MRS of Transgenic Mice

Gülin Öz, PhD

**Center for Magnetic Resonance Research,
University of Minnesota, Minneapolis, MN, USA**

Neurochemical profiling by in vivo ^{1}H MRS has experienced rapid improvements in recent years (1). This was primarily due to the increased sensitivity and spectral dispersion achieved at high magnetic fields and development of sophisticated spectral deconvolution methods (2). Together these improvements facilitate non-invasive quantification of up to 20 metabolites in small volumes-of-interest in the mouse brain (3). Such neurochemical profiles can provide multiple biomarkers to monitor disease progression and reversal in transgenic models of human diseases (4-6). For example, concentrations of neurotransmitters (glutamate, γ-aminobutyric acid, aspartate), antioxidants (glutathione, vitamin C) and energy metabolites (glucose, lactate, creatine/phosphocreatine) can provide measures of biochemical processes relevant to many neurodegenerative diseases, such as excitotoxicity, oxidative stress and energy failure (7, 8). However, such potential MRS biomarkers need to be validated extensively for successful translation of the findings from transgenic mouse models to human applications.

First, alterations in neurochemical profiles with disease need to be similar in the model species and humans. Transgenic models of hereditary conditions are advantageous in this respect since they usually faithfully reproduce multiple aspects of the human disease. Hence, the pathology of patients and mouse models that have the same genetic defect tends to be similar, potentially leading to parallel neurochemical alterations in both species. Next, the MRS biomarkers need to be sensitive to subtle and early biochemical alterations due to pathology, as well as reliably gauge the progression of pathology. Since biochemical alterations associated with neurodegeneration precede symptoms and irreversible cell death (9), MRS has great potential for detecting the earliest indications for neuronal dysfunction. The sensitivity of MRS biomarkers to early and progressive pathology can be established by parallel MRS and histological examination of the same brains. The advantage of the non-invasive MRS technique is that these data can be obtained longitudinally and disease progression can be monitored in individual animals. With careful experimental design, the MRS data can be compared to histology in a subset of the animals monitored for different lengths of time. Finally, the MRS biomarkers need to be sensitive to disease reversal such that they can be used in preclinical and clinical trials to monitor treatment effects. Conditional transgenic mouse models where the expression of the mutant protein can be turned on and off at will, e.g. by doxycycline administration (10), provide the ideal opportunity to investigate the sensitivity of MRS biomarkers to disease reversal. Examples for these points will be given with data obtained from transgenic models of spinocerebellar ataxia type 1 (SCA1), a hereditary movement disorder caused by the expansion of a polyglutamine repeat in the affected protein (11).

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