Glutamate Receptors

The central nervous system utilizes various substances as neurotransmitters. Among them, glutamate and gamma aminobutyric acid (GABA) are the major neurotransmitters for excitatory and inhibitory function, respectively. In the cerebral cortex, approximately 70%–80% of neurons are glutamatergic neurons, with the remainder comprising GABAergic interneurons . Thus, it is evident that glutamatergic and GABAergic neurons primarily compose basic neuronal networks, especially in the cortex. Cortical pyramidal neurons possess approximately 30,000 synapses, of which 95% are excitatory synapses, indicating that glutamate is the principal excitatory neurotransmitter in the brain, and also that GABAergic inhibition influences neuronal activity in an efficient manner. Recently, it has been demonstrated that glutamate is also utilized as a gliotransmitter, released from glial vesicles and channels, with evidence suggesting that glutamate released from glial cells modulates synaptic efficiency and controls the release of various biological molecules, including cytokines . Therefore, it is possible that glutamate may contribute to various physiological/pathological conditions.

Several types of ionotropic glutamate receptors have been identified. Three of these are ligand-gated ion channels called **NMDA receptors, AMPA receptors, and kainate receptors**

. These glutamate receptors are named after the agonists that activate them:

NMDA (*N*-methyl-D-aspartate),

AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate),

Kainic acid.

All of the ionotropic glutamate receptors are nonselective cation channels, allowing the passage of Na^+ and K^+, and in some cases small amounts of Ca^{2+}. AMPA, Kainate, and NMDA receptor activation always produces excitatory postsynaptic responses.

Like other ligand-gated channel receptors, AMPA/kainate and NMDA receptors are formed from the association of several protein subunits that can combine in many ways to produce a large number of receptor isoforms .

Ionotropic Glutamate receptors has 4 subunits assembly, each with pore loop.
There are 16 different receptor subunits -
NMDA receptors- 7 types of subunits (GluN1,GluN2A, GluN2B, GluN2C, GluN2D, Glu3A and Glu3B).
AMPA receptors-4 types of subunits(GluA1-4)
Kainate receptors-5 types of subunits(GluK 1-5).

NMDA and Kainate receptors also presynaptic

Cortex ,Basal ganglia and sensory pathways

NMDA,AMPA generally colocalised.

The NMDA subfamily of glutamate receptors also form multisubunit, nonselective cation channels similar to most other ligand-gated ion channel receptors . These receptors, however, have especially interesting properties. Perhaps most significant is the fact that NMDA receptor ion channels allow the entry of Ca^{2+} in addition to monovalent cations such as Na^{+} and K^{+}. As a result, EPSPs produced by NMDA receptors can increase the concentration of Ca^{2+} within the postsynaptic neuron; the Ca^{2+} concentration change can then act as a second messenger to activate intracellular signaling cascades . Other unique properties of NMDA receptors are that opening the channel requires the presence of a co-agonist (the amino acid glycine), and that extracellular Mg^{2+} blocks the channel at hyperpolarized, but not depolarized, voltages . Hence, NMDA receptors allow the passage of cations only when the Mg^{2+} block is removed by the depolarization of the postsynaptic cell, either by a large number of excitatory inputs or by the repetitive firing of the presynaptic cell. These properties are widely thought to be the basis for some forms of information storage at synapses.

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While some glutamatergic synapses have only AMPA or only NMDA receptors, most have both AMPA and NMDA receptors. The synaptic currents produced by NMDA receptors are slower and longer-lasting than the those produced by AMPA/kainate receptors .

Glutamate receptors are best known for mediating glutamate's role in learning and memory through plasticity, or modification, of channel properties; enhanced glutamate neurotransmission; and gene expression . Not only are NMDA receptors highly expressed on neurons, but they are also expressed on astrocytes . The human brain's expansive capacity for plasticity, learning, memory, and recovery from injury is attributed to improvement in synaptic anatomy and physiology of NMDA signaling, most notably in the hippocampus and other regions of the mammalian CNS . The basic mechanisms underlying plasticity include neurogenesis, activity-dependent refinement of synaptic strength, and pruning of synapses.

The AMPARs also act as one of the gatekeepers of NMDAR-dependent synaptic plasticity by relieving their voltage-dependent channel block by Mg2+ , allowing the postsynaptic Ca2+entry that initiates changes in synaptic strength . At some synapses, AMPARs can also mediate calcium influx directly, triggering various forms of postsynaptic plasticity .

Follow the Table below

Table 38.1 Properties of ionotropic glutamate receptors

	NMDA		AMPA	Kainate
Subunit composition	Tetramers consisting of GluN1–3 subunits		Tetramers consisting of GluA1–4 subunits (variants splicing and RNA editing)	Tetramers consisting of GluK1–5 subunits
	Receptor site	*Modulatory site (glycine)*		
Endogenous agonist(s)	Glutamate Aspartate	Glycine D-Serine	Glutamate	Glutamate
Other agonist(s)[a]	NMDA	Cycloserine	AMPA Quisqualate	Kainate Domoate[b]
Antagonist(s)[a]	AP5, CPP	7-Chloro-kynurenic acid, HA-966	NBQX	NBQX ACET
Other modulators	Polyamines (e.g. spermine, spermidine) Mg^{2+}, Zn^{2+}		Cyclothiazide Perampanel Piracetam CX-516	–
Channel blockers	Dizocilpine (MK801) Phencyclidine, ketamine Remacemide Memantine Mg^{2+}		–	–
Effector mechanism	Ligand-gated cation channel (slow kinetics, high Ca^{2+} permeability)		Ligand-gated cation channel (fast kinetics; channels possessing GluA2 subunits show low Ca^{2+} permeability)	Ligand-gated cation channel (fast kinetics, low Ca^{2+} permeability)
Location	Postsynaptic (some presynaptic, also glial) Wide distribution		Postsynaptic (also glial)	Pre- and postsynaptic
Function	Slow epsp Synaptic plasticity (long-term potentiation, long-term depression) Excitotoxicity		Fast epsp Wide distribution	Fast epsp Presynaptic inhibition Limited distribution

[a]Structures of experimental compounds can be found in Brauner-Osborne et al. (2002).
[b]A neurotoxin from mussels (see Ch. 40).
ACET, -(*S*)-1-(2-amino-2-carboxyethyl)-3-(2-carboxy-5-phenylthiophene-3-yl-methyl)-5-methylpyrimidine-2,4-dione; AP5, 2-amino-5-phosphonopentanoic acid; CPP, 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid; CX-516, 1-(quinoxalin-6-ylcarbonyl)-piperidine; epsp, excitatory postsynaptic potential; NBQX, 2,3-dihydro-6-nitro-7-sulfamoyl-benzoquinoxaline. (Other structures are shown in Figure 38.3.)

Long term potentiation- Prolonged enhancement of synaptic transmission following presynaptic stimulation

Excitotoxicity—High amount of glutamate causes neuronal cell death.

To correctly transfer information, neuronal networks need to continuously adjust their synaptic strength to extrinsic stimuli. This ability, termed synaptic plasticity, is at the heart of their function and is, thus, tightly regulated. In glutamatergic neurons,

synaptic strength is controlled by the number and function of AMPA receptors at the postsynapse, which mediate most of the fast excitatory transmission in the central nervous system. Their trafficking to, at, and from the synapse, is, therefore, a key mechanism underlying synaptic plasticity.

NMDA receptors (NMDARs) are both ligand- and voltage-gated: their activation depends not only on the binding of glutamate, but also on the concomitant depolarization of the postsynaptic membrane following neuronal activity, which relieves the block of their ion channel by magnesium. AMPA receptors (AMPARs), on the other hand, are ligand-gated only and the primary mediators of fast excitatory transmission.

Compiled and prepared