Review

A Review of Glutamate Receptors I: Current Understanding of Their Biology

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Abstract: Seventy years ago it was discovered that glutamate is abundant in the brain and that it plays a central role in brain metabolism. However, it took the scientific community a long time to realize that glutamate also acts as a neurotransmitter. Glutamate is an amino acid and brain tissue contains as much as 5 – 15 mM glutamate per kg depending on the region, which is more than of any other amino acid. The main motivation for the ongoing research on glutamate is due to the role of glutamate in the signal transduction in the nervous systems of apparently all complex living organisms, including man. Glutamate is considered to be the major mediator of excitatory signals in the mammalian central nervous system and is involved in most aspects of normal brain function including cognition, memory and learning. In this review, the basic biology of the excitatory amino acids glutamate, glutamate receptors, GABA, and glycine will first be explored. In the second part of this review, the known pathophysiology and pathology will be described. (*J Toxicol Pathol* 2008; **21**: 25–51)

Key words: glutamate, glycine, GABA, glutamate receptors, ionotropic, metabotropic, NMDA, AMPA, review

Introduction and Overview

In the first decades of the 20th century, research into the chemical mediation of the “autonomous” (autonomic) nervous system (ANS) was an area that received much research activity. In England, William Maddock Bayliss, Ernest Henry Starling, Henry Dale and T.R. Elliot were investigating the actions and properties of this system following the recent identification of acetylcholine and adrenaline. In Vienna, Austria, Otto Loewi provided the first reliable evidence for the existence of chemical transmission by acetylcholine in 1921, then other chemical mediators between 1929 and 1936. Loewi doubted that neurotransmitters operated in the voluntary nervous system, but the discovery that acetylcholine is also a neurotransmitter in the neuromotor synapse, and that preganglionic synapses in the ANS are all cholinergic, in contrast with the postganglionic cholinergic or adrenergic receptors, proved him incorrect. Later it was found that the transmitter acting in adrenergic synapses was not adrenalin (epinephrine) but noradrenalin (norepinephrine)¹. We now recognize three major categories of substances that act as neurotransmitters. These are amino acids (primarily glutamic acid, γ -amino butyric acid, aspartic acid and

glycine), peptides (vasopressin, somatostatin, neurotensin, etc.), and monoamines (norepinephrine, dopamine and serotonin) plus acetylcholine.

Glutamatergic synaptic transmission in the mammalian central nervous system (CNS) was slowly established over a period of some 20 years, dating from the 1950s^{2–4}. Realization that glutamate and similar excitatory amino acids (EAAs), such as domoic acid, mediated their excitatory actions via multiple receptors preceded establishment of these receptors as synaptic transmitter receptors⁵. EAA receptors were initially classified as N-methyl-D-aspartate (NMDA) and non-NMDA receptors.

Non-NMDA glutamate receptors were subdivided into α -amino-3-hydroxy-5-methylisoxazole-4- propionic acid (also known as AMPA receptor, AMPAR, or quisqualate receptor) and kainate (Ka) receptors following experiments with agonists that appeared to activate these receptors preferentially. In addition, their sensitivity to a range of differentially acting antagonists was understood during the 1970s. NMDA receptors were definitively shown to be synaptic receptors on spinal neurons by the sensitivity of certain excitatory pathways in the spinal cord to a range of specific NMDA receptor antagonists. However, specific NMDA receptor antagonists appeared to be less effective at synapses in higher centers. In contrast, antagonists that also blocked non-NMDA as well as NMDA receptors were almost universally effective at blocking synaptic excitation within the brain and spinal cord, establishing both the existence and ubiquity of non-NMDA synaptic receptor systems throughout the CNS⁶.

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In the early 1980s, NMDA receptors were shown to be involved in several central synaptic pathways, acting in concert with non-NMDA receptors under conditions where a protracted excitatory postsynaptic potential was seen in response to intense stimulation of presynaptic fibers. Such activation of NMDA receptors together with non-NMDA receptors led to the phenomenon of long-term potentiation (LTP)⁷. LTP is associated with lasting changes in synaptic efficacy (synaptic plasticity) and has been considered to be an important process in memory⁸ and learning⁹.

During the same period, it was shown that certain glutamate receptors (GluRs) in the brain mediated biochemical changes that were not susceptible to NMDA or non-NMDA receptor antagonists. This dichotomy was resolved in the early 1990s using molecular biology, which identified two families of glutamate binding receptor proteins: *ionotropic* (iGluR) and *metabotropic* (mGluR) glutamate receptors¹⁰. Development of antagonists binding to specific protein subunits is currently enabling precise identification of discrete iGluR or mGluR subtypes¹¹ that participate in a range of central synaptic processes, including synaptic plasticity^{12–14}.

It is the purpose of this review to summarize the biological activities of the glutamate system (Part I) and to relate changes in these receptors to normal physiology and disease entities (Part II). Efforts have been made to address the toxicologic pathology of these receptors wherever possible; however, although the literature has a number of examples of receptor visualization by immunohistochemistry, the role of these receptors in abnormal morphology is still under intense investigation.

The Glutamate System

A number of authors have discussed the importance of the glutamate system, e.g.,^{15–18}, and its regulation^{19,20}. The following discussion not only addresses, glutamate, GABA, and glycine but also details how excitatory amino acids may interact with the glutamate system.

Excitatory amino acids (EAAs)

Glutamate (Glu) and aspartate (Asp) are amino acids (AAs) that act as major excitatory neurotransmitters in the mammalian central nervous system^{21–25} by stimulating or exciting postsynaptic neurons. Although these AAs are primarily involved in intermediary metabolism and other non-neuronal functions, their most important role is as neurotransmitters. It is estimated Glu mediates nearly 50% of all the synaptic transmissions in the CNS and its involvement is implicated in nearly all aspects of normal brain function including learning, memory, movement, cognition and development^{21,26–34}.

These EAAs and their various analogues can be neurotoxic, particularly when they excessively stimulate the same excitatory receptors, which is a phenomenon known as excitotoxicity^{21,22,24,25,35,36}. At elevated concentrations, Glu acts as a neurotoxin capable of inducing severe neuronal

damage and necrosis by causing over excitation of neurons^{37–41}. Previously it was thought that hypoxia played a part in the neurotoxicity of Glu, particularly in the white matter; however, it has now been shown that hypoxic injury and GluRs over stimulation are independent of one another⁴².

EAAs access the brain tissue of the circumventricular organs located outside the blood brain barrier (BBB)^{43–45}. Despite the BBB protective mechanisms, the local or circulating concentrations of these excitatory compounds may be great enough to induce damage leading to neurotoxic exposure levels. The toxicity of each EAA compound varies according to the potency, the chemical availability, the rate of absorption, the affinity to specific receptors and the particular anatomical target site^{46–48}. In addition, the susceptibility, genetic predisposition and health status of the individual are also important factors.

Excitotoxicity

The neurotoxic effects of the EAAs are dependent on the species, developmental stage of the animal, type of agonist, duration of exposure to the agonist and the cellular expression of the GluR subtypes. Regardless, neurons under various conditions can become so over stimulated by Glu that it actually kills them through receptor-mediated depolarization and calcium (Ca^{++}) influx^{49,50}. There are five main factors necessary for the transition of Glu and Asp from neurotransmitters to excitotoxins. These include inadequate neuronal ATP levels, inadequate neuronal levels of magnesium (Mg^{++}); high concentrations of inflammatory prostaglandins; excessive free radical formation^{51,52}, and inadequate removal of synaptic Glu^{53,54}.

An array of GluRs is known to be present on pre- and post-synaptic membranes that are used to transduce integrated signals using an increased ion flux and second messenger pathways^{21,24,25,33,34,55–57}. It is the excessive activation of these receptors that leads to neurotoxicity, often referred to as “excitotoxicity”⁵⁸. In addition, it has been postulated that excitotoxicity is involved in the pathogenesis of many types of acute and chronic insults to the CNS⁵⁹ and peripheral tissues^{60,61}.

The AAs, Glu and Asp, including structurally similar compounds, can be dietary excitotoxins⁶². Domoic acid (DA) is one of the most potent neurotoxins in seafood that can enter our food supply⁶³. Contamination of mussels by the sea diatoms producing DA was found to be the reason for the outbreak of the lethal shellfish poisoning that occurred in Canada in 1987^{65–67}. The clinical manifestations of DA intoxication are related to its effect in the brain including severe seizures^{63–71} and survivors of severe cases suffered permanent loss of short-term memory, a phenomenon that lead to the term amnesic shellfish poisoning⁶⁶. However, the other clinical symptoms such as gastrointestinal disturbances, cardiovascular collapse and cardiac arrhythmia^{43,63,70,72} have also been noted, and could be related to the DA poisoning⁶⁰. Recently, DA poisoning in California Sea Lions has been reported⁷³.

Disturbance of Glu homeostasis probably plays a pivotal role in the execution of pathological changes in many disease states involving the tissues listed above. There may be a number of factors that trigger the neurotoxic potential of endogenous Glu including increase in Glu release, malfunctioning of neuronal and glial uptake, energy deficits, neuronal depolarization, changes in GluR properties or expression patterns, free radical formation and others^{49,50,74–77}. Excitotoxicity has also been suggested as a central mechanism in fluoride neurotoxicity^{78,79}.

Such excitotoxic effects can be pronounced during acute events such as ischemic stroke and trauma, or milder but prolonged in chronic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis^{76,80–82}. As will be discussed in the second article of this series, glutamatergic dysfunction is also involved in the symptomatology of disorders such schizophrenia, anxiety, and depression^{50,74}. In addition, glutamatergic dysfunction has been regarded as part of the development of disorders associated with long-term plastic changes in the CNS such as chronic pain, drug tolerance, dependence, addiction, partial complex seizures and tardive dyskinesia^{50,74,83,84}.

It has been suggested that monosodium glutamate (MSG) is toxic and can exert its toxicity via similar mechanisms to L-glutamate (L-Glu). Administration of MSG during the neonatal period produces marked cognitive effects due to the loss of synaptic plasticity in rodents⁸⁵; however, the effect of MSG on long-term brain function in humans has been questioned⁸⁶. The route of administration can explain the differences in these findings, where human exposure is much lower occurring via the oral route.

Glutamate, gamma aminobutyric acid, and glycine

Historically, AAs (including Glu and Asp) were studied in the context of their importance in protein synthesis, but in the 1950s the focus of research shifted as AAs became recognized as putative neurotransmitters. For compounds to be classified as neurotransmitters they show several characteristics in common^{87,88}. These characteristics are: the neurotransmitter is synthesized, stored, and released from the presynaptic terminal; specific neurotransmitter receptors are localized on the postsynaptic cells; and there exists a mechanism to stop neurotransmitter release and clear molecules from the cleft. Glu was found to fulfill the requirements above and thus was named a neurotransmitter⁸⁹.

Although many AAs play a role in neurotransmission, Glu, glycine (Gly), and γ -aminobutyric acid (GABA) are among the more common and better-understood neurotransmitters^{74,90,91}. They are all metabolic intermediates and neurotransmitters, where Glu is the major excitatory neurotransmitter, and Gly and GABA are the major inhibitory neurotransmitters, in the CNS⁹². Glu, which is synthesized, stored, and released from the presynaptic terminal, has specific neurotransmitter receptors localized on the postsynaptic cells, and is eliminated from

Fig. 1. The structure of glutamic acid

Table 1. Biological Functions of Glutamate

Functions of glutamate
1. Substrate for protein synthesis
2. Precursor of glutamine
3. N transport (muscle-glutamine; brain)
4. Neurotransmitter (and γ -aminobutyrate)
5. Polyglutamate and cell signaling
6. D-Carboxylation of glutamate
7. Substrate for glutathione production
8. Precursor of N-acetylglutamate
9. Active sites of enzymes
10. Inhibitor of glutaminase reaction
11. Citric acid cycle intermediate
12. Energy source for some tissues (mucosa)

Fig. 2. The synthesis of glutamate

the synaptic cleft by specific transporters: it is a neurotransmitter.

L-Glu acts through both ligand-gated ion channels at ionotropic receptors (iGluR) and at G-protein coupled metabotropic receptors (mGluR). As will be discussed in more detail later, activation of these receptors is responsible for basal excitatory synaptic transmission and many forms of synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD), which are thought to underlie learning and memory⁹¹.

1) Glutamate

Glu has a number of functions that are listed in Table 1.

a) Glutamate synthesis

Glu is enzymatically created from α -ketoglutarate via GABA transaminase as is shown in Fig. 2⁹³.

N-Acetyl-aspartyl-glutamate (NAAG) is abundant in the mammalian CNS, which has led to the hypothesis that this dipeptide is the storage form of Glu. The membrane bound metalloproteinase NAALADase (N-acetyl-a-linked-acidic dipeptidase, or glutamate carboxypeptidase II, E.C.

3.4.17.21) is co-localized with NAAG in the CNS and converts NAAG to N-Acetyl-aspartate (NAA) and Glu⁹⁴. It seems likely that NAAG is also a weak partial agonist at N-methyl-D-aspartic acid (NMDA)⁹⁵. This effect is seen at concentrations beyond therapeutically relevant levels. Inhibition of NAALADase could be useful in numerous CNS disorders associated with disturbances in glutamatergic transmission by decreasing the concentration of Glu and increasing the concentration of NAAG⁹⁶.

b) Glutamate uptake

Brain tissue has a remarkable ability to accumulate Glu, an ability resulting from glutamate transporter proteins (GluTP) present in the plasma membranes of both glial cells and neurons⁹⁷. Glu and its structural analogues may enter the food supply during preparation or processing as contaminants or additives in its free form or bound to peptides and proteins^{64–77,98–101}. These analogues include monosodium glutamate (MSG), L-aspartate, L-cysteine, related sulfur AAs, B-N-oxalamino-L-alanine (BOAA or ODAP), B-N-methyl-amino-L-alanine (BMAA) and the seafood toxin domoic acid (DA)^{21,63,64,99–104}.

From Glu labeling studies, the average concentration of Glu in ganglion cells is five mM¹⁰⁵. Physiological studies using isolated cells indicate that only μ M levels of Glu are required to activate GluR^{106–108}. Thus, the amount of Glu released into the synaptic cleft is several orders of magnitude higher than the concentration required for activating most postsynaptic receptors.

c) Glutamate metabolism

Two key goals of brain AA handling are to maintain a very low intrasynaptic concentration of glutamic acid and also to provide the system with precursors from which to synthesize Glu. The intrasynaptic Glu level must be kept low to maximize the signal-to-noise ratio upon the release of Glu from nerve terminals, and to minimize the risk of excitotoxicity consequent to excessive glutamatergic stimulation of susceptible neurons. Additionally, the brain must also provide neurons with a constant supply of Glu, which both neurons and glia robustly oxidize. Astrocytes, which are in close approximation to brain capillaries, probably are the initial site of metabolism of Glu. Astrocytes release the cognate ketoacid [α -ketoisocaproate (KIC)] to neurons, which have a cytosolic branched-chain aminotransferase that reaminates the KIC to leucine, in the process consuming Glu and providing a mechanism for the buffering of Glu if concentrations become excessive¹⁰⁹.

The liver is the major site of gluconeogenesis, the major organ of AA catabolism and the only organ with a complete urea cycle¹¹⁰. It has been suggested that these AAs are oxidized in the liver; however, total oxidation cannot occur within the confines of hepatic oxygen uptake and ATP homeostasis. Rather, most AAs are oxidized only partially in the liver, with the bulk of their carbon skeleton being converted to glucose. The nitrogen is converted to urea and, to a lesser extent, to glutamine. The integration of the urea cycle with gluconeogenesis ensures that the bulk of the reducing power (NADH) required in the cytosol for

gluconeogenesis can be provided by ancillary reactions of the urea cycle¹¹¹.

Glu is at the center of these metabolic events. It is central because of the well-described transamination system involving aminotransferases and Glu dehydrogenase, where Glu plays a key catalytic role in the removal of α -amino nitrogen from AAs. In addition, the “glutamate family” of AAs (arginine, ornithine, proline, histidine and glutamine) requires the conversion of these AAs to Glu for their metabolic disposal. Finally, Glu serves as substrate for the synthesis of N-acetylglutamate, an essential allosteric activator of carbamyl phosphate synthetase I, a key regulatory enzyme in the urea cycle¹¹².

d) Glutamate clearance

It has been calculated that a 70-kg man has a daily Glu intake of approximately 28 g that is derived from the diet and from the breakdown of gut proteins. The daily Glu turnover in the body is about 48 g. Glu is eliminated from the synaptic cleft by specific transporters. Despite this large turnover, the total pool of Glu in blood is quite small, approximately 20 mg, because of its rapid extraction from and utilization by various tissues, particularly muscle and liver^{113,114}. In the CNS, Glu clearance and, as a consequence, Glu concentration and diffusion in the extracellular space, is associated with the degree of astrocytic coverage of its neurons¹¹⁵.

e) Glutamate transporters (GluTPs)

Brain tissue has a remarkable ability to accumulate Glu, an ability due to GluTPs present in the plasma membranes of both glial cells and neurons. GluTPs represent the only significant mechanism for removal of Glu from the extracellular fluid and are important for the long-term maintenance of low and non-toxic concentrations of Glu and appear to have more sophisticated functions in the modulation of neurotransmission⁹⁷. They may modify the time course of synaptic events¹¹⁶, the extent and pattern of activation and desensitization of receptors outside the synaptic cleft and at neighboring synapses (intersynaptic cross talk).

The genes encoding GluTPs have been cloned both from rats and humans^{117,118}. The human transporters EAAT1 and EAAT2 (rat equivalents GLAST and GLT1) are found in astroglia and microglia widely distributed throughout the CNS. The highest concentration can be found in the cortex. Human EAAT3 (rat EAAC1) is thought to be restricted to neurons; however, it also has been found outside of the CNS. More restrictively, human EAAT4 is expressed only by cerebellar neurons. Further investigation into the neuronal vesicular Glu transporter uncovered VGLUT1, which is only expressed in glutamatergic neurons^{119,120}.

GluTPs provide Glu for synthesis of GABA, glutathione and protein, which can be used structurally, or for energy production⁹⁷. Glu uptake appears to be modulated molecularly on virtually all possible levels including DNA transcription, mRNA splicing and degradation, protein synthesis and targeting, actual AA transport activity and associated ion channel activities. A number of soluble

Fig. 3. Diagram showing glutamate transport across the cell wall

compounds, including Glu, cytokines, and growth factors, influence the GluTP expression and activities¹²¹.

GluTPs have been identified in a number of neural tissues where they assist in maintaining appropriate concentrations of Glu at its synaptic site. Many tissues demonstrate Glu, GluR and GluTPs, including but not limited to, CNS¹²², autonomic and sensory ganglia¹²³, peripheral nerves—myelinated and unmyelinated^{124,125}, vagus and other cholinergic nerves¹²⁴, tachykinin containing sensory nerves and vestibular tissues^{126,127}, retinal photoreceptors^{128–130}, Muller cells^{128,131}, adrenal medulla^{123,133}, pituitary¹³⁴, pineal gland¹³⁵, endocrine pancreas^{136–147}, immune system¹⁴⁸, taste buds^{149,150}, esophagus¹⁵¹, gut^{70,100,152–154}, ileal longitudinal muscle^{155–157}, hepatocytes^{68,158}, kidney, spleens, ovaries^{48,159}, lungs^{60,99,145,148,154,158–165}, heart^{60,99,145,148,154,158–165}, bone^{159,165}, bone marrow¹⁵⁹, rat glabrous skin¹⁶⁶, and keratinocytes¹⁶³.

In the CNS, high affinity GluTPs located on adjacent neurons and surrounding glial cells rapidly remove Glu from the synaptic cleft to prevent cell death^{167–169}. Five GluTPs, EAAT-1 (or GLAST), EAAT-2 (or GLT-1), EAAT-3 (or EAAC-1), EAAT-4, and EAAT-5, have been cloned^{169–174}.

GluTPs are pharmacologically distinct from both iGluRs and mGluRs and L-Glu, L-Asp, and D-Asp are substrates for the transporters^{129,130,175}; GluR agonists^{129,130,175,176} and antagonists^{130,177} are not. Glu uptake can be blocked by the transporter blockers dihydrokainate (DHKA) and DL-threo- β -hydroxyaspartate (HA)^{130,177}.

GluTPs incorporate Glu into cells along with the co-transport of three Na^+ ions^{175,178} and the antiport of one K^+ ion^{178,179} and either one OH^- or one HCO_3^- ion¹⁷⁹. The excess Na^+ ions generate a net positive inward current, which drives the transporter^{175,178}. In addition, a Glu-elicited chloride current is also associated with some transporters^{174,179}.

GluTPs located in the plasma membrane of neuronal and glial cells are different from the GluTPs located on synaptic vesicles within presynaptic terminals. The transporters in the plasma membrane transport Glu in a Na^+ and voltage-dependent manner independent of Cl^- ^{168,175,178}. L-Glu, L-Asp, and D-Asp are substrates for these transporters¹⁷⁵. In contrast, the vesicular transporter selectively concentrates Glu into synaptic vesicles in a Na^+ -independent, ATP-dependent manner^{180–182} that requires Cl^- ^{181–185}.

The pharmacology of GluR is similar to that described for GluTPs, as the Glu-elicited current is dependent upon external Na^+ , reduced by transporter blockers, and insensitive to Glu agonists and antagonists. However, altering internal Na^+ concentration does not change the reversal potential¹⁸³ or the amplitude^{185,186} of the Glu-elicited current, suggesting GluR is distinct from GluTPs.

2) Gamma-Aminobutyric Acid (GABA)

In 1950, γ -Aminobutyric acid (GABA) was independently identified in the vertebrate brain^{187,188}. These investigators also demonstrated the presence of glutamic acid decarboxylase (GAD) in mouse brain and showed that the active enzyme, capable of decarboxylating Glu to GABA, required pyridoxal 5-phosphate (PLP) as cofactor¹⁸⁹.

Early electrophysiological work carried out, primarily in crustaceans, firmly established GABA as an inhibitory neurotransmitter in invertebrates¹⁹⁰. Although GABA was originally shown to be present in very high, up to millimolar, concentrations in the vertebrate CNS, it proved considerably more difficult to unequivocally establish its role as a neurotransmitter in the mammalian brain. However, by the early 1970s, GABA had been shown to satisfy all of the classical criteria of a neurotransmitter^{191,192}.

The establishment of the role of GABA as a neurotransmitter was hampered by the widespread distribution of GABAergic neurons throughout the CNS, and the lack of suitable reagents to positively identify GABAergic neurons. The role of GABA as a neurotransmitter is that of inhibitory neurotransmission, although this property has been questioned recently¹⁹³. Following the purification of GAD and the generation of GAD antisera, immunohistochemical studies revealed that many GABAergic neurons in the brain are interneurons and are therefore uniquely able to alter the excitability of local circuits within a given brain region¹⁹². From these and other studies it was confirmed that 30–40% of all CNS neurons utilize GABA as their primary neurotransmitter.

a) GABA: Synthesis, uptake, and metabolism

GABA is formed *in vivo* via a metabolic pathway called the “GABA shunt”. The initial step in this pathway utilizes α -ketoglutarate formed from glucose metabolism via the Krebs cycle. α -Ketoglutarate is then transaminated by α -oxoglutarate transaminase (GABA-T) to form Glu, the immediate precursor of GABA. Finally, Glu is decarboxylated to form GABA by the GAD^{189,192}. GAD is expressed only in GABAergic neurons and in certain

Table 2. A summary of the Functions and Molecular Structure of GABA Receptors

Receptor	Function	Molecular structure	Other actions
GABA _A and GABA _C	GABA binding opens Cl ⁻ channels.	Heteropentamers of α 1-6, β 1-4, γ 1-4, δ , and ρ primarily in the retina. Many receptor subtypes contain α , β , and γ in a pentameric arrangement.	In recombinant systems, both the α and β subunits are required for the benzodiazepine (valium and librium) site. Barbiturates (Phenobarbital, pentobarbital) bind to α and β subunits. Both of these drugs enhance channel opening and the effect of the drugs at any given synapse depends on the subunit composition of the GABA receptors there.
GABA _B	These receptors are largely inhibitory by opening K ⁺ channels or closing Ca ⁺⁺ channels.	G _{i/o}	Widely distributed throughout the brain

peripheral tissues, which are also known to synthesize GABA.

Like most neurotransmitters, GABA is stored in synaptic vesicles and is released in a Ca⁺⁺-dependent manner upon depolarization of the presynaptic membrane. Following release into synaptic cleft, GABA's actions are terminated principally by reuptake into presynaptic terminals and surrounding glia. GABA is also metabolized by GABA-T to form succinic semialdehyde. This transamination regenerates Glu when it occurs in the presence of α -ketoglutarate. Next, succinic semialdehyde is oxidized by succinic semialdehyde dehydrogenase (SSADH) to succinic acid, which then reenters the Krebs cycle.

The reuptake of GABA occurs via highly specific transmembrane transporters, which have recently been shown to be members of a large family of Na⁺-dependent neurotransmitter transporters. GABA uptake is temperature- and ion-dependent and both Na⁺ and Cl⁻ ions are required for optimal uptake.

Affinity purification of the GABA transporter protein has recently led to its molecular cloning¹⁹⁴. The principal neuronal GABA transporter is a 70- to 80-kDa glycoprotein that contains 12 hydrophobic membrane-spanning domains. To date, at least two other GABA transporter cDNAs have been cloned¹⁹⁵, but the physiological and pharmacological significance of this heterogeneity is unknown. Nonetheless, specific inhibitors of GABA uptake that directly bind to the transporter itself have been synthesized, and several have been shown to have anticonvulsant and antinociceptive properties in laboratory animals^{196,197}.

b) GABA receptors

GABA is a highly flexible molecule and, thus, can exist in many low-energy conformations. Conformationally restricted analogues of GABA have been used to help identify three major GABA receptors, termed GABA_A, GABA_B and GABA_C receptors¹⁹⁸⁻²⁰⁰. GABA_A and GABA_C receptors are members of a superfamily of transmitter-gated ion channels that include nicotinic acetylcholine, strychnine-sensitive glycine and 5HT₃ receptors^{201,203}. On the other hand, GABA_B receptors are seven transmembrane receptors that are coupled to G-proteins and activate second messenger systems and Ca⁺⁺ and K⁺ ion channels. These receptors

Fig. 4. Biotransformation of glutamic acid to GABA

resemble mGluRs and develop before GluR²⁰³.

c) GABA_A receptors: physiology to pharmacology

GABA_A receptors are hetero-oligomeric chloride channels that are selectively blocked by the alkaloid bicuculline and modulated by steroids, barbiturates and benzodiazepines^{204,205}. To date, 16 human GABA_A receptor cDNA have been cloned. They are ionotropic receptors leading to increased Cl⁻ ion conductance²⁰⁶. Activation of the GABA_A receptor by an agonist results in an increase in Cl⁻ ion conductance via the receptor-gated ion channel or pore. This increase in Cl⁻ ion conductance, which requires the binding and cooperative interaction of two molecules of GABA, is actually due to an increase in the mean open time of the Cl⁻ ion channel itself²⁰⁶. The increase in Cl⁻ ion conductance observed following activation of GABA_A receptors results in a localized hyperpolarization of the neuronal membrane and therefore leads to an increase in the threshold required for excitatory neurotransmitters to depolarize the membrane in order to generate an action potential. This decrease in neuronal membrane excitability results in the inhibitory actions of GABA¹⁹⁸.

A variety of GABA receptor agonists have been discovered and have been shown to selectively activate GABA_A receptors. Muscimol, a rigid GABA analogue isolated from the hallucinogenic mushroom *Amanita muscaria*, is one of the most selective and potent GABA agonists known. Muscimol is also not a substrate for the GABA transporter, which makes it useful for electrophysiological and biochemical studies. Both competitive and noncompetitive GABA_A receptor antagonists also have been described²⁰⁷.

d) GABA_A and GABA_C receptor agonists and antagonists

It is believed that the GABA_A receptor is a heteropentameric glycoprotein of approximately 275 kDa²⁰². Many compounds have been shown to augment GABA-mediated Cl⁻ ion conductance selectively at pharmacologically relevant concentrations. There is now considerable evidence that a number of other sedative-hypnotic-anesthetic drugs also interact with GABA_A receptors e.g., benzodiazepines, and several other compounds such as barbiturates, alcohols and anesthetics, have been shown to bind to, and affect, other receptors and channels as well. Therefore, the GABA_A receptor can be positively or negatively modulated by compounds, which range in activity from full agonists to full inverse agonists^{208,209}. Full agonists have sedative-anesthetic properties, whereas full inverse agonists are convulsants²¹⁰. It is now thought that GABA_A receptors are involved in at least some forms of human anxiety.

The large numbers of drug recognition sites associated with GABA_A receptors, which are clearly distinct from those that recognize GABA itself, have led several investigators to propose the existence of endogenous receptor ligands. Several have been identified; however, with the possible exception of two, there is little compelling evidence at present that any interact with GABA_A receptors *in vivo*. One of these ligands is an endogenous peptide diazepam-binding inhibitor (DBI), which was shown to interact with GABA_A receptors and to have anxiogenic properties similar to inverse agonists²¹¹. The other postulated endogenous ligands include two natural reduced steroid metabolites of progesterone and deoxycorticosterone: allopregnanolone and allotetrahydrodeoxycorticosterone²¹².

These neuroactive steroids bind with high affinity to GABA_A receptors and have barbiturate-like actions in augmenting GABA-mediated responses²¹³. The plasma and brain levels of these neuroactive steroids increase dramatically following exposure of rats to various stressors. Plasma allopregnanolone levels are also quite high during the third trimester of pregnancy, and they decrease dramatically following parturition²¹³. However, none of these putative natural ligands have yet been unequivocally demonstrated to sub serve any physiological function.

Bicuculline is the prototypical competitive antagonist and directly competes with GABA for binding to the receptor complex. Bicuculline reduces both the frequency and mean open time of the GABA-gated Cl⁻ ion channel. Picrotoxin and other extremely potent cage convulsants such as t-butylbicyclophosphorothionate (TBPS) are noncompetitive GABA receptor antagonists that do not compete directly with GABA for its recognition sites but, instead, bind to separate and distinct recognition sites associated with the receptor complex²¹⁴.

Other selective antagonists, such as the imidazobenzodiazepine Ro15-1788 (flumazenil), bind with high affinity to GABA_A receptors but are devoid of intrinsic activity of their own²⁰⁹. However, these antagonists completely block the actions of benzodiazepine receptor

agonists in augmenting GABA-mediated responses. Selective antagonists such as flumazenil also reverse the actions of inverse agonists. Not surprisingly, both classes of GABA_A receptor antagonists produce seizures when administered to laboratory animals. The affinity of convulsants for GABA_A receptors is so high that they have proven to be useful radioligands for measuring GABA_A receptors *in vitro* and for their subsequent biochemical and pharmacological characterization²¹⁴.

Ethanol has been shown by several investigators to augment GABA-activated Cl⁻ ion conductance in a variety of intact and isolated neuronal membrane preparations²¹⁵. Concentrations of ethanol (10–100 mM) weakly augment GABA-activated Cl⁻ ion conductance, as do longer chain-length alcohols and general anesthetics^{216,217}. Moreover, several imidazobenzodiazepine inverse agonists of the benzodiazepine receptor have been reported to antagonize the sedative effects of ethanol²¹⁵. This finding is further evidence implicating the GABA_A receptor as one of the key central sites mediating at least some of ethanol's neuropharmacological effects. The effects of ethanol on GABA_A receptors, coupled with its more recently described actions in inhibiting Glu (NMDA) receptor-mediated depolarizing events²¹⁷, likely contribute to the anxiolytic and sedative effects of alcohols.

To date, five distinct classes of polypeptide subunits (α , β , γ , δ , and ρ) have been cloned and multiple isoforms of each have been shown to exist²¹⁸. There is approximately 70% sequence identity between the polypeptide subunits within a given class, but only approximately 30% between classes^{219–221}. Subunit heterogeneity seems also to be relevant to the pharmacological differences observed between drugs that interact with GABA_A receptors such as the benzodiazepines^{222,223}.

Several of the subunits of the GABA_A receptor have been cloned^{201,205}. The deduced AA sequences of the α - and β -subunit cDNAs isolated indicated that each subunit was approximately 50–60 kDa in size and had four α -helical hydrophobic membrane-spanning sequences of approximately 20–30 AAs. The predicted structure of the receptor was based on strong evidence that the GABA_A receptor is a member of a large superfamily of ligand-gated ion channels, which includes the nicotinic-cholinergic, ionotropic Glu, and glycine receptors^{201,202}.

In contrast, GABA_C receptors represent a relatively simple form of transmitter-gated Cl⁻ ion channel made up of a single type of protein subunit. Two human GABA_C receptor cDNA have been cloned²⁰⁰. These receptors are not blocked by bicuculline nor do steroids, barbiturates or benzodiazepines modulate them. Instead, GABA_C receptors are selectively activated by the conformationally restricted analogues of GABA in the folded conformation cis-4-aminocrotonic acid and (1 S, 2 R)-2-(aminomethyl)-1-carboxycyclopropane. (1,2,5,6-Tetrahydropyridine-4-yl) methylphosphinic acid, a methylphosphinic acid analogue of GABA in a partially folded conformation, is a selective antagonist at GABA_C receptors^{198,224}.

e) GABA_B receptors

GABA_B receptors are seven transmembrane receptors that are coupled to G-proteins and activate second messenger systems and Ca⁺⁺ and K⁺ ion channels²²⁵. Three GABA_B receptor proteins have been cloned and these resemble metabotropic GluRs^{199,226}. GABA_B receptors are hetero-oligomeric receptors made up of a mixture of a combination of the subunits, which are selectively activated by baclofen and CCGP27492 and are blocked by phaclofen, the phosphonic acid analogue of baclofen; hence, GABA_B is found in central and peripheral nervous tissue²²⁶.

3) Glycine

Glycine (Gly), also known as aminoethanoic acid, is a non-polar, sweet tasting, AA derived from the alkaline hydrolysis of gelatin. It is the simplest of the AAs as its side chain is only a hydrogen atom. More complex AAs are constructed on the basic glycine structure. Since Gly has no side chain, it can enter spaces where no other AA can, e.g., only glycine can be the internal AA of the collagen helix accounting for about one third of the mass of collagen. Gly is conserved among species at certain positions in some proteins, e.g., cytochrome c, myoglobin, and hemoglobin²²⁷.

a) Glycine: synthesis and uptake

Gly is the major inhibitory neurotransmitter in the brainstem and spinal cord, where it participates in a variety of motor and sensory functions. It also functions as a co agonist at the NMDA subtype of GluR in the forebrain, where it promotes the actions of Glu, the major excitatory neurotransmitter. Thus, Gly subserves both inhibitory and excitatory functions within the CNS.

Gly is formed from serine by the enzyme serine hydroxymethyltransferase (SHMT) and like GABA, is released from nerve endings in a Ca⁺⁺-dependent fashion. Its uptake has been demonstrated in the brainstem and spinal cord in regions where there are also high densities of inhibitory glycine receptors. The actions of Gly are terminated primarily by reuptake via Na⁺/Cl⁻-dependent, high-affinity glycine transporters.

Glycine transporters have been cloned and expression shown in the CNS and in peripheral tissues^{228,229}. These glycine transporters are members of the large family of Na⁺/Cl⁻-dependent neurotransmitter transporters, and both share approximately 50% sequence identity with the GABA transporters discussed above. Two glycine-cloned transporters have been named GLYT-1 and GLYT-2 both of which have similar kinetic and pharmacological properties²²⁸. Studies have inferred that GLYT-1 is primarily a glial glycine transporter whereas GLYT-2 is primarily a neuronal transporter. The mapping of both glycine transporter mRNAs, as well as the glycine receptor subunit mRNAs, confirm the importance of this neurotransmitter in the brainstem and spinal cord, but support a more widespread distribution in supraspinal brain regions than was previously suspected²³⁰.

b) Glycine receptors

The glycine receptor was first successfully dissolved

Fig. 5. Structure of glycine, which is a simple amino acid

and purified using affinity purification over an affinity matrix derivatized with aminostyrychne²³¹. This affinity-purified glycine receptor was shown to consist of two polypeptide subunits of approximately 48 kDa (α) and 58 kDa (β), respectively.

Reconstitution of these polypeptide subunits into lipid vesicles resulted in functional receptors, and intramolecular cross-linking experiments suggested that the native glycine receptor is a pentameric structure. Photo affinity labeling of the glycine receptor with [³H]strychnine revealed that both the strychnine and Gly binding sites are located on the 48-kD α subunit. As would be expected, purification of the α - and β -receptor subunits was followed closely by their molecular cloning²³¹.

The deduced AA sequences of the α - and β -glycine-receptor subunits predict structures quite homologous to the subunits of other ligand-gated ion channels, including the GABA_A receptor²³². Each subunit has four hydrophobic membrane-spanning sequences, and each shares considerable sequence identity with the other. Several glycine-receptor α -subunit variants have been identified (α 1–4), and, not surprisingly, they differ in their pharmacological properties and level of expression. As mentioned, both the agonist and antagonist binding sites are located on the α -subunit, but at different AAs²³³.

Interestingly, glycine receptors comprised of α 1 subunits are efficiently gated by taurine and β -alanine, whereas α 2-containing receptors are not²³¹. The α 1 and α 2 genes are expressed in the adult and neonatal brain, respectively. Here the β -subunit transcript is expressed at relatively high levels in the cerebral cortex and cerebellum, where no α transcripts or specific [³H]strychnine binding sites have been observed. Co expression of β subunits with α -subunits, as opposed to homo-oligomeric α -subunit glycine receptors, results in glycine receptors with pharmacological properties quite similar to native glycine receptors. Nonetheless, the widespread distribution of β -subunit mRNA in the brain suggests that other, perhaps strychnine-insensitive glycine receptor isoforms will be found.

The expression of α 1 and α 2 subunits is regulated developmentally with a switch from the neonatal α 2 subunit [strychnine-insensitive] to the adult α 1 form [strychnine-sensitive] at about 2 weeks postnatally in the mouse²³¹. The timing of this switch over corresponds with the development of spasticity in the mutant spastic mouse²³⁴, prompting speculation that insufficient expression of the adult isoform

Table 3. The Function and Structure of Glycine Receptors

Receptor	Function	Molecular structure	Other actions
Glycine	Glycine binding opens Cl ⁻ channels.	Heteropentamers of α 1-4, and β .	Strychnine is the most potent and selective competitive antagonist.

may underlie some forms of spasticity²³⁰.

Electrophysiological studies in rodent spinal cord neurons have demonstrated that Gly activates the Cl⁻ ion conductance²³¹. Like GABA, this increase in Cl⁻ ion conductance results in a hyperpolarization of the neuronal membrane and an antagonism of other depolarizing stimuli. As indicated above, other α - and β -AAs, including β -alanine and taurine, also activate glycine receptors, but with lower potency^{231,235}. Inhibitory glycine receptors are blocked by the plant alkaloid strychnine, which was also first used to label glycine receptors in spinal cord membranes^{217,236}. Strychnine poisoning results in muscular contractions and tetany as a result of glycinergic disinhibition and over excitation.

c) Glycine as a co-agonist

Gly is a co-agonist at NMDA receptors at a strychnine-insensitive recognition site (glycine B) and its presence at moderate nM concentrations is a prerequisite for channel activation by Glu or NMDA²³⁷. Physiological concentrations reduce one form of relatively rapid NMDA receptor desensitization.

Recently it has been suggested that D-serine may be more important than Gly as an endogenous co-agonist at NMDA receptors in the telencephalon and developing cerebellum. There is still some debate as to whether the glycine B site is saturated *in vivo*²³⁷ but it seems likely that the degree of NMDA receptor activation varies depending on regional differences in receptor subtype expression and local Gly or D-serine concentrations. Moreover, Gly concentrations at synaptic NMDA receptors could be finely modulated by local expression of specific glycine transporters such as GLYT1²³⁸.

Glutamate Receptors

Glutamate receptors (GluRs), which are important in neural plasticity, neural development, and neurodegeneration^{239–241}, have been individually characterized by their sensitivity to specific Glu analogues and by the features of the Glu-elicited current. GluR agonists and antagonists are structurally similar to Glu, which allows them to bind onto the same receptors^{242–244}. Activation of GluRs has been shown to mediate a large number of neuronal processes such as long-term potentiation and ischemic damage²⁴⁵.

Two classes of GluRs have been characterized based on studies in the CNS: ionotropic (iGluRs) and metabotropic (mGluRs). These receptor types are similar in that they both bind Glu, and Glu binding can influence the permeability of ion channels. However, there are several differences

between the two classes²⁴⁶. Their cloning has revealed the molecular diversity of the gene families encoding various receptor types that are responsible for the pharmacological and functional heterogeneity in the brain and other tissues^{21,24–26,31,33,55,56,156}.

Ionotropic glutamate receptors (iGluRs)

The iGluRs are ligand-gated ion channels that mediate the vast majority of excitatory neurotransmission in the brain. The iGluRs contain integral cationic channels associated with ligand binding sites that mediate rapid synaptic transmission. The structure and how it relates to the function of these receptors has received recent attention and the reader is directed to these publications for further details^{247–249}.

The iGluR family is classified into three major subtypes according to their sequence similarities, their electrophysiological properties, and their affinity to selective agonists: *N*-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate (Ka) receptors^{21,22,25,26}.

All iGluRs can form heteromeric subunit assemblies, composed of different subunits, which have different physiological and pharmacological properties and are differentially distributed throughout the CNS^{25,50,237,250–253}. Both AMPA²⁵⁴ and NMDA receptors²⁵⁵ are probably largely formed from tetrameric, heteromeric assemblies of different subunits²⁵⁶. Changes in these receptors are probably mediated through nuclear transcription factors²⁵⁷.

The membrane channels associated with these receptors exhibit varied pharmacological and electrophysiological properties, including ionic channel selectivity to sodium (Na⁺), potassium (K⁺) and Ca⁺⁺^{21,22,25,26,33}. The non-NMDA receptors control a nonselective cationic channel permeable to Na⁺ and K⁺, whereas NMDA is more permeable to Ca⁺⁺ ions than either AMPA or Ka^{21,22,25,26}.

Recombinant technology has identified several gene families encoding iGluRs: AMPA family is composed of GluR 1-4 (GluRA-D); Ka family includes GluR 5-7 and Ka 1-2; NMDA includes NMDAR 1 and NMDAR 2A-D.

NMDAR 1, the most tightly regulated neurotransmitter receptor, forms the channel where other subunits (NMDA 2A-D) are involved in the receptor modulation. It is the most intensively studied and complex receptor and is linked to the Na⁺ and Ca⁺⁺ ion channel that has 5 distinct binding sites for endogenous ligands that influence the opening of these channel^{21,22,25,33}. These binding sites include 2 different agonist recognition sites, one for Glu and one for Gly, a polyamine regulatory site that promotes receptor activation. The remaining sites are separate recognition sites for Mg⁺⁺,

Fig. 6. Relationship of glutamate receptors to one another

Fig. 7. Relationship of ionotropic glutamate receptors to one another

Zn⁺⁺, and phencyclidine (PCP), which inhibits ion flux through agonist bound receptors^{21,22,25,26,33,250}.

The complexity of these iGluR families is further increased by alternate splicing, RNA editing and post-translational modifications such as phosphorylation, glycosylation and palmitoylation. Each of these modifications is important in the regulation of channel functions^{247,248}.

Within each family, GluRs subunits can also form homo-oligomeric or heteroligomeric channels that exhibit different functional properties depending on the subunit composition. For example, the presence of the GluR 2 subunit decreases Ca⁺⁺ permeability of AMPA channels^{21,22,25,33}. Table 4 lists the iGluRs.

Learning and memory depend on persistent changes in synaptic strength that require neuronal gene expression. AMPA- and NMDA-type GluRs have distinct roles in controlling synaptic strength: AMPA receptors effect short-term changes in synaptic strength, whereas NMDA receptors regulate genes that are required for the long-term maintenance of these changes²⁵⁹.

1) Diversity of the ionotropic glutamate receptors

The iGluRs are an extremely diverse group of receptors, a diversity that is generated both before and after gene

transcription. Glu binding onto an iGluR directly influences ion channel activity because the receptor and the ion channel form one complex. These receptors mediate fast synaptic transmission between neurons. Each iGluR is formed from the co-assembly of multimeric individual subunits, the structures of which affect the receptor function²⁴⁹.

The assembled subunits may or may not be homologous, with the different combinations of subunits, e.g., NR2A-D is produced from four genes, resulting in channels with different characteristics^{57,240,260-263}. However, following gene transcription, the resultant pre-mRNA may be modified. For example, different regions of this mRNA molecule can be spliced together, giving rise to multiple mRNAs that are translated into different proteins.

This phenomenon is known as “splice variation” and is a very common finding among neuroreceptors. The C-terminus of the iGluRs is the site of extensive splice variation, which could have important functional consequences, as the C-terminus is also the site for multiple protein-protein interactions, e.g., GluR2. Thus, different splice variants may interact differently with the same set of proteins leading to, for instance, differential subunit localization²⁴⁶.

A further modification leading to diversification is RNA editing, in which selected nucleotides in the mRNA sequence transcribed from the gene sequence are enzymatically modified, changing the AA for which it was coded. Such an event has fundamental consequences for the Ca⁺⁺ permeability of subunits such as the AMPA type subunit GluR2 and the Ka receptor subunit GluR5²⁶⁴.

2) Synaptic plasticity

In many regions of the CNS, limited Ca⁺⁺ influx through NMDA receptors can trigger two forms of synaptic plasticity: LTP and LTD. LTP and LTD are believed to resemble some elementary features of memory formation at the neuronal level^{191,265-269}.

Voltage-dependent blockade of NMDA receptors by Mg⁺⁺ and their high Ca⁺⁺ permeability renders them inherently suited for their role in mediating synaptic plasticity²⁷¹. NMDA receptor channels are only activated in the presence of a local strong depolarization induced by strong AMPA receptors activation and concurrent GABAergic disinhibition via feedback effects of GABA on GABA_B autoreceptors.

As a result, the Mg⁺⁺ blockade of NMDA receptors is transiently fully relieved allowing Ca⁺⁺ to flow into the postsynaptic neuron. This Ca⁺⁺ influx triggers a cascade of secondary messengers which ultimately activate a number of enzymes such as protein kinase C (PKC), phospholipase A2 (PLA2), phospholipase C (PLC), Ca⁺⁺-calmodulin-dependent protein kinase II (CaM kinase II), and others²⁷²⁻²⁷⁸. Consequently, these processes lead to fixation of changes in postsynaptic AMPA receptors such as an increase in their affinity and number²⁷⁹⁻²⁸³, and possibly through retrograde signals from arachidonic acid and nitric oxide²⁸⁴, modulate presynaptic glutamatergic terminals influencing

Table 4. Ionotropic Receptors, Their Subunits, Agonists and Antagonists

Receptor	NMDA	AMPA	Kainate
Subunits	NR1, NR2A, NR2B, NR2C, NR2D	GLUR1, GLUR2, GLUR3, GLUR4	GLUR5, GLUR6, GLUR7, KA1, KA2
Agonists	N-Methyl-D-aspartate	α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid	Kainate
Antagonists	D (-)-AP-5, D(-)-AP-7	CNQX, DNQX	CNQX, DNQX

Table 5. Summary of iGluRs, Their Function and Structure

Receptor	Function	Molecular structure	Other actions
NMDA	Glu binding opens cation-selective channels. The receptors are identified pharmacologically by the agonist action of N-methyl-D-aspartate (NMDA). Ca^{++} is an important charge carrier at depolarized potentials. Thus, activation of NMDA receptors can raise intracellular Ca^{++} , which can act as a second messenger. The kinetics of gating is relatively slow compare to those of the AMPA/kainate receptors. The entry of Ca^{++} (and Na^+) through the channels is subject to a voltage dependent block by Mg^{++} such that there is significant Ca^{++} entry only if the neuron is depolarized. The depolarization can be achieved by the action of the AMPA receptor channels and, to a lesser extent, by the NMDA receptor channels. The channels also require the presence of glycine as a coagonist.	Heterotetramers or heteropentamers of R1, R2A, R2B, R2C, and R2D. Alternatively known as NR1, NR2A-NR2D and MDAR1, NMDAR2A-NMDAR2D. Numerous splice variants can be mixed and matched.	
AMPA/ Kainate (Ka) (non-NMDA)	AMPA and kainate are a family of ligand-gated that are activated physiologically by Glu. They are identified pharmacologically by agonist actions of AMPA and kainate and their insensitivity to NMDA. Agonist binding opens cation channels that pass Na^+ , K^+ , and sometimes Ca^{++} . The kinetics of the response is fast (quick on and quick off) compared to those of NMDA receptors. Thus, they are very effective at depolarizing neurons and mediate fast EPSCs. Previously, what is now called AMPA/kainate receptors formed two classes based on pharmacology: kainate receptors and AMPA/kainate/quisqualate receptors. More recently, molecular classification has grouped these into a single group.	Multi subunit tetramers or pentamers of GluR1 - GluR7, KA1, KA2. There is a variety of molecular mechanisms result in numerous splice variants of these proteins. In addition, the GluR and Ka proteins can combine in numerous ways. The presence of a Ka subunit is sufficient but not necessary to make a channel with high sensitivity to kainate.	Kainate is a potent convulsant and neurotoxin. AMPA antagonists are neuroprotective in animal models of cerebral ischemia.

transmitter release^{285–290}.

There is accumulating evidence that LTP and LTD share some common mechanisms, although LTD occurs with increases in postsynaptic Ca^{++} , which are insufficient to induce LTP^{291–300}. LTP and LTD have been extensively studied as cellular models of learning and memory.

Although hippocampal LTP and spatial learning are impaired by NMDA receptor blockade²⁷⁰, learning deficits can be almost completely prevented if rats are previously trained in a different water maze^{301,302}. Therefore, NMDA receptors may not be required for encoding the spatial representation of a specific environment but rather in other forms of memory important for learning this task³⁰³. Further evidence indicates that LTP is not only important for synaptic plasticity in the mature CNS but also in the formation of conducting glutamatergic synapses in the developing mammalian brain³⁹⁷.

One form of hippocampal LTP involves the activation of the NMDA receptors and a rise in postsynaptic Ca^{++} in the

CA1 region but there is still considerable debate as to the site at which the increase in synaptic strength is expressed^{304–307}. Presynaptic mechanisms, which can be measured at excitatory synapses on cultured hippocampal neurons by analysis of the progressive block of NMDA receptor-mediated synaptic currents by the irreversible open channel blocker, dizocilpine ((+) MK-801), should be reflected in a change in release probability³⁹⁸.

This technique was used to demonstrate that release probability was not affected after the induction of LTP, making a presynaptic mechanism unlikely³⁰⁸. In fact, other authors indicate that a high proportion of synapses in hippocampal area CA1 transmit through NMDA receptors but not AMPA receptors, making these synapses effectively non-functional at normal resting potentials due to Mg^{++} blockade^{309–312}. These silent synapses acquire AMPA-type responses following LTP induction.

This form of LTP is accompanied by an increase in the conductance of postsynaptic AMPA receptors³¹³. When

viewed together, these findings challenge the dogma that LTP in CA1 involves a presynaptic modification, and suggest instead a simple postsynaptic mechanism for both induction and expression of LTP.

3) NMDA receptors

The NMDA receptor is perhaps the best characterized of the iGluR^{251,314}, in part due to the existence of selective agonists and antagonists. NMDA receptors are ubiquitous³¹⁵ and are found with relative ease in the cerebral cortex within the Schaffer collaterals of the CA3 - CA1 projection within the hippocampus. These receptors play a role in LTP; a phenomenon associated with learning and memory function and increased neuronal activity such as in "kindling."

NMDA receptors are quite diverse³¹⁶ and are composed of assemblies of NR1 subunits and NR2 subunits, which can be one of four separate gene products (NR2A-D). Expression of *both* subunits is required to form functional channels. The Glu-binding domain of the receptor is formed at the junction of NR1 and NR2 subunits; hence, the need for expression of both subunits. In addition to Glu, the NMDA receptor requires a co-agonist, Gly, to bind to allow the receptor to function. The Gly-binding site is found on the NR1 subunit. The NR2B subunit also possesses a binding site for polyamines, regulatory molecules that modulate the functioning of the NMDA receptor³¹⁷.

NMDA receptors are inactive at resting membrane potentials due to a voltage-dependent block of ion flow through the channel pore by Mg⁺⁺ ions. Sustained activation of AMPA receptors by a train of impulses arriving at a pre-synaptic terminal depolarizes the post-synaptic cell, releasing the channel inhibition and thus allowing NMDA receptor activation. Unlike GluR2-containing AMPA receptors, NMDA receptors are permeable to Ca⁺⁺ and other ions. Therefore NMDA receptor activation leads to a Ca⁺⁺ influx into the post-synaptic cells.

Glu binding onto an NMDA receptor also opens non-selective cation channels, resulting in a conductance increase. However, the high conductance channel associated with these receptors is more permeable to Ca⁺⁺ than Na⁺ ions³¹⁸ and NMDA-gated currents typically have slower kinetics than kainate- and AMPA-gated channels. As the name suggests, NMDA is the selective agonist at these receptors. The compounds MK-801, AP-5 (2-amino-5-phosphonopentanoic acid), and AP-7 (2-amino-7-phosphoheptanoic acid) are NMDA receptor antagonists.

NMDA receptors are structurally complex, with separate binding sites for Glu, Gly, Mg⁺⁺, Zn⁺⁺, and a polyamine recognition site. There is also an antagonist-binding site for PCP and MK-801³¹⁹. The Glu, Gly, and Mg⁺⁺ binding sites are important for receptor activation and gating of the ion channel. In contrast, the Zn⁺⁺ and polyamine sites are not needed for receptor activation, but affect the efficacy of the channel.

Zn⁺⁺ blocks the channel in a voltage-independent manner³²⁰, whereas the polyamine site^{321,322} binds compounds such as spermine or spermidine, either

potentiating^{321,322} or inhibiting³²² the activity of the receptor. Potentiation or inhibition depends on the combination of subunits forming each NMDA receptor³²².

The Glu, Gly, and Mg⁺⁺ binding sites confer both ligand-gated and voltage-gated properties onto NMDA receptors. NMDA receptors are ligand-gated because the binding of GluR (ligand) is required to activate the channel with the presence of micromolar concentrations of Gly, which must also be present^{323,324}. The requirement for both Glu and Gly makes them co-agonists³²⁴ at NMDA receptors. Mg⁺⁺ ions provide a voltage-dependent block of NMDA-gated channels³²⁵.

NMDA receptors are highly permeable for Ca⁺⁺ ions. They show slower gating kinetics with the channel blocked in a voltage and use-dependent manner by physiological concentrations of Mg⁺⁺ ions³²⁵. These properties make them ideally suited for their role as a coincidence detector underlying synaptic plasticity in learning, chronic pain, drug tolerance and dependence^{83,84,90,91,252,266}.

NMDA receptors were originally thought to belong exclusively in neurons. However, recent studies have found functional NMDA receptors in brain microglia, astrocytes, and oligodendrocytes, but glial and neuronal NMDA receptors are functionally and structurally different. Glial receptors are weakly sensitive to the extracellular Mg⁺⁺ block in comparison to neurons, indicating a predominant expression of the NR3 receptor subunit.

In the cortex, astroglial NMDA receptors are activated upon physiological synaptic transmission. The physiological relevance of NMDA receptors in the white matter remains unknown; their activation upon ischemia triggers Ca⁺⁺-dependent damage of oligodendrocytes and myelin³²⁶.

a) NMDA subunits

Two major subunit families of NMDA designated NR1, NR2, as well as a modulatory subunit designated NR3, have been cloned. Most NMDA functional receptors are formed by combination of NR1 and NR2 subunits, which express the Gly and Glu recognition sites respectively^{327,328}. NR1 is more concentrated in rostral structures such as cortex, caudate, and hippocampus, while the latter are principally found in more caudal regions such as thalamus³²⁹, colliculi, locus coeruleus and cerebellum³³⁰. The NR2 subfamily consists of four individual subunits: NR2A to NR2D²⁶³. Various heteromeric NMDA receptor channels formed by combinations of NR1 and NR2 subunits are known to differ in gating properties, Mg⁺⁺ sensitivity, and pharmacological profile³³¹. Of the NR2 group, NR2A is distributed ubiquitously, as is NR1, with greatest densities occurring in hippocampal regions. NR2B is expressed predominantly in forebrain but not in cerebellum where NR2C predominates. The spinal cord expresses high levels of NR2C and NR2D³³² and these subunits may form heteroligomeric receptors with NR1 plus NR2A, which would provide a basis for the development of drugs selectively aimed at spinal cord disorders³³³. NR3 (NRL or Chi-1) is expressed predominantly in the developing CNS. NR3 does not seem

to form functional homomeric Glu-activated channels, but the co-expression of NR3 with NR1 plus NR2 subunits decreases any response magnitude^{334–337}.

4) AMPA receptors

AMPA receptors are involved in mediating most forms of fast glutamatergic neurotransmission, which corresponds to a Ca^{++} influx³³⁸, and the inward rectification of both AMPA and kainate subtype GluRs are generated by polyamine-mediated ion channel block³³⁹. In fact, AMPA receptor activates a G-protein that suppresses a cGMP-gated current³⁴⁰.

Four known subunits GluR1 to GluR4, sometimes referred to as GluRA to GluRD, are widely, but differentially, distributed throughout the CNS²⁵. The types of subunits forming these receptors determine their biophysical properties and pharmacological sensitivity.

Two alternative splice variants of GluR1 to GluR4 subunits designated as 'flip' and 'flop' have been shown to differ in their expression throughout the brain and during development and to impart different pharmacological properties. AMPA receptors also play an important role in memory function^{341,342}. They are localized in the hippocampus and striatum and also may play a role in the generation of seizures^{263,338,343}.

Like all iGluR subunits, but in contrast to other ligand gated ion channel subunits such as those forming the GABA_A receptor, iGluR subunits have an extracellular N-terminus and an intracellular C-terminus. The ligand-binding domain is made up from N-terminal regions S1 and S2, although it is possible that the binding site is spread across more than one subunit like the NMDA receptor. All AMPA receptor subunits exist as two splice variants, flip and flop. The alternative splice cassette is found at the C-terminal end of the loop between TMIII and TMIV. Although only a few AAs are changed in the receptor subunits, the effect can be quite dramatic resulting in altered desensitization kinetics.

Native AMPA receptor channels are impermeable to Ca^{++} , a function controlled by the GluR2 subunit. The Ca^{++} permeability of the GluR2 subunit is determined by post-transcriptional editing of the GluR2 mRNA, which changes a single AA in the TMII region from glutamine (Q) to arginine (R). This event is the so-called Q/R editing site - GluR2(Q) is Ca^{++} permeable whilst GluR2(R) is not. Almost all the GluR2 protein expressed in the CNS is in the GluR2(R) form, giving rise to Ca^{++} impermeable AMPA receptors. This observation, along with the interactions with other intracellular proteins, makes GluR2 perhaps the most important AMPA receptor subunit.

5) Kainate receptors

Kainate (Ka) receptors constitute a separate group from the NMDA and AMPA receptors, although they share many of the same structural characteristics³⁴⁴. Ka and AMPA receptors are localized in the hippocampus and striatum and also may play a role in the generation of seizures³⁴⁵. Ka is

used as a neurotoxin in basic research due to its ability to destroy cells at the site of injection while leaving axons of passage intact.

Ka receptors are built from multimeric assemblies of GluR5-7 and KA-1/2 subunits. Like the other iGluRs, they possess an extracellular N-terminus. This terminus forms the ligand binding domain and a re-entrant loop (TMII), together with a loop between TMIII and TMIV, which forms the lining of the pore region in the ion channel. Ka also undergoes both splice variation and RNA editing, giving rise to a large number of possible receptors with differing pharmacological and functional properties³⁴⁶.

Ka receptors were previously believed to be largely presynaptic. Activation of these Ka receptors facilitated transmitter release at such sites as the dorsal root ganglia³⁴⁷. Short-term synaptic facilitation is reduced in knockout mice lacking the GluR6, but not the GluR5, Ka receptor subunit suggesting that Ka receptors act as presynaptic autoreceptors on mossy fiber terminals to facilitate synaptic transmission³⁴⁸, but inhibition of GABA release³⁴⁹. Also they are involved post synaptically in neurotransmission in some pathways^{345,350–352}.

Metabotropic glutamate receptors (mGluRs)

The mGluRs were discovered and established as a new type of excitatory AA receptor by their unique coupling mechanism and pharmacological characteristics. mGluRs are a family of eight single polypeptide chain receptors that function via coupling to G-proteins³⁵³. Members of this family have unique pharmacological properties and function to modulate the presynaptic release of Glu and the post-synaptic sensitivity of the cell to Glu excitation^{22,25,33,34,354,356}. They exert their effects either on the second messengers or ion channels via the activation of the GTP-binding proteins and regulate the synthesis of different intracellular second messengers such as IP₃, cAMP or cGMP^{22,25,33,34,56}. Single mGluR proteins can cross talk with multiple second messengers in the same cell.

The mGluRs are densely expressed in medium spiny projection neurons of striatum. They have both chemical and electrical signaling properties³⁵⁵. Glu binding onto an mGluR opens non-selective cation channels more permeable to Na^{+} and K^{+} ions than Ca^{++} ³¹⁸. mGluR binding elicits a rapidly activating inward and outward current and Ka, quisqualate, and AMPA are the specific agonists at these receptors; CNQX (6-cyano-7-nitroquinoxaline-2, 3-dione), NBQX (1,2,3,4-tetrahydro-6-nitro-2,3-dione-benzo[f]quinoxaline-7-sulfonamide), and DNQX (6,7-dinitroquinoxaline-2,3-dione) are the antagonists^{107,356–361}.

In common with other G-protein coupled receptors (GPCRs), the mGluRs possess a 7 transmembrane domain motif (7-TMR) and an extracellular N-terminus and intracellular C-terminus. However, the mGluRs are much larger than GPCRs of the adrenergic type and the ligand-binding domain is located in the N-terminus, rather than in a pocket formed from the clustering of the 7-TMR region³⁶². The eight functionally distinct mGluR subtypes are localized

to specific neuron types at presynaptic and postsynaptic membranes, their physiological functions involving the generation of slow excitatory and inhibitory synaptic potentials, modulation of synaptic transmission, synaptic integration, and plasticity.

As with iGluRs, the mGluRs are classified into 4 groups (Group I – IV) based on AA sequence similarities, agonist pharmacology and the signal transduction pathways to which they are coupled²⁴⁰. Each receptor is formed from the co-assembly of several subunits^{239,240,363}. To date, eight subunits (named mGluR1 through mGluR8) have been cloned^{239,260,262–267}.

Briefly, Group I (mGluR 1, 5, and 6) stimulates inositol phosphate metabolism and mobilization of intracellular Ca^{++} , Group II (mGluR 2 and 3) and Group III (mGluR 4, 6–8) are coupled to adenylyclase^{22,25,33,56}, and Group IV is coupled to the activation of phospholipase D (PLD)³⁶⁸. The latter class is more efficiently activated by L-cysteine-sulfonic acid (L-CSA) rather than Glu, which suggests that L-CSA may serve as an endogenous agonist of this receptor⁵⁵.

As with the iGluRs, the mGluRs also have a unique distribution in the CNS and retina, which reflects a diversity of function in normal and pathological processes. The mGluRs have certain features that distinguish them from the iGluRs. First, the mGluRs modulate the activity of neurons rather than mediate fast synaptic neurotransmission. Second, the distribution of the mGluRs is highly diverse and heterogeneous. Different subclasses are localized uniquely at both the anatomical and cellular levels. For example, mGluR 2 and 3 are found in high density in the cerebral cortex, whereas mGluR 4 is found in high density in the thalamus but not in the cortex and mGluR 6 is almost exclusively found in the retina.

Activation of mGluRs alters local transmitter release and behaviors of experimental animals. In particular, mGluRs regulate phosphorylation of several key signaling proteins, including protein kinases and transcription factors, resulting in significant changes in immediate early gene and neuropeptide gene expression in striatal neurons. The prominent involvement of mGluRs in genomic responses to synaptic stimulation is considered to play a pivotal role in the development of synaptic and neuronal plasticity underlying long-term adaptive changes in cellular physiology related to a variety of neurological disorders. mGluR also regulates dopamine transmission, an important factor in many neurological disorders³⁶⁹.

Motor neuron activity changes significantly after administration of mGluR antagonists. Antagonists for Group II and for Group III mGluR enhance synaptic currents in rat spinal lumbar and cervical motor neurons^{370–372}. This increased current is presumably caused by the blockade of presynaptic receptors, suggesting that endogenous activation of these receptors attenuates synaptic transmission. In phrenic motor neurons, the Group I mGluR antagonist (R,S)-1-aminoindan-1,5-dicarboxylic acid (AIDCA) significantly reduces excitatory postsynaptic currents amplitude,

Fig. 8. The relationship of metabotropic glutamate receptors to one another

suggesting that postsynaptic Group I mGluR, along with various ionotropic receptors^{373,374}, are activated by endogenously released Glu during inspiration. Three groups of mGluR are functionally expressed in motor neurons to mediate differential effects on intrinsic and synaptic properties via distinct mechanisms operating at pre- or post-synaptic sites. The diversity of actions mediated by various receptor subtypes provides a wide dynamic range for modulation of motor neuron excitability.

The glutamate system: agonists and antagonists

1) iGluRs and mGluRs

As Glu, GluR, and GluTP are ubiquitous and have a plethora of effects, antagonists to GluR are under evaluation for a number of diseases. So far most efforts have been directed toward antagonism to the iGluR, but some effects have also been made with respect to the mGluR. Glu, NMDA, AMPA and Ka are the most commonly used GluR agonists. The purpose of developing antagonists is two fold: to enable investigation into the mechanism of action of the GluR and to hopefully develop new drugs targeting diseases know to have basis in altered Glu activity⁴⁷. A summary of a sample of the GluR agonists and antagonists available can be seen in Table 7.

The side effects of agonist over stimulation have been previously discussed under the section on excitatory amino acids (EAAs). Antagonists, which completely block NMDA receptors, cause numerous side effects such as memory impairment, psychomimetic effects, ataxia and motor incoordination as they impair normal synaptic transmission³⁷⁵.

2) Glycine

Most full glycineB antagonists, without intrinsic partial agonist activity, show very poor penetration to the CNS, although some agents with improved, but by no means optimal pharmacokinetic properties, have now been developed. Glycine_B antagonists have been reported to lack many of the side effects classically associated with NMDA receptor blockade such as no neurodegenerative changes in the cingulate and retrosplenial cortex even after high

Table 6. Metabotropic Glutamate Receptors Function and Structure

Receptor	Function	Molecular structure	Other actions
mGlu	Activation of many of these receptors leads to inhibition of postsynaptic Ca^{++} and Na^{+} channels.	G protein $\text{G}_{q/11}$ or $\text{G}_{i/o}$	Unlike the excitatory ionotropic glutamate receptors, the metabotropic receptors cause slower responses that can either increase or decrease the excitability of the postsynaptic neuron.

Table 7. Summary of Selective iGlu and mGlu Ligands

Ionotropic (iGlu) receptors			
Receptor type	NMDA	AMPA	Kainate
Agonists	NMDA; Tetrazolylglycine	AMPA; LY404187; (S)-5-fluorowillardiine	Kainate; ATPA; (S)-5-iodowillardiine; LY339434; SYM 2081
Antagonists	CPP (selective NR2A/NR2B vs. NR2C/NR2D); PEAQX (selective NR2A vs. NR2B); Ro-25-6981; (NR2B selective)	NBQX; LY293558; (S)-ATPO; GYKI53655	LY382884; UBP302; NS 3763
Metabotropic (mGlu) receptor ligands			
Receptor type	Group I	Group II	Group III
Agonists	(S)-DHPG; CHPG (mGlu 5); (3S,2R)-ACPD; Ro (+) 01-6128 (mGlu1); (-) DFB (mGlu 5); CBPG (mGlu5)	LY354740; LY487379; CCG-1; APDC.	LY379268; (S)-AP4; DCPG (mGlu 8); (+)PHCC (mGlu4); CCG-1; (L)-AP4; PPG.
Antagonists	LY367385 (mGlu1); (S)-MCPG; (-)MPEP; (mGlu5); (-)MTEP (mGlu5); (-) CPEOEt (mGlu1); (-)BAY36-7620 (mGlu)	LY341495; EGLU	CPPG; UBP1112

doses³⁷⁶ and no psychomimetic-like or learning impairing effects at anticonvulsive doses^{237,377–380}. The improved neuroprotective therapeutic profile of glycine_B full antagonists could be due to their ability to reveal glycine-sensitive desensitization³⁸¹.

Kynurenic acid is an endogenous glycine_B antagonist but it seems unlikely that concentrations are sufficient to interact with NMDA receptors under normal conditions^{237,382}. However, concentrations are raised under certain pathological conditions^{237,382} and interactions with other receptors such as $\alpha 7$ neuronal nicotinic have been reported at lower concentrations^{237,382,383}.

D-cycloserine and (+R)-HA-966 are partial agonists at the glycine_B site with different levels of intrinsic activity of 57% and 14% respectively in cultured hippocampal neurons³⁸⁴. Although these systemically active partial agonists do not induce receptor desensitization^{384–386}, they have favorable therapeutic profiles in some *in vivo* models^{387,388}. In part this positive effect may be due to their own intrinsic activity as agonists at the glycine_B site, which would serve to preserve a certain level of NMDA receptor function even at very high concentrations^{389–391}.

Although ACPC has been reported to be a partial agonist with very high intrinsic activity, it is probably really a full agonist at the glycine_B site and actually behaves as an antagonist in some *in vivo* models, resulting in neuroprotection and anticonvulsive effects, which are likely to be mediated via competitive antagonistic properties at higher concentrations³⁹². The consistent observation that chronic treatment with ACPC is neuroprotective could be

because it desensitizes or uncouples NMDA receptors^{393,394} or may be related to an increase in the relative levels of NR2C expression³⁹⁰.

Dose-response

D-cycloserine shows agonist like features at low doses, while with increasing dosing antagonistic effects predominate³⁸⁷. Such findings are often falsely interpreted to be “typical” for partial agonists: agonism at low and antagonism at high doses. However, partial agonism actually means that an agent reaches a ceiling, non-maximal effect at higher doses. That is its intrinsic activity is limited compared with a full agonist, so that it will antagonize receptor activation at high concentrations but facilitate at low concentrations^{384,385}.

The consistent biphasic effects of D-cycloserine seen *in vivo* may be related to different affinities and intrinsic activities at NMDA receptor subtypes. D-cycloserine is a partial agonist for the murine equivalents of NR1/2A and NR1/2B heteromers [38% and 56% intrinsic activity compared to Gly 10 μM] but is more effective than Gly at NR1/2C (130%)³⁹⁵. This effect is accompanied by higher affinity at NR1/2C receptors - NR1/2C > NR1/2D >> NR1/2B > NR1/2A³⁹⁵. In contrast, similar data showed that the intrinsic activity at NR1/2C was even higher (192%)³⁹⁶. Therefore, it is likely that the biphasic effects seen *in vivo* are due to agonistic actions at NR1/2C receptors at lower doses and inhibition of NR1/2A and NR1/2B containing receptors at higher doses.

In conclusion, the glutamate system is central to many

neurotransmission processes, and this review has attempted to summarize some aspects of the complex glutamate system. As we learn more regarding this system, it is probable that current and future development of agonists and antagonists for treatment of a number of diseases will occur. The second part of this review will address the pathophysiology and pathology of the GluRs.

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