The Journal of Physiology

TOPICAL REVIEW

Structure and gating of tetrameric glutamate receptors

Alexander I. Sobolevsky

Department of Biochemistry & Molecular Biophysics, Columbia University, 650 West 168th Street, Black Bldg. 513, New York, NY 10032, USA

Abstract Ionotropic glutamate receptors (iGluRs) are ligand-gated ion channels that open their ion-conducting pores in response to the binding of agonist glutamate. In recent years, significant progress has been achieved in studies of iGluRs by determining numerous structures of isolated water-soluble ligand-binding and amino-terminal domains, as well as solving the first crystal structure of the full-length AMPA receptor in the closed, antagonist-bound state. These structural data combined with electrophysiological and fluorescence recordings, biochemical experiments, mutagenesis and molecular dynamics simulations have greatly improved our understanding of iGluR assembly, activation and desensitization processes. This article reviews the recent structural and functional advances in the iGluR field and summarizes them in a simplified model of full-length iGluR gating.

Introduction Ionotropic glutamate receptors (iGluRs) are ligand-gated ion channels that mediate the majority of excitatory neurotransmission in the central nervous system (Traynelis et al. 2010). iGluRs are implicated in nearly all aspects of nervous system development and function, and their dysfunction is associated with devastating chronic neurodegenerative conditions such as Alzheimer’s and Parkinson’s diseases, psychiatric disorders such as schizophrenia and depression and acute disorders such as brain trauma and stroke (Bowie, 2008; Traynelis et al. 2010; Paoletti et al. 2013). The iGluR family includes three major subtypes: AMPA, kainate (KA) and NMDA receptors. Each subtype is represented by several subunits including GluA1–4 for AMPA receptors, GluK1–5 for KA receptors and GluN1, GluN2A–D and GluN3A–B for NMDA receptors. Although iGluR subtypes exhibit diverse kinetic and pharmacological properties and play disparate roles in cognition, they share common structural features.

iGluRs function as assemblies of four subunits. Whereas the majority of iGluRs in the nervous system are heterotetramers composed of at least two types of subunits, AMPA and select KA subunits can form functional homotetramers. Each iGluR subunit has a modular design (Fig. 1A) and includes a large extracellular amino-terminal domain (ATD) that plays a fundamental...
role in subtype-specific receptor assembly, trafficking and modulation; a ligand-binding domain (LBD) responsible for agonist/antagonist recognition; a transmembrane domain (TMD) that forms the membrane-spanning ion channel; and a cytoplasmic C-terminal domain (CTD) involved in synaptic localization, trafficking, mobility and receptor regulation. Structural information on iGluRs is limited to high resolution crystal structures of genetically excised, water-soluble ATDs (Furukawa, 2012) and LBDs (Gouaux, 2004) as well as the first 3.6 Å resolution crystal structure of the full-length AMPA receptor in the closed, antagonist bound state (Sobolevsky et al. 2009). This review discusses recent advances in the iGluR field and summarizes them in the context of the full-length receptor. Many important questions related to structure, function and assembly of iGluRs remain beyond the scope of this review but have been nicely reviewed elsewhere (Bowie, 2010; Jackson & Nicoll, 2011; Ogden & Traynelis, 2011; Paoletti, 2011; Paoletti, 2011; Lu & Roche, 2012; Popescu, 2012; Herguedas et al. 2013; Kumar & Mayer, 2013).

**Structure**

The structure of the full-length AMPA receptor is shaped like the capital letter ‘Y’ with layered arrangement of domains: ATDs at the top, LBDs in the middle and TMDs at the bottom (Fig. 1B). TMDs of all four subunits assemble together to form a single ion channel. Interfaces between TMDs are the largest interfaces in the structure (~2800 Å² per subunit), suggesting strong contribution of the ion channel to the tetrameric stability of iGluR subunit assembly. Supporting this view, mutations at the TMD interfaces disrupt proper oligomerization of iGluR subunits (Salussolia et al. 2013) or produce drastic changes in the functional characteristics of the iGluR channel, such as single-channel conductance, allosteric modulation, alcohol sensitivity, Ca²⁺ permeability and ion channel block (Siegler Retchless et al. 2012; Lopez et al. 2013; Ren et al. 2013). ATDs and LBDs form two pairs of dimers each. The intradimer interfaces for ATD (~1300 Å² per dimer) and LBD (~900 Å² per dimer) are the next largest after the TMD interfaces and conclude the

![Figure 1. Structure of iGluR](image)

*Figure 1. Structure of iGluR*

*A, topology of iGluR subunit. B, structure of AMPA subtype rat GluA2 receptor in the closed antagonist bound state (3KG2). The four subunits (A to D) are coloured differently. The antagonist ZK 200775 molecules are shown as space-filling models. Strong and weak interfaces are shown as large and small ovals, respectively. C, model of the assembly of four three-compartmental sausages with strong interactions holding together (1) all four bottom compartments, (2) left and right pairs of the top compartments and (3) front and back pairs of the middle compartments. D, LBD-TMD linkers – the iGluR gating transmission domain – include S1–M1, M3–S2 and S2–M4, of which S1–M1 and S2–M4 are shown transparent. The M3–S2 linkers, the central element of the gating machinery, have different conformations and secondary structures for the two diagonal pairs of subunits, A/C and B/D.*
list of interfaces that mediate strong interactions between iGluR subunits.

The four iGluR subunits (A to D) form two conformationally distinct but chemically identical diagonal pairs (A/C and B/D) that underlie two fundamental properties of iGluR subunit assembly. First, they allow functionally important transformation of the fourfold rotational symmetry of the ion channel to the twofold rotational symmetry of the extracellular domains. The overall twofold rotational symmetry of the tetrameric iGluR is exceptional; generally, ion channels with \( n \) subunits per oligomer have \( n \)-fold rotational symmetry (Supplemental Fig. 1). Second, the conformationally different pairs of iGluR subunits underlie swapping of domains between dimers of ATD (AB and CD) and LBD (AD and BC). With domain swapping, the available number of strong intersubunit interactions is sufficient to keep the four iGluR subunits together (Fig. 1C). Such an assembly allows exceptional conformational flexibility, consistent with versatile physiological functions and regulation of iGluRs. In certain conditions, this flexibility might even be higher because of possible breakage of LBD intradimer interfaces leading to separation of LBDs (Schauder et al. 2013).

Several smaller interfaces also contribute to the stability of iGluR tetrameric assembly, possibly limiting its conformational flexibility: intrasubunit ATD–LBD interfaces in subunits A and C (\( \sim 300 \text{ Å}^2 \) per subunit) as well as interdimer interfaces between ATD dimers AB and CD (\( \sim 330 \text{ Å}^2 \)) and between LBD dimers AD and BC (\( \sim 220 \text{ Å}^2 \)). The intrasubunit ATD–LBD interfaces help maintain the upright orientation of these domains relative to one another, while the interdimer interfaces prevent ATD and LBD dimers from separating. Whether these dimers can separate from each other in other iGluR subtypes or gating conformations remains controversial. While one of the earlier electron microscopy (EM) studies proposed separation of ATD dimers during desensitization (Nakagawa et al. 2005), other EM studies (Midgitt et al. 2012; Schauder et al. 2013) and crystallographic data (Clayton et al. 2009; Jin et al. 2009; Kumar et al. 2009, 2011; Kumar & Mayer, 2010) argue for the stability of the ATD dimer–dimer interface. On the other hand, several reported iGluR conformations have the LBD dimer–dimer interface either apparently modified (Lau et al. 2013) or absent (Midgitt et al. 2012; Schauder et al. 2013).

**Gating**

The term ‘gating’ refers to a series of conformational changes in iGluR protein that relate the binding/unbinding of ligands to the opening/closure of the ion channel. Whole-cell currents in response to application of agonist glutamate reveal three apparent gating processes – activation, desensitization and deactivation (Fig. 2A) – that convert iGluR from closed to open, open to desensitized and open/desensitized to closed states (or gating conformations), respectively. Although detailed kinetic analysis of whole-cell and single-channel currents resolves many more gating conformations and the transitions between them (Popescu & Auerbach, 2003; Robert & Howe, 2003; Vance et al. 2013), the corresponding structural data remain limited.

**Gating initiation domain: LBD – activation.** iGluR activation begins with the binding of agonist glutamate to the clamshell-shaped gating initiation domain LBD. The LBD is formed by two stretches of polypeptide, S1, located between ATD and the first transmembrane domain M1, and S2, located between the transmembrane domains...
M3 and M4 (Fig. 1A). A construct of isolated S1 and S2 connected by a glycine–threonine linker (S1S2 construct) can be expressed in bacteria and folds into a bilobe structure of the ‘clamshell’ with the upper lobe D1 and lower lobe D2 (Armstrong & Gouaux, 2000). Since this soluble S1S2 construct is capable of binding different iGluR ligands and can be studied using X-ray crystallography and NMR, it has become a model system for understanding LBD structure–function relationships. Despite the power of this divide-and-conquer approach, the results of experiments with S1S2 should be interpreted with caution because LBD conformation in the context of the full-length receptor might be influenced significantly by other domains (Lau & Roux, 2011; Ylilauri & Pentikainen, 2012; Hansen et al. 2013).

Unliganded (apo) or antagonist bound structures of S1S2 – models of the LBD in the iGluR closed state – typically adopt the maximally open clamshell conformation (Fig. 2B). In contrast, S1S2 structures in complex with full agonists – models of LBD in the iGluR open state – often have the maximally closed clamshell conformation where D2 undergoes ~25°-rotation towards D1 (Fig. 2C). Partial agonists, ligands that have only partial efficacy in eliciting iGluR currents compared to full agonists, often induce intermediate clamshell conformations, as shown in both AMPA (Jin et al. 2003) and KA (Mayer, 2005; Nayeem et al. 2011) receptors. Comparison of different GluA2 AMPA receptor S1S2 crystal structures resulted in one of the earliest structural hypotheses of activation, namely that the agonist-induced LBD clamshell closure leads to opening of the ion channel and that the degree of clamshell closure is proportional to the extent of iGluR activation (Armstrong & Gouaux, 2000). The back-to-back dimer arrangement of LBDs held together by the D1–D1 interface, first discovered in the S1S2 crystal structures and later recapitulated in the full-length GluA2 structure, elegantly explained how the closure of individual clamshells can cause separation of the D2 lobes, in turn leading to opening of the ion channel (Fig. 2B and C, Supplemental Movie 1).

Since the first published model of LBD (Armstrong et al. 1998), numerous S1S2 structures, apo (unliganded) or bound to different ligands, have become available, covering the whole spectrum of clamshell conformations from maximally open to maximally closed. The increasing number of available S1S2 structures has made it obvious that, in contradiction to the original hypothesis (Armstrong & Gouaux, 2000), a single ligand can produce structures of isolated LBD with different clamshell closures (Maltsev et al. 2008; Poon et al. 2011), while ligands producing different functional effects can induce identical clamshell closures (Inanobe et al. 2005; Ahmed et al. 2011; Poon et al. 2011; Hansen et al. 2013). Moreover, a rich diversity of LBD conformations, of which only a small portion is represented by the S1S2 crystal structures and consistent with the original hypothesis, have been revealed by studies using NMR (Fenwick & Oswald, 2010; Ahmed et al. 2013), single-molecule fluorescence resonance energy transfer (FRET; Landes et al. 2011; Ramaswamy et al. 2012), solution X-ray scattering (Madden et al. 2005), chemical crosslinking (Plested & Mayer, 2009) and molecular dynamics simulations (Lau & Roux, 2007, 2011; Postila et al. 2011; Ylilauri & Pentikainen, 2012; Yao et al. 2013).

The complicated structural dynamics of LBD can in part be reconciled by dividing the activation process into multiple steps, including binding of a ligand, LBD clamshell closure and formation of hydrogen bonds across the lobe interface (Ahmed et al. 2013). Only a weak correlation has been established between the free energy associated with LBD closure and the extent of LBD closure observed in crystal structures of GluA2, suggesting that the extent of closure, by itself, cannot account for the free energy associated with the protein’s conformational transition (Lau & Roux, 2011). Rather, the extent of iGluR activation depends on the probability of the LBD clamshell to occupy its maximally closed conformation (Zhang et al. 2008; Ahmed et al. 2011; Landes et al. 2011; Lau & Roux, 2011; Maclean et al. 2011). According to this new view, the efficacy of a ligand to activate iGluR depends on its ability to stabilize the maximally closed LBD clamshell conformation. Additional tuning of iGluR activation might occur via effects of agonists on the LBD dimer interface (Nayeem et al. 2011).

While the principle activation mechanism is likely to be shared across all iGluRs, some features are certainly subtype specific. A striking example is NMDA receptors that typically have a single conductance level and concerted contribution of subunits to channel opening (Banke & Traynelis, 2003; Kussius & Popescu, 2009) versus non-NMDA receptors that demonstrate multiple single-channel conductances contributed by individual subunits (Rosenmund et al. 1998; Smith & Howe, 2000; Jin et al. 2003; Poon et al. 2010, 2011; Prieto & Wollmuth, 2010). Computed conformational free energy landscapes suggested that agonists of NMDA receptors bind via a conformational selection mechanism, while agonists of AMPA receptors bind via an induced-fit mechanism (Yao et al. 2013). The structural bases underlying differences between NMDA and non-NMDA receptors are not yet understood, but might involve ATD–LBD interdomain interactions (Hansen et al. 2013).

Gating initiation domain: LBD – desensitization. Desensitization – a gating process that is typically slower than activation – leads to closure of the ion channel pore and appears as a reduction of iGluR-mediated currents in the continuous presence of glutamate (Fig. 2A). Desensitization represents a natural way of suppressing
iGluR activity to protect neurons from the excessive entry of excitotoxic calcium. Similar to activation, crystal structures of S1S2 have played a crucial role in developing current models of desensitization. In AMPA receptors, allosteric modulators, such as cyclothiazide, aniracetam and CX614, attenuate or block desensitization, presumably by binding at and stabilizing the LBD intradimer interface (Sun et al. 2002; Jin et al. 2005). Similarly, covalent crosslinks or single point mutations strengthening/perturbing the LBD intradimer interface in AMPA (Sun et al. 2002) or KA (Weston et al. 2006; Nayeem et al. 2009) receptors reduce/enhance desensitization, respectively. It has been concluded that desensitization occurs through a rearrangement of the dimer interface that disengages the agonist-induced conformational change in the LBD from the ion channel gate (Sun et al. 2002).

Experiments on crosslinking the D2 lobes of GluA2 S1S2 via the S729C substituted cysteines further examined the decoupling of agonist binding from ion channel gating (Armstrong et al. 2006). In the crosslinked S1S2, the individual clamshells maintain their maximally closed conformation, similar to the open state, while the D1 lobes undergo significant separation (Fig. 2D). According to this model, desensitization leads to rupture of the D1–D1 interface, which allows the D2 lobes and the linkers to the ion channel to adopt a closed state-like conformation (Supplemental Movie 2).

Rupture of the D1–D1 interface during desensitization is consistent with luminescence resonance energy transfer measurements in AMPA (Gonzalez et al. 2010) and NMDA receptors (Rambhadran et al. 2010). In KA receptors, the stability of the LBD dimer interface depends on the occupancy of the ion binding sites it harbours (Plested & Mayer, 2007; Plested et al. 2008; Nayeem et al. 2009; Veran et al. 2012; Dawe et al. 2013). A complete rupture of the intradimer interface and separation of LBDs during desensitization was proposed for GluK2 KA receptors (Schauder et al. 2013).

On the other hand, GluN1–GluN2A NMDA receptors with the crosslinked upper D1 lobes had intact desensitization but their activation was deeply impaired: their open probabilities were lowered 200-fold due to increased barriers to activation and unstable open states (Borschel et al. 2011). In KA receptors, covalent crosslinking of the dimer interface prevented access to the main open state but permitted lower conductance states, suggesting that significant rearrangements of the dimer interface are also required for activation (Daniels et al. 2013). Mutations of non-conserved residues in the D2 lobe of GluA2 distal from the intradimer interface conferred slow recovery from desensitization on AMPA receptors (Carbone & Plested, 2012). One of these mutations, E713T, increased the stability of the isolated S1S2 measured by thermal unfolding (Ahmed et al. 2013), possibly due to altered interaction between hydrophobic elements of D2 that might affect both AMPA receptor desensitization and activation.

Given the above examples of seemingly conflicting results, the LBD dimer interface may have adapted to fulfill different tasks as distinct iGluR subtypes emerged during evolution (Daniels et al. 2013). It is clear that more structural and functional work is required to fully understand the role of LBD in iGluR gating.

**Gating effector domain: ion channel.** The ion channel – the iGluR gating effector domain – has only been characterized structurally within the context of the full-length GluA2 receptor (Fig. 1B). The TMD of each iGluR subunit contributes three transmembrane helices M1, M3 and M4 and a reentrant loop M2 containing a C-terminal helical region and an N-terminal extended region that lines the ion channel pore (Fig. 3A). A short pre-M1 helix oriented nearly parallel to the membrane acts as a cuff around the extracellular portion of the ion channel.

---

**Figure 3. Ion channel**

A, GluA2 ion channel (3KG2) viewed parallel to membrane. The subunits are coloured similarly to Fig. 1B. The transmembrane segments M1 to M4 and the calf helix pre-M1 are labelled. B, superposition of the GluA2 channel (3KG2, cyan) and KcsA (1BL8, orange). C, GluA2 channel viewed from the extracellular side of membrane. The diagonal pairs of subunits, A/C and B/D, are shown in light green and purple, respectively. Molecule surface representation emphasizes that the channel is in the closed conformation. D, Shaker K+ channel in the open state (2A79) viewed from the intracellular side of membrane. Colouring of subunits is similar to the GluA2 channel in C. Comparing the structures of the closed GluA2 channel in C and the open Shaker channel in D, one can imagine how transmembrane helices of iGluR can bend and splay away from the central axis of the channel, mimicking the iris-like opening of K+ channels.
and serves as a binding site for non-competitive inhibitors (Balannik et al. 2005) and allosteric regulators (Ogden & Traynelis, 2013). Since GluA2 was crystallized in the presence of competitive antagonist ZK, the ion channel is in an apparently closed conformation (Fig. 3C). The narrowest portion of the pore is formed by the bundle crossing of M3 helices. This region bears high structural homology to the corresponding region in K⁺ channels (Fig. 3B) and similarly was proposed to serve as an activation gate (Chang and Kuo, 2008; Moore et al. 2013). Whether the extended portion of M2, which defines iGluR permeation and channel block but is apparently disordered in the GluA2 structure, also contributes to the activation gate (Sobolevsky et al. 2002) remains uncertain.

The structure of the iGluR channel in the open state is not yet available. During activation, a significant portion of the channel may transition from fourfold symmetry to twofold symmetry (Sobolevsky et al. 2004) but the overall character of conformational changes will likely follow the iris-type opening in structurally homologous K⁺ channels (cf. Fig. 3C and D). There is no structure of the iGluR channel in the desensitized state either, but its non-conducting conformation is expected to be similar to the closed state.

Gating transmission domain: LBD–TMD linkers. The LBD–TMD linkers – the iGluR gating transmission domain – include three types of polypeptides, S1–M1, M3–S2 and S2–M4 (Fig. 1D), that convert ligand-induced conformational changes in LBD to opening/closure of the ion channel. Since these linkers also convert twofold rotational symmetry of the extracellular domain to fourfold rotational symmetry of the ion channel, one diagonal pair of each linker type differs significantly from the second diagonal pair. This is especially evident for the M3–S2 linkers, which not only have different conformations, but also distinct secondary structures; the M3 helices of subunits A and C are 4 residues (one α-helical turn) longer than those of subunits B and D. The three linker types all play an important role in gating, and restraining their movement results in impaired iGluR function (Yelshansky et al. 2004; Talukder et al. 2011; Talukder & Wollmuth, 2011; Kazi et al. 2013). The LBD–TMD linkers also form the entry portals for the permeant ions, and their amino acid composition affects the binding sites and permeation of Ca²⁺ through the channel pore (Watanabe et al. 2002; Dai & Zhou, 2013).

Gating modulatory domain: ATD. The ATD – the iGluR gating modulatory domain – plays an important role in the allosteric modulation of NMDA receptors. Allosteric modulators that interact with NMDA receptors include polyamines and GluN2-specific agents like ifenprodil and Zn²⁺ (Mony et al. 2009; Furukawa, 2012). Recent advances in crystallization of NMDA receptor ATDs successfully identified binding sites for Zn²⁺ inside the clamshell cleft of GluN2B (Karakas et al. 2009) and for ifenprodil and related compounds at the GluN1–GluN2B interface (Karakas et al. 2011). Both GluN1 and GluN2 ATDs are mobile regulatory domains and are dynamically involved...
in NMDA receptor allosteric modulation (Gielen et al. 2009; Yuan et al. 2009; Zhu et al. 2013). Allosteric modulators acting at non-NMDA ATDs have not yet been identified. In fact, extensive interfaces between the upper and lower lobes of ATD dimers typically observed in crystal structures of isolated AMPA (Jin et al. 2009) and KA (Kumar et al. 2009; Kumar & Mayer, 2010) receptor ATDs essentially immobilize individual ATD clamshells. Nevertheless, the somewhat different clamshell conformations observed in GluA3 ATD crystal structures, the normal mode analysis and electron density detected in the interlobe cleft of a high resolution crystal structure of GluA2 ATD (Sukumaran et al. 2011) argue for a possibility that such modulators might be identified in the future.

The transmission of allosteric modulatory signals from ATD to LBD must occur through the ATD–LBD linkers and ATD–LBD interfaces. Perhaps, the latter ones play a more important role in AMPA receptors, as a six-residue deletion in the ATD–LBD linker did not produce appreciable changes in GluA2 structure and function (Sobolevsky et al. 2009). Given the significantly different conformations and dynamic properties of ATDs in NMDA and non-NMDA receptors (Furukawa, 2012), the structure and role of ATD–LBD linkers and interfaces in ATD–LBD communication might be strongly subtype specific. Structural mechanisms that transmit allosteric modulation from ATD to the ion channel have yet to be identified for any iGluR subtype. Further structural and functional experiments are needed to solve this puzzle.

**Model of full-length iGluR gating**

In summary, a simplified model of iGluR gating at the level of the full-length receptor (Fig. 4) can be constructed based on the following assumptions: (1) the closed state is represented by the antagonist-bound structure of the full-length GluA2; (2) in the open and desensitized states, the LBD has conformations of glutamate-bound S1S2 with and without the S729C mutation, respectively; (3) the ATD dimer of dimers does not change conformation and stays the same in all three conformational states; and (4) in the desensitized state, the ion channel has a conformation identical to the closed state, but has a Shaker-like conformation in the open state. According to this model, the full-length iGluR undergoes twisting and shortening upon activation and untwisting and elongation during desensitization (Supplemental Movie 3).

While this model almost certainly represents an over-simplification of reality, it can nevertheless serve as a guide for deriving experimentally testable hypotheses. Further development of the model in terms of energetic feasibility will require molecular modelling. Molecular modelling studies have already made a number of important predictions including vertical movement of TMDs during gating in AMPA receptors (Dong & Zhou, 2011) and a stronger contribution of GluN2 compared to GluN1 to NMDA receptor gating (Dai & Zhou, 2013). They have also identified molecular determinants of the toxin binding site in Ca\(^{2+}\)-permeable AMPA receptors and the mechanism of toxin trapping in the channel (Barygin et al. 2011), distinguished five groups of residues in AMPA receptors that regulate glutamate binding affinity (Su et al. 2013) and revealed the structure of the extracellular Ca\(^{2+}\) binding site that contributes to high Ca\(^{2+}\) permeability of NMDA receptor channels (Dai & Zhou, 2013). Model-predicted conformational dynamics can be tested experimentally using various structural and functional approaches including electrophysiology, X-ray crystallography, NMR, site-directed mutagenesis and FRET. Future modifications and corrections to this oversimplified model will allow us to gain a more nuanced understanding of the iGluR gating mechanism.

**Conclusions**

Based on structural and functional work of the last two decades, a fuzzy picture of iGluR gating in the full-length receptor begins to appear. There are still more questions than answers; for example: What do full-length structures of NMDA and KA receptors look like? What is the arrangement of subunits in heteromeric iGluRs? What do structures in activation states other than the closed state look like? What is the structural mechanism of iGluR assembly? Are there allosteric regulators acting at the ATD domains of non-NMDA receptors? What are the structural mechanisms of iGluR interaction with auxiliary subunits? What is the structural origin of sub-conductance states? We are entering an exciting era of deciphering the fundamental structural principles of iGluR function. Better understanding of these principles will aid the development of new drug design strategies for the treatment of numerous neurological diseases.

**References**


Talukder I & Wollmuth LP (2011). Local constraints in either the GluN1 or GluN2 subunit equally impair NMDA receptor pore opening. J Gen Physiol 138, 179–194.


Additional information

Competing interests

None declared.

Funding

A.I.S. was supported by the Klingenstein Fellowship Award in the Neurosciences and by National Institutes of Health grant NS083660.

Acknowledgements

The author thanks Eric Green, Maria Yelshansky and Kei Saotome for valuable comments on the manuscript. Structural illustrations were made using the PyMOL Molecular Graphics System (Schrodinger, LLC).