McKernan, R. M., and Whiting, P. J. (1996). Which GABAA-receptor subtypes really occur in the brain? *Tends Neurosci.* 19, 139–143.

Park, I. S., Kim, J. S., An, J. Y., Kim, Y. L., and Lee, K. S. (2009). Excellent response to oral zolpidem in a sporadic case of the myoclonus dystonia syndrome. *Mov. Disord.* 24, 2172–2173.

Sanna, E., Busonero, F., Talani, G., Carta, M., Massa, F., Peis, M., Maciocco, M., and Biggio, G. (2002). Comparison of the effects of zaleplon, zolpidem, and triazolam at various GABA(A) receptor subtypes. *Eur. J. Pharmacol.* 451, 103–110.

Sheehy, M. P., and Marsden, C. D. (1982). Writer's cramp: a focal dystonia. *Brain* 105, 461–480.

Starr, P. A., Turner, R. S., Rau, G., Lindsey, N., Heath, S., Volz, M., Ostrem, J. L., and Marks, W. J. Jr. (2006). Microelectrode-guided implantation of deep stimulators into the globus pallidus internus for dystonia: techniques, electrode locations, and out comes. *J. Neurosurg.* 104, 488–501.

Weiss, E. M., Hershey, T., Karimi, M., Racette, B., Tabbal, S. D., Mink, J. W., Paniello, R. C., and Perlmutter, J. S. (2006). Relative risk of spread of symptoms among the focal onset primary dystonias. *Mov. Disord.* 21, 1175–1181.

Young, J., Kim, J. S., Kim, Y. I., and Lee, K. S. (2008). Successful treatment of the Meige syndrome with oral zolpidem monotherapy. *Mov. Disord.* 23, 1619–1620.

Conflict of Interest Statement: 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.

Received: 06 October 2011; accepted: 28 March 2012; published online: 17 April 2012.

Citation: Miyazaki Y, Sako W, Asanuma K, Izumi Y, Miki T and Kaji R (2012) Efficacy of zolpidem for dystonia: a study among different subtypes. Front. Neur. 3:58. doi: 10.3389/fneur.2012.00058

This article was submitted to Frontiers in Movement Disorders, a specialty of Frontiers in Neurology.

Pre-operative Inclusion and Exclusion Criteria for Deep Brain Stimulation in Dystonia

Helen Bronte-Stewart, MD MSE,[1] Takaomi Taira, MD,[2] Francesc Valldeoriola, MD,[3] Marcello Merello, MD,[4] William J. Marks, Jr., MD,[5] Alberto Albanese, MD,[6] Susan Bressman, MD,[7] Elena Moro, MD, PhD[8]

[1] Department of Neurology and Neurological Sciences, Stanford University, Stanford, California, USA
[2] Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan
[3] Servei de Neurologia, Institut Clínic de Neurociències, Hospital Clínic, Barcelona, Spain
[4] FLENI, Department of Movement Disorders, Buenos Aires, Argentina
[5] Department of Neurology, University of California, San Francisco, California, USA
[6] Istituto Neurologico Carlo Besta and Università Cattolica, Milano, Italy
[7] Mirken Department of Neurology, Beth Israel Medical Center, New York, NY, USA
[8] Movement Disorders Center, Division of Neurology, TWH, University of Toronto, UHN, Toronto, Ontario, Canada

Corresponding author:
H. Bronte-Stewart
SUMC, Rm A343, Department of Neurology and Neurological Sciences, Stanford University, 300 Pasteur Drive, Stanford, 94305 CA, USA
Tel. 650 498 4328
E-mail: hbs@stanford.edu

Financial Disclosures: the authors of this article have received no compensation for the research covered in this article.
H. Bronte-Stewart: none
T. Taira
F. Valldeoriola
M. Merello
WJ Marks
A. Albanese
S. Bressman
E. Moro has received honoraria for consulting services and lecturing from Medtronic. She has also received research grant support from CurePSP, St. Jude Medical and Canadian Institute of Health Research

ABSTRACT

When considering a patient with dystonia for deep brain stimulation (DBS) surgery several factors need to be considered. However, to date the selection criteria for DBS - specifically in terms of patient features (severity and nature of symptoms, age, time of evolution, or any other demographic or disease aspects) - have not been assessed in a systematic fashion. In general, dystonia patients are not considered for DBS unless medical therapies have been previously and extensively tested, including different groups of drugs, botulinum toxin injections, and physiotherapy. The vast majority of reported patients have had DBS surgery when the disease was provoking important disability, with loss of independence and impaired quality of life. Current evidence suggests that subjects with primary generalized dystonia (PGD) should undergo DBS at an early age and sooner rather than later after disease onset to gain the optimal benefit from DBS. There does not appear to be an upper age limit nor a minimum age limit, although there are no published data regarding the outcome of globus pallidus internus (GPi) DBS for dystonia in children younger than seven years of age. All motor features and associated pain in primary dystonia are potentially responsive to GPi DBS, although response of speech has been less consistent. While dystonic features may improve, spasticity and other neurological deficits in secondary dystonias do not respond to DBS. Previous ablative procedures, such as thalamotomy, pallidotomy, and peripheral denervation, should not prevent consideration of DBS.