Molecular and Metabolic Imaging in Multiple Sclerosis

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KEYWORDS

• Multiple sclerosis • MR imaging • Spectroscopy • PET • Molecular • Metabolic

KEY POINTS

- Molecular and metabolic imaging techniques assess dynamically and in vivo the pathogenetic mechanisms that lead to MS pathology and reflect the heterogeneity of pathologic abnormalities occurring in MS.
- ^{1}H-MR spectroscopy estimates brain levels of several metabolites, which reflect important biologic processes, such as mitochondrial function and/or neuronal integrity (*N*-acetyl-aspartate), and glial cell activation and proliferation (*myo*-inositol).
- ^{23}Na MR imaging estimates the total concentration of sodium within regions-of-interest in the brain. Increased total sodium concentration is thought to reflect axonal impaired energy metabolism and neurodegeneration.
- PET permits the characterization of the biologic processes occurring at the cellular and molecular levels. The following radioligands are often used: ^{18}F-fluoro-2'-deoxyglucose to investigate inflammation, translocator protein tracers to study microglia activation, amyloid tracers to study demyelination, and ^{11}C-flumazenil to investigate neuronal damage.
- Although technically challenging and expensive, the translation of these techniques to clinical trials and the clinical setting may allow stratification of patients for treatments.

INTRODUCTION

Recent advances in conventional MR imaging have remarkably improved the diagnosis of multiple sclerosis (MS), which can now be achieved earlier and with greater precision. T2 lesions and brain atrophy estimated with MR imaging are currently used in clinical trials as outcome measures. However, conventional neuroimaging techniques lack of specificity with regard to different pathophysiologic substrates of MS, and are not able to explain the heterogeneous and long-term clinical evolution of this disease.[1–4]

MS usually starts with a relapsing–remitting course (RRMS), characterized by the subacute occurrence of neurologic symptoms (namely relapses) that may be followed up by a clinical improvement. In view of this, the presence of focal areas of inflammatory demyelination in the white

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matter (WM), known as plaques and responsible for relapses, has been considered the main pathologic feature of MS. After 15 to 25 years from disease onset, the clinical course of MS typically shifts into a progressive course, which is termed secondary progressive MS (SPMS). However, a small group of patients (10%–15%) develop a progressive course of the disease since onset, and this type of MS is called primary progressive MS (PPMS).

The main pathologic mechanism underling the progressive course of MS is thought to be neurodegeneration. The occurrence of neurodegenerative features is considered to be a consequence of the inflammatory activity,[1,5,6] and a primary neurodegenerative component.[7] Neurodegeneration occurs diffusely in the brain and spinal cord of patients with MS, and is reflected by changes in structural imaging parameters that are measured within and outside lesions, namely in the normal appearing WM (NAWM) and gray matter (GM).[8]

The pathogenesis of MS is not fully understood, and it is thought that there is a series of pathobiologic events, starting with focal lymphocytic infiltration and microglia activation, and ending with demyelination and neuroaxonal degeneration (Fig. 1). In particular, a primary stimulus (either endogenous or exogenous) may be responsible for an inflammatory, demyelinating response, which induces a compensatory response within neurons. This response, which includes the redistribution of sodium channels along the demyelinated axolemma and increased mitochondrial metabolism, might have a transient functional benefit, but may be deleterious in the long-term. Specifically, oxidative stress, mitochondrial injury, and ion channel dysfunction have been suggested as possible "maladaptive" changes, leading to neuroaxonal damage (see Fig. 1).[1,9] Molecular and metabolic imaging have the unique ability to reflect in vivo some of the molecular and metabolic pathways involved in the development and progression of neurodegeneration in MS.[2,10]

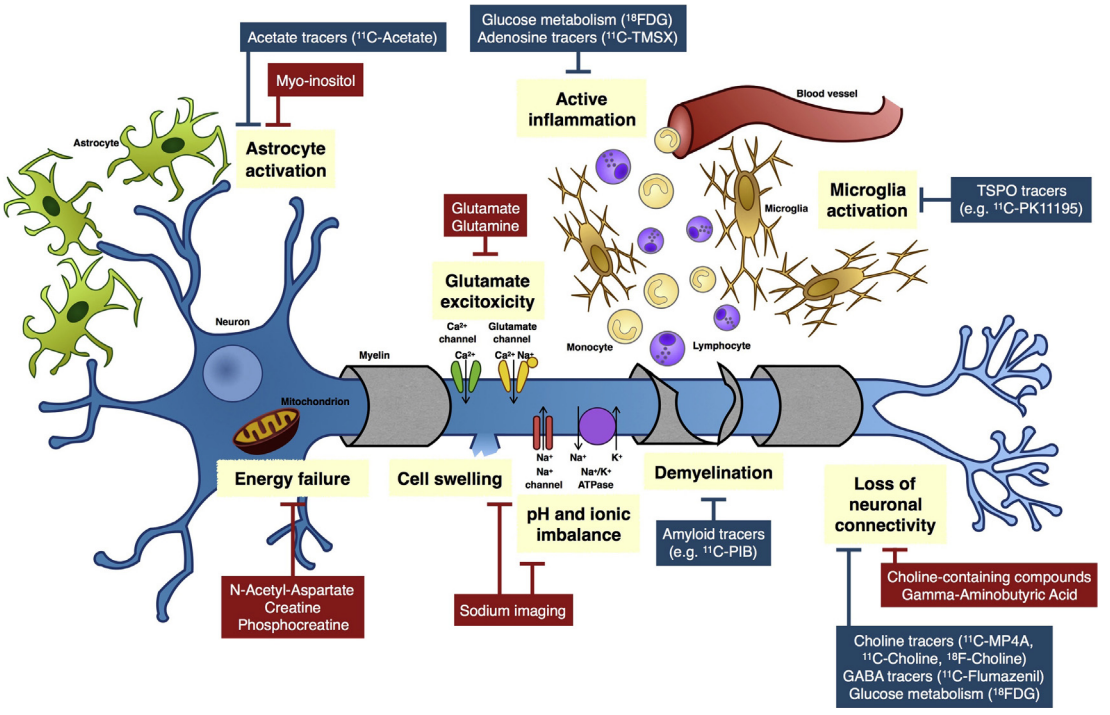

Fig. 1. Mechanisms of neurodegeneration and the molecular and metabolic imaging targets studied in MS. Inflammatory cells (eg, lymphocytes, monocytes, microglia) produce reactive oxygen species and reactive nitrogen species, which contribute to mitochondrial injury. This leads to metabolic stress, energy deficiency, and progressive loss of neuroaxonal function. Activation and proliferation of astrocytes occur to restore neuroaxonal function, although reactive astroglial cells also have harmful consequences on axonal survival. After acute demyelination, there is a redistribution of ion channels (eg, Na^+ channels) that, along with accumulation of glutamate (the main excitatory neurotransmitter of the central nervous system), promotes ionic imbalance, with increased intracellular concentration of calcium and consequent neuronal apoptosis. The metabolites most commonly studied in MS are highlighted in the red boxes, and the targets of PET radioligands are shown in the blue boxes. TSPO, translocator protein.