A slip 'twixt the cup and the lip: a new way to impair function of transmitter-gated channels

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PERSPECTIVES

A slip 'twixt the cup and the lip: a new way to impair function of transmitter-gated channels

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The glycine-gated receptor is a member of the nicotinic receptor family, often overshadowed by its cousins the nicotinic, GABA-ergic and even serotonin type 3 receptors. Glycine receptors are found in many regions of the nervous system (Lynch, 2004), but are best known as the targets for the convulsant poison strychnine. By blocking glycine receptors in the spinal cord, strychnine produces tonic paralysis. In humans and laboratory animals, the major feature of deficient glycine receptor expression or function is an exaggerated response to sudden stimuli, or excessive tone in muscles. One of the spontaneous mutations identified in mouse is named *spasmodic*, which produces tremor, exaggerated startle and some gait abnormalities. This results from a missense mutation in the glycine receptor $\alpha 1$ subunit, A52S. *Spasmodic* is a loss-of-function mutation, and results in a shift in the concentration–response relationship to larger concentrations of glycine and a more rapid decay of responses (Graham *et al.* 2006). In an article in this issue of *The Journal of Physiology*, Plested *et al.* (2007) explore in elegant kinetic detail the functional deficit produced by this mutation, resulting in a very interesting insight into the repertoire of mechanisms for reduction of receptor activation.

Earlier work from this group examined wild-type glycine receptors (Burzomato *et al.* 2004), and provided strong evidence for a particular activation scheme (Scheme 1). In this scheme, a receptor has three states: resting (C), 'flipped' (F) and open channel (O). In each case, up to three glycine (A) molecules may bind to a receptor. The flipped state has a closed channel, and is interposed between the resting receptor (top row) and the open channel form (bottom row). Channel gating steps occur between the middle and bottom rows. The scheme is based on the 'concerted transition' or MWC allosteric model, and relies on the idea that the receptor as a whole undergoes a transition from C to F. The binding sites have identical microscopic affinities for glycine, while the affinity for sites of receptors in the F state is higher than in the C state.

Plested *et al.* (2007) demonstrate that the functional abnormality in the *spasmodic* receptor is a consequence of an effect on the closed channel isomerization from A_iC to A_iF. The effect can be stated in two ways. First, in the *spasmodic* receptor the equilibrium ratio of A_iF to A_iC changes very little between singly and triply liganded receptors (only ~3-fold, *versus* 5000-fold for wild-type receptors). Second, the affinity for glycine in the flipped state is reduced in the *spasmodic* receptor (to ~800 μM from ~8 μM), and the affinity in the flipped state is only ~2-fold better than in the resting state, as compared to ~65-fold. The predicted activation curve is shifted to higher concentrations of glycine, as observed. When miniature inhibitory postsynaptic currents are simulated they are predicted to decay more rapidly, also as observed. A possible reason for the more rapid decay is that the rate for moving from A_3F to A_3C is increased ~6-fold while the channel opening rate from A_3F is reduced ~2-fold in the *spasmodic* receptor. Finally, the *spasmodic* receptor also shows less change in apparent glycine affinity as a function of occupancy (less apparent cooperativity in binding). Burzomato *et al.* (2004) argued that the existence of the flipped conformation provides a plausible explanation for the observed apparent cooperativity: the concerted conformational change allows (un)occupied sites to sense the occupancy of relatively distant sites. Accordingly, the deficit in the flipped conformation provides a simple and elegant explanation for the reduced cooperativity.

So, receptor function can be compromised (and possibly enhanced?) not only by effects on resting or open channel receptors, but by an action on an intervening state. The duration of the closed dwells associated with the flipped conformation appears to be longer for the glycine receptor than for other family members, but it seems plausible that analogous states are present for other receptors. Indeed, an interposed closed channel transition in the activation pathway has been postulated for NMDA (Banke & Traynelis, 2003) and $GABA_A$ (Lema & Auerbach, 2006) receptors. Hence, this mechanism may not only be new, but may prove applicable to additional situations.

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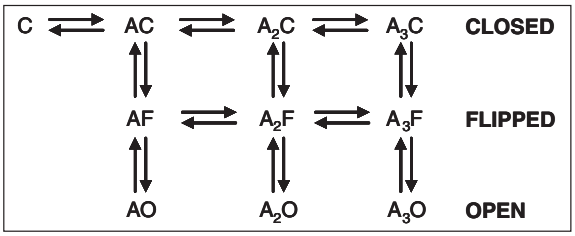

Scheme 1

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