



Loss of inhibition in sensorimotor networks in focal hand dystonia



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ABSTRACT

Objective: To investigate GABA-ergic receptor density and associated brain functional and grey matter changes in focal hand dystonia (FHD).

Methods: 18 patients with FHD of the right hand and 18 age and gender matched healthy volunteers (HV) participated in this study. We measured the density of GABA-A receptors using [¹¹C] Flumazenil and perfusion using [¹⁵O] H₂O. Anatomical images were also used to measure grey matter volume with voxel-based morphometry (VBM).

Results: In FHD patients compared to HV, the vermis VI of the right cerebellum and the left sensorimotor cortex had a decrease of Flumazenil binding potential (FMZ-BP), whereas the striatum and the lateral cerebellum did not show significant change. Bilateral inferior prefrontal cortex had increased FMZ-BP and an increase of perfusion, which correlated negatively with disease duration. Only the left sensorimotor cortex showed a decrease of grey matter volume.

Interpretation: Impairments of GABAergic neurotransmission in the cerebellum and the sensorimotor cortical areas could explain different aspects of loss of inhibitory control in FHD, the former being involved in maladaptive plasticity, the latter in surround inhibition. Reorganization of the inferior prefrontal cortices, part of the associative network, might be compensatory for the loss of inhibitory control in sensorimotor circuits. These findings suggest that cerebellar and cerebral GABAergic abnormalities could play a role in the functional imbalance of striato-cerebello-cortical loops in dystonia.

1. Introduction

Focal hand dystonia (FHD) is clinically characterized by involuntary muscular co-contraction causing incoordination and abnormal posturing of the hand during skillful movements that are over-trained. A common hypothesis to explain the pathophysiology of FHD is a reduction of inhibitory control over the cortical motor areas that would cause sustained muscle contraction (Beck and Hallett, 2011; Hallett, 2011; Marsden, 1995; Mink, 2003). Yet, there is at present no direct demonstration of what would cause such a phenomenon. In this study, we seek to better understand the pathophysiology of inhibitory control in FHD.

Inhibitory control in the human brain is achieved through the

neurotransmitter gamma-aminobutyric acid (GABA). Pharmacological work using Flumazenil, a benzodiazepine antagonist that binds to GABA-A receptors, showed GABAergic impairments in the thalamus and the cerebellum in animal models of dystonia (Ledoux and Lorden, 2002; Zhang et al., 2011; Zhao et al., 2011). GABAergic dysfunctions in the striatum and the cerebellum have been suggested in FHD (Ceballos-Baumann et al., 1995a; Krystkowiak et al., 1998; Lehericy et al., 1996; Shakkottai et al., 2016). A flumazenil study found GABAergic deficits in the sensorimotor cortex but none in the cerebellum and putamen in dystonic patients (Garibotto et al., 2011). A majority of the patients in this study had DYT1 dystonia and all had impairments affecting several body parts except for two with focal dystonia. DYT1 dystonia differs from FHD, which is typically sporadic, acquired after intensive and

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repetitive motor practice, and affects a specific type of skillful hand movements.

GABAergic neuromodulation is involved in the fine tuning of brain networks (Popa et al., 2013). It is conceivable that altered GABAergic neuromodulation would be associated with functional abnormalities in the sensorimotor network. For instance, FHD patients are known to have functional impairments in the primary and secondary motor cortices, in the striatum and cerebellum (Wu et al., 2010; Butz et al., 2006; Garraux et al., 2004). Task-related activation studies cannot easily isolate functional changes primarily related to the disease, because they often involve groups with different motor performances or task-induced compensatory mechanisms. Resting state represents a useful tool to isolate disease-related changes, and abnormal resting state activity has been observed in striato-cortical and the cerebello-cortical loops in FHD (Dresel et al., 2014; Hinkley et al., 2013). In addition to functional changes, GABAergic deficits in sensorimotor areas could be associated with structural changes as already found in this patient population (Delmaire et al., 2007; Gibb et al., 1992). Loss of grey matter volume in areas showing GABAergic deficits would suggest that abnormal inhibitory control could be related to neuronal loss.

In a homogeneous patient population of FHD with focal symptoms in the right dominant hand and matching healthy controls, we used a multimodal imaging protocol including (1) Positron Emission Tomography (PET) with flumazenil binding; (2) PET with [¹⁵O]-H₂O to investigate cerebral activation of brain areas with abnormal GABAergic receptor density; and (3) MRI voxel-based morphometry to verify whether areas with abnormal GABAergic receptor density would have abnormal grey matter volume. We hypothesize that the functional imbalance of striato-cerebello-cortical loops are due to decreases in inhibition in the contralateral striatum, contralateral sensorimotor cortex, and the ipsilateral cerebellum.

2. Methods

2.1. Subjects

We studied eighteen patients with focal hand dystonia and eighteen healthy volunteers. Patient ages ranged from 24 to 65 years (3 women, 15 men; mean age \pm standard deviation = 53.94 \pm 12.04 years); eighteen control subjects were matched for age from 22 to 65 years and sex (3 women, 15 men; mean age \pm standard deviation = 53.29 \pm 12.79 years). All subjects had normal neurologic examinations apart from FHD diagnosis in the patient group. The duration of FHD ranged from 3 to 41 years (mean \pm standard deviation = 13.8 \pm 9 years). All patients were also evaluated with the Fahn-Marsden scale (FMS, score range from 2 to 4) to assess for the severity and specificity (restricted to the hand) of symptoms. Patients who participated in the study did not present any symptoms at rest so that there was no interference with the scanning procedure. Patients were off any medication affecting the central nervous system during the study and for at least 3 months before the study. Specifically, none of the subjects were on benzodiazepine medication, which binds GABA-A receptors and competes directly with flumazenil for binding; baclofen which binds GABA-B receptors; flunitrazepam, a benzodiazepine receptor agonist; or triazolam, a partial allosteric modulator of GABA-A receptors. All patients had their last injection of botulinum toxin (BoNT) at least 3 months before the study. The study was approved by the Institutional Review Board of the National Institutes of Health. All participants gave their informed consent.

2.2. MRI and PET procedures

For all subjects, high-resolution structural T1-weighted images were acquired for anatomical co-registration with a 3 T GE scanner (9 min, TR = 6.172 ms, TE = 3.2 ms, slice thickness = 1.3 mm, no gap, FOV = 240 \times 240 mm², 256 \times 256 matrix, in-plane

resolution = 0.9375 \times 0.9375 mm²). For the PET scan acquisition, participants were scanned using a General Electric Advance Scanner (GE Medical Systems, Waukesha, WI). Images were acquired in axial order (FOV = 150 \times 150 mm², 35 contiguous slices were acquired, plane separation = 4.25 mm; spatial resolution of raw PET images was 6 to 7 mm full width at half maximum (FWHM)). An 8-min transmission scan for attenuation correction was obtained at the beginning of the session (see Lerner et al., 2007; Lerner et al., 2012). Subject motion during the PET acquisition was corrected with mutual-information registration of each scan timeframe to a standard frame before attenuation correction (Andersson et al., 1995). Based on the calculated motion, the transmission images were resliced and projected for final reconstruction and realignment (matrix size of 256 \times 256 matrix, in plane resolution = 2 \times 2 mm²). To minimize head movements during the scans, an individually molded thermoplastic mask was placed on the face and head of each subject. Subjects were instructed to lie still while relaxing with their eyes closed, to think of nothing in particular and not to fall asleep. The entire duration of the PET procedures was two hours, one hour for [¹⁵O] H₂O to measure regional cerebral blood flow (rCBF), and one hour for flumazenil to measure GABA-A receptors.

During the first hour, all subjects received 5 intravenous boluses of 10 mCi of [¹⁵O] H₂O at 10-minute intervals. The distribution of cerebral radioactivity was measured in a 60-second emission scan after each bolus injection. No arterial line was inserted because of the equivalence in errors in measuring tissue radioactivity and in the calculated rCBF (Herscovitch et al., 1983; Lerner et al., 2007; Lerner et al., 2012). During the second hour, and after the injection of 20 mCi of [¹¹C] flumazenil, 60-min dynamic emission images of the brain were acquired.

2.3. Data analysis

2.3.1. PET

Binding potential images for flumazenil (FMZ-BP) were created using the 2-step version of the simplified reference tissue model (SRTM2) (Wu and Carson, 2002). The input kinetics for the reference tissue were derived from the pons (drawn on each individual's MR image), where the [¹¹C] flumazenil binding is predominantly accounted for by free and non-specifically bound radiotracer (Lerner et al., 2007; Lerner et al., 2012; Millet et al., 2002; Odano et al., 2009). FMZ-BP images were corrected for partial volume effects and grey-white matter ratios on a pixel by pixel basis (Giovacchini et al., 2005). FMZ-BP images (already transformed to MR space) were normalized to the standard Montreal Neurological Institute (MNI) PET template (Ashburner and Friston, 1999) using AFNI (<http://afni.nimh.nih.gov/afni>, Bethesda, MD), smoothed (FWHM of 10 mm) and analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, UCL, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>) implemented in Matlab (Mathworks Inc., Natick, MA). To test our hypothesis, a between group analysis was performed (2 sample *t*-test) to show the brain areas that had a decrease or an increase of FMZ-BP in patients when compared with healthy subjects at the level of the whole brain. Age and sex were included in this analysis as nuisance covariates. An additional region of interest (ROI) analysis was run for contralateral striatal (putamen and caudate nuclei) regions involved in sensorimotor functions using the a-priori masks of the YEB atlas normalized in MNI space (Lehéricy et al., 2006), and ipsilateral cerebellar lobules V, VI and VIII containing a representation of the hand (Schmahmann et al., 1999; Küper et al., 2012; Schlerf et al., 2010).

The image processing and analysis of resting state rCBF levels were performed using Statistical Parametric Mapping SPM8. The images were realigned to the first volume. The resliced volumes were normalized to a standard PET template based on the MNI reference brain in MNI space (Talairach and Tournoux, 1988). Additionally, we used an atlas for the cerebellum (Schmahmann et al., 1999) for the spatial localization of the clusters. The normalized images of 2 \times 2 \times 2 mm³

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