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Increased expression of glutaminase and glutamine synthetase mRNA in the thalamus in schizophrenia

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Abstract

Numerous molecules enable the handling of glutamate that is destined for neurotransmitter release, including transporters, receptors and glutamatergic enzymes. Previous work in our lab has shown altered levels of transcript expression of excitatory amino acid transporters and a vesicular glutamate transporter in the thalamus in schizophrenia. These changes suggest that molecules that facilitate the release and reuptake of glutamate may be abnormal in schizophrenia. In this study we determined the levels of expression of phosphate activated glutaminase (PAG), which converts glutamine to glutamate, and glutamine synthetase (GS), which converts glutamate to glutamine, with the hypothesis that thalamic PAG and GS transcript expression is altered in schizophrenia. We investigated expression of PAG and GS mRNA using in situ hybridization in six different thalamic nuclei (anterior, dorsomedial, centromedial, ventral anterior, ventral and reticular) from 13 persons with schizophrenia and 8 comparison subjects and found that transcripts for PAG and GS were significantly increased in schizophrenia. Increased PAG and GS transcripts suggest enhanced glutamatergic neurotransmission in the thalamus and its efferent targets in schizophrenia.

Keywords: Glutamate; Mental illness; Transcript; Enzyme; In situ hybridization

1. Introduction

Schizophrenia is a severe mental illness that typically manifests itself in early adulthood, affecting approximately 1% of the population (Sadock and Sadock, 2000). Persons with schizophrenia exhibit a myriad of debilitating symptoms including delusions, hallucinations and paranoia, as well as disorganized

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thought processes, flattened affect and deficits in executive functioning (Goff and Coyle, 2001; Goff and Wine, 1997; Tsai and Coyle, 2002). A glutamate hypothesis of schizophrenia has emerged, supported by a number of recent studies demonstrating region-specific alterations in transcript and protein expression of molecules involved in glutamatergic neurotransmission in schizophrenia. The glutamate hypothesis of schizophrenia was originally based on the pharmacological activity of phenylcyclidine (PCP) on the *N*-methyl D-aspartate (NMDA) subtype of glutamate receptor (Itil et al., 1967; Luby et al., 1962). PCP, a non-competitive antagonist of the NMDA receptor, can precipitate many of the symptoms of schizophrenia in non-psychotic subjects and exacerbate psychotic symptoms in patients with schizophrenia (Hollmann and Heinemann, 1994; Itil et al., 1967; Luby et al., 1962).

The synthesis, packaging, release and reuptake of glutamate involve a number of molecules essential for glutamatergic neurotransmission (Fig. 1). Glutamate is packaged into vesicles in presynaptic neurons by vesicular transporters (VGLUTs) (Bellocchio et al., 2000; Takamori et al., 2000). Following release into the synapse, glutamate may bind metabotropic (mGluRs) or ionotropic (kainate, AMPA, NMDA) glutamate receptors (Hollmann and Heinemann, 1994). Glutamate is removed from the synapse by a family of plasma membrane transporters (EAATs) located on the postsynaptic and glial cell plasma membranes (Arriza et al., 1993; Furuta et al., 1997; Rothstein et al., 1994, 1996; Utsunomiya-Tate et al., 1996). In glial cells, glutamate can be converted to glutamine by glutamine synthetase (GS), or converted to α-ketoglutarate by glutamate dehydrogenase (GLUD) and removed from the releasable pool. Glutamine is taken up by the presynaptic neuron by a family of glutamine transporters (GlnTs), and converted back into glutamate by phosphate activated glutaminase (PAG) for packaging into secretory vesicles (Danbolt, 2001).

Numerous studies have implicated alterations in the thalamus in schizophrenia. Imaging studies in schizophrenia have found alterations in the shape, structure

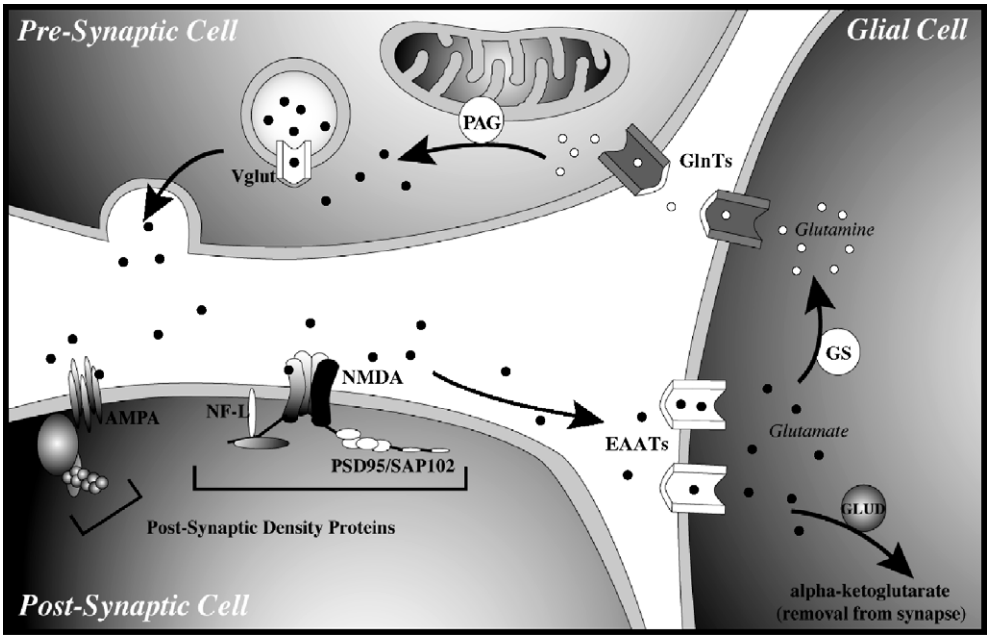

Fig. 1. Key molecules of the glutamate synapse. Abbreviations: vesicular glutamate transporter (VGLUT), glutamine transporter (GlnT), excitatory amino acid transporter (EAAT), postsynaptic-density protein-95 (PSD95), neurofilament light (NF-L), synapse-associated protein-102 (SAP102), glutamate dehydrogenase (GLUD), phosphate-activated glutaminase (PAG), glutamine synthetase (GS). Messenger RNA for molecules in white has been found in this and previous studies to be increased, while *N*-methyl D-aspartate receptor (NMDAR) subunit expression and binding sites (in black) have been found to be decreased in the thalamus in schizophrenia.