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Vitamin A_1/A_2 chromophore exchange: Its role in spectral tuning and visual plasticity

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ABSTRACT

Vertebrate rod and cone photoreceptors detect light via a specialized organelle called the outer segment. This structure is packed with light-sensitive molecules known as visual pigments that consist of a G-protein-coupled, seven-transmembrane protein known as opsin, and a chromophore prosthetic group, either 11-*cis* retinal ('A_1') or 11-*cis* 3,4-didehydroretinal ('A_2'). The enzyme cyp27c1 converts A_1 into A_2 in the retinal pigment epithelium. Replacing A_1 with A_2 in a visual pigment red-shifts its spectral sensitivity and broadens its bandwidth of absorption at the expense of decreased photosensitivity and increased thermal noise. The use of vitamin A_2-based visual pigments is strongly associated with the occupation of aquatic habitats in which the ambient light is red-shifted. By modulating the A_1/A_2 ratio in the retina, an organism can dynamically tune the spectral sensitivity of the visual system to better match the predominant wavelengths of light in its environment. As many as a quarter of all vertebrate species utilize A_2, at least during a part of their life cycle or under certain environmental conditions. A_2 utilization therefore represents an important and widespread mechanism of sensory plasticity. This review provides an up-to-date account of the A_1/A_2 chromophore exchange system.

1. Introduction

Vertebrate rod and cone photoreceptors mediate vision in dim- and bright-light environments, respectively (Fig. 1A and B). The light-sensitive molecule of a photoreceptor cell, known as the visual pigment, consists of two components: a G-protein-coupled, seven-transmembrane apo-protein known as opsin, and a chromophore prosthetic group bound via a Schiff base linkage to the side chain of a lysine within the opsin's chromophore binding cleft (Fig. 1B). Absorption of a photon of light by the chromophore induces a *cis*-to-*trans* isomerization in the molecule, which in turn effects a conformational change in the opsin that initiates the phototransduction cascade. In vertebrates, two different chromophores are found: 11-*cis* retinal (derived from vitamin A_1 and henceforth referred to as 'A_1') and 11-*cis* 3,4-didehydroretinal (derived from vitamin A_2 and henceforth referred to as 'A_2') (Wald, 1939; Bridges, 1972). The only functional difference between the two chromophores is the presence of an additional double bond within the β-ionone ring of A_2 (Fig. 1C). Replacing A_1 with A_2 in a visual pigment has four main effects: (1) it red-shifts the spectral absorption curve of the visual pigment; (2) it broadens the spectral bandwidth of absorption; (3) it decreases the pigment's photosensitivity; and (4) it increases thermal noise (Fig. 1D–F) (Bridges, 1972; Donner, 2020). The wavelength of maximal sensitivity of a visual pigment (referred to as λ_{max}) can be tuned toward shorter or longer wavelengths via two primary mechanisms: changes in the amino acids of the opsin; or exchange of one chromophore for the other. Opsin tuning via amino acid replacement has become an important model system for the study of molecular evolution in recent years (Carleton et al., 2020; Yokoyama, 2000; Altun et al., 2011; Hunt et al., 2009; Hart and Hunt, 2007; Osorio and Vorobyev, 2005; Kenaley et al., 2014). In contrast, nearly a half century has elapsed since publication of the most recent comprehensive review of the vitamin A_1/A_2 chromophore exchange system (Bridges, 1972). The present review therefore aims to provide an up-to-date account of our understanding of the A_1/A_2 system and how it impacts spectral tuning and visual plasticity.

2. The discovery of vitamin A_1/A_2 chromophore exchange

Scientists first studied purified extracts of vertebrate visual pigments toward the end of the 19th century. They found that solutions of visual pigments obtained from aerial and terrestrial species had a striking rose-pink color which rapidly bleached upon exposure to light. This visual pigment was named 'rhodopsin' based on the ancient Greek words,

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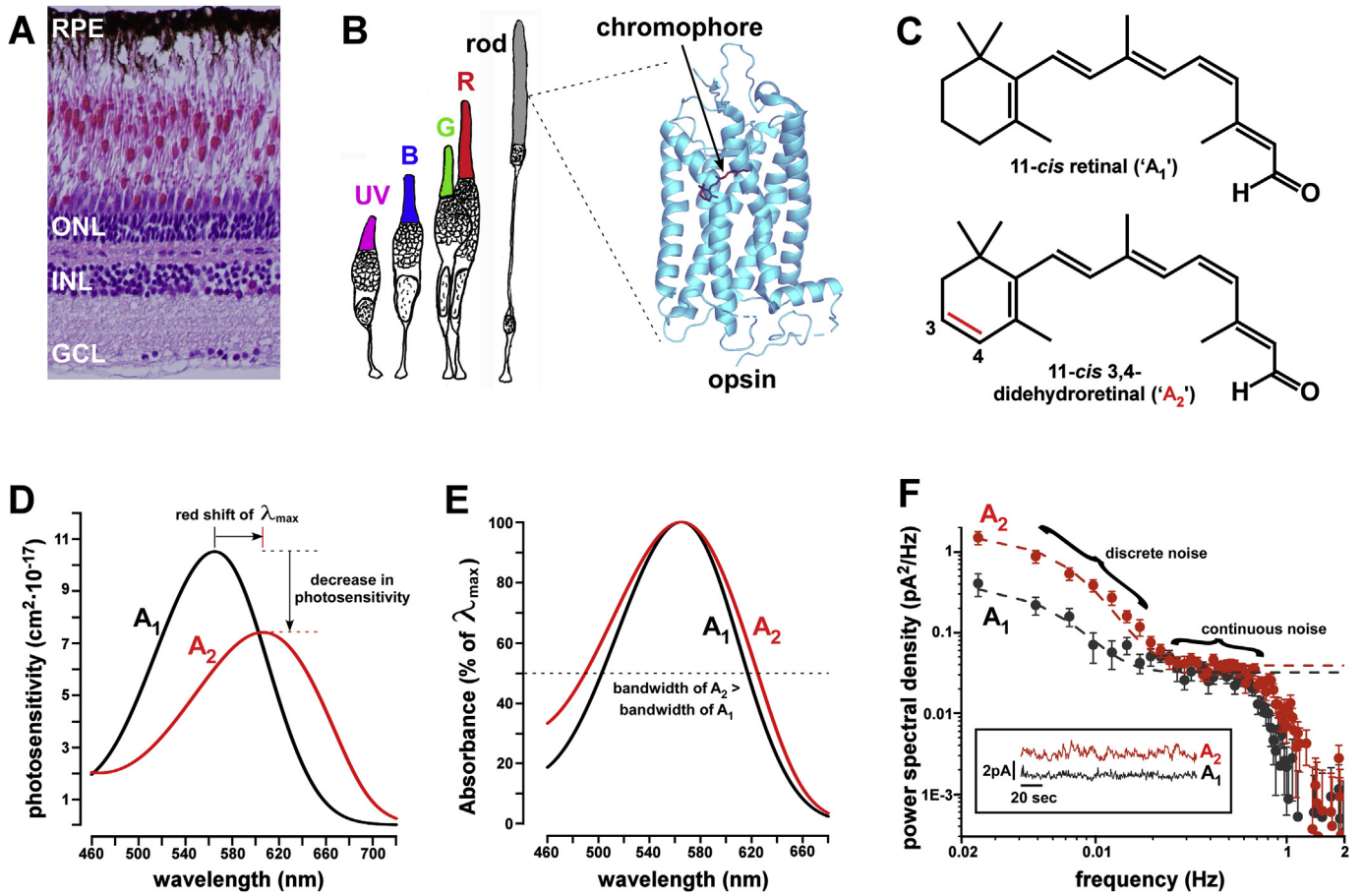

Fig. 1. The vitamin A_1/A_2 chromophore exchange system. (A) H&E-stained histologic section of adult zebrafish retina. The photoreceptor cell bodies reside in the outer nuclear layer (ONL). INL = inner nuclear layer; GCL = ganglion cell layer; RPE = retinal pigment epithelium. **(B)** Drawing of rod and cone photoreceptor subtypes of adult zebrafish: UV = ultraviolet cone; B = blue cone; G = green cone; and R = red cone. Also shown is the crystal structure of bovine rhodopsin (RH1) with the 11-*cis* retinal (A_1) chromophore in red. PDB code = 1F88 (Palczewski et al., 2000). **(C)** Chemical structure of 11-*cis* retinal (A_1) and 11-*cis* 3,4-didehydroretinal (A_2). Note the position of the additional double bond (in red) within the terminal β-ionone ring of A_2. **(D)** Photosensitivity curves of a typical LWS visual pigment either with A_1 (λ_{max} = 565 nm) or A_2 (λ_{max} = 606 nm). Curves are based on templates in Govardovskii et al. (2000). Note that the λ_{max} of the A_2 pigment is red-shifted by 41 nm relative to the A_1 form in accordance with the formula in Fig. 3A. In addition, the photosensitivity of the A_2 pigment is only ~70% that of the A_1 form. **(E)** A_2-based visual pigments have a wider bandwidth than A_1 forms as shown here by superimposing the absorbance curves of A_1 and A_2 pigments with identical λ_{max} = 565 nm. Dotted line indicates half-maximal absorbance. **(F)** This figure shows the noise power spectral density from electrical recordings of the light-sensitive current of individual larval tiger salamander (*Ambystoma tigrina*) rods either in their native A_2-predominant form (red trace; A_1:A_2 ratio is ~0.26:0.74) or after regeneration with A_1 (black trace; A_1:A_2 ratio is ~0.91:0.09) (Ala-Laurila et al., 2007). Note that the A_2-based visual pigment is noisier than the A_1 form. Photoreceptor 'dark noise' has discrete (low frequency) and continuous (high frequency) components. Discrete noise results from thermal isomerization events which occur with greater frequency in A_2-based visual pigments. Continuous noise arises in components of the phototransduction cascade downstream of the visual pigment and occurs at similar rates in A_1-and A_2-based pigments. The inset shows recordings of a rod in the 'A_2' state (red trace) and the 'A_1' state (black trace). Note the large, lower-frequency deviations in the A_2 trace that are absent from the A_1 recording. Panel F is adapted, with permission from the author, from Ala-Laurila et al. (2007).

ῥόδον, rose, and ὄψις, vision (Ewald and Kühne, 1878). In 1880, Kühne and Sewall first noticed that visual pigment extracts from some species of fish were not rose-colored but purple (Kühne and Sewall, 1880). This new visual pigment was subsequently named 'porphyropsin', based on the Greek term for the gastropod mollusks used in antiquity to produce 'royal purple' dye (πορφύρα, purple-fish, and ὄψις, vision) (Wald, 1937, 1939; Ziderman, 1986). In 1896, Köttgen and Abelsdorff showed that the absorption spectra of visual pigments derived from reptiles, birds, and mammals peaked around 500 nm, whereas those of freshwater fish were red-shifted, peaking around 540 nm (Köttgen and Abelsdorff, 1896). George Wald later demonstrated that 'rhodopsins' contain an A_1 chromophore whereas 'porphyropsins' contain A_2 (Wald, 1939). He also showed that replacement of A_1 with A_2 in the same opsin produces a red shift in the λ_{max} of the visual pigment (Wald, 1939). While the terms 'rhodopsin' and 'porphyropsin' were once used to refer to any visual pigment containing A_1 and A_2, respectively, the subsequent discovery of cone opsins made this terminological distinction obsolete. The term 'rhodopsin' is now only used to refer to 'rod opsins' (i.e., RH1 opsins), whereas 'porphyropsin' is rarely used.

3. Species distribution and uses of vitamin A_1/A_2 chromophore exchange

The use of vitamin A_2-based visual pigments is strongly associated with the occupation of aquatic habitats, particularly those with red-shifted or highly variable ambient light (Bridges, 1972). The spectral distribution of light under water is determined, in part, by the presence of dissolved substances which selectively absorb certain wavelengths or by the presence of suspended matter which scatters light and increases turbidity. While A_2-based visual pigments have never been identified in any species of bird, mammal, or fully terrestrial reptile [with the exception of two lizards, *Anolis carolinensis* and *Podarcis siculus* (Provencio et al., 1992)], these pigments are widely distributed among fishes, amphibians, aquatic reptiles, and lamprey (Bridges, 1972). Indeed, data

suggest that the vast majority of freshwater fishes utilize A_2-based visual pigments (Toyama et al., 2008). While early studies showed A_2 to be common in diadromous species (i.e., salmon, trout, eels, and lamprey) during the freshwater phase of their life cycle (Bridges, 1972; Wald, 1937, 1941, 1957; Beatty, 1966, 1984), they found the use of A_2 to be rare among fully marine species. Subsequent studies, however, have demonstrated the use of A_2-based visual pigments in marine fishes from multiple families (Toyama et al., 2008; Wald, 1941; Lythgoe, 1972; Munz and McFarland, 1977; Cummings and Partridge, 2001; Ali and Heumann, 1970; Kondrashev and Lamash, 2019; Munz, 1958; White et al., 2004; Cohen et al., 1990), especially nearshore species inhabiting spectrally variable environments (Cummings and Partridge, 2001). It is therefore unwise to assume *a priori* that a marine species does not utilize A_2-based visual pigments. In total, it is likely that more than a quarter of all vertebrate species utilize A_2-based visual pigments, at least during a part of their life cycle or under certain environmental conditions.

The vitamin A_1/A_2 chromophore exchange system is sometimes referred to as a 'switch', implying that organisms toggle between the use of one chromophore or the other in an all-or-none fashion. In fact, many species utilize both chromophores simultaneously, adjusting the A_1/A_2 ratio in response to physiological or environmental cues in a continuous manner (Bridges, 1972). The presence of both A_1-and A_2-based visual pigments in a single outer segment endows a photoreceptor with a broad, unimodal spectral response curve with a λ_{max} intermediate between those of the pure A_1- and A_2- based pigments (Bridges, 1972). Thus, by adjusting the A_1/A_2 ratio, the organism can continuously tune λ_{max} on a physiological time scale. It appears that some species (e.g., the ninespine stickleback, *Pungitius pungitius*) can independently tune the A_1/A_2 ratio in rods and cones and even within cone subtypes in the same retina (Saarinen et al., 2012). Interestingly, A_1/A_2 ratio can vary among individual fish of a single species caught at the same time and place (Beatty, 1966; Bridges, 1964a, 1966). One author suggested that this phenomenon is particularly notable in schooling species and proposed that the broadening of spectral sensitivity of the school as a whole by individually variable A_1/A_2 ratios might confer a selective advantage in detecting predators (Bridges, 1972; Bridges, 1966).

Fishes inhabiting clear, optically pure waters tend to utilize A_1-based visual pigments, while those found in turbid and red-shifted environments tend to have a high proportion of A_2 in their eyes. However, classifying fish species as either 'A_1' or 'A_2' is overly simplistic, because most published reports describe fish collected at a single location at only one time of the year, and thus ignore potential temporal dynamics of chromophore usage. For example, most published studies [with one exception (Endeman et al., 2013)] indicate that zebrafish (*Danio rerio*) almost exclusively utilize A_1-based pigments under standard laboratory conditions (Enright et al., 2015; Allison et al., 2004). Yet, the zebrafish's native streams and ponds in India and Bangladesh are likely subject to conditions of widely varying turbidity, particularly during the monsoon season (Spence et al., 2006; Arunachalam et al., 2013; Parichy, 2015). It is possible, and even likely, that zebrafish utilize A_2-based visual pigments in the wild when they encounter turbid, red-shifted environments. Indeed, laboratory studies have demonstrated that application of thyroid hormone (TH) to the water of zebrafish can induce a complete switch to A_2-based visual pigments (Enright et al., 2015; Allison et al., 2004), revealing a latent capacity to synthesize A_2. Clearly, one cannot rule out the use of A_2-based visual pigments by a given species based on examination of individuals caught at one time or in a single locale.

Species utilize A_1/A_2 exchange to fine-tune spectral sensitivity in accordance with season, migration status, and developmental stage (Bridges, 1972; Temple et al., 2006). Longitudinal studies have shown that A_2 levels tend to be highest during the winter months and lowest during the summer, even at a single location (Beatty, 1966; Dartnall et al., 1961; Bridges, 1964b; Makino et al., 1983). Some have speculated that the increase in A_2 during the winter may be a response to red-shifting of the ambient light spectrum caused by decreased solar elevation (Bridges, 1972; Beatty, 1966). Alternatively, colder water temperatures may play a role since lower temperatures are known to increase A_2 levels in several species (Beatty, 1984; Allen and McFarland, 1973; Cristy, 1976; McFarland and Allen, 1977; Tsin, 1979a, 1979b; Tsin and Beatty, 1977, 1978, 1980). Colder habitats might also favor A_2 usage since the lower temperature mitigates the increased thermal noise associated with A_2-based pigments (see below) (Aho et al., 1988). As mentioned above, migratory species (salmon, trout, eels, and lamprey) alternate between A_1 and A_2-based pigments, shifting to A_1 upon entering clear marine environments, and favoring A_2 upon entering more turbid, inland waterways (Bridges, 1972; Wald, 1937, 1941, 1957; Beatty, 1966, 1975, 1984). Some species switch between A_1 and A_2 according to developmental stage (Cohen et al., 1990; Liebman and Entine, 1968; Wilt, 1959a; Crescitelli, 1959; Reuter, 1969). For example, the northern leopard frog (*Lithobates pipiens*) utilizes A_2-based pigments during the aquatic tadpole stage and then switches to A_1 upon metamorphosis into a semiterrestrial adult (Liebman and Entine, 1968). In contrast, amphibians that remain aquatic as adults, such as the African clawed toad (*Xenopus laevis*), appear to have A_2-predominant retinas throughout life (Bridges, 1972). One study reported an increasing proportion of A_2 in the eyes of older individuals of the common rudd (*Scardinius erythrophthalmus*) under controlled lighting conditions (Bridges and Yoshikami, 1970a), but the relationship between A_2 levels and age has not been examined in other species.

Several species use A_2-based pigments for specialized purposes. For example, unlike most anurans, the American bullfrog (*Lithobates catesbeianus*) retains A_2-based pigments in the dorsal third of its retina, even as an adult (Reuter et al., 1971). Bullfrogs spend considerable time with their eyes positioned right above the surface of the water (Surface, 1913). Thus, the A_2-rich dorsal retina enables downward vision into the turbid, red-shifted aquatic environment, while the A_1-rich ventral retina scans the aerial milieu. Similarly, the four-eyed fish (*Anableps anableps*) inhabits the surface of turbid waterways, viewing the aquatic and aerial environments with its dorsal and ventral retinas, respectively (Miller, 1979; Owens et al., 2012). Despite marked morphologic differences between the dorsal and ventral retina and the expression of red-sensitive LWS opsin exclusively in the dorsal retina (Owens et al., 2012), the distribution of A_2 in the four-eyed fish's retina is currently unknown (Bridges, 1982). One might speculate that the LWS opsin expressed in the dorsal retina is likely to be paired with an A_2 chromophore to enhance aquatic vision. In contrast, some other fishes have been reported to have a higher proportion of A_2 in the ventral retina, indicating that intraretinal distribution of A_2 is species-specific (Denton et al., 1971; Muntz and Northmore, 1971).

A specialized optical adaptation in certain shallow-water, nearshore fishes favors the use of A_2. More than 100 species of fish can reversibly pigment their corneas upon exposure to bright light (Orlov and Kondrashev, 1998). Corneal pigmentation is mediated by the movement of yellow and red carotenoid-containing organelles within specialized chromatophores whose processes extend across the pupil (Orlov and Kondrashev, 1998). While the adaptive function of corneal pigmentation is debated and might differ between species (Kondrashev, 2008, 2019), in the masked greenling (*Hexagrammos octogrammus*), pigment density can be so high that the cornea acts as a long-pass spectral filter, precluding the transmission of light less than 520 nm (Kondrashev, 2008). This species has adopted the use of A_2-based visual pigments to red-shift their medium- and long-wavelength-sensitive opsins and thereby enhance their ability to detect the longer wavelengths that are passed by the corneal filter, even in summertime when A_2 levels in most species are low (Kondrashev and Lamash, 2019; Kondrashev, 2008).

Another interesting optical adaptation found in three genera of deep-sea dragonfish (Stomiidae) involves the use of A_2-based visual pigments. In addition to the blue-green (450–500 nm) bioluminescent signals typically emitted by deep-sea fishes (Herring, 1983), these dragonfishes emit a far-red (>700 nm) signal from periorbital photophores (Widder et al., 1984; Herring and Cope, 2005; de Busserolles et al., 2020). Since most deep-sea fishes are blind to long-wavelength light, far-red emission endows

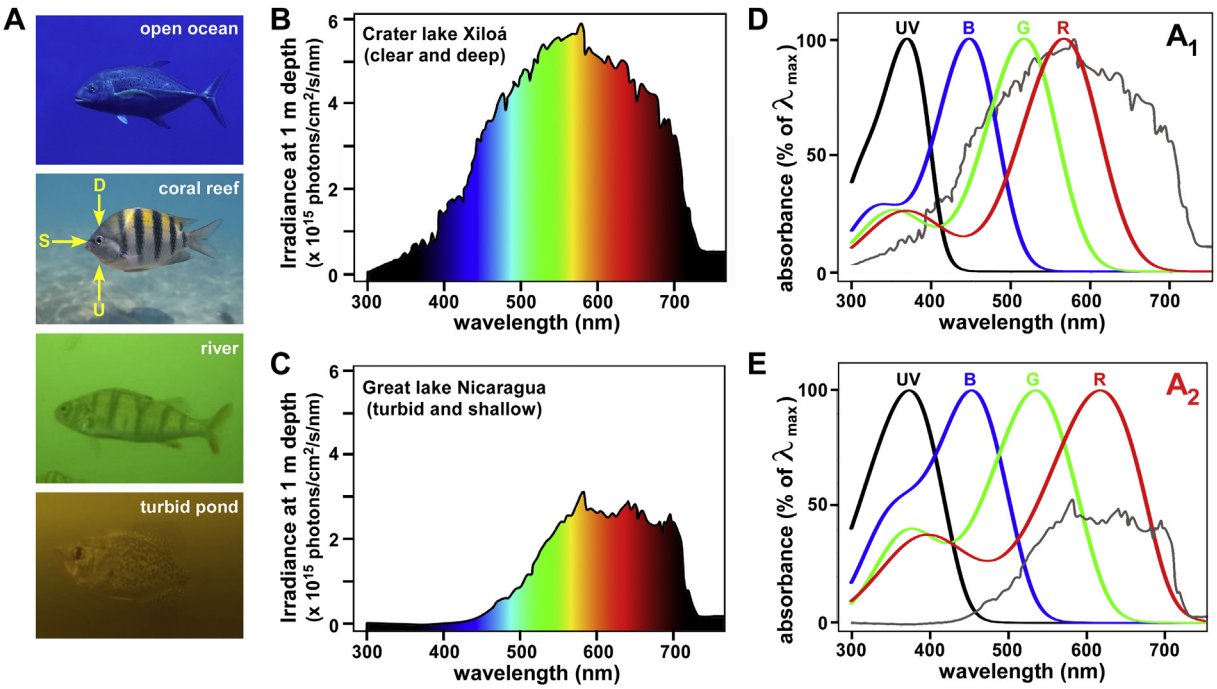

Fig. 2. Light in aquatic habitats is highly variable. (A) Aquatic species experience widely varying and labile photic environments in which the transmission of light is modulated by both suspended and dissolved matter in the water column. Light variability was likely a major impetus for the evolution of the A_1/A_2 chromophore system. D = downwelling light; S = sidewelling light (i.e., the horizontal visual field); U = upwelling light. Photo credits (from top to bottom): Humberto Chavez, Matthew T. Rader, Andreas Steinhoff, Patrick Moreno. **(B, C)** Spectral irradiance in two Central American cichlid habitats with marked differences in water clarity. Turbidity decreases the amount of light available for vision and preferentially absorbs shorter wavelengths, effectively red-shifting the spectral distribution. A recent study showed that expression of *cyp27c1* (the enzymes that converts A_1 into A_2) in the eyes of cichlids correlates with the spectral distribution of light in these habitats (Härer et al., 2018). **(D, E)** The spectral absorbance curves of the A_1 (D) and A_2 (E) forms of the four cone visual pigments of the goldfish, a typical tetrachromatic teleost. The curves are based on templates in Govardovskii et al. (2000), using the following values for λ_{max} from Parry and Bowmaker (2000): A_1 forms (370.1, 447.2, 515.9, 565.9 nm); A_2 forms (381.9, 454.1, 534.9, 617.5 nm). The irradiance curves from panels B and C (gray) are superimposed on the spectral absorbance curves in D and E, respectively. Note how the λ_{max} of the A_1 and A_2 forms of the red cone (LWS) pigment are well-positioned to capture the predominant wavelengths of light in clear and turbid habitats, respectively. This figure demonstrates how switching between A_1 and A_2 allows an organism to tune its spectral sensitivity to match the predominant wavelengths in its environment. The spectral irradiance curves in panels B and C are adapted, with permission of the author, from Torres-Dowdall et al. (2017).

dragonfishes with the potential for covert prey illumination or 'private' signaling between individuals (Douglas et al., 2016). To detect this signal, dragonfishes have evolved rod opsins (RH1) with red-shifted λ_{max} (Douglas et al., 1998a). These fishes couple their red-shifted opsin with an A_2 chromophore in a sub-population of rods, thereby enhancing sensitivity to far-red signals (Douglas et al., 1998a; Bowmaker et al., 1988; Partridge and Douglas, 1995; Partridge et al., 1989). Remarkably, the dragonfish *Malacosteus niger* red-shifts sensitivity even further by using derivatives of bacteriochlorophyll as photosensitizers (Douglas et al., 1998b, 1999, 2016).

4. Environmental factors controlling the A_1/A_2 ratio

What accounts for the widespread utilization of A_1/A_2 chromophore exchange among aquatic organisms and its rarity among terrestrial species? The most likely answer is the variable and labile quality of light in aquatic, and especially freshwater, habitats (Fig. 2). Light transmission in water can be affected by both biotic and abiotic factors (e.g., chlorophyll-containing plankton, suspended inorganic particles, and dissolved compounds). These factors modify both the amount and spectral distribution of light available for vision (Fig. 2B). Opsin switching (i.e., changes in the expression of opsin genes) and A_1/A_2 chromophore exchange are the primary mechanisms whereby species modify their spectral sensitivity in response to changes in their photic environment (Carleton et al., 2020). It is therefore not surprising that evolution has favored the emergence of both A_1/A_2 chromophore exchange and highly diverse opsin gene repertoires in fishes (Bridges, 1972; Carleton et al., 2020; Lin et al., 2017). Despite the established role of water temperature in controlling A_1/A_2 ratio in some fishes (Beatty, 1984; Allen and McFarland, 1973; Cristy, 1976; McFarland and Allen, 1977; Tsin, 1979a, 1979b; Tsin and Beatty, 1977, 1978), there is broad consensus that light intensity, duration (i.e., day length), and wavelength are the most important environmental variables determining A_1/A_2 ratio in the majority of species (Bridges, 1972). Environments with less light of shorter duration and longer wavelengths tend to favor an increase in A_2 levels (Bridges, 1972). Indeed, emerging evidence from the evolutionarily diverse cichlid fishes (Cichlidae) indicates that selection for higher A_2 levels has likely played a key role in adaptation to turbid or otherwise red-shifted environments (Fig. 2B and C) (Härer et al., 2018; Torres-Dowdall et al., 2017; Terai et al., 2006, 2017; Carleton and Yourick, 2020; Escobar-Camacho et al., 2019).

Given the outsized importance of light quality and quantity in determining opsin and A_1/A_2 usage, it is surprising that so few studies of fish vision have included ambient light measurements. In studies that do incorporate such measures, the data are often limited to quantification of up- or downwelling light at varying depths (Härer et al., 2018; Munz and McFarland, 1977; Saarinen et al., 2012; McFarland and Munz, 1975; Munz and McFarland, 1975). While certainly laudable, such studies do not typically measure the light that actually reaches the animal's eye. Yet, in surfperches (Embiotocidae) photoreceptor spectral tuning most strongly correlates with sidewelling irradiance (i.e., the horizontal visual field), not up- or downwelling light (Fig. 2A, second subpanel) (Cummings and Partridge, 2001). Since changes in spectral tuning via opsin or chromophore exchange occur over days to weeks (Bridges, 1972; Beatty, 1966), these changes likely reflect cumulative light exposure at the

retinal surface. Ideally, studies of spectral sensitivity should include a 'fish eye' view of light (Zimmermann et al., 2018), summated over time via a miniature head-mounted camera or spectrophotometer, perhaps with special weighting of visual features critical to organismal fitness [e.g., the reflectance spectra of predators or potential mates (Schneider et al., 2020)]. Such an approach would likely reveal much stronger correlations between spectral tuning and light exposure than have heretofore been observed using more indirect measures of ambient light.

5. The enzymatic mechanism and transcriptional control of vitamin A_1-to-A_2 conversion

The existence of an enzyme that converts vitamin A_1 into A_2 was proposed more than a half century ago (Bridges, 1972). Early studies showed a strong correlation between A_2 levels in retina and in retinal pigment epithelium (RPE) (Tsin and Beatty, 1980; Reuter et al., 1971; Bridges and Yoshikami, 1970b), suggesting that A_2 might be synthesized in the RPE and then passed to the retina during the visual cycle (Palczewski and Kiser, 2020). To identify the enzyme mediating A_2 synthesis, my lab used RNA-seq to compare the transcriptomes of RPE from TH-treated zebrafish vs. untreated controls as well as the transcriptomes of dorsal vs. ventral bullfrog RPE (Enright et al., 2015). We identified a single gene that was both upregulated in TH-treated zebrafish RPE and enriched in the dorsal bullfrog RPE, the cytochrome P450 family member, *cyp27c1* (Enright et al., 2015). P450 enzymes are involved in the metabolism of a wide range of xenobiotic compounds and endogenous small molecules, including retinoids (Coon, 2005). Thus, cyp27c1 was an excellent candidate for the long-hypothesized 'vitamin A_1 3,4-dehydrogenase'. Subsequent analysis demonstrated that this enzyme is localized to the RPE in zebrafish and American bullfrog, and that its expression correlates with the presence of A_2 (Enright et al., 2015). We also showed that cyp27c1 is sufficient to convert vitamin A_1 and its congeners into their corresponding A_2 forms (Enright et al., 2015; Kramlinger et al., 2016). Lastly, we engineered zebrafish with mutations in *cyp27c1* and showed that the gene is required for endogenous synthesis of A_2 (Enright et al., 2015). Knock-out of *cyp27c1* also eliminates the zebrafish's ability to red-shift its photoreceptor spectral sensitivity in response to TH treatment and reduces its ability to see and respond to near-infrared light of 770 nm (Enright et al., 2015). Some fishes display differences in the A_1/A_2 ratio between photoreceptor classes, suggesting that *cyp27c1* might be differentially expressed in individual photoreceptor subtypes in these species, rather than exclusively in the RPE (Saarinen et al., 2012; Bowmaker et al., 1988). Differences in the A_1/A_2 ratio between rods and cones might also be accounted for by expression of *cyp27c1* in Müller glia which support cone, but not rod, pigment regeneration (Wang and Kefalov, 2011). Interestingly, there does not appear to be an enzyme that converts A_2 into A_1. Instead, a switch from A_2 to A_1 likely occurs via progressive turnover of the retinoid pool in the RPE.

Despite the apparent absence of A_2-based visual pigments in some groups (i.e., birds and mammals), orthologs of *cyp27c1* are found in all vertebrate classes. Expression of *cyp27c1* strongly correlates with the presence of A_2 in the retina of the sea lamprey (*Petromyzon marinus*) (Morshedian et al., 2017), an agnathan that diverged from jawed vertebrates during the Cambrian period ~500 million years ago (Kuraku and Kuratani, 2006). The sea lamprey switches between A_1-and A_2-predominance at different stages of its migratory life cycle (Wald, 1957), suggesting that the capacity for A_2 production may have facilitated the initial invasion of turbid inland waterways by early vertebrates (Morshedian et al., 2017; Halstead, 1985). As expected, *cyp27c1* orthologs are nearly ubiquitous among the sequenced genomes of fishes, amphibians, and reptiles. More surprisingly, nearly all sequenced bird genomes also retain an intact copy of *cyp27c1*. The role of this enzyme in birds is currently unknown, but studies suggest potential functions outside of the eye. For example, 3,4-didehydroretinoic acid (a derivative of vitamin A_2), is the predominant form of 'retinoic acid' found in the developing chicken (*Gallus gallus*) embryo (Maden et al., 1998; Thaller and Eichele, 1990).

Orthologs of *cyp27c1* are present in most mammalian species including humans, but the gene appears to have been lost in three groups. BLAST searches using human *CYP27C1* as a query revealed loss of *cyp27c1* in bats (Chiroptera), rodents (Rodentia) with the exception of squirrel-related clades (Sciuromorpha), and Afrotheria (with the possible exception of manatees). The retention of *cyp27c1* orthologs among squirrel-like clades suggests early evolutionary branching of Sciuromorpha prior to *cyp27c1* loss, a finding consistent with recent phylogenetic studies (Churakov et al., 2010; Asher et al., 2019). Interestingly, *cyp27c1* orthologs appear to be absent from all sequenced Afrotheria genomes, with the exception of that of the West Indian manatee (*Trichechus manatus*) which retains a gene encoding a protein with ~68% amino acid identity to human CYP27C1 and with shared synteny (*BIN1 – CYP27C1 — ERCC3*). The retention of a possible ortholog of *cyp27c1* in West Indian manatee is intriguing, because this species inhabits turbid coastal waters, estuaries, and rivers and, along with the three other species of sea cow (Sirenia), represents the only fully aquatic sub-clade within Afrotheria (Gaspard et al., 2013). This finding raises the possibility that sea cows (and perhaps other aquatic mammals inhabiting turbid, red-shifted water such as river dolphins) might use A_2-based visual pigments. The presence of *cyp27c1* orthologs in terrestrial mammals is more puzzling, but the enrichment of both *CYP27C1* transcripts and 3,4-didehydroretinoids in human skin (Johnson et al., 2017; Rollman and Vahlquist, 1985; Torma and Vahlquist, 1985; Vahlquist, 1980), and the ability of human CYP27C1 to convert vitamin A_1 into A_2 (Kramlinger et al., 2016; Johnson et al., 2017), suggest a role for this enzyme in the integument.

No ortholog of *cyp27c1* has so far been identified in the genomes of invertebrates, despite the existence of an A_1/A_2 exchange system in the eyes of several crayfish species (Suzuki et al., 1984; Suzuki and Eguchi, 1987). In the Louisiana crayfish (*Procambarus clarkii*) A_2 levels increase in the winter or upon exposure to cold temperature in the laboratory (Suzuki et al., 1985), mirroring the seasonal changes in the A_1/A_2 ratio seen in many vertebrate species. Interestingly, Suzuki et al. have reported the presence of 3-hydroxyretinol in the eyes of the Louisiana crayfish, but only under conditions when A_2 was present (Suzuki and Miyata, 1991). Johnson et al. have similarly shown that human CYP27C1 produces trace amounts of 3-hydroxyretinol and 4-hydroxyretinol upon incubation with all-*trans* retinol as a substrate (Johnson et al., 2017). These findings suggest that the enzymatic mechanism used by crayfish to produce A_2 may be similar to that used by vertebrates.

Organisms dynamically modulate A_1/A_2 ratio in response to both physiological changes and environmental variables. In some species, such as salmon preparing to migrate, the initiation of the A_1-to-A_2 switch precedes the fish's entry into the new photic environment (Bridges, 1972; Beatty, 1966), suggesting that chromophore exchange is part of a suite of anticipatory physiologic changes and is therefore likely under systemic hormonal control. In other species, the A_1/A_2 ratio can be modulated locally within the eye. Bridges and Yoshikami showed that when held in constant darkness the common rudd converts nearly all chromophore to A_2 (Bridges and Yoshikami, 1970a, 1970b). Upon re-exposure to light the fish then reverts to A_1. This reversion can be prevented by placing an opaque plastic cap over one eye, while the uncapped eye reverts normally (Bridges and Yoshikami, 1970a, 1970b). Thus, in the rudd, changes in the photic environment can be sensed locally within a single eye and transduced into changes in the A_1/A_2 ratio independent of the other eye.

How do animals sense changes in their internal state or external milieu and transduce this signal into changes in *cyp27c1* expression? The answer to this question is currently unknown, but TH signaling appears to play a role, at least in some species. Studies in salmon, trout, zebrafish, goldfish (*Carassius auratus*), and shiners (*Richardsonius balteatus*, *Notemigonus crysoleucas*, and *Laxilus cornutus*) indicate that application of TH increases the percentage of A_2 in the eye (Beatty, 1984; Munz and Swanson, 1965; Jacquest and Beatty, 1972; Cristy, 1974; Allen, 1977; Allen, 1971; Beatty, 1969), while in sunfish (*Lepomis* sp.) and American bullfrog it has the opposite effect (Wilt, 1959a, 1959b; Naito and Wilt, 1962; Ohtsu et al., 1964). To identify the transcription factors that

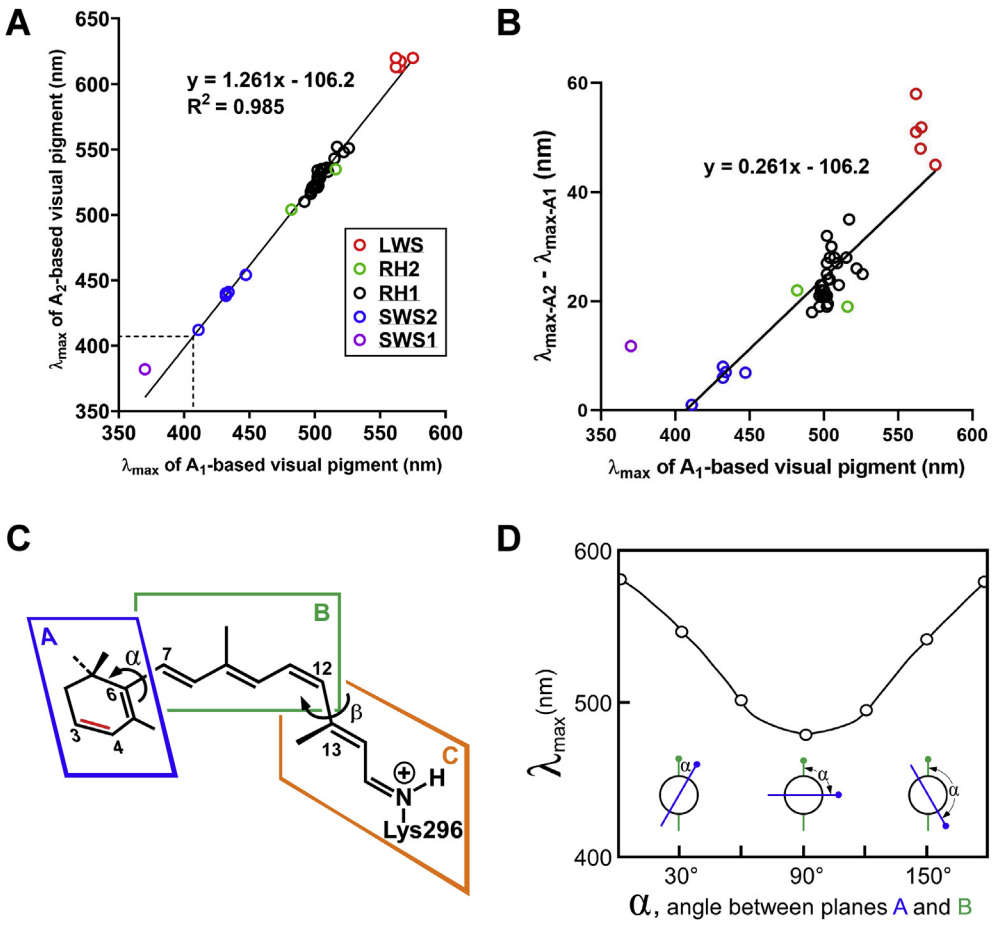

Fig. 3. The relationship between $\lambda_{max\text{-}A1}$ and $\lambda_{max\text{-}A2}$. **(A)** This graph shows the relationship between $\lambda_{max\text{-}A1}$ and $\lambda_{max\text{-}A2}$ for 57 different rod (RH1) and cone (SWS1, SWS2, RH2, LWS) visual pigment pairs from numerous species (primary data and references in Supplemental Table S1). The relationship is well described by a straight line ($R^2 = 0.985$; equation for the fitted line is shown). The dotted lines indicate the point at which $\lambda_{max\text{-}A1}$ and $\lambda_{max\text{-}A2}$ are equal (~407 nm). **(B)** The same data as in panel A but with $\lambda_{max\text{-}A1}$ plotted against $\lambda_{max\text{-}A2}$ - $\lambda_{max\text{-}A1}$ to highlight how the red shift increases with increasing $\lambda_{max\text{-}A1}$. The marked deviation of the one SWS1 pigment (purple) is discussed in the main text. Values for LWS pigments (red) also appear to deviate somewhat from the fitted line. It is not currently known whether this deviation is real or attributable to measurement errors. **(C)** The retinal chromophore consists of three planes (A, B, C) which can rotate relative to each other. Rotation about the C6–C7 bond (dihedral angle α) alters the degree of coplanarity between planes A and B, thereby modifying the extent of electron delocalization into the β-ionone ring. Blatz and Liebman have proposed that the relationship between $\lambda_{max\text{-}A1}$ and $\lambda_{max\text{-}A2}$ might be explained by differences in α across visual pigments (Blatz and Liebman, 1973). **(D)** A theoretical modeling analysis suggested that λ_{max} can be tuned over a range of ~100 nm by changing α, the dihedral angle between planes A and B (Honig et al., 1976; Nakanishi, 1991). Panel D is adapted from Honig et al. (1976).

mediate induction of *cyp27c1* in response to TH, my lab assayed zebrafish with mutations in the three known TH nuclear receptors (*thraa*, *thrab*, and *thrb*). We found that no single TH nuclear receptor is required for TH-mediated induction of *cyp27c1* but that deletion of all three completely eliminates *cyp27c1* expression and the resulting conversion of A_1 to A_2 (Volkov et al., 2020). Despite this knowledge, we still do not understand the mechanism whereby some species flip the polarity of the response, reducing A_2 levels upon exposure to TH (Wilt, 1959a, 1959b; Naito and Wilt, 1962; Ohtsu et al., 1964). We also do not know how changes in the light environment are sensed and transduced into changes in TH signaling in the RPE. These are important problems for future work.

In addition to controlling *cyp27c1* expression, TH signaling is required for red-sensitive LWS opsin expression in many vertebrates (Volkov et al., 2020; Ng et al., 2001; Eldred et al., 2018; Suzuki et al., 2013). In zebrafish, mutations in *thrb* cause LWS cone precursors to be transfated into UV cones (Volkov et al., 2020). TH signaling also appears to play a role in controlling expression of paralogous opsin genes, possibly in response to changes in the photic environment. Temple and colleagues showed that TH treatment of coho salmon (*Oncorhynchus kisutch*) can induce increased expression of a RH2 paralog with red-shifted λ_{max} (Temple et al., 2008). Another study demonstrated that TH treatment of zebrafish induces a shift in expression toward red-shifted RH2 and LWS paralogs (Mackin et al., 2019). Taken together, these findings suggest that TH signaling coordinates a multi-level response to changes in long-wavelength light in the environment. One might speculate that in early vertebrate evolution both A_1/A_2 exchange and the expression of red-shifted opsins came under the control of TH signaling as a mechanism of coordinating physiologic changes, perhaps in a jawless ancestor undergoing metamorphosis or in one preparing to migrate into fresh water.

6. The extent of red shift upon switching from A_1 to A_2 is correlated with λ_{max}

One of the most remarkable features of the A_1/A_2 system is that the longer the $\lambda_{max\text{-}A1}$, the greater the red shift upon switching to A_2 (Fig. 3A and B) (Bridges, 1972; Liebman and Entine, 1968; Dartnall and Lythgoe, 1965a, 1965b; Munz and Schwanzara, 1967). For example, in an early study of the northern leopard frog using microspectrophotometry (MSP) (Liebman and Entine, 1968), the authors found that the LWS pigment ($\lambda_{max\text{-}A1} = 575$ nm) underwent a red-shift of 45 nm upon switching from A_1 to A_2, whereas the RH1 pigment ($\lambda_{max\text{-}A1} = 502$ nm) underwent a red shift of 25 nm and the SWS2 pigment ($\lambda_{max\text{-}A1} = 432$ nm) a red shift of only 6 nm. The authors observed that these data fall on a straight line when graphed against $\lambda_{max\text{-}A1}$ [However, it should be noted that the LWS $\lambda_{max\text{-}A1}$ value obtained in this study differs significantly from that found later by Koskelainen et al. (1994)]. Multiple subsequent studies have confirmed a linear or nearly linear relationship between $\lambda_{max\text{-}A1}$ and $\lambda_{max\text{-}A2}$ (Parry and Bowmaker, 2000; Saarinen et al., 2012; Allison et al., 2004; Makino et al., 1990), at least for $407\text{ nm} < \lambda_{max\text{-}A1} < 550\text{ nm}$ (Fig. 3A and B). The functional consequence of this relationship is that switching from A_1 to A_2 results in a large extension of visual sensitivity into the far-red region without much of a corresponding loss of sensitivity at the short-wavelength end of the spectrum (Fig. 2D and E).

One implication of a linear relationship between $\lambda_{max\text{-}A1}$ and $\lambda_{max\text{-}A2}$ is that the red shift caused by an A_1-to-A_2 switch is predicted to be zero when the $\lambda_{max\text{-}A1}$ equals ~407 nm (see equation in Fig. 3A). Two published datasets are consistent with this prediction. First, an MSP study of zebrafish (*Danio rerio*) found no statistically significant red shift of the

λ_{max} of the SWS2 pigment ($\lambda_{max\text{-}A1} = 411$ nm) upon switching to A_2 ($\lambda_{max\text{-}A2} = 412$ nm) (Allison et al., 2004). The authors did, however, observe that the half-bandwidth of the absorption curve of the A_2-based SWS2 pigment was broader than that of the A_1-based, indicating that chromophore exchange had indeed occurred. In a second study, Makino and colleagues measured the λ_{max} of the SWS2 visual pigment of the tiger salamander (*Ambystoma tigrinum*) reconstituted with three different 9-*cis* retinals: 9-*cis* 5,6-dihydroretinal, which lacks double bonds in the β-ionone ring and is referred to by the authors as A_0; 9-*cis* retinal (referred to as A_1); and 9-*cis* 3,4-didehydroretinal (referred to as A_2) (Makino et al., 1999). As expected from the equation in Fig. 3A, the authors observed only very small red shifts of the SWS2 pigment upon addition of one or two double bonds to the β-ionone ring of the chromophore ($\lambda_{max\text{-}A0} = 415$ nm; $\lambda_{max\text{-}A1} = 418$ nm; $\lambda_{max\text{-}A2} = 422$ nm). Although more data are needed to precisely define the $\lambda_{max\text{-}A1}$ value at which the red shift equals zero, the published data strongly suggest that such a point exists near 407 nm.

A counterintuitive prediction of the equation in Fig. 3A is that at $\lambda_{max\text{-}A1} < 407$ nm, A_2-based pigments should absorb at shorter wavelengths than their A_1 counterparts! For example, an SWS1 pigment with $\lambda_{max\text{-}A1} = 370.1$ nm would be predicted to have $\lambda_{max\text{-}A2} = 360.5$ nm. Instead, measurements of the goldfish SWS1 pigment ($\lambda_{max\text{-}A1} = 370.1$ nm) indicate a red shift of nearly 12 nm upon switching to A_2 ($\lambda_{max\text{-}A2} = 381.9$ nm) (Parry and Bowmaker, 2000). This apparent deviation from linearity has led some authors to suggest that A_1/A_2 data would be better fit by a non-linear (e.g., parabolic) function (Parry and Bowmaker, 2000; Harosi, 1994; Whitmore and Bowmaker, 1989). Indeed, there is also some apparent deviation from strict linearity at $\lambda_{max\text{-}A1} > 550$ nm (Fig. 3A and B). It remains to be determined whether these deviation at longer $\lambda_{max\text{-}A1}$ are real or due to experimental error. How should we account for deviations from linearity at $\lambda_{max\text{-}A1} < 400$ nm?

I propose that deviations from linearity at very short λ_{max} might be due to fundamental differences in the mechanisms of spectral tuning used by visual pigments with an unprotonated Schiff base and those with a protonated Schiff base (Harosi, 1994; Zhu et al., 2013; Altun et al., 2008). It has long been known that all SWS2, RH1, RH2, and LWS visual pigments contain a protonated Schiff base linkage (Honig et al., 1976; Morton and Pitt, 1955; Honig and Ebrey, 1974). Furthermore, the presence of this positive charge on the chromophore and the distance of the counterion within the binding cleft play a major role in tuning the λ_{max} of the visual pigment (Honig et al., 1976; Kochendoerfer et al., 1999; Sekharan et al., 2012; Collette et al., 2018; Ernst et al., 2014). In contrast, SWS1-based visual pigments fall into two distinct spectral classes: those with $\lambda_{max\text{-}A1} < 400$ nm (i.e., ultraviolet-sensitive) and those with $\lambda_{max\text{-}A1} > 400$ nm (violet-sensitive) (Odeen and Hastad, 2003, 2013; Shi et al., 2001; Cuthill et al., 2000). Visual pigments in the former class contain an unprotonated Schiff base, whereas those in the latter class have a protonated Schiff base (Altun et al., 2011; Harosi, 1994). Given the fundamental role played by protonation in defining the electronic state of the chromophore and consequently its spectral tuning, it is reasonable to conclude that a visual pigment with an unprotonated Schiff base might be tuned differently (Zhu et al., 2013).

I therefore suggest that the relationship between $\lambda_{max\text{-}A1}$ and $\lambda_{max\text{-}A2}$ is linear (or nearly linear) for visual pigments with a protonated Schiff base, and that a different, and currently unknown equation describes the relationship between $\lambda_{max\text{-}A1}$ and $\lambda_{max\text{-}A2}$ for visual pigments with an unprotonated Schiff base. At the present time, there are very few high-confidence measurements of A_1/A_2 pairs of visual pigments with an unprotonated Schiff base. In fact, the above-mentioned study of the goldfish SWS1 pigment is the only high-quality data point I have found in this range (Parry and Bowmaker, 2000). Another study purporting to analyze A_1/A_2 pairs of ultraviolet pigments relied on paired A_1 and A_2 values derived from different species of fish (under the unproven assumption that the opsins were identical) or from the absorption spectra of pure A_1 and A_2 chromophores dissolved in ethanol (Harosi, 1994). Clearly, to define the relationship between $\lambda_{max\text{-}A1}$ and $\lambda_{max\text{-}A2}$ in the ultraviolet region, more high-quality measurements of A_1/A_2 pairs are needed, especially in the range $\lambda_{max\text{-}A1} = 350$–$385$ nm.

Why is the extent of red shift upon switching from A_1 to A_2 correlated with λ_{max} in visual pigments with a protonated Schiff base? A definitive answer to this question is not yet available and will depend on a deeper understanding of the physical mechanisms of visual pigment spectral tuning. Spectral tuning largely depends on the presence/absence of a protonated Schiff base and the extent of π-electron delocalization along the polyene chain and into the β-ionone ring of the chromophore (Kochendoerfer et al., 1999; Sekharan et al., 2012; Collette et al., 2018; Ernst et al., 2014; Honig et al., 1979). A greater number of conjugated double bonds (as in A_2-based visual pigments) and a greater extent of π-electron delocalization result in greater red shifts in λ_{max} (Blatz and Liebman, 1973; Honig et al., 1976; Altun et al., 2008; Rajamani et al., 2011). Charge delocalization is modulated by both electrostatic interactions between the chromophore and the amino acid side chains within the opsin, as well as by steric interactions that distort the geometry of the chromophore, in turn, affecting its electronic state (Honig et al., 1976; Altun et al., 2008; Kochendoerfer et al., 1999; Sekharan et al., 2012; Collette et al., 2018; Ernst et al., 2014).

Nearly fifty years ago, Blatz and Liebman proposed a simple mechanism to account for the relationship between $\lambda_{max\text{-}A1}$ and $\lambda_{max\text{-}A2}$ (Blatz and Liebman, 1973). They suggested that the extent of π-electron delocalization into the β-ionone ring is modulated by the degree of co-planarity between the plane of the β-ionone ring (plane A in Fig. 3C) and that of the polyene chain (plane B in Fig. 3C). When the two planes are entirely co-planar (i.e, when α, the dihedral angle between planes A and B, is equal to 0°), maximal π-electron delocalization into the β-ionone ring occurs, and a maximal red shift is achieved (Honig et al., 1976; Nakanishi, 1991; Zhu et al., 2013; Sekharan et al., 2012; Collette et al., 2018; Ernst et al., 2014). In contrast, when planes A and B are at a right angle to each other ($\alpha = 90°$ in Fig. 3C,D), π-electron delocalization cannot extend into the β-ionone ring, and a maximal blue shift results. Values of α between 0° and 90° would produce intermediate λ_{max} values.

This tuning mechanism could explain the observed relationship between $\lambda_{max\text{-}A1}$ and $\lambda_{max\text{-}A2}$ because the full effect of the additional double bond of the A_2 chromophore would be accessible for conjugation at $\alpha = 0°$, while neither of the ring double bonds would be accessible for conjugation at $\alpha = 90°$. Several modeling studies are consistent with a role for Blatz and Liebman's mechanism in spectral tuning (Honig et al., 1976; Zhu et al., 2013; Sekharan et al., 2012), and the crystal structure of the medium-wavelength-sensitive bovine rhodopsin (an RH1 opsin) demonstrates an 'intermediate' value of α as would be predicted by this model (Okada et al., 2004). Nonetheless, a number of experiments using 'locked' chromophores (Makino et al., 1990) (in which a chemical bridge prevents changes in α) or 5,6-dihydroretinals (Makino et al., 1999) (which lack ring double bonds) indicate that changes in α alone cannot account for the full-range of spectral tuning observed in naturally occurring visual pigments. In conclusion, the Blatz and Liebman mechanism may play a role in spectral tuning, particularly in the 'violet-blue' region of the spectrum, but further modeling and experiments are required to evaluate this idea.

7. The disadvantages of vitamin A_2-based visual pigments

The advantages of A_2-based pigments (red-shifted and broadened spectral sensitivity and the potential for continuous tuning of λ_{max}) are counterbalanced by two notable disadvantages: they have lower thermal stability and lower intrinsic photosensitivity than A_1-based pigments. *Cis*-to-*trans* isomerization of a visual pigment and consequent activation of the phototransduction cascade can be caused either by absorption of a photon (light) or by random thermal fluctuations (heat) (Ala-Laurila et al., 2007; Donner, 2020; Luo et al., 2011). Thermal isomerization is sometimes referred to as 'dark noise' or 'dark light' because the resultant activation of the phototransduction cascade is indistinguishable from that caused by light-induced isomerization (Donner, 2020). Dark noise

sets a fundamental limit to an organism's ability to detect photons at very low light levels, because it is impossible to distinguish between photoisomerization and thermal isomerization of the visual pigment (Barlow, 1956; Donner, 1992). Thus, visual detection in dim light is a signal-to-noise discrimination task: a switch from A_1 to A_2 might increase signal by more precisely matching λ_{max} to the predominant wavelengths of transmitted light, but this increase is offset by an increase in thermal noise (Ala-Laurila et al., 2007). Ala-Laurila and colleagues have estimated that replacing A_1 with A_2 in tiger salamander RH1 results in a red shift of 26 nm and a 36-fold increase in dark noise (Ala-Laurila et al., 2007). These antagonistic effects pose a conundrum for organisms in turbid environments in which the predominant wavelengths of light are red-shifted (favoring the use of A_2-based pigments) while the amount of transmitted light is simultaneously reduced (favoring less noisy A_1-based pigments).

The potential advantages of a switch to A_2 are further offset by a second factor: the lower photosensitivity of A_2-based visual pigments compared to those with A_1 (Ala-Laurila et al., 2007; Dartnall, 1972). Photosensitivity ($\alpha\gamma$) is a measure of the efficiency with which absorption of light by a visual pigment (or other molecule) induces a specific change in that pigment (Dartnall, 1972; Goodeve and Wood, 1938; Dartnall, 1968). It is the product of two terms: α, the absorption coefficient, which is a measure of the efficiency of light absorption, and γ, the quantum efficiency, which is a measure of the efficiency with which the absorbed light causes isomerization (Dartnall, 1968, 1972). Dartnall found that the average photosensitivity of A_1-based RH1 visual pigments was 10.5 ($cm^2 \times 10^{-17}$ per chromophore), while the average photosensitivity of A_2-based RH1 pigments was 7.4 (Dartnall, 1968). Thus, the photosensitivity of A_2-based visual pigments is only ~70% that of A_1-based pigments (Fig. 1D). Both increased noise and decreased photosensitivity counterbalance the advantages of A_2-based visual pigments in low light, but these disadvantages are likely of little consequence in bright light. It is therefore possible that the main selective advantage of A_2 is the large red shift (>40 nm) it confers on long-wavelength-sensitive cone opsins (e.g., Fig. 2E). However, Donner has noted that some A_2-utilizing species appear to have evolved RH1 opsins with greater thermal stability than species that do not use A_2 (Donner, 2020; Donner et al., 1990). The implication is that thermally stabilizing RH1 mutations act to counter the increased noise of the A_2 chromophore. Furthermore, the presence of such mutations implies that the species in question must use A_2 under low-light conditions where thermal noise would be selectively relevant. Overall, the nearly ubiquitous utilization of A_2 in red-shifted aquatic environments suggests that its advantages outweigh the disadvantages, irrespective of whether natural selection is acting primarily on the photopic or scotopic visual system.

8. Unsolved problems related to the A_1/A_2 chromophore system

In this section I recap what I consider to be the most interesting outstanding questions related to the A_1/A_2 system, listed in the order in which they arise in the main text. (1) Why are A_2-based visual pigments so rare among fully terrestrial vertebrates, and what is their role in the two species (*Anolis carolinensis* and *Podarcis siculus*) known to possess them? (2) What factors determine the distribution of A_2 usage among fully marine fishes? (3) What are the mechanisms that control differential A_2 utilization in different parts of the retina (e.g., in the American bullfrog, the four-eyed fish, etc.)? (4) What features of the environment (temperature; salinity; turbidity; light intensity, duration, and wavelength etc.) play the biggest role in determining A_1/A_2 ratio, and what is the best way to measure them? (5) What are the molecular mechanisms whereby environmental signals are sensed, transduced, and integrated into changes in A_1/A_2 ratio in the eye? (6) Are A_2-based visual pigments used by any birds or mammals? (7) What is the function of *cyp27c1* in species that do not use A_2 in the eye? (8) What enzyme converts A_1 to A_2 in crayfish? (9) What are the mechanisms that permit some species (e.g., deep-sea dragonfishes and ninespine sticklebacks) to differentially tune the A_1/A_2 ratio in individual photoreceptor subtypes? (10) Are there enzymes other than cyp27c1 that mediate production of A_2 in vertebrates? (11) Is TH signaling always involved in the control of *cyp27c1* expression or do TH-independent mechanisms exist? (12) Is the coordinate regulation of A_1/A_2 exchange and the expression of red-shifted opsins by TH signaling fortuitous or does it have a deeper physiologic or evolutionary significance? (13) What is the equation (or equations) that describes the relationship between $\lambda_{max\text{-}A1}$ and $\lambda_{max\text{-}A2}$, especially at wavelengths <400 nm, and what are the mechanisms of spectral tuning that underlie this relationship? (14) To what extent is visual pigment spectral tuning mediated by the degree of co-planarity between the β-ionone ring and the polyene chain of the chromophore? (15) To what degree does the lower photosensitivity and increased noise of A_2-based visual pigments limit their utility? (16) Is the selective advantage of A_2 utilization mainly attributable to its effects on rod or cone vision? (17) What is the magnitude of the selective advantage that A_2 utilization confers? (18) Can we identify mutations that independently control thermal stability and spectral tuning of opsins? (19) Are thermally stabilizing opsin mutations a necessary accompaniment of A_2 utilization?

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ydbio.2021.03.002.

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