Desensitizing interactions

The strength of synaptic responses is controlled by neurotransmitter receptor activation, deactivation, and desensitization. The structural basis of desensitization has not been well understood, but Yu Sun, Rich Olson, Eric Gouaux (Columbia University, New York, NY), and colleagues are getting a look at how subunit interactions determine whether glutamate receptors are activated or desensitized.

AMPA-sensitive glutamate receptors can either be activated or desensitized upon glutamate binding. Desensitization, in which the receptor is bound to ligand but inactive, allows for rapid cessation of signaling in the presence of agonist. AMPA receptors are arranged as heterotetramers, but Gouaux’s group has determined that the functionally relevant structure for the ligand-binding core for desensitization is that of dimers of dimers.

Using crystallographic and functional analyses of site-directed mutant subunits of GluR2, they show that the stability of the dimer interface at the ligand-binding core correlates linearly with the extent of receptor desensitization. Mutations that strengthen this interaction are more resistant to desensitization, whereas disruption of dimerization promotes desensitization.

Dimer interaction takes place between domain 1 of the ligand-binding core in each subunit. When these interactions are strong, conformational changes induced by glutamate binding are more likely to take place by movement of domain 2. This movement forces open the channel of the receptor. Weaker dimer interactions make it more likely that domain 1 will move upon glutamate binding, breaking the dimer interface. When that happens, the channel is left closed, and although the receptor is bound, Na⁺ ions cannot pass.

These studies also explain the mode of action of a drug that promotes AMPA activation, cyclothiazide (CTZ). CTZ binding in the ligand-binding core of the receptor stabilizes the dimer interface, thus reducing receptor sensitivity to desensitization.

Reference: Sun, Y., et al. 2002. Nature. 417:245–253.

Slow and steady moves the cell

More actin-based protrusion should mean more cell movement, or so it has been thought. Yet depletion of the Ena/VASP family of actin-binding proteins, which promote lamellipodial protrusion rates, actually causes cells to move faster. New results from James Bear, Tatyana Svitkina, Frank Gertler (MIT, Cambridge, MA), and colleagues explain this counterintuitive effect by putting the emphasis on the quality rather than the quantity of protrusions.

The group boosted Ena/VASP levels at the plasma membrane of fibroblasts and saw increases in protrusion velocity. But the protrusions were quickly withdrawn as ruffles. Within these lamellipodia, actin filaments were longer and less branched than normal and ran parallel to the membrane instead of perpendicular. “This tells us that the geometry of actin networks and had slower and more persistant protrusions. These are the cells that move more quickly. “The simplest viewpoint was that promoting actin assembly should increase the rate of cell movement,” says Gertler. “But it’s not that simple—you must look at the separate components of cell motility.” These include the rate of protrusion extension, the stability and adhesion of protrusions, cell contraction, and cell polarity. Gertler found that the duration, rather than the rate, of protrusions best correlated with translocation speed.

The Ena/VASP proteins bind to the barbed ends of actin filaments and antagonize the activity of capping proteins while allowing filament extension. This makes Ena/VASP the first anti-capping proteins identified. The inhibition of protrusion by Ena/VASP could be reversed by cytochalasin D treatment, indicating that the critical parameter is filament length, rather than branching. Filaments that are too long will extend along the membrane, whereas shorter filaments can push against the membrane as they polymerize.

Reference: Bear, J., et al. 2002. Cell. 109:509–521.