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Glutamate Receptors

Elek Molnár

Centre for Synaptic Plasticity, School of Physiology, Pharmacology and Neuroscience, University of Bristol, Biomedical Sciences Building, University Walk, Bristol, BS8 1TD, UK

Elek Molnár, Professor of Neuroscience

E-mail: Elek.Molnar@bristol.ac.uk

Synonyms

[Ionotropic glutamate receptors \(AMPA, kainate and NMDA receptors\)](#); [Metabotropic glutamate receptors](#)

Nomenclature of Glutamate Receptor Proteins

International Union of Basic and Clinical Pharmacology (IUPHAR) recommended and previous nomenclatures of glutamate receptor proteins

1. Ionotropic glutamate receptors (Traynelis et al. [2010](#))

- AMPA receptor subunits GluA1-4 (previously: GluR1-4; GluRA-D; GLU_{A1-4})
- Kainate receptor subunits GluK1-5 (previously: GluR5-7, KA-1/2; EAA3-5, EAA1/2; GLU_{K5-7}, GLU_{K1/2})
- NMDA receptor subunits GluN1, GluN2A-D, GluN3A-B (previously: NR1, NR2A-D, NR3A/B; GLU_{N1}, GLU_{N2A-D}, GLU_{N3A/B})
- δ receptor subunits GluD1-2 (previously: GluR δ 1/2)

2. Metabotropic glutamate receptors (Niswender and Conn [2010](#))

- mGlu1-8 (previously: mGluR1-8)

Historical Background

The excitatory neurotransmitter role of L-glutamate gradually emerged in the 1950s–1960s. Early studies indicated that L-glutamate: (1) was present in high concentrations throughout the mammalian central nervous system (CNS), (2) produced convulsions, and (3) excited single neurons (reviewed in Lodge [2009](#)). The development of increasingly specific pharmacological tools during the 1970s started to reveal considerable functional diversity. The family of glutamate-activated cation channels (ionotropic glutamate receptors [iGluRs]) was classified into three major pharmacological subfamilies, defined by their most selective agonists: α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors (Lodge [2009](#); Traynelis et al. [2010](#)). In the mid-1980s, evidence began to appear of the existence of another glutamate receptor (GluR) group termed metabotropic GluRs (mGluRs) that are directly coupled to second-messenger systems via GTP-binding proteins (Nicoletti et al. [2011](#)). However, iGluR and mGluR proteins remained elusive until the late 1980s. The application of the newly emerging expression cloning approach led to a breakthrough and provided the original sequence information for the first iGluR subunits GluA1 and GluN1 (Lodge [2009](#)). The first member of the family of mGluRs (mGlu1a) was also discovered by expression cloning (Nicoletti et al. [2011](#)). Successive cloning by sequence homology led to the identification of additional iGluR subunits, mGluR isoforms, and their splice variants (Traynelis et al. [2010](#); Niswender and Conn [2010](#)). Receptor localization studies in the 1990s–2000s, together with the development of a range of transgenic animals and more selective

pharmacological tools, started to reveal the mechanisms of glutamatergic signaling in the CNS. The availability of X-ray crystal structures, molecular modeling and site-directed mutagenesis studies provided much improved understanding of the molecular organization of iGluRs (Kumar and Mayer 2013) and mGluRs (Nicoletti et al. [2011](#)). A very diverse range of receptor phosphorylation–dephosphorylation events, auxiliary subunits, protein–protein interactions, and receptor trafficking have been identified as important regulators of GluR function and synaptic plasticity (Huganir and Nicoll 2013; Henley and Wilkinson 2016). Synaptic activity-induced changes in GluR responses have long been linked to learning and memory (Collingridge et al. 2013; Morris 2013). Furthermore, dysfunction of GluRs have been implicated in a wide range of neurological and psychiatric disorders (Nicoletti et al. [2011](#); Paoletti et al. 2013; Golubeva et al. 2015).

Key Features of the Glutamate Receptor Family

The amino acid L-glutamate is the predominant neurotransmitter of the vast majority of excitatory synapses in the mammalian CNS. This ubiquitous neurotransmitter acts via the activation of a number of ionotropic (ligand-gated ion channels) and metabotropic (G-protein-coupled) GluRs. These receptors are involved in nearly all aspects of nervous system development and function including many forms of synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD), mechanisms that are involved in learning and memory (Morris 2013; Huganir and Nicoll 2013). GluRs are also involved in a very wide range of neurological and psychiatric disorders including chronic neurodegenerative conditions (Lewerenz and Maher 2015; Miladinovic et al. 2015). They are thus also potential targets for therapies for CNS disorders (Nicoletti et al. 2011; Collingridge et al. 2013).

Ionotropic Glutamate Receptors

The related channel pore forming subunit proteins of glutamate-gated ion channels (iGluRs) are encoded by 18 genes in mammals. Based on their sequence homology, electrophysiological properties and pharmacological selectivity they are subdivided into four subtypes: AMPA, kainate, NMDA, and δ receptors (Fig. [1](#)). All iGluRs share a common basic structure, which differs from other ligand-gate ion channels. iGluRs are formed from the tetrameric assembly of homologous subunits around a central ion pore (Traynelis et al. [2010](#)). The membrane topology of the iGluR subunits consists of a large extracellular N-terminal domain and four hydrophobic membrane-associated domains (M1-4; Fig. [2a](#)). M2 is a re-entrant loop in the phospholipid bilayer and represents the channel pore-forming region (Kumar and Mayer 2013). Each subunit carries its own ligand-binding site, which consists of residues that are distributed throughout both the distal N-terminal domain (called S1) and the extracellular loop between M3 and M4 (called S2; Fig. [2a](#); Kumar and Mayer 2013). The S1S2 ligand-binding domain regions of some of the iGluR subunits have been isolated and crystalized with and without bound ligands (Kumar and Mayer 2013). X-ray analysis of these proteins and protein-ligand complexes elucidated fine molecular details of the binding site, and the conformational changes of different agonists and antagonists induce to open or block the ion channels or modulate the manifestation of their activity (Kumar and Mayer 2013). Crystallographic and cryogenic electron microscopy studies have provided detailed structures of the antagonist-bound tetrameric GluA2 (Sobolevsky et al. [2009](#)) and heteromeric GluA2/3 (Herguedas et al. 2016) AMPARs, which revealed complex subunit domain interactions within iGluRs (Fig. [2b](#)). Oligomerization of iGluR subunits plays a major role in their surface expression (Herguedas et al. 2013). Nonfunctional receptors are retained intracellularly, suggesting that glutamate binding and associated conformational changes are prerequisites for the forward trafficking of intracellular iGluRs following multimeric assembly (Herguedas et al. 2013). In addition to the pore-forming subunits, native iGluR protein complexes also contain auxiliary subunits and a wide variety of intracellular

interaction partners (Traynelis et al. [2010](#); Galaz et al. 2015). Auxiliary subunits are defined by four key criteria: (1) they are not an integral component of the transduction pathway, (2) they are stably associated with pore-forming subunits, (3) they affect multiple aspects of receptor pharmacology, function and subcellular trafficking or targeting, (4) their co-assembly is required for proper neuronal functionality of the receptor (Galaz et al. 2015; Howe 2015). In contrast, other interacting proteins are involved in transient and often dynamic interactions with iGluRs and they influence singular aspects of receptor function (e.g. biogenesis, trafficking or synaptic localization; Traynelis et al. [2010](#)). These interactions allow local signaling to proceed, providing the possibility of spatial and temporal specificity to receptor regulation. Functional and immunolocalization studies indicate that segregated populations of iGluRs are localized at diverse subcellular compartments (Henley and Wilkinson 2016).

AMPA receptors (AMPA) mediate fast synaptic transmission in the CNS and they are key components of the modifiable synaptic response. AMPARs are formed by co-assembly of the GluA1-4 channel pore-forming subunits (Fig. [1](#)), each of which can form functional homomeric receptors, although most native AMPARs contain both the GluA2 subunit and either GluA1, GluA3, or GluA4 (Traynelis et al. [2010](#)). All AMPAR subunits exist as two splice variants termed *flip* and *flop*. The alternatively spliced region is in the extracellular loop (S2) adjacent to the last transmembrane domain (M4; Fig. [2a](#)). The *flip* splice variants of GluA1-4 desensitize more slowly and to a lesser extent than the *flop* variants, which can influence the amplitude of the total AMPAR current (Traynelis et al. [2010](#)). The C-terminal domain of AMPAR subunits also undergo alternative splicing to yield short and long forms of the intracellular domain (Traynelis et al. [2010](#)). GluA2 undergoes editing in the M2 channel pore-forming region at the functionally significant Q/R site (Fig. [2a](#)). The GluA2 subunit in the edited form is responsible for the Ca²⁺ impermeability of AMPARs (Henley and Wilkinson 2016).

Auxiliary subunits play a critical role in the regulation of AMPAR function and trafficking. The currently identified auxiliary subunits of AMPARs are: transmembrane AMPAR regulatory proteins (TARPs), suppressor of lurcher (SOL), cornichon homologues (CNIHs), synapse differentiation-induced gene 1 (SynDIG 1), cysteine-knot AMPAR modulating proteins 44 (CKAMP44 or Shisa9), and germ cell-specific gene 1-like (GSG1L) protein (Haering et al. 2014).

AMPA receptors are highly mobile proteins that undergo constitutive and activity-dependent translocation to, and removal from, synapses (Henley and Wilkinson 2016). Increases in synaptic AMPAR function through changes in their number, subunit composition, and/or properties result in the long-term potentiation (LTP) of synaptic efficacy. Conversely, removal of synaptic AMPARs provides a mechanism for long-term depression (LTD) (Huganir and Nicoll 2013). Several functionally important phosphorylation sites have been identified in the C-terminal domains of AMPAR subunits (Traynelis et al. [2010](#); Diering et al. 2016). The effects of these phosphorylation/dephosphorylation events together with protein-protein interactions (e.g., α -actinin, AP2, GRIP, GRIP2, IQGAP1, mLIN-10, NSF, PICK1, PSD95, RIL, SAP97, Shank3, syntenin, 4.1; Traynelis et al. [2010](#)) are crucial in functional changes, localization and trafficking of these receptors so that they can fulfill their roles in synaptic transmission and plasticity (Huganir and Nicholl 2013; Henley and Wilkinson 2016).

Kainate receptors (KARs) are key players in the modulation of neuronal-network activity throughout the CNS (Lerma and Marques 2013). While other iGluRs (AMPA and NMDA receptors) mainly operate at postsynaptic sites, KARs are located at both presynaptic and postsynaptic sites where they modulate neurotransmitter release or mediate excitatory neurotransmission, respectively (Lerma and Marques 2013). KARs are also involved in neuronal differentiation, synaptic plasticity, epileptogenesis, chronic pain, neurodegeneration, neuronal cell death, migraine, schizophrenia, autism, bipolar disorders, mental retardation and periventricular leukomalacia (Lerma and Marques 2013). Some of the functions of KARs involve metabotropic action through coupling with a G-protein,

which does not require an ionotropic action. For instance, KARs regulate neuronal excitability by inhibition of Ca^{2+} -dependent K^+ channels (Lerma and Marques 2013).

Molecular cloning has identified five channel pore-forming KAR subunits, named GluK1-5 (Fig. 1; Traynelis et al. 2010; Lerma and Marques 2013). KAR subunits are subdivided into low-affinity (GluK1-3) and high-affinity (GluK4/5) kainate-binding subunits (Lerma and Marques 2013). Electrophysiological and biochemical analysis of recombinant KARs indicate that functional KAR channels are formed by both homomeric and heteromeric expression of GluK1-3 subunits. In contrast, the GluK4 and GluK5 subunits do not form functional homomeric channels, but they co-assemble with the GluK1-3 subunits (Lerma and Marques 2013). The diversity of KARs is increased by the existence of splice variants for GluK1 (1a-d, 2a-c), GluK2 (a-c), and GluK3 (a,b) subunits (Fig. 1; Traynelis et al. 2010). GluK1 and GluK2 are subject to mRNA editing at the functionally significant Q/R site in the channel pore forming domain (Fig. 2a). Q/R editing of GluK1 and GluK2 subunits reduces Ca^{2+} -permeability of KARs (Traynelis et al. 2010).

Studies with recombinant receptors in cell lines and cultured neurons have started to define rules for the trafficking of KARs to the plasma membrane. The relative level of their surface expression depends on subunit composition, alternative splicing of their C-terminal domains, and editing of the Q/R site in the pore forming M2 domain. Some subunits (GluK2a and GluK3a) contain a forward trafficking motif, whereas others (GluK1a, GluK1b, GluK2b, GluK3b, and GluK5) are retained in the endoplasmic reticulum due to retention signals (Traynelis et al. 2010).

Neuropilin and tolloid-like 1 and 2 (Neto1 and Neto2) were identified as KAR auxiliary subunits that are responsible for the characteristic slow kinetics and high agonist affinity of native KARs (Copits and Swanson 2012). KAR subunits and splice variants show great divergence in their C-terminal cytoplasmic domain, which has been identified as a region of interaction with a number of protein partners (Traynelis et al. 2010). Many KAR-interacting proteins have been identified (e.g., actipilin, calmodulin, CASK, COPI, cortactin, dynamin-1, dynamitin, G- α (q/11), GRIP/GRIP2, NSF, PICK1, profilin, PSD95, SAP97, SAP102, SNAP25, spectrin, SUMO, syntenin, VILIP1/3, 14-3-3). Some of these proteins have been implicated in trafficking, synaptic localization and modulation of the properties of KARs (Traynelis et al. 2010).

NMDA receptors (NMDARs) function as modulators of synaptic response and coincidence detectors (Collingridge et al. 2013). At resting membrane potentials, NMDARs are inactive. This is due to a voltage-dependent block of the channel pore by Mg^{2+} , preventing ion flows through it. Sustained activation of AMPARs by, for instance, a train of impulses arriving at a presynaptic terminal, depolarizes the postsynaptic cell, releasing the channel inhibition and thus allowing NMDAR activation. In addition to Na^+ and K^+ , NMDARs are also permeable to Ca^{2+} . Thus, NMDAR activation leads to a Ca^{2+} influx into the postsynaptic cells, a signal that is instrumental in the activation of a number of signaling cascades. Depending on the pattern of synaptic plasticity, NMDARs are responsible for a wide range of postsynaptic functions, including LTP and LTD (Collingridge et al. 2013). While the physiological significance remains to be determined, recent studies suggested a non-ionotropic signaling role for NMDARs, which is based on agonist-induced conformational changes in the receptor, independently of channel opening (Gray et al. 2016). Excessive activation of NMDARs leads to pathological processes (e.g., excitotoxic injury) in a number of acute and chronic neurological disorders (Miladinovic et al. 2015).

NMDARs are obligate heterotetramers formed from assemblies of GluN1 with GluN2A-D and GluN3A/B channel pore-forming subunits (Fig. 1). In addition, GluN3A can assemble with GluN1 (without other GluN2 subunits) to form excitatory, Ca^{2+} -impermeant glycine receptors. Eight possible variations of the GluN1 subunit arise by alternative splicing of a single gene transcript. The insertion of one splice cassette at the N-terminal region of GluN1 and the deletion of two independent consecutive splice variants at the C terminus have been identified (Sanz-Clemente et al. 2013). Therefore, a large number of different NMDARs with differing functional and pharmacological

properties exist in different parts of the brain or at different stages in development (Molnár [2008](#)). Unusually for the iGluR, L-glutamate is not the only agonist for the NMDAR. Glycine, another amino acid, is a co-agonist and both transmitters must bind in order for the receptor to function. The binding sites for glutamate and glycine are found on different subunits – glycine binds to the GluN1 subunit while glutamate binds to the GluN2 subunit. This is one reason why both subunit types are required to generate a fully functioning receptor. The GluN2B subunit also possesses a binding site for polyamines, regulatory molecules that modulate the functioning of NMDARs (Collingridge et al. 2013).

While previous studies raised the possibility that Neto1 and/or amyloid precursor protein (APP) are auxiliary subunits of NMDARs, further studies are necessary to confirm or discard these findings (Galaz et al. 2015). Like other iGluRs, NMDARs also interact with a wide range of cytoskeletal, scaffolding and signaling proteins (e.g., α -actin-2, AP2, calmodulin, CaMKII, CARPI, COPII, GPS2, LIN7, LIN10, MAP1S, PACSIN1, plectin, PSD95, RACK1, SALM1, SAP97, SAP102, S-SCAM; Traynelis et al. [2010](#); Collingridge et al. 2013).

δ receptors (GluD1 and GluD2) share 17-28% amino acid sequence identity with other iGluR subfamilies. Despite structural similarities and the presence of amino acid residues critical to ligand binding and Ca^{2+} permeability, GluD subunits do not function as conventional glutamate-gated ion channels. However, recent studies suggest that postsynaptic GluD subunits form a molecular bridge with presynaptic β -neurexin 1 via Cbln1 (a C1q-like synaptic organizer) and they are involved in higher brain functions through controlling synaptic connectivity and plasticity (Elegheert et al. 2016).

Metabotropic Glutamate Receptors

mGluRs are members of class C G-protein coupled receptor family and they play important roles in regulating the activity of many synapses in the CNS (Niswender and Conn [2010](#)). These receptors activate a multitude of signaling pathways; therefore, they are involved in a wide number of physiological and pathological processes: modulation of slow excitatory and inhibitory responses; the regulation of Ca^{2+} , K^+ , and nonselective cation channels; the inhibition and facilitation of transmitter release; the induction of LTP/LTD; the formation of various types of memory; the regulation of iGluR trafficking; modification of AMPAR-, NMDAR- and KAR-mediated synaptic transmission; the regulation of neuronal development; and signaling between neurons and glial cells (Gladding et al. [2009](#); Niswender and Conn [2010](#)). mGluRs are also implicated in various diseases such as epilepsy, anxiety and stress disorders, depression, schizophrenia, fragile X mental retardation, autism, Parkinson's disease, chronic pain, drug addiction, hypoxic brain damage, and excitotoxic neuronal death (Nicoletti et al. [2011](#); Golubeva et al. 2015).

The seven transmembrane-domain proteins mGluRs (Fig. [3](#)) are coupled to heterotrimeric GTP-binding proteins which link the receptors to downstream signaling pathways (Niswender and Conn [2010](#); Nicoletti et al. [2011](#)). The family of mGluRs comprises eight different subtypes (mGlu1-8 receptors; Fig. [1](#)) classified into three groups on the basis of sequence similarities, pharmacological properties, and intracellular signal transduction mechanisms (Niswender and Conn [2010](#)). Group I includes mGlu1 and mGlu5 receptors, which couple to G_q and activate signaling cascades involving phospholipase C (PLC), inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). In group II (mGlu2, mGlu3) and group III (mGlu4, mGlu6, mGlu7, and mGlu8) receptors couple to G_i/G_o and inhibit adenylyl cyclase (AC) (Niswender and Conn [2010](#)). Many of these receptors (mGlu1, mGlu3, mGlu5-8) exist as various isoforms with different intracellular C-termini generated by alternative splicing (Fig. [1](#); Niswender and Conn [2010](#)). The large N-terminal domain of the mGluRs contains the ligand-binding site, which is formed by two-hinged globular domains – the so-called Venus fly trap domain (Fig. [3a](#), b; Nicoletti et al. [2011](#); Rondard and Pin 2015). Binding of glutamate causes the two domains to close, providing the structural change in the transmembrane domains that

triggers intracellular G-protein activation. mGluRs form dimers stabilized by an inter-subunit disulfide bond (Fig. 3b). Only mGluR subtypes coupled to the same G-protein can form heterodimers (Nicoletti et al. 2011). The binding of a single agonist per dimer is sufficient for receptor activation (Nicoletti et al. 2011). mGluRs are expressed by neurons and glia, where they locate in the proximity of the synaptic cleft. In neurons, mGlu1/5 are mostly localized postsynaptically, mGlu4/7/8 at the presynapse, while mGlu2/3 do not show any preference. mGlu6 is only expressed in retinal bipolar cells postsynaptic to photoreceptors (Niswender and Conn 2010). Proteins interacting with mGluRs include: 4.1 G, adenosine receptor A1, Ca_v2.1, Ca²⁺-sensing receptor, calmodulin, caveolin-1/-2β, GABA_{B1} receptor, filamin-A, G-protein βγ, GRIP, GRK2, homer, optineurin, pias1, PICK1, PKA, PKC, PP1γ1, PP2α, siah-1A, syntenin, tamalin, α/β-tubulin (Niswender and Conn 2010).

Anti-GluR autoantibodies are present in a range of CNS disorders. A wide range of anti-GluR antibodies have been found in several different neurological and autoimmune diseases and they are much more prevalent than previously thought. Several studies have identified autoantibodies to GluA3, GluN1, GluN2A/B, mGlu1 and mGlu5 GluR proteins (reviewed in Levite 2014). The presence of these anti-GluR antibodies has been linked to neurological and psychiatric disorders, including epilepsy, encephalitis and stroke (Levite 2014). There is evidence that these autoimmune anti-GluR antibodies can bind to neurons in specific brain regions, activate GluRs, kill neurons by excitotoxicity and/or by complement-dependent mechanism (Levite 2014).

Summary

Glutamate is the most important excitatory neurotransmitter in the CNS, producing a wide range of synaptic responses through the activation of a mixed population of GluRs. While iGluRs are responsible for fast synaptic transmission, mGluRs modulate slow synaptic transmission through intracellular second messengers. Both iGluRs and mGluRs are critically important signaling molecules for normal brain function. They transduce the vast majority of excitatory neurotransmission and regulate the strength of both excitatory and inhibitory transmission in the CNS via complex interactions. Glutamatergic systems are dysfunctional in most neuropathologies, and aberrant receptor function appears to have causative roles in many neurological disorders. In addition to neurons, iGluRs and mGluRs have been identified in nonneuronal cells where they are involved in a broad range of signaling processes (Du et al. 2016). The full functional significance of these nonneuronal GluRs remains to be established. A confound in the study of GluRs has been the lack of congruence between the properties of recombinant receptors expressed in heterologous systems and those of native receptors studied in the brain tissue. This mismatch suggests that heterologously expressed receptors lack modulatory components that can influence essential properties. The discovery of auxiliary subunits for iGluRs (e.g., TARPS, Neto1/2; Galaz et al. 2015), dimerization of mGluRs (Rondard and Pin 2015), various interaction partners, phosphorylation/dephosphorylation and other covalent modifications of GluRs (Niswender and Conn 2010; Traynelis et al. 2010) has started to provide answers for many of these discrepancies. A better understanding of the specific functions and molecular interactions of native GluR subtypes and the development of more subtype/subunit-specific pharmacological tools are needed for future breakthroughs in the treatment of several neurological and psychiatric disorders.

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Figure legends

Glutamate Receptors, Fig. 1. IUPHAR recommended nomenclature, classification and sequence homology dendrograms of iGluR and mGluR proteins. The known splice variants and main signaling mechanisms are indicated next to the code name of the GluR proteins.

Glutamate Receptors, Fig. 2. (a) Schematic representation of iGluR subunit membrane topology. iGluR subunits composed of two extracellular domains: the N-terminal domain (NTD) and the ligand-binding domain (LBD) formed by the S1 and S2 segments. Unlike other ligand-gated ion channels (e.g., nicotinic acetylcholine receptors, GABA_A receptors), iGluRs contain three transmembrane domains (M1, M3, and M4). A membrane re-entrant loop (M2) forms the pore of the channel in iGluRs and contains the Q/R editing site in GluA2, GluK1, and GluK2 subunits. The intracellular C-terminal domain (CTD) contains phosphorylation sites and binds to intracellular proteins. See text for details. Schematic image was provided by Dr. Andrew Doherty. (b) Assembled iGluR subunits have an overall twofold symmetry perpendicular to the membrane plane; the extracellular N-terminal domains (NTDs) and ligand-binding domains (LBDs) are organized as dimers of dimmers, and the ion channel forming membrane-associated domains (M1-4) exhibit a fourfold symmetry (Sobolevsky et al. [2009](#)).

Glutamate Receptors, Fig. 3. Schematic representation of mGluR membrane topology (a) and diagram of the mGluR dimer (b). mGluRs contain large extracellular domains called the Venus flytrap domains (VFDs), which bind L-glutamate and other ligands. The cysteine-rich domain (CRD) links the VFD to the seven transmembrane domains (M1-7). The intracellular C-terminal domain (CTD) is often subject to alternative splicing to generate different C-terminal tails. The open state of the VFD is the inactive state and can be stabilized by antagonists. Schematic images were provided by Dr. Andrew Doherty.

Fig. 1.

Fig. 2.

Fig. 3.