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Dopamine and retinal function

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Abstract

This review summarizes the experimental evidence in support of dopamine's role as a chemical messenger for light adaptation. Dopamine is released by a unique set of amacrine cells and activates D1 and D2 dopamine receptors distributed throughout the retina. Multiple dopamine-dependent physiological mechanisms result in an increased signal flow through cone circuits and a diminution of signal flow through rod circuits. Dopamine also has multiple trophic roles in retinal function related to circadian rhythmicity, cell survival and eye growth. In a reciprocal way, the health of the dopaminergic neurons depends on their receiving light-driven synaptic inputs. Dopamine neurons appear early in development, become functional in advance of the animal's onset of vision and begin to die in aging animals. Some diseases affecting photoreceptor function also diminish day/night differences in dopamine release and turnover. A reduction in retinal dopamine, as occurs in Parkinsonian patients, results in reduced visual contrast sensitivity

Abbreviations: ACh–acetylcholine; CT–circadian time; DA–dopaminergic; D1R, D2R–D1 dopamine receptor, D2 dopamine receptor, etc.; DD–complete darkness; DOPAC–dihydroxyphenylacetic acid; ERG–electroretinogram; GABA–γ-aminobutyric acid; HVA–homovanillic acid; I_{Ca}–a calcium current; $I_{Cl(Ca)}$–a calcium-dependent chloride current; I_h–a hyperpolarization-activated current; INL–inner nuclear layer; IPL–inner plexiform layer; LD–light-dark cycle; L-DOPA–levo-dihydroxyphenylalanine; MAO–monoamine oxidase; 6-OHDA–6-hydroxydopamine; OPL–outer plexiform layer; PERG–pattern electroretinogram; RPE–retinal pigment epithelium; RCS–Royal College of Surgeons; STR–scotopic threshold response; TH–tyrosine hydroxylase; TTX–tetrodotoxin; VMAT2–vesicular monoamine transporter 2; ZT–zeitgeber time.

Introduction

Dopamine is only one of many neuroactive chemicals in the body and brain and yet it deserves special attention because of its involvement in a very diverse and very basic set of functions, including motor behavior, cognition and emotional states. When things go wrong with the dopamine system, the consequences for the body and the brain are severe – they include Parkinson's disease, Huntington's chorea, tardive dyskinesia, and schizophrenia. Many drugs associated with addictive behavior, such as amphetamines and cocaine, act through dopaminergic neurons.

Over the past 30 years or so, moreover, we have come to appreciate the importance and the complexity of dopamine's multiple roles in retinal function. The first general hypothesis that emerged is that dopamine is a chemical messenger for light adaptation. A second focus of interest, one that is still developing rapidly, concerns the involvement of dopamine in more trophic functions of the retina. These include growth, development, cell death, experimental myopia and the like. A general hypothesis about how dopamine carries out these trophic functions remains to be developed, but an interesting point conveyed by this body of research is that the interactions of the neural retina and the dopaminergic system are very much a two way

street. When, for example, photoreceptors degenerate, as they do in some inherited retinal diseases, the dopaminergic system shows a less pronounced daily rhythm of dopamine production and release. These experimental findings underscore that some aspects of retinal function are plastic, and they bear on studies of animal models of retinal diseases and on the diagnosis and treatment of certain retinal diseases in humans.

Before entering into the details it is worth mentioning that dopamine acts through G-protein coupled receptors, and that its most common action is to change the rate of cAMP production, either upwards or downwards. The complications arise because cAMP participates in a wide variety of cellular mechanisms and because cells respond to multiple neurotransmitters and neuromodulators whose actions overlap in time and space. Reviews of the literature are useful in collecting and organizing references to recent work, but as that literature becomes more complex and voluminous, it can be challenging to plow through. In this review I try to relate the findings to the two main questions posed above – how does dopamine fulfill its role as a chemical messenger for light adaptation, and how does dopamine carry out its trophic functions– in the hope that when the experimental details are linked to a general framework, the whole becomes more digestible. I have placed most emphasis on newer data from mammalian retinas; readers may consult [1, 2] for a discussion of the older literature, much of which deals with studies of cold-blooded vertebrates.

I begin with the first question, which requires a review of the dopaminergic neurons in the retina, their morphological appearance and the way in which they respond to light stimuli and release dopamine. Next we consider the receptors through which dopamine acts and their distribution in the retina (recently reviewed in [3, 4])

Form and synaptic connections of dopaminergic neurons in the retina

In mammalian retinas, the dopaminergic (DA) cell bodies are found among the layer of amacrine cells, at the border of the inner nuclear (INL) and inner plexiform layers (IPL) (Figure 1a). The density of DA neurons in vertebrate retinas is low, about 10–100 mm^{-2}, but each cell gives rise to multiple processes that radiate far enough to overlap with those of neighboring DA cells. DA processes are of two sorts: relatively thick and irregularly shaped dendrites whose arbor has a diameter of about 0.5 mm, and multiple fine axons bearing varicosities, which extend up to several mm from the cell body [5]. According to this study [5] , it is the axons which form the plexus of fine fibers illustrated in Figure 1b. Tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis, and dopamine itself are present throughout the cell, including the finest processes and terminals.

As Figure 1a makes clear, almost all of the dopaminergic processes extend in a narrow horizontal plane situated in the distal portion of the IPL, corresponding to the region in which OFF bipolar cells terminate [6]. A few processes emerging from the DA cell pass to more proximal layers of the IPL. Synaptic input to such processes would be a basis for signals from the ON pathway to modify DA neurons, but such inputs, if they exist, are sparse [7]. Marshak [8] has argued on functional grounds that even though the DA neurons receive bipolar cell input in the 'OFF' zone of the IPL, the bipolar cell in question is a special, so called 'giant bistratified' variety, [9, 10]. The way in which this bipolar cell responds to light is unknown. In my opinion, it is still not firmly established that the giant bistratified bipolar provides input to DA neuron and, moreover, DA neurons might receive input from more than one bipolar cell type. On the output side, DA neurons make morphologically defined synapses onto two types of amacrine cells, the AII and the A17 amacrines, both of which belong to the rod pathway (reviewed in [11]. The perikarya of these amacrines reside within rings of DA processes (Figure 1b). The DA neurons also contain the transmitter, GABA [12, 13]. Contini and Raviola [14], examining the interface between DA neurons and AII amacrines, found post-synaptic $GABA_A$ receptors on the AII amacrine in register with the GABA vesicular transporter on the DA neuron. The AII amacrine has receptors for dopamine of the D1 subtype. [15]. Together these indicate that DA cells make both dopaminergic and GABAergic synapses onto the AII neuron, perhaps at the same point, but this is not yet established.

These anatomical data can be integrated with the recent finding [16, 17] that DA neurons fire action potentials. In the absence of synaptic input the cultured DA cell fires spontaneously at a modest rate (<10 spikes/s); this rate is increased by exogenous kainate (acting at an AMPA receptor) and decreased by exogenous GABA and glycine [17]. DA neurons have been shown to possess glutamate receptors of the AMPA sub-type [18] and GABA receptors of the GABA-A subtype [19]. It is thus clear that the DA

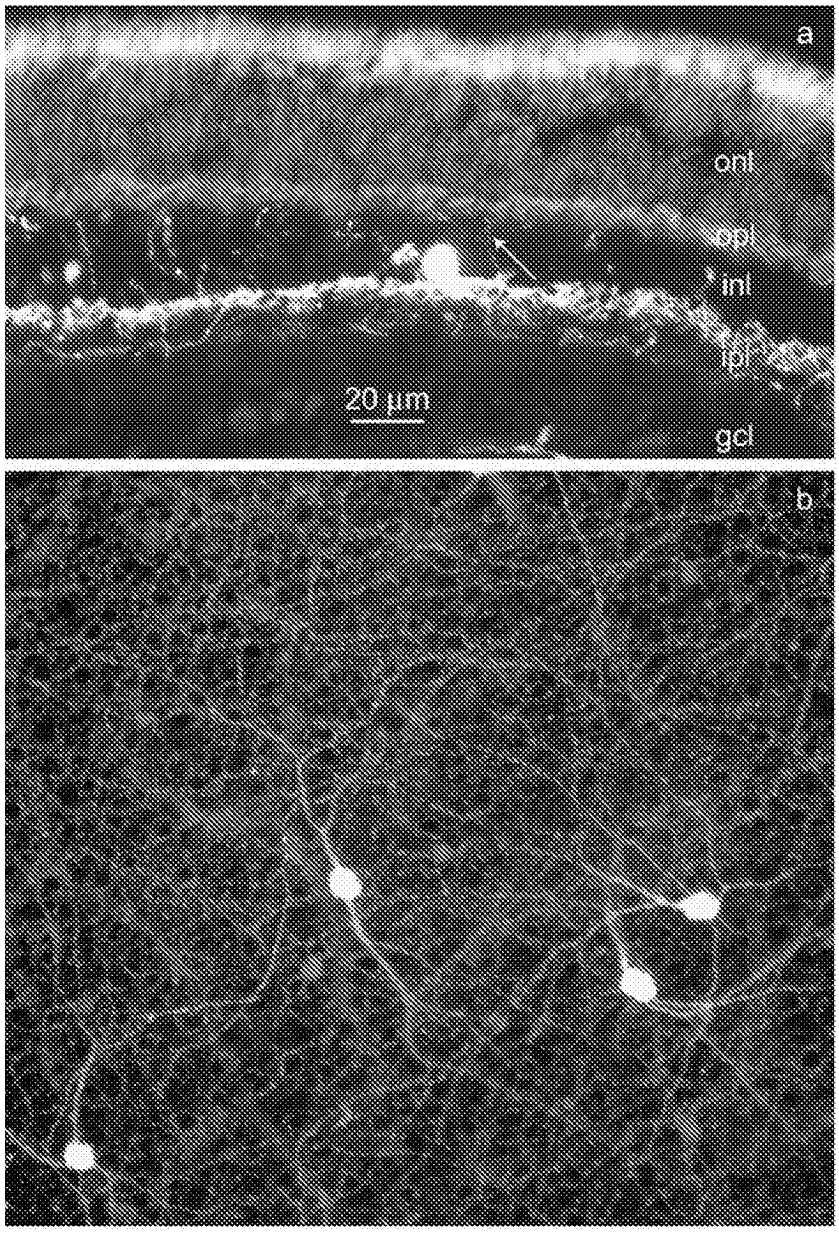

Figure 1. Structural organization of dopaminergic neurons in the rat retina. (a) Vertical section through the rat retina showing a DA perikaryon and DA processes visualized by immunocytochemical staining with an antibody against tyrosine hydroxylase. The arrow points to an ascending process which reaches the outer plexiform layer. (b) A horizontal view showing DA cell bodies, primary dendrites and fine processes disposed in rings in the distal portion of the inner plexiform layer. The 20 µm marker bar serves for both (a) and (b). gcl, ganglion cell layer; inl, inner nuclear layer; ipl, inner plexiform layer; onl, outer nuclear layer; opl, outer plexiform layer.

neuron receives a mix of excitatory (glutamatergic input from one or more type of bipolar cell) and inhibitory (GABAergic and glycinergic contacts from different amacrine cells) synaptic inputs to its dendrites which set the level of excitability of the cell. Spikes conducted along the multiple axons control the release of dopamine at multiple points along the axon.

Although, as just indicated, certain amacrines receive input from DA neurons at morphologically defined synapses [7], the vast majority of retinal cells respond to dopamine that reaches them by diffusion, a communication path referred to as paracrine or volume conduction. The diffusion path may be long, 10 s of microns, or it may be from less than a micron away. In that regard, a variable fraction of DA cells (the fraction varying with the species being studied) emit fine processes that run more or less vertically towards the outer plexiform layer (OPL) (arrow in Figure 1a) where they end in close association with photoreceptors, bipolars and horizontal cells [5, 7, 20]. Most studies of OPL DA processes indicate that they do not make morphologically defined synapses (but cf. [21] in goldfish and Cebus monkey and [7] in cat retina).

It is an interesting fact that all of the DA processes are filled with tyrosine hydroxylase and also with dopamine, as indicated by fluorescence studies [22], indicating that the DA cell makes dopamine throughout the cell and presumably releases dopamine at many points along the axon. Release of dopamine is a calcium-dependent process, suggesting that it is released from synaptic vesicles or from a similar membrane-bound packet. A reasonable idea is that the spike-induced depolarization of the axon increases Ca entry, and this gates transmitter release. Puopolo et al. [23] used a dopamine-sensitive electrode to show that small bursts of dopamine were emitted from DA perikarya. Release of dopamine was found to be dependent on spike firing; blockage of spikes with TTX led to a cessation of release [23]. The sites of release within DA perikarya have yet to be identified. There are no groups of vesicles and the vesicular monoamine transporter (VMAT2) is sparse [14]. It is probable that, *in vivo*, most dopamine is released from the DA axons, which is where most of the vesicular monoamine transporter, VMAT2, is located (Witkovsky, unpublished findings).

To summarize, the anatomy and physiology of the DA cell coalesce in the following interpretation of how the DA neurons respond to light and release dopamine. The cell has an intrinsic spike firing rate (the *in vivo* rate has yet to be determined and might well vary between day and night). Dendrites receive excitatory (glutamatergic) and inhibitory (gabaergic and glycinergic) inputs that raise or lower the intrinsic firing rate and in this way modify the rate of dopamine release. The cell body and its dendrites are electrotonically compact, meaning that dendritic EPSPs and IPSPs will be sufficiently large to influence the spike generating zone in the perikaryon. Axons carry the spike message to distant sites of release, assuring that all parts of the cell respond similarly. The extensive overlap of dendrites and axons in the inner plexiform layer means that dopamine will be released more or less evenly at every point and also that the dopaminergic signal could not convey spatial information, except on a very crude level.

Dopamine receptors

To begin to understand what dopamine does when it reaches a target cell, we next examine the dopamine receptors. Dopamine acts through five receptor subtypes (D1–D5) [24, 25], all of which belong to the superclass of G-protein coupled, 7-transmembrane loop receptors. Dopamine receptors are grouped into two families: the D1-like receptors, which include D1R and D5R, and the D2-like receptors, D2R, D3R and D4R. Each receptor is encoded by a different gene located on different chromosomes (Table 1). The amino acid sequences of the receptors are known, revealing a substantial overall similarity, particularly in the highly conserved transmembrane regions. Additional variants of dopamine receptors are created through post-translational splicing (Table 1). An interesting finding is that the D1R family is intronless, whereas the D2R family contains introns, most of which are in the coding region of the receptor, thus allowing for alternate splice variants [25].

Dopamine receptors are coupled to a few different G-proteins, suggesting that they activate different cascades. The main functional difference is that the D1 family is linked to activation of adenylate cyclase and an increase in cAMP, whereas activation of D2Rs leads to inhibition of adenylate cyclase and a drop in cAMP. Other cascades involving phospholipase C or arachidonic acid have been suggested, but there is still no strong evidence that these underlie any of dopamine's actions in the retina.

Dearry et al. [26, 27] cloned D1- and D2Rs and expressed them in COS-7 cells. In that expression system, the D1R activated adenylate cyclase in

Table 1. Properties of dopamine receptors in humans

Sub-type	Amino acids	Chromosome	G-Protein	G-Protein coupling
D1	446	5	G_s, G_o	↑ Adenylate cyclase[a]
D5 (D1b)	477	4	G_s	↑ Adenylate cyclase
D2 short	414	11	G_i, G_z	↓ Adenylate cyclase[b]
D2 long	443	11	G_i, G_o	↓ Adenylate cyclase
D3	400	3	G_s, G_z, g_i	↓ or ↑ Adenylate cyclase
D4 (many alleles)	387–515	11	G_i, G_o	↓ Adenylate cyclase

[a] Also reported to increase phosphoinositide turnover.
[b] Also reported to increase $[Ca^{2+}]_i$ through phosphoinositide hydrolysis or to increase arachidonic acid release. For more details, consult Ref. [22–26].

a concentration-dependent manner, with a threshold near 10^{-8} m dopamine. The D2R inhibited adenylate cyclase, again in a concentration-dependent way with a threshold near 10^{-9} M. These values are important in relation to the concentration of dopamine seen extracellularly in the retina. Functional studies in brain [28] show that D3Rs inhibit adenylate cyclase activity. The D3R is the least studied dopamine receptor and has so far not been identified in the retina, at least in its prototypical form, but it is certainly possible that new hybrid varieties of dopamine receptor will be uncovered. For example, a recent study [29] used D2/D3 chimeras to show that if the third cytoplasmic loop has a D2R sequence the receptor couples to the inhibitory G-protein, G_i; a D3R sequence in that same region results in coupling to the excitatory G-protein, G_s.

Autoradiography using specific D1- or D2-family receptors or immunocytochemistry using dopamine receptor-specific antibodies have been used to probe where in the retina the different receptors are located. The results are that the retinal pigment epithelium has a D5 receptor [30], both rod and cone photoreceptors have D2 family receptors [31], which are D4 receptors in the mouse [32] and have not been sufficiently characterized in other species. Bipolar, horizontal, amacrine and ganglion cells have D1 receptors [15, 33]. One exception is that the DA neuron itself has a D2 receptor [34], the so-called autoreceptor [35], which functions to inhibit dopamine release. In addition to its neurons, vertebrate retinas have Mueller glial cells which are a target of the DA system [36], and in mammalian retinas the pericytes of retinal blood vessels appear to receive a dopaminergic input [37]. The techniques for identifying dopamine receptors still are relatively crude, generally indicating their presence in layers rather than specific retinal neurons. One may therefore anticipate changes in our understanding of the distribution of dopamine receptors in the retina as more refined techniques are brought to bear.

Many organizational features of the retinal dopaminergic system favor its working through volume conduction.The spatial separation of the source of dopamine from its retinal receptors has been mentioned [38]. Another point relates to the inactivation of dopamine, which occurs first by recapture via a high affinity dopamine transporter located on the dopaminergic neuron itself. In this context the essentially two-dimensional configuration of the dopamine neurons (cf. Figure 1) means that once dopamine escapes recapture at the INL/IPL border, it is free to diffuse both towards the vitreous and towards the distal retina. Recaptured dopamine is metabolized by MAO and other enzymes [39], giving rise to a metabolic by-product, DOPAC (dihydroxyphenylacetate). The DA/DOPAC ratio is a good indicator of dopamine turnover. In the striatum where dopaminergic processes invade every corner of the tissue, DOPAC/Dopamine is 1000:1 or less, meaning that 999 of each 1000 dopamine molecules released are recaptured and metabolized by DA processes. In the retina, DOPAC/dopamine is very much lower [40, 41], around 1:1, indicating that 50% of the dopamine escapes recapture. A corollary is that extracellular [dopamine] is much higher in retina than in the striatum. A study combining a diffusion model for dopamine combines with direct measures of [dopamine] in the extracellular fluid of the retina indicate values between 100 and 1000 nM [41], which is in the right concentration range to activate the dopamine receptors[26, 27]. This need not mean that striatal receptors operate in a different concentration range of DA, but rather that the local concentration of dopamine directly opposite the point of release is more important than the average concentration in the extracellular fluid.

The differing sensitivities to dopamine of the dopamine receptors also contribute to their relative activation. Dopamine concentrations are not constant, either in space or time. A circadian rhythm of dopamine production and release increases dopamine during daytime hours and lowers it at night [42]. Local diffusion barriers and variable distance from the source of dopamine influence extracellular [dopamine] in the retina. Thus the finding that D5Rs are 10–20× more sensitive to dopamine than D1Rs [22, 23] may be important, given that D5Rs are found on the RPE, which is the retinal cell most distant from the source of dopamine. Similarly the finding that D2Rs are more sensitive to dopamine than D1Rs may allow them to be modulated by dopamine at night, when dopamine concentrations are low. In relation to considerations of dopamine receptor sensitivity, it has been shown that dopamine receptors undergo desensitization as a result of prolonged exposure to agonist [43], a factor that might be operative in the retina, where dopamine is being released continuously. On the other hand, the numbers and/or the sensitivity of dopamine receptors are subject to up-regulation when dopamine concentrations are very low. There is suggestive evidence that these sorts of regulation of dopamine receptors occur in retina [44, 45].

Daily rhythms of dopamine production and release

As a point of clarification, the term 'circadian', meaning 'about one day', refers to a rhythm that persists in the absence of external cues. For the retina the most important cue is light, so to claim a circadian rhythm for the retina requires the experimenter to show that it persists in complete darkness (DD). In such experiments subjective time is indicated as circadian time (CT), and CT 12 indicates the onset of activity. This is not to say that light has no influence on circadian rhythms; in fact light, when presented during subjective night, resets the clock, as shown for example in running patterns of rodents [46]. Other rhythms may be regulated by light but lack a circadian component; rhythm studies carried out in a light/dark cycle are marked in 'zeitgeber' (time-giver) time (ZT) where ZT 0 indicates onset of light and ZT 12 onset of darkness.

The daily rhythm of dopamine production and release depends on an interaction between photoreceptors and DA neurons. Amphibian retinal photoreceptors have a circadian clock which controls the activity of the enzyme, *N*-acetyltransferase, the rate-limiting enzyme in the synthesis of serotonin and melatonin [47]. Cahill and Besharse [48] showed that the rhythm of melatonin production persisted in a cultured eyecup containing a reduced retina consisting only of photoreceptors. Melatonin acts to suppress dopamine release, whereas dopamine, acting through D2-like receptors on the photoreceptor cells, inhibits melatonin production [49]. The result is two rhythms in counterphase, with melatonin being high at night, dopamine high in daytime. Is the production and release of dopamine therefore a circadian process? The experimental tests of this question have not led to a uniform answer. The problem depends, in part, on what is measured and under what conditions. Some studies have looked at total retinal dopamine content (i.e., the amount stored in DA neurons), but this is not always a reliable measure, because catecholamine systems throughout the body balance production and release, keeping catecholamine content steady (reviewed in [39]). A better way is to examine either daily variations in **extracellular** dopamine concentration (a measure of [release – reuptake]), or in the production of dopamine metabolites, such as DOPAC or homovanillic acid (HVA).

In the mammalian eye, there is good evidence that dopamine release and DOPAC production are higher in light than in darkness [40]. At this juncture it is worth emphasizing that dopamine is released in both light and darkness. The term 'darkness' moreover needs to be carefully specified because it relates both to the day/night cycle and to the absence of illumination. For an animal exposed to a normal day/night cycle, dopamine release at 09:00 will be greater than at 02:00, even if in both cases the animal is in the dark. Recently Tosini and Menaker [50] found a circadian clock regulating melatonin production in the mouse eye and Doyle et al. [51] reported that if rats were maintained for 14 days in complete darkness, a retinal rhythm of DOPAC and HVA production persisted, although somewhat damped by reference to values in LD. It seems fair to conclude that mammalian eyes have a circadian rhythm of dopamine release and metabolism, one that is reinforced by light.

Melatonin appears to act in two ways: as an antioxidant and through G-protein coupled receptors (reviewed in [52, 53]). The antioxidant role has been little explored, but Marchiafava and Longoni [54] describe its action in preventing oxidation of a dye injected into frog photoreceptors and suggest it may protect against the oxidative effects of light. Three Mel1 receptor subtypes (Mel1a-c) have been cloned [52] and of these, there is evidence that at least the Mel1a/b subtype is

found in the mammalian retina [53, 55, 56]. The distribution of melatonin receptors within the guinea pig retina has been studied [56] and located on dopaminergic and gabaergic amacrine cells. A general action of such receptors is to reduce [cAMP], but exactly how they act in retina remains to be worked out. What is clear is their high sensitivity: Dubocovich et al. [55] found that 20 pM melatonin inhibited [^{3}H]dopamine release by 50%, which correlates well with the affinity of the Mel1b receptor for 2-[^{125}I]iodomelatonin.

Dopamine is not required to maintain a circadian rhythm of melatonin production, since that rhythm persists in an isolated layer of photoreceptors [48], but the dopamine rhythm does appear to depend on melatonin. In balb/c mice, which cannot synthesize melatonin, the rhythm of dopamine utilization is lost in DD [40]. A rhythm of dopamine utilization is present in LD, however, indicating that light operates on dopamine through multiple pathways (see below). In a strain of mice (C3H/rd) in which rods undergo degeneration during post-natal development, the loss of rods results not in the disappearance of melatonin, but in the loss of rhythmic synthesis [57]. Thus rods appear to have components of the biological clock required to set the rhythm.

In that regard, much recent work has been directed towards identifying components of the biological clock in the retina. This fascinating subject is too complex to be reviewed here (cf. [58, 59]), but two points need to be made in relation to the retinal functions of dopamine. The first is that clock proteins now have been identified in many retinal neurons besides photoreceptors [60, 61], and one of these is the dopaminergic neuron [62]. The other is that there are visual pigments in the retina beyond the Vitamin A-based opsins, and they, like the clock proteins, are found in multiple classes of retinal neuron [63–65]. These additional pigments appear to account for the finding that nominally blind rodents still retain rhythms of locomotor activity [66] and still show light-dependent entrainment of the suprachiasmatic nucleus (SCN) [67], where the main clock of the body is located [68]. Possibly signals initiated by these novel pigments impinge on the functioning of the retinal DA system.

To summarize all the above, dopamine is released by a unique set of dopaminergic amacrine/interplexiform neurons. A combination of circadian rhythmicity and light ensures that retinal dopamine levels rise around dawn, the time at which vision switches from being rod-mediated to cone-mediated. Rod vision is characterized by high sensitivity, but low acuity; cone circuits by the reverse. Cone circuit function is measured by contrast, color and motion detection, properties that are related to the receptive field organization of retinal neurons, which are in turn derived from their synaptic inputs and the neuromodulatory influences they receive. So to understand how dopamine interacts with the retinal network to facilitate information flow through cone circuits and to suppress that through rod circuits, we next focus on synaptic mechanisms and related phenomena involved in synaptic maintenance, e.g., transporters, calcium currents, inter alia.

Dopamine in the outer retina

This section begins with the photoreceptor, deferring the retinal pigment epithelium to the section on trophic influences. Photoreceptor transduction allows light absorption by visual pigment to trigger a set of biochemical reactions, ultimately resulting in a fall in [cGMP] and a closing of a number of cGMP-gated membrane channels (reviewed in [69]). In darkness these channels permit a steady inflow of cations which keep the photoreceptor relatively depolarized. Light, by reducing the flow of 'dark' current, hyperpolarizes rods and cones. The dark current influx is balanced by a Na/K ATPase which expels Na and retains K. Shulman and Fox [70] report that dopamine, acting through a D4 receptor, inhibits the Na/K ATPase of rat rods. One expects this action ultimately to result in a fall in dark current, a hyperpolarization of the rod and a reduced light response, but whether this is so still awaits a direct test, as does whether the same mechanism operates in cones.

Photoreceptors are subject to a number of other dopamine-mediated mechanisms, all of which have been studied in amphibian rods and cones. The coupling between rods and cones is increased [71], the voltage-gated calcium current of rods is increased and that of cones is decreased [72] and a hyperpolarization-dependent current, I_h is decreased [73]. All of these mechanisms depend on a D2-like dopamine receptor, consistent with the identification of D2Rs on amphibian photoreceptors [31]. Dopamine evidently remodels photoreceptor physiology, but are the various effects consistent in diminishing rod and increasing cone activity? Rod-cone coupling allows cone signals to flow into rods, making the rod response more cone-like. At the same time, inhibition

of I_h diminishes the rod's own response to light. Both these effects result in a relative diminution of the rod's independently generated response to light. What still needs to be examined is the degree to which rods communicate the cone-like signal to second order cells, in relation to direct cone to second-order cell synaptic transfer.

A more puzzling aspect of dopamine's actions is its effect on Ca currents [72]. A priori, an increased calcium current means more transmitter release, so a dopamine-mediated elevation of rod calcium current appears to go against the central hypothesis. Thoreson et al. [74] tested this directly and found that although rod Ca signals were elevated, rod input to second order cells was diminished. They provide evidence for a complex feedback pathway, whereby Ca activates a Ca-dependent chloride current, $I_{Cl(Ca)}$, leading to efflux of Cl^-, resulting in a subsequent fall in I_{Ca}, because it depends on $[Cl]_i$ in the photoreceptor. When $I_{Cl(Ca)}$) was blocked, the D2 agonist, quinpirole, no longer inhibited rod inputs to horizontal and bipolar cells. It is still unknown whether any of the above applies to mammalian retinas. For example, Schneeweis and Schnapf [75] provide strong evidence for rod-cone coupling in primate retina, but this coupling apparently is unaffected by dopamine.

In cells post-synaptic to photoreceptors, dopamine has been linked to two important cell functions: a decrease in cell to cell coupling among horizontal cells and an increase in current flow through AMPA type glutamate receptors. A comprehensive physiological study of dopamine's actions on horizontal cell coupling was carried out by de Vries and Schwartz [76]. They recorded from pairs of catfish horizontal cells in culture and showed that cell to cell communication was decreased by dopamine or by a D1 agonist, that it was mimicked by cAMP or by agents such as forskolin that increased cAMP production and was inhibited by blockers of protein kinase A. McMahon and Brown [77] extended this work to single channels, showing that dopamine reduced the open probability of horizontal cell gap junctional channels 2- to 3 fold, by reducing both the frequency and the duration of single channel openings. Parenthetically these data suggest why a D2 agonist should increase rod-cone coupling [71]. The D1 mechanism increases adenylate cyclase activity, whereas the D2 mechanism decreases it, presumably resulting in more open channels.

The substrate for cell to cell coupling is the gap junction, a specialized electrotonic synapse created from specialized proteins called connexins. Six connexins assemble into a connexon, and connexons in two cells join to create a cytoplasmic bridge between cells. Typically multiple connexons assemble in close proximity, creating an electrical synapse. An older, but still commonly encountered, term for this assembly is a gap junction. It is reasonable to suppose that the horizontal cell and photoreceptor cell connexins (of which there are many subtypes; reviewed in [78]) have phosphorylation sites and we can suppose that phosphorylation decreases the conductance of the junction whereas dephosphorylation increases it (this still has to be proven). Although no one has carried out this sort of research on horizontal cells in mammalian retinas, modulation of their coupling by dopamine has been shown, using as a metric the cell to cell diffusion of a tracer molecule injected into one cell. When Lucifer yellow or Neurobiotin is injected into one horizontal cell it passes to neighboring cells by permeating the gap junctions. He et al. [79] showed that dopamine or cAMP reduced coupling in mouse horizontal cells, whereas the D1 antagonist increased it, a result clearly consistent with the physiological data [76]. Xin and Bloomfield [80] examined the relation between light and coupling in rabbit retinal horizontal cells. Maximum coupling was seen in dim (scotopic) illumination, and was decreased by brighter light, consistent with the finding that dopamine release is increased by light. However, coupling was also decreased in complete darkness, a result not readily reconcilable with the dopamine hypothesis, but in this regard it is important to remember that other neuroactive chemicals besides dopamine influence cell to cell coupling in the retina, e.g., nitric oxide, cGMP and retinoic acid [81–83]. In the retina, nitric oxide has been reported to inhibit dopamine release [84, 85] but it has independent actions as well (reviewed in [86]).

A distinct dopaminergic mechanism relating to glutamate channels was first demonstrated by Knapp and Dowling [87]. Fish horizontal cells in culture respond to kainate with an inward current. Dopamine applications by themselves do nothing, but within a few minutes they greatly increase the response to kainate, associated with an increase in conductance. Further study showed that exposure to dopamine prolonged the time the channel spent in the open state. This mechanism is triggered by a D1 receptor and similarly depends on cAMP and protein kinase A. Witkovsky et al. [88, 89] found that for an amphibian horizontal cell, receiving direct input from both rods and cones, dopamine or a D1 agonist increased the cone input and diminished that of the rod. In

the mammalian retina, the situation is slightly different, in that horizontal cells connect to cones via perikaryal dendrites, but to rods through expansions of an axon terminal. It is generally considered that the fiber joining cell body to axon terminal is too fine for electrical communication and that rod signals seen in the horizontal cell body [90] arrive there via rod-cone coupling [91]. With this in mind we can interpret the data of Hankins and Ikeda [92] who examined the actions of dopamine on rat retinal horizontal cells. Dopamine depolarized horizontal cells, consistent with an increase in conductance of the glutamatergic synapse between cones and HC. That is, cones release glutamate in darkness; an increased conductance allows more glutamate-gated current to flow, and since the reversal potential for that current is near zero, the driving force will cause depolarization. Next these investigators showed that dopamine decreased the size of rod-generated responses. Again, this result is consistent with a short-circuiting of rod signals by cones. In effect, the rod light response is equivalent to the injection of a small hyperpolarizing current into the cone, and the relative effect of that current will be less if the conductance of the glutamate channels is increased. Finally, Hankins and Ikeda reported that the HC response to a small flash was increased, but that to an annulus was decreased. This is precisely what one would expect if dopamine decreased horizontal cell coupling. A full explanation of the underlying mechanism is given in Piccolino et al. [93]. We can conclude that mammalian horizontal cells manifest the same dopaminergic mechanisms studied in horizontal cells of lower vertebrates. In the salamander retina, Maguire et al. [94] found that OFF bipolar cells, which respond to glutamate through AMPA receptors, have the same D1 mechanism described for horizontal cells [87].

Uncoupling and alteration of glutamatergic transmission does not exhaust the list of dopamine-dependent activities in horizontal and bipolar cells. In amphibian horizontal cells, dopamine, acting through a D1 receptor, reduces a $GABA_c$-mediated response [95]. Since in the outer retina GABA is released by the horizontal cells themselves, dopamine may be modulating an autofeedback response. In amphibian bipolar cells, dopamine inhibits another $GABA_c$-dependent response, in this case an inhibition that reduces Ca^{2+}influx and transmitter release [96]. This action was mimicked by a D1 dopamine agonist, SKF 38393. Such studies collectively indicate how dopamine fine tunes retinal synaptic currents at both pre- and post-synaptic sites.

Another general category of dopamine's actions is modulation of voltage-gated channels. Its effects on Ca channels of photoreceptors already have been described. Similar alterations have been described for Ca channels in horizontal cells [97] and ganglion cells [98]; modulatory actions on K channels are reported for Muller glial cells [36] and bipolar cells [99, 100]. Ca and K channels are vital to many neuronal properties, including transmitter release, transporter function and the light-evoked spiking patterns of retinal ganglion cells.

Possible dopaminergic actions on mammalian bipolar cells have not yet been studied, except indirectly through the electroretinogram (ERG, see below). Given two well described dopamine-dependent mechanisms for altering signal transmission in the outer retina – enhancement of glutamate currents at AMPA receptors and uncoupling of horizontal cell gap junctions – is it possible to construct a consistent story for dopamine favoring cone circuitry? The best analysis bearing on this point is provided by Hare and Owen ([101] and Figure 2) in a study of the receptive fields of bipolar cells in the salamander retina. In essence, the end result wrought by dopamine was to preserve the basic center-surround organization but to make it spatially more compact, a result which predicts that spatial contrast detection in the outer retina is improved in the presence of dopamine.

Dopamine actions in inner retina

In the inner retina of mammals most attention has focused on dopaminergic modulation of the AII amacrine neuron, a subtype of amacrine cell that is an integral component of the circuit processing rod signals. This unusual neuron receives an excitatory glutamatergic input input from rod depolarizing (ON) bipolar cells, and its light-evoked response is depolarizing [11]. The population of AII amacrines are interconnected through homologous gap junctions and to cone ON bipolar cells through heterologous gap junctions. Depolarizing current flow from AII amacrines to cone ON bipolars is thought to increase excitatory input into ON ganglion cells, allow them to process rod signals. On the other hand, AII amacrines are glycinergic and make inhibitory synapses onto OFF ganglion cells [11]. Dopamine, acting through a D1 dopamine receptor, decreases the electrical coupling among

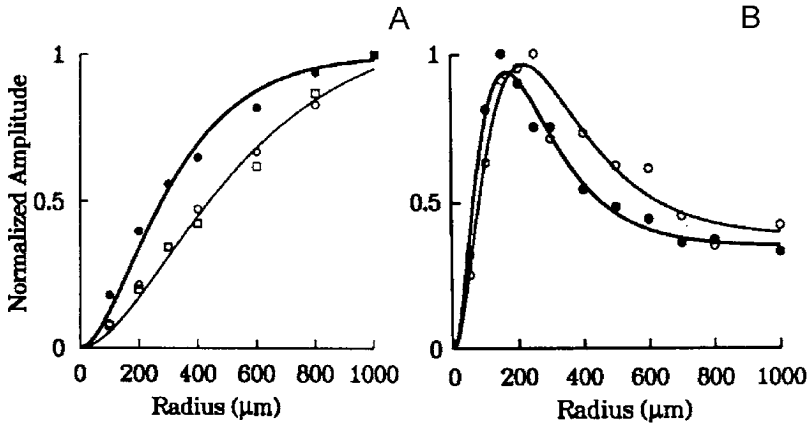

Figure 2. Modification by dopamine of bipolar cell receptive field organization. Left hand panel. The relative amplitude of horizontal cell light-evoked responses when stimulated with test spots of different radii. (○) Control; (●) during exposure to 20 μm dopamine; (□) after a wash in dopamine-free Ringer. Right hand panel. The same set of measurements upon an OFF-bipolar cell. For both cells, dopamine elicited a reduction in the integration area. Solid lines through the points in the left hand panel are generated by equations describing the spatial profile of the horizontal cell. For the right hand panel, the equations reflect the difference between bipolar and horizontal cell spatial profiles. Adapted from [101] with permission of the authors and the press.

AIIs [102], but is without effect on AII to cone ON bipolar cells [82]. Possibly a dopamine-induced reduction in spatial integration by AII amacrines results in reduced excitation to ON bipolars. At any rate, in a connexin 36 knock out mouse, AII amacrine cells are uncoupled, and in this animal there is no transmission of dim light-initiated rod signals to ganglion cells [103]. Another possibility raised by the new data of [14] described earlier is that the dopaminergic cell releases GABA onto the AII, resulting in a reduction of its light response. This is an additional mechanism besides uncoupling through which the dopaminergic cells might reduce rod signal flow through the retinal network. Overall, these AII-related findings appear to be consistent with the idea of dopamine acting as a chemical messenger for light-adaptation.

A study [104] carried out on organotypic cultures of rat retina showed that dopamine slowly increased $GABA_A$currents in amacrine cells of unidentified type(s). Dopamine's action depended on a D1 receptor coupled to adenylate cyclase and leading to the activation of Protein Kinase A. The ultimate target was the $GABA_A$receptor, which when phosphorylated had an increased affinity for GABA. Another target of dopamine in inner retina is the acetylcholine (ACh) system. ACh is released by mirror symmetrical starburst amacrine cells [105]. Dopamine is reported to increase ACh release by cultured retinal neurons [106] and to stimulate release of [^{3}H]ACh [107, 108]. In a reciprocal way, the ACh agonist, carbachol, induces dopamine-like changes in retinal neurons [101].

Dopamine and ganglion cells

One would have thought that ganglion cells, being the final common pathway for retinal signal processing, would have been thoroughly examined in relation to dopamine, but in spite of several promising early investigations, some important questions remain unanswered. In the retinas of the best studied mammals, cats and rabbits, ganglion cells have a maintained discharge in darkness or in weak steady light. This so-called 'spontaneous' activity reflects a tonic glutamatergic excitation of the ganglion cell. Light-driven activity is referred to a concentric center-surround receptive field [109], which may be ON-center (excited by a small light spot centered over the ganglion cell) or OFF-center (inhibited by a centered light spot). Further subdivision into transient/sustained or X–Y categories is based on the spike firing pattern and the linearity or non-linearity of summation in the receptive field center (reviewed in [110]).

The receptive field surround arises in two ways. The first is organized in the outer retina by horizontal

cells. Hyperpolarizing current passed into horizontal cells elicits surround responses in ganglion cells [111, 112]. Amacrine cells may contribute additional surround inputs. Barlow et al. [113] found that although light-adapted (i.e., cone-driven) ganglion cells had vigorous surrounds, as the retina dark-adapted the surround responses tended to weaken.

The circuitry outlined in Figure 3 illustrates how dopamine might act on ganglion cells. Under scotopic conditions in which only rods respond to light, all retinal inputs to ganglion cells are processed through the rod bipolar cell to AII amacrine cell pathway. (For the purposes of this discussion I will ignore the alternative route of rod signals reaching cones through rod-cone electrical coupling, since, in mammals, that pathway apparently is not subject to modulation by dopamine [75]).

Muller et al. [114] examined the 'rod circuit' in the cat retina. They showed that under dark-adapted conditions, APB, a metabotropic glutamate agonist which selectively blocks rod to rod bipolar cell communication, inhibited the light responses of both ON and OFF center ganglion cells. Moreover, the maintained discharge of ON cells was suppressed while that of OFF ganglion cells was increased. In addition, the glycine antagonist, strychnine, blocked the light responses of dark-adapted OFF-center cells and prevented the effects of APB when applied simultaneously. All these findings are basically consistent with a circuit showing obligatory signal transfer from rods to ganglion cells through rod bipolar cells and AII amacrines. Suppression of the AII amacrine response is thought to block a depolarizing input to cone ON bipolar cells, stopping the maintained discharge, but relieves a glycinergic inhibition of cone OFF bipolar cells. Some uncertainties arise, however, when we examine this circuit more closely. Patch clamp studies of AII amacrines show that their membrane potential in darkness is about –60 mV, consistent with a light-evoked discharge that sometimes contains spikes. Cone ON bipolar cells, on the other hand, are more depolarized in darkness, perhaps around –40 mV. In darkness, therefore, the AII network cannot inject a depolarizing current through its gap junctions with cone ON bipolar cells; in fact it would be expected that AIIs would hyerpolarize them. With regard to the OFF cone bipolars/OFF ganglion cells, in order for strychnine to act there must be a tonic release of glycine in darkness. Earlier studies of glycine and strychnine on cat retinal ganglion cells indicate this is the case [115].

In the rabbit retina, Jensen and Daw [116, 117] and Daw et al. [118] reported that dopamine increased the maintained discharge of OFF-center cells, but reduced that of ON-center cells, and they interpreted their findings in terms of a dopaminergic inhibition of the AII amacrine cell network. In addition they found that dopamine decreased the light sensitivity of ganglion cells, in effect by eliminating rod inputs. Their data raise the question whether a dopamine-mediated uncoupling of AII amacrines can explain a decrease in the maintained discharge of ON ganglion cells. Current flow in a coupled system depends on a driving voltage; in the absence of such a voltage, there will be no net current flow. In darkness, in order to generate a voltage difference between any two AII amacrines we have to suppose that their tonic synaptic inputs are different. There is as yet no evidence to support this. At present, therefore, it is difficult to reconcile uncoupling of AII amacrines with the observed effect seen on the maintained activity of ganglion cells.

Another cell type, the so-called A17 cell may also receive a dopaminergic input [11] and it has its output on rod bipolar cells. If dopamine were to cause the A17 to decrease a GABAergic feedback to rod bipolars, AII amacrines would receive more excitation and depolarize. This would have the desired effect on cone ON bipolars, but would work in the wrong way for the glycinergic inhibition of cone OFF bipolars and ganglion cells. On the other hand the connexin 36 knock out study [103] indicates that a loss of AII coupling somehow prevents rod responses to dim light from reaching ganglion cells. We may conclude therefore that the data support the idea that dopamine diminishes information flow through the rod pathway, even if the mechanisms are not perfectly understood.

Jensen [119, 120] built on these data to study dopamine's actions on the ganglion cell receptive field. He reported that under fully light-adapted conditions, the D1 antagonist, SCH 23390, selectively blocked the surround mechanism of OFF-center ganglion cells, but had little or no effect on the central mechanism. Drugs that increased cAMP counteracted SCH23390, as did strychnine. The interpretation is that the AII cell functions under light-adapted conditions, but is suppressed by dopamine through a D1-dependent mechanism directed at glycine release. Blocking the D1 receptor with SCH 23390 allows glycine to inhibit the ganglion cell, eliminating the surround. These provocative findings require additional assumptions beyond the circuitry of Figure 3 and raise additional questions. For example, if the surround is organized in the outer retina [112] it

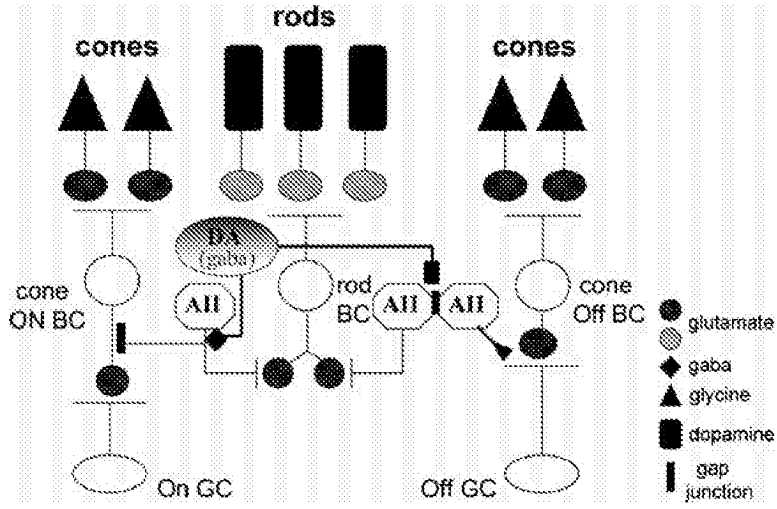

Figure 3. A schematic of the rod circuit in the mammalian retina. Rods synapse upon rod bipolar cells (rod BC) which in turn provide a glutamatergic input to AII amacrine cells (AII). AIIs are connected by gap junctions to cone ON bipolars (cone On BC) which drive On ganglion cells (On GC). AIIs release the inhibitory transmitter glycine onto cone Off bipolar cells (cone Off BC), resulting in inhibition of Off ganglion cells (Off GC). The dopamine (DA) neuron colocalizes GABA. It makes a GABAergic synapse onto the AII cell, and also releases dopamine which inhibits AII-AII coupling. The key to the various transmitters and junctions is indicated at right.

will be conveyed to the OFF ganglion cell by OFF bipolars, with the expectation that glycine should block both center and surround responses. Secondly it is unknown how cAMP might suppress glycine release. More work is called for here to fill in the lacunae in our understanding.

Dopamine and field potentials

Several field potentials are used in evaluating retinal performance. The flash electroretinogram (ERG) taken from humans and most mammals is a measure primarily of rod (a-wave) and rod bipolar cell (b-wave) under conditions of dim to moderate illumination because of the numerical dominance of rods. Special measures need to be taken to isolate cone contributions to the ERG; when those are imposed the ERG samples cones (a-wave), cone ON bipolar cells (b-wave) and cone OFF bipolar cells (d-wave). The ERG c-wave and light peak are signs of retinal pigment epithelium activity. The pattern ERG (PERG; [121]) reflects the activity of inner retinal neurons, the amacrine and ganglion cells. All of these have been utilized in studying actions of dopamine, or in evaluating animal models of retinal diseases and humans with impaired retinal function.

In this section concerned with whether the data are consistent with dopamine acting as a chemical messenger for light adaptation, we consider the ERG. For a true evaluation of dopamine's action, the adaptational state of the retina has to be defined, i.e., the responses must be characterized as originating in rods, cones or both. An exemplary analysis in that regard is by Naarendorp et al. [122]. In the completely dark-adapted cat eye, very dim stimuli evoke a 'scotopic threshold response [STR]', which appears at intensities 2–3 log units weaker than those needed to evoke a scotopic b-wave. 6-Hydroxydopamine (6-OHDA), a drug which weakens and ultimately destroys dopam inergic and adrenergic neurons [123, 124] increases the STR. Analysis of the intraretinal ERG [125, 126] indicates that the STR arises in the inner retina, probably from amacrine cells. Thus we may conclude that under dark-adapted conditions, some rod-connected amacrines generate the STR and these amacrines are inhibited by dopamine. The obvious candidates are the AII and/or A17 amacrines, the ones known to receive a dopaminergic input, as described earlier. GABA also inhibits the STR, but the interpretation of this action is

complicated by the fact that GABA suppresses dopamine release. Other studies of the AII [127] and A17 cells [128] show they receive GABA-mediated inhibitory inputs, thus exogenous GABA would be expected to decrease the STR.

With regard to the scotopic b-wave, it is inhibited by dopamine and increased by GABA [129], the latter action disappearing when the retina is first exposed to a dopaminergic blocker, haloperidol, or to 6-OHDA. Thus in the case of the scotopic b-wave the main action of GABA is to inhibit dopamine release. The rod bipolar cells which underlie this ERG component [130] are not reported to have a dopamine receptor. It is also conceivable that dopamine, acting through a D2-like receptor, inhibits rod responses by inhibiting their Na/K-ATPase [70]. In that case one would expect a reduction in the ERG a-wave by dopamine; although this proposition has not been tested directly, Skandries and Wässle [131]showed that 6-OHDA greatly increased both scotopic a- and b-waves. It is possible, moreover, that dopamine acted to reduce transmitter release from the rod, in which case a reduction in the a-wave would not be expected. We don't yet know whether dopamine alters calcium currents in mammalian photoreceptors as has been reported for amphibian rods and cones [72]. The pharmacology, moreover, is not clear; for example, it is reported [132] that both D1 and D2 dopamine antagonists increase the rod b-wave. Corroborative data of dopamine actions on rod-driven b-waves were obtained [123, 131].

To summarize the electrophysiological findings, in spite of many uncertainties concerning details and mechanisms, it seems fair to conclude that dopamine interacts with retinal circuitry to suppress signal flow through rod circuits and enhance that through cone circuits. Up-regulation of dopamine release at dawn contributes to the potency of dopamine's actions during daytime hours. Thus the overall hypothesis that dopamine is a chemical messenger for light adaptation is substantiated. It is worth noting that other neuroactive chemicals, e.g., nitric oxide, influence the same retinal circuitry and can be presumed to have a role in light/dark adaptation (reviewed in [86]).

Dopamine actions in fish retinas

Before concluding this evaluation of dopamine's role as a chemical messenger for light adaptation, it is worth paying special attention to the many studies of fish retina. The particular reason is that some publications prior to 1991 indicated that dopamine promoted dark-adaptation in cone-connected horizontal cells (e.g., [133]) whereas others, looking for example at retinomotor movements concluded that dopamine promoted light-adaptation [134]. The underlying changes in relative rates of dopamine release in light and darkness were largely inferred from the physiology. Subsequently, Weiler et al. [135] directly measured endogenous dopamine release and reported that it was increased by flickering, but not steady light. Correspondingly, Umino et al. [136] found that flickering light uncoupled cone horizontal cells , an action blocked by the non-specific dopamine antagonist, haloperidol. In contrast, reduction of horizontal cell receptive fields by steady light was not blocked by a dopamine antagonist.

These studies are basically consistent with the general hypothesis about dopamine favoring cone circuits, but there are some additional points to be brought out. The first is that although so-called cone horizontal cells receive direct synaptic input only from cones, when sufficiently dark-adapted they also receive inputs from rods. [137]. A reasonable presumption is that the rod input arrives via rod-cone coupling, but this has yet to be demonstrated in fish retina. The resultant dark-adaptational change is reflected in a marked fall in light-evoked responsiveness and a spectral sensitivity shift from red-sensitive cones to green-sensitive rods. Mangel and co-workers have used these changes to examine circadian rhythms in the dopamine system [137, 138]. They find a shift from rod-domination to cone-domination occurs even in complete darkness and can be mimicked by exogenous dopamine. They report, moreover, that there is a circadian rhythm in dopamine production, leading to increased dopamine production during subjective day. They state [ref. –, p.808] that 'destruction of dopaminergic cells following pre-treatment with 6-hydroxydopamine increased rod input and decreased cone input during the subjective day'. Li and Dowling [139] studied circadian rhythms in the zebrafish and came to rather different conclusions. They devised a behavioral escape response to monitor rod and cone thresholds and used it to generate a typical two-phase dark-adaptation curve following exposure to a bright, desensitizing light. When, however, they depleted the retina of dopaminergic neurons by 6OHDA treatment, the dark-adaptation function indicated that only cones were functioning, i.e., that dopamine depletion led to a **loss** of rod function. Further study showed, however, that it was not the rod receptors themselves which

were dysfunctional, nor rod to ON-bipolar cell communication (as judged by the ERG b-wave), but rather some inner retinal circuit, and not excluding further effects central to the retina. Thus there is no formal contradiction between the results of Rabelayga et al. [138] and those of Li and Dowling [139] because the former study looked at outer retinal changes, whereas the latter pinpointed changes in inner retina. Still it is counterintuitive that the absence of dopamine should increase rod output to horizontal cells but block rod signals in inner retina. In summary, it seems that fish retinas reflect similar dopamine-dependent changes **in outer retina** as have been reported for representative species of other vertebrate classes, although with some differences whose bases require further experimentation and analysis. It is worth noting that dopaminergic cells in fish differ somewhat from those of other vertebrates in having a more extensive arbor in the outer plexiform layer and a much reduced one at the border of inner nuclear and inner plexiform layers (reviewed in [140]).

Trophic actions of dopamine

The layer of DA neurons reacts to light and to a variety of neuroactive chemicals by modifying dopamine production and release. A key player in this process is TH, the rate-limiting enzyme for catecholamine production. TH is made up of four identical sub-units, each having three phosphorylation sites near the N-terminus at serines 19, 31 and 40 (reviewed in [141, 142] Phosphorylation of serine 40, which is dependent on cAMP and Protein Kinase A [143, 144] seems to be the most important site in relation to dopamine production. It results in TH having a greater affinity for its tetrahydrobiopterin co-factor and, in consequence, a higher turnover rate. Thus, any influence impinging on the DA cell which influences cAMP can help regulate dopamine production. What effect, if any, phosphorylation at serines 19 and 31 might have on TH activity is still under investigation. A few peptides, such as PACAP and VIP, strongly increase retinal [cAMP], and amacrine cells containing these peptides have processes in the appropriate part of the IPL to contact the DA cell. In reciprocal fashion, dopamine is implicated in controlling the release of a group of three peptides (enkephalin, neurotensin and somatostatin) which, in the chicken retina, are colocalized within a subtype of amacrine cell [145]. Possible interactions between the DA neurons and peptidergic amacrine cells is a topic that needs further study. One known example is somatostatin which would be expected to decrease cAMP; receptors for this peptide are found on the DA cell [146]. In the salamander retina, photoreceptors have one subtype of somatostatin receptor and it works in the opposite direction of DA by increasing calcium current in cones, but decreasing it in rods [147].

Synaptic influences also modify TH phosphorylation; specifically, light and glutamate agonists increase phosphorylation, whereas GABA decreases it [148]. Acetylcholine has a selective effect on phosphorylation at serine 31, but the physiological significance of this datum is undetermined, as noted above. Excitatory chemicals also increase dopamine release [17]. A probable mechanism is related to the calcium-dependence of dopamine release. That is, one may suppose that the spiking activity of the DA neuron depolarizes the membrane and increases the probability of calcium channel opening, leading to Ca influx and increased release. By extension, any agent affecting the intracellular [Ca] of DA neurons will modulate dopamine release.

These data and inferences suggest a general feedback loop whereby synaptic activity helps regulate dopamine. The anatomy of the DA neurons indicates their primary synaptic inputs come from cone connected bipolar cells and the amacrine neurons driven by those bipolars. As mentioned above, the location of DA processes in the OFF zone of the IPL indicates input from OFF bipolars, but Marshak [8] has suggested they may be ON bipolars based on the finding that APB, a metabotropic glutamate agonist which antagonizes the light response of ON bipolars, inhibits dopamine release [149]. On the other hand, Witkovsky et al. [148] found that APB had no effect on TH phosphorylation. Whatever the resolution of this particular point, in mesopic and photopic ranges, cone circuits help control the spiking activity and Ca flux of the DA cells. Critz and Marc [150] showed that in relation to K^+-evoked DA release, relief from GABA inhibition was more important than excitation via glutamatergic inputs. Rod circuits also may influence dopamine production and release. As noted above, in dim scotopic illumination rod input depolarizes rod bipolar cells, activating the AII circuits and possibly one or more synaptic pathways impinging on DA neurons (cf. [8]).

With this background information we can explore whether the normal light responsiveness of the retina has an impact on dopamine production, release and turnover. It is a universal finding that light in-

creases dopamine release, and this diurnal effect interacts with a circadian rhythm governing dopamine release, as discussed earlier. In the mouse retina, Nir et al. [40] showed that steady state levels of dopamine do not change significantly between night and day. At dawn, however, there is a sudden increase in dopamine synthesis (measured by accumulation of L-Dopa in the presence of a L-Dopa decarboxylase inhibitor) and dopamine utilization (as indicated by residual dopamine after inhibiting dopamine production). This level of activity declines somewhat during the day but remains at a level higher than what is found at night. What happens when this daily patterning is disturbed? Several studies [151–154] have examined dopamine metabolism in dystrophic (retinal degeneration slow or rds) mice and in a mutant lacking dopamine D4 receptors. In the homozygous dystrophic mice, although dopamine levels were as high as controls, light-induced utilization of dopamine was much lower than in BALB/c mouse controls. In heterozygous rds mice, an early morning increase in dopamine production was noted, but at a level lower than control. Correspondingly, cAMP production in photoreceptors, which is lowered by dopamine or light in controls [155], is unaffected in homozygous rds mice. The resultant maintained high level of photoreceptor [cAMP] may contribute to photoreceptor pathology, since cAMP-dependent protein kinase phosphorylates cGMP phosphodiesterase [156], a crucial element in the phototransduction cascade. In an analogous way, in mice lacking dopamine D4 receptors [154], the D2/D4 antagonist, quinpirole, failed to modulate photoreceptor cAMP levels. Light, acting through a dopamine-independent mechanism lowered photoreceptor [cAMP] in control, but not in D4 knockout mice; the authors speculate that dopamine normally modulates a cascade relating membrane potential changes to adenylyl cyclase activity, thereby possibly affecting the expression of crucial proteins, e.g. calmodulin. Physiological data consistent with the idea of an interaction between retinal circuits and the DA system is provided by Hankins and Ikeda [157]. They studied RCS rats and found that during the period in which photoreceptors degenerate, the D1 dopamine antagonist, SCH 23390, hyperpolarized horizontal cells in recessive controls, indicating a relatively high level of endogenous dopamine, but not in age-matched dystrophic retinas. The data of these diverse studies are at the heart of the notion that photoreceptor and dopaminergic function are mutually interactive and controlled by the day/night cycle. The interactions between melatonin and dopamine production already discussed are another example of this interaction. Further research is required to arrive at a general mechanistic scheme of how the interactions are mediated.

Dopamine interactions with the retinal pigment epithelium

The retinal pigment epithelium (RPE) is a secretory layer. Passage of ions and metabolites between the subretinal space and the choroid must occur by transport, since the intercellular space is sealed by tight junctions and zonulae adherentes. Steinberg et al. [158] showed that apical and basal layers of the RPE interact to produce a DC trans-epithelial potential, the standing potential, and both layers generate currents in relation to discrete transport activities, giving rise to the c-wave of the ERG and to the light peak. The c-wave, which results from activity of the apical face of the RPE, is generated within a few seconds, whereas the light-peak takes several minutes to develop fully and it reflects activity of the basal face of the RPE (reviewed in [158]).

Dopamine affects **both** faces of the RPE [159–162], although the dopamine receptor subtype(s) on the basal face of the RPE has not been identified, whereas the apical face has D5 receptors [30]. The specific actions of dopamine on the RPE are somewhat complicated, but appear to involve alterations in cAMP and to interact with an anion conductance in the RPE membrane [160–161]. From the standpoint of this review the salient fact is that activity-dependent changes in retinal dopamine are signaled to the RPE. This finding is of interest in the context of indicating a possible role for dopamine in some forms of myopia.

Some of the experimental work on myopia has been carried out on primates [163], but a more popular animal model is the young chick. The animals are fitted with frosted goggles that create blur (form deprivation myopia) or with unfrosted goggles carrying plus or minus lenses that induce hypermetropia or myopia, respectively. Evidently the neural retina senses well-focused images containing appropriate spatial frequencies and contrast, and generates a signal that inhibits scleral expansion when the eye is emmetropic. Biasing this mechanism by form deprivation leads to myopia. An early finding, which held for both primate and chick retinas, was that form deprivation myopia (FDM) was accompanied by a reduction in ret-

inal dopamine levels and reduced dopamine synthesis and turnover [164–165]. This datum is in line with results discussed above that the retinal dopaminergic system is sensitive to the flow of information through the retina. But the converse proposition is more intriguing: that a retinal signal involving dopamine somehow initiates a cascade resulting in altered scleral growth. The first suggestion came from reports that apomorphine, a non-specific dopamine agonist, counteracted FDM [166, 167]. How might this work? Dopamine might interact with the RPE, leading to a trans-RPE signal that affected choroid and/or the sclera. In support of this idea, Seko et al. [168] found that chick RPE cells, when co-cultured with scleral chondrocytes, greatly increase their mitotic rate. Apomorphine added to the culture system decreased the RPE-dependent stimulation of scleral chondrocytes, whereas apomorphine alone had little effect on the scleral cells. Some doubts about the role of dopamine in visual control of eye growth persist, however, because (1) dopamine-receptor antagonists by themselves might be expected to cause myopic eye enlargement, but are reported to have little or no effect on ocular growth and refraction [164, 167], (2) destruction of dopaminergic neurons by 6-OHDA [169] prevents deprivation myopia, rather than causing myopia as might be expected; and (3) depletion of retinal dopamine by reserpine, a blocker of vesicular monoamine transport, also does not cause myopia [170]. Other studies, moreover, indicate that dopamine is just one of several factors influencing eye growth. In the chick, retinoic acid has been implicated because FDM alters its levels in retina [171, 172] and in choroid [172], and it affects scleral growth [173]. Another retinal neurochemical influenced by eye growth in chick is glucagon, possibly turned on by an immediate early gene [174]. In that regard, the DA neurons are induced by stroboscopic flicker to express c-fos. They also have receptors for fibroblast growth factor, but so does practically every retinal cell and scleral cells have them as well [165, 175]. Given the present state of understanding it seems fair to say that many retinal neurochemicals, dopamine among them, are both affected by eye growth and may contribute to the feedback loop(s) whereby signal flow through the retina regulates scleral growth.

Parkinson's disease affects the dopamine system of the retina

Parkinson's disease is a late onset pathology in which dopaminergic neurons of the brain die, resulting in a characteristic tremor and other movement disorders. The most standard therapy is administration of the dopamine precursor, L-Dopa, since it crosses the blood–brain barrier. One report of autopsied human brains reported a lowered retinal content of dopamine in the Parkinsonian patient group compared to age-matched controls, using patients who had not received L-Dopa in the 5 days preceding death [176]. Nguyen-Legros et al. [177] carefully studied the retinal DA neurons of Parkinsonian patients and noted no loss of DA neurons, although the intensity of TH staining was lower in the fine DA processes and there was a loss of DA processes in the foveal region. One test of retinal function that has been applied to many Parkinsonian patients is the pattern ERG (PERG, cf. [121]). This test, performed under photopic conditions, consists of a moving pattern, which could be sign-reversal of a checkerboard or a drifting grating. In either case the relevant variable is that the frequency of change or movement alters without a change in overall luminance. It was shown in cases of optic nerve atrophy or optic nerve section, followed by degeneration of the ganglion cells, that the PERG was extinguished [178], whereas the full-field ERG was unaltered. Although this clearly indicates that ganglion cells contribute to the PERG and probably constitute its major source, other work (cf. [121] for details) indicates contributions from additional subtypes of retinal neuron. PERG responses have two main components, a positive wave at 50 ms and a negative wave at 95 ms; the amplitudes of these components change as a function of stimulus frequency. A plot of PERG amplitude against frequency provides a spatial tuning function, and this function shows a reduction in the middle range (2.5 – 4.0 cycles/deg) in the Parkinsonian patient. Peppe et al. [179] compared PERGs in Parkinsonian patients before and after L-Dopa treatment and found that L-Dopa led to a recovery of the normal spatial tuning function. Stanzione et al. [180] reported that the D2 antagonist, sulpiride, caused a reduction in PERG responses at 4 cycles/deg. The possibility that sulpiride acted at the autoreceptor is unlikely. The D2 autoreceptor acts to reduce dopamine release so that an antagonist would be expected to increase dopamine release, and yet sulpiride had an anti-dopamine effect. The only other identified D2-like receptors in the ret-

ina are in the photoreceptors, an unlikely source for a frequency-dependent defect in ganglion cell responsiveness. Akamine et al. [181] examined the actions of the non-specific dopamine antagonist, haloperidol, on K currents of rat ganglion cells. They found a reduction in the apamin-sensitive, calcium-dependent K current. Conceivably blockage of this K current could slow spike frequency by delaying the repolarization of the ganglion cell membrane following spike-initiated depolarization. Their findings fit in a general way with the haloperidol-induced loss of PERG; however, that loss occurred at lower frequencies than what is found in Parkinsonian patients [182]. Moreover, it still needs to be demonstrated that the haloperidol effects acted through dopamine receptors. Earlier, Guenther et al. [183] reported that haloperidol reduced calcium currents in rat retinal ganglion cells isolated into culture, and that this inhibition occurred in the absence of dopamine.

Other evidence indicates that the retinal dopaminergic system influences PERG responses. For example, monkeys treated with MPTP develop a Parkinsonian syndrome and a characteristic mid-frequency loss in PERG amplitude [184]. Recovery from MPTP is associated with an improvement in PERG response.

Retinal dopamine in relation to development and aging

Some aspects of this area of investigation are reviewed in [3]. The dopaminergic neurons are among the first neurochemical systems to appear in the developing retina. In the amphibian, Xenopus, dopaminergic neurons appear coincident with amino acid transmitter systems [185], at a tadpole stage immediately prior to when outer segments first appear [186]. Dopamine function, as judged by release and reuptake, is delayed until a later stage at which ganglion cells just begin to show light-evoked responses [187]. In the rat eye, amacrine cells destined to become dopaminergic stop dividing between embryonic days 16–20, but sufficient dopamine to yield a fluorescence image is evident only after post-natal day 10 [188]. In mouse retina, an assay of DA content by HPLC with electrochemical detection, which is more sensitive than fluorescence, showed a steady increase of dopamine beginning at post-natal day 6 and increasing sharply thereafter [189]. This is still in advance of the day (PN 15) when the rat or mouse opens its eyes. In human embryos, TH immunoreactivity is seen already at 24 weeks [190]. In the chick retina, D1 receptors coupled to increases in cAMP appear about the time that retinal synaptogenesis begins [191]. In a culture of chick retinal neurons, forskolin-stimulated cAMP evoked growth and maturation of TH (presumably DA) neurons, whereas exogenous dopamine reduced the TH cell population [192]. Collectively these developmental studies are consistent in showing that DA neurons appear early in development, overlapping the time periods at which glutamatergic, gabaergic, glycinergic and cholinergic systems appear and begin to mature, indicating that the DA neurons begin to receive synaptic input early in development, and depend on interactions with other retinal cell types for their growth and maturation. Confirmatory evidence is provided by the finding that light increases DA turnover in rat retina beginning at post-natal day 7, i.e., before the eyes open [193]. The maturation of the melatonin system involved in day/night regulation of the DA neurons has not been documented. In view of the apparent interdependence of DA neurons and retinal neurons coupled to other transmitter systems, the report [194] that dopamine neurons in RCS rats mature and survive identically to those in normal rats, in spite of photoreceptor degeneration, is somewhat surprising. In the rd mouse, a still more surprising finding [195] is that dopamine contributes to the degeneration of the photoreceptors. Eliminating dopaminergic cells with 6-OHDA or blocking dopamine actions with D1 or D2 receptor antagonists permitted photoreceptor survival.

As the animal passes through maturity towards senescence, the number of dopamine neurons decreases and the level of TH immunoreactivity is diminished. In a human autopsy study [196], it has been found that retinas from individuals aged 65–89 had, on average, only half the number TH neurons found in individuals aged 19–64. Obviously many factors might contribute to the loss of DA cells and DA function, considering how intricately the system depends on synthesis, release, re-uptake, receptor systems and so forth. One indication is the study [197] showing a loss of dopamine transporter activity in aged rats and its remediation by treatment with a ganglioside.

Perspective

In this review I have tried to address some general issues relating to the multiple roles of dopamine in retinal function . One, which arose some years ago in the

context of many new studies of dopamine function, all conducted on retinas of lower vertebrates, was that the phenomena were interesting but perhaps not applicable to the mammalian retina. This mistaken notion I believe has been firmly put to rest. Mammalian retinas have the same system of DA cells as found in lower vertebrates, they respond to the same circadian and synaptic influences and their outputs onto other retinal neurons act similarly to bias retinal circuits in favor of cone vision. The mammalian retina, moreover, has become the favored place to look at genetic manipulations which impinge upon dopaminergic function and to examine animal models of retinal diseases involving dopamine.

Secondly I wanted to emphasize the plastic nature of retinal function in the context of two special features of its operation. One is the switch between rod and cone vision, the other is the retina's ceaseless activity. We have, I believe, just begun to explore and uncover these mechanisms, but the early signs are that they involve an unusual degree of interdependence between classical amino acid transmitters and a large number of other neurochemicals. Some of the latter operate through G-protein coupled receptors, others such as growth factors employ different strategies. They interact not just in terms of information processing, but also cell survival. Dopamine plays a unique role in this network because of its interactions with multiple neurochemical systems. The DA neurons have receptors for excitatory and inhibitory transmitters, for a variety of peptides, for melatonin, for neurotrophins [198] and for growth factors. They have immediate early genes like c-fos whose genomic targets are still unidentified. They have components of the biological clock. In turn, at least some members of every major class of retinal neuron have dopamine receptors, as do retinal pigment epithelial cells, Muller glial cells and pericytes. Diffusion carries dopamine to the remotest corners of the retina. Somehow the multiple actions of dopamine are coordinated to produce an integrated result, which is to prepare the retina for daytime vision. In this review I have discussed some components of that integrated response and tried to indicate how the unraveling of the dopamine system, whether brought about experimentally, naturally, as in the case of aging, or clinically, leads to predictable deficits in retinal function.

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