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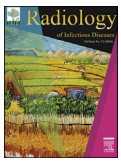

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Review

# Magnetic resonance imaging of glutamate in neuroinflammation

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**Abstract**

Inflammation in central nervous system (CNS) is one of the most severe diseases, and also plays an impellent role in some neurodegenerative diseases. Glutamate (Glu) has been considered relevant to the pathogenesis of neuroinflammation. In order to diagnose neuroinflammation incipiently and precisely, we review the pathobiological events in the early stages of neuroinflammation, the interactions between Glu and neuroinflammation, and two kinds of magnetic resonance techniques of imaging Glu (chemical exchange saturation transfer and magnetic resonance spectroscopy).


*Keywords:* Glutamate; GluCEST; $^{1}$H-MRS; Microglia; Neuroinflammation

## 1. Introduction

As we know, an efficient immune response is required for the defense against invading pathogens. However, neuroinflammation is considered a challenging clinical problem with substantial case fatality rates [1]. An inflammatory response in the CNS may contribute to a great number of acute or chronic neurological diseases (for example, multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy). Moreover, it is also thought to be closely related to some psychiatric diseases, including schizophrenia and depression [2]. These notorious diseases can clearly underscore the significance of the early detection of neuroinflammation.

The pathogenesis of neuroinflammation is characterized by a cascade of pathobiological events. Though histological analysis after biopsy can give us a precise picture at the actual stage of inflammation within a relatively small lesion area, molecular imaging shows us its great potentiality in diagnosing the lesion development in time and space.

What distinguished molecular imaging from high achievers, apart from assessing the accurate pathobiological event in vivo, was its high specificity and resolution. Molecular imaging referred in this review comprises the techniques that explore the magnetic resonance properties of protons, including amide and hydroxyl protons. It is undeniable that PET make a great contribution to achieving the possibility to visualize and study some neurotransmitters or their transporters under physiologic and pathologic conditions, like metabotropic Glu receptor subtype 5 [3], but it is restricted by its radiation exposure, low resolution and imaging logistics. In this review, we focus on a relatively new approach, namely

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chemical exchange saturation transfer (CEST), and a classical one, proton magnetic resonance spectroscopy ($^1$H-MRS). CEST is a modern MRI technique contributes to detect the slow-to-intermediate exchange rate of protons associated with proteins and neurochemicals with water. $^1$H-MRS has been used in clinical studies for many years, which estimates the concentrations of molecules that contain different numbers of protons.

In this review, we demonstrate the interaction between activated microglia and astrocytes in the early stages of neuroinflammation and summarize the insights provided by $^1$H-MRS and CEST. Experimental (preclinical) studies and clinical applications (when available) are reviewed to emphasize the contributions of H-MRS and CEST in understanding the pathogenesis in the early stages of neuroinflammation. We aim at showing the feasibility of $^1$H-MRS and CEST in assisting understanding the pathophysiology and evolution in the early stages of neuroinflammation.

## 2. Pathobiological events in the early stages of neuroinflammation

The central nervous system (CNS) is composed of neurons and the following three types of glial cells: microglia, astrocytes and oligodendrocytes [4]. Microglia are the primordial innate immune cells primarily activated in response to inflammatory stimulation in the CNS [5,6]. Microglia exist in at least two functionally discernable states once “activated” by inflammation, namely a phagocytic phenotype (innate activation) or an antigen presenting phenotype (adaptive activation) [7]. Once activated by certain pathogens, microglia secrets numerous glutamate [8–10] and other pro-inflammatory innate cytokines, characterized by pro-inflammatory cytokine production and adaptive activation of T cells. Experimental studies have shown that astrocytes may be colluded with by the activated microglia to cause the elevation of extracellular Glu in the early stages of neuroinflammation [10]. There are some Glu transporters in astrocytes, like GLAST (EAAT1 in humans) and GLT-1 (EAAT2), which are the major functional Glu transporters, playing an important role in maintaining extracellular Glu concentrations in the CNS below glutamate excitotoxic levels [11].

Glu is the major free amino acid present in the brain and has been regarded as one of the most important excitatory neurotransmitters in CNS. The central role of Glu in learning, memory and many other ways have been well reported [12,13]. However, glutamate excitotoxicity, caused by the elevated extracellular Glu concentration, has been reported in in vivo and in vitro inflammation models which suggest that concentrations of Glu increase in a range of neurologic disorders associated with inflammation, for example, multiple sclerosis (MS) [14–17], amyotrophic lateral sclerosis (ALS) [18] and epilepsy [19–21]. Meanwhile, impairments of Glu transporter function also have been reported in a large number of neurological diseases associated with inflammation [18–24].

Microglia, astrocytes and Glu play important roles in the early stages of neuroinflammation. Preclinical studies show us that in the early stages of neuroinflammation, activated microglia release Glu voluntarily to trigger the elevation of extracellular Glu, and astrocyte Glu transporters will be downregulated causing the elevation of astrocytic intracellular Glu levels. And as a result of these events, the extracellular Glu will increase to a great extent (Fig. 1) [10]. So that we draw a conclusion that extracellular glutamate concentrations rise as a result of the interaction between activated microglia and astrocytes in the early stages of neuroinflammation.

## 3. Insights provided by $^1$H-MRS and CEST

### 3.1. $^1$H-MRS

Proton magnetic resonance spectroscopy ($^1$H-MRS) is adept in analyzing the information of spin density, spin–spin couplings, molecular tumbling and properties related to the chemical environment of the proton. The present development of $^1$H-MRS has enabled the *invivo* study of certain chemical compounds or metabolites, which reflect a variety of pathological processes. Based on this, $^1$H-MRS has been widely used in studying the physiological or pathological changes in brain which are associated with inflammation during diseases progression [25–32]. For example, dedicated editing $^1$H-MRS

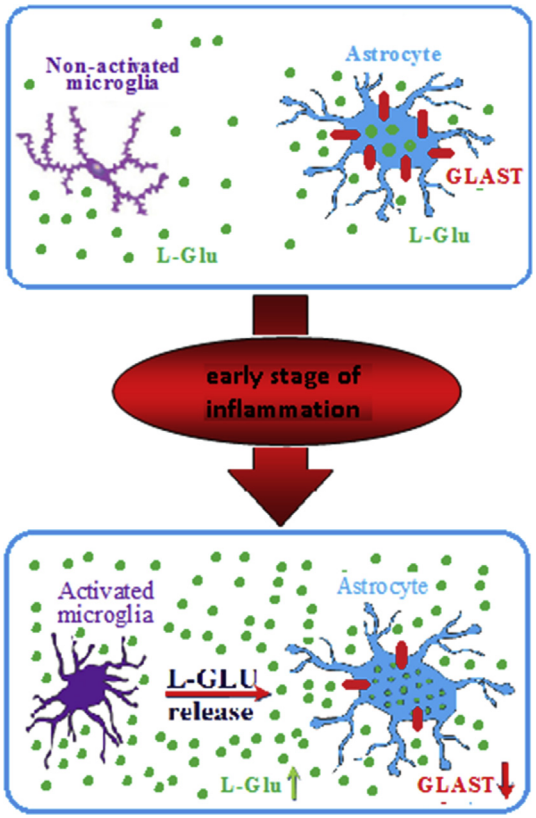


Fig. 1. Activated microglia release L-Glu. 2. The extracellular L-Glu causes the elevation of astrocytic intracellular L-Glu. 3. The GLAST expression is downregulated by the elevation of astrocytic intracellular L-Glu. 4. The interaction between activated microglia and astrocytes in the early stages of neuroinflammation results in evaluating the extracellular glutamate concentrations [10].

imaging techniques is capable of quantifying glutamate and separating it from the strongly overlapping glutamine signal. Short echo times along with spectral editing techniques will be valuable for $^{1}$H-MRS in detecting Glu's signature groups [33,34].

Clinical studies showed that Glu concentrations (estimated at 3 T) increased in active, enhancing lesions, and remained normal by contrast in chronic lesions, in multiple sclerosis, infiltrated by inflammation (Fig. 2) [35]. Other experimental studies suggest that increased inflammation probably is related to the Glu in active lesions, because active MS lesions show high glutaminase expression (glutaminase is a marker of Glu production) in microglia, linked cheek by jowl to the dystrophic axons [36]. And in the brain, previous work has shown higher Glu content in gray matter than white matter [37,38]. Therefore, studies of Glu in vivo will make the changes of this neurotransmitter associated with the pathogenesis of neuroinflammation identifiable. And it seems valuable to detect the changes of Glu's concentrations by $^{1}$H-MRS to alarm us that the inflammation has begun to infiltrate CNS.

Unfortunately, sometimes some clinical studies fall short of expectations. At 1.5 T, with different protocols and patients with different characteristics, other clinical studies show different results. Productive changes in Glu concentrations were reported neither between the normal-appearing white matter and control white matter, nor between the gray matter of patients with MS and that of healthy controls [38]. These negative studies can be attributed to the low extracellular concentration of Glu (0.1−1 mmol/L) [9], and low magnetic field which struggled with a lack of internal capability in its resolving power efforts. What is more, though $^{1}$H-MRS has been widely used to monitor the Glu changes in diseases associated with inflammation (for example, MS, AD, PD, etc) [1], it is criticized because of poor spatial resolution and long acquisition time. In a word, the blemishes of $^{1}$H-MRS make it particularly difficult to map the differences of Glu between gray and white matter in brain intuitively.

Therefore, a high spatial resolution imaging is requisite to spatially map Glu to assist understanding the pathophysiology and evolution in the early stages of neuroinflammation.

### 3.2. CEST

Since the amount of protons in tissue metabolites (like Glu) is much smaller than that of water protons, when $^{1}$H-MRS is applied to living tissue to obtain noninvasive biochemical information on small and mobile metabolites (for example, the concentration of Glu) and physiological parameters, it is strongly limited in terms of signal-to-noise ratio (SNR), spatial resolution and scanning time in vivo. Sherry AD et al. [39] applied chemical exchange saturation transfer (CEST) contrast agents for magnetic resonance imaging to augment the dependence of the exchange rates on physical and physiological parameters that characterize the microenvironment such as metabolite concentration, restriction in motion, temperature, and pH.

Recently, it is reported that pH in liver [40], glycosaminoglycan in cartilage [41], gene expression [42], and myo-inositol in brain [43] can be detected by CEST, which is associated with amide and hydroxyl protons from different amino acids, proteins and other molecules. Besides, recent studies showed that at the asymmetric magnetization transfer ratio ($MTR_{asymmetry}$) of 3 ppm, we could find a large fraction of Glu signal, with the relative amount depending on the saturation power used [44]. We used 3 ppm as the GluCEST resonance saturation frequency, and our phantom studies at 7.0T (Fig. 3) demonstrated a similar result that the GluCEST effect depends on different concentrations compared with the studies in Philadelphia [44]. In brain, in-vivo human GluCEST maps showed a similar distribution pattern of Glu compared

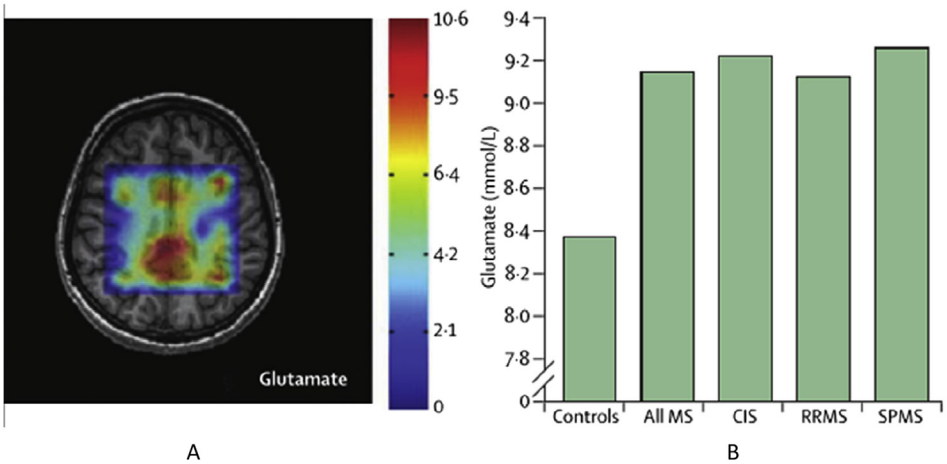


Fig. 2. **Glutamate concentrations in multiple sclerosis**. Glutamate concentrations (mmol/L) in the white matter are shown, with differences between patients and healthy controls. (A) Chemical-shift imaging using echo time (TE)-average point resolved spectroscopy (PRESS) at 3T, which is an editing technique used to highlight glutamate signal; warmer colors show higher glutamate concentrations, whereas cooler colors show lower metabolite concentrations. (B) Differences in glutamate concentrations between all patients with multiple sclerosis, each multiple sclerosis group, and healthy controls. MS = multiple sclerosis. SPMS = secondary-progressive multiple sclerosis. RRMS = relapsing-remitting multiple sclerosis. CIS = clinically isolated syndrome [35].

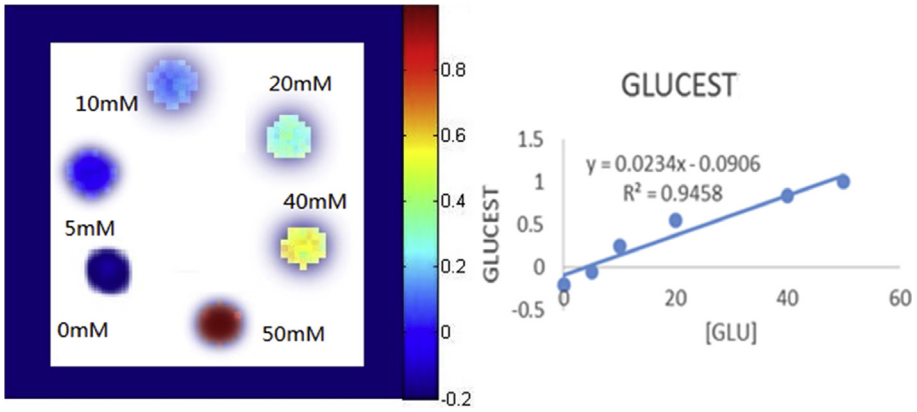


Fig. 3. **GluCEST images at 7T of a phantom** consisting of test tubes with different concentrations of L-Glu solutions (pH 7.0) immersed in a beaker containing PBS. All the experiments were performed at 37 °C.

with that of metabotropic glutamate receptor subtype 5-PET (Fig. 4) [44], which is higher in gray matter compared to white matter [44]. Early applications of GluCEST to animal models of Alzheimer's disease have been reported, which showed a decrease in GluCEST contrast in age-matched transgenic mouse model of Alzheimer's disease (AD) (APP-PS1) relative to wild-type (WT) mouse brain (Fig. 5) [45]. Thanks to these preclinical studies and clinical applications, detecting the changes in Glu concentration is becoming increasingly practicable.

Though GluCEST has begun to be translated from experimental studies to patient studies, it is still a relatively immature imaging technique so far, and there are lots of problems remained, like the phenomenon of intermediate to fast exchange (κ Δω) which mediates the maximum of asymmetry plot occurred at 1.2 ppm, but not 3.00 ppm at pH 7, and the

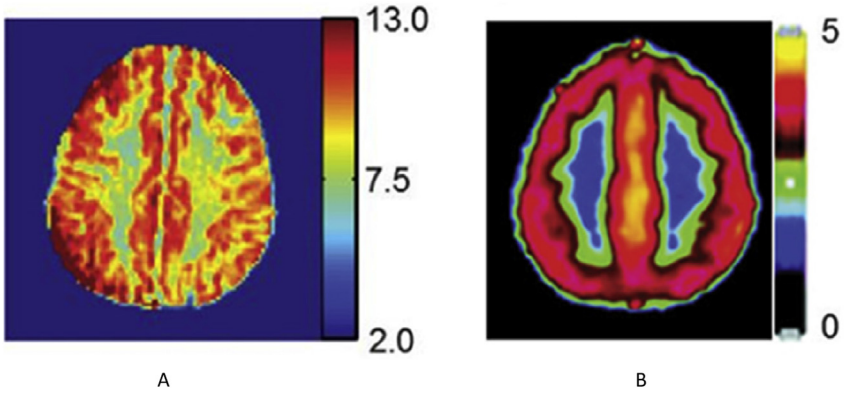


Fig. 4. **GluCEST imaging from a healthy human brain acquired at 7T** (A) B1 and B0 corrected GluCEST contrast map (Color bar represents GluCEST contrast in percentage) (B) Map of distribution volumes (DVs) of metabotropic Glu receptor subtype 5 from a PET image [2,44].

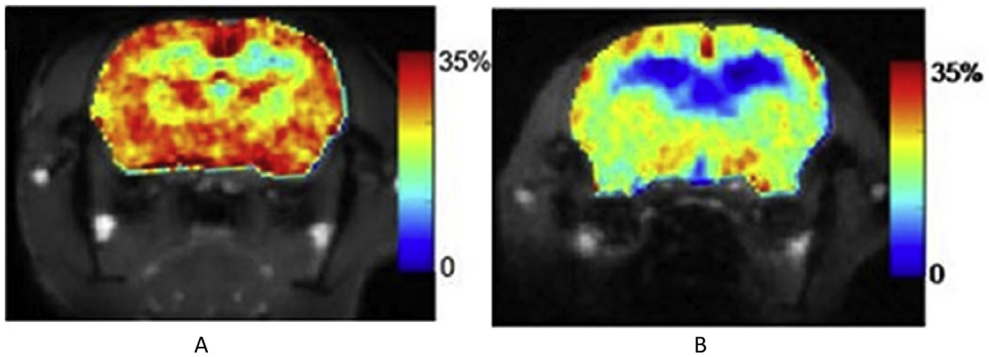


Fig. 5. **Glutamate chemical exchange saturation transfer (GluCEST) mapping of wild-type (WT) mouse (A) and age-matched transgenic mouse model of Alzheimer's Disease (AD) (APP-PS1) (B).** (A)The corresponding GluCEST map of WT mouse. (B)The corresponding GluCEST map of APP-PS1, which shows the decreased GluCEST contrast compared with the wild-type (WT) [45].

unified mechanism of correcting the B1 and B0 map is still indeterminated. Despite of these limitations, based on abundant theories and data from preclinical or clinical studies, GluCEST has possessed its glamour of mapping relative changes of Glu concentration.

## 4. Conclusions

Neuroinflammation is associated with lots of notorious diseases (for example, MS, AD, PD, epilepsy), so it is important to diagnose it incipiently and precisely. Experimental (preclinical) studies and clinical applications have shown us that extracellular glutamate concentrations rise as a result of the interaction between activated microglia and astrocytes in the early stages of neuroinflammation. With high specificity and resolution, some kinds of molecular imaging, like $^{1}$H-MRS and CEST, help to assess these events accurately in vivo. $^{1}$H-MRS makes the changes in this neurotransmitter identifiable, and little by little, GluCEST begins to be translated from experimental studies to patient studies. There are some ineluctable limitations of detecting the changes of L-Glu concentrations by $^{1}$H-MRS because of its poor spatial resolution and long acquisition time. Though GluCEST provides markedly increased spatial and temporal resolution than $^{1}$H-MRS, it is still struggling to solve the problems mentioned above. Notwithstanding these limitations, GluCEST and $^{1}$H-MRS could ameliorate these issues by efforts from everyone to apply high field MRI machines, solve the shimming aporia, and come up with a true and unified mechanism of correcting the B1 and B0 map. All in all, with dramatic potential, $^{1}$H-MRS and GluCEST are feasible of assisting understanding the pathophysiology in the early stages of neuroinflammation.

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