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Editorial: The decade of the retina

Neuroscience emerged only twenty years ago as a discipline defined by a broad range of experimental and conceptual problems involving the nervous system and its relation to behavioral and mental functions. In recognition of the remarkable progress achieved thus far and the potential for major advances in virtually every major field that neuroscience encompasses, the Senate and House of Representatives of the United States recently passed a resolution designating the decade beginning January 1, 1990, as "The Decade of the Brain." President Bush has further issued a proclamation that calls upon "... all public officials and the people of the United States to observe such decade with appropriate programs and activities."

One of the major goals of neuroscience is to attain a comprehensive understanding of how the nervous system encodes and organizes our knowledge of the world, and how it uses its enormous computational powers to extract and interpret information from the sense organs. Leading the explosive growth and development of new knowledge in neuroscience has been the rapid pace of research directed toward understanding the neural processes that underlie visual perception and visually guided behaviors. In retrospect, the 1980's might justifiably be remembered as the "The Decade of the Retina," for it has yielded a multitude of major discoveries at virtually every synaptic level. The development and application of a host of new physiological, neuropharmacological and immunohistochemical techniques, together with increased utilization of cell culture and retinal-slice preparations have contributed to what might be termed "a great leap forward" in retinal neurobiology. Modern molecular genetic techniques have been used for the first time to successfully isolate the genes that specify individual photopigments present in rods and three types of cones in the human retina. The development of antibodies which recognize different cone opsins has permitted analysis of the distribution of cone types in the retinas of a variety of species and provided new insights into the evolutionary, comparative and physiological bases of color vision.

One of the most remarkable accomplishments has been measurement of the minute currents generated by individual photoreceptor outer segments, providing the first direct information about the kinetics of the transduction process itself. Consequently, future prospects for understanding some of the most fundamental properties associated with luminosity, chromatic, temporal and spatial dimensions of visual experience have been greatly enhanced. Equally compelling has been the accumulation of evidence that cyclic GMP plays a central role in phototransduction by regulating ionic conductance in the surface membrane of both rods and cones, thereby supplanting the heuristically powerful calcium hypothesis which previously dominated studies on retinal transduction. Now, it appears that calcium may regulate both the gain and kinetics of the nucleotide cascade and thus, remain a crucial factor in these initial events in phototransduction.

Over the past decade, substantial evidence has accumulated that identifies L-glutamate as the most likely candidate for photoreceptor neurotransmitter, acting at three different receptor sites on horizontal cells and on both hyperpolarizing and depolarizing bipolar cells. Also, striking similarities have been demonstrated recently between photoreceptors and pinealocytes in the ability to synthesize melatonin in darkness. Unlike the stimulus-induced release of glutamate, melatonin has a much slower response time and thus, may act in neurohumoral fashion to regulate dark-adaptation processes throughout the retina. Both melatonin and dopamine may serve as paracrine effector signals in the control of retinomotor responses, rod disc shedding at the dark-light transition and perhaps, in cone disc shedding as well. Thus, a circadian timing mechanism exists within the vertebrate retina itself, with major effects upon the control of visual sensitivity.

New evidence of electrical coupling at photoreceptor gap junctions indicates that light strengthens the association between rods and cones and that adaptation-induced changes in the strength of coupling occur as background illumination is altered. Also, single rods in the mammalian retina show light adaptation effects at illumination levels just below that at which the cones become fully functional, and suppressive rod-cone interactions expressed as a tonic influence upon cone pathways by dark-adapted rods (most probably via horizontal cell feedback onto cones) can be removed by selective light adaptation of rods. Thus, psychophysical demonstrations of such interactions may have their origins at the earliest synaptic level in the visual pathway.

A complex pattern of neurotransmitters and neuropeptides is now emerging from analysis of the inner nuclear and plexiform layers where, depending upon the species, 20–40 types of amacrine cells mediate bipolar cell actions upon 16–22 types of ganglion cell. Ramon Y Cajal proposed that the retina could best be understood as a laminar structure and, in particular, that the sublaminar pattern of the inner plexiform layer is directly related to the number and size of bipolar cells in a given species. Excitatory amino acids act upon both amacrine and ganglion cells, while inhibitory amino acids are now well-established as crucial agents in the orchestration of motion, velocity, directional, orientational, and size-selectivity responses of ganglion cells, as well as in the opponent-process mechanisms of the inner retinal layers. A number of neuropeptides also occur in amacrine cells, some of which coexist with conventional neurotransmitters and perhaps, with each other. To further complicate matters, recently described cholinergic amacrine cells

appear to synthesize both acetylcholine *and* GABA—a peculiar push-me, pull-you kind of arrangement with neurotransmitters having opposite modes of postsynaptic action.

Amacrine cells are the most diverse neurons in the retina, and several subpopulations with multiple axons originating from the dendritic arbor are now recognized. These axonal and dendritic components may have independent synaptic functions which are electrically isolated from each other. The former may give rise to spikes that propagate over considerable distance within the inner plexiform layer. Feedback from the inner plexiform layer to the outer nuclear layer via dopaminergic interplexiform neurons adds yet another level of complexity to this multiplex circuitry, as does the discovery of a new type of "biplexiform" ganglion cell which makes dendritic contact with rod photoreceptor terminals as well as with amacrine and bipolar cells. Clearly, a new level of sophistication in network and computational analysis will be required in order to fully understand the functional significance of these cellular, neurochemical and synaptic interrelationships.

The value of the vertebrate retina as a readily accessible neural substrate for investigating the integrative and functional organization of neural circuits remains unsurpassed. In this final decade of the twentieth century, the creativity and achievements of visual neuroscientists should continue to provide major contributions to the greatest endeavor of all—the human brain striving to understand itself.

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