Preclinical MR biomarkers in Parkinson's disease models

Alexandra Petiet*[1]

[1]Institut du Cerveau et de la Moëlle Epinière = Brain and Spine Institute – Institut National de la Santé et de la Recherche Médicale : U1127, CHU Pitié-Salpêtrière [APHP], Sorbonne Universite : UM75, Centre National de la Recherche Scientifique : UMR7225 – France

Résumé

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Alexandra Petiet
Sorbonne Universités, UPMC Paris 06, Brain and Spine Institute, ICM, Hôpital de la Pitié Salpêtrière, Inserm UMR S 1127, CNRS UMR 7225, Paris, France
Center for Neuroimaging Research, Brain and Spine Institute, Paris, France

Introduction

Magnetic Resonance (MR) biomarkers play a crucial role in the diagnosis and monitoring of disease progression and treatment. A variety of MR methods are available to characterize neurodegeneration, iron accumulation and metabolic changes in animal models of Parkinson's disease (PD). This review aims at giving an overview of the MR methods that have been used in the 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) rodent models of PD. It further presents emerging methods that develop biomarkers of inflammation based on diffusion-weighted spectroscopy (DWS) and others that should allow the delivery of therapeutical agents based on the blood-brain barrier opening with MR-guided transcranial focused ultrasound.

Animal models

The most used models of neurodegeneration are based on injections of neurotoxins such as 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl1,2,3,6-tetrahydropyridine (MPTP) to produce degeneration of dopamine neurons in the substantia nigra (SN) and subsequently of the nigrostriatal pathway (1). Depending on the site of injection, 6-OHDA intoxication leads to rapid and massive cell death (medial forebrain bundle and SN injections) or to slow and progressive loss (striatal injection).

Microstructural markers

Diffusion imaging has been used to evaluate microstructural changes in those models. Fractional anisotropy (FA) was shown to decrease and the mean diffusivity (MD) was shown to increase in the SN of 6-OHDA rats, which was consistent with neurodegeneration and with human findings (2). Furthermore, FA was shown to increase in the striatum (STR)

*Intervenant

of 6-OHDA rats, which was consistent with neurodegeneration in a crossing-fiber structure such as STR (3).

Functional connectivity markers

Resting-state functional MRI has been used to explore functional connectivity (FC) changes in the nigrostriatal pathway. Decreased FC was found in the interhemispheric caudate putamen (CPu) (2), in the ipsilateral cortices (4), and between the ispilateral motor cortex (M1) and contralateral thalamus (TH) of 6- OHDA rats (3), which are presumably due to direct lesioning effects. Increased FC was found between the CPu and the sensorimotor cortex of both hemispheres (2), in the TH of both hemispheres (4), between the ipsilateral STR and globus pallidus (GP), the contralateral M1 and GP, and the interhemispheric STR and GP of 6-OHDA rats (3), which could be due to compensatory effects and reorganization, like it has been observed in PD patients.

Discrepancies are found in diffusion MRI and in rs-fMRI studies, which can be explained by the differences in the injection site, which produces different types of degeneration – massive or partial, rapid or progressive; or to the anesthesia protocols – Isoflurane or medetomidine alone or a combination of both, which alters neuronal activation in different ways; or to the sensitivity of the measures coming from different magnetic field strengths (from 7T to 11.7T) and different spatial resolutions.

Iron deposit markers

Iron deposits can be detected with conventional T2* imaging in the SN of 6-OHDA rats by measuring hyposignal levels (5).

Metabolic markers

MR spectroscopy can be used to assess brain metabolic changes. For example, increased GABA levels have been measured in the STR of MPTP mice and in 6- OHDA rats – consistent with human data, which makes it a good translational biomarker in PD (6,7).

Inflammation markers

Diffusion-weighted MRS can probe intracellular metabolite diffusion. Myoinositol diffusivity has been proposed as a specific marker of astrogliosis (8).

MR-guided Transcranial focused ultrasound for blood-brain barrier opening

Focused ultrasound coupled to microbubbles can be used to transiently open the blood-brain barrier and target specific brain regions for the delivery of therapeutical agents (9).

Conclusions

All of those imaging biomarkers provide insight into the physiopathology of PD however they do not replicate the entire complexity of the disease. The results should therefore be interpreted with this knowledge. Some discrepancies are found in the literature that can be attributed mainly to experimental conditions. Promising techniques emerge such as myo-inositol diffusivity as a marker of astrogliosis and blood-brain barrier opening for the delivery of drugs.

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Mots-Clés: Parkinson, imaging, MRI, biomarkers