Journal of Pharmacological Sciences xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Pharmacological Sciences

journal homepage: www.elsevier.com/locate/jphs

Survey Review

Dopaminergic modulation of retinal processing from starlight to sunlight

Suva Roy, Greg D. Field*

Department of Neurobiology, Duke University School of Medicine, Durham, NC, USA

ARTICLE INFO

Article history:
Received 20 December 2018
Received in revised form
13 March 2019
Accepted 29 March 2019
Available online xxx

Keywords:
Neuromodulation
Gap junction
Adaptation
Scotopic
Vision

ABSTRACT

Neuromodulators such as dopamine, enable context-dependent plasticity of neural circuit function throughout the central nervous system. For example, in the retina, dopamine tunes visual processing for daylight and nightlight conditions. Specifically, high levels of dopamine release in the retina tune vision for daylight (photopic) conditions, while low levels tune it for nightlight (scotopic) conditions. This review covers the cellular and circuit-level mechanisms within the retina that are altered by dopamine. These mechanisms include changes in gap junction coupling and ionic conductances, both of which are altered by the activation of diverse types of dopamine receptors across diverse types of retinal neurons. We contextualize the modulatory actions of dopamine in terms of alterations and optimizations to visual processing under photopic and scotopic conditions, with particular attention to how they differentially impact distinct cell types. Finally, we discuss how transgenic mice and disease models have shaped our understanding of dopaminergic signaling and its role in visual processing. Cumulatively, this review illustrates some of the diverse and potent mechanisms through which neuromodulation can shape brain function.

Introduction

From nightlight to daylight, the retina switches from processing rod to cone signals. This switch presents challenges for retinal circuits if both rod and cone signals are to be processed effectively. For example, rod and cone responses have distinct kinetics (~500 and ~50 ms, respectively) and distinct forms of adaptation.[1,2] Additionally, the signal and noise of visual inputs are distinct between night and day. At night, photons are scarce with only one in a thousand rods receiving a photon each second.[3,4] Thus, a rod absorbing a photon will tend to be anticorrelated with neighboring rods because they are unlikely to absorb a photon. During day, photons are plentiful, mitigating Poisson noise in photon absorptions, while natural scenes correlate signals produced by nearby cones.[5] Thus, seeing in starlit and sunlit conditions involves switching from an anticorrelated input across photoreceptors that is noise dominated, to a correlated input that is signal dominated. This switch between night and day vision is facilitated by the neuromodulator dopamine. Dopamine modulates cellular, synaptic and gap-junction signaling in various circuit elements, effectively changing how signals are processed by retinal circuits and altering retinal output. In this review, we cover the major actions of dopamine in the retina and we attempt to contextualize their role in tuning retinal function for nighttime and daytime vision.

Neural circuitry of the retina

We begin by briefly summarizing the organization of the retina to provide an anatomical and functional context for the impact of dopamine on retinal processing (Fig. 1). Light is transduced into electrochemical signals by rod and cone photoreceptors.[6] Cone signals diverge to ~14 distinct bipolar cell types.[7,8] Bipolar cells are excitatory interneurons and can be divided into two broad classes: ON and OFF cells. ON cells depolarize in response to an increment of light; OFF cells depolarize in response to decrements. Bipolar cell signals further diverge (and converge) to 30–40 distinct retinal ganglion cell (RGC) types, contacting them in the ON and OFF layers of the IPL (Fig. 1).[9–11] Each RGC type tiles the retina with its dendritic fields and conveys a distinct message about the visual scene to the brain. Interposed between photoreceptors, bipolar cells, and

* Corresponding author.
E-mail address: field@neuro.duke.edu (G.D. Field).
Peer review under responsibility of Japanese Pharmacological Society.

https://doi.org/10.1016/j.jphs.2019.03.006

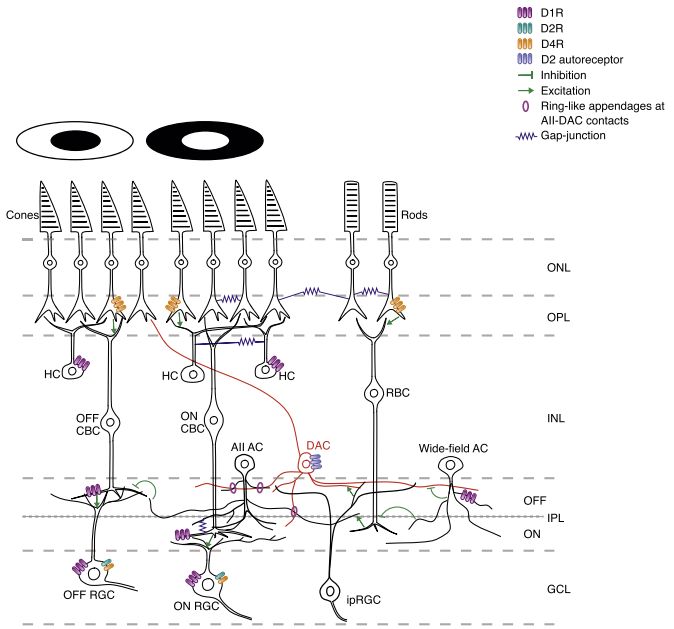

Fig. 1. Schematic of the retinal circuitry with cell types expressing specific dopamine receptors in the rodent retina. Dopamine receptors D1R, D2R, D4R and D2 autoreceptors localized on various cell types, are indicated in purple, green, yellow and violet. The dopaminergic amacrine cell (in red) stratify primarily in the outermost layers of IPL, and send axon like dendritic projections to cone terminals in the OPL and to the inner layers of the IPL where they contact AII ACs via ring-like appendages (in magenta). Synaptic excitation and inhibition are illustrated by arrow and bar-line (in green) respectively. Gap-junctions are shown by resistor-like symbols (in blue). The concentric dark-bright circles at the top represent OFF center ON surround and ON center OFF surround, and are aligned with the cone bipolar cells responding to the corresponding polarities. Abbreviations: ONL: Outer Nuclear Layer. OPL: Outer Plexiform Layer. INL: Inner Nuclear Layer. IPL: Inner Plexiform Layer. GCL: Ganglion Cell Layer. DAC: Dopaminergic Amacrine Cell. HC: Horizontal Cell. RBC: Rod Bipolar Cell. CBC: Cone Bipolar Cell. AC: Amacrine Cell. RGC: Retinal Ganglion Cell. ipRGC: intrinsically photosensitive Retinal Ganglion Cell.

RGCs are two classes of inhibitory interneurons: horizontal and amacrine cells. Horizontal cells provide feedback and feedforward inhibition onto photoreceptors and bipolar cells, respectively.[12–14] They consist of one or two cell types depending on mammalian species.[15,16] Amacrine cells typically have no axon and provide feedback and feedforward inhibition via their dendrites onto bipolar cells and RGCs, respectively.[17–19] Some amacrine cell types, in addition to providing glycinergic or GABAergic inhibition, also co-release neuropeptides including somatostatin and vasointestinal polypeptide, that can modulate retinal function.[20–22] The precise number of amacrine cell types remains unclear, but is likely between 30 and 40 types.[23–25]

Dopamine is released by a specialized cell type in retina

Dopaminergic amacrine cells (DACs) are the principal sources of dopamine in the retina. DACs typically form two distinct functional types: type-1 and type-2[26–28]; the morphology of the two types is conserved across species including amphibians, fish, birds, and mammals.[29–33] DAC somata are restricted to the INL and DAC dendrites ramify extensively in the outermost sublamina of the inner plexiform layer. Depending on the species, DAC processes can extend to the outer plexiform layer and/or the ganglion cell layer (Fig. 1).[34,35] The dendrites can reach up to several millimeters away from the soma and are dotted by a dense plexus of varicosities and spines. These varicosities and spines serve as conduits for synaptic output and input, respectively.[29] Thus, DACs can receive synaptic input as well as release dopamine over a large volume of the retina, thereby influencing the responses of distant and diverse cell types (Fig. 1).[36–38] Most of the action of dopamine in the retina is likely extra-synaptic, or paracrine in nature.[39,40]

The activity of DACs is regulated by excitatory and inhibitory inputs from several retinal cell types. DACs receive excitatory input from both cone bipolar cells (CBCs) and intrinsically photosensitive (ip)RGCs.[41,42] CBCs provide DACs with both the rod-mediated input they receive from AII ACs and cone-mediated input. ipRGCs provide input to DACs via axon collaterals that retrogradely extend into the IPL.[42–45] DACs also receive GABAergic and glycinergic inhibition from AII and other ACs types.[46] Rod and cone mediated input to DACs allows them to respond transiently to short timescale changes in light intensity, while inputs from ipRGCs allow DACs to respond in a slow modulatory fashion to changes in mean light intensity.[43,47] Input from all three photoreceptor types, thereby allows DACs to regulate retinal dopamine over a broad range of light levels and timescales.

Locations at which dopamine acts in retina

Retinal neurons sense changes in extracellular dopamine via a diverse set of receptors. These receptors fall into two classes: D1-type and D2-type. D1-type includes D1Rs and D5Rs; D2-type includes D2Rs, D3Rs, D4Rs.[48] These two classes are distinguished by their ligand binding properties and by their action on the regulatory enzyme adenylyl cyclase.[49] Activation of these receptors by dopamine triggers a wide array of intracellular changes that eventually alter the neural response.[50,51]

Most major cell classes in the retina express at least one type of dopamine receptor (Fig. 1). In the outer retina, rods and cones express D4Rs and may express D2R in some species.[50] In the inner retina, horizontal cells (HCs), cone bipolar cells (CBCs) and a few subtypes of amacrine cells (ACs) express D1Rs.[52–54] A special variant of D2Rs, called D2 autoreceptors, are located presynaptic to the DACs and regulate release of dopamine and it's reuptake by dopamine transporters.[55]

Antibody staining and mRNA assays indicate RGCs express both D1-type and D2-type receptors, where D2-type receptors may be more sparsely expressed.[56–59] How these expression patterns differ across the 30–40 RGC types remains to be determined. In particular, melanopsin expressing ipRGCs have been shown to express D1Rs and D4Rs,[60] providing a conduit by which dopamine can modulate the activity of cells that signal changes in the phase of the circadian cycle. Controversy regarding the cellular expression patterns for D1Rs and D2Rs due to antibody specificity and differences in genetic models still remains. Regardless, the widespread expression of DARs in the retina indicates that dopamine is likely to impact almost every stage of retinal processing. Below, we highlight specific ways that dopamine can shape retinal processing.

Impact of dopamine on gap junction coupling

One of the most well studied mechanisms by which changes in dopamine concentration alter retinal processing is modulation of gap-junction-mediated electrical coupling between neurons. Just as every major class of retinal neuron expresses dopamine receptors, every major class expresses at least one type of connexin: the proteins that form gap junctions.[61,62] In mammalian retina, cones and likely rods express connexin36 (Cx36), horizontal cells express Cx57, and particular types of bipolar cells, amacrine cells, and RGCs express Cx36 and/or Cx45.[63] Notably, there is a high degree of correspondence between cell types that express one or more connexins and cell types that express one or more dopamine receptor types (see previous section). These connexins mediate

Please cite this article as: Roy S, Field GD, Dopaminergic modulation of retinal processing from starlight to sunlight, Journal of Pharmacological Sciences, https://doi.org/10.1016/j.jphs.2019.03.006

both homotypic coupling within a cell type (e.g. cones to other cones) as well as heterotypic coupling across cell types (e.g. amacrine cells to bipolar cells). This means that dopaminergic modulation of gap junctions can alter retinal processing in two very different ways. By modulating homotypic coupling, dopamine can promote or limit the summation of signals within a set of neurons that perform the same function. By modulating heterotypic coupling, dopamine can promote or limit crosstalk between distinct retinal circuits. Below, we describe how coupling modulation by dopamine can tune the integration of signals to optimize the signal-to-noise ratio or change connectivity between circuits to alter circuit computations.

Photoreceptors

In many species, including primates, rods and cones are homotypically and heterotypically coupled to one another.[63,64] The strength of this coupling is dependent on the time of the day, light level, and the level of dopamine in the retina.[65–67] Dopamine in particular, under the control of circadian clocks and/or light, activates D4Rs, which signal via the inhibitory G-protein G_i, adenylyl cyclase, cAMP, and protein kinase A to limit rod-cone coupling.[65,68] Similarly, when D4Rs are inactivated, rod-cone coupling is increased. Because rods are likely to express Cx36, similar behavior is also expected in the coupled rod network.

Why might modulating photoreceptor coupling be useful? On a starlit night, photons are scarce: only one rod in ~1000 receives a photon.[4,69] Thus, signals are sparse across the array of rods and these signals will be overwhelmed if linearly pooled with noise from the dozens to hundreds of neighboring rods that fail to absorb a photon.[70–72] Under these conditions, optimal processing dictates that rods are minimally coupled to one another and to cones. This prevents sparse signals from mixing with noise across photoreceptors. However, as the light level increases to moonlight or dawn/dusk, the rate of photon absorption increases by several orders of magnitude across the array of rods. At this light level, the photons are also more spatially correlated due to the correlations in natural scenes.[73] A stronger coupling among rods would therefore be potentially advantageous, as the signal-to-noise ratio can be increased by averaging the spatially correlated inputs together while averaging out their uncorrelated noise (e.g. Poisson fluctuations in photon absorption). Furthermore, an increase in rod to cone coupling near dawn/dusk conditions, allows the potentially more sensitive rod signals to infiltrate cones, thereby providing additional drive to downstream RGCs, via the 'secondary' rod pathway (see Fig. 1).[65,74,75] Recent evidence suggests, contrary to expectations, that rod-rod coupling and rod-cone coupling are high for illumination less than ~1R* and low for illumination above ~1R*.[76] High to modest coupling in rods surprisingly does not appear to interfere with the ability to detect single-photons at these light levels.[76] Rod-cone coupling is also decreased in the presence of D4R agonists and increased in the presence of D4R antagonists, mimicking the effects produced by light and darkness respectively.[77] Thus rod-rod coupling attenuates response fluctuations even at the level of single photon detection. Whether at high scotopic light levels, the benefit of avoiding response saturation by utilizing the secondary rod pathway outweighs the benefit of noise averaging in coupled rods, which might necessitate weaker coupling, remains to be determined.

Similar benefits can be achieved by controlling cone-to-cone coupling. Under low photopic conditions, spatially correlated cone signals suffer from residual noise due to Poisson fluctuations in photon absorption and cellular noise from phototransduction. Thus, pooling neighboring cone signals to average out this noise can improve the signal-to-noise ratio.[78,79] However, this benefit comes at the cost of acuity, which is decreased when cone signals are spatially pooled. Thus, at high sunlight conditions, optimal processing considerations suggest that cones may reduce their coupling. While evidence for such as reduction has not been found yet for cones, several other retinal cell types exhibit decreases in coupling at high light levels and presumed high dopamine levels (see below).

Horizontal cells

In addition to photoreceptors, HCs exhibit homotypic coupling, and this coupling is modulated by dopamine. In primates, activation of D1R uncouples H1-type horizontal cells.[80–82] This indicates that under photopic conditions when the dopamine level is elevated, H1 cells will be minimally coupled. Furthermore, in dark-adapted retina examined during circadian day, D1R receptor antagonists have been shown to increase H1 coupling, suggesting that tonic daytime dopamine release (in the absence of light) promotes decoupling.[81,83]

What is the potential benefit for retinal processing of modulating H1 cell coupling? Coupling increases the spatial receptive field size of individual H1 cells.[80] Thus, at lower light levels, H1 coupling will generate a broader antagonist surround at the level of photoreceptors and bipolar cells. Broader surrounds may be beneficial at low photopic light levels for greater integration of signals across the array of noisy cones. Narrower surrounds may be beneficial at higher light levels because it allows for smaller receptive fields to support higher acuity. Importantly, recent work shows that nonlinearities in transmission between bipolar cells and RGCs, as well as differential temporal processing among different bipolar cell types, cause feedback from H1 cells to have diverse influences on the output of different RGC types.[84] Furthermore, a recent study in mouse found minimal changes in RGC function when Cx57 was conditionally knocked out in horizontal cells.[85,86] Thus, it remains a direction for future research to determine the full impact of modulating horizontal cell coupling on retinal output.

Amacrine cells

DACs form close structural interactions such as perisomatic rings with a variety of amacrine cell types,[87] suggesting that DACs likely modulate the activity and coupling of several amacrine cell types. However, a full catalog of the amacrine cell types that express dopamine receptors and which types are homotypically and/or heterotypically coupled has yet to be obtained. Thus, our understanding of how dopaminergic modulation of amacrine cell coupling shapes retinal output is shallow. Yet, an instructive example for the potency of modulating coupling among amacrine cells is provided by AII amacrine cells, the most numerous amacrine cell in most mammalian retinas. AIIs exhibit immunoreactivity for D1 receptors as well as both homotypic and heterotypic coupling.[49,63] Furthermore, AIIs lie at a critical junction between circuits that process rod versus cone signals. They receive rod-mediated visual signals from rod-bipolar cells; AIIs feed these signals to ON cone bipolar cells via gap junctions and to OFF cone bipolar cells (and some OFF RGCs) via glycinergic disinhibition.[88,89] We describe below how the retina modulates coupling among AIIs to influence the processing and transmission of signals under both scotopic and photopic conditions.

Under fully dark-adapted conditions (e.g. starlight), AIIs exhibit weak homotypic coupling mediated by Cx36. Under these conditions, neurobiotin diffusion is limited to ~20 nearby AIIs.[90,91] At higher scotopic light levels, AII coupling is greatly expanded: neurobiotin diffusion reveals a coupled network of ~200 AIIs. These changes in coupling produce concomitant changes in receptive field size.[92,93] At higher light levels that enter the photopic range, AII coupling is diminished back to small groups of ~20 cells. The increase in coupling from darkness to dim light conditions is

Please cite this article as: Roy S, Field GD, Dopaminergic modulation of retinal processing from starlight to sunlight, Journal of Pharmacological Sciences, https://doi.org/10.1016/j.jphs.2019.03.006

signaled by a dopamine-independent pathway involving activated NMDA receptors on AIIs, which drives the phosphorylation of Cx36 by a CaMKII-mediated signaling pathway.[94,95] However, AII decoupling at higher light levels is signaled by dopamine released from DACs, which binds D1Rs on AIIs and acts through protein phosphatase 2A to dephosphorylate Cx36.[94,95]

What are the benefits of modulating AII coupling to the processing of rod and cone mediated signals? At low light levels, AII cells receive substantial noise from rod bipolar cells and few of those bipolar cells carry the signal of an absorbed photon. Pooling this noise by strongly coupling AIIs is likely to overwhelm the sparser, photon-generated signal.[72] Thus, these conditions favor a decoupled network of AIIs.

At moderate to high scotopic light levels (moonlight to dawn/dusk), most rod bipolar cells will be activated by absorbed photons across the array of rods. Thus, higher light levels produce a correlated visual signal across the array of rod bipolar cells. This produces an advantage to averaging AII signals by reducing (averaging out) the negative consequences of noise (e.g. uncorrelated Poisson noise in photon absorption between nearby rods). These conditions promote coupling across the network of AIIs, but likely come at the cost of reduced visual acuity.

At moderate to high photopic conditions, uncorrelated Poisson noise in visual input diminishes relative to the signal. This allows spatial receive fields of RGCs to begin to shrink and surround antagonism to increase.[96,97] These are beneficial because smaller receptive fields support higher acuity vision and surround antagonisms reduces signal redundancy across RGCs.[98] Under daylight conditions, AIIs serve as a route by which signals from ON bipolar cells inhibit (via glycine) OFF bipolar cell and OFF RGC signals. If AIIs remained strongly coupled, the spatial pooling of this 'cross-over inhibition' would be mismatched to the receptive fields of RGCs.[99] Thus, these constraints likely promote AII decoupling under photopic conditions.

These considerations illustrate the potential utility to retinal processing for modulating amacrine cell coupling by dopamine. The story of AII coupling recapitulates many features of coupling among photoreceptors. What is the utility of modulating this coupling both in the outer and inner retina? A likely explanation is that the receptive fields of photoreceptors are small, while the receptive fields of AIIs are much larger. The light level at which neighboring photoreceptor signals become correlated versus neighboring AII signal will thus be quite different: neighboring AII signals will be correlated at a lower light levels.[75] Thus, separately modulating coupling in the inner and outer retina allows the processes to be tuned to different light levels and different degrees of signal convergence.

Retinal ganglion cells

Dopamine can also modulate coupling among the RGCs, which send signals from retina to brain. Homotypic gap junction coupling is somewhat common among RGCs: one study identified 7 of 22 morphologically defined RGC types in mouse exhibit neurobiotin tracer coupling with homotypic RGCs.[100] Heterotypic coupling with amacrine cells is also relatively common: 15 of 22 morphologically defined types in mouse exhibit neurobiotin coupling with one or more types of amacrine cells.[100] The extent to which this homotypic and heterotypic coupling across RGC types is under the modulatory control of dopamine is unclear. However, at least some of this coupling is likely under the control of dopamine. For example, homotypic coupling among OFF alpha RGCs in mouse and rabbit retina is increased by activation of D1 receptors.[101] Interestingly, this increase in coupling has minimal impact on spontaneous activity, but does increase stimulus-driven synchronous spiking among neighboring OFF alpha RGCs.[101] The functional implications of this modulation in coupling are not clear. One explanation is that an increase in the strength of homotypic coupling among RGCs at high light level may promote the transmission of correlated signals from the retina to the primary visual cortex via the LGN.[102–104] Several studies in bullfrog retina have also demonstrated dopamine dependent changes in RGC correlated spiking, suggesting this is a conserved mechanism.[105,106] D1 receptor activation can also modulate heterotypic coupling between RGCs and amacrine cells.[41,107] In principle, modulation of RGC coupling changes the basic circuit mediating RGC responses, thereby changing the information content that is transmitted to the brain.

Interestingly, dopamine-dependent modulation of coupling among RGCs (homotypic and heterotypic) has been recently observed to be engaged by spontaneous waves of activity that propagate across the retina during development.[108] Dopamine release is driven by spontaneous (light-independent) retinal waves, which thereby promotes electrical coupling between ipRGCs and other retinal neurons. This describes a mechanism initiated by retinal waves and promoted by dopamine, that shapes the extent of light-driven signals during retinal development. Understanding the impact of this process on the visual processing by different retinal circuits is an important avenue for future research and highlights the ways in which dopaminergic modulation of gap junctions plays diverse and critical roles in the retina, including during development.

In summary, dopamine modulates gap junction coupling at nearly every stage of retinal processing in the mature retina and plays important roles in development. Modulation of homotypic coupling likely serves to tune spatial integration to optimize the signal-to-noise of retinal signals under different lighting conditions. At the level of RGCs, modulation of homotypic coupling will control the extent of fine time-scale synchronous spiking activity, which may improve the efficiency with which visual signals are processed across populations of RGCs.[109,110] In contrast, modulation of heterotypic coupling may serve as a switch to regulate communication across diverse cell types and circuits in the retina.

Impact of dopamine on intrinsic cellular conductances

In addition to modulating gap-junction conductances, dopamine also modulates intrinsic ionic conductances in different retinal cell types.[56,111,112] Depending on the cell type, dopamine can alter ionic flow by acting directly on ion channels via sensing receptor elements, or by acting indirectly via cAMP-PKA pathway and/or auxiliary regulatory elements such as calmodulin.[51] Ligand binding studies show that dopamine can have wide-ranging effects on ligand- and voltage-gated channels, thereby regulating cell excitability.[58,113,114] To understand how dopamine impacts the excitability of retinal neurons, we focus on a few instructive examples.

Photoreceptors

Photoreceptors in most species express D4Rs,[115] and activation of these receptors on photoreceptors modulate cellular conductances in addition to coupling. In the salamander retina, a light induced hyperpolarization in rods and 'small' cones triggers I_h (hyperpolarization-activated nonspecific cation current), which tends to restore the membrane back to its resting potential. But concomitant D4R activation increases the calcium current which suppresses I_h, keeping the rods and 'small' cones hyperpolarized. In 'large' cones however, activation of D4Rs reduces calcium currents, thus allowing I_h to relieve the hyperpolarization. This likely promotes stronger responses in 'large' cones while suppressing responses in rods and 'small cones. Notably, in the salamander retina, a D4R-mediated change in calcium current was found to be

Please cite this article as: Roy S, Field GD, Dopaminergic modulation of retinal processing from starlight to sunlight, Journal of Pharmacological Sciences, https://doi.org/10.1016/j.jphs.2019.03.006

dependent on cAMP-PKA regulatory elements. In chick, frog, mouse and human retinas, activation of D2Rs/D4Rs is also likely to reduce rod responses and enhance cone responses,[66,116–118] but the role of cAMP-PKA regulatory elements remains unclear. Together, these findings suggest that dopamine receptor activation in photoreceptors induces changes in conductances which can elevate or suppress light responses, and that the underlying mechanisms may be species specific.

Horizontal cells

Another instructive example is HCs, which in most species express D1Rs.[119] Two lines of evidence suggest that HC excitability is significantly modulated by dopamine. First, when dopamine activates D1Rs on HCs, it triggers the cAMP-PKA signaling cascade which phosphorylates glutamate sensing kainate receptors in these cells.[114] This enhances the effective sensitivity of horizontal cells to glutamate released from photoreceptors. Second, D1R mediated cAMP-PKA signaling cascade also produces a suppression in voltage gated calcium currents specifically in H1s.[120] It is conceivable that these competing effects shape the horizontal cell feedback to cones in ways that allow subtraction of spatially averaged light, thereby changing the gain of the photoreceptor response.[121,122]

Amacrine cells

With the exception of how dopamine modulates gap-junction coupling in AIIs (see also previous section),[90–93] relatively little is known about the role dopamine plays in modulating the ionic conductances of ACs. However, a few studies provide clues that dopamine changes AC conductances to shape signal processing in the retina. For example, AII ACs express D1Rs that are activated by synaptic and extra-synaptic dopamine released from DACs.[87] This pathway appears to inhibit spontaneous and K^+ evoked release of glycine, potentially mitigating rod signals in the OFF pathway.[123] Dopamine is also thought to increase $GABA_A$ receptor mediated Cl^- currents in ACs, via increased affinity of $GABA_A$ receptors by PKA-mediated phosphorylation.[124] Finally, wide-field ACs, expressing D1Rs, regulate GABA release onto rod bipolar cells, thereby shaping dim light sensitivity.[54] While the cellular mechanisms underlying these changes remain to be understood, these studies suggest that dopamine is altering cellular conductances in a variety of ACs types, thus potentially tuning inhibition in the inner retina for daytime and nighttime vision.

Retinal ganglion cells

Dopamine can modulate the spike generating mechanisms in RGCs, and thereby directly tune the transmission of visual information from the retina to the brain. Dopamine modulates RGC spiking activity via two primary mechanisms: (1) modulating membrane conductance of RGCs to various ions, and (2) modulating coupling strength among homotypically coupled RGCs (see above). In whole-cell recordings, D1R agonist SKF81297 was found to decrease spontaneous spiking in RGCs while D1R antagonist SCH23390 was found to increase it. In both cases, RGC excitability was dominated by a D1R mediated change in inward Na^+ currents.[56] D1R activation also enhances temporal summation of excitatory signals in RGC dendrites.[125,126] Thus, by locally modulating the flow of ions, D1Rs on RGCs mediate both signal integration in dendrites and spike generation near the soma. Extracellular recordings from RGCs also suggest that dopamine mediates changes in spike latency, with differential change between ON and OFF RGC types.[127,128] Together, these studies point to a number of intrinsic mechanisms that dopamine regulates - potentially tuning RGCs to process cone-mediated signals. Experiments that link these cellular and circuit-level changes in responsivity to light-adaptation and efficient coding[98] are important directions for future work.

Cellular conductances in amacrine cells[63] and bipolar cells[129] are also influenced by dopamine, though the exact mechanisms driving these changes are poorly understood. As with RGCs, it is likely that this neuromodulation serves visual encoding under different lighting conditions, but more experiments are needed to discover the impact of these cellular changes on visual signaling. What is becoming increasingly clear is that there is a great diversity of ways in which dopamine modulates neuronal conductances in the retina, and that this offers an opportunity to understand the relationship between neuromodulation and sensory processing.

Lessons from disease models and genetically modified animals

Transgenic animals have been a powerful tool for investigating the impact of dopamine on vision. For example, genetic ablation or pharmacological inhibition of D1Rs in mouse retina results in diminished ERG b-wave amplitudes at rod and cone light levels.[130,131] This suggests that D1Rs are critical to maintaining rod and cone signal transmission through bipolar cells. Meanwhile, genetic ablation of D4Rs in dark-adapted mice completely abolished the rhythmic changes in ERG,[131] suggesting that D4Rs in photoreceptors are involved in generating or maintaining circadian rhythm in the retina. When dopamine signaling was abolished in the retina using a retina-specific knockout of tyrosine hydroxylase, the circadian component of the ERG was also eliminated.[131] These results suggest that dopamine plays a key role in mediating both light and circadian dependent signaling in the retina. Transgenic mice have also been useful for morphological characterization of DACs, especially in elucidating the spatial distribution of their processes and determining their synaptic partners.[28,132]

Diseases associated with dopamine dysfunction or dysregulation have also been informative about the neuromodulatory and neurotropic roles of dopamine in the retina. For example, Parkinson's patients exhibit apoptosis of dopaminergic neurons (DACs) in the retina[133] - confirmed by post-mortem studies.[134] The retinas of these patients have morphological abnormalities such as thinning of the inner nuclear layer and ganglion cell layer, and degeneration of the retinal lattice.[135] In addition, these patients suffer from reduced light sensitivity, reduced spatial acuity and diminished color vision.[136,137] Rodent models of Parkinson's exhibit similar deficiencies in the retina.[138,139] These studies support the idea that dopamine plays a major role in tuning visual processing and further suggest that dopamine may play an important role in the overall health of the retina.

Discussion

We have reviewed how dopamine modulates gap junction coupling and other cellular conductances across light levels. We have also hypothesized potential benefits of dopaminergic modulation for processing visual signals under the distinct regimes of photon absorption that dominate night and day-time vision. In particular, we have argued that these signaling regimes demand different processing strategies in different retinal circuits for accurately and reproducibly encoding visual scenes. Finally, we suggest that dopamine release in the retina is key to tuning visual processing to meet the constraints imposed by different light levels.

This perspective on the role of dopamine in light adaptation is far from conclusive or complete. There is a dearth of experiments that clearly demonstrate the impact of dopaminergic signaling on the spatial or temporal receptive fields of retinal neurons. Nor are there clear demonstrations that dopaminergic signaling alters the quality and quantity of information about natural scenes that RGCs

Please cite this article as: Roy S, Field GD, Dopaminergic modulation of retinal processing from starlight to sunlight, Journal of Pharmacological Sciences, https://doi.org/10.1016/j.jphs.2019.03.006

send to the brain. For example, if dopamine tunes retinal processing to ambient light levels, blocking dopamine signaling at high light levels should reduce the information RGC spike trains convey about visual scenes. Furthermore, moderate to high dopamine levels would be predicted to favor multi-photon responses from cones over single-photon responses from rods to influence RGC spiking.

Comparing the relative impact of different dopamine-induced changes in different cell types also remains a challenge for future studies. For example, how does the impact of dopamine-mediated changes in the balance of ionic conductances within individual neurons compare to the impact of dopamine-mediated changes in gap junction coupling? And how pronounced are the effects of dopamine-mediated coupling modulation in different cell classes such as photoreceptors, horizontal cells and RGCs?

A key set of technological, pharmacological and genetic tools may be pivotal in addressing these questions. First, a comprehensive understanding of the structure and dynamics of GPCRs facilitated by technologies such as X-ray crystallography, cryo-EM and NMR spectroscopy, is within reach[140] - offering promise for targeted and effective modulation of DAR activity in-vitro and in-vivo.[141] This could increase the specificity of drug-target interactions, reducing off-target effects. Second, genetic tools allow precise manipulation of dopamine signaling at the level of individual receptor types within individual types of neurons. Retina restricted DAR specific knockouts and dopamine precursor enzymes such as tyrosine hydroxylase knockouts are now available[131]; providing an opportunity for assaying the role of different DAR types in modulating signal processing in distinct retinal circuits. Third, large-scale electrical and calcium imaging technologies have enabled monitoring activity of hundreds to thousands of neurons simultaneously.[142,143] Using these technologies in mice genetically engineered to express fluorescent reporters conjugated to specific DARs[52] or conjugated to specific gap-junction connexin molecules[144,145] will allow precise manipulation of dopamine signaling, identification of impacted cell types, and measurements of response perturbations in those cell types. Additionally, chemogenetic tools such as PSAM, DREADD and DART,[146–148] offer the promise of gaining temporal control over dopaminergic signaling with cell type and receptor type precision. Thus, we anticipate the union of these technologies will greatly advance our understanding of how dopaminergic neuromodulation tunes visual processing in the next decade.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

Disclosures

The authors have no financial interests in this work.

Acknowledgements

We would like to thank Christophe P. Ribelayga, A.P. Sampath, Nicholas C. Brecha, and Jon Cafaro for commenting on drafts of this article. This work was supported by a grant from the National Institutes of Health and the National Eye Institute, EY024567 (G.D.F.) and a fellowship from the Ruth K. Broad Biomedical Research Foundation (S.R.).

References

1. Schnapf JL, Copenhagen DR. Differences in the kinetics of rod and cone synaptic transmission. *Nature*. 1982;296(5860):862–864.
2. Corey DP, Dubinsky JM, Schwartz EA. The calcium current in inner segments of rods from the salamander (Ambystoma tigrinum) retina. *J Physiol*. 1984;354:557–575.
3. Baylor DA, Nunn BJ, Schnapf JL. The photocurrent, noise and spectral sensitivity of rods of the monkey Macaca fascicularis. *J Physiol*. 1984;357:575–607.
4. Field GD, Sampath AP, Rieke F. Retinal processing near absolute threshold: from behavior to mechanism. *Annu Rev Physiol*. 2005;67:491–514.
5. Wachtler T, Doi E, Lee T, Sejnowski TJ. Cone selectivity derived from the responses of the retinal cone mosaic to natural scenes. *J Vis*. 2007;7(8):6.
6. Dowling JE. *The retina : an approachable part of the brain*. Cambridge, Mass: Belknap Press of Harvard University Press; 1987.
7. Helmstaedter M, Briggman KL, Turaga SC, Jain V, Seung HS, Denk W. Connectomic reconstruction of the inner plexiform layer in the mouse retina. *Nature*. 2013;500(7461):168–174.
8. Euler T, Haverkamp S, Schubert T, Baden T. Retinal bipolar cells: elementary building blocks of vision. *Nat Rev Neurosci*. 2014;15(8):507–519.
9. Sanes JR, Masland RH. The types of retinal ganglion cells: current status and implications for neuronal classification. *Annu Rev Neurosci*. 2015;38:221–246.
10. Baden T, Berens P, Franke K, Roman Roson M, Bethge M, Euler T. The functional diversity of retinal ganglion cells in the mouse. *Nature*. 2016;529(7586):345–350.
11. Field GD, Sher A, Gauthier JL, et al. Spatial properties and functional organization of small bistratified ganglion cells in primate retina. *J Neurosci*. 2007;27(48):13261–13272.
12. Thoreson WB, Babai N, Bartoletti TM. Feedback from horizontal cells to rod photoreceptors in vertebrate retina. *J Neurosci*. 2008;28(22):5691–5695.
13. Wu SM. Input-output relations of the feedback synapse between horizontal cells and cones in the tiger salamander retina. *J Neurophysiol*. 1991;65(5):1197–1206.
14. Yang XL, Wu SM. Feedforward lateral inhibition in retinal bipolar cells: input-output relation of the horizontal cell-depolarizing bipolar cell synapse. *Proc Natl Acad Sci U S A*. 1991;88(8):3310–3313.
15. Peichl L, Gonzalez-Soriano J. Morphological types of horizontal cell in rodent retinae: a comparison of rat, mouse, gerbil, and Guinea pig. *Vis Neurosci*. 1994;11(3):501–517.
16. Wassle H, Boycott BB, Rohrenbeck J. Horizontal cells in the monkey retina: cone connections and dendritic network. *Eur J Neurosci*. 1989;1(5):421–435.
17. Wong-Riley MT. Synaptic organization of the inner plexiform layer in the retina of the tiger salamander. *J Neurocytol*. 1974;3(1):1–33.
18. Muller JF, Marc RE. GABA-ergic and glycinergic pathways in the inner plexiform layer of the goldfish retina. *J Comp Neurol*. 1990;291(2):281–304.
19. Marc RE, Liu W. Fundamental GABAergic amacrine cell circuitries in the retina: nested feedback, concatenated inhibition, and axosomatic synapses. *J Comp Neurol*. 2000;425(4):560–582.
20. Wassle H, Boycott BB. Functional architecture of the mammalian retina. *Physiol Rev*. 1991;71(2):447–480.
21. Cristiani R, Petrucci C, Dal Monte M, Bagnoli P. Somatostatin (SRIF) and SRIF receptors in the mouse retina. *Brain Res*. 2002;936(1–2):1–14.
22. Witkovsky P, Shi XP. Slow light and dark adaptation of horizontal cells in the Xenopus retina: a role for endogenous dopamine. *Vis Neurosci*. 1990;5(4):405–413.
23. MacNeil MA, Masland RH. Extreme diversity among amacrine cells: implications for function. *Neuron*. 1998;20(5):971–982.
24. MacNeil MA, Heussy JK, Dacheux RF, Raviola E, Masland RH. The shapes and numbers of amacrine cells: matching of photofilled with Golgi-stained cells in the rabbit retina and comparison with other mammalian species. *J Comp Neurol*. 1999;413(2):305–326.
25. Lin B, Masland RH. Populations of wide-field amacrine cells in the mouse retina. *J Comp Neurol*. 2006;499(5):797–809.
26. Mariani AP, Hokoc JN. Two types of tyrosine hydroxylase-immunoreactive amacrine cell in the rhesus monkey retina. *J Comp Neurol*. 1988;276(1):81–91.
27. Wang HH, Cuenca N, Kolb H. Development of morphological types and distribution patterns of amacrine cells immunoreactive to tyrosine hydroxylase in the cat retina. *Vis Neurosci*. 1990;4(2):159–175.
28. Contini M, Lin B, Kobayashi K, Okano H, Masland RH, Raviola E. Synaptic input of ON-bipolar cells onto the dopaminergic neurons of the mouse retina. *J Comp Neurol*. 2010;518(11):2035–2050.
29. Dacey DM. The dopaminergic amacrine cell. *J Comp Neurol*. 1990;301(3):461–489.
30. Keeley PW, Reese BE. Morphology of dopaminergic amacrine cells in the mouse retina: independence from homotypic interactions. *J Comp Neurol*. 2010;518(8):1220–1231.
31. Pourcho RG. Dopaminergic amacrine cells in the cat retina. *Brain Res*. 1982;252(1):101–109.
32. Marshak DW, Carraway RE, Ferris CF. Characterization of immunoreactive substance P and neurotensin in the goldfish retina. *Exp Eye Res*. 1987;44(6):839–848.
33. Dowling JE, Ehinger B. The interplexiform cell system. I. Synapses of the dopaminergic neurons of the goldfish retina. *Proc R Soc Lond B Biol Sci*. 1978;201(1142):7–26.
34. Tauchi M, Madigan NK, Masland RH. Shapes and distributions of the catecholamine-accumulating neurons in the rabbit retina. *J Comp Neurol*. 1990;293(2):178–189.
35. Versaux-Botteri C, Martin-Martinelli E, Nguyen-Legros J, Geffard M, Vigny A, Denoroy L. Regional specialization of the rat retina: catecholamine-containing

amacrine cell characterization and distribution. *J Comp Neurol*. 1986;243(3):422–433.
36. Contini M, Raviola E. GABAergic synapses made by a retinal dopaminergic neuron. *Proc Natl Acad Sci U S A*. 2003;100(3):1358–1363.
37. Dumitrescu ON, Pucci FG, Wong KY, Berson DM. Ectopic retinal ON bipolar cell synapses in the OFF inner plexiform layer: contacts with dopaminergic amacrine cells and melanopsin ganglion cells. *J Comp Neurol*. 2009;517(2):226–244.
38. Hokoc JN, Mariani AP. Tyrosine hydroxylase immunoreactivity in the rhesus monkey retina reveals synapses from bipolar cells to dopaminergic amacrine cells. *J Neurosci*. 1987;7(9):2785–2793.
39. Witkovsky P, Nicholson C, Rice ME, Bohmaker K, Meller E. Extracellular dopamine concentration in the retina of the clawed frog, Xenopus laevis. *Proc Natl Acad Sci U S A*. 1993;90(12):5667–5671.
40. Puopolo M, Hochstetler SE, Gustincich S, Wightman RM, Raviola E. Extrasynaptic release of dopamine in a retinal neuron: activity dependence and transmitter modulation. *Neuron*. 2001;30(1):211–225.
41. Hoshi H, Liu WL, Massey SC, Mills SL. ON inputs to the OFF layer: bipolar cells that break the stratification rules of the retina. *J Neurosci*. 2009;29(28):8875–8883.
42. Zhang DQ, Wong KY, Sollars PJ, Berson DM, Pickard GE, McMahon DG. Intraretinal signaling by ganglion cell photoreceptors to dopaminergic amacrine neurons. *Proc Natl Acad Sci U S A*. 2008;105(37):14181–14186.
43. Prigge CL, Yeh PT, Liou NF, et al. M1 ipRGCs influence visual function through retrograde signaling in the retina. *J Neurosci*. 2016;36(27):7184–7197.
44. Zhang DQ, Belenky MA, Sollars PJ, Pickard GE, McMahon DG. Melanopsin mediates retrograde visual signaling in the retina. *PLoS One*. 2012;7(8):e42647.
45. Zhao X, Wong KY, Zhang DQ. Mapping physiological inputs from multiple photoreceptor systems to dopaminergic amacrine cells in the mouse retina. *Sci Rep*. 2017;7(1):7920.
46. Qiao SN, Zhang Z, Ribelayga CP, Zhong YM, Zhang DQ. Multiple cone pathways are involved in photic regulation of retinal dopamine. *Sci Rep*. 2016;6:28916.
47. Liu LL, Spix NJ, Zhang DQ. NMDA receptors contribute to retrograde synaptic transmission from ganglion cell photoreceptors to dopaminergic amacrine cells. *Front Cell Neurosci*. 2017;11:279.
48. Seeman P, Van Tol HH. Dopamine receptor pharmacology. *Trends Pharmacol Sci*. 1994;15(7):264–270.
49. Nguyen-Legros J, Simon A, Caille I, Bloch B. Immunocytochemical localization of dopamine D1 receptors in the retina of mammals. *Vis Neurosci*. 1997;14(3):545–551.
50. Witkovsky P. Dopamine and retinal function. *Doc Ophthalmol*. 2004;108(1):17–40.
51. Neve KA, Seamans JK, Trantham-Davidson H. Dopamine receptor signaling. *J Recept Signal Transduct Res*. 2004;24(3):165–205.
52. Farshi P, Fyk-Kolodziej B, Krolewski DM, Walker PD, Ichinose T. Dopamine D1 receptor expression is bipolar cell type-specific in the mouse retina. *J Comp Neurol*. 2016;524(10):2059–2079.
53. Popova E. Role of dopamine in distal retina. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol*. 2014;200(5):333–358.
54. Travis AM, Heflin SJ, Hirano AA, Brecha NC, Arshavsky VY. Dopamine-dependent sensitization of rod bipolar cells by GABA is conveyed through wide-field amacrine cells. *J Neurosci*. 2018;38(3):723–732.
55. Wang Y, Harsanyi K, Mangel SC. Endogenous activation of dopamine D2 receptors regulates dopamine release in the fish retina. *J Neurophysiol*. 1997;78(1):439–449.
56. Hayashida Y, Rodriguez CV, Ogata G, et al. Inhibition of adult rat retinal ganglion cells by D1-type dopamine receptor activation. *J Neurosci*. 2009;29(47):15001–15016.
57. Koulen P. Postnatal development of dopamine D1 receptor immunoreactivity in the rat retina. *J Neurosci Res*. 1999;56(4):397–404.
58. Ogata G, Stradleigh TW, Partida GJ, Ishida AT. Dopamine and full-field illumination activate D1 and D2-D5-type receptors in adult rat retinal ganglion cells. *J Comp Neurol*. 2012;520(17):4032–4049.
59. Veruki ML. Dopaminergic neurons in the rat retina express dopamine D2/3 receptors. *Eur J Neurosci*. 1997;9(5):1096–1100.
60. Van Hook MJ, Wong KY, Berson DM. Dopaminergic modulation of ganglion-cell photoreceptors in rat. *Eur J Neurosci*. 2012;35(4):507–518.
61. Vaney DI. Many diverse types of retinal neurons show tracer coupling when injected with biocytin or Neurobiotin. *Neurosci Lett*. 1991;125(2):187–190.
62. Volgyi B, Kovacs-Oller T, Atlasz T, Wilhelm M, Gabriel R. Gap junctional coupling in the vertebrate retina: variations on one theme? *Prog Retin Eye Res*. 2013;34:1–18.
63. Bloomfield SA, Volgyi B. The diverse functional roles and regulation of neuronal gap junctions in the retina. *Nat Rev Neurosci*. 2009;10(7):495–506.
64. Fain G, Sampath AP. Rod and cone interactions in the retina. *F1000Research*. 2018;7.
65. Ribelayga C, Cao Y, Mangel SC. The circadian clock in the retina controls rod-cone coupling. *Neuron*. 2008;59(5):790–801.
66. Jackson CR, Chaurasia SS, Zhou H, Haque R, Storm DR, Iuvone PM. Essential roles of dopamine D4 receptors and the type 1 adenylyl cyclase in photic control of cyclic AMP in photoreceptor cells. *J Neurochem*. 2009;109(1):148–157.
67. Jin NG, Ribelayga CP. Direct evidence for daily plasticity of electrical coupling between rod photoreceptors in the mammalian retina. *J Neurosci*. 2016;36(1):178–184.
68. Tosini G, Dirden JC. Dopamine inhibits melatonin release in the mammalian retina: in vitro evidence. *Neurosci Lett*. 2000;286(2):119–122.
69. Barlow HB. Retinal noise and absolute threshold. *J Opt Soc Am*. 1956;46(8):634–639.
70. Baylor DA, Lamb TD, Yau KW. Responses of retinal rods to single photons. *J Physiol*. 1979;288:613–634.
71. van Rossum MC, Smith RG. Noise removal at the rod synapse of mammalian retina. *Vis Neurosci*. 1998;15(5):809–821.
72. Field GD, Rieke F. Mechanisms regulating variability of the single photon responses of mammalian rod photoreceptors. *Neuron*. 2002;35(4):733–747.
73. Simoncelli EP, Heeger DJ. Representing retinal image speed in visual cortex. *Nat Neurosci*. 2001;4(5):461–462.
74. Ribelayga C, Wang Y, Mangel SC. Dopamine mediates circadian clock regulation of rod and cone input to fish retinal horizontal cells. *J Physiol*. 2002;544(Pt 3):801–816.
75. Bloomfield SA, Dacheux RF. Rod vision: pathways and processing in the mammalian retina. *Prog Retin Eye Res*. 2001;20(3):351–384.
76. Jin NG, Chuang AZ, Masson PJ, Ribelayga CP. Rod electrical coupling is controlled by a circadian clock and dopamine in mouse retina. *J Physiol*. 2015;593(7):1597–1631.
77. Li H, Zhang Z, Blackburn MR, Wang SW, Ribelayga CP, O'Brien J. Adenosine and dopamine receptors coregulate photoreceptor coupling via gap junction phosphorylation in mouse retina. *J Neurosci*. 2013;33(7):3135–3150.
78. DeVries SH, Qi X, Smith R, Makous W, Sterling P. Electrical coupling between mammalian cones. *Curr Biol*. 2002;12(22):1900–1907.
79. Tessier-Lavigne M, Attwell D. The effect of photoreceptor coupling and synapse nonlinearity on signal:noise ratio in early visual processing. *Proc R Soc Lond B Biol Sci*. 1988;234(1275):171–197.
80. Zhang AJ, Jacoby R, Wu SM. Light- and dopamine-regulated receptive field plasticity in primate horizontal cells. *J Comp Neurol*. 2011;519(11):2125–2134.
81. Xin D, Bloomfield SA. Dark- and light-induced changes in coupling between horizontal cells in mammalian retina. *J Comp Neurol*. 1999;405(1):75–87.
82. Mangel SC, Dowling JE. The interplexiform-horizontal cell system of the fish retina: effects of dopamine, light stimulation and time in the dark. *Proc R Soc Lond B Biol Sci*. 1987;231(1262):91–121.
83. He S, Weiler R, Vaney DI. Endogenous dopaminergic regulation of horizontal cell coupling in the mammalian retina. *J Comp Neurol*. 2000;418(1):33–40.
84. Drinnenberg A, Franke F, Morikawa RK, et al. How diverse retinal functions arise from feedback at the first visual synapse. *Neuron*. 2018;99(1):117–134. e111.
85. Dedek K, Pandarinath C, Alam NM, et al. Ganglion cell adaptability: does the coupling of horizontal cells play a role? *PLoS One*. 2008;3(3):e1714.
86. Stroh S, Puller C, Swirski S, et al. Eliminating glutamatergic input onto horizontal cells changes the dynamic range and receptive field organization of mouse retinal ganglion cells. *J Neurosci*. 2018;38(8):2015–2028.
87. Debertin G, Kantor O, Kovacs-Oller T, et al. Tyrosine hydroxylase positive perisomatic rings are formed around various amacrine cell types in the mammalian retina. *J Neurochem*. 2015;134(3):416–428.
88. Muller F, Wassle H, Voigt T. Pharmacological modulation of the rod pathway in the cat retina. *J Neurophysiol*. 1988;59(6):1657–1672.
89. Demb JB, Singer JH. Intrinsic properties and functional circuitry of the AII amacrine cell. *Vis Neurosci*. 2012;29(1):51–60.
90. Hampson EC, Vaney DI, Weiler R. Dopaminergic modulation of gap junction permeability between amacrine cells in mammalian retina. *J Neurosci*. 1992;12(12):4911–4922.
91. Bloomfield SA, Xin D. A comparison of receptive-field and tracer-coupling size of amacrine and ganglion cells in the rabbit retina. *Vis Neurosci*. 1997;14(6):1153–1165.
92. Taylor WR. TTX attenuates surround inhibition in rabbit retinal ganglion cells. *Vis Neurosci*. 1999;16(2):285–290.
93. Bloomfield SA, Xin D. Surround inhibition of mammalian AII amacrine cells is generated in the proximal retina. *J Physiol*. 2000;523(Pt 3):771–783.
94. Kothmann WW, Massey SC, O'Brien J. Dopamine-stimulated dephosphorylation of connexin 36 mediates AII amacrine cell uncoupling. *J Neurosci*. 2009;29(47):14903–14911.
95. Kothmann WW, Trexler EB, Whitaker CM, Li W, Massey SC, O'Brien J. Non-synaptic NMDA receptors mediate activity-dependent plasticity of gap junctional coupling in the AII amacrine cell network. *J Neurosci*. 2012;32(20):6747–6759.
96. Barlow HB, Fitzhugh R, Kuffler SW. Change of organization in the receptive fields of the cat's retina during dark adaptation. *J Physiol*. 1957;137(3):338–354.
97. Rodieck RW, Stone J. Analysis of receptive fields of cat retinal ganglion cells. *J Neurophysiol*. 1965;28(5):833–849.
98. Atick JJ, Redlich AN. What does the retina know about natural scenes. *Neural Comput*. 1992;4(2):196–210.
99. Manookin MB, Beaudoin DL, Ernst ZR, Flagel LJ, Demb JB. Disinhibition combines with excitation to extend the operating range of the OFF visual pathway in daylight. *J Neurosci*. 2008;28(16):4136–4150.

Please cite this article as: Roy S, Field GD, Dopaminergic modulation of retinal processing from starlight to sunlight, Journal of Pharmacological Sciences, https://doi.org/10.1016/j.jphs.2019.03.006

100. Volgyi B, Chheda S, Bloomfield SA. Tracer coupling patterns of the ganglion cell subtypes in the mouse retina. *J Comp Neurol*. 2009;512(5):664–687.
101. Hu EH, Pan F, Volgyi B, Bloomfield SA. Light increases the gap junctional coupling of retinal ganglion cells. *J Physiol*. 2010;588(Pt 21):4145–4163.
102. Neuenschwander S, Singer W. Long-range synchronization of oscillatory light responses in the cat retina and lateral geniculate nucleus. *Nature*. 1996;379(6567):728–732.
103. Usrey WM, Reid RC. Synchronous activity in the visual system. *Annu Rev Physiol*. 1999;61:435–456.
104. Shlens J, Field GD, Gauthier JL, et al. The structure of multi-neuron firing patterns in primate retina. *J Neurosci*. 2006;26(32):8254–8266.
105. Bu JY, Li H, Gong HQ, Liang PJ, Zhang PM. Gap junction permeability modulated by dopamine exerts effects on spatial and temporal correlation of retinal ganglion cells' firing activities. *J Comput Neurosci*. 2014;36(1):67–79.
106. Li H, Liang PJ. Stimulus discrimination via responses of retinal ganglion cells and dopamine-dependent modulation. *Neurosci Bull*. 2013;29(5):621–632.
107. Mills SL, Xia XB, Hoshi H, et al. Dopaminergic modulation of tracer coupling in a ganglion-amacrine cell network. *Vis Neurosci*. 2007;24(4):593–608.
108. Arroyo DA, Kirkby LA, Feller MB. Retinal waves modulate an intraretinal circuit of intrinsically photosensitive retinal ganglion cells. *J Neurosci*. 2016;36(26):6892–6905.
109. Meister M. Multineuronal codes in retinal signaling. *Proc Natl Acad Sci U S A*. 1996;93(2):609–614.
110. Schnitzer MJ, Meister M. Multineuronal firing patterns in the signal from eye to brain. *Neuron*. 2003;37(3):499–511.
111. Thoreson WB, Stella Jr SL, Bryson EI, Clements J, Witkovsky P. D2-like dopamine receptors promote interactions between calcium and chloride channels that diminish rod synaptic transfer in the salamander retina. *Vis Neurosci*. 2002;19(3):235–247.
112. Lasater EM, Dowling JE. Dopamine decreases conductance of the electrical junctions between cultured retinal horizontal cells. *Proc Natl Acad Sci U S A*. 1985;82(9):3025–3029.
113. Vaquero CF, Pignatelli A, Partida GJ, Ishida AT. A dopamine- and protein kinase A-dependent mechanism for network adaptation in retinal ganglion cells. *J Neurosci*. 2001;21(21):8624–8635.
114. Knapp AG, Schmidt KF, Dowling JE. Dopamine modulates the kinetics of ion channels gated by excitatory amino acids in retinal horizontal cells. *Proc Natl Acad Sci U S A*. 1990;87(2):767–771.
115. Vuvan T, Geffard M, Denis P, Simon A, Nguyen-Legros J. Radioimmunoligand characterization and immunohistochemical localization of dopamine D2 receptors on rods in the rat retina. *Brain Res*. 1993;614(1–2):57–64.
116. Ivanova TN, Alonso-Gomez AL, Iuvone PM. Dopamine D4 receptors regulate intracellular calcium concentration in cultured chicken cone photoreceptor cells: relationship to dopamine receptor-mediated inhibition of cAMP formation. *Brain Res*. 2008;1207:111–119.
117. Akopian A, Witkovsky P. D2 dopamine receptor-mediated inhibition of a hyperpolarization-activated current in rod photoreceptors. *J Neurophysiol*. 1996;76(3):1828–1835.
118. Kawai F, Horiguchi M, Miyachi E. Dopamine modulates the voltage response of human rod photoreceptors by inhibiting the h current. *Invest Ophthalmol Vis Sci*. 2011;52(7):4113–4117.
119. Nguyen-Legros J, Versaux-Botteri C, Vernier P. Dopamine receptor localization in the mammalian retina. *Mol Neurobiol*. 1999;19(3):181–204.
120. Liu X, Grove JC, Hirano AA, Brecha NC, Barnes S. Dopamine D1 receptor modulation of calcium channel currents in horizontal cells of mouse retina. *J Neurophysiol*. 2016;116(2):686–697.
121. Kamermans M, Kraaij D, Spekreijse H. The dynamic characteristics of the feedback signal from horizontal cells to cones in the goldfish retina. *J Physiol*. 2001;534(Pt 2):489–500.
122. Verweij J, Hornstein EP, Schnapf JL. Surround antagonism in macaque cone photoreceptors. *J Neurosci*. 2003;23(32):10249–10257.
123. Pycock CJ, Smith LF. Interactions of dopamine and the release of [3H]-taurine and [3H]-glycine from the isolated retina of the rat. *Br J Pharmacol*. 1983;78(2):395–404.
124. Feigenspan A, Bormann J. Facilitation of GABAergic signaling in the retina by receptors stimulating adenylate cyclase. *Proc Natl Acad Sci U S A*. 1994;91(23):10893–10897.
125. Chen L, Yang XL. Hyperpolarization-activated cation current is involved in modulation of the excitability of rat retinal ganglion cells by dopamine. *Neuroscience*. 2007;150(2):299–308.
126. Cui P, Li XY, Zhao Y, et al. Activation of dopamine D1 receptors enhances the temporal summation and excitability of rat retinal ganglion cells. *Neuroscience*. 2017;355:71–83.
127. Jensen RJ, Ziv OR, Rizzo 3rd JF. Thresholds for activation of rabbit retinal ganglion cells with relatively large, extracellular microelectrodes. *Invest Ophthalmol Vis Sci*. 2005;46(4):1486–1496.
128. Xiao L, Zhang PM, Gong HQ, Liang PJ. Effects of dopamine on response properties of ON-OFF RGCs in encoding stimulus durations. *Front Neural Circuits*. 2014;8:72.
129. Maguire G, Werblin F. Dopamine enhances a glutamate-gated ionic current in OFF bipolar cells of the tiger salamander retina. *J Neurosci*. 1994;14(10):6094–6101.
130. Herrmann R, Heflin SJ, Hammond T, et al. Rod vision is controlled by dopamine-dependent sensitization of rod bipolar cells by GABA. *Neuron*. 2011;72(1):101–110.
131. Jackson CR, Ruan GX, Aseem F, et al. Retinal dopamine mediates multiple dimensions of light-adapted vision. *J Neurosci*. 2012;32(27):9359–9368.
132. Gustincich S, Feigenspan A, Wu DK, Koopman LJ, Raviola E. Control of dopamine release in the retina: a transgenic approach to neural networks. *Neuron*. 1997;18(5):723–736.
133. Nguyen-Legros J. Functional neuroarchitecture of the retina: hypothesis on the dysfunction of retinal dopaminergic circuitry in Parkinson's disease. *Surg Radiol Anat*. 1988;10(2):137–144.
134. Harnois C, Di Paolo T. Decreased dopamine in the retinas of patients with Parkinson's disease. *Invest Ophthalmol Vis Sci*. 1990;31(11):2473–2475.
135. Hajee ME, March WF, Lazzaro DR, et al. Inner retinal layer thinning in Parkinson disease. *Arch Ophthalmol (Chicago, Ill*. 2009;127(6):737–741, 1960.
136. Price MJ, Feldman RG, Adelberg D, Kayne H. Abnormalities in color vision and contrast sensitivity in Parkinson's disease. *Neurology*. 1992;42(4):887–890.
137. Tagliati M, Bodis-Wollner I, Yahr MD. The pattern electroretinogram in Parkinson's disease reveals lack of retinal spatial tuning. *Electroencephalogr Clin Neurophysiol*. 1996;100(1):1–11.
138. Bodis-Wollner I. Visual electrophysiology in Parkinson's disease: PERG, VEP and visual P300. *Clin EEG (Electroencephalogr)*. 1997;28(3):143–147.
139. Onofrj M, Bodis-Wollner I. Dopaminergic deficiency causes delayed visual evoked potentials in rats. *Ann Neurol*. 1982;11(5):484–490.
140. Shimada I, Ueda T, Kofuku Y, Eddy MT, Wuthrich K. GPCR drug discovery: integrating solution NMR data with crystal and cryo-EM structures. *Nat Rev Drug Discov*. 2018;18:59–82.
141. Gray DL, Allen JA, Mente S, et al. Impaired beta-arrestin recruitment and reduced desensitization by non-catechol agonists of the D1 dopamine receptor. *Nat Commun*. 2018;9(1):674.
142. Tsai D, Sawyer D, Bradd A, Yuste R, Shepard KL. A very large-scale microelectrode array for cellular-resolution electrophysiology. *Nat Commun*. 2017;8(1):1802.
143. Weitz AC, Behrend MR, Lee NS, et al. Imaging the response of the retina to electrical stimulation with genetically encoded calcium indicators. *J Neurophysiol*. 2013;109(7):1979–1988.
144. Falk M. Genetic tags for labelling live cells: gap junctions and beyond. *Trends Cell Biol*. 2002;12(9):399–404.
145. Kick DR, Schulz DJ. Cell communication: studying gap junctions with PARIS. *eLife*. 2019;8:e45207.
146. Armbruster BN, Li X, Pausch MH, Herlitze S, Roth BL. Evolving the lock to fit the key to create a family of G protein-coupled receptors potently activated by an inert ligand. *Proc Natl Acad Sci U S A*. 2007;104(12):5163–5168.
147. Shields BC, Kahuno E, Kim C, et al. Deconstructing behavioral neuropharmacology with cellular specificity. *Science*. 2017;356(6333). New York, NY.
148. Sternson SM, Roth BL. Chemogenetic tools to interrogate brain functions. *Annu Rev Neurosci*. 2014;37:387–407.

Please cite this article as: Roy S, Field GD, Dopaminergic modulation of retinal processing from starlight to sunlight, Journal of Pharmacological Sciences, https://doi.org/10.1016/j.jphs.2019.03.006