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Overview of Glutamatergic Neurotransmission in the Nervous System

Mark J. Niciu, M.D., Ph.D.[a,b], **Benjamin Kelmendi, B.S.**[c], and **Gerard Sanacora, M.D., Ph.D.**[a,b]

[a]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, United States

[b]Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, New Haven, CT, United States

[c]University of Vermont School of Medicine, Burlington, VT, United States

Abstract

This introductory article to the special edition on glutamate neurotransmission in neuropsychiatric disorders provides an overview of glutamate neurotransmitter system physiology and pharmacology. Glutamate was only relatively recently recognized as the major excitatory neurotransmitter in the mammalian brain, in part due to its ubiquitious nature and diverse metabolic roles within the CNS. The extremely high concentration of glutamate in brain tissue paired with its excitotoxic potential, require tight physiological regulation of extracellular glutamate levels and receptor signaling in order to assure optimal excitatory neurotransmission but limit excitotoxic damage. In order to achieve this high level of control, the system has developed a complex physiology with multiple regulatory processes modulating glutamate metabolism, release, receptor signaling, and uptake. The basic physiology of the various regulatory components of the system including the rich receptor pharmacology is briefly reviewed. Potential contributions from each of the system's components to the pathophysiology of neuropsychiatric illnesses are briefly discussed, as are the many new pharmacological targets for drug development provided by the system, especially as they pertain to the proceeding preclinical and clinical articles in this issue.

INTRODUCTION

The monoaminergic hypothesis of psychiatric disorders arose in the wake of the serendipitous discovery that tricyclic antidepressants and monoamine oxidase inhibitors had beneficial effects on mood, anxiety and psychosis via monoamine neurotransmitter (dopamine, serotonin and norepinephrine) reuptake, degradation and receptor dynamics. Monoamingergic research progressed apace, resulting in many important preclinical and clinical discoveries, enhancing our understanding of the pathophysiological mechanisms

Address correspondence to: Gerry Sanacora, M.D., Ph.D., Department of Psychiatry, Yale University School of Medicine, Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, 34 Park St., New Haven, CT 06519, Telephone: +1 203-974-7535, Fax: +1 203-974-7662, gerard.sancora@yale.edu.

Conflicts of Interest

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underlying many neuropsychiatric disorders and improving our ability to treat these devastating illnesses. However, several recent large clinical studies have made us increasingly aware of the limitations of our current armamentarium of psychotropic medications [STAR*D (Gaynes et al., 2009; Rush et al., 2006), STEP-BD (Perlis et al., 2006; Sachs et al., 2003), CATIE (Lieberman et al., 2005; Swartz et al., 2008)].

Presently, mounting evidence suggesting that the glutamatergic system also contributes to the pathophysiology of neuropsychiatric disorders is opening opportunities for the development of new models of pathogenesis, improved diagnostic tools and novel treatment strategies. A more complete understanding of glutamates roles in the pathogenesis and pathophysiology of neuropsychiatric disorders may allow for an increasingly rational approach to drug development for these common, disabling illnesses. The following review will briefly outline the extremely complex physiology and pharmacology of the glutamatergic neurotransmitter system, highlighting specific areas of interest to clinical neuroscience and drug discovery.

GLUTAMATE METABOLISM

Although glutamate was known to have central nervous system (CNS) effects for more than 75 years, it was not until 1984 that it was truly acknowledged as fulfilling the criteria of a neurotransmitter (Fonnum, 1984). Glutamate was originally speculated to serve a metabolic function in the CNS (Krebs, 1935), as it was found within numerous intracellular compartments including the cytosol and mitochondria of all CNS cell types. However, it is now known that despite its ubiquitous nature, levels of extracellular glutamate are indeed tightly regulated, thus allowing glutamate to function as the major excitatory neurotransmitter in the mammalian CNS. The tight control of glutamatergic neurotransmission is an energy-costly process, requiring multiple regulatory processes and high levels of glucose and oxygen consumption.

Like all amino acids, glutamate has a C-terminus and an N-terminus; the C-terminus and carbon backbone derive from glucose. Glucose crosses the blood-brain barrier via astrocytic end feet and, once intracellular, is broken down via glycolysis to pyruvic acid in the cytosol. Pyruvic acid enters the tricarboyxlic acid (TCA) cycle, which generates α-ketoglutarate and is later transaminated to receive an amino group from a branched chain amino acid donor, *e.g.* leucine, isoleucine and valine, and various amino group donors, *e.g.* aspartate, γ-aminobutyric acid (GABA) and alanine (Pellerin & Magistretti, 2004). It is important to note that in addition to it role as a neurotransmitter, glutamate also serves as a metabolic precursor to GABA and as a component of various amino acid-based derivatives, *e.g.* the antioxidant glutathione. Consistent with glutamate's key role in multiple aspects of brain physiology, metabolic studies have determined that virtually all of the glucose that enters the CNS is eventually converted to glutamate (Shen et al., 1999).

GLUTAMATE RELEASE

Cytosolic glutamate crosses the vesicular membrane via the activity of vesicular glutamate transporters (VGLUTs) (Takamori, 2006). VGLUTs are multimeric proton/glutamate antiporters. To date, three VGLUTs have been cloned. VGLUT1 and 2 are primarily expressed in glutamatergic neurons; whereas, VGLUT3 is somewhat unique in that it has been detected in GABAergic, cholinergic and monoaminergic neurons, although the function of VGLUT3 in these non-glutamatergic neuronal populations is unclear (Fremeau et al., 2004b). Interestingly, VGLUT1 and 2 are also expressed in glial cells and may play a role in the recently-identified release of glutamate from depolarized astrocytes (Bezzi et al., 2004; Montana et al., 2004). The loss of VGLUT expression via targeted knockout strategies results in the loss of glutamate packaging into synaptic vesicles and deleterious

neuropsychiatric sequelae (Fremeau et al., 2004a; Gras et al., 2008; Moechars et al., 2006; Seal et al., 2008; Wallen-Mackenzie et al., 2006; Wallen-Mackenzie et al., 2010; Wojcik et al., 2004). In a Ca^{2+} and soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-dependent manner (Pang & Sudhof, 2010; Sudhof & Rothman, 2009), glutamate is released into the synaptic cleft to bind to and elicit its effects on postsynaptic receptors. Recent studies demonstrating that the packaging and release of vesicular glutamate are modulated by stress and psychotropic drugs (Musazzi et al., 2010), lead to speculation that this could be a critical site in relation to stress-related pathophysiology and possibly a target for drug development.

GLUTAMATE CLEARANCE AND CYCLING

Dysregulated excitatory neurotransmission, resulting in high concentrations of extracellular glutamate, and especially increased levels of extrasynaptic glutamate, leads to cellular damage (hence, the term “excitotoxicity”) (Hardingham et al., 2002; Ivanov et al., 2006; Leveille et al., 2008; Vanhoutte & Bading, 2003; Xu et al., 2009). Therefore, the rapid removal of extracellular glutamate must occur on a millisecond time scale to avoid cellular damage. Glutamate is actively removed from the synaptic cleft and transported into the cytosol against its concentration gradient via excitatory amino acid transporters (EAATs), primarily found on synaptically-associated astrocytic processes. Five such high-affinity transporters have been identified to date (O’Shea, 2002). EAAT1 is abundantly detected in the neocortex and cerebellum but appears to be restricted to astrocytes. EAAT2, the chief glutamate transporter in the forebrain, is expressed mostly in astrocytes but also, to a limited extent, in neurons. EAAT3 is neuron-specific and enriched in GABAergic presynaptic nerve endings. EAAT4 has only been detected in the dendrites of cerebellar Purkinje neurons. Finally, EAAT5 is retina-specific. In rodents, the homologues of EAAT1–3 are referred to as GLAST, GLT and EAAC1, respectively. The location of the EAATs relative to the geometry of synapse places them in a critical position to prevent glutamate spillover and activation of extrasynaptic glutamate transporters (Zheng et al., 2008). Considering individual astrocytes serve large numbers of synapses with minimal overlap in the synapses served by neighboring astrocytes, the failure of a single astrocyte could impair glutamate removal at thousands of synapses in some brain regions (Bushong et al., 2002). Interestingly, dysfunction of EAATs has specifically been implicated in the pathology of several neurodegenerative disorders (Beart & O’Shea, 2007), and has recently been related to learned helplessness behavior in rodent models (Zink et al., 2010). Other studies have identified reduced levels of EAATs in the brains of patients with mood and psychotic spectrum disorders (Bernard et al., 2010; Choudary et al., 2005; McCullumsmith & Meador-Woodruff, 2002; Sequeira et al., 2009).

Once in the cysotol, glutamine synthetase, an astrocyte and oligodendrocyte-specific enzyme, converts glutamate into glutamine in an ATP-requiring reaction with ammonia. Both astrocytes and neurons contain glutamine transporters that, under appropriate electrophysiological conditions, lead to the net exchange of glutamine from astrocytes-to-neurons. In neurons, the mitochondrial phosphate-specific enzyme, glutaminase, reconverts inert glutamine-to-glutamate for subsequent repackaging into synaptic vesicles. The cycling of glutamate/glutamine in astrocytes and neurons has been termed “the glutamine cycle” (see Figure for schematic). Thus, there are two pathways for the production of neuronal glutamate: (1.) the *de novo* production of glutamate from glucose and amino acid derivatives via energy metabolism and (2.) the recycling of glutamate from glutamine via glutamate reuptake, enzymatic activity of glutaminase and the activities of the glutamine transporters (Erecinska & Silver, 1990). Recent work has demonstrated a decreased rate of glutamate/glutamine cycling following chronic unpredictable stress exposure in rodents (Banasr et al., 2010), and suggests that glutamate clearance and cycling could be targets for future

psychotropic drug development (Banasr et al., 2010; Mineur et al., 2007; Sattler & Rothstein, 2007).

In addition to stimulated vesicular release of glutamate, some level of extracellular glutamate is maintained by a cystine-glutamate antiporter called system x-C. This antiporter exchanges extracellular cystine for intracellular glutamate in a 1:1 ratio. System x-C is highly expressed in the rodent and human brain, and most CNS cell types (neurons, astrocytes, microglia, vascular endothelial cells, ependymal cells of the choroid plexus and leptomeninges) express detectable levels of this antiporter. System x-C consists of a specific light chain, xCT, and a heavy chain, 4F2, linked by a disulfide bridge (Albrecht et al., 2010), and its activity is inhibited in the context of numerous neuropsychiatric insults including *in vitro* oxygen deprivation and *in vivo* chronic cocaine exposure (Baker et al., 2003; Fogal et al., 2007; Madayag et al., 2007). Interestingly, the activity of system x-C has been restored by numerous agents, *e.g.* interleukin 1-β (Jackman et al., 2010), N-acetylcysteine (Moussawi et al., 2009) and ceftriaxone (Knackstedt et al., 2010). In addition to it role in regulating levels of extracellular glutamate, system x-C is also the rate-limiting step in the formation of the potent antioxidant, glutathione (McBean, 2002).

GLUTAMATERGIC NEUROTRANSMISSION

As described, glutamatergic synapses serve as excitatory relay stations between presynaptic nerve terminals and postsynaptic dendritic spines (axo-dendritic synapses) or adjacent nerve endings (axo-axonal synapses). Axo-dendritic glutamatergic synapses are easily recognizable via electron microscopy due to the thickened appearance of the postsynaptic membrane. These postsynaptic "densities" (PSDs) are ~50 nm thick conglomerations of membrane receptors, scaffolding proteins and second messenger effectors; some estimates suggest that each PSD may contain up to 100 proteins. Glutamate receptors may be divided into two broad categorizations: ionotropic and metabotropic receptors (see figure 2). Ionotropic glutamate receptors are ion channels that flux cations (Ca^{2+}, Na^{+}). Conformational changes "open" the channel in response to agonist binding. Metabotropic receptors, on the other hand, activate or inhibit second messenger systems via interactions with cognate G-proteins.

Ionotropic Glutamate Receptors

Three classes of ionotropic glutamate receptors have been identified, which were named on the basis of agonist selectivity: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) and kainate (KA). Ionotropic glutamate receptors form tetrameric complexes of individual/heteromeric subunits. One of the most intriguing features of ionotropic glutamate receptors is their diversity of channel properties based on subunit composition and expression profile in the mammalian brain.

NMDA Receptors—NMDA receptors have the highest affinity for glutamate (EC_{50} 1 μM). Three families of NMDA receptor subunits have been identified: (1.) NR1 (2.) NR2A-D (3.) NR3A-B. Via *in situ* hybridization studies, NR1 expression appears to be ubiquitous and obligatory in the brain; it is critical for neurodevelopment, as NR1 knockout mice die shortly after birth due to respiratory demise. Interestingly, hippocampal CA1-specific NR1-knockout mice display grossly normal development but impaired long-term potentiation (LTP), the molecular and electrophysiological correlate of learning and memory in CA1 hippocampal pyramidal neurons and impaired spatial memory in the Morris water maze (Tsien et al., 1996). NR2 mRNA displays differential expression and appears to be developmentally-regulated (Monyer et al., 1994). NR2A expression predominates in the neocortex and hippocampus while NR2B is primarily expressed in the forebrain. In contrast, NR2C and NR2D are intensely expressed in the cerebellum and diencephalon/lower brain

stem (Nakanishi, 1992). NR3A is predominantly expressed in the neocortex and displays neurodevelopmental regulation; dysregulated NR3A development been proposed to contribute to the pathogenesis of schizophrenia (Das et al., 1998; Henson et al., 2008). Finally, NR3B mRNA expression is evident in the brainstem and alpha motor neurons of spinal cord (Chatterton et al., 2002; Matsuda et al., 2003; Matsuda et al., 2002; Nishi et al., 2001). More recently, NR3B has been detected in the cerebellum and hippocampus (Andersson et al., 2001; Bendel et al., 2005).

NMDA receptors are among the most tightly regulated in the mammalian brain and unique in requiring co-agonists for activation. At least six binding sites have been identified that regulate the probability of ion channel opening, *viz.*, sites for two obligatory co-ligands (glutamate and glycine), polyamines and cations (Mg^{2+}, Zn^{2+} and H^{+}). NMDA receptor ligands are short-chain dicarboxlic amino acids (NMDA, glutamate, aspartate, *etc.).* Glutamate, the most potent neurochemical agonist identified in the CNS, and several competitive antagonists of the NMDA receptor including D-2-amino-5-phosphonopentanoic acid (D-AP5) and 3-(2-carboxypiperazin-4-yl)1-propeny-1-phosphonic acid (2R-CPPene) bind to the NR2 subunit of the tetrameric receptor complex. In contrast, glycine binds to a site on the NR1 subunit (Dingledine et al., 1999; Kleckner & Dingledine, 1988). The glycine-binding site on the NR1 subunit has gained clinical significance due to D-cycloserine's binding at the same $glycine_B$ site. D-cycloserine is a partial agonist that has been proposed as a novel neuromodulatory agent to enhance the efficacy of evidence-based psychotherapies like exposure and response prevention in anxiety disorders (Danysz & Parsons, 1998; Krystal et al., 2009; Sheinin et al., 2001). Glycine transport requires the activity of specific glycine transporters (GlyT). Two such transporters have been identified to date, GlyT1 and GlyT2. Recent studies suggest GlyT inhibitors may provide an efficacious augmenting strategy in treatment-refractory schizophrenia (Lane et al., 2006; Lane et al., 2010).

Extracellular Mg^{2+} acts as an open-channel, voltage-dependent "pore blocker" to preclude cation flux (Nowak et al., 1984). Interestingly, Zn^{2+}, while also a divalent cation, does not block the pore of the NMDA receptor. Instead, Zn^{2+} is an important allosteric modulator of some glutamate receptors and colocalizes to synaptic vesicles and is co-released with glutamate in select populations of synaptic vesicles, which possibly provides an additional mechanism to regulate glutamate receptor activation. Several additional NMDA receptor antagonists also exert their influence in an analogous voltage-dependent manner, *e.g.* phencyclidine (PCP), ketamine and MK-801. These noncompetitive antagonists have recently garnered significant attention both for their psychotomimetic (Balla et al., 2001; Javitt, 2007; Javitt et al., 2004; Krystal et al., 1994; Moghaddam & Adams, 1998; Patil et al., 2007; Umbricht et al., 2000) and rapidly-acting antidepressant-like properties (aan het Rot et al., 2010; Berman et al., 2000; Diazgranados et al., 2010; Mathew et al., 2009; Price et al., 2009; Valentine et al., 2011; Zarate et al., 2006).

Hydrogen ions (H^{+}) are also critical endogenous allosteric modulators of glutamate receptors. At physiological pH, the presence of H^{+} decreases the frequency of channel opening due to H^{+} binding to NR2B. The polyamine regulatory sites of ionotropic glutamate receptors also play an important pH-dependent modulatory role. The binding of polyamines (spermine, spermidine) relieves the H^{+}-mediated block and increases cation flux; however, the effect of polyamines reverses at higher concentrations (Traynelis et al., 1995). These pH-dependent effects may modulate NMDA receptor functioning in the context of increased metabolic demands and neurophysiological insults, *e.g.* excessive stimulation/activity, hypoxia and acidosis. Additionally, Ca^{2+} dependent calmodulin inactivation of NR1 subunits has also been proposed as a negative feedback mechanism leading to decreased channel open time/probability (Ehlers et al., 1996). Moreover, the Ca^{2+}-calmodulin

dependent phosphatase calcineurin inhibits the activity of ionotropic glutamate receptors via receptor dephosphorylation following the Ca^{2+}-dependent activation of calmodulin (Tong et al., 1995).

Finally, glutamatergic neurotoxicity is increasingly thought to be mediated by the differential activation of extrasynaptic relative to synaptic NMDA receptors (Hardingham & Bading, 2010; Hardingham et al., 2002; Ivanov et al., 2006; Leveille et al., 2008; Vanhoutte & Bading, 2003; Xu et al., 2009). A recent series of studies suggests that excessive activation of extrasynaptic pathways specifically induces apopotic signal transduction cascades promoting neuronal cell death, while activation of synaptic NMDA receptors creates a "neuroprotective shield" via Ca^{2+}-mediated signal transduction pathways promoting neuronal survival. The opposing neuroprotective and neurotoxic effects induced by activation of the synaptic and extrasynaptic NMDA receptors, respectively, are mediated by complex regulatory actions on several protective (anti-apoptotic, pro-survival and antioxidant) and pro-apoptotic genes (Hardingham et al., 2001a, 2001b; Papadia et al., 2008; Wu et al., 2001). Interestingly, memantine, a noncompetitive NMDA receptor antagonist, displays differential effects on synaptic and extrasynaptic NMDA receptors (Chen & Lipton, 2006). At low doses, memantine does not accumulate in the synaptic cleft to antagonize synaptic NMDA receptors; instead, it antagonizes extrasynaptic NMDA receptors which spares their exposure to high levels of extracellular glutamate in pathological states like ischemia and other neuropsychiatric processes (Chen et al., 1998; Xia et al., 2010).

AMPA/Kainate Receptors—AMPA receptors are also widely expressed in the mammalian CNS and mediate fast excitatory neurotransmission in response to glutamate binding (Palmer et al., 2005). AMPA receptor subunits are called GluR1–4; kainate receptor subunits are GluR5–7 and KA1–2. GluRs, in contrast to other amino acid and monoaminergic neurotransmitter receptors, contain an unusually large extracellular N-terminus. Upon forming a tetrameric complex of GluR1–4s, AMPA receptors mediate fast excitatory neurotransmission that can be blocked by specific quinoxalinediones including 6-nitro-7-sulphamobezo(f)quinoxaline-2,3-dione (NBQX), a potent and selective AMPA receptor antagonist. Kainate receptors are also tetrameric complexes of GluR5–7 and KA1–2 subunits. When expressed in heterologous systems, homomeric KA1 and/or KA2 containing-receptors are virtually inactive, and, therefore, appear to serve a modulatory function in contrast to the GluR5–7 subunits, which generate functional ligand-gated receptors (Alt et al., 2004; Herb et al., 1992; Howe, 1996).

The release of even small and brief (<1 millisecond) concentrations of glutamate into the synaptic cleft generates robust excitatory postsynaptic potentials (EPSPs). AMPA-mediated currents generate a fast upstroke and rapid current decay while NMDA-receptor activation provides a more prolonged phase of depolarization that can last several hundred milliseconds. EPSP generation is hypothesized to be controlled by AMPA receptor de/activation while the longer pharmacokinetics of NMDA receptor sensitization provides ample opportunity for spatial and temporal summation at numerous postsynaptic inputs. The higher affinity of glutamate for NMDA-to-AMPA receptors likely explains these pharmacokinetic differences, as prolonged receptor activation is often the result of slower dissociation of agonist and receptor.

AMPA receptor trafficking has been widely studied, especially its intracellular cycling and its potential physiological sequelae. Like all membrane receptors, AMPA receptors are synthesized in the soma and transported to the cell surface via the secretory pathway involving multiple membrane sorting steps and cytoskeleton transport proteins (Kapitein et al., 2010; Kennedy & Ehlers, 2006). Dendritic AMPA receptor localization to synapses is regulated via two mechanisms: (1) exocytic and endocytic trafficking and recycling,

respectively, in the secretory pathway and (2) membrane diffusion from extrasynaptic-to-synaptic localizations (Groc & Choquet, 2006; Hoogenraad et al., 2010; Newpher & Ehlers, 2008; Wang et al., 2008).

A physiological role for AMPA receptor trafficking and surface diffusion has been hypothesized in learning and memory. An LTP-like strengthening of neocortical synapses occurs after sensory stimulation *in vivo* (Holtmaat & Svoboda, 2009; Kessels & Malinow, 2009), and this process appears dependent on AMPA receptor number, localization and facilitation at synapses (Takahashi et al., 2003). Learning in the hippocampus also appears to be regulated by AMPA receptor dynamics (Whitlock et al., 2006) as evidenced by the recruitment of AMPA receptors to mushroom-shaped dendritic spines in the CA1 region of the hippocampus 24 hours after fear conditioning (Matsuo et al., 2008). Stress hormones have recently been recognized to play a role in AMPA receptor trafficking (Groc et al., 2008; Krugers et al., 2010; Yuen et al., 2011), and may provide a mechanism for the dose-dependent ("inverted U") facilitative and suppressive effects of corticosteroid hormones on synaptic plasticity and cognition (Martin et al., 2009). Further complexity in the regulation of ionotropic glutamatergic neurotransmission is provided by molecular variability at the transcriptional and post-transcriptional level. RNA editing of AMPA and kainate receptor subunits (Higuchi et al., 1993) and alternative splicing of mRNA transcripts (Sommer et al., 1990) modulate second messenger cascades critical for downstream intracellular effects.

METABOTROPIC GLUTAMATE RECEPTOTRS

Unlike ionotropic glutamate receptors that depend on cation flux, metabotropic glutamate receptors exert their effects via the recruitment and activation of intracellular trimeric G-proteins and downstream signal transduction pathways. Like all G-protein coupled receptors, metabotropic glutamate receptors are seven transmembrane domain-spanning receptors with an extracellular N-terminus and intracellular C-terminus, and, like AMPA receptors, they possess an especially large N-terminus. The metabotropic receptors (except mGluR8) localize primarily to perisynaptic and extrasynaptic locales on neurons and glial cells and modulate synaptic activity and plasticity. To date, eight metabotropic glutamate receptors have been identified (mGluR1–8), which have been further subdivided into three functional groups on the basis of amino acid homology, agonist binding and activated downstream signal transduction cascades (Kim et al., 2008). Group I metabotropic glutamate receptors consist of mGluR1 and mGluR5. They elicit their downstream effects by two mechanisms: (1.) phospholipase Cvia inositol-1,4,5-triphosphate (IP_3) to release Ca^{2+} from intracellular stores and (2.) diacylgycerol (DAG) to stimulate protein kinase C. Group II metabotropic glutamate receptors (mGluR2 and mGluR3) and group III metabotropic glutamate receptors (mGluR4–8) are coupled to inhibitory G-proteins (G_i) that decrease intracellular cyclic adenosine monophosphate (cAMP) via inhibition of the adenylyl cyclase/protein kinase A pathway. Members of each class share approximately 70% sequence homology; across classes, there is approximately 45% sequence homology (Conn & Pin, 1997). Similar to ionotropic glutamate receptors, glutamate activates metabotropic glutamate receptors with varying degrees of affinity/avidity, and fairly selective agonists, antagonists and modulators have been identified and developed for the various receptor classes and subtypes.

Postsynaptic activation of metabotropic glutamate receptors has been demonstrated to modulate ion channel activity, and, as predicted, whether agonist binding to metabotropic glutamate receptors potentiates or inhibits channel activity depends on whether their cognate downstream signal transduction cascades. Tissue and cell type-specificity also exists in this regard (Kuzmiski & Bains, 2010). Metabotropic glutamate receptors localized to presynaptic membranes have been demonstrated to decrease both excitatory glutamatergic and inhibitory

GABAergic neurotransmission (Pinheiro & Mulle, 2008). Although the precise mechanism(s) mediating presynaptic modulation has not been conclusively demonstrated, metabotropic glutamate receptors appear to elicit their diverse effects via the modulation of voltage-dependent presynaptic Ca^{2+} channels, thereby influencing quantal neurotransmitter release in a SNARE-dependent manner (Takahashi et al., 1996). There is presently intense effort to develop both positive and negative modulators of presynaptic group II and III metabotropic glutamate receptors in an effort to treat a plethora of neuropsychiatric illnesses (Nicoletti et al., 2010).

There is also great interest in developing strategies to modulate group I metabotropic glutamate receptor activity. Beyond its enhancing effects on ionotropic glutamate receptor activation, mGluR5 has been demonstrated to play a role in regulating local mRNA translation in dendritic spines (Weiler & Greenough, 1993; Weiler et al., 1997). Local protein synthesis at synapses is required for the long-lasting physiological and pathophysiological sequelae of group I metabotropic glutamate receptor activation including some receptors proposed in mediating metaplasticity. (Abraham, 2008; Aschrafi et al., 2005; Banko et al., 2006; Huber et al., 2000; Karachot et al., 2000; Merlin et al., 1998; Raymond et al., 2000; Vanderklish & Edelman, 2002). After initially discovering that group I metabotropic glutamate receptor signaling-dependent LTD is impaired in the hippocampus of FMR1 (Fragile X Mental Retardation gene 1) knock-out mice (Huber et al., 2002) and that the gene product of FMR1, FMRP (Fragile X Mental Retardation Protein), is a potent transcriptional repressor (Aschrafi et al., 2005; Bolduc et al., 2008; Dolen et al., 2007; Huber et al., 2002; Laggerbauer et al., 2001; Z. Li et al., 2001; Qin et al., 2005), Bear and colleagues proposed that the loss of FMRP in Fragile X Syndrome (FXS) leads to excessive local protein translation owing to the dysregulated mGluR5 stimulated-protein synthesis, and that antagonism of mGluR5 may abrogate the neurophysiatric sequalae of this disorder. There are now multiple studies confirming these hypotheses, especially mGluR5's activation and downstream signal transduction hypersensitivity as critical pathogenic factors in FXS (Dolen & Bear, 2008; Osterweil et al., 2010). Other studies have demonstrated marked effects of mGluR5 modulators in a variety of animal models of neuropsychiatric and neurodegenerative disorders making this one of the most active areas in CNS drug discovery (Bird & Lawrence, 2009; Carroll, 2008; Cook, 2010; Gasparini et al., 2008; Krystal et al., 2010; Lindsley & Emmitte, 2009; Rodriguez & Williams, 2007; Simonyi et al., 2010)

INTRACELLULAR SIGNAL TRANSDUCTION FROM THE POSTSYNAPTIC DENSITY TO THE NUCLEUS

As mentioned, ionotropic and metabotropic glutamate receptors interact with postsynaptic proteins through their intracellular C-termini. Among the first discovered postsynaptic elements is the critically important "scaffolding" protein, postsynaptic density protein of 95 kDA (PSD-95). PSD-95 has been demonstrated to mechanically stabilize the synapse via the presynaptic-to-postsynaptic interaction of neuroligin and β-neurexin (Futai et al., 2007; Irie et al., 1997; Levinson et al., 2005; Nam & Chen, 2005; Schapitz et al., 2010; Song et al., 1999). PSD-95 also bridges glutamate receptors to the cytoskeleton. The C-terminus of the glutamate receptor subunit NR2 binds to PSD-95, and PSD-95 binds to α-actinin/F-actin, one of the major contributors to dendritic spine morphogenesis. PSD-95 also binds to postsynaptic signal transduction effectors via the activation of calmodulin/calmodulin-dependent kinase II (CaMKII). CAMKII mediates the phosphorylation of various protein kinases and, as discussed above, the translocation of AMPA receptors from more intracellular compartments to the PSD. A similar cycling process also occurs with KA receptors through PSD-95 and other scaffolding proteins with PDZ domains, *e.g.* glutamate receptor activating protein (GRIP) and SAP-97 (synapse-activating protein of 97 kDa). Metabotropic glutamate receptors, on the other hand, are found at more perisynaptic and

extrasynaptic sites due to their interactions with similarly-localized “scaffolding” proteins (e.g. shank and homer). As such, presynaptic glutamate receptors are localized via these intracellular scaffolds, *e.g.* mGluR7 binds to the PDZ domain of protein interacting with C kinase-1 (PICK-1) (Bertaso et al., 2008; Boudin et al., 2000; Dev et al., 2000; El Far et al., 2000; Suh et al., 2008) and impaired mGluR7a-PICK1 interaction leads to absence-like seizures (Bertaso et al., 2008). Additionally, several recent studies have identified altered expression of postsynaptic proteins in rodent models and individuals suffering from a variety of neuropsychiatric diseases (Karolewicz et al., 2009; Kristiansen et al., 2010; Sifonios et al., 2009; Toro & Deakin, 2005), increasing their pathophysiological intrigue.

Scaffolding proteins directly or indirectly regulate small monomeric GTPases, and GTPases can either activate or silence transcription based on their specific downstream effectors. GTPases cycle between active GTP-bound and inactive-GDP bound forms, which are regulated by activating GEFs (guanyl exchange factors) and inhibiting GAPs (GTPase activating proteins). GEFs activate GTPases by promoting the exchange of bound GDP-for-GTP while GAPs inhibit GTPases by hydrolyzing bound GTP-to-GDP. As an example, a Ras-specific GEF associates with NR2B (Krapivinsky et al., 2003), and a Ras-specific GAP, synGAP, binds to PSD-95. If the Ras-specific GEF is activated via NR2B, GDP is exchanged for GTP, and this stimulates intracellular signal transduction cascades including the Raf-MEK-ERK and PI3K (phosphoinositide 3-OH kinase) pathways. Phosphorylated ERK translocates from the cytosol to the nucleus, where it activates the transcription factors CREB and Elk. The PI3K pathway activates protein kinase B (Akt/PKB), which stimulates nuclear translocation of the transcription factors, NFκB and CREB. The PI3K pathway also activates the MEKK-JNKK-JNK signal transduction cascade; via nuclear translocation of JNK, the transcription factors c-Jun, c-Fos and ATF2 are stimulated. Activation of these immediate-early genes mediates the transcription and translation of cytoskeletal proteins, enzymes of intermediary metabolism and neurotransmitter receptor subunits. In contrast, if Ras activity is inhibited via synGAP, the above signal transduction cascades are inhibited and transcription of the same target genes is reduced.

Cytoskeletal modulation is a critical mediator of glutamatergic receptor signaling because, as mentioned above, increased synaptic activity leads to morphological, biochemical and electrophysiological effects on the order of minutes. The Rho-family small GTPases Rac1 and Cdc42 promote dendritic spine morphogenesis via actin polymerization while Rho itself facilitates spine retraction via actin depolymerization (Krapivinsky et al., 2003). Numerous scaffolding proteins bind to RhoGEFs, *e.g.* PSD-95, and other scaffolds contain RhoGEF domains *within* their structure itself, *e.g.* kalirin (Alam et al., 1997) and trio (Debant et al., 1996). When overexpressed, GluR2 increases the size and density of dendritic spines while deletion of this subunit leads to spine retraction (Passafaro et al., 2003). Interestingly, acute ketamine exposure was recently shown to induce rapid dendritic spine morphogenesis via the activation of mammalian target of rapamycin (mTor), a serine/threonine protein kinase that signals though PI3K. Spine morphogenesis and the rapid antidepressant response of ketamine is speculated to occur via enhanced AMPA receptor activity, which is induced by the increased release of presynaptic glutamate in the context of acute NMDA receptor blockade (N. Li et al., 2010).

CONCLUSIONS

Glutamate is the main excitatory neurotransmitter in the mammalian CNS. Mostly due to the serendipitous discovery of antidepressants and antipsychotics that modulate monoaminergic neurontransmission and the relatively recent discovery of glutamate’s role as a true neurotransmitter, glutamate was initially understudied in neuropsychiatric disease. The discovery of ischemia-mediated glutamatergic excitotoxicity in stroke sparked initial interest

in the glutamatergic system's contribution to the pathophysiology of neuropsychiatric illnesses. Since this time, the number of studies implicating glutamatergic signaling in the diseased brain has swelled, and recent research has focused on glutamatergic neurotransmission as a rational therapeutic approach to disorders as diverse as schizophrenia, major depressive disorder, cocaine use disorders, FXS and amytrophic lateral sclerosis (ALS). The authors of the following articles will review the preclinical and clinical evidence for aberrant glutamatergic neurotransmission in neuropsychiatric disease and outline important future directions in diagnosis, prognosis and rational therapeutics.

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Highlights

- This manuscript provides a general overview of Glutamate receptors and transporters
- It provides a model of physiological regulation of glutamatergic neurotransmission
- The manuscripts reviews how impaired physiological regulation of the glutamatergic receptors and transporter can be related to neuropsychiatric disorders
- The manuscript describes specific viable drug targets within the glutamatergic system

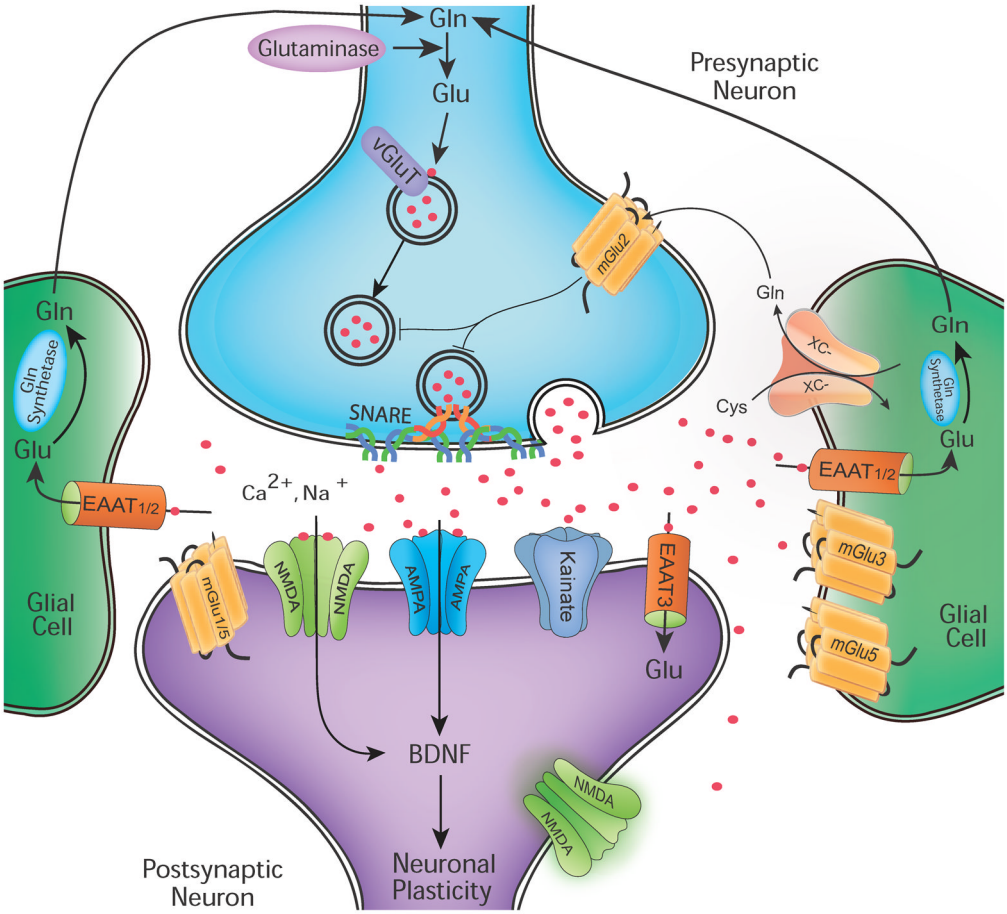

Figure 1. Glutamatergic Neurotransmission

Due to the risk of excitotoxic damage in the wake of excessive glutamatergic stimulation, precise physiological control of glutamate must be maintained in the mammalian CNS. Glutamine (Gln) is converted to glutamate (Glu) by glutaminase [though glutamate may also be derived from the TCA cycle (not shown)]. Glu is packaged into presynaptic vesicles by vesicular Glu transporter (VGLUT) proteins and synaptically released in an voltage-dependent manner through vesicular interactions with SNARE proteins. Synaptically-released Glu is recycled from the extracellular space by excitatory amino acid transporters (EAATs) expressed predominantly on astroglia. In astrocytes, Glu is converted to Gln by Gln synthetase and exported extracellularly to be taken up again by neurons. Additionally, system x-C is a cystine/glutamate antiporter expressed on glia that also contributes to Glu recycling. Glu receptors are present on presynaptic and postsynaptic neurons as well as on glial cells. These include both ionotropic receptors (NMDA, AMPA/KA) and metabotropic receptors (mGluRs). The effect of Glu is determined by the receptor subtype, localization (synaptic, perisynaptic and extrasynaptic), and interactions with various scaffolding and signaling proteins (not shown) in the postynaptic density. Glu receptor stimulation results not only in rapid ionotropic effects but also synaptic plasticity, e.g. long-term potentiation (LTP) and long-term depression (LTD), via cognate signal transduction cascades.

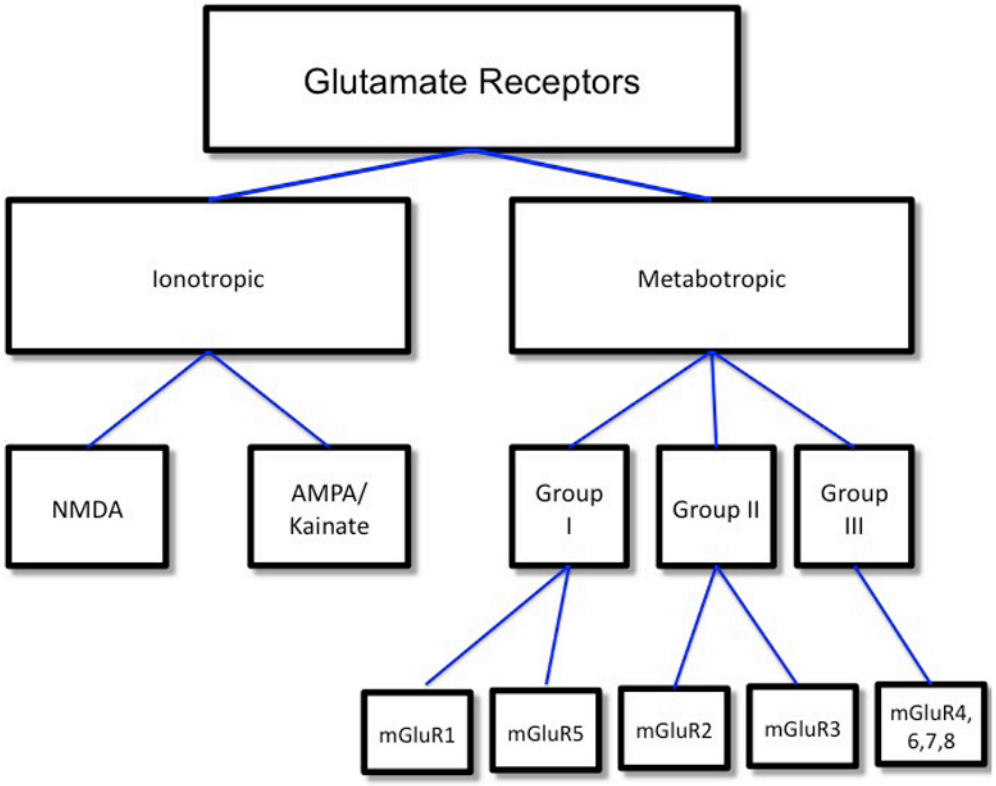

Figure 2.