their light responses when introduced *via* the patch-pipettes. Recent direct measurements of the free $Ca^{2+}$ rise by fluorescence imaging of initially dark-adapted carp retinal slices have confirmed a large increase in free $Ca^{2+}$ with light in the outer plexiform layer.[18] This rise was suppressed by 2-amino-4-phosphonobutyrate, a selective agonist for the ON-bipolar cell mGluR.[19] Transient $Ca^{2+}$-rises of 30–40 μM have been reported in cerebellar Purkinje cell dendrites.[20] A rise in $Ca^{2+}$ of this order highly localized to ON-bipolar cell dendrites would not be excessive given the likely locus of cGMP-activated channels and the components of the cGMP-cascade. Just how $Ca^{2+}$ reduces ON-bipolar cell sensitivity remains to be determined.

The decrease in input conductance accompanying the suppression of inward dark current and light responses with elevated free $Ca^{2+}$ suggests that there may be an action on the channels, either direct or perhaps mediated by $Ca^{2+}$/calmodulin-dependent protein kinase,[21,22] but this cannot as yet be distinguished from a reduction in cGMP levels induced by phosphodiesterase (PDE) activation or guanylate cyclase (GC) inhibition. On equilibration with BAPTA, an inward shift in dark current was observed which would be consistent with an increase in GMP-activated conductance mediated by a fall in intracellular $Ca^{2+}$. Inward current shifts and rebounds on flash responses have also been observed in rods on equilibration with BAPTA,[12] reflecting similarites between the mGluR-linked system expressed in ON-bipolar cells and phototransduction.

The role of $Ca^{2+}$ in light adaptation of photoreceptors has been well characterized.[23] The reduction in light sensitivity in rods is due to a decrease in intracellular free $Ca^{2+}$ below the dark level resulting from the closure of $Ca^{2+}$-permeable cGMP-activated channels[24] and persistent $Ca^{2+}$ extrusion.[25,26] $Ca^{2+}$ prolongs the lifetime of photoexcited rhodopsin by reducing rhodopsin kinase activity.[27,28] $Ca^{2+}$ has been shown to inhibit particulate GC activity,[29] but ON-bipolar cells express only the soluble form of GC which is activated by NO.[30] $Ca^{2+}$ decreases the apparent affinity of rod cGMP-activated channels for cGMP.[31] This latter action is far more pronounced in olfactory receptor cells, which also possess a cyclic-nucleotide-gated conductance.[21] Raising intracellular $Ca^{2+}$ more than the order of 1 μM in both olfactory receptors[32] and photoreceptors[33] also acts to reduce their sensitivity.

The question therefore arises as to where light adaptation of the visual system occurs. The rise in increment threshold of ON-ganglion cells in cat retina by background light was orders of magnitude greater than that displayed by photoreceptors.[34] This is paralleled by a 3000-fold elevation in human visual threshold following light adaptation of the rod system, whilst at the same time the reduction in gain in phototransduction is only some 5-fold.[35] The b-wave of the electroretinogram, which derives from the population of ON-bipolar cell responses[36] displays the same shift of adaptive characteristics as ON-ganglion cells[37] and human subjective visual changes. These observations have given rise to the concept of adaptation of the rod pool or network adaptation, due to the release of some "desensitizing substance", possibly $K^+$, being released and accumulating in the inner layer of the retina.[37] However, there is no evidence for a rise in $K^+$ of the correct magnitude in the inner retina. The present observations would rule out this possibility, since in ON-bipolar cells, cGMP-activated channels tend to close with background adaptation reducing depolarizing drive throughout the inner retina.

The results presented here point to a light-induced rise in intracellular $Ca^{2+}$ in ON-bipolar cells as the "desensitizing substance". A $Ca^{2+}$-induced reduction in the voltage gain of synaptic transmission could be achieved by reducing the biochemical gain of the ON-bipolar cell cGMP cascade, which would effectively couple mGluRs to the control of a smaller number of cGMP-activated channels.[3] A reduction in biochemical gain would change the glutamate concentration-current response relation from linearity at high glutamate concentrations (in the dark-adapted condition) into a curve showing saturation. $Ca^{2+}$-dependent reduction in the cGMP-gated conductance would also reduce voltage gain. Thus there are two gain control systems in series: a high gain control at the level of ON-bipolar cells where rod signals are pooled, and a lower sensitivity system in rods. Together, they give rise to the wide operating range of the scotopic visual system.[38]

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