Published in final edited form as:

Exp Eye Res. 2010 December ; 91(6): 788–792. doi:10.1016/j.exer.2010.08.013.

Retinol Dehydrogenases (RDHs) in the Visual Cycle

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Abstract

The isomerization of 11-*cis* retinal to all-*trans* retinal in photoreceptors is the first step in vision. For photoreceptors to function in constant light, the all-*trans* retinal must be converted back to 11-*cis* retinal via the enzymatic steps of the visual cycle. Within this cycle, all-*trans* retinal is reduced to all-*trans* retinol in photoreceptors and transported to the retinal pigment epithelium (RPE). In the RPE, all-*trans* retinol is converted to 11-*cis* retinol, and in the final enzymatic step, 11-*cis* retinol is oxidized to 11-*cis* retinal. The first and last steps of the classical visual cycle are reduction and oxidation reactions, respectively, that utilize retinol dehydrogenase (RDH) enzymes. The visual cycle RDHs have been extensively studied, but because multiple RDHs are capable of catalyzing each step, the exact RDHs responsible for each reaction remain unknown. Within rods, RDH8 is largely responsible for the reduction of all-*trans* retinal with possible assistance from RDH12. retSDR1 is thought to reduce all-*trans* retinal in cones. In the RPE, the oxidation of 11-*cis* retinol is carried out by RDH5 with possible help from RDH11 and RDH10. Here, we review the characteristics of each RDH in vitro and the findings from knockout models that suggest the roles for each in the visual cycle.

1. Introduction

The photoisomerization of 11-*cis* retinal to all-*trans* retinal in photoreceptors is the first step in vision. Of equal importance, however, are a series of enzymatic steps that replenish chromophore levels in photoreceptors by converting all-*trans* retinal back into 11-*cis* retinal. This process, known classically as the visual cycle, includes reduction and oxidation reactions carried out by retinol dehydrogenases (RDHs) in the photoreceptors and retinal pigment epithelium (RPE), respectively (Fig. 1). In the photoreceptor outer segment (OS), all-*trans* retinal is reduced to all-*trans* retinol by RDHs, and after all-*trans* retinol is transferred to the RPE and converted to 11-*cis* retinol, an oxidation reaction carried out by RDHs converts 11-*cis* retinol to 11-*cis* retinal. The multiple RDHs that function in the visual cycle are found in the retina and RPE (Fig. 2). In addition to the classical visual cycle, a cone-specific visual cycle (see below) is thought to exist in the retina to provide cones with a privileged source of 11-*cis* retinal, but the RDHs associated with the cone visual cycle have not been identified.

Visual cycle RDHs belong to the short-chain dehydrogenase/reductase (SDR) super-family of proteins. SDRs are divided into multiple families, but visual cycle RDHs fall into Clusters

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C2 and C3 of the classical SDRs (Bray et al., 2009). RDHs utilize NAD(H) or NADP(H) as cofactors in reactions that catalyze a hydride transfer between the nicotinamide group (S-face of the C₄ position) and the retinoid substrate (Lukacik et al., 2006). The stereospecificity, substrate, and cofactor of known RDHs in the visual cycle are summarized in Table 1. Here, we review both the function of individual RDHs in vitro and the murine visual cycle in vivo in the absence of different RDHs.

2. all-*trans* Retinal Reduction in Photoreceptors

The reduction of all-*trans* retinal to all-*trans* retinol occurs in the photoreceptors. Both rods and cones contain multiple RDHs capable of catalyzing this reaction. RDH8 and RDH12 are found in the OS and inner segment (IS), respectively, of rods and cones and contribute to all-*trans* retinal reduction.

2.1 RDH8 (prRDH)

RDH8 (prRDH) is localized to the photoreceptor OS, where it constitutes 0.2–0.5% of the total ROS protein (Rattner et al., 2000). Purified mouse RDH8 displays a substrate preference for all-*trans* retinal (Rattner et al., 2000) and a cofactor preference for NADPH (Palczewski et al., 1994), which support its role as an all-*trans* RDH.

Studies in *Rdh8*^{−/−} mice have confirmed its role in all-*trans* retinal reduction but have also shown that it is not exclusively required for visual cycle function. In many ways, *Rdh8*^{−/−} mice are unremarkable, as retina morphology and ERGs are normal through 8 months of age (Maeda et al., 2005). Although 11-*cis* retinal production is unimpeded in the absence of RDH8, all-*trans* retinal accumulation in rods slows the recovery of ERG responses. Thus, the phenotype of *Rdh8*^{−/−} differs only mildly from wild-type (Wt) mice, but slower all-*trans* retinal reduction and a corresponding decrease in retinyl esters exist (Maeda et al., 2005). As such, RDH8 contributes to all-*trans* retinal reduction but is not essential for the reaction.

2.2 RDH12

RDH12 is localized to the IS of both rods and cones (Haeseleer et al., 2002). Recombinant human RDH12 utilizes both *cis*- and *trans*-retinoids as substrates (Haeseleer et al., 2002) and is also active towards medium chain aldehydes (Belyaeva et al., 2005). NADP(H) is the preferred cofactor (Haeseleer et al., 2002). While capable of all-*trans* retinal reduction in vitro, isolated ROS from *Rdh12*^{−/−} and Wt mice have similar all-*trans* RDH activity, suggesting that the majority of all-*trans* retinal is not reduced by RDH12 (Maeda et al., 2006).

Although RDH12 mutations are associated with LCA (Janecke et al., 2004), the mild phenotype in *Rdh12*^{−/−} mice suggests that the physiological role of RDH12 is not entirely homologous in murine and human retinae. *Rdh12*^{−/−} mice have normal retina morphology through 7 months, although OS reductions appear after 10 months (Maeda et al., 2006; Kurth et al., 2007). As would be expected from an all-*trans* RDH, dark adaptation is slower, and all-*trans* retinal accumulates after extensive bleaching (Maeda et al., 2006). The effects, however, are less dramatic than those in seen in *Rdh8*^{−/−} mice (Maeda et al., 2005), and it appears that RDH12 contributes to all-*trans* retinal reduction to a lesser extent than RDH8.

One theory regarding RDH12 function is that RDH12 protects the retina from excessive all-*trans* retinal accumulation during persistent illumination. In the presence of continuous illumination, photoreceptor loss occurs in the central retina of *Rdh12*^{−/−} mice, and with intense illumination, photoreceptors in *Rdh12*^{−/−} mice are more susceptible to apoptosis (Maeda et al., 2006). Regardless of its small contribution to all-*trans* retinal reduction under

normal conditions, RDH12 appears to be important for photoreceptor health in the presence of excessive illumination.

2.3 RDH8 AND RDH12 in the rod visual cycle

Studies of *Rdh8*^{-/-}*Rdh12*^{-/-} mice provide additional information about the process of all-*trans* retinal reduction in the visual cycle and suggest a cooperative role for these two enzymes. Like single knockouts, six-week-old *Rdh8*^{-/-}*Rdh12*^{-/-} mice have normal retina morphology and ERGs, but shortened OS and diminished ERGs are seen by 3 months (Maeda et al., 2007). Additionally, all-*trans* RDH activity is 2% of Wt levels in *Rdh8*^{-/-}*Rdh12*^{-/-} retinæ. RDH8 accounted for 70% of the total all-*trans* RDH activity in the retina after the first five minutes of the reaction (Maeda et al., 2007). Thus, both the RDH8 and RDH12 exhibit all-*trans* RDH activity, but RDH8 is the main contributor to total all-*trans* RDH activity in the retina.

3. Oxidation of 11-*cis* retinol in the RPE

A critical step of the visual cycle is the production of 11-*cis* retinol in the RPE, but to regenerate chromophore, 11-*cis* retinol must be oxidized to 11-*cis* retinal by RDH's. RDH5 is largely responsible for this reaction, but 11-*cis* retinol oxidation is also facilitated by other RDH's, among them RDH11.

3.1 RDH5

In the eye, RDH5 is most abundant in the RPE (Simon et al., 1995). RDH5 has no activity towards all-*trans* retinal (Simon et al., 1995), but it is capable of oxidizing or reducing all of the common *cis*-retinoid isomers (Romert et al., 1998). RDH5 is thought to oxidize *cis*-retinoids through an NAD⁺-dependent reaction in the RPE (Simon et al., 1995).

Studies in *Rdh5*^{-/-} mice suggest that RDH5 contributes to 11-*cis* retinol oxidation but is not required for the reaction. Retina histology and ERGs are normal in *Rdh5*^{-/-} mice, and ERG recovery following a bleach is similar to Wt (Driessen et al., 2000). Likewise, 11-*cis* retinol oxidation still occurs at a reduced rate in RPE membranes from *Rdh5*^{-/-} mice. While function remains normal, retinoid profiles are unique in *Rdh5*^{-/-} mice. Dark adapted retinoid profiles show increased levels of 11-*cis* retinol and *cis*-retinyl esters (Kim et al., 2005), and the recovery of ERG responses after intense bleaching is delayed (Driessen et al., 2000). Together, elevated levels of 11-*cis* retinol, retinyl esters, and delayed dark adaptation show that RDH5 does play a significant role in 11-*cis* retinol oxidation in the RPE. Similarly, human studies in a patient with an RDH5 R157W null mutation (Cideciyan et al., 2000) show that rod ERG amplitude and thresholds were unaffected, suggesting that the absence of RDH5 activity does not reduce the number or length of rod OS. Bleaches (0.5%) that expose early portions of rod dark adaptation were normal, but recovery of sensitivity from bleaches >2% were slowed, suggesting that RDH5 is needed for normal recovery from bleaches of >2%.

3.2 RDH11

RDH11 is found in the RPE, Müller cells (Haeseleer et al., 2002), and photoreceptor IS of mice (Kasus-Jacobi et al., 2003). Like other Cluster 2B RDHs, RDH11 can utilize both *cis*- and *trans*-retinoid substrates (Haeseleer et al., 2002). Mouse RDH11 (SCALD) can also utilize short-chain saturated aldehydes (such as nonanal) as substrates, but has no steroid activity (Kasus-Jacobi et al., 2003). Because nonanal is reduced faster than most retinoids, RDH11 is hypothesized to play a role in removing toxic aldehydes from the retina (Kasus-Jacobi et al., 2003). With regards to the visual cycle, both human (Belyaeva et al., 2003) and mouse (Kedishvili et al., 2002) RDH11 appear to be more efficient as retinal reductases than

as retinal dehydrogenases, and NADP(H) is the preferred cofactor (Haeseleer et al., 2002). In the RPE, RDH11 is thought to facilitate 11-*cis* retinol oxidation.

Rdh11^{-/-} mice have normal retinal morphology and ERGs under baseline conditions (Kasus-Jacobi et al., 2005), and retinoid profiles are equivalent to Wt (Kim et al., 2005). Dark adaptation studies, however, show that the kinetics of rod recovery is slowed in *Rdh11*^{-/-} mice, but retinoid profiling shows that 11-*cis* retinal production is not impeded after bleaching (Kasus-Jacobi et al., 2005). Based on these findings, the etiology of delayed dark adaptation in *Rdh11*^{-/-} mice is uncertain, but studies in *Rdh5*^{-/-}*Rdh11*^{-/-} mice suggest that diminished 11-*cis* RDH activity in the RPE does exist (*see below*).

3.3 Combined Effects of RDH5 and RDH11

While data about RDH11's role as an 11-*cis* RDH are conflicting, studies in *Rdh5*^{-/-}*Rdh11*^{-/-} mice suggest a cooperative role between RDH5 and RDH11. Like *Rdh5*^{-/-} and *Rdh11*^{-/-} mice, *Rdh5*^{-/-}*Rdh11*^{-/-} mice have normal retina morphology, but only *Rdh5*^{-/-}*Rdh11*^{-/-} mice have diminished rod ERGs (Kim et al., 2005). Similarly, the recovery of rod responses measured with paired flash ERGs is normal in *Rdh5*^{-/-} and *Rdh11*^{-/-} mice but slow in *Rdh5*^{-/-}*Rdh11*^{-/-} mice (Kim et al., 2005). Retinoid profiling also suggests that both RDH5 and RDH11 contribute to 11-*cis* retinal production. After bleaching, a progressive attenuation of *a*-wave recovery among the three strains exists (*Rdh11*^{-/-} < *Rdh5*^{-/-} < *Rdh5*^{-/-}*Rdh11*^{-/-}) that correlates with 11-*cis* retinal concentrations measured after the same bleaching procedure (Kim et al., 2005). Thus, it appears that RDH11 plays a minor but complementary role to RDH5 in the flow of retinoids during dark adaptation.

4. Oxidation and reduction reactions in the cone visual cycle

A second visual cycle exists in the retina to provide cones with a privileged source of 11-*cis* retinal (Wang et al., 2009). This cone visual cycle begins with the reduction of all-*trans* retinal in the OS. all-*trans* Retinol is then transported to Müller cells, isomerized to 11-*cis* retinol (Mata et al., 2005), and transported to cones for oxidation to 11-*cis* retinal (Jones et al., 1989). As such, the cone visual cycle, like the classical visual cycle, involves one reduction and one oxidation reaction involving RDH enzymes.

4.1 retSDR1

Only one of the visual cycle RDHs is known to be cone-specific—retSDR1. Analogous to RDH8 in the OS of both rods and cones, retSDR1 is found in the OS of all murine cones (Haeseleer et al., 1998). As such, rod OS contain RDH8, while cone OS contain RDH8 and retSDR1. Like RDH8, the main function of retSDR1 appears to be all-*trans* retinal reduction. Recombinant retSDR1 reduces all-*trans* retinal to retinol but has no activity against 11-*cis* retinal or steroid compounds (Haeseleer et al., 1998). NADP(H) is the preferred cofactor and is not replaceable with NAD(H). Thus, retSDR1 appears to be analogous to RDH8 in the OS (Haeseleer et al., 1998), but this hypothesis is not supported by *in vivo* functional data.

4.2 RDH8 and RDH12 in Cone Function

RDH8 and RDH12 are located in the OS and IS of cones, respectively. In the OS, both RDH8 and retSDR1 utilize NADPH to reduce all-*trans* retinal to all-*trans* retinol. The presence of redundant all-*trans* retinal reductases in the cone OS might be needed for rapid all-*trans* retinal reduction under photopic conditions. Work is limited on RDH8's role in cone function, but cone ERGs are normal in *Rdh8*^{-/-} mice lacking the transducin alpha subunit necessary for rod photoreceptor signaling (*Gnat1*^{-/-}*Rdh8*^{-/-} mice). Similarly,

studies of cone function are limited in mice lacking RDH12, but cone ERGs in *Gnat1*^{-/-}*Rdh12*^{-/-} mice are also normal (Maeda et al., 2007). However, it remains to be seen if the absence of RDH12 affects cone function under photopic conditions. Another possible role for RDH12 in cone function is the oxidation of 11-*cis* retinol in the cone visual cycle. RDH12 belongs to the sub-family of RDH enzymes with RDH11-14 with dual substrate specificity (Haeseleer et al., 2002). As such, RDH12 has the ability to reduce all-*trans* retinol or oxidize 11-*cis* retinol. Whether or not this role belongs to RDH12 or an unidentified oxidase has not been determined.

4.3 RDH5 and RDH11 in Cone Function

RDH5 and RDH11 are thought to be the main RDH's responsible for 11-*cis* retinol oxidation in the RPE. While the cone visual cycle is believed to be independent of the RPE, the absence of cone function in the cone-like photoreceptors of *Nrl*^{-/-}*Rpe65*^{-/-} mice suggests that cones do rely on the RPE for some level of chromophore (Wenzel et al., 2007). As such, RDH5 and RDH11 have plausible roles in cone function. While photopic ERGs are normal in *Rdh5*^{-/-}*Rdh11*^{-/-} mice (Kim et al., 2005), cone function was found to be abnormal in a human patient containing a homozygous mutation of RDH5 (Cideciyan et al., 2000). Most interestingly, recovery of L/M cones following bleaching was delayed with a biphasic recovery that was 34x slower than normal. Thus, RDH5 does contribute to retinoid metabolism in human cones, and additional studies of cone function may reveal roles for RDH5 and RDH11 in murine cone function.

5. Additional RDHs in the Eye

Studies of knockout mice have helped identify specific roles of RDHs in the classical visual cycle, but other RDHs in the eye have unidentified functions. RDH10 is located in both the RPE (Wu et al., 2002) and Müller cells (Wu et al., 2004), and as such, has the potential to contribute to the classical visual cycle. Studies of recombinant RDH10 show that NAD⁺ is the preferred cofactor in vivo (Belyaeva et al., 2008a). While in vitro studies have shown that RDH10 can function as an oxidoreductase (Takahashi et al., 2009), the enzyme exhibits a preference for oxidation reactions and can utilize both *cis*- and *trans*-retinols similarly as substrates (Belyaeva et al., 2008a). Because RDH10 can substitute for RDH5 under experimental conditions (Farjo et al., 2009), it is possible that RDH10 accounts for the remaining 11-*cis* RDH activity in *Rdh5*^{-/-}*Rdh11*^{-/-} mice. Because of RDH10's extra-ocular roles, *Rdh10* deletions are lethal and knockouts cannot be studied.

RDH13 and RDH14 are expressed in the retina and have no known role in the classical visual cycle, but both are elevated in the retinae of *Nrl*^{-/-} mice and may be important for cone function (Kanan et al., 2008). RDH13 is capable of utilizing retinoids as substrates, but its localization in the mitochondria seems to preclude its role as a visual cycle RDH (Belyaeva et al., 2008b). RDH14 has activity towards all-*trans* and 11-*cis* retinoids, and therefore, may participate in the oxidation of 11-*cis* retinol in the cone visual cycle.

6. Conclusion

RDHs are responsible for the oxidation and reduction reactions in the classical visual cycle. While knowing the preferred substrate, cofactor, and localization of RDHs suggests specific roles for each, studies of the visual cycle in knockout mice have increased our understanding of RDH function in vivo (Table 2) and revealed an amazing amount of redundancy in the oxidation and reduction reaction of the visual cycle. Thus, the absence of one RDH in knockout mice is often compensated for by others, and attempts to assign individual RDHs to specific reactions are difficult. Regardless, work in knockout mice has provided valuable

information about RDH activity in the visual cycle and future studies will undoubtedly contribute further to our understanding of retinoid metabolism in the eye.

Acknowledgments

We thank Dr. Luanna Bartholomew for editorial assistance. Work was supported by grants from NIH EY04939 (to R.K.C.), EY14793 (MUSC vision core); Foundation Fighting Blindness, Inc. (Owings Mills, MD) (to R.K.C.); and an unrestricted award to the Department of Ophthalmology at MUSC from Research to Prevent Blindness (RPB; New York); R.K.C. is an RPB Senior Scientific Investigator. R.O.P. is the recipient of a RPB Medical Student Eye Research Fellowship.

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Fig. 1.

Oxidation and Reduction Reactions of the Visual Cycle. The classical visual cycle involves reduction and oxidation reactions carried out in the photoreceptors and retinal pigment epithelium (RPE), respectively. RDH enzymes are responsible for both reactions. In the photoreceptor OS, RDHs carry out the NADPH-dependent reduction of all-*trans* retinal (atRAL) to all-*trans* retinol (atROL). In the RPE, RDHs are responsible for the NAD⁺-dependent oxidation of 11-*cis* retinol (11cROL) to 11-*cis* retinal (11cRAL).

Fig. 2.

Distribution of Visual Cycle RDHs in the Eye. Multiple RDHs found in the eye contribute to retinoid metabolism. The proposed role of many RDHs is based on their location in the retinal pigment epithelium (RDH5, RDH11, RDH10), photoreceptor outer segments (RDH8, retSDR1), photoreceptor inner segments (RDH11, RDH12), and Müller cells (RDH10).

Table 1

RDHs Associated with the Visual Cycle^a

RDH	Location	Proposed Visual Cycle Substrate	Proposed Visual Cycle Cofactor	Additional Substrates	Stereospecificity		Disease
					Cofactor	Retinoid	
RDH8	ROS, COS	all- <i>trans</i> retinal	NADPH	—	Pro-S	Pro-R	—
RDH12	RIS, CIS	all- <i>trans</i> retinal	NADPH	aldehydes	Pro-S	Pro-R	LCA
retSDR1	COS	all- <i>trans</i> retinal	NADPH	—	Pro-S	Pro-R	—
RDH5	RPE	11- <i>cis</i> retinol	NAD ⁺	—	Pro-S	Pro-S	FA
RDH11	RPE, IS	11- <i>cis</i> retinol	NADP ⁺	aldehydes	Pro-S	Pro-R	—

^aReferences are also noted in text but are as follows for each RDH: RDH8 (Palczewski et al., 1994; Jang et al., 2000; Rattner et al., 2002; Janecke et al., 2004; Belyaeva et al., 2005), retSDR1 (Haeseleer et al., 1998), RDH5 (Simon et al., 1995; Romert et al., 1998; Yamamoto et al., 1999; Jang et al., 2001), RDH11 (Haeseleer et al., 2002; Kedishvili et al., 2002; Kasus-Jacobi et al., 2003). Abbreviations: ROS (rod outer segment), COS (cone outer segment), CIS (rod inner segment), RIS (rod inner segment), RPE (retinal pigment epithelium), IS (inner segment, undefined), LCA (Leber's Congenital Amaurosis), FA (fundus albipunctatus).

Table 2

Summary of RDH Knockout Mouse Studies^a

Model	Morphology	ERG	Dark Adaptation (ERG)	Retinoid Profile (dark)	Retinoid Profile (bleach)
<i>Rdh8</i> ^{-/-}	Normal	Normal	↑↑ Delayed	Normal	↑ all- <i>trans</i> retinal ↓ retinyl esters
<i>Rdh12</i> ^{-/-}	↓ OS (10 months)	Normal	↑ Delayed	Normal	↑↑ all- <i>trans</i> retinal
<i>Rdh8</i> ^{-/-} <i>Rdh12</i> ^{-/-}	↓ OS (3 months)	Decreased	↑↑↑ Delayed	Normal	↑ all- <i>trans</i> retinal
<i>Rdh5</i> ^{-/-}	Normal	Normal	↑↑ Delayed	↑ 11- <i>cis</i> retinol ↑ <i>cis</i> -retinyl esters	↑ 11- <i>cis</i> retinol ↑ <i>cis</i> -retinyl esters
<i>Rdh11</i> ^{-/-}	Normal	Normal	↑ Delayed	Normal	Normal
<i>Rdh5</i> ^{-/-} <i>Rdh11</i> ^{-/-}	Normal	Decreased	↑↑↑ Delayed	↑ <i>cis</i> -retinyl esters	↑ <i>cis</i> -retinyl esters

^aReferences are noted in text but are as follows for each knockout: *Rdh8*^{-/-} (Maeda et al., 2005), *Rdh12*^{-/-} (Maeda et al., 2006; Kurth et al., 2007; Maeda et al., 2007), *Rdh8*^{-/-}*Rdh12*^{-/-} (Maeda et al., 2007), *Rdh5*^{-/-} (Driessen et al., 2000; Kim et al., 2005), *Rdh11*^{-/-} (Kedishvili et al., 2002; Kasus-Jacobi et al., 2005; Kim et al., 2005), *Rdh5*^{-/-}*Rdh11*^{-/-} (Kim et al., 2005)