World Journal of Psychiatry

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5498/wjp.v6.i1.31

World J Psychiatr 2016 March 22; 6(1): 31-42
ISSN 2220-3206 (online)

REVIEW

Role of astrocytic glutamate transporter in alcohol use disorder

Jennifer R Ayers-Ringler, Yun-Fang Jia, Yan-Yan Qiu, Doo-Sup Choi

Jennifer R Ayers-Ringler, Neurobiology of Disease PhD Program, Mayo Graduate School, Mayo Clinic, Rochester, MN 55905, United States

Yun-Fang Jia, Yan-Yan Qiu, Doo-Sup Choi, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic College of Medicine, Rochester, MN 55905, United States

Author contributions: All authors contributed equally to conception and design of the manuscript, analysis and interpretation of data, drafting, and making critical revisions of the manuscript; all authors gave final approval of the version of the article to be published.

Supported by Mayo Graduate School, NIAAA, No. AA018779; SC Johnson Genomics of Addiction Program, Ulm Family Foundation, Center for Individualized Medicine at Mayo; and David Lehr Research Award from American Society for Pharmacology and Experimental Therapeutics.

Conflict-of-interest statement: No potential conflicts of interest.

Correspondence to: Doo-Sup Choi, PhD, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, United States. choids@mayo.edu
Telephone: +1-507-2845602
Fax: +1-507-2841767

Received: August 29, 2015
Peer-review started: September 6, 2015
First decision: November 11, 2015
Revised: December 18, 2015
Accepted: January 8, 2016
Article in press: January 11, 2016

Published online: March 22, 2016

Abstract

Alcohol use disorder (AUD) is one of the most widespread neuropsychiatric conditions, having a significant health and socioeconomic impact. According to the 2014 World Health Organization global status report on alcohol and health, the harmful use of alcohol is responsible for 5.9% of all deaths worldwide. Additionally, 5.1% of the global burden of disease and injury is ascribed to alcohol (measured in disability adjusted life years, or disability adjusted life years). Although the neurobiological basis of AUD is highly complex, the corticostriatal circuit contributes significantly to the development of addictive behaviors. In-depth investigation into the changes of the neurotransmitters in this circuit, dopamine, gamma-aminobutyricacid, and glutamate, and their corresponding neuronal receptors in AUD and other addictions enable us to understand the molecular basis of AUD. However, these discoveries have also revealed a dearth of knowledge regarding contributions from non-neuronal sources. Astrocytes, though intimately involved in synaptic function, had until recently been noticeably overlooked in their potential role in AUD. One major function of the astrocyte is protecting neurons from excitotoxicity by removing glutamate from the synapse *via* excitatory amino acid transporter type 2. The importance of this key transporter in addiction, as well as ethanol withdrawal, has recently become evident, though its regulation is still under investigation. Historically, pharmacotherapy for AUD has been focused on altering the activity of neuronal glutamate receptors. However, recent clinical evidence has supported the animal-based findings, showing that regulating glutamate homeostasis contributes to successful management of recovery from AUD.

Key words: Alcohol; Addiction; Glutamate; Astrocyte; Excitatory amino acid transporter type 2; Glia; Striatum

Core tip: Review of astroglial involvement in alcohol use disorder and potential for astrocyte-specific glutamate transporter excitatory amino acid transporter type 2 (EAAT2, Slc1a2)/GLT-1 in pharmacological treatment, including alcohol withdrawal symptoms.

Ayers-Ringler JR, Jia YF, Qiu YY, Choi DS. Role of astrocytic glutamate transporter in alcohol use disorder. *World J Psychiatr* 2016; 6(1): 31-42 Available from: URL: http://www.wjgnet.com/2220-3206/full/v6/i1/31.htm DOI: http://dx.doi.org/10.5498/wjp.v6.i1.31

INTRODUCTION

Substance abuse and addiction is a pervasive problem at all socioeconomic levels worldwide. Alcohol, though one of the most common addictive substances, is recreationally used by many people without incident. Alcohol use disorder (AUD) or alcohol addiction often results in one of the most lethal sets of withdrawal symptoms, including seizures, hallucinations, and delirium tremens, termed alcohol withdrawal syndrome (AWS). As with most addictive substances, craving and relapse rates are high, and predictability, and even recognition, of addiction is difficult to ascertain. This makes alleviation of withdrawal symptoms the primary focus on treating AUD.

Like other neuropsychiatric conditions, AUD involves dysfunction of normal signaling pathways. Importantly, neurons are not the only cells involved in neural signaling. The majority of cells in the central nervous system (CNS) are of the glial lineage[1]. Two of the major glial cell types, oligodendrocytes and microglia, have been well characterized, as they are relatively monofunctional: Oligodendrocytes myelinate neurons, and microglia regulate the CNS immune response[2]. Ironically, the most abundant glia, the astrocyte, is not as well understood. Its diverse role in maintaining vascular integrity and metabolic homeostasis, and regulating synaptogenesis and immune response[1,3], means that its morphology and gene expression vary greatly depending on its location, local contacts, and microenvironment[4,5].

AWS is attributed to elevated extracellular glutamate levels in certain brain regions, such as the striatum and hippocampus[6-8]. These regions are part of the mesocorticolimbic circuit, which is highly implicated in addiction disorders[9,10]. Astrocytes provide critical regulation of synaptic glutamate concentrations in these regions through bi- and uni-directional transporters. Glutamate, the most important excitatory neurotransmitter in the CNS, serves to stimulate action potentials by activating its cognate ionotropic receptors on the postsynaptic neurons, and modulate synaptic connectivity through its cognate metabotropic receptors. Astrocytes are responsible for removing glutamate from the extracellular space, thereby limiting its effects. Within the astrocyte, glutamate is converted to glutamine *via* glutamine synthetase, and released back out to the extracellular environment for uptake by presynaptic neurons, which convert it back to glutamate to be packaged into vesicles for synaptic release. In AWS, this glutamatergic tone is dysregulated, resulting in a hyperglutamatergic state that can lead to neuronal excitotoxicity. Clinically, benzodiazepines are often used to alleviate withdrawal symptoms, but patients can become physically dependent on these, as well[11].

Animal models have been extremely useful in studying addiction. The rodent corticolimbic circuitry is very similar to human, and thus provides an effective method for studying various aspects of the addiction and withdrawal processes. Certain species are useful for studying behaviors of different points and aspects of the addiction process, including consumption, preference, learning, tolerance, and withdrawal[12]. Additionally, through genetic manipulation of specific components of glutamatergic signaling, we have come to understand ethanol's effects on involved neuronal glutamate receptors, such as NMDA and AMPA receptors[13-17]. This review will focus on the role of glia in neuronal function, both normal and pathological, and illuminate the importance of understanding astrocyte function in neuropsychiatric disorders, like AUD.

GLIAL FUNCTION IN NEUROPSYCHIATRIC DISORDERS

Glial cells are mostly known for their contributions to physiological processes and pathological involvement. There are many more glial cells than neurons (glia to neuron ratio = 4:1), and they are generally smaller[18]. Three subtypes have been identified in the CNS: Astrocytes, microglia and oligodendrocytes. The major function of glial cells is to maintain homeostasis in the CNS, including supporting blood vessels, providing nutrition and oxygen to neurons, regulating neurotransmitter metabolism and modulating the immune response. Therefore, balance disruption derived from any of these cell types could be associated with multiple kinds of psychiatric disorders.

Oligodendrocytes are one of the more numerous than the types of glial cells. Their primary role is to myelinate axons, which increases the resistance and reduces the effective capacitance of axonal membranes, accelerating the transmission of electrical signals. They arise from a large population of oligodendrocyte precursor cells (OPCs), a source of replacement cells for damaged oligodendrocytes after injury or in disease. There are multiple trophic and growth factors that maintain oligodendrocyte survival and myelination[19]. One therapeutic option is to increase and amplify this OPC pool once the pathologically activated signa-

ling pathways are identified[20]. Moreover, mounting evidence shows that oligodendrocytes may also play a critical role in neuropsychiatric disorders[21].

Astrocytes represent highly heterogeneous mediators that interact directly with neurons, which is crucial for maintaining brain function. Astrocytes play an essential role in neurogenesis and the development of the CNS, energy metabolism, synaptic signaling, immune defense, amino acid neurotransmitter clearance, neurotrophin production and ionic homeostasis[22]. More recently, many studies have suggested that astrocyte dysregulation is associated with neuropsychiatric disorders, such as Wernicke's encephalopathy[23] and Korsakoff psychosis[24], schizophrenia[25], depression and addiction[26].

Microglia originates from hematopoietic progenitors and have been considered the resident immune cells in CNS. However, recent evidence has provided a notion that microglia are not only activated by inflammatory challenge or neuronal damage, but that they extend an array of physiological functions through synaptic maturation[27], maintenance of CNS homeostasis, memory processes and neurogenesis[28]. Additionally, disturbance of microglia responding to minor pathological intrusion is implicated in multiple neuropathological and neuropsychiatric disorders.

Pathological potential of neuroglia in AUD

Astrocytes play critical roles in CNS abnormalities associated with ethanol-induced neurotoxicity. Chronic ethanol exposure profoundly affects the expression of GFAP, an astroglial stress fiber, as well as the function of astrocytes. One interesting study found that by increasing astrocyte number by injecting purified astrocytes into rat forebrain learning and memory abilities associated with cholinergic signal recovery were improved[29]. It is well known that alcohol and its metabolite acetaldehyde show direct neurotoxicity by disturbing thiamine-related enzymes, resulting in thiamine deficiency and damage to astrocytes[30]. Our laboratory demonstrated the importance of adenosine signaling in regulating alcohol-related behaviors. Mice lacking type 1 equilibrative nucleoside transporter (ENT1), the glial transporter responsible for maintaining adenosine tone in the synapse, consume more ethanol in two bottle choice experiments when compared to wild-type littermates[31]. In addition, antagonists and agonists acting on the adenosine A_{2A} receptor ($A_{2A}R$) modulate ethanol preference and withdrawal symptoms. Moreover, inhibition of $A_{2A}R$ in the dorsomedial striatum promoted goal-directed behavior and increased sucrose or ethanol drinking[32]. We revealed that deletion of ENT1 decreased the expression of astrocytic glutamate transporter GLT-1, the protein responsible for regulating extracellular glutamate concentration in the striatum. Adenosine-mediated glutamate signaling in neuroglial interaction in ethanol intoxication and preference has been thoroughly described elsewhere[33,34].

Microglia are the resident macrophages and are distributed ubiquitously throughout the CNS. Alterations in microglia have even been noted in AUD models. After intensive chronic ethanol intoxication in rats, there were structural lesions in the CNS, including infiltration of mononuclear cells and lymphocytic-microglial nodules[35]. Changes in immune-related genes have been found in human alcoholic brain, including chemokines (Ccl2, Ccl3) and chemokine receptors (Ccr5, Ccr1 motif)[36]. Consumption and preference of ethanol decreased in mice after deleting either chemokines (Ccl2 or Ccl3) or chemokine receptors (Ccr2). Particularly the proinflammatory cytokine, CCL2, was extensively higher in alcoholics[37]. Also, consecutive 10-d injection of ethanol increased pro-inflammatory cytokine TNFα in the brain. Meanwhile, ethanol enhanced LPS-induced increases in TNFα, MCP-1, and IL-1β in brain[38]. Previous studies indicated that TLR4 response might be a vital mechanism of chronic ethanol-induced neuroinflammation. The signaling pathways related to IL-1RI/TLR4 receptors were facilitated by chronic ethanol treatment[39], while the deletion of TLR4 prevented ethanol-induced glial activation and production of inflammatory mediators[40].

Regarding oligodendrocytes, alcohol appears to have different effects, but much of the evidence points toward reduced oligodendrocyte function. Prenatal alcohol exposure decreased the level of myelin basic protein (MBP) expression[41], consequently leading to a reduction in brain myelination that may contribute to the development of fetal alcohol syndrome[42]. Protein kinase C was activated after ethanol exposure, which delays MBP expression in differentiating CG-4 oligodendrocytes. Oligodendrocyte myelin glycoprotein was significantly decreased in rat hippocampus by chronic ethanol exposure[43]. This deficit may explain the demyelination observed in human alcoholics[44]. Recent studies showed that premyelinate oligodendrocytes and myelin-associated protein were decreased in medial prefrontal cortex (mPFC) during chronic intermittent ethanol vapor exposure (CIE). However, protracted abstinence increased MBP levels in the mPFC, possibly a compensatory effect after CIE[45]. In contrast, the activity of enzyme 2', 3'-cyclic nucleotide 3'-phosphodiesterase, a maker for oligodendrocytes, was increased in ethanol-treated cultures[46].

Neuroglia pathology in other psychiatric conditions

Glial pathology is also implicated in other neuropsychiatric conditions, like schizophrenia and bipolar disorder (BD). One study demonstrated decreased astrocytic gene expression in the deep layers of the anterior cingulate gyrus, including excitatory amino acid transporter 2 (EAAT2)[47]. In this regard, animal models have been somewhat helpful in investigating structural changes, glycogen metabolism and glutamate signaling[48].

BD, like AUD, involves the corticostriatal circuit. Morphometric postmortem and neuroimaging studies found decreased glial cell density in the mPFC of

patients with BD[49]. Recent studies indicate that chronic treatment with anti-bipolar drugs could inhibit astroglial glutamate release[50]. Additionally, S100β, a neurotrophic factor mainly released by astrocytes, was increased after chronic lithium treatment, although astrocytes or interaction between neurons and astrocytes were unaffected[51].

Regarding microglia, studies in schizophrenia patients have yielded more consistent results. Microglia are activated along with increased cell population in the postmortem brains of schizophrenic patients[52]. Consistently, the level of cytokines, IL-1β, IL-6, and TGF-β, were elevated in schizophrenia. Interestingly, these alterations were reversed by antipsychotic treatment[53]. The dysfunction of microglia is associated with impairment of nervous system development, synaptic formation and pruning[27,54], processes that may also affect neural circuitry in AUD.

Neuroinflammation has also been linked to BD. The level of IL-1β was increased in cerebrospinal fluid of euthymic BD patients when compared with normal controls, and even higher in those who had recently experienced one or more manic/hypomanic episodes[55]. In addition, microglia activation induced higher levels of IL-1β, which was associated with increased suicide behavior in BD patients[56]. Moreover, concentrations of pro-inflammatory cytokines, which are associated with increased activation of MAPK and NF-κB pathways in BD patients, were higher, as well. These results suggest that microglia play a potentially crucial role in BD. Interestingly, there is an increased incidence of BD in patients with the autoimmune disorder, multiple sclerosis, where oligodendrocytes are targeted by the immune system. And, oligodendrocytic markers are down regulated in patients with BD[57].

Multiple studies have confirmed oligodendrocytes and myelination are impaired in schizophrenia[58-60]. Oligodendrocytic and myelination abnormalities damage saltatory conduction and information transfer between neurons in schizophrenia[61]. White matter anomalies were found in schizophrenia patients from maternal and early postnatal immune challenge[62], perinatal hypoxia[63], and during childhood and adolescence[58,64], suggesting that damage to axonal integrity and conduction velocity may play a causal role in schizophrenia.

Taken together, studying glial cells is warranted for understanding neuropsychiatric disorders in regards to glutamatergic abnormalities.

SYNAPTIC, PERISYNAPTIC AND EXTRASYNAPTIC ASTROCYTIC PROCESSES IN REGULATING GLUTAMATE SIGNALING

Neurons connect to each other with a kind of chemical junction called a synapse, which consists of the presynapse, post-synapse, and synaptic cleft as a key information communication relay and central functional element of the nervous system[65,66]. Each neuron can receive a number of synaptic inputs and these synapses have diverse properties, including the type of neurotransmitter and the number of postsynaptic receptors. Neurotransmitter vesicles accumulate in the presynaptic terminal, while the neurotransmitter receptors located in the postsynaptic neurons are recruited to the postsynaptic.

Synaptic astrocytic processes

Astrocytes were widely thought to provide only metabolic and physical support for neurons, but now they are demonstrated to directly participate in neuronal signaling, even locally at synapses[67,68]. Many investigations have shown that astrocytes exhibit unique biophysical and functional electrical properties, are sensitive to neuronal activity and are actually involved in the control of synaptic transmission. Astrocytes are indeed equipped to sense and integrate neuronal information through ionic channels, neurotransmitter receptors and transporters, and intracellular signaling pathways[69]. Astrocytes are also known to influence synaptic activity *via* synthesizing and recycling glutamate[70] and responding to synaptic release of neurotransmitters[68,71,72]. Glutamate, as a major neurotransmitter in the brain, exerts a critical role in mediating synaptic activity and also causing a response in astrocytes[73,74]. Importantly, the involvement of astrocytes in glutamatergic regulation is very widespread, as most glutamate is taken up by transporters expressed on astrocytic membranes when it is released into the extracellular space between neurons[75,76], and it is estimated that only 20% of synaptic glutamate is taken up by transporters on the postsynaptic neurons[77]. Astrocytes can synchronize with neuronal activity, and subsequently regulate glutamate transmission between neurons[78]. Astrocyte-to-neuron glutamate signaling may mediate activity-dependent modulation of inhibitory synapses in the hippocampus, with glial glutamate release taking place at some distance from the synapse[79]. The increases in calcium (Ca^{2+}) evoked by neuronal activity results in a release of glutamate from astrocytes[80,81]. This release of glutamate process is known to be a Ca^{2+}-dependent exocytic pathway[82]. In addition, during synaptic activity neurons or astrocytes release ATP, which cause an increase in intracellular (Ca^{2+}), mediated by the P2Y1 type purinergic receptors (P2Y1Rs) in hippocampal astrocytes[83]. As a G protein coupled receptor, P2Y1R signaling in astrocytes is coupled to Ca^{2+}-dependent glutamate exocytosis[84,85].

Glutamate is able to induce a wide range of effects in astrocytes *via* metabotropic glutamate receptors (mGluR), NMDA receptors, and AMPA receptors[86]. Hippocampal astrocytes express functional AMPA receptors[87], the properties of which can be changed by astrocytes during postnatal development. It has been reported that immature astrocytes had a prolonged activation of the AMPA receptors, while glutamate

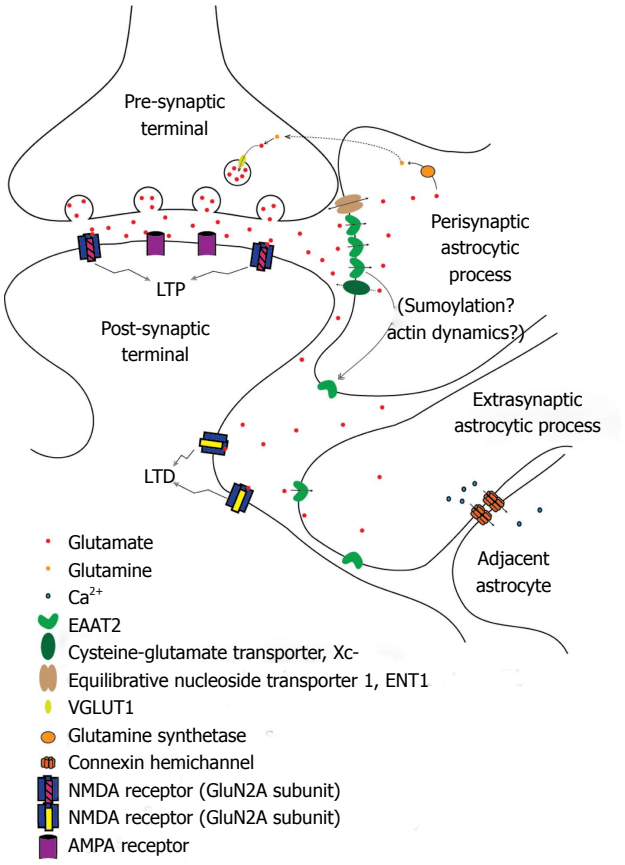

Figure 1 Fine regulation of glutamate levels and excitatory amino acid transporter 2 localization in neuron-glial interaction. The perisynaptic astrocytic process contains a higher concentration of EAAT2 immediately adjacent to the synapse. The EAP also contains EAAT2, but in lower concentrations. Glutamate spillover results in activation of GluN2B-containing NMDA receptors (increasing LTD response in the post-synaptic neuron), increased EAAT2 surface expression on and migration of EAPs, and activation of adjacent astrocytes via calcium waves propagated through connexin channels. LTP: Long term potentiation; LTD: Long term depression; EAAT2: Excitatory amino acid transporter 2; Xc-: Cysteine-glutamate transporter; ENT1: Equilibrative nucleoside transporter 1; VGLUT1: Vesicular glutamate transporter 1; NMDA: N-Nitrosodimethylamine; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EAP: Extrasynaptic astrocytic process.

responses were greatly increased as astrocytes matured. In addition, the presynaptic NMDA receptors are activated and the excitatory communication between neurons is increased once astrocytic glutamate is released[85]. Additionally, astrocytes also use the mGluRs to modulate neuronal activity. However, previous results suggest developmental changes in the expression of mGluRs in astrocytes[88], predicting its important role in development. Reports reveal that synaptic glutamate stimulates astrocytic mGluRs and subsequently triggers glutamate release from astrocytes[80,89].

Perisynaptic astrocytic processes

It has recently been recognized that astrocytes act as a third partner in synaptic processes, leading to the description of a "tripartite synapse[90]", with the astrocytic processes in close apposition to the synaptic cleft[91]. Perisynaptic astrocytic processes (PAPs), assumed to mediate this communication, may detect glutamate spillover and other substances from active synapses[76,92]. Glutamate can also cause structural alterations of astrocytes, driving them to extend and modify their own processes[73,93] (Figure 1). It is thought that PAPs position next to the synaptic cleft, as the effectors of glia-neuronal crosstalk at the synapse, to exert their roles in ion buffering and transmitter uptake, thus keeping a low diffusion distance[94]. Glutamine synthetase is mainly expressed in the PAPs around identified glutamatergic synapses[95].

There have been a few approaches that described peripheral astrocyte processes related to synapses using direct or indirect observations. Glial gamma-aminobutyricacid (GABA) receptor channels could be of functional importance in buffering extracellular Cl^- in the perisynaptic microenvironment using patch-clamp techniques, and might relate to mechanisms not present in the peripheral processes[96]. Electrically stimulated parallel fibers increased intracellular calcium concentration in peripheral processes of Bergmann glia, astrocytic cells located in the cerebellum[97]. The transmitter release is affected by reduction in glutamate clearance through modulation of presynaptic mGluR. Therefore, astrocytic wrapping of neurons may contribute to the regulation of synaptic efficacy in the CNS[98]. Glia-synaptic interactions can be attributed to the astrocytic peripheral processes in the perisynaptic microenvironment. As the functions of PAPs displayed might not be representative of the astrocyte as a whole, they could be recognized as a specialized astroglial compartment[94].

Extrasynaptic astrocytic processes

In some instances, glutamate may escape from the synaptic cleft, generating extrasynaptic glutamate dynamics[99,100]. The kinetic simulations of extrasynaptic glutamate uptake show that glutamate can bind to several subtypes of receptors, but transporters rapidly reduce the free concentration of transmitter[101]. Extrasynaptic glutamate dynamics is believed to regulate a variety of important neural and glial functions including synaptic transmission[102], synaptic plasticity[103], synaptic crosstalk[104,105], nonsynaptic neurotransmission[106], neuronal survival[107], and gliotransmitter release[108].

Synaptic "spillover", or extracellular diffusion of transmitters and modulators after extrasynaptic release in the local circuit regions, is an important short distance form of volume neurotransmission. The neurotransmitters bind to extrasynaptic neuronal and glial receptors and then activate related signaling pathways in the neuroglial networks of the brain (Figure 1). G protein-coupled receptor heteromers play a major role in the integrative processes of extrasynaptic signaling on glutamatergic synapses. The balance of activity in the different types of projection neurons is determined by the diverse distributions of high affinity receptors on the neurons and glia, where both neuronal extrasynaptic and long distance volume transmission signaling can be involved[109]. Temporal resolution at axon terminals of

fast-spiking neurons might be due to rapid glutamate receptor desensitization. Transmitter diffusion is partly responsible for transmitter clearance from the synaptic cleft[76]. The glutamate transient duration seen at a distance from the release site can be greatly increased if interactions between glutamate and extrasynaptic binding sites reduce the effective diffusion constant, resulting in a greater probability of NMDA receptor activation[110]. Relatively small amounts of glutamate are likely to activate extrasynaptic receptors, especially if the diffusion coefficient in the extracellular medium is low[101]. Extrasynaptic glutamate spillover implies significant cross-talk between neighboring synapses, which could have major repercussions for information processing[111].

GLUTAMATE TRANSPORTERS IN AUD

Glutamate is arguably the most important neuroexcitatory amino acid in the CNS. As such, its concentration, both intra- and extra-cellularly, is tightly regulated by membrane transporters. Within neurons, the vesicular glutamate transporters, of which there are three known subtypes[112], pack glutamate from the cytosol into presynaptic vesicles utilizing the proton electrochemical gradient[113]. In glia, the cysteine-glutamate transporter (Xc-) is the major transporter responsible for releasing glutamate into the extracellular space, while a family of sodium-dependent transporters, called excitatory amino acid transporters (EAAT), removes glutamate from the extracellular environment. The function of these latter transporters is critical, as excessive synaptic glutamate can lead to neuronal excitoxicity and/or death. There are five mammalian EAAT subtypes (EAAT1-EAAT5) that have been identified to date. EAAT1 and EAAT2 (in rodents, designated glutamate and aspartate transporter, GLAST, and glutamate transporter 1, GLT-1, respectively) are the primary subtypes responsible for extracellular glutamate clearance throughout the CNS during neurotransmission, and are predominantly expressed in astrocytes[114,115]. EAAT1 is most abundantly expressed in the cerebellum, while EAAT2 has a more ubiquitous expression pattern, which is strongest in the forebrain[116]. EAAT3 (EAAC1 in rodents) is the most widely distributed, expressed in peripheral tissues, as well as in both neurons and astrocytes[117]. EAAT4 is most strongly expressed in cerebellar Purkinje cells[118], and EAAT5 is almost exclusively expressed in the retina[119].

In recent years, EAAT2 has received increasing attention in addiction research, as it is the primary EAAT subtype expressed in the striatum, a component of the basal ganglia that has been implicated in addiction and other psychiatric disorders, and is responsible for clearance of at least 90% of extracellular glutamate. Conceptually, alterations in EAAT2 surface expression should impact neurotransmission, and indeed, this has been demonstrated[120,121].

Structure, function and localization

Structurally, EAATs contain eight transmembrane segments. The N-terminal structures are involved in intersubunit contacts, while the C-terminal half is implicated in substrate transport[122]. EAATs appear to be oligomeric, and EAAT2 tends to form homotrimers and heterotrimers with its other isoforms[123,124], generating a bowl-shaped complex with the aqueous, concave side facing the extracellular space and the pointed side facing the cytoplasm. Interestingly, between the subunits on the hydrophobic transmembrane sides are distinct crevices that allow lipids to interact with key functional domains of the transporter[122], suggesting a role for lipid modulation of EAAT2 activity.

EAATs are capable of transporting both glutamate and aspartate. With one molecule of glutamate, they co-transport three sodium ions and one proton in exchange for one potassium ion[122]. Mouse EAAT2 (GLT-1) shares 97% sequence homology with humans and 99% with rats[125]. The Km of EAAT2 is fairly small (for D-aspartate, 17 ± 5 μmol/L for mouse[126], 54 ± 9 μmol/L for human[127]). Synaptic levels of glutamate can be as high as 1 mmol/L[128], so transport of glutamate out of the synapse occurs very rapidly. In this way, EAAT2 maintains low extracellular glutamate concentrations, preventing it from reaching excitotoxic levels.

In the striatum, EAAT2 is primarily located on the membrane surface of astrocytes, but can also be found on the outer mitochondrial membrane, on rough endoplasmic reticulum, and on polyribosomes[129]. EAAT2 tends to concentrate at cellular processes adjacent to glutamatergic synapses (PAPs; Figure 1) and in astrocytic endfeet near capillaries in the neurovascular unit[1]. It is tightly associated with cholesterol-rich lipid rafts[130,131], and it has been suggested that it may be part of a macromolecular complex that also contains Kir4.1 and AQP4 at capillary endfeet, implying a combined effort for glutamate and potassium ion homeostasis[132].

Glutamate transporter regulation

EAAT2, like most proteins, can be regulated by multiple methods. It is subject to transcriptional regulation by transcription factors and differential splicing, epigenetically by histone modifications and DNA methylation, post-translationally by various residue modifications, and functionally by certain toxins, membrane lipid composition, and cytoskeletal rearrangements[115,131,133-137] (Table 1 provides a more complete list of modulators).

The EAAT2 promoter contains several transcription factor binding sites, including CREB, KBBP, NF-κB, N-myc, Sp1 and Yin Yang 1[115,134,138]. The most studied of these, NF-κB, has been shown to be an effective regulator of EAAT2 expression, though by different mechanisms depending on the initiation factor[139-145]. For example, EGF-receptor stimulation induces increased EAAT2 transcription, but not *via* IκB degradation[115], whereas Ceftriaxone, a β-lactam antibiotic, does appear to

Table 1 Modulators of excitatory amino acid transporter 2 expression and/or function

Compound	Demonstrated effect on EAAT2	Process/pathway	Ref.
17β-estradiol	Increased expression	Activation of both NF-κB and CREB	Lee *et al*[142]
cAMP/bromo-cAMP/dB-cAMP	Increased expression	PKA pathway, PI-3K and NF-κB	Su *et al*[115]
Ceftriaxone	Increased expression	Conventional NF-κB activation	Lee *et al*[146]; Rothestein *et al*[143]
EGF	Increased expression	Non-canonical NF-κB activation	Zelenaia *et al*[144]
PACAP	Increased expression	PKA and PKC activation	Figiel *et al*[139]
Parawixin1	Increased transport speed	Allosteric enhancement of receptor function	Fontana *et al*[133]
Raloxifene	Increased expression	Activation of both NF-κB and CREB	Karki *et al*[135]
Riluzole	Increased expression and activity	Multiple pathways, mediated by estrogen receptors and HSF1	Karki *et al*[135]; Liu *et al*[137]
Tamoxifen	Increased expression	Activation of both NF-κB and CREB	Karki *et al*[141]
TGF-α	Increased expression	Tyrosine Kinase activation	Lee *et al*[136]; Su *et al*[115]
TNFα	Decreased expression	Co-activation of NF-κB and N-myc	Sitcheran *et al*[145]

Listed in this table are agents that have been demonstrated to affect EAAT2 expression and/or function, and their mechanism of action. EAAT2: Excitatory amino acid transporter 2; cAMP: Cyclic adenosine monophosphate; CREB: cAMP response element-binding protein; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PI-3K: Phosphatidylinositol 3-kinase; PKA: Protein kinase A; EGF: Epidermal growth factor; PACAP: Pituitary adenylate cyclase-activating peptide; TGF-α: Transforming growth factor alpha; TNFα: Tumor necrosis factor alpha.

activate EAAT2 through the canonical NF-κB pathway[146]. However, NF-κB has also been shown to reduce EAAT2 transcription through co-activation of the TNFα-mediated NF-κB activation and N-myc activation, converting NF-κB to a repressor[145] (Table 1). One intriguing method of EAAT2 up regulation is through an as yet unknown mechanism driven by the presence of neurons or neuronal supernatant in cultured astrocytes, involving NF-κB and the kappa B-motif binding phosphoprotein (KBBP)[147]. Interestingly, in cultured astrocytes, transcription factor Ying Yang 1 appears to act as a repressor by recruiting histone deacetylases, coordinating an epigenetic method of silencing the gene[134]. Hypermethylation of EAAT2 promoter DNA is another epigenetic mechanism for EAAT2 down regulation that has been suggested[147,148].

Several post-translation modifications have been suggested to control EAAT2 levels and cellular localization. EAAT2 is internalized and degraded through Nedd-2 dependent ubiquitination at its C-terminus[149]. Sumoylation may also be involved, as non-sumoylated EAAT2 is primarily localized to the plasma membrane while only sumoylated EAAT2 is found in intracellular compartments[150] (Figure 1).

Functionally, EAAT2 has been show to exhibit reduced glutamate uptake when membrane cholesterol levels are reduced[130], as suggested by the inter-subunit crevices revealed by its structure. Additionally, certain exon-skipping EAAT2 splice variants appear to have an effect on EAAT2 function and surface localization[123].

In neuropathology, EAAT1 and EAAT2 have been shown to be reduced in several neurodegenerative disorders, such as amyotrophic lateral sclerosis, Alzheimer's disease, and Huntington's disease, where it was causally related to excitotoxic neuronal cell death[151]. In AUD, one genetic variant of human EAAT2, G603A, has been associated with antisocial[152] and cirrhotic alcoholics[153]. Rodent models, however, have provided an excellent tool for studying EAAT2 in AUD. The mouse EAAT2 gene (*slc1a2*) is located near a quantitative trait loci on chromosome 2 (E2)[125] that modulates seizure frequency and neuro-excitability in mouse models of epilepsy and alcohol withdrawal[154]. Many mouse studies have supported the involvement of EAAT2 in both the acute and chronic effects of ethanol, as well as the symptoms of withdrawal. Mulholland *et al*[155] showed disruption of NMDA and EAAT2 dependent Kv2.1 potassium channels by acute ethanol in the hippocampus. Several studies have demonstrated increased glutamatergic tone in regions of the cortico-striatal circuit[156], but there are only a handful of publications providing strong support for a correlating decrease in EAAT2. Increased EAAT2 expression and/or function alleviates withdrawal symptoms and reduces ethanol consumption[157,158], highlighting the importance of EAAT2 in regulating synaptic glutamate signaling.

CONCLUSION

According to the DSM-5® (diagnostic and statistical manual of mental disorders), alcohol use becomes a disorder when at least two of eleven specific criteria are met, including uncontrolled consumption, alcohol craving, or a development of tolerance. Addiction is a chronic, relapsing disorder characterized by the progression from occasional, controlled use to uncontrolled use and behavior over seeking and consumption, to chronic relapse after protracted abstinence. This process involves neuroplastic changes, primarily in the mesolimbic dopamine system, going from impulsive, positively reinforced behaviors (euphoria, social aspects) to compulsive, negatively reinforced behaviors (removing withdrawal symptoms)[10,159].

Understandably, early research in the field of addiction was focused on the ascending monoamine pathways of the dopaminergic reward system (mesocorticolimbic and extended amygdala), including the involvement of GABA and serotonin, all of which are

important in the early stages of addiction. In the past two decades, increased focus has shifted to glutamatergic signalling, as glutamate receptors in this system are greatly altered, and highly implicated in all stages of addiction, especially the later stages of dependence and withdrawal. The effects of alcohol on all types of glutamate receptors are under intense investigation, and much has been learned to date on how the dysregulated synaptic glutamate alters synaptic plasticity[66,67,86,121] (Figure 1). This shift in focus coincides with the success of clinical pharmacotherapies that alter the glutamatergic system. Acamprosate, a homo-taurine derivative similar in structure to GABA, especially when used with naltrexone, an opioid antagonist, has been one of the most effective drugs in preventing relapse in AUD[160]. However, the mechanistic understanding of these drugs is still not well understood. But, because of these relative successes, we are increasing our efforts in understanding synaptic glutamate modulation. For example, ceftriaxone, a beta-lactam antibiotic, has been shown not only to increase EAAT2 transcript levels, but also to attenuate ethanol consumption and withdrawal symptoms[157,158,161].

Regulation of EAAT2 and glutamate is complex, and understanding how to effectively control astrocytic EAAT2 function and/or expression could be the key to successfully treating AUD. By maintaining stable synaptic glutamatergic tone to ease withdrawal symptoms and allow re-establishment of non-pathological connections in the mesocorticolimbic circuit, recovery from addiction could be greatly ameliorated. In conclusion, a medication targeting an astrocytic glutamate transporter, especially EAAT2, will be an appropriate treatment option for AUD patients with pathologically increased glutamate levels.

REFERENCES

1 **Kandel ER**, Schwarz MJ, Jessell TM. Principles of neural science. McGraw-Hill, 2000

2 **Volterra A**, Meldolesi J. Astrocytes, from brain glue to communication elements: the revolution continues. *Nat Rev Neurosci* 2005; **6**: 626-640 [PMID: 16025096 DOI: 10.1038/nrn1722]

3 **Barnett SC**, Linington C. Myelination: do astrocytes play a role? *Neuroscientist* 2013; **19**: 442-450 [PMID: 23131748 DOI: 10.1177/1073858412465655]

4 **Pannasch U**, Rouach N. Emerging role for astroglial networks in information processing: from synapse to behavior. *Trends Neurosci* 2013; **36**: 405-417 [PMID: 23659852 DOI: 10.1016/j.tins.2013.04.004]

5 **Heller JP**, Rusakov DA. Morphological plasticity of astroglia: Understanding synaptic microenvironment. *Glia* 2015; **63**: 2133-2151 [PMID: 25782611 DOI: 10.1002/glia.22821]

6 **Rossetti ZL**, Carboni S. Ethanol withdrawal is associated with increased extracellular glutamate in the rat striatum. *Eur J Pharmacol* 1995; **283**: 177-183 [PMID: 7498307]

7 **Dahchour A**, De Witte P. Effect of repeated ethanol withdrawal on glutamate microdialysate in the hippocampus. *Alcohol Clin Exp Res* 1999; **23**: 1698-1703 [PMID: 10550004]

8 **Saellstroem Baum S**, Huebner A, Krimphove M, Morgenstern R, Badawy AA, Spies CD. Nicotine stimulation on extracellular glutamate levels in the nucleus accumbens of ethanol-withdrawn rats in vivo. *Alcohol Clin Exp Res* 2006; **30**: 1414-1421 [PMID: 16899045 DOI: 10.1111/j.1530-0277.2006.00169.x]

9 **Everitt BJ**, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 2005; **8**: 1481-1489 [PMID: 16251991 DOI: 10.1038/nn1579]

10 **Koob GF**, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology* 2010; **35**: 217-238 [PMID: 19710631 DOI: 10.1038/npp.2009.110]

11 **Amato L**, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the Alcohol Withdrawal Syndrome. *Cochrane Database Syst Rev* 2011; **(6)**: CD008537 [PMID: 21678378 DOI: 10.1002/14651858.CD008537.pub2]

12 **Ripley TL**, Stephens DN. Critical thoughts on current rodent models for evaluating potential treatments of alcohol addiction and withdrawal. *Br J Pharmacol* 2011; **164**: 1335-1356 [PMID: 21470204 DOI: 10.1111/j.1476-5381.2011.01406.x]

13 **Szumlinski KK**, Lominac KD, Oleson EB, Walker JK, Mason A, Dehoff MH, Klugmann M, Cagle S, Welt K, During M, Worley PF, Middaugh LD, Kalivas PW. Homer2 is necessary for EtOH-induced neuroplasticity. *J Neurosci* 2005; **25**: 7054-7061 [PMID: 16049182 DOI: 10.1523/jneurosci.1529-05.2005]

14 **Cowen MS**, Schroff KC, Gass P, Sprengel R, Spanagel R. Neurobehavioral effects of alcohol in AMPA receptor subunit (GluR1) deficient mice. *Neuropharmacology* 2003; **45**: 325-333 [PMID: 12871650]

15 **Boyce-Rustay JM**, Holmes A. Functional roles of NMDA receptor NR2A and NR2B subunits in the acute intoxicating effects of ethanol in mice. *Synapse* 2005; **56**: 222-225 [PMID: 15803501 DOI: 10.1002/syn.20143]

16 **Gordey M**, Mekmanee L, Mody I. Altered effects of ethanol in NR2A(DeltaC/DeltaC) mice expressing C-terminally truncated NR2A subunit of NMDA receptor. *Neuroscience* 2001; **105**: 987-997 [PMID: 11530236]

17 **Kiefer F**, Jahn H, Koester A, Montkowski A, Reinscheid RK, Wiedemann K. Involvement of NMDA receptors in alcohol-mediated behavior: mice with reduced affinity of the NMDA R1 glycine binding site display an attenuated sensitivity to ethanol. *Biol Psychiatry* 2003; **53**: 345-351 [PMID: 12586454]

18 **Yamamuro K**, Kimoto S, Rosen KM, Kishimoto T, Makinodan M. Potential primary roles of glial cells in the mechanisms of psychiatric disorders. *Front Cell Neurosci* 2015; **9**: 154 [PMID: 26029044 DOI: 10.3389/fncel.2015.00154]

19 **Casaccia-Bonnefil P**. Cell death in the oligodendrocyte lineage: a molecular perspective of life/death decisions in development and disease. *Glia* 2000; **29**: 124-135 [PMID: 10625330]

20 **Gallo V**, Deneen B. Glial development: the crossroads of regeneration and repair in the CNS. *Neuron* 2014; **83**: 283-308 [PMID: 25033178 DOI: 10.1016/j.neuron.2014.06.010]

21 **Nave KA**. Myelination and support of axonal integrity by glia. *Nature* 2010; **468**: 244-252 [PMID: 21068833 DOI: 10.1038/nature09614]

22 **Ransom BR**, Ransom CB. Astrocytes: multitalented stars of the central nervous system. *Methods Mol Biol* 2012; **814**: 3-7 [PMID: 22144296 DOI: 10.1007/978-1-61779-452-0_1]

23 **Burda JE**, Sofroniew MV. Reactive gliosis and the multicellular response to CNS damage and disease. *Neuron* 2014; **81**: 229-248 [PMID: 24462092 DOI: 10.1016/j.neuron.2013.12.034]

24 **Bernstein HG**, Steiner J, Guest PC, Dobrowolny H, Bogerts B. Glial cells as key players in schizophrenia pathology: recent insights and concepts of therapy. *Schizophr Res* 2015; **161**: 4-18 [PMID: 24948484 DOI: 10.1016/j.schres.2014.03.035]

25 **Barley K**, Dracheva S, Byne W. Subcortical oligodendrocyte- and astrocyte-associated gene expression in subjects with schizophrenia, major depression and bipolar disorder. *Schizophr Res* 2009; **112**: 54-64 [PMID: 19447584 DOI: 10.1016/j.schres.2009.04.019]

26 **Armstrong V**, Reichel CM, Doti JF, Crawford CA, McDougall SA. Repeated amphetamine treatment causes a persistent elevation of glial fibrillary acidic protein in the caudate-putamen. *Eur J Pharmacol* 2004; **488**: 111-115 [PMID: 15044042 DOI: 10.1016/j.ejphar.2004.02.001]

27 **Paolicelli RC**, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, Giustetto M, Ferreira TA, Guiducci E, Dumas L, Ragozzino

D, Gross CT. Synaptic pruning by microglia is necessary for normal brain development. *Science* 2011; **333**: 1456-1458 [PMID: 21778362 DOI: 10.1126/science.1202529]
28 **Sierra A**, Encinas JM, Deudero JJ, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, Tsirka SE, Maletic-Savatic M. Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell* 2010; **7**: 483-495 [PMID: 20887954 DOI: 10.1016/j.stem.2010.08.014]
29 **Arendt T**. Impairment in memory function and neurodegenerative changes in the cholinergic basal forebrain system induced by chronic intake of ethanol. *J Neural Transm Suppl* 1994; **44**: 173-187 [PMID: 7897389]
30 **Butterworth RF**. Pathophysiology of alcoholic brain damage: synergistic effects of ethanol, thiamine deficiency and alcoholic liver disease. *Metab Brain Dis* 1995; **10**: 1-8 [PMID: 7596324]
31 **Choi DS**, Cascini MG, Mailliard W, Young H, Paredes P, McMahon T, Diamond I, Bonci A, Messing RO. The type 1 equilibrative nucleoside transporter regulates ethanol intoxication and preference. *Nat Neurosci* 2004; **7**: 855-861 [PMID: 15258586 DOI: 10.1038/nn1288]
32 **Nam HW**, Hinton DJ, Kang NY, Kim T, Lee MR, Oliveros A, Adams C, Ruby CL, Choi DS. Adenosine transporter ENT1 regulates the acquisition of goal-directed behavior and ethanol drinking through A2A receptor in the dorsomedial striatum. *J Neurosci* 2013; **33**: 4329-4338 [PMID: 23467349 DOI: 10.1523/JNEUROSCI.3094-12.2013]
33 **Ruby CL**, Adams CA, Knight EJ, Nam HW, Choi DS. An essential role for adenosine signaling in alcohol abuse. *Curr Drug Abuse Rev* 2010; **3**: 163-174 [PMID: 21054262]
34 **Sari Y**, Sreemantula SN, Lee MR, Choi DS. Ceftriaxone treatment affects the levels of GLT1 and ENT1 as well as ethanol intake in alcohol-preferring rats. *J Mol Neurosci* 2013; **51**: 779-787 [PMID: 23893122 DOI: 10.1007/s12031-013-0064-y]
35 **Jedrzejewska A**, Staff-Zielińska E, Wierzba-Bobrowicz T, Poszwińska Z, Olejniczak P. [Histology of the central nervous system in rats after intensive chronic ethanol intoxication]. *Neuropatol Pol* 1990; **28**: 93-99 [PMID: 2097539]
36 **Lewohl JM**, Wang L, Miles MF, Zhang L, Dodd PR, Harris RA. Gene expression in human alcoholism: microarray analysis of frontal cortex. *Alcohol Clin Exp Res* 2000; **24**: 1873-1882 [PMID: 11141048]
37 **Blednov YA**, Bergeson SE, Walker D, Ferreira VM, Kuziel WA, Harris RA. Perturbation of chemokine networks by gene deletion alters the reinforcing actions of ethanol. *Behav Brain Res* 2005; **165**: 110-125 [PMID: 16105698 DOI: 10.1016/j.bbr.2005.06.026]
38 **Qin L**, He J, Hanes RN, Pluzarev O, Hong JS, Crews FT. Increased systemic and brain cytokine production and neuroinflammation by endotoxin following ethanol treatment. *J Neuroinflammation* 2008; **5**: 10 [PMID: 18348728 DOI: 10.1186/1742-2094-5-10]
39 **Blanco AM**, Guerri C. Ethanol intake enhances inflammatory mediators in brain: role of glial cells and TLR4/IL-1RI receptors. *Front Biosci* 2007; **12**: 2616-2630 [PMID: 17127267]
40 **Alfonso-Loeches S**, Pascual-Lucas M, Blanco AM, Sanchez-Vera I, Guerri C. Pivotal role of TLR4 receptors in alcohol-induced neuroinflammation and brain damage. *J Neurosci* 2010; **30**: 8285-8295 [PMID: 20554880 DOI: 10.1523/JNEUROSCI.0976-10.2010]
41 **Ozer E**, Sarioglu S, Güre A. Effects of prenatal ethanol exposure on neuronal migration, neuronogenesis and brain myelination in the mice brain. *Clin Neuropathol* 2000; **19**: 21-25 [PMID: 10774947]
42 **Bichenkov E**, Ellingson JS. Ethanol exerts different effects on myelin basic protein and 2',3'-cyclic nucleotide 3'-phosphodiesterase expression in differentiating CG-4 oligodendrocytes. *Brain Res Dev Brain Res* 2001; **128**: 9-16 [PMID: 11356257]
43 **Bichenkov E**, Ellingson JS. Protein kinase C inhibitors counteract the ethanol effects on myelin basic protein expression in differentiating CG-4 oligodendrocytes. *Brain Res Dev Brain Res* 2002; **139**: 29-38 [PMID: 12414091]
44 **Okamoto H**, Miki T, Lee KY, Yokoyama T, Kuma H, Wang ZY, Gu H, Li HP, Matsumoto Y, Irawan S, Bedi KS, Nakamura Y, Takeuchi Y. Oligodendrocyte myelin glycoprotein (OMgp) in rat hippocampus is depleted by chronic ethanol consumption. *Neurosci Lett* 2006; **406**: 76-80 [PMID: 16905253 DOI: 10.1016/j.neulet.2006.07.023]
45 **Navarro AI**, Mandyam CD. Protracted abstinence from chronic ethanol exposure alters the structure of neurons and expression of oligodendrocytes and myelin in the medial prefrontal cortex. *Neuroscience* 2015; **293**: 35-44 [PMID: 25732140 DOI: 10.1016/j.neuroscience.2015.02.043]
46 **Aspberg A**, Tottmar O. Ethanol-induced increase in catalase activity in reaggregation cultures of rat brain cells is due to increased oligodendrocyte differentiation. *Alcohol Clin Exp Res* 1994; **18**: 620-624 [PMID: 7943665]
47 **Katsel P**, Byne W, Roussos P, Tan W, Siever L, Haroutunian V. Astrocyte and glutamate markers in the superficial, deep, and white matter layers of the anterior cingulate gyrus in schizophrenia. *Neuropsychopharmacology* 2011; **36**: 1171-1177 [PMID: 21270770 DOI: 10.1038/npp.2010.252]
48 **Xia M**, Abazyan S, Jouroukhin Y, Pletnikov M. Behavioral sequelae of astrocyte dysfunction: focus on animal models of schizophrenia. *Schizophr Res* 2014; Epub ahead of print [PMID: 25468180 DOI: 10.1016/j.schres.2014.10.044]
49 **Savitz JB**, Price JL, Drevets WC. Neuropathological and neuromorphometric abnormalities in bipolar disorder: view from the medial prefrontal cortical network. *Neurosci Biobehav Rev* 2014; **42**: 132-147 [PMID: 24603026 DOI: 10.1016/j.neubiorev.2014.02.008]
50 **Liu Z**, Song D, Yan E, Verkhratsky A, Peng L. Chronic treatment with anti-bipolar drugs suppresses glutamate release from astroglial cultures. *Amino Acids* 2015; **47**: 1045-1051 [PMID: 25676933 DOI: 10.1007/s00726-015-1936-y]
51 **Emamghoreishi M**, Keshavarz M, Nekooeian AA. Chronic lithium treatment increased intracellular S100ß levels in rat primary neuronal culture. *Acta Med Iran* 2015; **53**: 89-96 [PMID: 25725177]
52 **Radewicz K**, Garey LJ, Gentleman SM, Reynolds R. Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics. *J Neuropathol Exp Neurol* 2000; **59**: 137-150 [PMID: 10749103]
53 **Miller BJ**, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry* 2011; **70**: 663-671 [PMID: 21641581 DOI: 10.1016/j.biopsych.2011.04.013]
54 **Schafer DP**, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, Yamasaki R, Ransohoff RM, Greenberg ME, Barres BA, Stevens B. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron* 2012; **74**: 691-705 [PMID: 22632727 DOI: 10.1016/j.neuron.2012.03.026]
55 **Söderlund J**, Olsson SK, Samuelsson M, Walther-Jallow L, Johansson C, Erhardt S, Landén M, Engberg G. Elevation of cerebrospinal fluid interleukin-1ß in bipolar disorder. *J Psychiatry Neurosci* 2011; **36**: 114-118 [PMID: 21138659 DOI: 10.1503/jpn.100080]
56 **Monfrim X**, Gazal M, De Leon PB, Quevedo L, Souza LD, Jansen K, Oses JP, Pinheiro RT, Silva RA, Lara DR, Ghisleni G, Spessato B, Kaster MP. Immune dysfunction in bipolar disorder and suicide risk: is there an association between peripheral corticotropin-releasing hormone and interleukin-1β? *Bipolar Disord* 2014; **16**: 741-747 [PMID: 24862833 DOI: 10.1111/bdi.12214]
57 **Konradi C**, Sillivan SE, Clay HB. Mitochondria, oligodendrocytes and inflammation in bipolar disorder: evidence from transcriptome studies points to intriguing parallels with multiple sclerosis. *Neurobiol Dis* 2012; **45**: 37-47 [PMID: 21310238 DOI: 10.1016/j.nbd.2011.01.025]
58 **Chew LJ**, Fusar-Poli P, Schmitz T. Oligodendroglial alterations and the role of microglia in white matter injury: relevance to schizophrenia. *Dev Neurosci* 2013; **35**: 102-129 [PMID: 23446060 DOI: 10.1159/000346157]
59 **Dracheva S**, Davis KL, Chin B, Woo DA, Schmeidler J, Haroutunian V. Myelin-associated mRNA and protein expression deficits in the anterior cingulate cortex and hippocampus in elderly schizophrenia patients. *Neurobiol Dis* 2006; **21**: 531-540 [PMID:

16213148 DOI: 10.1016/j.nbd.2005.08.012]
60 **Takahashi N**, Sakurai T, Davis KL, Buxbaum JD. Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. *Prog Neurobiol* 2011; **93**: 13-24 [PMID: 20950668 DOI: 10.1016/j.pneurobio.2010.09.004]
61 **Nave KA**. Myelination and the trophic support of long axons. *Nat Rev Neurosci* 2010; **11**: 275-283 [PMID: 20216548 DOI: 10.1038/nrn2797]
62 **Paintlia MK**, Paintlia AS, Contreras MA, Singh I, Singh AK. Lipopolysaccharide-induced peroxisomal dysfunction exacerbates cerebral white matter injury: attenuation by N-acetyl cysteine. *Exp Neurol* 2008; **210**: 560-576 [PMID: 18291369 DOI: 10.1016/j.expneurol.2007.12.011]
63 **Oorschot DE**, Voss L, Covey MV, Goddard L, Huang W, Birchall P, Bilkey DK, Kohe SE. Spectrum of short- and long-term brain pathology and long-term behavioral deficits in male repeated hypoxic rats closely resembling human extreme prematurity. *J Neurosci* 2013; **33**: 11863-11877 [PMID: 23864676 DOI: 10.1523/JNEUROSCI.0342-12.2013]
64 **Huang H**, Gundapuneedi T, Rao U. White matter disruptions in adolescents exposed to childhood maltreatment and vulnerability to psychopathology. *Neuropsychopharmacology* 2012; **37**: 2693-2701 [PMID: 22850736 DOI: 10.1038/npp.2012.133]
65 **Choquet D**, Triller A. The role of receptor diffusion in the organization of the postsynaptic membrane. *Nat Rev Neurosci* 2003; **4**: 251-265 [PMID: 12671642 DOI: 10.1038/Nrn1077]
66 **Faissner A**, Pyka M, Geissler M, Sobik T, Frischknecht R, Gundelfinger ED, Seidenbecher C. Contributions of astrocytes to synapse formation and maturation - Potential functions of the perisynaptic extracellular matrix. *Brain Res Rev* 2010; **63**: 26-38 [PMID: 20096729 DOI: 10.1016/j.brainresrev.2010.01.001]
67 **Allen NJ**, Barres BA. Signaling between glia and neurons: focus on synaptic plasticity. *Curr Opin Neurobiol* 2005; **15**: 542-548 [PMID: 16144764 DOI: 10.1016/j.conb.2005.08.006]
68 **Witcher MR**, Kirov SA, Harris KM. Plasticity of perisynaptic astroglia during synaptogenesis in the mature rat hippocampus. *Glia* 2007; **55**: 13-23 [PMID: 17001633 DOI: 10.1002/Glia.20415]
69 **Dallérac G**, Chever O, Rouach N. How do astrocytes shape synaptic transmission? Insights from electrophysiology. *Front Cell Neurosci* 2013; **7**: 159 [PMID: 24101894 DOI: 10.3389/Fncel.2013.00159]
70 **Hertz L**, Zielke HR. Astrocytic control of glutamatergic activity: astrocytes as stars of the show. *Trends Neurosci* 2004; **27**: 735-743 [PMID: 15541514 DOI: 10.1016/j.tins.2004.10.008]
71 **Pascual O**, Casper KB, Kubera C, Zhang J, Revilla-Sanchez R, Sul JY, Takano H, Moss SJ, McCarthy K, Haydon PG. Astrocytic purinergic signaling coordinates synaptic networks. *Science* 2005; **310**: 113-116 [PMID: 16210541 DOI: 10.1126/science.1116916]
72 **Schipke CG**, Kettenmann H. Astrocyte responses to neuronal activity. *Glia* 2004; **47**: 226-232 [PMID: 15252811 DOI: 10.1002/Glia.20029]
73 **Cornell-Bell AH**, Thomas PG, Smith SJ. The excitatory neurotransmitter glutamate causes filopodia formation in cultured hippocampal astrocytes. *Glia* 1990; **3**: 322-334 [PMID: 1699891 DOI: 10.1002/glia.440030503]
74 **Glaum SR**, Holzwarth JA, Miller RJ. Glutamate receptors activate Ca2+ mobilization and Ca2+ influx into astrocytes. *Proc Natl Acad Sci USA* 1990; **87**: 3454-3458 [PMID: 1970637]
75 **Bergles DE**, Jahr CE. Synaptic activation of glutamate transporters in hippocampal astrocytes. *Neuron* 1997; **19**: 1297-1308 [PMID: 9427252 DOI: 10.1016/S0896-6273(00)80420-1]
76 **Rusakov DA**, Zheng K, Henneberger C. Astrocytes as regulators of synaptic function: a quest for the Ca2+ master key. *Neuroscientist* 2011; **17**: 513-523 [PMID: 21536839 DOI: 10.1177/1073858410387304]
77 **Swanson RA**. Neuroglia. 2nd ed. New York, NY, USA: Oxford University Press, 2005: 346-350
78 **Amiri M**, Bahrami F, Janahmadi M. Functional contributions of astrocytes in synchronization of a neuronal network model. *J Theor Biol* 2012; **292**: 60-70 [PMID: 21978738 DOI: 10.1016/j.jtbi.2011.09.013]
79 **Kang J**, Jiang L, Goldman SA, Nedergaard M. Astrocyte-mediated potentiation of inhibitory synaptic transmission. *Nat Neurosci* 1998; **1**: 683-692 [PMID: 10196584 DOI: 10.1038/3684]
80 **Bezzi P**, Carmignoto G, Pasti L, Vesce S, Rossi D, Rizzini BL, Pozzan T, Volterra A. Prostaglandins stimulate calcium-dependent glutamate release in astrocytes. *Nature* 1998; **391**: 281-285 [PMID: 9440691 DOI: 10.1038/34651]
81 **Parpura V**, Basarsky TA, Liu F, Jeftinija K, Jeftinija S, Haydon PG. Glutamate-mediated astrocyte-neuron signalling. *Nature* 1994; **369**: 744-747 [PMID: 7911978 DOI: 10.1038/369744a0]
82 **Mazzanti M**, Sul JY, Haydon PG. Glutamate on demand: astrocytes as a ready source. *Neuroscientist* 2001; **7**: 396-405 [PMID: 11597099 DOI: 10.1177/107385840100700509]
83 **Bowser DN**, Khakh BS. ATP excites interneurons and astrocytes to increase synaptic inhibition in neuronal networks. *J Neurosci* 2004; **24**: 8606-8620 [PMID: 15456834 DOI: 10.1523/JNEUROSCI.2660-04.2004]
84 **Domercq M**, Brambilla L, Pilati E, Marchaland J, Volterra A, Bezzi P. P2Y1 receptor-evoked glutamate exocytosis from astrocytes: control by tumor necrosis factor-alpha and prostaglandins. *J Biol Chem* 2006; **281**: 30684-30696 [PMID: 16882655 DOI: 10.1074/jbc.M606429200]
85 **Jourdain P**, Bergersen LH, Bhaukaurally K, Bezzi P, Santello M, Domercq M, Matute C, Tonello F, Gundersen V, Volterra A. Glutamate exocytosis from astrocytes controls synaptic strength. *Nat Neurosci* 2007; **10**: 331-339 [PMID: 17310248 DOI: 10.1038/nn1849]
86 **Ota Y**, Zanetti AT, Hallock RM. The role of astrocytes in the regulation of synaptic plasticity and memory formation. *Neural Plast* 2013; **2013**: 185463 [PMID: 24369508 DOI: 10.1155/2013/185463]
87 **Zhou M**, Kimelberg HK. Freshly isolated hippocampal CA1 astrocytes comprise two populations differing in glutamate transporter and AMPA receptor expression. *J Neurosci* 2001; **21**: 7901-7908 [PMID: 11588163]
88 **Sun W**, McConnell E, Pare JF, Xu Q, Chen M, Peng W, Lovatt D, Han X, Smith Y, Nedergaard M. Glutamate-dependent neuroglial calcium signaling differs between young and adult brain. *Science* 2013; **339**: 197-200 [PMID: 23307741 DOI: 10.1126/science.1226740]
89 **Bezzi P**, Gundersen V, Galbete JL, Seifert G, Steinhäuser C, Pilati E, Volterra A. Astrocytes contain a vesicular compartment that is competent for regulated exocytosis of glutamate. *Nat Neurosci* 2004; **7**: 613-620 [PMID: 15156145 DOI: 10.1038/nn1246]
90 **Araque A**, Parpura V, Sanzgiri RP, Haydon PG. Tripartite synapses: glia, the unacknowledged partner. *Trends Neurosci* 1999; **22**: 208-215 [PMID: 10322493 DOI: 10.1016/S0166-2236(98)01349-6]
91 **Peters, A,** Palay SL, and Webster HD. The fine structure of the nervous system: neurons and their supporting cells. New York: Oxford University Press, 1991
92 **Diamond JS**. Deriving the glutamate clearance time course from transporter currents in CA1 hippocampal astrocytes: transmitter uptake gets faster during development. *J Neurosci* 2005; **25**: 2906-2916 [PMID: 15772350]
93 **Hirrlinger J**, Hülsmann S, Kirchhoff F. Astroglial processes show spontaneous motility at active synaptic terminals in situ. *Eur J Neurosci* 2004; **20**: 2235-2239 [PMID: 15450103 DOI: 10.1111/j.1460-9568.2004.03689.x]
94 **Derouiche A**, Anlauf E, Aumann G, Mühlstädt B, Lavialle M. Anatomical aspects of glia-synapse interaction: the perisynaptic glial sheath consists of a specialized astrocyte compartment. *J Physiol Paris* 2002; **96**: 177-182 [PMID: 12445894 DOI: 10.1016/S0928-4257(02)00004-9]
95 **Derouiche A**, Frotscher M. Astroglial processes around identified glutamatergic synapses contain glutamine synthetase: evidence for transmitter degradation. *Brain Res* 1991; **552**: 346-350 [PMID: 1680531 DOI: 10.1016/0006-8993(91)90103-3]
96 **Bormann J**, Kettenmann H. Patch-clamp study of gamma-aminobutyric acid receptor Cl- channels in cultured astrocytes. *Proc Natl Acad Sci USA* 1988; **85**: 9336-9340 [PMID: 2461568 DOI:

10.1073/pnas.85.23.9336]
97 **Grosche J**, Matyash V, Möller T, Verkhratsky A, Reichenbach A, Kettenmann H. Microdomains for neuron-glia interaction: parallel fiber signaling to Bergmann glial cells. *Nat Neurosci* 1999; **2**: 139-143 [PMID: 10195197 DOI: 10.1038/5692]
98 **Oliet SH**, Piet R, Poulain DA. Control of glutamate clearance and synaptic efficacy by glial coverage of neurons. *Science* 2001; **292**: 923-926 [PMID: 11340204 DOI: 10.1126/science.1059162]
99 **Barbour B**. An evaluation of synapse independence. *J Neurosci* 2001; **21**: 7969-7984 [PMID: 11588170]
100 **Kullmann DM**, Erdemli G, Asztély F. LTP of AMPA and NMDA receptor-mediated signals: evidence for presynaptic expression and extrasynaptic glutamate spill-over. *Neuron* 1996; **17**: 461-474 [PMID: 8816709 DOI: 10.1016/S0896-6273(00)80178-6]
101 **Rusakov DA**, Kullmann DM. Extrasynaptic glutamate diffusion in the hippocampus: ultrastructural constraints, uptake, and receptor activation. *J Neurosci* 1998; **18**: 3158-3170 [PMID: 9547224]
102 **Scanziani M**, Salin PA, Vogt KE, Malenka RC, Nicoll RA. Use-dependent increases in glutamate concentration activate presynaptic metabotropic glutamate receptors. *Nature* 1997; **385**: 630-634 [PMID: 9024660 DOI: 10.1038/385630a0]
103 **Humeau Y**, Shaban H, Bissière S, Lüthi A. Presynaptic induction of heterosynaptic associative plasticity in the mammalian brain. *Nature* 2003; **426**: 841-845 [PMID: 14685239 DOI: 10.1038/nature02194]
104 **Arnth-Jensen N**, Jabaudon D, Scanziani M. Cooperation between independent hippocampal synapses is controlled by glutamate uptake. *Nat Neurosci* 2002; **5**: 325-331 [PMID: 11896395 DOI: 10.1038/nn825]
105 **Marcaggi P**, Attwell D. Endocannabinoid signaling depends on the spatial pattern of synapse activation. *Nat Neurosci* 2005; **8**: 776-781 [PMID: 15864304 DOI: 10.1038/nn1458]
106 **Szapiro G**, Barbour B. Multiple climbing fibers signal to molecular layer interneurons exclusively via glutamate spillover. *Nat Neurosci* 2007; **10**: 735-742 [PMID: 17515900 DOI: 10.1038/nn1907]
107 **Hardingham GE**, Fukunaga Y, Bading H. Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. *Nat Neurosci* 2002; **5**: 405-414 [PMID: 11953750 DOI: 10.1038/nn835]
108 **Zhang JM**, Wang HK, Ye CQ, Ge W, Chen Y, Jiang ZL, Wu CP, Poo MM, Duan S. ATP released by astrocytes mediates glutamatergic activity-dependent heterosynaptic suppression. *Neuron* 2003; **40**: 971-982 [PMID: 14659095 DOI: 10.1016/S0896-6273(03)00717-7]
109 **Fuxe K**, Borroto-Escuela DO, Romero-Fernandez W, Diaz-Cabiale Z, Rivera A, Ferraro L, Tanganelli S, Tarakanov AO, Garriga P, Narváez JA, Ciruela F, Guescini M, Agnati LF. Extrasynaptic neurotransmission in the modulation of brain function. Focus on the striatal neuronal-glial networks. *Front Physiol* 2012; **3**: 136 [PMID: 22675301 DOI: 10.3389/fphys.2012.00136]
110 **Kullmann DM**, Asztely F. Extrasynaptic glutamate spillover in the hippocampus: evidence and implications. *Trends Neurosci* 1998; **21**: 8-14 [PMID: 9464678 DOI: 10.1016/S0166-2236(97)01150-8]
111 **Asztely F**, Erdemli G, Kullmann DM. Extrasynaptic glutamate spillover in the hippocampus: dependence on temperature and the role of active glutamate uptake. *Neuron* 1997; **18**: 281-293 [PMID: 9052798 DOI: 10.1016/S0896-6273(00)80268-8]
112 **Danbolt NC**. Glutamate uptake. *Prog Neurobiol* 2001; **65**: 1-105 [PMID: 11369436]
113 **Liguz-Lecznar M**, Skangiel-Kramska J. Vesicular glutamate transporters (VGLUTs): the three musketeers of glutamatergic system. *Acta Neurobiol Exp* (Wars) 2007; **67**: 207-218 [PMID: 17957901]
114 **Amara SG**, Fontana AC. Excitatory amino acid transporters: keeping up with glutamate. *Neurochem Int* 2002; **41**: 313-318 [PMID: 12176072]
115 **Su ZZ**, Leszczyniecka M, Kang DC, Sarkar D, Chao W, Volsky DJ, Fisher PB. Insights into glutamate transport regulation in human astrocytes: cloning of the promoter for excitatory amino acid transporter 2 (EAAT2). *Proc Natl Acad Sci USA* 2003; **100**: 1955-1960 [PMID: 12578975 DOI: 10.1073/pnas.0136555100]
116 **Gegelashvili G**, Schousboe A. High affinity glutamate transporters: regulation of expression and activity. *Mol Pharmacol* 1997; **52**: 6-15 [PMID: 9224806]
117 **Kanai Y**, Hediger MA. Primary structure and functional characterization of a high-affinity glutamate transporter. *Nature* 1992; **360**: 467-471 [PMID: 1280334 DOI: 10.1038/360467a0]
118 **Fairman WA**, Vandenberg RJ, Arriza JL, Kavanaugh MP, Amara SG. An excitatory amino-acid transporter with properties of a ligand-gated chloride channel. *Nature* 1995; **375**: 599-603 [PMID: 7791878 DOI: 10.1038/375599a0]
119 **Arriza JL**, Eliasof S, Kavanaugh MP, Amara SG. Excitatory amino acid transporter 5, a retinal glutamate transporter coupled to a chloride conductance. *Proc Natl Acad Sci USA* 1997; **94**: 4155-4160 [PMID: 9108121]
120 **Murphy-Royal C**, Dupuis JP, Varela JA, Panatier A, Pinson B, Baufreton J, Groc L, Oliet SH. Surface diffusion of astrocytic glutamate transporters shapes synaptic transmission. *Nat Neurosci* 2015; **18**: 219-226 [PMID: 25581361 DOI: 10.1038/nn.3901]
121 **Filosa A**, Paixão S, Honsek SD, Carmona MA, Becker L, Feddersen B, Gaitanos L, Rudhard Y, Schoepfer R, Klopstock T, Kullander K, Rose CR, Pasquale EB, Klein R. Neuron-glia communication via EphA4/ephrin-A3 modulates LTP through glial glutamate transport. *Nat Neurosci* 2009; **12**: 1285-1292 [PMID: 19734893 DOI: 10.1038/nn.2394]
122 **Yernool D**, Boudker O, Jin Y, Gouaux E. Structure of a glutamate transporter homologue from Pyrococcus horikoshii. *Nature* 2004; **431**: 811-818 [PMID: 15483603 DOI: 10.1038/nature03018]
123 **Gebhardt FM**, Mitrovic AD, Gilbert DF, Vandenberg RJ, Lynch JW, Dodd PR. Exon-skipping splice variants of excitatory amino acid transporter-2 (EAAT2) form heteromeric complexes with full-length EAAT2. *J Biol Chem* 2010; **285**: 31313-31324 [PMID: 20688910 DOI: 10.1074/jbc.M110.153494]
124 **Shigeri Y**, Seal RP, Shimamoto K. Molecular pharmacology of glutamate transporters, EAATs and VGLUTs. *Brain Res Brain Res Rev* 2004; **45**: 250-265 [PMID: 15210307 DOI: 10.1016/j.brainresrev.2004.04.004]
125 **Kirschner MA**, Copeland NG, Gilbert DJ, Jenkins NA, Amara SG. Mouse excitatory amino acid transporter EAAT2: isolation, characterization, and proximity to neuroexcitability loci on mouse chromosome 2. *Genomics* 1994; **24**: 218-224 [PMID: 7698742 DOI: 10.1006/geno.1994.1609]
126 **Sutherland ML**, Delaney TA, Noebels JL. Molecular characterization of a high-affinity mouse glutamate transporter. *Gene* 1995; **162**: 271-274 [PMID: 7557442]
127 **Arriza JL**, Fairman WA, Wadiche JI, Murdoch GH, Kavanaugh MP, Amara SG. Functional comparisons of three glutamate transporter subtypes cloned from human motor cortex. *J Neurosci* 1994; **14**: 5559-5569 [PMID: 7521911]
128 **Augustine JA**, Fitzpatrick D, Hall WC, LaMantia A, McNamara JO, Mooney RD, Platt ML, Purves D, Simon SA, White LE, Williams SM. Neuroscience. Fourth ed. Sunderland, MA, USA: Sinauer Associates, Inc., 2008: 129
129 **Roberts RC**, Roche JK, McCullumsmith RE. Localization of excitatory amino acid transporters EAAT1 and EAAT2 in human postmortem cortex: a light and electron microscopic study. *Neuroscience* 2014; **277**: 522-540 [PMID: 25064059 DOI: 10.1016/j.neuroscience.2014.07.019]
130 **Butchbach ME**, Tian G, Guo H, Lin CL. Association of excitatory amino acid transporters, especially EAAT2, with cholesterol-rich lipid raft microdomains: importance for excitatory amino acid transporter localization and function. *J Biol Chem* 2004; **279**: 34388-34396 [PMID: 15187084 DOI: 10.1074/jbc.M403938200]
131 **Takahashi K**, Foster JB, Lin CL. Glutamate transporter EAAT2: regulation, function, and potential as a therapeutic target for neurological and psychiatric disease. *Cell Mol Life Sci* 2015; **72**: 3489-3506 [PMID: 26033496 DOI: 10.1007/s00018-015-1937-8]
132 **Hinson SR**, Roemer SF, Lucchinetti CF, Fryer JP, Kryzer TJ, Chamberlain JL, Howe CL, Pittock SJ, Lennon VA. Aquaporin-4-binding autoantibodies in patients with neuromyelitis optica impair glutamate transport by down-regulating EAAT2. *J Exp Med* 2008;

205: 2473-2481 [PMID: 18838545 DOI: 10.1084/jem.20081241]
133 **Fontana AC**, de Oliveira Beleboni R, Wojewodzic MW, Ferreira Dos Santos W, Coutinho-Netto J, Grutle NJ, Watts SD, Danbolt NC, Amara SG. Enhancing glutamate transport: mechanism of action of Parawixin1, a neuroprotective compound from Parawixia bistriata spider venom. *Mol Pharmacol* 2007; **72**: 1228-1237 [PMID: 17646426 DOI: 10.1124/mol.107.037127]
134 **Karki P**, Webb A, Smith K, Johnson J, Lee K, Son DS, Aschner M, Lee E. Yin Yang 1 is a repressor of glutamate transporter EAAT2, and it mediates manganese-induced decrease of EAAT2 expression in astrocytes. *Mol Cell Biol* 2014; **34**: 1280-1289 [PMID: 24469401 DOI: 10.1128/MCB.01176-13]
135 **Karki P**, Webb A, Zerguine A, Choi J, Son DS, Lee E. Mechanism of raloxifene-induced upregulation of glutamate transporters in rat primary astrocytes. *Glia* 2014; **62**: 1270-1283 [PMID: 24782323 DOI: 10.1002/glia.22679]
136 **Lee E**, Sidoryk-Wegrzynowicz M, Yin Z, Webb A, Son DS, Aschner M. Transforming growth factor-α mediates estrogen-induced upregulation of glutamate transporter GLT-1 in rat primary astrocytes. *Glia* 2012; **60**: 1024-1036 [PMID: 22488924 DOI: 10.1002/glia.22329]
137 **Liu AY**, Mathur R, Mei N, Langhammer CG, Babiarz B, Firestein BL. Neuroprotective drug riluzole amplifies the heat shock factor 1 (HSF1)- and glutamate transporter 1 (GLT1)-dependent cytoprotective mechanisms for neuronal survival. *J Biol Chem* 2011; **286**: 2785-2794 [PMID: 21098017 DOI: 10.1074/jbc.M110.158220]
138 **Yang Y**, Gozen O, Watkins A, Lorenzini I, Lepore A, Gao Y, Vidensky S, Brennan J, Poulsen D, Won Park J, Li Jeon N, Robinson MB, Rothstein JD. Presynaptic regulation of astroglial excitatory neurotransmitter transporter GLT1. *Neuron* 2009; **61**: 880-894 [PMID: 19323997 DOI: 10.1016/j.neuron.2009.02.010]
139 **Figiel M**, Engele J. Pituitary adenylate cyclase-activating polypeptide (PACAP), a neuron-derived peptide regulating glial glutamate transport and metabolism. *J Neurosci* 2000; **20**: 3596-3605 [PMID: 10804201]
140 **Karki P**, Smith K, Johnson J, Lee E. Astrocyte-derived growth factors and estrogen neuroprotection: role of transforming growth factor-α in estrogen-induced upregulation of glutamate transporters in astrocytes. *Mol Cell Endocrinol* 2014; **389**: 58-64 [PMID: 24447465 DOI: 10.1016/j.mce.2014.01.010]
141 **Karki P**, Webb A, Smith K, Lee K, Son DS, Aschner M, Lee E. cAMP response element-binding protein (CREB) and nuclear factor κB mediate the tamoxifen-induced up-regulation of glutamate transporter 1 (GLT-1) in rat astrocytes. *J Biol Chem* 2013; **288**: 28975-28986 [PMID: 23955341 DOI: 10.1074/jbc.M113.483826]
142 **Lee E**, Sidoryk-Wêgrzynowicz M, Wang N, Webb A, Son DS, Lee K, Aschner M. GPR30 regulates glutamate transporter GLT-1 expression in rat primary astrocytes. *J Biol Chem* 2012; **287**: 26817-26828 [PMID: 22645130 DOI: 10.1074/jbc.M112.341867]
143 **Rothstein JD**, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE, Jin L, Dykes Hoberg M, Vidensky S, Chung DS, Toan SV, Bruijn LI, Su ZZ, Gupta P, Fisher PB. Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. *Nature* 2005; **433**: 73-77 [PMID: 15635412 DOI: 10.1038/nature03180]
144 **Zelenaia O**, Schlag BD, Gochenauer GE, Ganel R, Song W, Beesley JS, Grinspan JB, Rothstein JD, Robinson MB. Epidermal growth factor receptor agonists increase expression of glutamate transporter GLT-1 in astrocytes through pathways dependent on phosphatidylinositol 3-kinase and transcription factor NF-kappaB. *Mol Pharmacol* 2000; **57**: 667-678 [PMID: 10727511]
145 **Sitcheran R**, Gupta P, Fisher PB, Baldwin AS. Positive and negative regulation of EAAT2 by NF-kappaB: a role for N-myc in TNFalpha-controlled repression. *EMBO J* 2005; **24**: 510-520 [PMID: 15660126 DOI: 10.1038/sj.emboj.7600555]
146 **Lee SG**, Su ZZ, Emdad L, Gupta P, Sarkar D, Borjabad A, Volsky DJ, Fisher PB. Mechanism of ceftriaxone induction of excitatory amino acid transporter-2 expression and glutamate uptake in primary human astrocytes. *J Biol Chem* 2008; **283**: 13116-13123 [PMID: 18326497 DOI: 10.1074/jbc.M707697200]
147 **Yang Y**, Gozen O, Vidensky S, Robinson MB, Rothstein JD. Epigenetic regulation of neuron-dependent induction of astroglial synaptic protein GLT1. *Glia* 2010; **58**: 277-286 [PMID: 19672971 DOI: 10.1002/glia.20922]
148 **Perisic T**, Holsboer F, Rein T, Zschocke J. The CpG island shore of the GLT-1 gene acts as a methylation-sensitive enhancer. *Glia* 2012; **60**: 1345-1355 [PMID: 22593010 DOI: 10.1002/glia.22353]
149 **García-Tardón N**, González-González IM, Martínez-Villarreal J, Fernández-Sánchez E, Giménez C, Zafra F. Protein kinase C (PKC)-promoted endocytosis of glutamate transporter GLT-1 requires ubiquitin ligase Nedd4-2-dependent ubiquitination but not phosphorylation. *J Biol Chem* 2012; **287**: 19177-19187 [PMID: 22505712 DOI: 10.1074/jbc.M112.355909]
150 **Foran E**, Rosenblum L, Bogush A, Pasinelli P, Trotti D. Sumoylation of the astroglial glutamate transporter EAAT2 governs its intracellular compartmentalization. *Glia* 2014; **62**: 1241-1253 [PMID: 24753081 DOI: 10.1002/glia.22677]
151 **Lauriat TL**, McInnes LA. EAAT2 regulation and splicing: relevance to psychiatric and neurological disorders. *Mol Psychiatry* 2007; **12**: 1065-1078 [PMID: 17684493 DOI: 10.1038/sj.mp.4002065]
152 **Sander T**, Ostapowicz A, Samochowiec J, Smolka M, Winterer G, Schmidt LG. Genetic variation of the glutamate transporter EAAT2 gene and vulnerability to alcohol dependence. *Psychiatr Genet* 2000; **10**: 103-107 [PMID: 11204345]
153 **Foley PF**, Loh EW, Innes DJ, Williams SM, Tannenberg AE, Harper CG, Dodd PR. Association studies of neurotransmitter gene polymorphisms in alcoholic Caucasians. *Ann N Y Acad Sci* 2004; **1025**: 39-46 [PMID: 15542698 DOI: 10.1196/annals.1316.005]
154 **Crabbe JC**, Belknap JK. Behavior genetic analyses of drug withdrawal. *Alcohol Alcohol Suppl* 1993; **2**: 477-482 [PMID: 7748342]
155 **Mulholland PJ**, Carpenter-Hyland EP, Woodward JJ, Chandler LJ. Ethanol disrupts NMDA receptor and astroglial EAAT2 modulation of Kv2.1 potassium channels in hippocampus. *Alcohol* 2009; **43**: 45-50 [PMID: 19185209 DOI: 10.1016/j.alcohol.2008.10.001]
156 **Griffin WC**, Haun HL, Hazelbaker CL, Ramachandra VS, Becker HC. Increased extracellular glutamate in the nucleus accumbens promotes excessive ethanol drinking in ethanol dependent mice. *Neuropsychopharmacology* 2014; **39**: 707-717 [PMID: 24067300 DOI: 10.1038/npp.2013.256]
157 **Abulseoud OA**, Camsari UM, Ruby CL, Kasasbeh A, Choi S, Choi DS. Attenuation of ethanol withdrawal by ceftriaxone-induced upregulation of glutamate transporter EAAT2. *Neuropsychopharmacology* 2014; **39**: 1674-1684 [PMID: 24452391 DOI: 10.1038/npp.2014.14]
158 **Medrano MC**, Mendiguren A, Pineda J. Effect of ceftriaxone and topiramate treatments on naltrexone-precipitated morphine withdrawal and glutamate receptor desensitization in the rat locus coeruleus. *Psychopharmacology* (Berl) 2015; **232**: 2795-2809 [PMID: 25787747 DOI: 10.1007/s00213-015-3913-2]
159 **Rao PS**, Bell RL, Engleman EA, Sari Y. Targeting glutamate uptake to treat alcohol use disorders. *Front Neurosci* 2015; **9**: 144 [PMID: 25954150 DOI: 10.3389/fnins.2015.00144]
160 **Feeney GF**, Connor JP, Young RM, Tucker J, McPherson A. Combined acamprosate and naltrexone, with cognitive behavioural therapy is superior to either medication alone for alcohol abstinence: a single centres' experience with pharmacotherapy. *Alcohol Alcohol* 2006; **41**: 321-327 [PMID: 16467406]
161 **Sari Y**, Sakai M, Weedman JM, Rebec GV, Bell RL. Ceftriaxone, a beta-lactam antibiotic, reduces ethanol consumption in alcohol-preferring rats. *Alcohol Alcohol* 2011; **46**: 239-246 [PMID: 21422004 DOI: 10.1093/alcalc/agr023]

P- Reviewer: Romani A, Zhang ZM
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Jiao XK

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com