A multimodal imaging approach for phenotyping of dynein heavy chain mutant mice CrA1 using MRI and PET/CT

D. Stiller¹, T. Kaulisch¹, S. Bucher¹, J. Tillmanns¹, D. Kind¹, H. G. Niessen¹, K. Rona-Vörös², K. E. Braunstein², H-P. Müller², L. Dupuis³, and A. C. Ludolph²

¹In-Vivo Imaging, Dept. of Drug Discovery Support, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, BW, Germany, ²Dept. of Neurology, University of Ulm, Ulm, BW, Germany, ³ISERM U692, Strasbourg, France

Introduction

In 2003 a mouse model containing a point mutation in the DNCHC-1 gene (dynein cytoplasmic heavy chain 1) was described [1,2]. Dyneins are motorproteins expressed in cells of the central nervous system and within them responsible for various types of motion: retrograde axonal transport, protein distribution, movement of vesicles and organelles. The Cra-1 mutation leads to a disturbed function of the dynein complex and thereby to a disturbed retrograde transport. Overall the mouse model is characterized by the occurrence of abnormal reflexes due to neonatal sensory neuropathy and by progressive motor and behavioural abnormalities in the absence of motor neuron degeneration [3]. In the brain the striatum, an important coordination center for movement, is the main structure affected by the dynein mutation. Previous results had shown the occurrence of striatal astrocytosis occurring with age along with gene expression alterations reminiscent of striatal dysfunction. However, no in-vivo characterization of the brain has been performed so far. In this contribution we describe the longitudinal, multimodal phenotyping of Cra1 mice using in vivo MR imaging and [18F]-Fallypride PET to investigate structural and functional alterations in the mouse brain.

Animal Handling and Methods

Throughout all imaging experiments four groups of mice were measured: mutant and wildtype, both separated in male and female (group strength n = 10 for all groups). MRI data were acquired on a Biospec 47/40 scanner (Bruker BioSpin, Ettlingen, Germany) at 4.7 Tesla (200 MHz ¹H-Frequency). Mice were anaesthetized through continuous inhalation of 1.2-1.5% isoflurane (in 70:30 N₂O:O₂) and fixed in a stereotactic head holder. For anatomical analysis of the mouse brain contiguous sets of axial (20 slices) and horizontal (10 slices) T₂-weighted images were acquired using a RARE sequence [4]. Imaging parameters were: TR 2500 ms, TE 12.5 ms, TE eff 50 ms, slice thickness 600 µm (no gap), FOV 28.1 mm x 26.6 mm, matrix size 256 x 256, RARE factor 8, 8 averages. PET imaging was performed on an Inveon PET/CT system (Siemens Molecular Imaging, Erlangen, Germany) using the D₂ receptor ligand [18F]-Fallypride [5]. While MR images were acquired at an animal age of 5 and 10 months, PET measurements were only performed at the latest time point. MR data were analyzed using a custom-made software for volumetric analysis, which allows for the automated analysis of the ventricle volume. PET data were analyzed using the Siemens Inveon Research Workplace Package by a simplified reference tissue model (SRTM) to assess alteration in the Fallypride binding potential (BP) between wildtype and mutant mice [6].

Results

Figures above show typical MR and PET images of a mouse from this study. Sizes of ventricles (fig. 1a) and striatum (fig. 1b) were analyzed in the MR images, whereas PET images (fig. 3) yielded the uptake of the specific D₂-receptor ligand Fallypride. Compared to wildtype mice, in mutant mice the size of the striatum was significantly decreased and that of the ventricles increased (fig. 2a and 2b, respectively). Nevertheless, significant correlations between the two parameters exist. PET imaging revealed a significantly reduced uptake of Fallypride in the striatum (see graph in the bottom row), supporting the theory of cell loss in the structure.

References