Spine-Tingling Excitement from Glutamate Receptors

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(Published 25 November 2003)

AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid), kainate, and NMDA (*N*-methyl-D-aspartate) receptors are ligand-gated ion channels that mediate synaptic transmission throughout the central nervous system. Countless papers on excitatory amino acid receptors begin with this theme; however, there is a growing realization that these receptors can do more than just open their built-in channels. Fresh evidence for atypical signaling by glutamate receptors comes from two recent papers. One paper, from Lerma's group (*1*), adds to the evidence for metabotropic signaling by ionotropic kainate receptors. A second paper, from Sheng's lab (*2*), identifies a role for the GluR2 subunit of AMPA receptors in the formation of dendritic spines, the short appendages on neuronal dendrites that receive excitatory synaptic connections. Ever since their discovery by Ramón y Cajal more than 100 years ago, spines have captured the imagination of neuroscientists. Although their function has been debated over the years, it is now generally believed that spines represent a biochemical compartment (*3, 4*) that is distinct from the parent dendrite and is crucial for regulation of the strength of excitatory inputs—a process critical to memory formation. Not all excitatory synapses occur on spines, and there are a number of neuronal cell types, including many inhibitory interneurons, that are entirely devoid of spines (*5*).

Working with cultured hippocampal neurons, the Sheng lab showed (*2*) that overexpression of the GluR2 subunit enhanced spine size and number on presumptive excitatory neurons and, most surprisingly, stimulated the production of spines on a population of inhibitory neurons, which normally lack them in culture. GluR2 is one of four related subunits that can constitute AMPA receptors (*6*). As noted above, AMPA receptors are ion channels that bind glutamate released from the presynaptic terminal and provide a pathway for ion entry, thereby depolarizing the postsynaptic cell. Each of the four subunits of AMPA receptors contains a binding site for glutamate and a portion of the ion pore. Functional AMPA receptor channels are thought to require four of these subunits (*7*), arranged as either a homomeric or a heteromeric tetramer.

GluR2 is notable among AMPA receptor subunits because of its role in regulating the ion selectivity of the channel pore (*8*). All AMPA receptors conduct monovalent sodium and potassium ions. AMPA receptors that lack GluR2 also display high permeability to calcium ions, whereas receptors that include one or more GluR2 subunits are much less permeable to calcium (*9, 10*). This control of selectivity depends on a single amino acid substitution within the channel pore (*8*). The GluR2 subunit includes a positively charged arginine at this location, whereas the other three subunits contain a glutamine residue. Mutation of GluR2 to impose a glutamine residue at this site, which prevented its inhibition of calcium permeation, did not alter its enhancement of spines (*2*), which suggests that the signaling that underlies spine formation does not depend on the ion selectivity of the channel.

Prior work (*11*) suggests that long-term spine maintenance depends on activation of AMPA receptors by agonist. Chronic blockade of AMPA receptors with competitive antagonists, or presynaptic blockade of transmitter release with botulinum toxin, reduces spine density along the dendrites of hippocampal neurons in cultured slices (*11*). The effect of botulinum toxin is reversed by chronic exposure of the slices to low concentrations of AMPA, but it remains unclear whether this reversal depends on current flow through AMPA receptors, or simply on conformational changes induced by agonist binding. Transfection with a dominant negative GluR2 subunit (*12*) with mutated residues in the channel pore that block permeation (*13*) might provide a way to resolve this question. In contrast to these effects produced by chronic manipulation of AMPA receptor activity, acute blockade of AMPA receptors promotes spine formation within a period of several hours in hippocampal slices from mature rats (*14*). And, on an even shorter time scale, time-lapse studies (*15*) show that exposure to AMPA for several minutes inhibits rapid spine motility in cultures and in slices via a mechanism that requires Na entry through the activated channels. It remains to be determined how these effects, observed on a time scale of minutes to hours, relate to longer term changes in spine appearance and distribution, such as those observed with chronic blockade or GluR2 overexpression.

Analysis of hybrid subunits and deletion mutants by Sheng's group (*2*) identified the region of GluR2 that is responsible for spine enhancement. Surprisingly, the extracellular N-terminal domain was necessary and sufficient for the effects of GluR2 overexpression on spine morphology. Swapping this domain between the GluR2 and GluR1 subunits showed that spine-enhancing activity was completely transferred with the N-terminal portion of GluR2. The remainder of GluR2 had no effect on spines when its N-terminal domain was replaced with that of GluR1. The N-terminal extracellular region of AMPA receptor subunits, which precedes the glutamate-binding site (Fig. 1) (*16, 17*), exhibits homology with bacterial periplasmic binding proteins (*18*). It has been suggested that this domain facilitates the assembly of subunits into functional receptors (*19*) and the subsequent trafficking of these receptors to the surface membrane (*20*); however, complete deletion of this region does not preclude the construction of working channels (*21*). Overexpression of GluR2 that lacked the N-terminal domain reduced spine dimensions (*2*), possibly through competition with endogenous full-length GluR2 for delivery to synaptic locations. In addition, spine formation was inhibited by expression of the GluR2 N-terminal domain fused to the immunoglobulin constant region (*2*), or by adding this construct to the medium as a

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soluble protein. These findings suggest that absorption of an unknown endogenous partner that binds the N-terminal domain may limit signaling by GluR2.

How the N-terminal domain of GluR2 influences spine formation and morphology remains obscure; however, a number of possibilities exist (*22*). Binding of either soluble or membrane-attached proteins to the extracellular N-terminal domain of GluR2 could trigger spine elaboration (Fig. 1). In principle, such binding partners could arise from either the postsynaptic or presynaptic neuron or from enveloping glia; however, a presynaptic origin seems most attractive because it could provide built-in specificity. For example, excitatory presynaptic cells that need to make synapses onto spines might elicit postsynaptic spine formation by expressing the appropriate binding partner for the GluR2 N-terminal domain. In addition, the conformational changes associated with glutamate binding might promote this interaction, which could explain the requirement for agonist exposure in spine maintenance (*11*). Signaling that the extracellular interaction has occurred could be transmitted directly into the postsynaptic cell through a cytoplasmic domain of GluR2; however, this seems doubtful because GluR2 subunits lacking their cytoplasmic C-terminal tails remained fully active in regulating spine morphology (*2*). Instead, the N-terminal domain of GluR2 may interact laterally with the extracellular domains of other postsynaptic proteins (Fig. 1C), or it might elicit changes in the presynaptic terminal that indirectly enhance postsynaptic spine production and maintenance (Fig. 1E).

Prior work has identified a number of additional candidate molecules involved in the formation of spines and the clustering and delivery of glutamate receptors to excitatory synapses, including proteins such as the ephrins (*23-25*) and NARP (neuronal activity-regulated pentraxin) (*26, 27*), which could potentially interact with the N-terminal domain of GluR2 (Fig. 1, B to D) or could be involved with spine production downstream of the GluR2 N-terminal domain interaction (Fig. 1E). Among these players, the ephrin A-EphA receptor pair are negative regulators of spine number and morphology, whereas the ephrin B-EphB receptor pair interact with NMDA receptors (*28, 29*) and promote spine formation (*23, 24*). Activation of EphA4, a receptor tyrosine kinase, on pyramidal cells leads to rapid spine shrinkage and a reduction in spine number, whereas knockout of EphA4 results in longer spines with abnormal morphology (*25*). Interestingly, ephrin A3, the probable ligand for the EphA4 receptor, is produced by astrocytes, the nonneuronal cells that surround excitatory synapses, rather than by the presynaptic partner (*25*). In contrast to the ephrin A-EphA4 system, EphB2 receptor activation enhances spine morphology through phosphorylation of downstream targets that include the Rho-GEF (Rho guanine nucleotide exchange factor) kalirin (*24*) and the cell surface proteoglycan syndecan-2 (*23*). In addition, EphB2 receptor activation by ephrin B leads to a direct interaction of EphB2 with the NMDA receptor NR1 subunit extracellular domain (*28*). This initial association is independent of tyrosine phosphorylation by the EphB receptor (*28*), but subsequent changes in synapse number and in NMDA receptor-mediated calcium influx require tyrosine kinase activity by EphB (*28, 29*). Although manipulation of EphB2 signaling alters spine morphology in vitro, knockout mice that lack this receptor exhibit apparently normal spines in vivo (*30, 31*), possibly owing to developmental compensation by other Eph receptor family members. How the effects on spine formation mediated by GluR2 interact with these other determinants of spine morphology will be an active topic of future research.

The secreted pentraxin family member NARP interacts with the extracellular domains of several AMPA receptor subunits, including GluR2 (*26*). This interaction promotes the clustering of AMPA receptors at synapses made on cultured spinal cord and hippocampal neurons (*26, 27*); however, NARP, which selectively localizes to excitatory synapses on dendritic shafts (*32*), seems unlikely to be involved in spine formation. NARP was recently shown to form a complex with another pentraxin family member, NP1 (neuronal pentraxin 1) (*33*). NP1 alone had only a modest effect on AMPA receptor clustering, but when it was complexed with NARP, cluster formation was enhanced relative to either protein alone. In contrast to NARP, NP1 is relatively more abundant at synapses made on spines (*33*), where it might interact with the external domain of GluR2, possibly together with additional proteins other than NARP, and play a role in spine formation. The ability of NARP to cluster GluR2 at shaft synapses suggests that mere expression of GluR2 is not the sole factor responsible for spine formation. In addition, the fact that overexpression of recombinant GluR2 enhances the spininess of cells that already possess endogenous GluR2 demonstrates that the underlying mechanism is sensitive to relative levels of this subunit within the cell, and possibly sensitive to the stoichiometry of GluR2 within a population of heteromeric receptors (*34*).

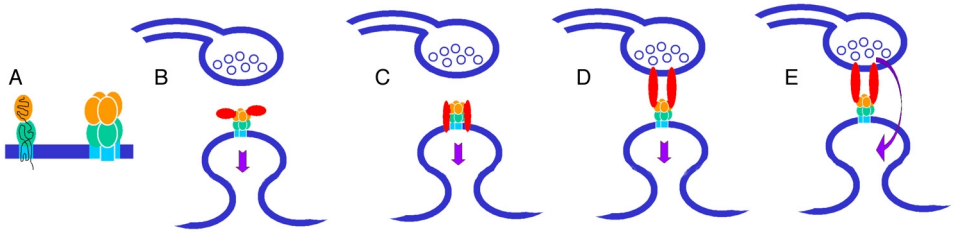

Fig. 1. Configuration of ionotropic glutamate receptor subunits (**A**) and possible interactions (*20*) involved in spine formation (**B** to **E**). (A) Diagram of ionotropic GluR subunit topology (*6*), left, showing the N-terminal domain (orange), the agonist binding domain (green), and the channel-forming domain (light blue) within the membrane (dark blue). Functional channels are tetrameric assemblies of related subunits, right. A postsynaptic spine-promoting signal elicited by interaction of the GluR2 N-terminal domain with its hypothetical binding partners (red) that are (B) soluble in the extracellular fluid, (C) present in the postsynaptic membrane, (D) attached to the presynaptic terminal, and (E) transducing the signal in the presynaptic terminal and promoting spines indirectly (arrow).

Both the level of expression and the subcellular distribution of GluR2 might influence spine dynamics. The synaptic expression of GluR2 increases during development (*35, 36*), and the inclusion of GluR2 within synaptic receptors can be regulated by the level of input activity (*37-39*). Even within single cells, the prevalence of calcium-impermeable AMPA receptors, which

contain GluR2, can be differentially regulated at synapses received from different presynaptic partners (*40*). Further studies will be required to determine how these differences in AMPA receptor composition correlate with spine production. In addition, it will be important to analyze dendritic morphology in GluR2 knockout mice (*41*) and mice engineered to overexpress GluR2 in interneurons (*42*).

Inhibitory interneurons represent a particularly interesting population in which to investigate the involvement of GluR2 in spine formation. Interneurons generally express less GluR2 than do excitatory cells (*43*). In addition, many, but not all, interneurons lack dendritic spines. Surprisingly, a study of inputs to CA3 interneurons in rat hippocampus (*40*) found a positive correlation between spine density and calcium-permeable synaptic AMPA receptors, which presumably lacked GluR2. Thus, spiny interneurons received a much higher proportion of synaptic inputs mediated through calcium-permeable AMPA receptors than did cells lacking spines (*40*). This relationship is exactly opposite to what would be predicted from the results of Sheng and colleagues (*2*). Clearly, more work is needed to understand the relationship between GluR2 expression and spine production.

Sheng and colleagues (*2*) suggest that the selective induction of spines by GluR2 might involve a metabotropic signaling mechanism. Sporadic reports presenting evidence for metabotropic actions triggered by classical ionotropic glutamate receptors have appeared in the past several years (*44-48*), with the most recent data coming in a study by Lerma's lab of rat dorsal root ganglion (DRG) sensory neurons (*1*). Earlier work (*49*) demonstrated that a subset of DRG cells express ionotropic kainate receptors, which regulate transmitter release from the cells' presynaptic terminals in the dorsal horn of the spinal cord (*50, 51*). Working on sensory neurons in culture, Lerma and colleagues (*1*) show that exposure to kainate evokes a rise in cytoplasmic calcium, which is sensitive to competitive antagonists of ionotropic kainate receptors, as well as to the heterotrimeric GTP-binding protein (G protein) inhibitor pertussis toxin. Calcium entry through voltage-gated calcium channels in the plasma membrane contributes to this rise, but an additional component involves calcium release from internal stores. In addition to triggering a rise in calcium, kainate application inhibited currents through voltage-gated calcium channels and suppressed the elevation in cytosolic calcium produced by subsequent depolarization with high concentrations of potassium. Pertussis toxin blocked both of these effects, and inhibitors of protein kinase C prevented kainate's inhibition of the calcium elevation produced by high K^+ (*1*). More important, these effects of kainate were absent in sensory neurons from knockout mice lacking GluR5 (*52*), the subunit that is required for production of functional kainate receptor channels in DRG cells (*52, 53*). This result by Lerma's group (*1*) provides the strongest evidence yet that a known ionotropic receptor subunit is directly necessary for producing a metabotropic effect, and it appears to rule out the nagging possibility that kainate was acting on some hitherto unidentified receptor.

On the other hand, the mechanistic connection between ionotropic receptors and downstream metabotropic effects remains unclear. Lerma and colleagues (*1*) provided several lines of evidence that ion channel function and metabotropic actions are independent of each other. Thus, kainate regulated voltage-gated calcium currents and suppressed calcium elevation after K^+ stimulation in cells that had no detectable current through kainate receptor channels. In addition, the distribution of kainate-evoked rises in calcium concentration within neurites was distinct from the locations at which kainate suppressed calcium elevation in response to high K^+ (*1*). Both of these observations raise the possibility that the subunits responsible for these metabotropic effects may not be integrated into functional ionotropic channels, but instead may be linked with other proteins that signal to downstream effectors.

Whether AMPA receptor subunits such as GluR2 can operate outside of their normal home within channels will also need to be examined. Interaction of AMPA receptors with the protein tyrosine kinase Lyn involves the SH3 (Src homology 3) domain of Lyn and the cytoplasmic C terminus of GluR2 (*44*), but the domains required for G protein stimulation by AMPA (*46*) or kainate (*1*) receptor subunits have not yet been identified. As mentioned above, the effects of GluR2 on spine morphology do not require the cytoplasmic portion of the subunit (*2*), casting doubt on the involvement of Lyn in this process.

Collectively, these recent studies (*1, 2*) put noncanonical signaling by ionotropic receptors on firmer ground, but they leave unresolved many questions about the linkage with downstream effectors. The evidence to date suggests that ability to pass current through functional ionotropic channels is not a prerequisite for metabotropic actions. Instead, it appears likely that the conformational changes initiated by agonist binding are sensed by other proteins directly in contact with the ionotropic receptor subunits. Identifying these interacting partners and determining how they operate is the next key step toward understanding these unconventional signaling mechanisms. Although spines may come and go with experience (*54*), atypical signaling by ionotropic glutamate receptors is here to stay.

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Citation: J. E. Huettner, Spine-tingling excitement from glutamate receptors. *Sci. STKE* **2003**, pe53 (2003).