NESTED FEEDBACK AND CONCATENATED INHIBITIONS IN THE RABBIT INNER PLEXIFORM LAYER

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Purpose: The goals of this study were to determine [1] the topologies of inhibitory amacrine cell (AC) circuits that shape bipolar cell (BC) → ganglion cell (GC) transmission in the mammalian retina and [2] the extents to which they mirror nested feedback and concatenated inhibitory configurations described in the *cyprinid* retina (Marc & Liu, 2000, *J Comp Neurol 425:560-582*).

Methods: Ultrathin sections of osmium-ferricyanide post-fixed rabbit retina were serially imaged for ultrastructure and GABA signals by overlay microscopy and examined for concatenated and nested synaptic relationships. GABA signals were derived from silver-intensified immunogold labeling of an adjacent 90 nm section. The GABA image was registered to the EM master image with PCI remote sensing code (Richmond Hill, Ontario, CA).

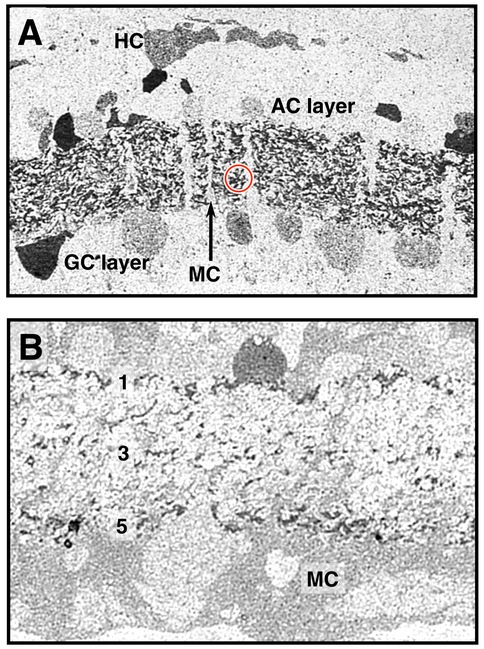

Figure 1. Most GABAergic amacrine cells receive bipolar cell drive. Panels A and B display GABA signals in thin resin sections of rabbit retina. The GABA signal (Panel A) constitutes ≈60% of the inner plexiform layer (IPL). Kainate activation of AMPA receptors results in reverse-transport mediated GABA efflux from a >85% of GABAergic processes in the IPL (Panel B). We presume that AMPA receptor drive reveals endogenous bipolar cell drive and conclude that most GABAergic cells receive direct synaptic input from bipolar cells. A few kainate insenstive processes remain in sublayers 1, 3 and 5, while released GABA accumulates in Müller cells (MC). The red ring in Panel A marks a region of the IPL examined by overlay microscopy in Figure 3.
HC, horizontal cell.

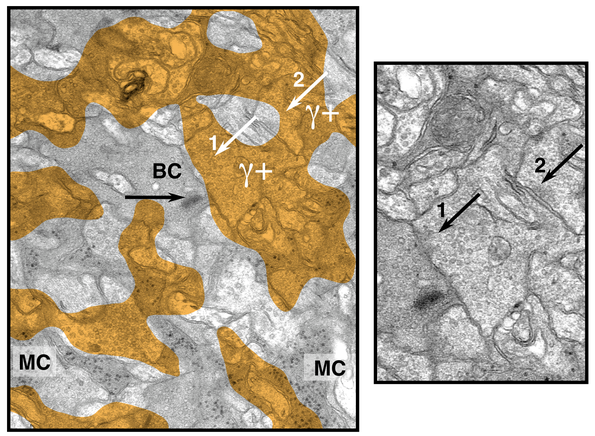

Figure 2. Nested feedback onto an OFF-center cone bipolar cell in sublayer 2 of the IPL. The arrow 1 points to the reciprocal ribbon contact. White arrows point to synapses formed by GABAergic amacrine cells (γ+, orange overlay). Contacts enlarged at right.

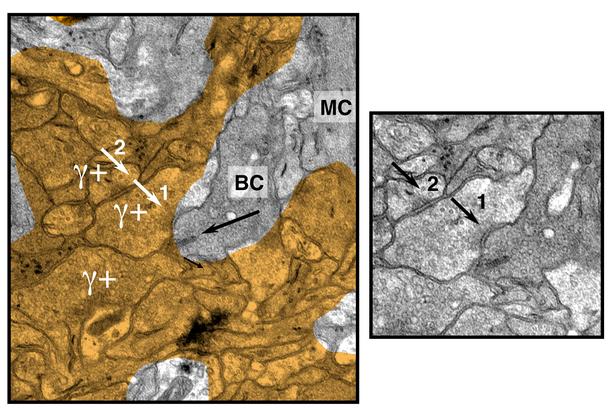

Figure 3. Nested feedback onto an ON-center cone bipolar cell in sublayer 3/4 of the IPL. Arrow 1 points to the reciprocal ribbon contact. White arrows point to synapses formed by GABAergic amacrine cells (γ+, orange overlay). Contacts enlarged at right. The ring in panel A of figure 1 marks the position of this assembly.

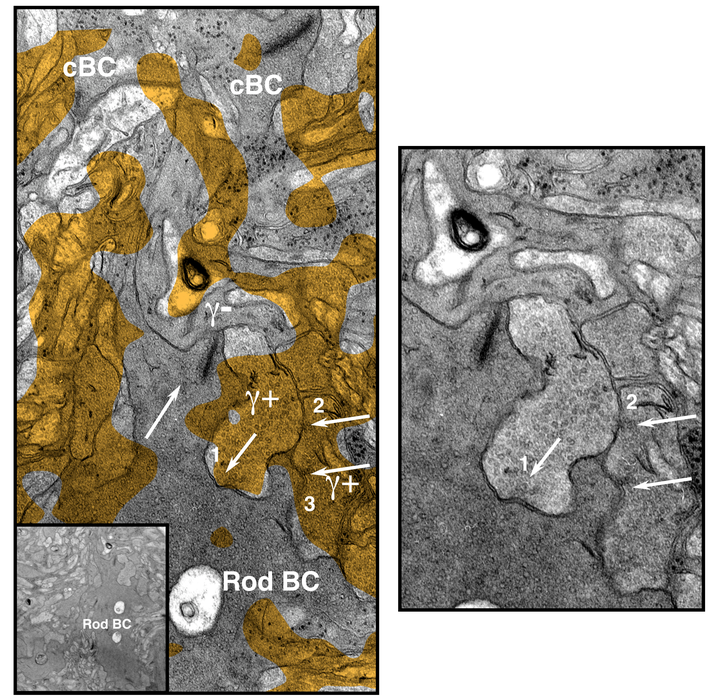

Figure 4. Nested feedback onto a rod bipolar cell in sublayer 5 of the IPL. Arrow 1 points to a reciprocal ribbon contact, arrow 2 to the nested contact, and arrow 3 to a feedback contact. Contacts enlarged at right. The second member of the ribbon dyadic pair is GABA negative (γ−) and is likely a glycinergic AII amacrine cell. The insert in the lower left corner shows the full extent of the rod bipolar ending. cBC, cone bipolar cell endings in sublayer 4.

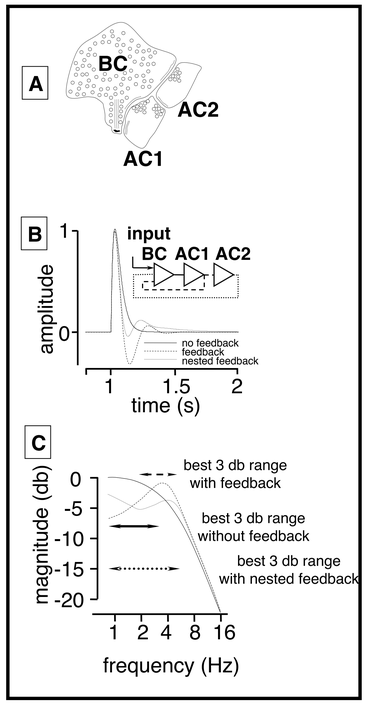

Fig. 5. Theoretical properties of nested feedback patterns. A: A typical nested feedback arrangement involving two separate AC processes. B: Modeled impulse responses using a noninverting input to a BC stage, a noninverting BC → AC1 input and sign-inverting inputs for all other paths. A monophasic response was generated through the model BC alone, followed by simple reciprocal feedback and nested feedback. C: Power spectra for the three configurations, displaying rolloff features and best 3 db ranges.

Results and Conclusions. The elements of nested feedback/feedforward were observed for OFF-center, ON-center and rod bipolar cells. These include reciprocal synaptic contacts between bipolar cells and amacrine cells (AC→AC↔BC loops) and concatenated micronetworks of AC→AC and AC→AC→AC chains. Overlay microscopy revealed that both OFF- and ON-center cone bipolar cells and rod bipolar cells receive γ+ reciprocal feedback from amacrine cells that were themselves the target of γ+ elements (γ+→γ+ ↔ BC). Although most AC profiles were γ+, some members of these chains were γ− and are most likely glycinergic.

Concatenated inhibitory chains and nested feedback loops are common in the rabbit retina, arguing that true simple feedback may be rare. Nested feedback can significantly alter the spatiotemporal processing of bipolar cell to ganglion cell signal transfer. Such circuits also have profound implications for developmental processes, as they can be generated with random synaptic targeting within a given level of the inner plexiform layer.