Principles and Practice of Clinical Electrophysiology of Vision

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Pharmacological Effects in Retinal Electrophysiology

Günter Niemeyer

Drugs typically reach the neural retina via the choroidal and retinal circulation by passage or transport through the blood-retina interface (blood-retina barrier, analogous to the blood-brain barrier).[36, 64] From the side of the richly fenestrated choroidal capillaries, this interface consists of the basal membrane and tight junctions of the retinal pigment epithelium (RPE). The retinal component of the blood-retina interface consists of the nonfenestrated walls of retinal capillaries and surrounding glial cells that separate the vascular from the neural structure. Passive permeability as well as active transport characterize this complex boundary. In experimental situations, substances may be directly injected into the vitreous. They must then diffuse through the "unstirred" vitreous and the retina before reaching a target site, and this means the effective concentration is reduced and the effect may be delayed. These problems are reduced if isolated superfused retina is used as an experimental tool.

The RPE can be affected by a large number of active agents that cannot easily pass into the neural retina. Typically, the majority of transmitter-related agents used in the arterially perfused eye in our laboratory change the standing potential (recorded between the scleral surface and the vitreous) in a dose-dependent way, and many of them reduce or even abolish the light peak[7, 20–23] in a dose-dependent manner, even though the drug may have no effect on retinal field potentials, the optic nerve, or single neurons.

The retina consists of a large variety of highly specialized neurons embedded in a glial matrix, and to a considerable extent, rod and cone function is separable,[44, 47] as schematically illustrated in Figure 20–1. Pharmacological effects can be described on two levels: (1) that of retinal circuitry and potentially multiple neural, glial, and vascular structures and (2) on the molecular level, where the target is to characterize the membrane-bound receptors (e.g., for neurotransmitters, neuromodulators, or vasoactive compounds); glial elements have also been shown to contain receptors for various neurotransmitters and neuromodulators.[8, 11, 16, 32, 52]

EXPERIMENTAL PREPARATIONS, DRUG APPLICATION, AND INTERPRETATION OF EFFECTS

Topical application of active agents in clinical therapy (such as eye drops) can reach the retina via diffusion through the cornea[49, 50] and via absorption into the circulation through the conjunctiva and the large surface of the lacrimal system. Subconjunctival and parabulbar injections would be expected to generate higher intraocular concentrations. The local injection of steroids, much like systemic application, can induce substantial increase in the amplitude of the electroretinogram (ERG) b-wave[87] and thus cover up ERG alteration due to disease. Oral and parenteral application of ocular therapeutic agents

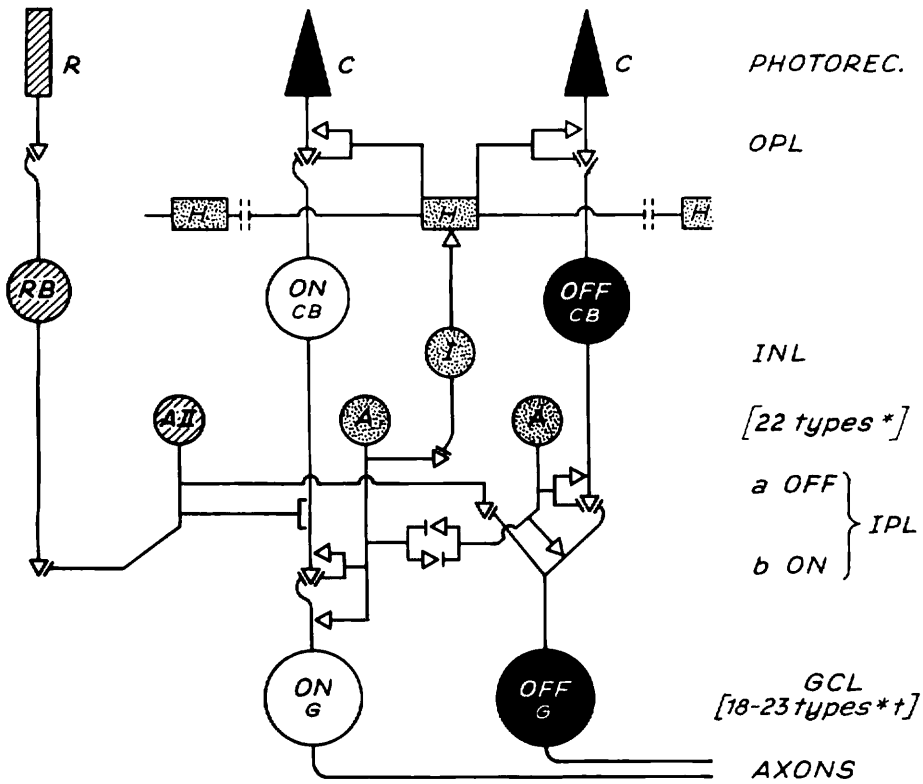

FIG 20–1.
Scheme of retinal circuits. Elements of the rod pathway *(hatched)* including a rod *(R)*, a rod bipolar *(RB)* and an amacrine cell *(AII)* feed into an on-center ganglion cell *(ON G)*. One cone on-pathway *(empty circles)* and a cone off-pathway *(black)* are schematically shown with interspersed horizontal *(H)*, amacrine *(A)* and inner plexiform *(I)* cells; the RPE, rod-to-cone connections at the synaptic level, and glial (Müller) cells are not included (*OPL* = outer plexiform layer; *INL* = inner nuclear layer; *IPL* = inner plexiform layer; *GCL* = ganglion cell layer). (Adapted from Massey SC, Redburn DA: *Prog Neurobiol* 1987; 28:55–96.[47])

may also affect the electrophysiology of the retina and visual pathway. Systemic treatment can induce ocular side effects resulting in functional changes of the RPE, retina, or optic nerve. Intravitreal injection of antibiotics can cause toxic damage to the retina.

In experiments additional ways are used to apply active agents to induce the accumulation of metabolites or to block specific neuronal circuits. These include intra-arterial injection near the ocular circulation[76, 85] or injection into the perfusion stream of isolated eyes,[55, 57] intravitreal injection, bath application in isolated superfused retina,[2, 42] vapor administration to isolated retina, pressure ejection, or iontophoretic release of chemicals near single cells during electrophysiological recording.

Among preparations used for pharmacological testing we distinguish between the in vivo and in vitro approaches. In vivo, anesthetized animals with intact eyes, in situ eyecups, and in situ preretinal perfusion[45] provide extended experimental time and also a chance to monitor systemic responses, i.e., of the cardiorespiratory system, to a given drug. However, it can become difficult to overview the role of extraocular metabolism and potential effects on retinal function of compensatory systemic mechanisms.

In vitro preparations include isolated intact arterially perfused mammalian eyes[15, 25, 40, 53–55, 57]; isolated retina-RPE-choroid sheets in double chambers[51]; isolated superfused retina, possibly with the optic nerve attached[2]; retinal slices[84]; and tissue cultures of RPE or retinal cells. Isolated organ or tissue preparations of this type provide advantages such as mechanical stability, the absence of extraocular metabolism, control over the chemical "input" (i.e., over the concentration of applied agents), and the washout thereof. Isolated retinal preparations provide easier access to the numerous types of small neurons in mammals as well as simple diffusion of applied agents, but they lack the possibility of monitoring interactions with the RPE and the vascular system.

A problem arises in estimating the actual *concen-*

tration at the target tissue, specifically at the synapses. Reasons for the difficulty in making such assessments (e.g., after the administration of eye drops) include the barrier properties of the blood-retina interface, diffusion through the retina or vitreous, the extent of binding to serum proteins, recycling in the systemic circulation, and finally, extraocular metabolism. The individual sensitivity of the subject or experimental animal to a drug and the time of application within the diurnal rhythm of, for example, changes in receptor density[6, 30, 82 83] are additional factors in determining the effective dosage.

An *interpretation* of pharmacologically induced electrophysiological changes should consider anatomical aspects addressed in the beginning of this chapter and a number of factors that can influence the results. The application of active agents can induce the following:

- Systemic and local changes in circulation
- Changes in intraocular pressure (crucial in the case of intravitreal injections)
- Changes in osmolarity
- Changes in acid-base balance[20, 81]

Such factors can indirectly alter light-evoked electrical responses from the RPE, retina, and optic nerve. Any interpretation of drug-induced changes in these responses should take into account the possibility that glial and vascular as well as neural receptors might be involved. The kinetics of receptor binding and the possible interaction between specific transmitter systems also complicate the picture. A comparison of these retinal effects to those observed in cerebral pharmacology often facilitates the interpretation of results in spite of marked differences in the distribution of subtypes of receptors.

EXPERIMENTAL NEUROPHARMACOLOGY OF THE RETINA

In most pharmacological experiments the major objectives are control over all extraneous variables, steady-state baseline condition, effects in response to an agent, and recovery. Recordings in the control phase should reveal stable sensitivity, defined adaptation, and homeostasis of parameters such as temperature, pO_2, pCO_2, pH, and the flow rate of perfusate or superfusate, respectively.[56, 58]

Electrical responses used in neuropharmacology of the retina consist of *clinical* (noninvasive) recording of the ERG and electro-oculogram (EOG) and monitoring the activity along the visual pathway in visual evoked cortical responses (VECRs). Specific techniques concerning rod-cone separation, focal ERG, pattern ERG (PERG), and scotopic threshold response (STR) are discussed thoroughly in the respective chapters of this volume.

The *experimental* approach to studying neuropharmacology in animals and in isolated tissue widens the spectrum of applicable electrophysiological tools; this is illustrated in part in Figure 20–2. Intravitreal direct corneal recording (DC) allows one to monitor the standing potential and the light peak directly with adequate stability.[40, 55] Regarding the b-wave of the ERG, it is of interest to compare the voltage-vs.-log intensity functions across different vertebrates and preparations (Fig 20–3). Following threshold at low stimulus intensity, there is a steep dynamic range that reveals a tendency to saturation at high stimulus intensity. Although these data were obtained under nonidentical conditions in vivo (left), a highly similar slope of the V/log I functions indicates the same underlying mechanism. This can also be shown in in vitro recording from arterially perfused cat and dog eyes (Fig 21–3, right panel). The V/log I function thus represents a useful monitor of retinal sensitivity and gain of the b-wave generator under experimental[55] and clinical conditions.[48]

Local ERGs recorded with microelectrodes under focal stimulation provide information on small retinal areas as well as on selected layers.[10, 75]

The optic nerve's light-evoked, temporally dispersed action potential, referred to simply as optic nerve response (ONR) can serve as a useful tool in experimental pharmacology.[55, 58, 59] A typical ONR recording from a perfused cat eye is shown in Figure 20–2,E. Distinct features are labeled as the rapid on-component, followed by a slightly declining and often oscillatory plateau phase during illumination and the more complex, often polyphasic off-component. We interpret this complex waveform as resulting from extracellular summation of the histograms of all on-going changes in excitation of the axons underlying the recording electrodes. Ratemeter recordings of the firing of ganglion cells closely resemble configurations—or at least components of the ONR.[59] Changes in amplitude and configuration of the ONR represent subtle indicators of drug actions; these facilitate assessment of the effective dose range and reversibility of effects of agents that alter retinal information processing.

Adequate characteristics of the tips of electrolyte-filled microcapillary electrodes allow *intracellular* recording from a variety of mammalian retinal neu-

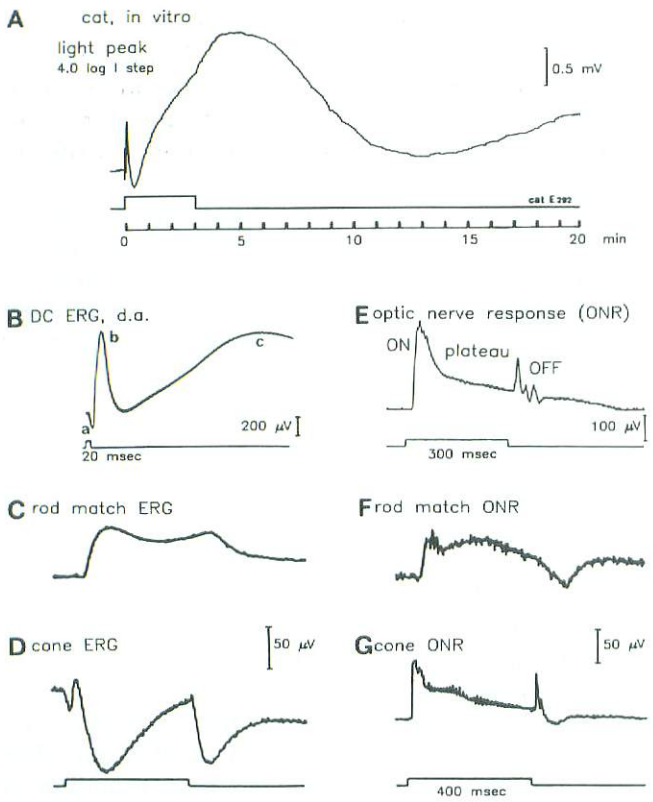

FIG 20–2.
Typical field potentials recorded in vitro from isolated, arterially perfused cat eyes. **A,** a light peak recorded intravitreally from a dark-adapted eye was elicited by a step increase of 4 log units (white light). The a-, b-, and c-waves appear compressed at this slow time scale, the slight hump (fast oscillation) after 1.5 to 2 minutes is not pronounced in this trace, and the actual light peak culminates after 4 to 5 minutes. **B,** an ERG displayed at a faster sweep speed. **C,** near threshold intensity, a pulse of 400 ms in duration elicits univariant ERGs for a given amplitude at different wavelengths. This trace is a response to a stimulus at 620 nm and an intensity of about 1.5 log units above the b-wave threshold. **D,** under adaptation to a rod-saturating white or yellow background,[77] the cone ERG matched for b-wave amplitude (but not for waveform) reveals small b-waves but a large a-wave and slow PIII. Note the strong photopic (negative) off-response. **E,** typical optic nerve response (ONR) at high stimulus intensity with the spike-shaped on-component; the falling, sometimes oscillatory plateau component; and the complex off-component. **F,** small ONRs can be recorded as univariant responses in rod-matched, dark-adapted conditions. **G,** light-adapted ONR revealing a large, spike-shaped off-component.

rons. Intracellular recordings from the RPE and from horizontal cells reveal responses to step changes in light as graded changes of their resting membrane potential; for spike-generating ganglion cells (see Fig 7 in Niemeyer[55]), extracellular monitoring suffices

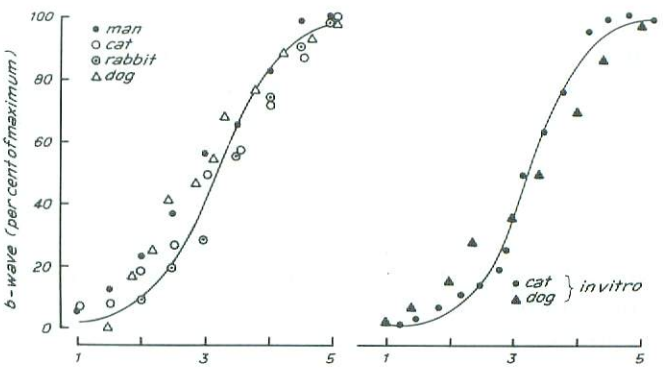

FIG 20–3.
V-log intensity curves of normalized b-wave amplitudes of dark-adapted eyes in vivo *(left)* and in arterially perfused preparations *(right)*. The position on the abscissa (log relative intensity) has been shifted for best fit by eye to the S-shaped function, that was drawn for $V = V_{max}\, I^n/(I^n + \delta^n)$, the intensity for $V_{max}/2$ was 3.3 log units, and the exponent n was 0.85 for the *left* curves; $V_{max}/2 = 3.45$ and $n = 1.0$ for the in vitro data *(right)*. (Data from Niemeyer G: *J Neurosci Methods* 1981;[55] 3:317–337, and for dog, in vitro, Schmidt B: *Graefes Arch Clin Exp Ophthalmol* 1986; 176:61–75.)

and is technically easier. If single-cell recordings are sufficiently stable before, during, and after the application of an active agent, the presence or absence of changes in the light-evoked signal helps, by comparison with changes in field potentials, in assessing the *site* of pharamcological action.

The chemistry of synaptic mechanisms in the vertebrate retina often requires very brief applications, e.g., by local iontopheresis. This topic has been reviewed recently by Dowling,[26] who documents, in a condensed form, the action of excitatory and inhibitory neurotransmitters, their analogues, and their antagonists. I should like to concentrate on slightly more clinically oriented experiments by selecting as examples phosphodiesterase (PDE) inhibitors, β-adrenergic therapeutic agents, and finally the effects of adenosine in relation to the effects of monoamines on the retina and on the RPE.

Phosphodiesterase Inhibitors and Cyclic Nucleotides

Interest in changing the retinal level of cyclic guanosine monophosphate (cGMP) or cyclic adenosine monophosphate (cAMP) arose from the importance of these nucleotides for signal generation within rods and cones, respectively.[13] Also, the possible involvement of cyclic nucleotides in the generation of the light peak has been tested experimentally. Several inhibitors of PDE have been used to transiently elevate the retinal levels of cGMP and cAMP.

Following the application of isobutylmethylxanthine (IBMX) to perfused cat eyes, Gouras and de Monasterio[38] reported an increase in a-wave amplitude. Gouras et al.[39] describe an increase in rod b-wave amplitude and discuss a possible link between the effects of elevated cGMP levels and rare cases of cone dystrophy associated with night blindness. The patients exhibited decreased b-waves at low stimulus intensities and increased b-waves at high ones; Yagasaki et al.[86] reported in 1986 two unrelated patients with clinical and ERG features similar to those described by Gouras et al.[39]

To test effects of elevated cyclic nucleotide levels on rod responses, Sandberg et al.[70] applied IBMX in 0.1M to 1mM concentrations to perfused cat eyes and observed a dose-dependent effect. Low doses of IBMX increased rod b-wave amplitudes, but only at high stimulus intensities. Higher doses reduced the ERG. The latter results and the increased implicit times of the a- and b-waves resembled the ERG pattern of retinal degenerations associated with night blindness.[66]

Schneider and Zrenner,[71] using four different inhibitors of PDE, including theophylline and ARL 115 BS, found increases in the cat's rod a- and b-wave amplitudes and implicit times. The cone data revealed a decrease in short-wavelength cone response amplitudes and a slight increase in long-wavelength cone response amplitudes. The amplitude of the ONR was diminished under rod stimulus conditions. However, the L-cone plateau and off-components of the ONR elicited in the L-cone system were enhanced.

Studying effects on the standing potential and light peak, Dawis and Niemeyer[21–23] applied dibutyryl cAMP and theophylline in micromolar concentrations to perfused cat eyes. Dibutyryl cAMP induced an increase in b-wave amplitude as well as in the standing potential and abolished the light peak reversibly. The data are indicative of cAMP regulation of some steps of light-induced responses of the photoreceptor-RPE complex. Theophylline had effects similar to those described for cAMP on the perfused cat eye: there was a dose-dependent increase in b-wave amplitude, a transient increase in the standing potential and c-wave, and abolishment of the light peak.[23] These data corroborate previous studies that indicated that cyclic nucleotides act on receptors in the RPE and in the retina of the cat eye.

The mosaic of these results from different laboratories can contribute to our basic understanding of parts of the retinal machinery and of models for the clinically relevant field of tapetoretinal degenerations.[52]

β-Adrenergic Mechanisms in the Retina

Therapeutically used β-adrenergic agents include the agonist nylidrin (analogous to buphenine) as a vasodilator, the β_2-agonist clenbuterol for the treatment of bronchospasm, and the spectrum of β-blockers used to lower intraocular pressure and in cardiac therapy. We examined whether β-agonists affected retinal electrophysiology (Fig 20–4) and retinal vessels and also whether β-blockers influenced

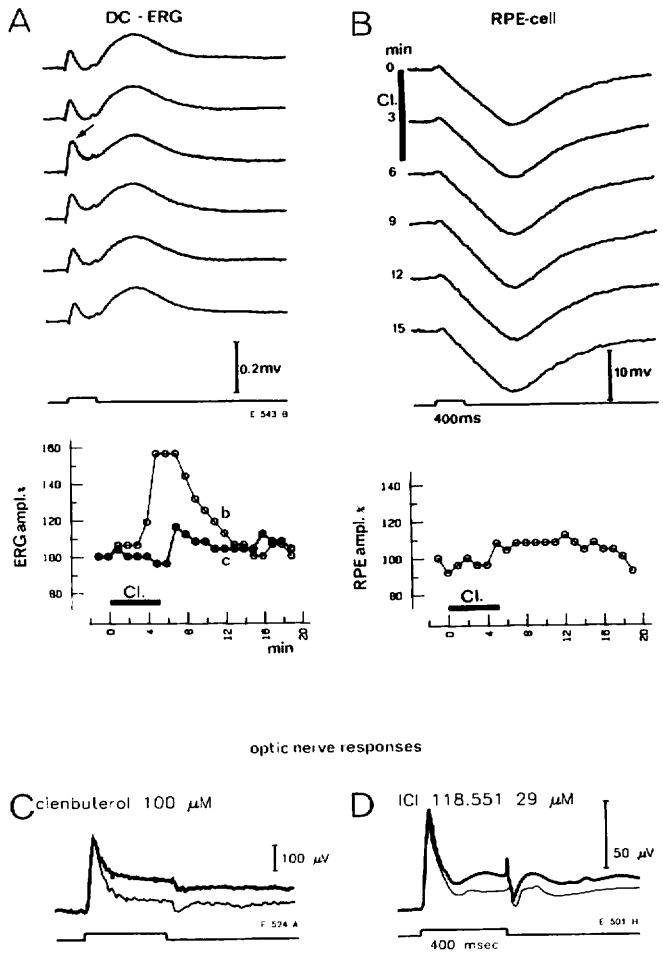

FIG 20–4.
Changes in extracellularly and intracellularly recorded light-evoked signals induced by the β_2-adrenergic agonist *clenbuterol (Cl)* in a perfused cat eye. The changes in amplitude of the plots can be read below *panels* **A** and **B. C**, depression of the ONR under clenbuterol (*thin* trace) vs. control (*heavy* trace). **D**, effects of a β_2-selective blocker, ICI 118.551, also reveal a depression of the ONR *plateau and* off-components.

the action of putative endogenous adrenergic transmitters.

Action of Agonists

The nonselective β-agonist nylidrin and the selective β_2-agonist clenbuterol were added for 10 minutes in micromolar concentrations to the intraarterial perfusate and were shown to increase the rod b-wave in a dose-dependent manner.

The on-component of the ONR was little affected, whereas the plateau phase and off-component were markedly depressed at higher concentrations.[60, 63] Cone-mediated responses were similarly affected.[77] Although β-agonists are known as peripheral vasodilators, there was no evidence of the decreased vascular resistance that would become evident as an increase in the flow rate of perfusate. Correspondingly, we failed to find measurable changes in the diameter of retinal arteries and veins.[17] Therefore, the changes in the optic nerve action potential and in b-wave amplitude are interpreted as responses mediated by neural and possibly by glial elements, respectively.

No β-agonist–induced changes in the intracellular responses of RPE and horizontal cells occur,[60] which suggests that the middle and inner retinal layers are the sites of action for β-adrenergic agonists rather than the other layers (Fig 20–4,B).

Action of Antagonists to Adrenergic Transmitters

Propranolol is the most effective agent, followed in descending order by ICI 118.551, timolol, and metoprolol. Propranolol had different effects on the rod and cone b-waves. The former were enhanced, whereas the latter were depressed, usually in a dose-dependent manner.[34, 35, 61] A qualitative overview is given in Figure 20–5.

These experiments thus reveal functional evidence for β-adrenergic mechanisms within the retinal rod and cone circuitry. Electrophysiological data point to the inner rather than the outer retina as the site of action. A comparison of the effects of β-blockers on the b-wave–generating mechanism vs. the purely neural ONR suggests more than one β-adrenergic receptor site in the cat retina, but further study is required.

Retinal Effects of Adenosine and Monoamines

Recent evidence shows release[27] and localization of adenosine by uptake autoradiography[7–9] in mammalian retinas and localization of adenosine in the human RPE.[32] We[7, 33, 62] found a decrease in vascular resistance of the perfused cat eye preparation (indicating vasodilation) and a corresponding increase in the perfusion flow rate (Fig 20–6, top) in the range of 4% to 25%, with reasonable dose-dependency. In DC recordings of the standing potential we observed a dose-dependent, reversible increase of 0.2 to 2 mV. The application of adenosine in 15μM and higher concentrations decreased and eventually abolished the light peak. The ERG b-wave increased in amplitude without a clear dose relation in the 0.5μM to 20μM range, as illustrated in the middle example in Figure 20–6. The most clear-cut, reproducible, and dose-dependent effects occured in ONR recordings, where all components were depressed by adenosine under selective rod or cone stimulation, e.g., in Figure 20–6, 20μM adenosine depressed the on-component of the ONR by

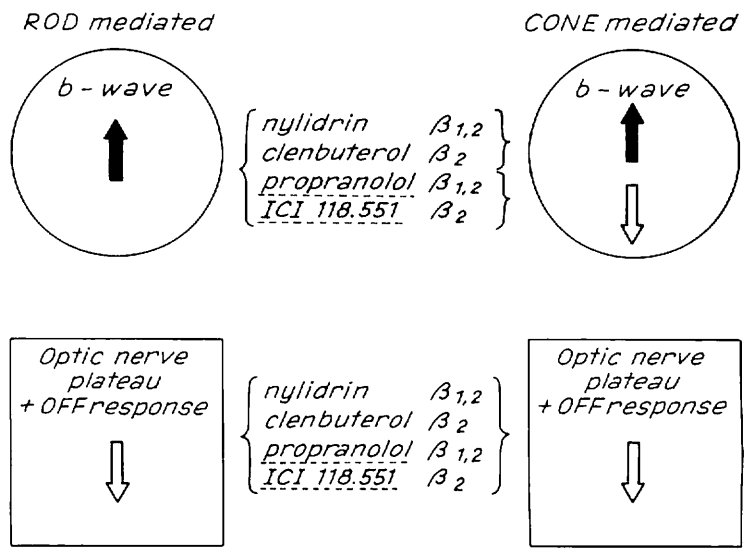

FIG 20–5.
Summary of effects of β-adrenergic agents on the ERG b-wave *(circles)* and on the ONR *(squares)*. On the *left*, rod-matched signals and, on the *right*, cone-matched signals are summarized, with *arrows* symbolizing increases and decreases in amplitude. Propranolol was used as a nonselective β-antagonist, and ICI 118.551 was used as a β_2-antagonist. L-timolol (unselective β-antagonist), metoprolol (β_1-blocker), and phentolamine (α-blocker) had no or minimal effects on the ERG and ONR.

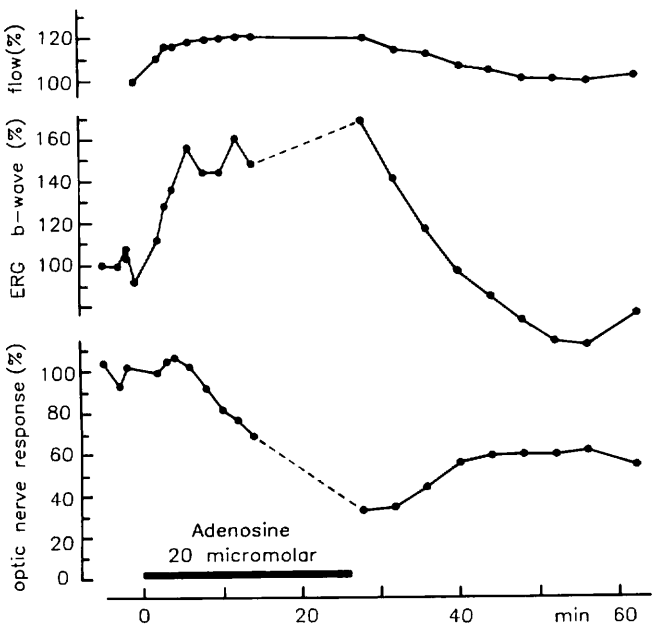

FIG 20–6.
Effects of adenosine on the perfusate flow rate *(top)*, ERG b-wave *(middle)*, and ONR on-component *(bottom)* in a perfused cat eye. Normalized values of synchronously recorded data are plotted vs. time; light-evoked electrical signals were not recorded when a light peak was elicited *(dotted lines)*. The increase in flow of perfusate, the marked increase in b-wave amplitude in dark-adapted preparations, and the profound depression of the ONR represent typical effects of adenosine.

70%. Changes in the rate of perfusion cannot be the sole and primary cause of the increase in b-wave amplitude and would be expected to increase, not decrease the ONR. The increase in standing potential and depression of the light peak are indicative of the presence of adenosine receptors in the cat's RPE. The different effects described suggest multiple receptor sites in the cat retina and thereby a complex modulatory role for adenosine. To differentiate between the involvement of A_1 vs. A_2 receptors, we applied cyclohexyl adenosine (CHA), an analogue that is known to interact with A_1 receptors at several orders of magnitude lower concentration than with A_2 receptors.[19] The results showed effects of CHA in the same dose range and direction as described above for adenosine. We therefore conclude that the effects described involve mainly A_2 receptor–mediated stimulation of adenylate cyclase in the cat retina.

Monoamines applied in a similar range of concentrations to the same preparation revealed comparable and marked effects on the standing potential and on the light peak: we found an increase in the standing potential and abolition of the light peak with 20μM to 140μM dopamine[21] and with 20μM norepinephrine, melatonin, and serotonin.[22] Similarly, 480μM dibutyryl cAMP increased the standing potential and abolished the light peak reversibly.[21] These data suggest that the monoamines, adenosine, and cAMP interfere with the messenger or intracellular RPE mechanisms that generate the light peak, possibly in a saturating fashion. A common factor for these active agents might be action via changes in cyclic nucleotide metabolism.

ELECTROPHYSIOLOGY AND CLINICAL PHARMACOLOGY OF THE RETINA

This topic appears not to exist as a coherent entity; pharmacology of the eye largely emphasizes therapy for glaucoma with cholinergic and adrenergic drugs and with inhibitors of carboanhydrase. The systemic effects of topically applied ocular therapeutic agents and, more importantly, the ocular side effects of systemically applied drugs only on rare occasions involve the RPE and the retina and, because they exceed the limits of this discussion, are treated under general pharmacology.

Obviously, textbooks listing systemic effects of ocular drugs and ocular side effects of systemic drugs are best suited to answer the reader's specific questions.[31, 72, 74] Special topics such as dopamine, chloroquine, and ethambutol are treated in other chapters of this book, and specific articles are scattered in a variety of journals. Therefore only arbitrarily selected issues can be briefly addressed here. When related to electrophysiological testing, experimental work on animals frequently provides the basis for the understanding of pharmacological mechanisms, an example once more of the interrelation between basic and clinical research. I should like to point out that clinically relevant effects on retinal function might reflect the complex interaction of mechanisms involving neural, glial, and vascular receptor sites. The multiple routes of modifying postsynaptic neuronal activity include a change in transport and reuptake of the transmitter (i.e., via autoreceptors, action of an endogenous substance on the release process, presynaptic inhibition via an axoaxonic synapse, and mechanisms that change ionic conductances of the presynaptic and postsynaptic membranes.[16]

Topical Application

For active agents large and variable concentration gradients between eye drops and aqueous humor can be measured.[49] A further significant dilution can

be expected before a retinal concentration has arisen. The penetration of agents through the cornea varies with factors such as lipophilicity vs. hydrophilicity, surfactant additives, and possible inflammatory preconditions of the tissue.[50] The clinical dosage of topical drugs can be compared with experimentally applied concentrations by useful tables that list the milligrams of substance per drop.[74] The comparison to experimental dosage becomes pertinent when addressing the issue of whether eye drops can cause functional changes in the retina or in other parts of the central nervous system (CNS). The first possibility is difficult to test since agonists or antagonists of endogenous retinal neurotransmitters and neuromodulators might induce subtle changes in specific visual functions such as receptive field center–surround balance, contrast sensitivity, temporal resolution, adaptation, thresholds, or color discrimination. The assessment of changes in these functions would require a considerable and specific effort in clinical testing. CNS symptoms, however, are not uncommon. They occur mainly as signs of muscarinic blockage following enhanced absorption of the anticholinergic cyclopentolate HCl or atropine with symptoms of restlessness, disorientation, and hallucinations or as signs of β-adrenergic blockade with symptoms of anxiety.[65, 73]

Systemic Drugs and Retinal Side Effects

A general list of potentially retinotoxic, systemically applied drugs includes quinolines, phenothiazines, tetracyclines, glycosides, carotinoids, antimetabolites (i.e., vinca-alkaloids), and the occasionally neurotoxic drugs ethambutol, isoniazid, sulfonamides, streptomycin, and disulfiram. The retinal toxicity of chloroquine appears to be more frequent than that of the other groups and is discussed in depth in Chapter 78.[29] The toxicity of phenothiazines and quinine, including electrophysiological changes, is documented in older reports.[73] The effects on retinal function in Parkinson's disease and after treatment with L-dopa are discussed in Chapter 114.

Retinoids

A comprehensive description of the physiological role of vitamin A including some retinoids, its use in therapy, and its potential toxicity (hypervitaminosis) is given by Mandel and Cohn[46] and by Chader.[5] Weleber et al.[80] extensively examined patients treated with 13-*cis*-retinoic acid (isotretinoin, Accutane) for severe acne and found relevant symptoms in 3 of 50 subjects. These included poor vision, glare sensitivity, elevated cone or rod thresholds in dark adaptometry, and changes in the ERG; there was a decrease in b-wave amplitude that was also seen in a compression of the Naka-Rushton V/log I function with an elevation of the half-saturation intensity by 0.7 log units (1 patient) as well as a depression of the oscillatory potentials. The electrophysiological changes remained abnormal for 6 to 12 months after the cessation of therapy.

Adverse effects on structures in the outer eye and teratogenic consequences of treatment with isotretinoin have been summarized by Fraunfelder and Meyer.[31] Kaiser-Kupfer et al.[43] reported reversible depression of the rod ERG that was induced by another analogue of vitamin A, fenretinide, used in the treatment of basal cell carcinoma.

Canthaxanthine is a food colorant that is related to β-carotene. Orally administered canthaxanthine and β-carotene were widely available as a means of producing a skin coloration (an artificial tan) that has a protective action in certain photodermatoses. Canthaxanthine-induced crystalline deposits in the retina have been described by several authors (for a review see Barker[4]). In a proportion of patients, this causes the dramatic appearance of spectacularly reflective golden crystals. While these may slowly vanish, they can remain for years after the end of canthaxanthine administration. In all, canthaxanthine is deposited as a phospholipid complex in the inner retinal layers, in abnormal cisternae associated with Müller cells.[78] Weber et al.[79] reported electrophysiological changes in patients treated mainly for erythropoietic porphyria. Normal EOG Arden ratios suggested an absence of functional changes in the RPE, which is in keeping with the histological findings in humans. The ERG, in contrast, revealed dose-dependent changes: in the course of dark adaptation low doses of carotenoids tended to enhance the b-wave amplitude, while higher doses (75 to 100 mg/day) depressed the b-wave to subnormal values. The amplitudes of the oscillatory potentials were decreased, and the implicit times of the a- and b-waves were prolonged with the highest dose levels. However, contrary findings have been reported. Arden et al.[3] monitored ERGs and other functions in a number of patients over several years and determined that the only observable change was a decrease in the V_{max} of the scotopic b-wave that returned to normal during the winter months when drug administration was discontinued. When it began in the summer months, the reduction was associated with doses of 60 mg/day, and the best correlation was with the appearance of crystals, not with

the total dose or blood level. Implicit times, photopic ERGs, and a-waves were unaffected. These authors consider that the effects on the retina are thus confined to the Müller cells and may be accounted for if the ionic "funneling" of these cells is reduced when they accumulate canthaxanthine and exocytose it to form the crystals; this explanation agrees with the known histology. The absence of canthaxanthine in the outer retina and the fact that the condition is always asymptomatic are difficult to reconcile with reports of a 2 log unit loss of retinal sensitivity[80] without the dramatic alteration in the ERG that would be expected. However, higher dosages in animals can cause damage to the outer retina, and adverse reactions that might imply neural damage have only been reported with high dosage. There is a likelihood that canthaxanthine accumulates in eyes in which the RPE is already damaged,[3] and crystals have been reported in persons who have never taken the compound for medical reasons.

Iron Chelators

Deferoxamine (Desferal) is used in the treatment of thalassemia and, if given nightly by slow subdermal infusion, prevents to a considerable degree the siderosis that previously caused severe damage to the myocardium, pancreas, liver, hypothalamus, etc. Desferal was thought to be a relatively safe drug and not only prolonged life but increased its quality: children so treated had normal stature and entered puberty, although a high proportion became diabetic. However, after many years, a severe retinopathy was reported.[19a] Inspection of the original toxicological data showed that only on one occasion had it been given intravitreally, which then destroyed the eye within a day or so; this suggests that the reported lack of any ocular toxicology (which allowed this compound to be marketed) was due to the fact it could not penetrate the blood-retina barrier. Analysis of human data[3a] showed that the reductions in the b-wave were correlated to the diabetic state of the patients. Diabetic retinopathy of course causes breaches in this barrier; thus the drug was preserving life (by preventing cardiomyopathy), although the siderosis, which was only partially reversible by Desferal, was rendering the patients diabetic, and this caused changes that allowed the toxicity of Desferal to become evident. This conclusion was reinforced by reports that in patients with rheumatoid disease Desferal causes a variety of severe CNS symptoms after only a few days' administration.[41] In rabbits anesthetized with urethane, which opens the blood-retinal barrier, the intravenous (IV) infusion of Desferal caused a change in the b-wave that amounted to light adaptation: sensitivity declined, and the V/log I curve shifted to the right. The c-wave was also reduced, but these effects were reversible.[69] The incidence of the retinopathy has been reduced by abandoning the practice of giving the drug IV; the subcutaneous route appears safer, for the drug combines with iron rapidly, so the free concentration in the blood is very low. Monitoring of thalassemics treated with iron chelators by serial PERG and visual evoked response (VER) is now recommended.

Vinca Alkaloids

Vincristine and vinblastine, successfully applied in the treatment of malignant tumors, can induce marked side effects, mainly in the peripheral nervous system. However, acute visual problems have been reported as retinal[67] or suspected cortical[12] blindness. The changes in visual function are in most reports considered to be potentially reversible. Experimental studies include retinal changes in the pigeon,[28] rabbit,[41] and cat.[69] The fundamental mechanism of action of vincristine in the CNS appears to be based on morphological changes in microtubules that resulted in compromised axoplasmatic flow; this was described for the pigeon's visual systems after intravitreal applications with attenuation of postsynaptic evoked potentials in the tectum—changes that were reversible within several weeks.[28] Ripps et al.[69] studied the effects of vincristine in isolated, perfused cat eyes and addressed questions on the ultrastructure, blood-retina barrier, and effects on the ERG and on the kinetics of rhodopsin. Vincristine-containing (20 to 100 μg) perfusate was substituted for control perfusate for 60 to 90 minutes. Horseradish peroxidase was used in some experiments to assess the status of the blood-retina barrier before and after application of the agent. Briefly, the results of the various studies in the perfused cat eye revealed major changes in retinal morphology and in the ERG but no changes in the kinetics of rhodopsin.[68] We have evidence that vincristine can compromise the blood-retina barrier, which may explain why CNS and, in particular, visual side effects are only occasionally observed in patients. Histological examination revealed paracrystals in the visual cells, less frequently in the nerve fiber layer, and only occasionally in the RPE. The microtubular system was markedly changed in the axons of photoreceptors.

The ERG underwent characteristic and dose-dependent changes consisting of an early decrease in the amplitude of the c-wave and standing poten-

tial followed by a decrease in b-wave amplitude. These changes occurred later and were less pronounced at lower arterial concentrations of vincristine. In preliminary experiments, reversibility of the changes described above could be seen within hours following shorter injections of the active agent (Niemeyer, Peachy, and Ripps, unpublished observations). Similar electrophysiological changes in b-waves with well-maintained a-waves and slow PIII comparable in several respects to congenital stationary night blindness were described by Ripps et al.[68] in a patient presenting with night blindness following vincristine therapy. Thus the experimental study of the effects of vinca alkaloids and corresponding clinical observations not only provide insight into the mechanisms of action of a clinically important drug but may also enhance our understanding of aspects of inherited abnormalities of the function of the human retina.

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