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Abnormal Expression of Glutamate Transporters in Temporal Lobe Areas in Elderly Patients with Schizophrenia

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Abstract

Glutamate transporters facilitate the buffering, clearance and cycling of glutmate and play an important role in maintaining synaptic and extrasynaptic glutamate levels. Alterations in glutamate transporter expression may lead to abnormal glutamate neurotransmission contributing to the pathophysiology of schizophrenia. In addition, alterations in the architecture of the superior temporal gyrus and hippocampus have been implicated in this illness, suggesting that synapses in these regions may be remodeled from a lifetime of severe mental illness and antipsychotic treatment. Thus, we hypothesize that glutamate neurotransmission may be abnormal in the superior temporal gyrus and hippocampus in schizophrenia. To test this hypothesis, we examined protein expression of excitatory amino acid transporter 1-3 and vesicular glutamate transporter 1 and 2 in subjects with schizophrenia (n = 23) and a comparison group (n = 27). We found decreased expression of EAAT1 and EAAT2 protein in the superior temporal gyrus, and decreased EAAT2 protein in the hippocampus in schizophrenia. We didn't find any changes in expression of the neuronal transporter EAAT3 or the presynaptic vesicular glutamate transporters VGLUT1-2. In addition, we did not detect an effect of antipsychotic medication on expression of EAAT1 and EAAT2 proteins in the temporal association cortex or hippocampus in rats treated with haloperidol for 9 months. Our findings suggest that buffering and reuptake, but not presynaptic release, of glutamate is altered in glutamate synapses in the temporal lobe in schizophrenia.

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Conflict of interest

Dr James H Meador-Woodruff receives an honorarium as editor of *Neuropsychopharmacology*. The other authors declare no conflict of interest.

Keywords

excitatory amino acid transporter (EAAT); vesicular glutamate transporter (VGLUT); superior temporal gyrus; hippocampus; schizophrenia; glutamate

1. Introduction

Glutamate is synthesized in the cytoplasm and packaged into synaptic vesicles in the presynaptic terminal by vesicular glutamate transporters (VGLUTs) (Bellocchio et al., 2000; Liguz-Lecznar and Skangiel-Kramska, 2007; Takamori et al., 2000). Following its exocytotic release, glutamate activates ionotropic or metabotropic glutamate receptors on both neurons and astrocytes (Hollmann and Heinemann, 1994; Shigeri et al., 2004). Excitatory amino acid transporters (EAATs) help terminate glutamatergic neurotransmission by removing glutamate from the synaptic cleft (Danbolt, 2001; Masson et al., 1999). Alterations in expression of excitatory amino acid transporters could lead to changes in synaptic or perisynaptic glutamate levels attributable to diminished buffering and reuptake of glutamate (Tzingounis and Wadiche, 2007).

EAAT1 and EAAT2, primarily expressed in the plasma membranes of astrocytes and oligodendrocytes, are responsible for the majority of glutamate reuptake, whereas EAAT3 is primarily localized to post synaptic neurons, and in most regions has a minor contribution to glutamate reuptake. (Chaudhry et al., 1995; Rothstein et al., 1994; Maragakis and Rothstein, 2004; Sheldon and Robinson, 2007; Furuta et al., 1997a; Furuta et al., 1997b; Rothstein et al., 1994). Studies of glutamate transporter-deficient mice have clarified the role of each transporter in synaptic glutamate transmission. Knockout mice for EAAT1 (called GLAST in the rodent) exhibit abnormalities of behavioral measures considered endophenotypes for the positive (locomotor hyperactivity), negative (social withdrawal), and attentional/cognitive (impaired working memory) symptoms of schizophrenia (Karlsson et al., 2008; Karlsson et al., 2009). In EAAT2 (called GLT-1 in the rodent) knockout mice, synaptic glutamate levels are elevated, leading to increased susceptibility to acute cortical injury and death (Tanaka et al., 1997). In contrast, EAAT3 (called EAAC1 in the rodent) knockout mice have no abnormalities that would suggest increased glutamate levels (Peghini et al., 1997). Consistent with the transgenic mice studies, a rat study using antisense oligonucleotides to knockdown the expression of EAAT1 or EAAT2 confirmed increased extracellular glutamate levels and neurodegeneration (Rothstein et al., 1996). In addition to these preclinical studies, partial deletion of the EAAT1 gene has been found in a subject with schizophrenia (Walsh et al., 2008), while expression of a high-risk for schizophrenia allele of the GRM3 metabotropic glutamate receptor is associated with decreased EAAT2 mRNA expression in human prefrontal cortex (Egan et al., 2004; Walsh et al., 2008). Taken together, these findings suggest that abnormal expression of EAAT1 and EAAT2 may contribute to the pathophysiology of schizophrenia.

Converging evidence implicates temporal lobe areas in the pathophysiology of schizophrenia, including data from neuroimaging, postmortem, and animal model studies (Benes et al., 1991; Bogerts et al., 1990; Boyer et al., 2007; Bruder et al., 1999; Eastwood and Harrison, 2000; Fatemi et al., 2001; Harrison et al., 2003; Heckers, 2001; Heckers and Konradi, 2002; Le Corre et al., 2000; Lipska, 2004; Nelson et al., 1998; Ohnuma et al., 2000; Rajarethinam et al., 2004; Rajarethinam et al., 2000; Schroeder et al., 1999; Sokolov et al., 2000; Tseng et al., 2009; Uezato et al., 2009; Young et al., 1998). Volume reduction is one of the most consistent structural abnormalities found in the temporal lobe in schizophrenia (Nelson et al., 1998; Rajarethinam et al., 2004; Rajarethinam et al., 2000), and volume change in these regions correlate with the presence of severe thought disorder.

Changes in cellular density as well as expression of synaptic proteins have also been reported in the temporal lobe in this illness. These findings suggest that glutamate synapses may be remodeled due to a lifetime of severe mental illness and antipsychotic treatment. Thus, we tested the hypothesis that glutamate transmission may be abnormal by examining expression of glutamate transporter proteins in the STG and hippocampus in schizophrenia.

2. Materials and Methods

2.1 Subjects and Tissue Preparation

Postmortem brain samples were provided by the Mount Sinai Medical Center and Bronx Veterans Administration Medical Center Brain Bank (Table 1 and Supplemental Table 1) and consisted of twenty-three subjects with schizophrenia and twenty-seven nonpsychiatrically ill comparison subjects. Subjects were excluded for a history of alcoholism, death by suicide, or coma for more than 6 hours before death. Next of kin consent was obtained for each subject.

Brain samples obtained upon autopsy were sliced mid-sagittally and sectioned in 6-8 mm coronal slabs, immediately snap-frozen in liquid nitrogen-cooled isopentane, and stored at −80°C. The superior temporal gyrus was defined by sulcogyral position and dissected from frozen slabs. Anterior hippocampus was dissected from the 0.8mm thick coronal block at the level of the mammillary body. The dissected tissue was pulverized into a fine powder at −190°C, aliquoted into individual Eppendorf tubes, and stored at −80°C.

2.2 Animals

Twenty-two adult male Sprague-Dawley rats were ordered from Harlan (Indianapolis, Indiana, USA) at approximately 60 days of age and housed 2-3 to a cage with food and water ad libitum. Animals received subcutaneous injections of haloperidol dissolved in sesame oil (28.5 mg/kg) or vehicle (sesame oil) every 3 weeks for 9 months (n = 11 per group). 24 hours following the last injection, the animals were sacrificed, and brains were immediately removed, dissected, and snap-frozen in isopentane cooled to −25°C. For dissection, a brain blocker (David Kopf Instruments, Tujunga, California, USA) was used to block the brain into coronal planes containing the rostrocaudal extension of the region of interest. Temporal association cortex (TAC) and hippocampus were dissected using landmarks from The Rat Brain in Stereotaxic Coordinates. Specifically, brains were blocked from interaural 6.88mm to 4.48mm for HC and from interaural 2.28mm to 1.36mm for TAC. Immediately after dissection, tissue was homogenized (10% w/v) in 50 mM Tris-HCl with a Polytron homogenizer (Fisher Scientific International Inc., Pittsburg, Pennsylvania, USA) for 30 seconds and stored at −80°C in 0.5 ml aliquots.

2.3 Antibodies

Commercially available antisera for EAAT1 (1:1000, Santa Cruz Biotechnology, Santa Cruz, California, USA), EAAT2 (1:1000, Millipore, Billerica, Massachusetts, USA), EAAT3 (1:1000, Alpha Diagnostic International, San Antonio, Texas, USA), VGLUT1 (1:2000, Alpha Diagnostic International, San Antonia, Texas, USA) and VGLUT2 (1:1000, Synaptic Systems, Göttingen, Germany) were used for Western blot analyses. β-tubulin (1:10,000; Upstate, Lake Placid, New York, USA) was used as a loading control.

2.4 Western Blot Analysis

Postmortem brain samples (50mg) were homogenized in 1 ml of 5mM Tris-HCl (pH 7.4), containing one Complete, mini, ethylene diaminetetraacetic acid-free protease inhibitor cocktail tablet (Roche Applied Science, Indianapolis, Indiana, USA) per 10 ml, for 30 seconds with a PowerGen 125 homogenizer (Fisher Scientific International, Inc., Hampton,

New Hampshire, USA). Total protein concentration was determined with a bicinchoninic acid protein assay kit (Pierce Biotechnology, Inc., Rockford, Illinouis, USA), and absorbance was measured on a SpectraCount absorbance microplate reader (Packard/Perkin Elmer, Wellesley, Massachusetts, USA) at 562 nm. Homogenates were stored in 0.5 ml aliquots at −80°C until assayed.

For electrophoresis, samples were prepared by combining homogenate with sample buffer and sterile water, and then denatured at 95°C for 4 min. For VGLUT1-2, samples were loaded in duplicate on 7.5% or 12.5% precast Criterion polyacrylamide Tris-HCl gels (Bio-Rad, Hercules, California, USA). For EAAT1-3, Nupage BisTris gels were used (Invitrogen, Carlsbad, California, USA). Gels were run at 120V for 1.75 hours. Following transblot onto nitrocellulose (VGLUT1-2) or PVDF (EAAT1-3) membranes with a semidry transblotter (Biorad, Hercules, California, USA), blots were rinsed several times in distilled water and blocked in 3% dried milk phosphate buffered saline (PBS) (VGLUT1), 1% BSA in PBS (VGLUT2), or LiCor/Oddyssey blocking buffer (LiCor, Lincoln, Nebraska, USA) (EAAT1-3) while rocking at room temperature for 30 minutes. Blots were then exposed to the primary antibody in their respective blocking solutions while rocking overnight at 4°C. After two 5 minute washes in PBS, the blots for VGLUT1-2 were incubated with a horseradish peroxidase coupled goat anti-rabbit secondary antibody or goat anti-mouse secondary antibody (VGLUT1: 1:5000; VGLUT2: 1:5000; Upstate, Lake Placid, New York, USA) respectively in 3% dried milk PBS on a rocker for 2 hours at room temperature. For EAAT1-3, the blots were probed with IR-Dye labeled secondary antibodies (1:10000, LiCor, Lincoln, Nebraska, USA) in 0.1% Tween, 0.01% sodium dodecyl sulfate (SDS), LiCor/Oddyssey blocking buffer for 1 hour in the dark at room temperature, then blots were imaged with the LiCor Odyssey laser based imaging system followed by washing three times for 5 minutes each in 0.01% tween phosphate buffered saline, and briefly washing in water three times. VGLUT1-2 blots were saturated in enhanced chemiluminescence reagent (Pierce, Rockford, Illinois, USA), and exposed to film (ISC BioExpress, Kaysville, Utah, USA). All membranes were also probed with β-tubulin antibody.

We have previously tested VGLUT1-2, EAAT1-3, and β-tubulin Western blot assays using varying protein concentrations of human brain homogenate and determined that our assays are in the linear range of the concentrations correlated for each protein be assayed (Bauer et al., 2008; Oni-Orisan et al., 2008).

2.5 Data Analysis

For VGLUT1-2, developed films were digitally captured with a charge-coupled device based imaging system using Scion Imaging software 4.0.3 (Scion Corporation, Frederick, Maryland, USA). Gray scale values were obtained for bands at the expected molecular weight, and membrane background was subtracted. Gray scale values for duplicate samples were averaged and converted into optical density (OD). The mean ratio of VGLUT1: β-tubulin or VGLUT2: β-tubulin OD was used for data analysis. For EAAT1-3, digital images were obtained using a LiCor Odyssey scanner (LiCor, Lincoln, Nebraska, USA). Odyssey analytic software (3.0) was used to quantify raw integrated intensity for bands of interest. The ratio of EAAT: β-tubulin expression was used for data analysis.

Data were analyzed using Statistica (StatSoft, Tulsa, Oklahoma, USA). Multiple regression analysis was performed to probe for possible correlations between protein expression and age, postmortem interval, and/or tissue pH. Analysis of covariance (ANCOVA) was used to analyze the data when significant correlations were found, otherwise analysis of variance (ANOVA) was used. ANOVA was also performed to assess the effects of sex and antipsychotic status on the dependent measures. For antipsychotic status, subjects with schizophrenia were considered off antipsychotics if antipsychotics were not administrated

within 6 weeks of death. We also examined expression of the loading control β-tubulin (unnormalized) using ANOVA. For all tests, $\alpha = 0.05$.

3. Results

3.1 Postmortem Studies

We examined expression of EAAT1-3 proteins in the superior temporal gyrus and hippocampus (Figure 1). EAAT1 [$F(1, 26) = 40.2$, $P < 0.01$] and EAAT2 [$F(1, 25) = 32.4$, $P < 0.01$], but not EAAT3, were significantly decreased in the superior temporal gyrus in subjects with schizophrenia (Figure 1A). We also found that EAAT2 [$F(1, 20) = 7.40$, $P < 0.02$], but not EAAT1 or EAAT3, was significantly decreased in the hippocampus in subjects with schizophrenia (Figure 1B).

In order to determine whether changes in transporter expression extend to the presynaptic component of glutamate synapses, we examined expression of VGLUT1-2 proteins in the superior temporal gyrus and hippocampus (Figure 2). We didn't detect any changes in expression of VGLUT1 and VGLUT2 proteins in the superior temporal gyrus (Figure 2A) or hippocampus (Figure 2B) in subjects with schizophrenia.

Expression of β-tubulin protein in schizophrenia subjects was not changed compared to comparison subjects. No significant difference was found in subjects with schizophrenia on antipsychotic medications at the time of death, compared to subjects off medications for at least 6 weeks (data not shown).

3.2 Antipsychotic Rat Studies

The potential effects of antipsychotic medication on the protein expression of EAAT1 and EAAT2 were explored in rats treated with haloperidol for 9 months. There were no changes in expression of EAAT1 and EAAT2 proteins in rats treated with haloperidol (28.5 mg/kg) compared to rats administrated vehicle in the temporal association cortex (Figure 3A) or hippocampus (Figure 3B). No significant differences in β-tubulin expression were detected in our animal studies.

4. Discussion

In this study, we examined the expression of glutamate transporter proteins in temporal lobe areas in elderly patients with schizophrenia. Decreased expression of EAAT2 protein was found in the STG and hippocampus, while expression of EAAT1 protein was decreased in the STG in schizophrenia. Decreased expression of EAAT1 and/or EAAT2 protein may have profound effects of glutamate neurotransmission. These transporters are expressed at high levels on astrocytic membranes near excitatory synapses, where they either bind and release glutamate or bind and transport glutamate into the cell. Since the transport efficiency of bound glutamate is about 0.5, the transporters act as a buffer to limit glutamate spillover to extrasynaptic regions (Tzingounis and Wadiche, 2007). The transporters rapidly remove glutamate from the perisynaptic space, maintaining low basal levels of glutamate in the synaptic cleft and limiting the pool of glutamate available to spill out of the synapse. A decrease in this glutamate buffering and reuptake capacity may lead to spillover of glutamate, increasing glutamate levels in extrasynaptic microenvironments where the level of glutamate is tightly regulated (Bridges et al., 2012).

Increased extrasynaptic glutamate may impact neurotransmission in a number of ways (Danbolt, 2001; Tzingounis and Wadiche, 2007). Increased extrasynaptic glutmate levels could activate extrasynaptic glutamate receptors on neurons and astrocytes, modulating the responses of these cells. For example, activation of presynaptic metabotropic receptors (that

are localized to areas outside of the synaptic cleft) decreases glutamate release from the presynaptic terminal (Moghaddam and Adams, 1998). A decrease in astrocytic glutamate reuptake may also impact the activation of postsynaptic receptors within the synaptic cleft; prolonged exposure to higher glutamate levels, as well as increased baseline glutamate levels within the synapse, may impact the physiology of ionotropic glutamate receptor activiation, disrupting molecular correlates of learning and memory, including long-term potentiation or depression (Tzingounis and Wadiche, 2007). Finally, extrasynaptic glutamate may also spillover into adjacent synapses and activate receptors in those synapses, leading to a loss of input specificity (Bridges et al., 2012; Tzingounis and Wadiche, 2007).

Changes in EAAT1 expression and glycosylation have previously been reported in schizophrenia. We found decreased expression of EAAT1 protein in the DLPFC, as well as a change in EAAT1 glycosylation consistent with decreased localization of EAAT1 to the plasma membrane in the same region (Bauer et al., 2008; Bauer et al., 2010). In contrast to these protein studies, increased levels of EAAT1 mRNA were found in the anterior cingulate cortex (ACC) and thalamus (Bauer et al., 2008; Rao et al., 2012; Smith et al., 2001). Taken together, these data suggest a profound abnormality of EAAT1 protein expression, with a compensatory increase in EAAT1 mRNA expression in schizophrenia.

Since EAAT1 is mainly expressed in astrocytes, and not neurons, throughout the central nervous system, our data suggest an abnormality of astrocytes in schizophrenia (Bar-Peled et al., 1997; Lehre et al., 1995; Schmitt et al., 1997). Consistent with this hypothesis, we found decreased expression of glial fibrillary acidic protein (GFAP), an astrocyte marker, in the frontal cortex in this illness (Johnston-Wilson et al., 2000; Steffek et al., 2008). These data raise the question of whether changes in EAAT1 protein expression are due to a decrease in EAAT1 protein levels in astrocytes, or an overall decrease in the number of astrocytes where the remaining astrocytes are expressing normal levels of EAAT1 protein. Several studies have found decreased astroglial cell numbers in the PFC (Cotter et al., 2002; Rajkowska et al., 2002), ACC (Cotter et al., 2001a; Cotter et al., 2001b; Stark et al., 2004) and hippocampus (Falkai and Bogerts, 1986) in schizophrenia, supporting the hypothesis that decreases in EAAT1-2 protein expression may be secondary to diminished numbers of astrocytes.

Similar to EAAT1, EAAT2 protein expression is widely distributed throughout the brain in astroglial cell bodies and processes (Chaudhry et al., 1995; Rothstein et al., 1994). While there is some overlap of expression of EAAT1 and EAAT2 in the same astrocytes, these molecules are generally expressed in different populations of astroglia (Rothstein et al., 1996; Tanaka et al., 1997). Consistent with our findings, deceased EAAT2 mRNA expression was found in the hippocampus in schizophrenia (Ohnuma et al., 2000). In contrast to the hippocampus, divergent findings have been reported for the neocortex. In the frontal cortex, one study found decreased EAAT2 mRNA using *in situ* hybridization (ISH) (Ohnuma et al., 1998), while another found increased EAAT2 mRNA with QPCR (Matute et al., 2005) and three others found no changes using QPCR or ISH (Bauer et al., 2008; Lauriat et al., 2006; Rao et al., 2012). These conflicting data may be attributable to differences in methodology, tissue source and subject demographics, as well as differential treatment with antipsychotic medications.

In subjects from the same brain collection as the present study, we have previously measured EAAT2 protein expression in the DLPFC and ACC and detected no changes (Bauer et al., 2008). However, while we did not find changes in EAAT2 protein levels in these two regions, we did find an increase in G-protein pathway suppressor-1 (GPS1) in the frontal cortex (Bauer et al., 2008). GPS1 decreases EAAT2 mediated glutamate reuptake

through a direct protein-protein interaction by regulating surface trafficking through a leucine zipper-like motif (Watanabe et al., 2003).

EAAT-mediated glial reuptake of glutamate may also be regulated by posttranslational modifications including N-linked glycosylation (Conradt et al., 1995; Raunser et al., 2005). N-linked glycosylation of EAATs is associated with trafficking from the ER to plasma membrane, increased stability at the plasma membrane, and increased glutamate reuptake (Trotti et al., 2001). We found an alteration in EAAT2 glycosylation that may reflect retention of EAAT2 in the endoplasmic reticulum, which might indicate decreased trafficking of EAAT2 to the plasma membrane (Bauer et al., 2010).

Our previous findings of increased GPS1 protein expression and altered EAAT2 glycosylation suggest that while total EAAT2 levels are normal in the frontal cortex, there may in fact still be a decrease in EAAT2 mediated glutamate reuptake via mechanisms other than a change in regional EAAT2 protein expression. Taken together with our findings of decreased EAAT2 protein levels in the hippocampus and STG, these results suggest there are pervasive abnormalities of EAAT2 protein expression and trafficking in schizophrenia, via region-specific mechanisms, leading to impaired glutamate reuptake in temporal and frontal brain regions.

We did not detect changes in EAAT3 protein expression in the STG or hippocampus in schizophrenia. We previously reported increased expression of EAAT3 protein and mRNA in the ACC, while other studies have found changes in EAAT3 mRNA expression in the frontal cortex (increased), DLPFC (no change) and striatum (decreased) (Bauer et al., 2008; Horiuchi et al., 2012; Lauriat et al., 2006; McCullumsmith and Meador-Woodruff, 2002; Nudmamud-Thanoi et al., 2007; Rao et al., 2012). Our lack of findings for EAAT3 protein levels suggest that neuronal glutamate reuptake may be preserved in these regions in schizophrenia. However, EAAT3 protein is localized to regulatable cytosolic pools that may be rapidly mobilized to the plasma membrane in response to elevated synaptic glutamate levels (Kugler and Schmitt, 1999). Such a mechanism would suggest that EAAT3 activity may be regulated by modulating EAAT3 localization, rather than increasing or decreasing levels of EAAT3 protein in the cell. Thus, the possibility remains that there may be an alteration in EAAT3-mediated glutamate reuptake without a change in total EAAT3 protein levels.

In contrast to EAAT1-2, we did not find changes in the expression of VGLUT1-2 protein levels in the STG or hippocampus. Alterations in synaptic activity can be induced via regulation of the amount of glutamate released from presynaptic terminals, and VGLUT-mediated packaging of glutamate is a central control point for normal synaptic activity (Bellocchio et al., 2000; Shigeri et al., 2004; Takamori et al., 2000). Thus, measurement of VGLUT protein levels may indicate the relative strength of presynaptic innervation for a given brain region (Daniels et al., 2006; Daniels et al., 2004; Pothos et al., 2000; Wilson et al., 2005). We previously examined VGLUT mRNA expression in the hippocampal subfields in tissues from a different brain collection, and found no changes in VGLUT1 or VGLUT2 transcript expression. A different study, using tissues from a different source, found reduced VGLUT1 mRNA in a younger cohort with schizophrenia (Eastwood and Harrison, 2005; Uezato et al., 2009). In the present study we did not find an association between age and our dependent measures, while the study using the younger subjects reported an association between VGLUT1 expression and age, which may account for these divergent findings.

Since antipsychotic medications are known to influence glutamate transporter expression, we used two complimentary approaches to evaluate this potential confounding factor (De

Souza et al., 1999; Melone et al., 2001; Schneider et al., 1998). Our secondary analyses showed no differences in expression of EAAT1 and EAAT2 proteins between medicated patients and patients who had been free of antipsychotic medications for at least 6 weeks prior to death. We also investigated the effects of haloperidol on the expression of EAAT1 and EAAT2 protein levels in the rat brain. We chose haloperidol because the vast majority of our subjects who were on medications were receiving a typical antipsychotic. Consistent with our human data, following 9 months of treatment with haloperidol we did not detect changes in EAAT1 or EAAT2 protein expression in the rat brain. Taken together, these data suggest our findings are not due to treatment with antipsychotic medication.

The temporal lobe plays a central role in many symptoms associated with schizophrenia, including altered cognitive function, oversensitization to sensory stimuli, and auditory hallucinations (Boyer et al., 2007; Brady et al., 2010; Bruder et al., 1999; Fujimoto et al., 2012). Structural and functional abnormalities of STG and hippocampus have been reported in this illness, while quantitative investigations have demonstrated reductions in neuronal size, cortical glial cell number, as well as changes in neuronal density (Boyer et al., 2007; Bruder et al., 1999; Heckers, 2001; Rajarethinam et al., 2004; Rajarethinam et al., 2000; Steen et al., 2006); (Benes et al., 1991; Cotter et al., 2002; Heckers and Konradi, 2002; Uranova et al., 2004). Consistent with loss of volume and cellular pathology, a number of postmortem studies found altered expression of synaptic proteins in the temporal lobe, including decreased expression of complexin, synaptophysin, SNAP-25, VGLUT1 and several ionotropic glutamate receptor subunits (Eastwood and Harrison, 2000, 2005; Harrison et al., 2003; Sokolov et al., 2000; Young et al., 1998). Taken together with our findings, these data support the hypothesis that there are profound abnormalities of glutamate neurotransmission in excitatory circuits in the temporal lobe in schizophrenia.

In summary, we found that expression of astroglial glutamate transporters was abnormal in temporal lobe areas in schizophrenia. These data suggest a deficit of glutamate reuptake capacity that may lead to alterations in excitatory neurotransmission. We did not find any changes in expression of the neuronal glutamate transporter EAAT3 or the neuronal vesicular glutamate transporters VGLUT1 and VGLUT2, suggesting that aspects of neuronal function are preserved in the STG and hippocampus in this illness. Our findings indicate a critical role for glial glutamate reuptake in severe mental illness and suggest that elements of the glutamate reuptake pathway may be high yield targets for development of novel treatments for this illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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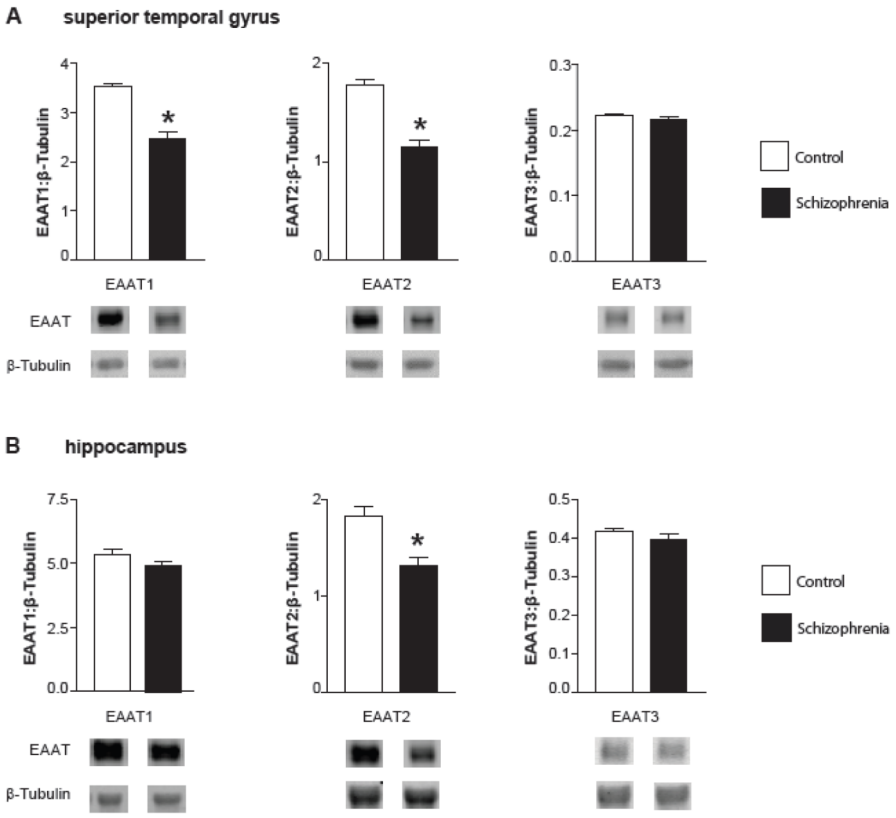

Figure 1.

Western blot analysis of EAAT1-3 normalized to β-tubulin in the (A) superior temporal gyrus (STG) and (B) hippocampus. Data are shown as mean ± standard deviation. *P < 0.05. A) EAAT1 and EAAT2 were significantly decreased in subjects with schizophrenia. No change was observed for EAAT3. B) EAAT2 was significantly decreased in subjects with schizophrenia. No changes were observed for EAAT1 or EAAT3. Abbreviation: excitatory amino acid transporter (EAAT).

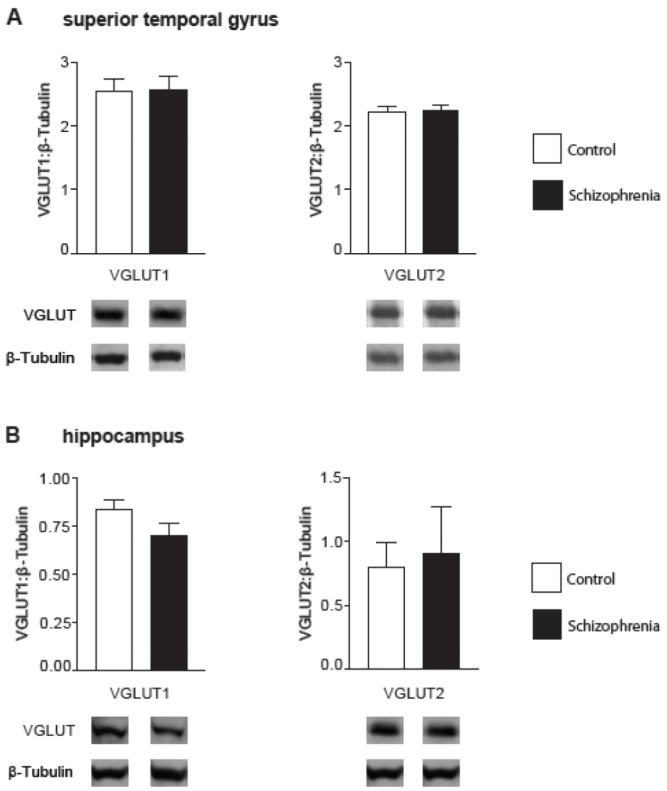

Figure 2.

Western blot analysis of VGLUT1-2 normalized to β-tubulin in the (A) superior temporal gyrus (STG) and (B) hippocampus. Data are shown as mean ± standard deviation. VGLUT1 and VGLUT2 were not changed in the (A) superior temporal gyrus or (B) hippocampus in subjects with schizophrenia. Abbreviation: vesicular glutamate transporter (VGLUT).

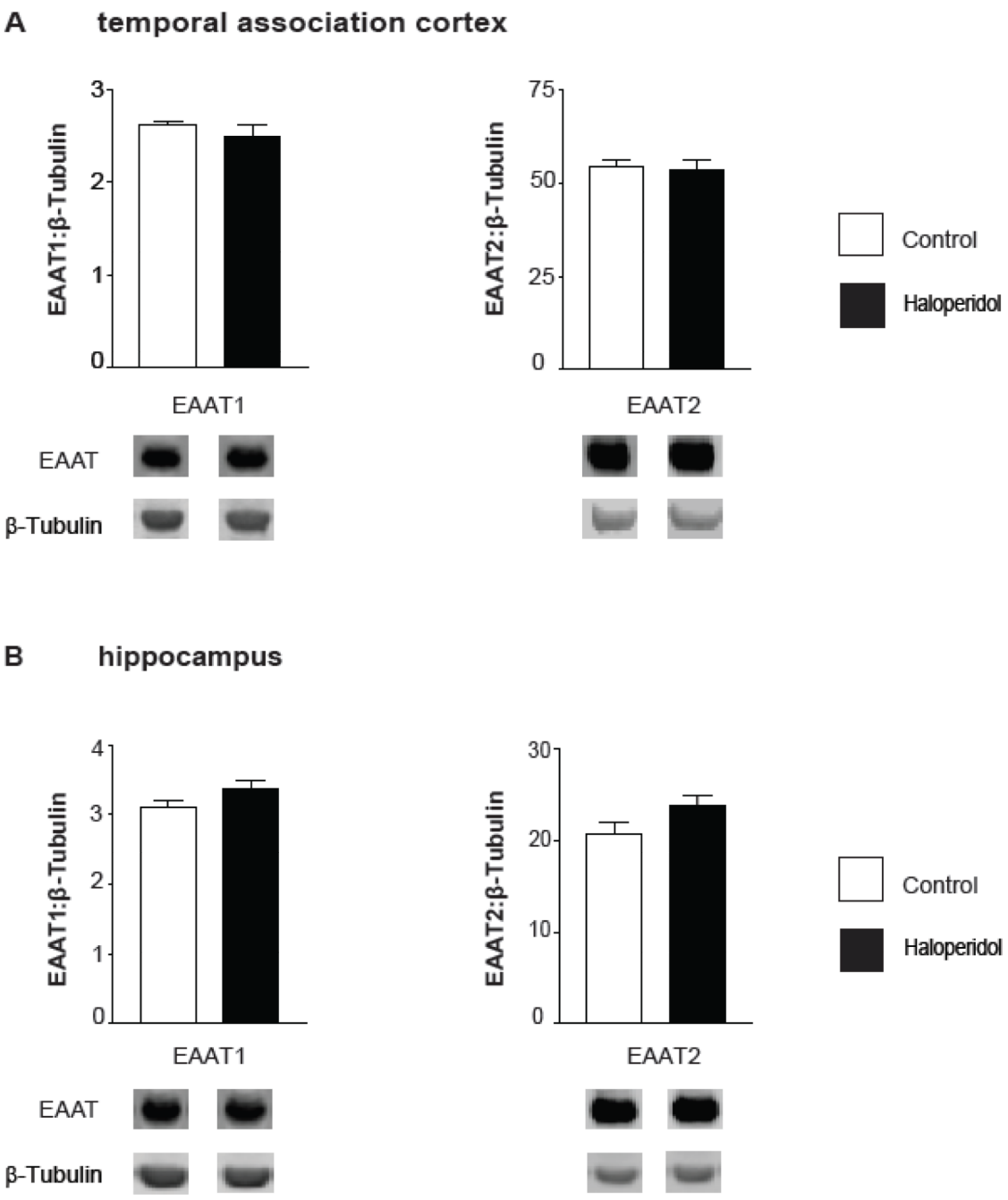

Figure 3.

Western blot analysis of EAAT1-2 normalized to β-tubulin in the (A) temporal association cortex (TAC) and (B) hippocampus in rats treated with haloperidol (28.5 mg/kg) or vehicle. Data are shown as mean ± standard deviation. There were no differences in EAAT1 or EAAT2 protein expression. Abbreviation: excitatory amino acid transporter (EAAT).

Table 1

Subject Characteristics

	STG/HPC	
	Comparison	Schizophrenia
N	27	23
Sex	14m/13f	16m /7f
AOD (years)	79 13	72 12
Tissue pH	6.5 0.2	6.5 0.3
PMI (hours)	7.6 6.8	14.6 8.9
Rx (on/o ff/un known)	0/27/0	16/6/1

Abbreviations: superior temporal gyrus (STG); hippocampus (HPC); female (f); male (m); age of death (AOD); post mortem interval (PMI); medications (Rx: on or off antipsychotic medication for at least 6 weeks at time of death). Values are presented as standard deviation.