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Review article

Evaluation of neuron-glia integrity by *in vivo* proton magnetic resonance spectroscopy: Implications for psychiatric disorders

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ABSTRACT

Proton magnetic resonance spectroscopy (^{1}H-MRS) has been widely applied in human studies. There is now a large literature describing findings of brain MRS studies with mental disorder patients including schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorders. However, the findings are mixed and cannot be reconciled by any of the existing interpretations. Here we proposed the new theory of neuron-glia integrity to explain the findings of brain ^{1}H-MRS stuies. It proposed the neurochemical correlates of neuron-astrocyte integrity and axon-myelin integrity on the basis of update of neurobiological knowledge about neuron-glia communication and of experimental MRS evidence for impairments in neuron-glia integrity from the authors and the other investigators. Following the neuron-glia integrity theories, this review collected evidence showing that glutamate/glutamine change is a good marker for impaired neuron-astrocyte integrity and that changes in *N*-acetylaspartate and lipid precursors reflect impaired myelination. Moreover, this new theory enables us to explain the differences between MRS findings in neuropsychiatric and neurodegenerative disorders.

Contents

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1. Introduction

Proton magnetic resonance spectroscopy (^{1}H-MRS) is evolved from the nuclear magnetic resonance spectroscopy in chemistry to determine the structure of molecules (Allen, 1990). One of the major motivations for using ^{1}H MRS is the greater sensitivity of the ^{1}H, compared with either ^{31}P or ^{13}C. This feature translates into relative sensitivities of about 10:1 relative to ^{31}P and about 64:1 relative to ^{13}C at equal concentrations of compounds and isotopic enrichments (Rosen and Lenkinski, 2007). Therefore, ^{1}H MRS uses the same hardware as standard magnetic resonance imaging (MRI), whereas observing nuclei other than ^{1}H requires the development of radio frequency (RF) coils and other specialized hardware tuned to their specific frequencies.

^{1}H-MRS has been sucessfully applied in the research of many brain disorders. Since the early 1990s, the non-invasive measurement of brain metabolite concentrations with ^{1}H MRS has provided a unique avenue for extending our understanding of the pathogenesis of neuropsychiatric disorders. There is now a large literature describing the findings of brain MRS studies in the major psychiatric disorders including schizophrenia, bipolar disorder (BD), major depressive disorder (MDD), and anxiety disorders. However, there is a great deal of inconsistency across findings from most of studies with mental disorders. Although discrepancies in methodologies applied in individual studies can partially explain the inconsistent findings, the main reason is due to the complexity of psychiatric disorders. Therefore, interpreting the mixed findings necessitates a new insight to or understanding of neurobiology behind the altered brain metabolites detected by ^{1}H MRS. The present review provided a neurobiological background of glia cells with a focus on neuron-glia contacts and introduced the neurochemical profile detected by ^{1}H MRS in the brain. Then, it proposed the neurochemical correlates of neuron-astrocyte integrity and axon-myelin integrity on the basis of update of neurobiological knowledge about neuron-glia communication and experimental evidence for impairments in neuron-glia integrity from the authors and the other investigators. Following this theory, it reviewed a great body of ^{1}H MRS studies that measured brain metabolites in patients with schizophrenia, BD, or MDD patients. Finally, it commented on the differences between MRS findings in neuropsychiatric and neurodegenerative disorders.

2. Glia cells and neuron-glia contacts

2.1. Astrocytes and their contacts with blood vessels and neurons

Astrocytes are the most abundant cells in the brain. The name derives from the 'star-like' shape of one kind of these cells–protoplasmic astrocytes which contain bundles of an abundant filamentous component of the cytoskeleton, the glial fibrillary acidic protein (Pereira and Furlan, 2010). The protoplasmic astrocytes mainly locate in the gray matter of the brain whereas fibrous astrocytes reside in the white matter. Individual astrocyte can contact with and ensheath thousands of synapses between neurons. This close spatial relationship has led to the term tripartite synapse (Fig. 1). In this neuron-astrocyte contact, astrocytes respond to pre-synaptic input by means of calcium waves and releasing gliotransmitters that modulate neuronal activity and synaptic plasticity. Briefly, the neurotransmitter released by neurons activates calcium-based signaling cascades in astrocytes which in turn release neuroactive substances that signal back to neurons. The different types of molecules secreted by astrocytes can either inhibit or enhance overall levels of neuronal activity (Allen and Barres, 2009).

Astrocytes participating in tripartite synapses are coupled by gap junctions forming a network that can support large-scale integrative functions of the brain, from dynamic glucose delivery (Rouach et al., 2008) to cognitive information processing (Perea and Araque, 2005; Robertson, 2002). The gap junctions are composed of connexins, which are channel-forming proteins and assemble astrocytes into functional syncytia permitting exchange of small molecules including metabolites, catabolites, and second messenger molecules (Reuss and Unsicker, 1998). Upon the gap junctions, the calcium wave propagates from astrocyte to astrocyte as described in the following. First, neuronal glutamate activates

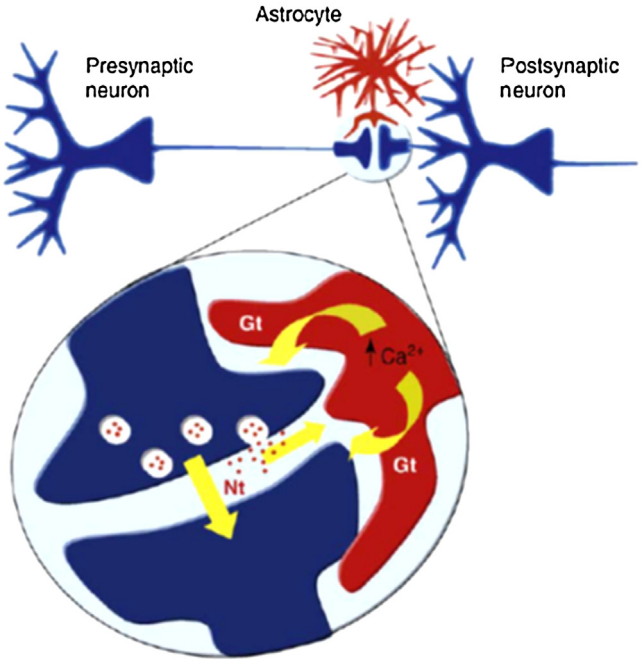

Fig. 1. Scheme of the tripartite synapse. Carton representing the transfer of information between neuronal elements and astrocyte at the tripartite synapse. Astrocytes respond with Ca^{2+} elevation to neurotransmitters (Nt) released during synaptic activity and, in turn, control neuronal excitability and synaptic transmission through the Ca^{2+}-dependent release of gliotransmitters (Gt). Figure was reproduced from Perea et al. with authorization of the publisher.