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Research article

Effects of repeated dizocilpine treatment on glutamatergic activity in the prefrontal cortex in an animal model of schizophrenia: An in vivo proton magnetic resonance spectroscopy study at 9.4 T

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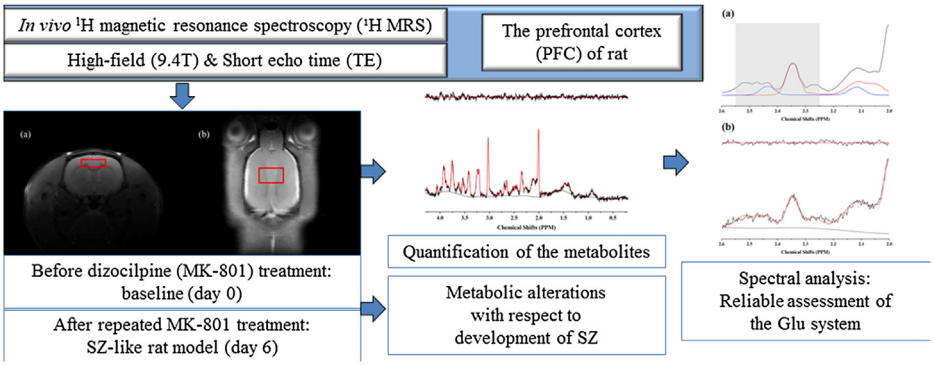
HIGHLIGHTS

- Accurate quantifications of glutamate and glutamine for assessment of Glu-activity.
- Developments of schizophrenia and metabolic alterations.
- High-field and Short-TE ^{1}H MRS for reduced cross-contamination of the metabolites.

GRAPHICAL ABSTRACT



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ABSTRACT

Repeated exposure to dizocilpine (MK-801) can be used as a model of schizophrenia that incorporates disease progression. Proton magnetic resonance spectroscopy (^{1}H MRS) has been widely used to investigate schizophrenia-related alterations in glutamate (Glu). The purpose of this study was to investigate metabolic alterations in the prefrontal cortex (PFC) in an animal model of schizophrenia by using in vivo ^{1}H MRS. Because of the spectral overlap of Glu and glutamine (Gln), high-field ^{1}H MRS with short echo time (TE) was used. A point-resolved spectroscopy sequence was used to measure the levels of Glu and Gln, and the brain metabolites in a volume of interest (22.5 μL) located in the PFC region of rats (n = 13) before and after 6 days of MK-801 (0.5 mg/kg) treatment. Analysis of the spectra showed that the cross-contamination of Glu and Gln can be considered to comparably low. No metabolic parameters were altered ($p > 0.05$). However, differences in Glu and N-acetylaspartate (NAA) levels between two times were significantly correlated ($p < 0.01$). The results showed both decreased (in 6 of the 13 rats) and increased (7 of the 13 rats) levels of Glu and NAA,

Abbreviations: SZ, schizophrenia; Glu, glutamate; PFC, prefrontal cortex; NMDA, N-methyl-D-aspartyl; ^{1}H MRS, proton magnetic resonance spectroscopy; Gln, glutamine; NAA, N-acetylaspartate; TE, echo time; SNR, signal-to-noise ratio; VOI, volume of interest; TR, repetition time; LCModel, linear combination of model; Cr, creatine; GPC, glycerophosphocreatine; PCho, phosphocholine; PCr, phosphocreatine; NAAG, N-acetylaspartylglutamate; tNAA, total NAA; Glx, glutamate-complex; tCho, total choline; tCr, total creatine; CRLB, Cramér-Rao lower bound.

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which suggested that these opposite metabolic alterations reflect two stage of disease progression. The results suggest that high-field and short TE in vivo ^{1}H MRS can quantify Glu and Gln with reliably low level of cross-contamination and that repeated exposure to MK-801 induces the progressive development of schizophrenia.

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1. Introduction

Schizophrenia (SZ), which affects about 1% of the total population [1], is a chronic and degenerative psychiatric disorder. The glutamate (Glu) hypofunction hypothesis of SZ is a generally accepted model of the pathophysiological of SZ that stems from the findings of Glu disturbances in cortical regions of patients with SZ [2–4]. The hypothesis postulated that psychosis is caused by Glu hyperactivity in the prefrontal cortex (PFC), which is induced by hypofunction of the *N*-methyl-D-aspartyl (NMDA) Glu receptor [1,5,6]. Localized in vivo proton magnetic resonance spectroscopy (^{1}H MRS) has been widely used to non-invasively investigate SZ-related alterations of the brain metabolites [7–10].

Many studies of SZ used in vivo ^{1}H MRS to investigate Glu activity in the PFC by quantifying Glu and glutamine (Gln) levels [9,10]. In addition to the Glu system, the disturbance in N-acetylaspartate (NAA) levels, which generally indicate neuronal density, and its' correlation to the Glu system in patients with SZ were investigated [11]. Because Glu is the major excitatory neurotransmitter and Gln is its precursor, investigations of both metabolites are required to accurately assess Glu activity. However, Glu and Gln have similar chemical shifts and J-coupling constants [12], and these similar responses to magnetic fields result in spectral overlap, which makes reliable quantification of their levels challenging [13,14]. In order to improve the quality of their quantification, the use of high-field ^{1}H MRS is advisable because of its enhanced sensitivity and spectral dispersion [15,16]. In addition, by applying a short echo time (TE), the T2 relaxation and J-evolution effects can be reduced, which results in an enhanced signal-to-noise ratio (SNR) [13,15,17–19]. Therefore, high-field (9.4T) short-TE ^{1}H MRS can be suitable for the reliable quantification of Glu and Gln levels with reduced cross-contamination.

Typically, the Glu hypofunction hypothesis was supported by the findings from ^{1}H MRS studies [7,8]. Although the findings in patients with SZ were mixed including no differences, a few studies reported increased (first-episode SZ) and decreased (chronic SZ) prefrontal Glu activity [7,8,11]. These contrasting changes reflected the stages of patient disease progression [11]. However, ^{1}H MRS conducted at a clinical field generally produces severe spectral overlapping of the Glu and Gln measures due to limited spectral dispersion [14,20]. It is necessary to quantify two metabolites with reduced cross-contamination to investigate Glu activity more accurately [21].

Preclinical studies of non-competitive NMDA receptor antagonists, including phencyclidine, ketamine, and dizocilpine (MK-801), consistently suggested that the drug-induced schizophrenic symptoms were related to the disturbances in Glu activity in the PFC [1,22–25]. However, these studies typically investigated only one stage of progression. It was reported that animal models consisting of repeated exposure to MK-801 induced SZ-like conditions including the development of illnesses ranging from first-episode to chronic SZ [23]. Additionally, extant studies indicated that repeated MK-801 administrations induced oxidative stress, increased apoptotic cells [26], and decreased white matter volume in animals [27], which were consistent with the findings in patients with SZ following the development of illnesses [11,28]. Therefore, this animal model can be important in investigating the pathophysiology and development of SZ.

Thus, the goal of this study was to investigate alterations of Glu in the PFC of an animal model of SZ induced by repeated exposure to MK-801 with high-field and short-TE ^{1}H MRS. Because of the enhanced spectral dispersion and SNR of these techniques, Glu and Gln levels can be quantified with reduced cross-contamination. Combining a high-field MR scanner with a short-TE sequence will enhance the diagnostic worth of ^{1}H MRS in investigations of Glu activity in SZ.

2. Materials and methods

2.1. Animal preparation and MK-801 treatment

All of the experimental and animal use protocols were approved by the Institutional Animal Care and Use Committee (IACUC) of the Asan Institute for Life Sciences of Asan Medical Center, which abides by the guidelines of the Institute of Laboratory Animal Resources. Male Sprague-Dawley rats (n = 13; Orient Bio Inc., Gyeonggi-Do, Korea) with an average weight of 300 g were used. All animals had free access to food and water. They were housed at 22–24 °C and a 12-h light/dark cycle with lights on at 08:00A.M. All rats received intraperitoneal injections of MK-801 (0.5 mg/kg; Sigma-Aldrich Co. LLC, St. Louis, MO, USA) once a day for six days. The MK-801 [(+)-MK-801 hydrogen maleate] was dissolved in a sterile 0.9% sodium chloride solution. The MK-801 dosage and administration schedule were based on a previous study [23].

2.2. MRI and ^{1}H MRS acquisition

MRI and in vivo ^{1}H MRS acquisition were conducted with a 9.4T/160 mm animal MR system (Agilent Technologies, Inc., Santa Clara, CA, USA) with a 160-mm horizontal bore magnet and 400-mT/m of actively shielded gradients and shims. For excitation, a birdcage volume coil of 72 mm was used, and a four-channel phased array surface coil was used as the receiver coil. MRI/MRS examinations were performed at baseline and after 6 days of MK-801 treatment. The examination was initiated 20 min after the last injection of MK-801. All rats were anesthetized with spontaneous inhalation of 2.0–2.5% isoflurane and a 1:2 mixture of O_2:NO_2 (250 mL/min) with an anesthesia unit. After anesthetization, the animals were positioned in the prone position in the handling system with a pressure sensor used for respiratory monitoring and a nose cone used to maintain anesthetization. During the 43-min examination, the body temperature of the animals was stabilized at 37.5 °C with an air heater system, and the respiratory rate was monitored to adjust the anesthetic concentration.

Multislice axial/coronal T2-weighted MR images were obtained with a fast spin echo sequence to localize the volume of interest (VOI), and the scan parameters were as follows: repetition time (TR), 4000 ms; effective TE, 32.95 ms; averages, 1; field of view, $30 \times 30\,mm^2$; matrix size, 256×256; and slice thicknesses, 1.5/1 mm (axial/coronal). A VOI of 22.5 μL ($5 \times 3 \times 1.5\,mm^3$) that mainly contained PFC was carefully determined. Localized shimming was performed, which resulted in a water line width range of

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