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Review

In vivo assessment of neurotransmitters and modulators with magnetic resonance spectroscopy: Application to schizophrenia

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ABSTRACT

In vivo measurement of neurotransmitters and modulators is now feasible with advanced proton magnetic resonance spectroscopy (^{1}H MRS) techniques. This review provides a basic tutorial of MRS, describes the methods available to measure brain glutamate, glutamine, γ-aminobutyric acid, glutathione, *N*-acetylaspartylglutamate, glycine, and serine at magnetic field strengths of 3 T or higher, and summarizes the neurochemical findings in schizophrenia. Overall, ^{1}H MRS holds great promise for producing biomarkers that can serve as treatment targets, prediction of disease onset, or illness exacerbation in schizophrenia and other brain diseases.

Contents

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1. Introduction

Proton magnetic resonance spectroscopy (^{1}H MRS) is a noninvasive technique that allows the quantification of certain biochemical concentrations in vivo. In the brain, these biochemicals reflect a wide variety of mechanisms that range from cellular function and viability to neurotransmission. The information provided by ^{1}H MRS is useful for researchers to understand pathological processes and treatment effects in brain diseases such as schizophrenia. The majority of ^{1}H MRS studies of schizophrenia measured *N*-acetylaspartate (NAA, a marker of neuronal viability and function), choline + phosphocholine + glycerophosphocholine or choline-containing compounds (Cho, reflective of membrane turnover), and creatine + phosphocreatine (Cr, an index of energy metabolism), simply because these biochemicals yield the most prominent peaks in the ^{1}H spectrum and therefore are the easiest to quantify. The consistent finding from ^{1}H MRS studies in schizophrenia is reduced frontal and temporal lobe NAA (Rowland et al., 2001; Steen et al., 2005; Brugger et al., 2011), plausibly reflecting neuronal dysfunction in these brain regions.

There are several neurochemicals that could prove fruitful in the elucidation of the pathophysiological processes that underlie schizophrenia and have potential to serve as biomarkers for treatment targets, prediction of disease onset, or exacerbation. However, reliable measurement of these biochemicals by ^{1}H MRS poses technical challenges because of their low concentrations and low sensitivity due to J-coupling which results in multiplet peaks in the spectrum as well as spectral overlap. Fig. 1 provides an illustration of a proton spectrum and corresponding metabolites. Major advances have been made in measuring these biochemicals using ^{1}H MRS, and these advances include higher sensitivity and spectral dispersion due to higher magnetic field strengths, greater reliability due to improved MR scanner hardware, new optimized pulse sequences for spectral acquisition, and improved spectral quantification algorithms and commercial software packages. This review will focus on the latest single voxel ^{1}H MRS techniques and their applications for measuring such biochemicals as glutamate (Glu), glutamine (Gln), glutathione (GSH), γ-aminobutyric acid (GABA), *N*-acetylaspartylglutamate (NAAG), glycine, and serine in schizophrenia at field strengths of 3 T or higher. Although this review focuses on schizophrenia, these ^{1}H MRS techniques would be useful in other psychiatric and neurological disorders.

2. ^{1}H MRS overview

2.1. ^{1}H MRS signal

^{1}H MRS uses the same hardware equipment as standard magnetic resonance imaging (MRI), in which the radiofrequency (RF) coils and receiver channels are all tuned to the proton (^{1}H) resonance frequency. The external magnetic field generated by the MR scanner is denoted by "B_0", and the strength typically ranges from 1.5 to 3 T for clinical settings. An explanation of the basic magnetic resonance (MR) principles can be found in (Haacke et al., 1999; Liang and Lauterbur, 2000; Brown and Semelka, 2010) while a detailed explanation of the principles of ^{1}H MRS can be found in (Drost et al., 2002; Zhu and Barker, 2011; De Graaf, 2007). NAA, Cho, and Cr yield the strongest signals in a normal ^{1}H spectrum of the human brain, and therefore have been most extensively studied using ^{1}H MRS. However, with higher magnetic field strengths, glutamate and glutamine that have complex spectral patterns due to coupling between their ^{1}H nuclei can also be quantified using short echo time (TE) pulse sequences (Gruetter et al., 1998; Petroff et al., 2000; Deelchand et al., 2010; Mekle et al., 2009; Wijtenburg and Knight-Scott, 2011; Mullins et al., 2008) or specifically tailored pulse sequences (Hurd et al., 2004; Schubert et al., 2004; Yang et al., 2008).

2.2. Spectroscopic localization techniques

There are two main types of spectroscopic acquisition techniques, single-voxel and spectroscopic imaging (SI) also known as chemical shift imaging (CSI). With single-voxel spectroscopy, the signal is acquired from a 3-dimensional volume called a "voxel" in a region of interest to produce a single spectrum. In contrast, SI is a combination of spectroscopy and imaging, whereby spectral information is acquired in a spatial matrix with corresponding spectra in multiple voxels. There are advantages and disadvantages to both techniques. Single-voxel spectroscopy is ideal for hypothesis-driven questions about specific regions, and to quantify metabolites that have short T_2 relaxation or strongly coupled spin systems such as glutamate, glutamine, and GABA. Commonly used non-editing acquisition sequences include the stimulated echo acquisition mode (STEAM) and point resolved excitation spin-echo sequence (PRESS) sequences (Frahm et al., 1987; Bottomley, 1987). There are two editing sequences commonly used to detect GABA: 2D JPRESS (Ryner et al., 1995) and the more frequently used Mescher-Garwood (MEGA)-PRESS sequence (Mescher et al., 1998). MEGA-PRESS combines the frequency-selective editing technique (MEGA) with a PRESS sequence and is employed for spectral editing of the metabolites with *J*-coupled spin systems, such as GABA (Terpstra et al., 2002), GSH (Terpstra et al., 2003), and NAAG (Edden et al., 2007). In recent years, improved editing efficiency of the traditional MEGA-PRESS sequence has been reported at higher magnetic fields (Edden and Barker, 2007; Kaiser et al., 2007). Compared to single voxel sequences, the spatial resolution is superior with SI and thus allows the investigator to assess more brain regions and smaller voxels that may allow a distinction between gray and white matter. However, SI is generally limited to the measurement of metabolites with longer T_2 relaxation such as NAA, Cho, and Cr. Metabolites with shorter T_2s may not be visible using long TE acquisition, which is typical for SI applications. Recent advances in the field do include the applications of short TE SI sequences (Otazo et al., 2007; Gruber et al., 2008), and for more detailed information regarding SI sequences, see (Posse et al., 2013; Zhu and Barker, 2011).

2.3. Spectroscopic data considerations

There are several important considerations for the evaluation and interpretation of proton spectroscopic data that include shimming, metabolite quantification, and reliability/reproducibility. An important factor when acquiring spectroscopic data is shimming. Shimming is the act of adjusting the currents of the shim coils in order to make the magnetic field homogeneous in the region of interest (ROI). A smaller line width is always desirable since it translates to better spectral resolution and therefore improved quantification. Often on 3 T MR systems, a water peak line width of 12 Hz or less is most desirable, which indicates the acquired