A light switch controlling Ca2+-permeable AMPA receptors in the retina

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J. Physiol. 2007;582;3-; originally published online Apr 26, 2007;

DOI: 10.1113/jphysiol.2007.135145

PERSPECTIVES

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At most excitatory, glutamatergic synapses in the brain, AMPA and NMDA-type glutamate receptors (AMPARs and NMDARs) make distinct contributions to the postsynaptic response: AMPARs mediate transient conductances that are well suited to fast information transfer; NMDARs associate glutamate binding with postsynaptic depolarization to mediate a slower conductance that, unlike that of most AMPARs, includes Ca^{2+} influx that can trigger long-lasting changes in synaptic strength. This delegation of postsynaptic roles has been blurred recently by evidence implicating Ca^{2+}-permeable AMPARs (CP-AMPARs) in different forms of synaptic transmission and plasticity. AMPARs are heterotetramers comprising various combinations of subunits GluR1–4, each of which is coded to express an uncharged glutamine in the pore region that permits permeation of divalent cations. In GluR2, RNA editing recodes this glutamine to a positively charged arginine, rendering GluR2-containing AMPARs Ca^{2+} impermeable (Dingledine *et al.* 1992). Many neurons, however, express AMPARs that lack GluR2 and are, consequently, Ca^{2+} permeable. Particularly in interneurons, CP-AMPARs often replace NMDARs as the primary source of postsynaptic Ca^{2+} influx. For example, Ca^{2+} influx through CP-AMPARs induces long-term potentiation (LTP) of excitatory synapses onto interneurons in the amygdala (Mahanty & Sah, 1998) and triggers GABA release from A17 amacrine cells in the retina (Chavez *et al.* 2006).

CP-AMPAR channels are distinguished electrophysiolgically via voltage-dependent block by (and eventual permeation of) endogenous intracellular polyamines that confers biphasic rectification on an otherwise linear *I–V* relationship (Bähring *et al.* 1997). CP-AMPARs also are blocked by exogenous extracellular polyamines such as philanthotoxin (Washburn *et al.* 1997). Ca^{2+} permeability and polyamine sensitivity typically go hand in hand, but a paper in this issue of *The Journal of Physiology* reports CP-AMPARs in rat retinal interneurons that are insensitive to philanthotoxin (Osswald *et al.* 2007). The expression of these receptors coincides with eye opening and is delayed by rearing animals in darkness, suggesting that they may participate in a critical phase of retinal development.

Functional CP-AMPARs are detected using cobalt staining and electrophysiology. Cobalt permeates CP-AMPARs and so fills cells expressing activated receptors. Following exposure to cobalt and glutamate, retinas were fixed according to a protocol that rendered cobalt-positive horizontal and amacrine cells a deep orange. Particularly strong staining was observed in AII amacrine cells, glycinergic interneurons known to express CP-AMPARs. Cobalt staining was not induced by membrane depolarization in the absence of glutamate and was unaffected by NMDAR and metabotropic glutamate receptor (mGluR) antagonists but was abolished by AMPAR antagonists, including philanthotoxin. During the third postnatal week, around the time of eye opening (~P14), cobalt staining persisted, but philanthotoxin sensitivity disappeared in horizontal cells and was reduced in AII cells, particularly in processes ramifying in the outer portion of the inner plexiform layer (IPL), where synapses transmitting 'OFF' visual signals are made. AII cells, but not horizontal cells, recovered philanthotoxin sensitivity 2 weeks later. Decreased philanthotoxin sensitivity did not occur in dark-reared animals, suggesting that light-induced activity may trigger the change.

Interestingly, voltage clamp recordings of spontaneous synaptic currents in AII cells also reflected the transient disappearance of philanthotoxin sensitivity. This, together with the morphological data described above, would suggest that most spontaneous activity in AIIs arises at synapses in the 'OFF' region of the IPL. This is a bit surprising, as most synapses onto AIIs are made by rod bipolar cells (RBCs) in the ON region, and spontaneous events in AIIs are indistinguishable from evoked quantal events from RBCs (Singer *et al.* 2004).

The molecular mechanism underlying this peculiar developmental switch remains unknown, but the authors propose the possibility of a novel AMPAR subtype (or novel RNA editing of known subunits), a reasonable suggestion given that other glutamate receptors (e.g. mGluR6) and transporters (e.g. EAAT5) appear unique to the retina. The functional impact of these philanthotoxin-insensitive CP-AMPARs also remains to be determined. Relief of polyamine sensitivity could change postsynaptic responsivity to patterns of synaptic input (Rozov & Burnashev, 1999) during a time when excitatory synaptic connections with bipolar cells are first being established (Horsburgh & Sefton, 1987). Alternatively, the authors suggest that these receptors may act as temporary molecular cues to direct formation of synaptic connections within specific sublaminae of the IPL, a critical step in the proper wiring of ON and OFF visual pathways.

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