Molecular Neurobiology

ISSN0893-7648/98/19(3): 181–204/$16.00

Dopamine Receptor Localization in the Mammalian Retina

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Abstract

After a short history of dopamine receptor discovery in the retina and a survey on dopamine receptor types and subtypes, the distribution of dopamine receptors in the retinal cells is described and correlated with their possible role in cell and retinal physiology. All the retinal cells probably bear dopamine receptors. For example, the recently discovered D_{1B} receptor has a possible role in modulating phagocytosis by the pigment epithelium and a D_4 receptor is likely to be involved in the inhibition of melatonin synthesis in photoreceptors. Dopamine uncouples horizontal and amacrine cell-gap junctions through D_1-like receptors. Dopamine modulates the release of other transmitters by subpopulations of amacrine cells, including that of dopamine through a D_2 autoreceptor. Ganglion cells express dopamine receptors, the role of which is still uncertain. Müller cells also are affected by dopamine. A puzzling action of dopamine is observed in the ciliary retina, in which D_1- and D_2-like receptors are likely to be involved in the cyclic regulation of intraocular pressure. Most of the dopaminergic actions appear to be extrasynaptic and the signaling pathways remain uncertain. Further studies are needed to better understand the multiple actions of dopamine in the retina, especially those that implicate rhythmic regulations.

Index Entries: Retina; dopamine receptors; mammals.

Introduction and History

The occurrence of dopamine receptors in the vertebrate retina, their pharmacology, and their physiological functions were reviewed in 1990 *(1)* but this research field is now growing rapidly and needs to be reexamined from a new perspective. The story of dopamine receptors in the retina began around the 1970s after a number of descriptions of catecholamine-fluorescent amacrine cells had accumulated throughout vertebrate species, from lamprey to human *(2)*. Parallel biochemical analysis had clearly established that dopamine was the major catecholamine in the retina of most species *(3)* whereas noradrenalin and adrena-

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lin occurred only as trace elements. Dopamine in the retina was demonstrated to fulfill the criteria of a neurotransmitter, and its inhibitory action on ganglion cell activity, as a result of complex interactions in retinal circuitry, was demonstrated in isolated retinas of rabbit and cat *(4,5)*.

A first step in the history of retinal dopamine was the demonstration of the accumulation of cyclic adenosine monophosphate (cAMP) in bovine retinal homogenates in response to catecholamines, and especially to dopamine, by Brown and Makman *(6)*. They also showed the existence of a cAMP-sensitive protein kinase and thought that they "may be dealing with a specific dopamine receptor." They further showed that the dopamine-sensitive adenylyl cyclase activity was inhibited by neuroleptic drugs *(7)*. Later, it was proposed that dopamine activation of adenylyl cyclase was mediated by D_1 receptors *(8)*.

It was the starting point of a search for agonists and antagonists *(9,10)* able to act on this newly discovered dopamine receptor coupled to adenylyl cyclase. Tritiated spiroperidol (a nonspecific antagonist) was extensively used to demonstrate binding sites in the retina throughout vertebrates species (*see* ref. *1* for a review). However, since domperidone, a more specific D_2 receptor ligand, did not bind to retinal extracts of goldfish and guinea pig *(11,12)* it was thought for a few years that the retina contained only D_1 receptors, either positively or negatively linked to adenylyl cyclase.

Progress in the discovery of more highly specific ligands led to the demonstration of D_1 and D_2 receptors in the retina as achieved in the brain *(13,14)*. However, their localization in retinal layers was more clearly demonstrated far further. The first attempts at receptor localization concerned the dopamine-sensitive adenylyl cyclase. The analysis of small punches of retina taken at different eccentricities in the four quadrants showed that the distribution of dopamine-sensitive adenylyl cyclase paralleled the density of dopamine cells in chick *(15)*. Subcellular fractionation studies provided other evidence of the presence of dopamine receptors in the retina. Retinal synaptosomes can be separated into two fractions according to density: The P1 fraction contains mostly the large synaptic terminals of photoreceptor cells, whereas the P2 fraction contains mostly the small synaptosomes of the second-order neurons. The dopamine-sensitive adenylyl cyclase was shown to concentrate in the P2 fraction as well as the spiroperidol binding sites *(16,17)*. Subsequently, G proteins were shown to localize to the outer (OPL) and inner (IPL) plexiform layers *(18)*. Autoradiography of labeled ligand bound to tissue sections was more informative: a strong labeling was observed in the IPL, whereas a faint labeling was sometimes detected in the OPL for D1 as well as for D_2 receptors in rat and human retinas *(19–23)*. The OPL labeling could be correlated with the demonstration that dopaminergic interplexiform cells (amacrine-like cells that project to both IPL and OPL) do exist in most mammalian species *(24)*. Cloning of dopamine receptors allowed for the obtention of nucleic acid probes as well as for highly specific antibodies that permitted a more precise and differential localization of D_1- and D_2-like receptors in retinal layers *(25–31)*. Receptor subtype localization is now progressing more quickly *(32–35)*.

Dopamine Receptor Classification: A Survey

This topic is developed in detail, together with an exhaustive bibliography in three recent books *(36–38)*. This short survey has been included for a better understanding of subjects presented later in this article.

The pharmacological classification proposed *(8)* distinguished two dopamine receptor classes, termed D_1 and D_2, characterized by different ligand-binding properties (benzazepines vs butyrophenones, respectively) and opposite action on adenylyl cyclase (activation vs inhibition, respectively). For each class, the existence of receptor subtypes was originally proposed on the basis of differential drug activities *(39)*.

This issue remained very controversial until it was conclusively demonstrated by molecular cloning that several dopamine receptor subtypes indeed existed. In addition, the distinctive features of these receptor sequences revealed they all belong to the same superfamily of G protein-coupled receptors. Dopamine receptors share with the majority of the other bioaminergic, peptidergic, and sensory receptors a similar structure and common functional properties. The primary structure of the receptor protein is characterized by the presence of seven transmembrane segments linked by three extracellular loops and three cytoplasmic loops, the amino-terminus of the protein being extracellular and the carboxy-terminus intracellular. From a functional point of view, these receptors are all able to favor the GDP/GTP exchange on the α subunit of the heterotrimeric G proteins *(40,41)*. This gene family membership implies that corresponding proteins are the products of related genes that duplicated during the course of vertebrate evolution.

Accordingly, the D_1 receptor class comprises two subtypes (named D_{1A} and D_{1B} or D_5), whereas the D_2 receptor class includes three subtypes (named D_2, D_3, D_4), each receptor subtype being encoded by a different gene in mammals. Phylogenetic analysis of the bioamine receptors has demonstrated that the D_1 and the D_2 classes of dopamine receptors are not more closely related to each other than they are from other classes of bioamine receptors, such as the α_1, α_2 or β receptor classes. This means that D_1 and D_2 receptor classes do not have a common evolutionary origin, and that their respective ancestors acquired independently and convergently the ability to bind dopamine. However, the hallmark of their divergence from a common ancestor gene is the structural and functional similarities exhibited by the receptor subtypes in each class. The precise definition of sequence identities as well as of shared pharmacological and biochemical characterisitics provides the best way to classify these receptor classes and subtypes *(42)*. Therefore, the term "subtype" defines a receptor molecule with sequences, pharmacological profile, and functional characteristics conserved throughout vertebrate species that is likely to correspond to a true functional entity in the dopamine systems *(43)*.

The availability of cloned receptor cDNAs allowed them to be heterologously expressed in different cell lines by transfection, in order to better understand their transduction properties. However, despite obvious advantages, the pathways activated by dopamine receptors in transfected cell lines depend on the promiscuous G proteins and effector proteins found in the cell lines, which do not always reflect what happens in original tissues (for a comprehensive discussion, *see* ref. *40*). It revealed that, in general, multiple transductional possibilities exist for each dopamine receptor subtype and that cell signaling may be adapted to transducer disponibility in each different cell in which a given subtype is expressed. The principal characteristics of D_1- and D_2 -like receptors are shown in Fig. 1.

D_1-Like Receptors

The D_1 dopamine receptor class comprises two subtypes in mammals, named D_{1A} and D_{1B}, but it includes three or four subtypes in most other jawed vertebrates (gnathostomes). Indeed, in addition to D_{1A} and D_{1B}, a D_{1C} receptor subtype is found in every gnathostome species in which it has been searched for so far *(43–45)*. The D_{1D} receptor subtype has been cloned in birds and crocodiles only (the archeosaurians) and is very likely to be a peculiarity of this group *(43,46)*. Whether additional D_1 receptor subtypes exist in mammals or whether mammalian ancestors have lost the D_{1C} subtype is still debated. As a matter of fact, all attempts to isolate other D_1 receptor subtypes from mammals have failed, whereas they have easily led to enlarge the family in all vertebrate phyla, therefore suggesting that mammals have indeed only two D_1 receptor subtypes.

All members of the D_1 receptor class are encoded by intronless genes. They also have a highly similar molecular structure remarkable

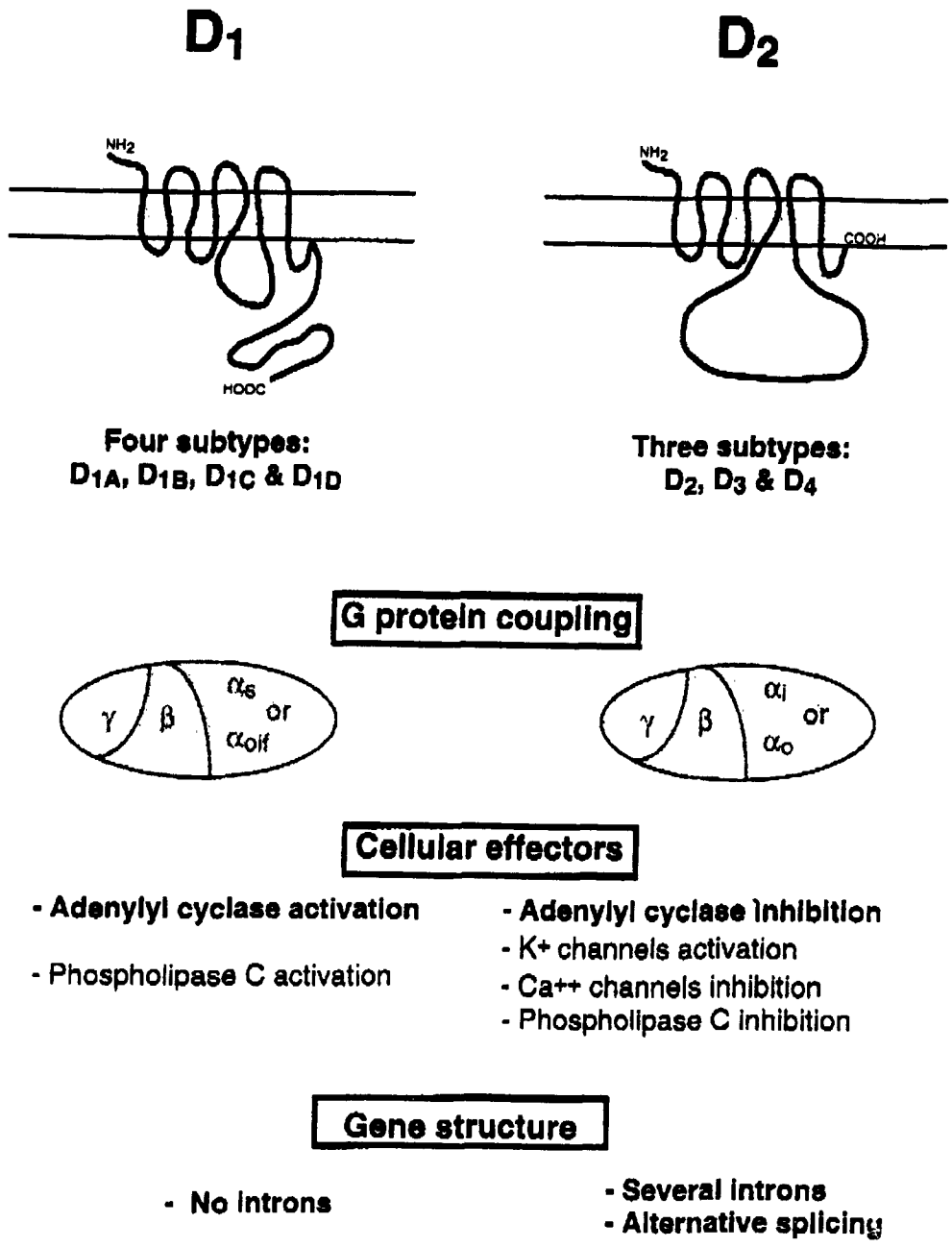

Fig. 1. Schematic representation of principal characteristics of D_1- and D_2-like receptors.

by a short third cytoplasmic loop and a long carboxy tail. From the pharmacological and functional point of view, both D_{1A} and D_{1B} share common properties, including a selective affinity for the D_1 generic benzazepine SCH 23393, the ability to efficiently activate adenylyl cyclase via a $G\alpha_s/G\alpha_{olf}$ protein (sensitive to cholera toxin), and a fast desensitization rate. Significant differences also exist among the subtypes, the D_{1B} receptor having a tenfold

higher affinity for dopamine than the D_{1A} subtype and exhibiting constitutive adenylyl cyclase activity. This constitutive activity is consistently inhibited by butaclamol or flupentixol acting as inverse agonists *(47)*. Additionally, depending on the tissues in which they are expressed or on the cell lines in which they have been transfected, D_1-like receptors are also able to activate phospholipase C, as are many other cyclase-activating receptors *(48)*. In other cells as well as in rat striatal slices and amygdala, a D_1-like receptor has been shown to open Ca^{2+} and Na^+ channels *(49)*. The effects are most likely indirect. A D_1-like receptor in kidney inhibits the amiloride-sensitive Na^+/H^+ exchanger *(50)*, and, in the chick retina, D_1 agonists also increase K^+ efflux independently of cAMP accumulation *(51)*. These different signaling pathways may be activated through unknown Gα subunits, may depend on βγ complex, or alternatively, as suggested by some authors, may involve unknown D_1-like receptor subtypes.

D_2-Like Receptors

Three subtypes of D_2-like receptors have been cloned in mammals and termed D_2, D_3, and D_4. The mammalian D_2 dopamine receptor is particularized by the existence of an alternative splicing of its premessenger RNA, which results in two isoforms, known as $D_{2(a)}$ for the long isoform and $D_{2(b)}$ for the short isoform. They differ respectively by the presence or the absence of 29 amino acids in the putative third cytoplasmic loop that may change the receptor-G protein interactions. The D_4 gene is highly polymorphic, at least in humans, exhibiting a 48-bp-long sequence that can be repeated two- to sevenfold in the third cytoplasmic loop, an insertion of four amino acid at the N-terminus in some individuals and several point mutations distributed in the whole sequence *(52)*.

The D_2-like receptor-encoding genes are interrupted by several introns whose positions are not conserved for all the subtypes. Structurally, the receptor proteins have a long third cytoplasmic loop and a short carboxy-terminal tail. The three D_2-like receptor subtypes have closely related pharmacological profiles with a generally high affinity for butyrophenone compounds. Additional selectivity may be achieved since the D_4 subtype exhibits especially high affinity for clozapine, D_2 and D_3 receptors preferentially bind nafadotride and atypic antipsychotic drugs *(53)*. Each of the D_2-like receptors can interact with multiple G proteins, resulting in the modulation of a variety of intracellular signals. They primarily interact with pertussis-toxin-sensitive G proteins, namely the three $G\alpha_i$ proteins, $G\alpha_{i1}$, $G\alpha_{i2}$, and $G\alpha_{i3}$, and the $G\alpha_o$ proteins. The distinctive effect of D_2-like receptors is the inhibition of adenylyl cyclase, and this activity may require $G\alpha_{i2}$ to occur. However, most of the D_2-like effect are cAMP independent. All three subtypes can promote sodium-dependent extracellular acidification via the amiloride-sensitive Na^+/H^+ exchanger or stimulate cell growth in transfected CHO cells *(53,54)*. Whereas the D_3 receptor seems able to stimulate cell division in many cell types, the D_2 receptor is often antimitotic, as is the case in prolactine pituitary cells. The effect of the D_2-like receptors on the activity of ionic channels is generally to activate K^+ channels via G_i proteins and to inhibit Ca^{2+} conductances via Ga_o both in natural situations and transfected cells *(55)*. D_2 and D_4 can also increase the release of arachidonic acid respectively in a cAMP-dependent and -independent, protein kinase C-dependent manner. Most of these effects depend of the signaling molecules present in the studied cells.

In the central nervous system (CNS), the D_2 and D_3 inhibit the release of dopamine, but the D_3 is more efficient and may be considered an autoreceptor in many locations *(53)*. D_2-like receptors mediate membrane hyperpolarization and inhibit neurotransmitter release in striatal neurons or pituitary cells, and may be regarded as generally inhibitory receptors *(55)*.

Dopamine Receptors in the Neural Retina

The most commonly used mammalian model, the rat, expresses all the cloned dopamine receptors in its retina except the D_3 subtype *(25,33)*. In addition, all the retinal cell types are affected by dopamine and they potentially bear dopamine receptors a well as the coupled $G\alpha_s$, $G\alpha_i$, and $G\alpha_o$ proteins. Moreover, four adenylyl cyclase isoenzymes (AC_1, AC_5, AC_7, and AC_8) have been demonstrated to exist in the bovine retina *(56)*. All these cyclases can be activated by $G\alpha_s$ and forskolin. Additionally, the isoenzymes AC_1 and AC_8 are activated by the Ca^{2+}/calmodulin complex, independently of $G\alpha_s$ activation; AC_1 is inhibited by $\beta\gamma$ subunit of G proteins; AC_5 is inhibited by low concentration of calcium; AC_7 can be regulated by both $G\alpha_s$ and $G\alpha_i$ and is stimulated by $\beta\gamma$ subunits and protein kinase C (PKC). There is no specificity of AC isoforms with receptor types but AC_5 is also especially enriched in the striatum, a dopamine recipient nucleus *(57)*.

Dopamine Receptors in the Retinal Pigment Epithelium

The retinal pigment epithelium (RPE) is the most external layer of the retina. It consists of a monolayer of melanized epithelial cells of neurectodermal origin and establishes intimate relationships with photoreceptor cells on which physiology depends. Among the major roles played by the RPE is phagocytosis of shed photoreceptor outer segment disks. While new disks are continuously assembled at the basis of outer segments, their tips are rhythmically shed and phagocytized by the RPE *(58,59)*. Several neuroactive substances released from the neural retina can influence the rhythm and intensity of phagocytosis through receptor binding on RPE membranes. Decreased phagocytosis is correlated with increased cAMP levels in RPE cells *(60)*. Accordingly, dopamine, which is involved in retinal rhythmic events *(61,62)*, could decrease RPE phagocytosis via D_1-like receptors. There is a coincidence between the rhythmic inhibition of phagocytosis and the rhythmic synthesis and release of dopamine in daytime *(63)*, and mice whose dopaminergic cells have been destroyed by the specific neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), accumulate large quantities of residual bodies in their RPE, resulting from hyperphagocytosis *(64)*. Recently, dopamine, and D_1-like agonist have been shown to decrease phagocytosis, as did the adenylyl cyclase activator forskolin and the phosphodiesterase inhibitor isobutyl-methyl-xanthine (IBMX) in cultured bovine RPE *(65)*. However, controversies remain about whether dopamine can really modulate cAMP content in the RPE *(66,67)*, and whether dopamine receptors or adrenergic receptors exist in the RPE of mammals *(68–70)*. Since dopamine and bromocriptine could not decrease forskolin-elevated cAMP it was proposed that the existence of D_2-like receptors in the rat RPE was highly improbable *(67)*, although $G\alpha_s$ and $G\alpha_i$ proteins can modulate RPE adenylyl cyclase activity.

Another action of dopamine suggests the presence of dopamine receptors in the RPE. The difference between the apical and basal membrane potentials of the RPE generates a current named the "standing potential." Upon light exposure, this current increases slowly to produce the "light peak" (LP) *(71)*. Exogenous dopamine can either mimic the LP or abolish it in the perfused cat eye, depending on doses and injection routes *(72)*. This action is blocked by flupenthixol and haloperidol (D_1/D_2 antagonists), suggesting the presence of dopamine receptors in the RPE. Since dibutyryl-cAMP produces the same effects as dopamine, the receptor would be of the D_1-like type. The integrity of the retinal layers is required for the generation of the LP, which coincides with the putative paracrine action of dopamine released from amacrine and interplexiform cells. Interestingly, the electro-oculogram (EOG, corresponding to LP in patients) is modified in parkinsonian patients with decreased retinal

dopamine *(73,74)*, and the EOG exhibits a circadian rhythm *(75)*, as does disk shedding. However, the existence of a dopamine receptor in the RPE is still questioned, although cAMP and IBMX were recognized to be active in the same way as dopamine, an observation suggesting that the receptor would be of the D_1 class *(76)*. It was proposed that instead dopamine may act primarily in the neural retina, then induce a second messenger that would reach the RPE. Photoreceptor cells may be the most likely candidates for mediating this action.

In this respect, dopamine receptor localization in the mammalian RPE remains highly controversial. These receptors do exist in nonmammals, where they mediate rhythmic and light-induced melanin pigment migration *(77–79)*. Binding sites for [^{3}H]-spiroperidol in mammals have been reported in the isolated RPE of cat *(80)* and cow *(81)*. D_2-like immunoreactivity was observed in the basal part of the bovine RPE, whereas in the same study it was not detected in other mammalian species *(26)*. The D_2 mRNAs were not found in the human RPE *(82)*. Recently, mRNAs for the D_{1B} receptor could be amplified by reverse transcriptase-polymerase chain reaction (RT-PCR) in the cultured bovine RPE and it was suggested that a D_{1B} receptor mediates the inhibition of phagocytosis by dopamine *(35)*, although the corresponding signaling pathway is still uncertain. Forskolin-binding sites indicate the presence of adenylyl cyclase in the RPE of rat and monkey *(83)*, and the AC7, activated by both $G\alpha_s$ and $G\alpha_i$ proteins, is specifically expressed in the bovine RPE *(56)*. Because dopamine and D_1 agonists decrease phagocytosis in the same range as does forskolin, it was suggested that coupling of D_{1B} receptor with adenylyl cyclase mediates the dopamine-induced phagocytosis inhibition, but a different signaling pathway may be involved because the D_{1B} receptor can also activate phospholipase C in the brain *(84)*, and the AC7 expressed in the RPE can be activated by PKC. Accordingly, increased PKC activity and/or increased Ca^{2+} reduce the ingestion of ROS by cultured rat RPE cells *(85)*.

Dopamine Receptors in Photoreceptor Cells: Dopamine/Melatonin Relationships

Dopamine plays a number of roles in photoreceptor cells. It predominantly regulates retinomotor reactions of cones through D_2-like receptors in nonmammals *(86)*. This function does not exist in mammals whose eyes are equipped with contractile pupils, but dopamine acting as a neurohormone modulates other functions of photoreceptors and evidence exists for the presence of D_2-like receptors in mammalian photoreceptor cells (Figs. 2A,B, 3A,B, 4B).

Dopamine Inhibition of Serotonin N-Acetyltransferase

As stated above, disk shedding and RPE phagocytosis are sequential steps of a single process: the renewal of photoreceptor outer segments. These events are rhythmic. In most mammalian species, rod disks are shed at light onset in the morning, whereas cone disks are shed at night *(58,59)*. This circadian rhythm has been well documented in the *Xenopus* eyecup *(86)*. It is governed by an intrinsic retinal oscillator and modulated by two neurohormones with an intimate relationship, dopamine and melatonin. The metabolism of dopamine is activated by light and undergoes a circadian rhythm that maintains the retinal dopamine content at higher levels during the day than at night. Dopamine inhibits serotonin *N*-acetyltransferase (NAT), the rate-limiting enzyme in melatonin synthesis. Concurrently, disk shedding is inhibited during the day. Conversely, melatonin is synthesized by photoreceptors at night. It inhibits dopamine synthesis and release *(87,88)* and thus potentiates shedding. Dopamine-melatonin antagonism on shedding activity also occurs in rat retina *(61)* and is quite independent of pineal melatonin *(89)*. Reportedly, dopamine slows the shedding process, whereas melatonin accelerates it *(90,91)*. We have already explained the ability of dopamine to slow down phagocytosis via a D_1-like receptor in RPE cells, but dopamine

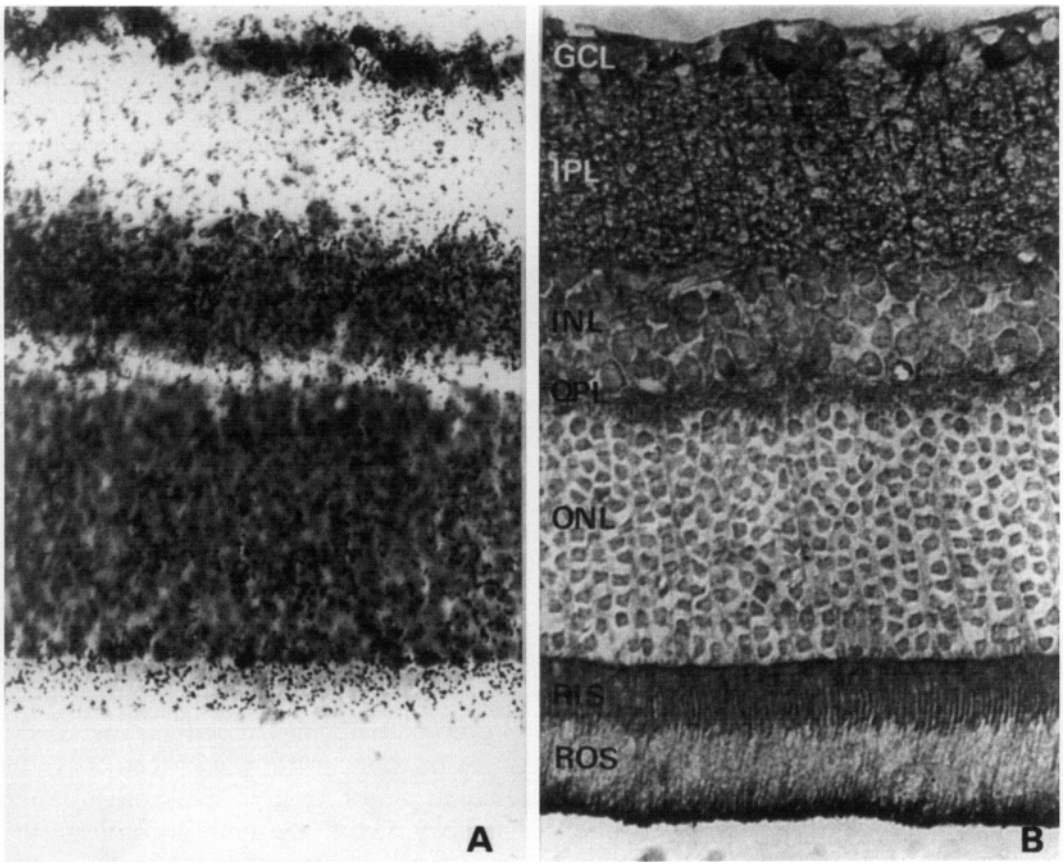

Fig. 2. Rat retina. **(A)** *In situ* hybridization with a mixture of three oligonucleotides of the D_2 mRNAs. Ganglion cells are heavily labeled. A label is also present over the inner nuclear layer (INL), whereas it is sparsely distributed over the ONL. A moderate labeling occurs over photoreceptor inner segments, which are out of focus. **(B)** Immunohistochemical localization of D_2-like receptors by use of anti-idiotypic antibody against dopamine. Ganglion cells are immunoreactive as are processes in the IPL. Cell bodies in the INL and ONL are only weakly labeled, whereas processes in the OPL are immunoreactive. The densest labeling is observed in photoreceptor inner segment. The heavy labeling of the outer segment tip may be a side effect.

also modulates disk shedding through NAT inhibition during the day. This action is mediated by a D_2-like receptor highly sensitive to clozapine in mice and rats *(32,92)*.

The occurence of D_2-like receptors was first suggested on isolated bovine rods *(93)*. It was confirmed by ligand binding on sections and immunocytochemistry in other mammalian species *(19,22,25,26)*, although confusion remains concerning their location on rods vs cones (or both), and outer vs inner segments (or both). In mice, melatonin synthesis seems to be restricted to cones, whereas rods are necessary for the maintenance of the rhythmic processes *(94)*. Dopamine receptors on photoreceptor cells of the mouse and rat retina were demonstrated to be of the D_4 subtype, decreasing adenylyl cyclase activity through $G\alpha_i$ protein *(32,34)*. This agrees with the blockade of this receptor by clozapine, which induces an increase of retinal melatonin in rats *(92)*. However, there are discrepancies about the subtype present on photoreceptor cells. A D_2/D_3 receptor has been recently localized on

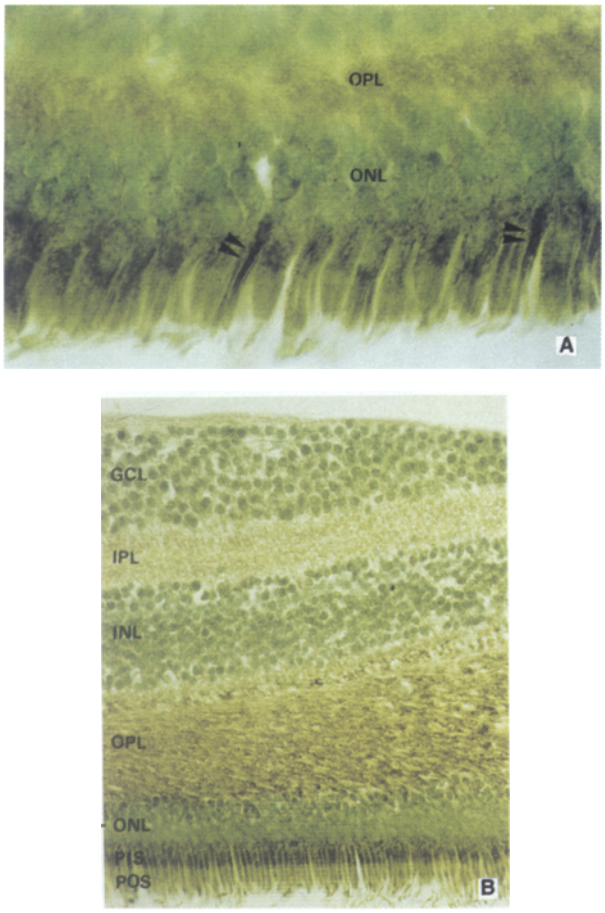

Fig. 3. Monkey retina. **(A)** Macaque monkey peripheral retina. Outer layers only. Immunohistochemical localization of D_2-like receptors. Rare slender photoreceptors are densely immunoreactive (double arrow heads). Their morphology and distribution suggest that they are blue cones. The OPL is moderately labeled. Methyl green/picric acid nuclear counterstain. **(B)** Part of the foveal slope (the foveal pit is on the right side). At this level, the retina is the thickest. Ganglion cells displaced from the foveal pit are numerous, as are the second-order neurons (INL). The OPL is especially thick because it contains the axons of the foveal cones (Henlé fibers). The inner segments of photoreceptors are all immunoreactive as are the Henlé fibers in the OPL. Methyl green/picric acid nuclear counterstain.

cones in the rat retina *(30)*. Using *in situ* hybridization, D_2 receptor mRNAs were observed in the outer nuclear layer (ONL) of the human retina *(82)*. In contrast, other authors failed to detect any signal on photoreceptor cells, either in human or in rat and monkey retinas *(95)*. Whether these differences are related to species differences in the expression of D_2-like receptor subtypes in the retina or to the adaptational state of the examined retinas remains to be explained. Indeed, dopamine receptor expression is modulated by light. Prolonged darkness induces receptor supersensitivity *(25, 96–98)*, and it may be hypothesized that the expression of these receptors exhibits a rhythm whose phase is opposite to that of tyrosine hydroxylase (TH, the rate-limiting enzyme in dopamine synthesis) activation and dopamine release.

The signaling pathway is not fully understood. The D_4-induced decrease of cAMP levels is not observed in *Rd* mutant mice (which are devoid of rods), indicating that the dopamine-sensitive adenylyl cyclase is mostly located in rods *(99)*. However, it has been proposed that NAT inhibition by dopamine is not caused by the coupling of a D_4 receptor to adenylyl cyclase in chick retina, but rather by an indirect linkage to the cAMP-generating system *(100)*. Retinal NAT activity is induced by Ca^{2+}-calmodulin activation of adenylyl cyclase in *Xenopus (101)*. Although mostly related to phototransduction, the components of the phosphoinositide signaling pathways, and especially a light-stimulated phospholipase C, are also present in photoreceptors *(102,103)* and may be part of the D_4 receptor-signaling pathway since dopamine acts as a light adaptive signal in retina. Indeed, lithium, which inhibits inositol monophosphatase (the enzyme that restores phosphatidylinositol from IP3), decreases retinal melatonin in frog *(104)*, inhibits the dopamine-induced accumulation of cAMP in rabbit *(105)*, and dampens the circadian rhythm of disk shedding in rats *(106)*. Retinal sensitivity to light and retinal input to the suprachiasmatic nucleus oscillator are diminished by lithium so that light therapy against seasonal depression must be prolonged in patients on lithium *(107)*. Since the calmodulin pathway is modulated by PKC, it could be supposed that dopamine reduces the

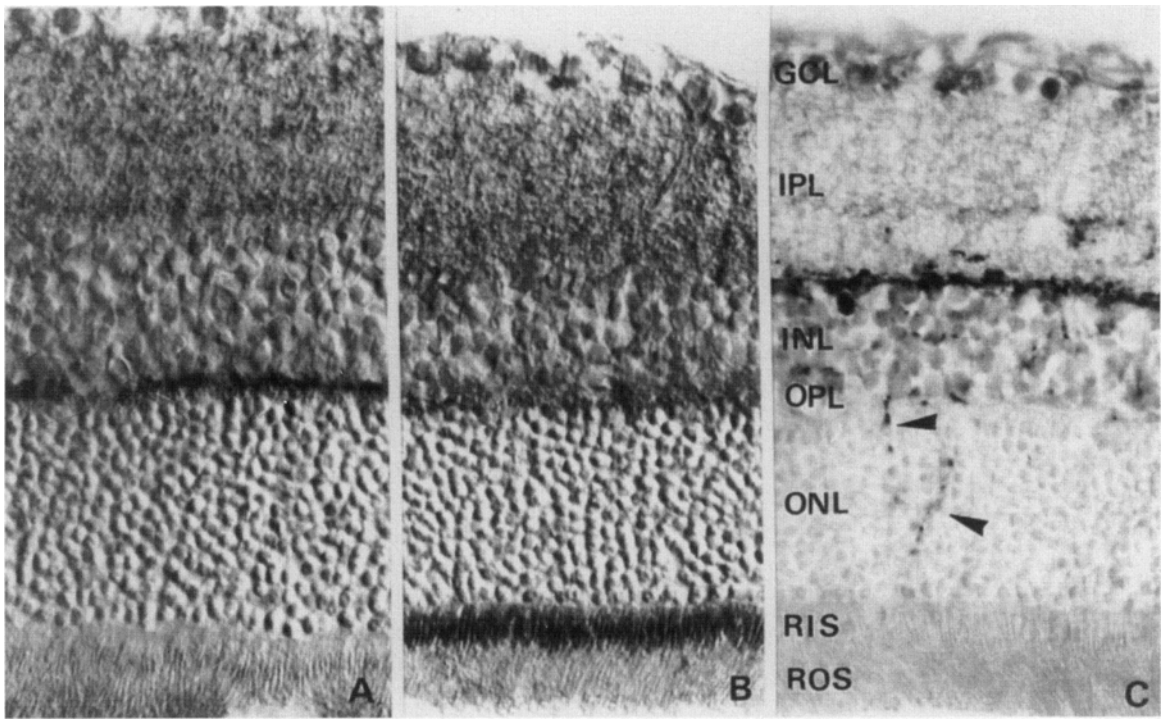

Fig. 4. Rat retina. Distribution of D_1-like **(A)** and D_2-like **(B)** receptor immunoreactivity, compared to that of TH-immunoreactivity **(C)**. (A) Several sublayers are weakly D_1 immunoreactive in the IPL (They are likely to be bands of bipolar cell terminals). The OPL is densely immunoreactive (most probably the horizontal cell processes). (B) The same pattern of D_2-like immunoreactivity as in Fig.2 is observed with the anti-D_2 antibody. The heaviest labeling is located in the rod inner segments (RIS). (C) TH-immunoreactivity. Cell bodies are not clearly observed in this section but two sublayers are labeled in the IPL. One is heavily labeled at the IPL/INL margin and corresponds to amacrine and interplexiform cell processes (dendrites and axons). The other is weakly labeled in the middle of the IPL and corresponds to the small weakly TH-immunoreactive amacrine cell processes. Outer processes of interplexiform cells are observed in the INL and ONL (arrow heads).

Ca^{2+}/calmodulin activation of NAT through the phospholipase C phosphatidylinositol pathway. Finally, photoreceptor cells may bear more than one dopamine receptor (D_2 or D_3) in cones vs D_4 in rods (as suggested by recent results), or alternatively, one receptor could activate several signaling pathways.

Dopamine Modulation of Rod Electric Activity

Dopamine has been shown to block the hyperpolarization-activated current in bovine rods through a D_4 receptor involving G proteins that inhibited adenylyl cyclase (*108*). However, in *Xenopus*, a similar dopamine inhibition is mediated by a D_2 receptor coupled via G proteins to Ca^{2+} movements instead of cAMP as a second messenger (*109*). Conversely, in rod inner and outer segment (RIS/ROS) preparation of the rat retina, dopamine was shown to inhibit Na^+/K^+-ATPase (*110*). By transporting Na^+ and K^+ against their electrochemical gradient, the Na^+/K^+-ATPase of photoreceptor cells maintains the "dark" current (Na^+ influx and K^+ release leading to depolarization). Thus, inhibition of this enzyme by dopamine may contribute to the hyperpolarizing response of rods

and reduce the rod to second order neuron transmission. This is in agreement with dopamine acting as a light-adaptive signal and favoring cone over rod pathways in response to light (*see* ref. *111* for review). Accordingly, rat photoreceptor cells predominantly express the α3-isoform mRNA of Na^+/K^+-ATPase, exclusively associated with the inner segment plasma membranes *(112)*. The dopamine inhibition would be mediated by a D_2-like receptor whose transduction signal is unknown, although cAMP is likely to be the best candidate. Whether the dopamine inhibition of Na^+/K^+-ATPase is related to the inhibition of the hyperpolarization-activated current observed in bovine rods remains to be clarified. Preliminary reports in the tiger salamander suggest that dopamine modulates transmitter release from rods through an opening of Ca^{2+} channels at their synaptic terminals *(113,114)*. Such an action requires confirmation in other species, including mammals.

Dopamine Receptors in Horizontal Cells: Modulation of Gap Junction Permeability

Several functions of horizontal cells in the retina of nonmammals are affected by dopamine through D_1-like receptors. Glutamate channels and L- and T-type calcium channels are modulated by dopamine in fish *(115,116)*. Also in fish, dopamine regulates spinule formation at the triad synaptic complex (one photoreceptor axon terminal facing three postsynaptic dendrites of bipolar and horizontal cells) *(117,118)*, but only the uncoupling action of dopamine on horizontal cell gap junctions has been documented in mammals *(119)*.

Horizontal cells of the retina are second-order neurons that mediate lateral inhibition and feedback to photoreceptor cells. Two types of horizontal cells participate in the first retinal synapse, according to rod- and cone-driven pathways. Each population of horizontal cells form a network (the so-called syncytium) resulting from a high degree of homologous cell coupling by the gap junctions. Uncoupling of the cone-driven horizontal cell network by dopamine was the first discovered cellular action of dopamine in the retina *(120–122)*. It occurs via a D_1-like receptor activating adenylyl cyclase and cAMP-sensitive protein kinase (PKA) in nonmammals *(123)*. A D_2-like receptor could also be involved in the turtle retina *(124)*. An identical action of dopamine has been recently shown to occur in rabbit axonless (cone-driven) horizontal cells. As in most mammals, synaptic input from dopaminergic cells to horizontal cells has not been observed in rabbit, so the uncoupling action is likely to be caused by diffusing dopamine. Surprisingly, a 1000-fold higher concentration of dopamine is needed in rabbit as compared to nonmammals *(119)*, suggesting that different receptor subtypes mediate this action in mammals vs nonmammals. D_1-like receptor immunoreactivity is associated with horizontal cell processes in the OPL of macaque, rat (Fig. 4A), mouse, and hamster retinas *(27–29,31)*, and based on the specificity of antibodies, the receptor seems to be of the D_{1A} subtype in mammals.

Dopamine Receptors in Bipolar Cells

The action of dopamine on retinal bipolar cells is poorly documented in mammals. In fish, dopamine has been demonstrated to enhance Ca^{2+} entry in axon terminals of isolated bipolar cells, thus potentiating the release of the transmitter *(125)*. This action seems to be mediated by D_1-like receptors that increase cAMP. Accordingly, synaptic terminals of the bipolar cells receive synaptic dopamine inputs in fish *(126)*. A similar action has not been demonstrated in mammals so far. Neither dopamine nor spiperone has been revealed to be efficient in modulating currents in isolated rod bipolar cells of the rabbit *(127)*.

However, D_{1A} receptor immunoreactivity has been shown on bipolar cells in rats and mice *(27,29)*. There is agreement for the presence of D_{1A} immunoreactivity on several subtypes of cone bipolar cells in both species,

whereas that of rod bipolar cells remains questionable *(27)*. Based on the observation that a band of immunoreactivity disappears from the IPL sublayer b (where the rod bipolar cell terminals are located) in dystrophic Royal college of surgeons (RCS) rats whose rod-driven pathways have degenerated, it was suggested that D_{1A} receptors may also be located on rod bipolar cell terminals *(29)*. Dopaminergic synapses onto bipolar cells have not been observed in the retina of any mammals and it is currently thought that the dopamine-induced facilitation of rod-driven pathway occurs through the dopaminergic input onto glycinergic "rod amacrine cells" *(see* Glycinergic AII Amacrine Cells*)*. Dendrites of these latter cells receive synaptic input from both rod bipolar cells and dopaminergic cells in the IPL b sublayer *(128,129)*, and the D_{1A} immunoreactivity observed in this sublayer may represent such an interaction *(29)*. Ca^{2+}-dependent PKC isoenzymes are largely distributed in retinal neurons, especially in bipolar cells, for which they are a good marker *(130–132)*. Some roles in the mechanisms of light/dark adaptation have been suggested for this enzyme since PKC migrates from somata to axon terminals of rod bipolar cells upon depolarization *(133)*. However, it is less probable that they will be involved in dopamine receptor signaling since the D_{1A} receptor subtype may rarely use the phospholipase C/phosphatidylinositol pathway in the brain *(84)*.

Dopamine Receptors in Amacrine Cells

Amacrine cells of the retina form a highly heterogenous population of axonless or short-axoned neurons in the innermost part of the INL, with lateral interactions at the second synapse level. Clearly, amacrine cells have a modulatory role in the retinal circuitry. Subpopulations of amacrine cells have been identified according to neurotransmitters, neuromodulators, and neuropeptides and colocalizations have been shown to occur. It is of interest to mention the occurrence of γ-aminobutyric acid (GABA) in dopaminergic cells of the mammalian retina, although its significance is still unknown *(134–138)*. Dopamine receptor localization could help us to better understand the influence of these local circuits. The dopaminergic amacrine and interplexiform cells are located in the amacrine cell layer and extend their dendrites close to this layer (Fig. 4C). Most of the synaptic output from dopaminergic cells goes to other amacrine cells, including other dopaminergic cells *(128,139,140)*.

Glycinergic AII Amacrine Cells

Dopamine inhibits the spontaneous and K^+-evoked release of glycine, and this action is blocked by butaclamol (a nonspecific D_1/D_2 antagonist) in the rat retina. Thus "..it may be predicted that dopaminergic cells may synapse on to glycine-containing amacrine cells..." *(141)*. Glycine immunoreactivity has been localized in the amacrine cells of the cat retina related to the rod-driven pathway, named AII *(142,143)*. The soma of these cells receive a massive synaptic input from dopaminergic neurons in rat and cat *(128,144)*. Moreover, they are interconnected by gap junctions that are uncoupled by dopamine, forskolin, IBMX, and SKF38393 (D_1 agonist), so that they were suspected to bear D_1-like receptors *(145)*. Surprisingly, they are not labeled by anti-D_{1A} receptor antibodies *(27,29)* leading to suppose that dopamine act on them through another D_1-like subtype.

Dopaminergic Amacrine and Interplexiform Cells

As in brain, dopamine release is modulated by an autoreceptor of the D_2-like family, presumably located on dopaminergic amacrine and interplexiform cells in the mammalian retina *(146,147)*. Activation of this receptor by D_2-like agonists inhibits both dopamine synthesis and release *(148)*. It is currently thought that this autoreceptor is of the D_2 subtype because D_3 mRNAs could not be amplified by RT-PCR in the rat retina *(25,33)*. A D_2/D_3 antibody was recently shown to colocalize with

TH in the rat retina *(30)*. D_2 receptor mRNAs in the human retina are expressed in the amacrine and ganglion cell layers where the dopaminergic cells are located, together with other dopamine recipient amacrine cells *(95)*. Because in 6-OHDA-treated rat retina the D_1-induced accumulation of AMPc increases as a consequence of receptor supersensitivity whereas D_2-induced inhibition does not, it is thought that the D_2 autoreceptor is not coupled to adenylyl cyclase *(149)*. Instead, this D_2-like receptor may regulate calcium influx at the nerve terminals. Interestingly, Ca^{2+}-dependent PKC immunoreactivity has been shown in dopaminergic cells of the mammalian retinas *(150)* and tyrosine hydroxylase is a good substrate for PKC phosphorylation, which, in turn is able to modify TH function.

The activity of aromatic L-amino acid decarboxylase (AADC, the enzyme that converts L-DOPA to dopamine), which is increased by light together with that of TH, is modulated by dopamine via a D_1-like receptor in the rat retina *(151)*. AADC colocalizes with TH in the dopaminergic cells and its regulation would implicate the presence of a D_1-like receptor on dopaminergic cells. This regulation could involve the interactions between dopaminergic cells, but AADC also occurs in photoreceptor cells, where it may participate in melatonin synthesis from tryptophan *(152)*. However, its activation by light is difficult to reconcile with such an effect because melatonin synthesis is abolished by light. Alternatively, serotonin (the product of AADC and substrate of NAT) may be synthesized in daytime and stored until NAT activation at night.

Cholinergic Amacrine Cells

A D_1-like receptor that increases cAMP elicits calcium-dependent release of acetylcholine from the isolated rabbit retina in vitro *(153,154)*. This receptor seems to be located on cholinergic amacrine cells because a similar action of dopamine is observed at synapses formed by retinal neurons cocultured with muscle cells *(155)*. Whether the dopamine-induced acetylcholine release is also a synaptic mechanism in retina is not known. Although the dopaminergic cells mostly contact amacrine cells in the IPL, synapses with cholinergic amacrine cells have not been identified so far. The cholinergic cell population is composed of amacrine cells, 50% of which are displaced to the ganglion cell layer (GCL) *(156)*. The processes of each subgroup form two sublayers in the IPL a and b sublayers, respectively, where several bands of D_1-like immunoreactivity are also observed in the rat retina *(29)*. However, double labeling with anti-ChAT and anti-D_{1A} receptor antibodies shows that there is no colocalization of the two markers *(27)*. It could be suggested that the D_1-like receptor mediating the release of acetylcholine is of the D_{1B}/D_5 subtype. Accordingly, the D_1 agonist SKF38393 was reported to behave as a partial agonist for this action *(157)*, and D_{1B} mRNAs are expressed in both GCL and INL, where the two subgroups of cholinergic amacrine cell somata are located *(33)*.

Other Amacrine Cells

Dopamine has been shown to facilitate GABAergic signaling by the mean of cAMP elevation and phosphorylation of the Cl^- channel ($GABA_A$ receptor) by PKA in retinal slices of the rat retina *(158)*. In addition, dopamine increases the Ca^{2+}-dependent glutamate-induced release of GABA from amacrine cells, possibly via a D_2-like receptor, in teleost fish retina *(159)*. This action has not yet been documented in mammals, but dopaminergic cells make synapses onto two amacrine cell types in the outermost sublayer of the IPL in cats *(128)*, one of which was identified as the A17 GABAergic cell *(160)*. D_1-like immunoreactivity (probably D_{1A}) colocalizes with the glutamate transporter GLT-1 in a few amacrine cells that may be among the suspected cells *(27)*. The whole amacrine cell layer express D_2 receptor mRNAs in the human retina *(95)*. Taken together, these observations suggest that dopamine receptors are located on a variety of amacrine cells in mammals.

Are There Dopamine Receptors on Retinal Ganglion Cells?

Intravenous L-DOPA depresses the evoked potential in the cat optic tract, and iontophoretically applied dopamine on cat eyecup ganglion cells reproduces the effect *(5)*. This suggests that dopamine decreases the transmission of retinal signals to the brain. In the isolated rabbit retina, dopamine was shown to decrease the spontaneous and light-evoked firing of about one-third of the ON and ON/OFF ganglion cells, whereas it increased that of OFF cells *(4)*. The effects of dopamine and dopaminergic drugs were not so clear in vivo. Conflicting results were obtained in cat *(161,162)* and rabbit *(163,164)* concerning the number and type of the responsive cells. However, an agreement can be made to state that dopamine attenuates the centre/surround organization of ganglion cell receptive fields, and favors cone- over rod-driven pathways in response to light *(163–165)*. This effect is partly antagonized by D_2-like blockers *(166)*. However, whether this results from a direct action of dopamine on ganglion cells or from interactions on local circuits remains questionable. Dopamine inhibits calcium currents in turtle peripheral ganglion cells via a cAMP-dependent mechanism that is mimicked by D_1-like agonists *(167)*. However, in patch-clamp recordings of isolated rat ganglion cells, haloperidol, spiperone, and SCH23390 all decreased calcium currents, but the recovery was so rapid and complete that the action was thought not to occur via dopamine receptors *(168)*.

In this respect, receptor localization studies are conflicting. Binding sites for D_1- as well as for D_2-specific ligands were observed over the rat GCL *(22)*, and rat ganglion cells stained with anti-idiotypic dopamine antibodies of unclear specificity *(25)*. D_{1A} immunoreactivity occurred as small patches on some cells in the GCL of rats *(27,29,31)*, and D_{1B} mRNAs were expressed in some ganglion cells of the human retina *(33)*. Concerning D_2-like receptors, ganglion cells were immunoreactive to an anti-D_2-like antisera in rat, rabbit, and cow *(26)*, and D_2 mRNAs were expressed in ganglion cells of the rat *(22)* (Fig. 2A) and human *(95)*. Interestingly, not all of the cells in the GCL are labeled by the two methods of receptor visualization, and concurrently, not all of the cells are responsive to dopamine in electrophysiological recordings. In most mammalian retinas, especially in rats, 50% of the cells in the GCL are displaced amacrine cells *(169)*, among which some are displaced cholinergic and dopaminergic cells that may bear dopamine receptors, as stated in Dopamine Receptors in Amacrine Cells. Whether dopamine receptor immunoreactivity and mRNA expression are located in ganglion cells or in displaced amacrine cells has not been addressed by double-labeling experiments. The nature of neurotransmitters and dopamine receptors present in subpopulations of ganglion cells will also require double-labeling experiments to be characterized. It was recently demonstrated in chicken that pineal activity, which depends on retinal information to the central oscillator, was changed by modifying the D_1 dopaminergic pathways in retina *(170)*. It may well be that at least the ganglion cells that compose the retino-hypothalamic pathway are sensitive to dopamine via D_1-like receptors in mammals. These retino-hypothalamic cells represent a very low percentage of the ganglion cells, and a few varicose processes of the dopaminergic cells run close to the GCL in the human, rat, and cat retinas *(128,171,172)*. However, synaptic contacts have not been observed *(128)*. A transient dopaminergic innervation of ganglion cells has been postulated in kittens *(173)*. If putative afferent dopaminergic synapses involve a small number of ganglion cells, they may have escaped electron microscopic observations. It should be remembered that dopaminergic cells are more frequently located presynaptically to amacrine cells. This synaptic organization better supports the inhibitory action of dopamine on ganglion cells as a result of interneuron interaction, leading researchers to propose another role for the observed dopamine receptors. It is thus possible that the α-cell uncoupling observed during light adaptation may be induced by dopamine *(174)*.

Although it is difficult to correlate the distribution pattern of the $G\alpha_o$ subunit immunoreactivity with any single transmitter candidate, the $G\alpha_o$ protein was also found in a few ganglion cells in rat, monkey, and human retinas *(18)*, and phorbol esters (PKC activators) binding sites localize in the GCL in those species *(19)* as well as the Ca^{2+}-dependent PKC-β*(130)*. No correlation of the distribution of these proteins with the action of dopamine has yet been made.

Dopamine and Müller Cells

The astrocyte-like glial cells of Müller extend radially into the whole thickness of the retina, with their somata located in the second-order neuron layer. They exhibit different physiological characteristics in their external and internal parts, respectively. One of their roles is to maintain homeostasis of the extracellular milieu, especially by regulating K^+ contents, and they possess numerous K^+-channels on their internal parts *(175)*. It has been shown electrophysiologically that isolated Müller cells of the rat and guinea pig respond to dopamine and to D_2 agonists by decreasing their K^+ conductance (closure of the inward rectifying K^+-channel). Accordingly, D_2-like immunoreactivity was demonstrated in Müller cells of the guinea pig, with the labeling being stronger in their internal part *(176)*. The signaling pathway activated by these receptors is unknown, but both isoforms of the D_2 receptor couple to G protein-activated K^+-channels in transfected cells *(177)* or in prolactine pituitary cells *(55)*. Interestingly, not all of the Müller cells were responsive to quinelorane (the D_2 agonist used in these recordings), suggesting that only a subpopulation of Müller cells bear such receptors. Moreover, some other cells may also express D_{1A} dopamine receptors because D_{1A}-like immunoreactivity has been recently shown to localize in the external part of some Müller cells of the mouse retina *(29)*. Additionally, DARPP32, a protein that is phosphorylated upon D_1-receptor activation, has also been observed in Müller cells of cat and primate retina *(178)*.

Dopamine Receptors in the Ciliary Retina

The neural retina is prolonged in the anterior part of the eye by the ciliary epithelium, whose main role is to synthesize aqueous humor. This secretion process follows a circadian rhythm in mammals, with a small anticipation of the light/dark cycle *(179–181)*. It is more active in the evening, resulting in a higher intraocular pressure (IOP) at night. This diurnal variation correlates with a parallel oscillation of cAMP content in aqueous humor, which is higher during the day *(182,183)*. There is evidence for an involvement of dopamine in this regulation. Dopamine, probably by diffusing from neural retina, is present in aqueous humor *(184,185)*, and is increased in glaucoma patients *(186)*. However, in animal experiments, dopamine was reported either to lower IOP or to increase it (or it may have a biphasic action) depending on the doses, routes of administration, and periods of the day, so its action remains very puzzling. Moreover, binding experiments do not always demonstrate dopamine receptors in the ciliary retina *(20,21,187)*. Since β-blockers are currently used to lower IOP in patients with glaucoma, it is thought that dopamine effects occur by acting on adrenoceptors *(188)* or by modulating noradrenalin release from the sympathetic nerves. However, the β-blocker timolol reduces the rate of aqueous flow only when applied during the dark period, suggesting a more elaborated mechanism related to circadian rhythms.

Recent experiments in rabbits and human volunteers with SDZ GLC-756, a new compound with both D_1-like antagonistic and D_2-like agonistic properties that lowers IOP, suggest a synergistic action of D_1- and D_2-like receptors in the regulation of IOP in mammals *(189,190)*. Increased cAMP or phosphodiesterase inhibition lower IOP. Moreover, DARPP32 has been found in the ciliary epithelium, suggesting the presence of D_1-like dopamine receptors *(191,192)*. Because the

action of dopamine disappears after sympathetic denervation, it is highly probable that these dopamine receptors are located on noradrenergic terminals and are few enough (or rhythmically expressed) to have escaped autoradiographic and immunohistochemical detection so far.

Concluding Remarks

A number of remarks can be made regarding this survey of dopamine receptor localization in the mammalian retina:

1. It is only the very beginning of dopamine receptor localization and understanding in the retina. It is still difficult to correlate the results of electrophysiology, pharmacology, and morphology, which have been obtained from different species and in various experimental conditions. The development of subtype-specific antibodies is needed to perform more accurate localizations at the cellular level, and the mammalian retina would be preferred to other vertebrates as a model to better understand human physiology.
2. There are both matched and mismatched distributions (mismatch being more frequent) of dopamine receptors and dopaminergic processes, leading to strengthen the hypothesis that dopamine primarily acts by diffusion in the retina. The most important synaptic input of dopaminergic cells to the AII glycinergic amacrine cells at the so-called "small rings" is not paralleled by a significant expression of dopamine receptors (at least those that could be demonstrated immunocytochemically so far). In contrast, horizontal cells and photoreceptors, which are located far from the dopaminergic processes (-even those of interplexiform cells a few number of which only reaches the ONL-), express, respectively, a high quantity of D_1- and D_2-like receptors. It is likely that the hypothesis of a paracrine action of dopamine, which has been raised to explain its action in the outer retina, must also be applied to the inner retina (ganglion cells and bipolar cell terminals) because of the scarcity of dopaminergic processes and the absence of synapses in this part.
3. Although the action of dopamine is not completely understood at the level of individual neurons, especially in mammals, our present knowledge may lead us to generalize the property of dopamine as a light-adaptive signal for the whole neural retina, and possibly also for the ciliary retina. Some convergent mechanisms shared by phototransduction and dopamine receptor signaling are clearly observed.
4. The role of dopamine in the regulation of retinal rhythms is now one of the most exciting directions open to further study. Indeed, the expression of neuropeptides, such as VIP, as well as nitric oxide and immediate early genes like c-*fos* and c-AMP-responsive element binding protein (CREB) is related to circadian rhythms and dopamine/melatonin relationships in the retina. The foundations for a retinal oscillator seem to be located in photoreceptor cells in mammals as well as in nonmammalian species. Cones could be especially relevant because melatonin synthesis, dopamine metabolism, and retino-hypothalamic information remains efficient in rd mice and RCS rats in which rods and rod-driven pathways have degenerated.
5. The signaling pathways modulated by dopamine receptors in the retina remain to be better understood, especially on account of the suspected synergy of D_1- and D_2-like receptors on several cellular mechanisms. The cases of disk shedding in the neural retina and IOP in the ciliary retina illustrate particularly well these possibilities and probabilities. The two dopamine receptor classes could compete for adenylyl cyclase activity to produce the oscillations of cAMP that result in the circadian rhythm of disk shedding and IOP, but the competition could also occur at other levels of the signaling process (α vs $\beta\gamma$ subunits of G protein, differential properties of adenylyl cyclase isoforms, and so forth). These studies are rendered difficult by the rhythmic variations in the expression and/or activity of most of the transducers and enzymes involved in neuronal signaling. It can be anticipated that, taking other oscillators as a model, these difficulties would now be rapidly vanishing.

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