Published in final edited form as:

Prog Mol Biol Transl Sci. 2015 ; 134: 249–267. doi:10.1016/bs.pmbts.2015.06.013.

Molecular and Biochemical aspects of the retina on refraction

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Abstract

Mutant mouse models with specific visual pathway defects offer an advantage to comprehensively investigate the role of specific pathways/neurons involved in refractive development. In this review, we will focus on recent studies using mouse models that have provided insight into retinal pathways and neurotransmitters controlling refractive development. Specifically, we will examine the contributions of rod and cone photoreceptors and the ON and OFF retinal pathways to visually driven eye growth with emphasis on dopaminergic mechanisms.

1. Retina

The retina is a complex ocular structure that converts wavelengths of light into neuronal signals that become perceived visual images. The mammalian retina is composed of approximately 55 morphologically distinct cell types, each with a different function [1]. From outer to inner retina, photoreceptors and horizontal cells, bipolar cells, amacrine cells and ganglion cells constitute the major neuronal populations in the mammalian eye [2, 3] (Figure 1). While describing how the retinal neurons are interconnected and the integrated eloquence by which a visual signal is created is beyond the scope of this review, several excellent reviews are available [1, 2, 4].

The retina is required for regulating visually-driven eye growth, yet our knowledge of what visual signals and retinal pathways control eye growth is lacking. In this review, we will focus on a few key retinal cells and neurotransmitters that have been implicated in myopia, and show how investigations to explore complex signaling pathways and retinal circuits using the mouse model have provided some remarkable insights into the retinal mechanisms of refractive development.

2. Retinal input essential for ocular growth

As previously discussed [5–17], a wide range of animal studies have shown that the visual environment influences refractive development of the eye. It has been established that eye growth regulation occurs at the retinal level in response to both diffusers and defocus lenses. Previous studies have shown that severing the optic nerve in young chicks does not prevent the development of myopia in response to both negative lenses [18, 19] and diffusers [20]. Furthermore, in both chicks [21] [7] and primates [22], if partial diffusers are imposed on only half of the visual field, only that corresponding half of the eye elongates and becomes myopic. Similarly, chick eyes compensate for both negative [21, 23] and positive [23] lenses

imposed on local retinal areas using hemi-field spectacle lenses with ocular growth restricted to the defocussed parts of the visual field. These studies demonstrate retinal, and not cortical processing, is sufficient to regulate refractive eye growth.

However, there is some evidence that cortical processing may also influence eye growth. While higher order visual processing was not required for compensation to hyperopic defocus in chickens, optic nerve [20] or optic nerve and ciliary nerve sections [24] induced hyperopia in chickens with normal visual input [20, 24]. Together these findings suggest that higher order processing within the visual system may influence ocular growth, but is not a requirement for visually-driven ocular growth. Given that the visual mechanisms regulating refractive development localize principally to the retina, any defect in visual transmission through the retina could potentially influence ocular growth, and may lead to development of refractive errors.

Several studies have suggested the role of various retinal cell types/pathways and neurotransmitters in normal refractive development of the eye. In chickens, physiological and morphological changes in photoreceptors are associated with experimentally induced myopia [25]. In addition, differential eye growth under both normal and FD conditions in response to neurotoxins blocking responses from the photoreceptors [26], ON and OFF pathways [27, 28] and the inner retina [29] have been shown. Several retinal neurotransmitters such as dopamine (DA) [30, 31], glucagon [32], acetylcholine [33], nitric oxide [34, 35] and retinoic acid [36, 37] have also been implicated in defocus induced ocular growth in animals. Abnormalities in visual transmission through the retina may result from mutations in retinal neurons/pathways, changes in various retinal neurotransmitters associated with the mutation, or a combination of both factors. Whilst these experiments demonstrate the influence of the retina in normal ocular development, these experimental approaches do not ensure complete and selective blockage of a single pathway or neuronal type. Mutant mouse models with specific visual pathway defects offer an advantage to comprehensively investigate the role of specific pathways/neurons involved in refractive development. In this review, we will focus on recent studies using mouse models that have provided insight into retinal pathways and neurotransmitters controlling refractive development.

3. Mouse – a novel animal model to explore retinal mechanism of refractive development

In the recent years, there has been a growing interest in using mouse models for investigating complex signaling pathways and retinal circuitries, and their influence on ocular refractive development [38–49]. Mouse models offer the advantage of altering both genes and environment in the same animal by using various knockout models that are generated by manipulating the mouse genome, combined with altered visual input with lenses or form deprivation. Additionally, close resemblance of the mouse retinal structure to humans, short gestational period and large litter sizes make them an excellent experimental model for refractive development research. However, small eye size, absence of fovea, nocturnal behavior, poor visual acuity [50] and large depth of field [51] are some limitations

of using murine models for refractive development studies (please see review [52]). Despite these limitations, the mouse eye responds to visual form-deprivation with temporal properties and magnitude comparable with other mammalian models (see review, [52]).

Studying the effects of visual manipulations in various mouse mutants provides a unique opportunity to examine the role of gene/environment interactions in refractive development. A number of previous studies have examined the effects of a specific gene defect using various mutant mice under normal and form-deprived visual conditions [41, 42, 47, 48, 53–58]. The mouse model provides the opportunity to investigate how the gene defect and/or the associated changes in the levels of retinal neurotransmitters alter refractive development with normal visual input, as well as the influence of the gene defect on myopia susceptibility. In view of these points, probing genetic and environmental interactions is the most promising aspect of using the mouse to provide important insights into the mechanisms regulating eye growth.

4. Retinal neurotransmitters and refractive development

Before describing studies of mouse models with retinal neuron defects, it is important to acknowledge the rich diversity of neurotransmitters present in the retina that have been associated with experimentally-induced refractive errors in animal models. In order for the rate of ocular growth to change, visual stimulation of the retina must activate signaling pathways that modulate scleral growth. Evidence from pharmacological and genetic studies suggests that several signaling pathways control refractive eye growth [59–61]. For instance, the expression level of ZENK in chickens or the mammalian homologue, Egr-1, has been shown to increase or decrease with hyperopic or myopic eye growth, respectively [62, 63].

A large body of previous studies has examined muscarinic acetylcholine receptor mechanisms in refractive development of the eye. Both non-selective (such as atropine) and partially selective (such as pirenzepine) muscarinic antagonists have been shown to have inhibitory effects on experimental myopia in chickens and mammals (see review, [60, 64]). Clinically, atropine [65–67] and pirenzepine [68–70] has been used to slow myopia progression in children. In both laboratory animals and children, anti-myopia effect of atropine has been found to be independent of the drug's action on accommodation [64]. Recent results using a mutant mouse suggest that loss of the muscarinic cholinergic receptor gene, M_2 , or pharmacological blocking M_2 will provide resistance to myopia by altering the scleral collagen composition [58].

Another possible signaling pathway candidate is adenosine which is known to be regulated by light and alters collagen synthesis [56]. All adenosine receptor subtypes are expressed in the retina, choroid and sclera of the mammalian eye [71], and have been suggested to play an important role in the regulation of eye growth in both mammalian [71, 72] and human eyes [73]. The adenosine A_{2A} receptor KO mice have relative myopia compared to WT littermates and altered scleral ultrastructure [56].

Nitric oxide, a gaseous neurotransmitter synthesized by both the retina and the choroid [74] is thought to be part of the signal cascade mediating ocular growth inhibition in response to

myopic defocus [75]. Studies on chickens have shown pharmacological inhibition of nitric oxide to prevent the increase in choroidal thickness normally induced by myopic defocus, resulting in myopic eye growth [34, 35, 76]. However, some earlier chicken studies have reported inconsistent results compared to these newer studies on the effects of nitric oxide in ocular growth regulation of chickens [77, 78]. The differences in results could be due to differences in drug concentrations used by these studies. Furthermore, a transient suppression of retinal nitric oxide synthase (NOS, enzyme catalyzing the production of nitric oxide) activity was observed in guinea pigs with acute form-deprivation, whereas chronic form-deprivation (about 14–21 days) was associated with significant upregulation of NOS levels in the posterior eye [79, 80]. Other potential candidates that either inhibit (such as glucagon [32]), or promote (such as retinoic acid [36, 37]) ocular growth in response to defocus have been suggested to be part of this signaling pathway.

4.1 Role of dopamine in refractive development and myopia susceptibility

In the retina, DA is synthesized and released by a subset of amacrine-interplexiform cells, known as the dopaminergic amacrine cells [81, 82]. Dopaminergic neurons convert tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) via tyrosine hydroxylase and L-DOPA to DA via aromatic L-amino acid decarboxylase [82]. DA is released by the neuron and metabolized to DOPAC, which is the main DA metabolite in the rodent retina [83].

DA has been implicated as a stop signal in refractive eye growth [61]. In both chicken and mammalian models, form deprivation decreases DA biosynthesis [30, 84, 85], whereas DA mimetic treatment (L-DOPA or receptor agonists) prevents form deprivation myopia (see [61] for review; [30, 31, 86]). Furthermore, particular DA receptor activation may be important for refractive development signaling, as D2R have been shown to be important for the inhibitory effects of form deprivation [87, 88], lens defocus [89] and bright lighting [90, 91] in chickens. In the mammalian guinea pig model of spontaneous myopia, D1-like receptors inhibit and D2-like receptors promote myopic growth [92]. However, the loss of D2R in mice prevents the form deprivation response [55]. It should be noted that some recent reports indicate unaltered retinal dopamine activity in mice with form-deprivation [93]. Together, these results indicate that more studies are needed to elucidate how dopamine modulates refractive development and myopia. Section 3.6 will review dopaminergic modulation of myopia susceptibility in retinal mouse mutants (discussed below).

5. Retinal neurons/pathways and refractive development in mutant mice

5.1 Photoreceptor input to myopia

Since the photoreceptors form the first layer of photo-sensory neurons in the retina, it is plausible that photoreceptors are involved in mechanisms sensing defocus and/or communicating that error signal across the retina to the RPE and the choroid. In fact, studies have suggested that, in emmetropia, the focal plane is located at the photoreceptor inner segments, and both the alignment and directionality of photoreceptors are important components for retinal blur detection [25]. Over the years, morphological changes of photoreceptors (elongation of rod outer segments) [94], reduction in photoreceptor cell density [95], changes in the outer segment shedding under various lighting conditions [96,

97] and changes in electroretinogram [98] associated with experimentally induced myopia have all pointed towards the possible role of photoreceptors in refractive development of the eye.

Whilst a number of studies have suggested that cone pathways are likely to dictate the signaling needed for proper eye development, there is also some evidence for the involvement of rods in regulating ocular growth. The requirement of a high acuity retinal image (largely attributed to cone mediated signaling) for emmetropization [99]; development of myopia under dim lighting conditions (when cones are less sensitive) in chickens [100]; increased and decreased susceptibility to form-deprivation myopia in cone and rod dominated animal models, respectively [101, 102]; and reduced response to experimental myopia in chickens treated with formoguanamine, a photoreceptor neurotoxin that causes significant damage to cone outer segments, all suggest the importance of cone activity in emmetropization [26]. However, normal response to form-deprivation myopia in monkeys treated with laser ablation at the cone-rich fovea [103], and similar myopic responses in monkeys with form-deprivation imposed on the rod-dominated peripheral regions or the entire visual field [104] suggest that cone pathways may not completely dominate the signaling for mammalian eye growth, a finding further supported by the following mouse studies of experimental myopia.

5.1.1 *rd1*–/– and *rd10*–/– mice – photoreceptor degeneration models—In a recent study, Park et al [47] found that under normal visual conditions, retinal degeneration causes significantly hyperopic refractive errors and shorter axial lengths in *rd1*–/– and *rd10*–/– mice compared to wild-type (WT) mice. *Pde6b*^{rd1/rd1} (*rd1*–/–, [105–107]) and *Pde6b*^{rd10/rd10} (*rd10*–/–, [108, 109]) mice with a mutation in the *Pde6b* gene are two frequently used mouse models of photoreceptor degeneration. *Pde6b* mutation disrupts encoding of the β -subunit of cyclic nucleotide phosphodiesterase-6 [110, 111], a mutation also seen in patients with RP [112, 113].

Interestingly, with form-deprivation, both degeneration strains show faster and greater susceptibility to form-deprivation myopia than WT mice (~ 6–7 D in 2 weeks in *rd1*–/– and *rd10*–/– mice vs ~ 3 D in 4–5 weeks in *rd1*+/+ and *rd10*+/+; Figure 2) [47]. In agreement with previous studies [114, 115], dopamine (DA) levels were altered. Levels of the DA metabolite, 3,4 dihydroxyphenylacetic acid (DOPAC) and the DOPAC/DA ratios (a measure of DA turnover) were significantly lower in *rd1*–/– and *rd10*–/– mice compared to the WT mice during normal visual experience, indicating a lower DA metabolism in degenerated mouse retinas [47]. Furthermore, both degenerations models exhibited a high correlation between lower basal levels of retinal DOPAC and greater susceptibility to form-deprivation myopia (Figure 3). These results indicate that retinal degeneration by itself may not cause myopia, but may reduce DA metabolism in the retina, which may lead to an increased susceptibility to myopia under myopigenic visual environments.

5.1.2 *Gnat1*–/– mice – non-functional rod model—The importance of rod pathways in visual processing under different light conditions, and their potential role in refractive error development is demonstrated by the presence of myopia in human patients with

congenital stationary night blindness due to abnormal visual transmission between rods and ON bipolar cells [116].

Recently, Park et al [53] reported abnormal refractive development in *Gnat1*^{-/-} mice with non-functional rod photoreceptors (genetic mutation in rhodopsin-associated G protein, transducin α 1, [117]). Unlike normal refractive development in WT mice, *Gnat1*^{-/-} mice do not show a relative increase in hyperopia with age, instead the refractive curve in *Gnat1*^{-/-} mice remains stable throughout the developmental period measured from 4 to 12 weeks. Additionally, *Gnat1*^{-/-} mice are unresponsive to form-deprivation and do not develop a myopic shift (Figure 2). In this study, the authors examined retinal dopamine and DOPAC levels across age, and found significantly lower (and stable) retinal DOPAC levels in *Gnat1*^{-/-} mice compared to WT mice throughout the period of development. Furthermore, *Gnat1*^{-/-} retinas exhibit significantly greater dopamine turnover (measured from DOPAC/DA ratio) at early ages of refractive development, which rapidly decline from the second week of development [53]. These results suggest that functional rods are critical to normal refractive development and form-deprivation response in mice, and that dopamine metabolism and tonic levels of dopamine during ocular development are important predictors of susceptibility to form-deprivation myopia in murine eyes. Future studies using *Gnat2*^{-/-} mutants with non-functional cones [118] may increase our understanding of how different photoreceptors might regulate normal refractive under different ambient lighting conditions.

5.2 ON and OFF pathway contributions to myopia

Effects of ON and OFF pathways on eye development have been examined using various neurotoxins that specifically block the ON and OFF responses to light [27, 28]. In chickens, elimination of the OFF pathway using intravitreal injections of the D isomer of a Müller cell gliotoxin α amino adipic acid (D α AAA) resulted in an enhanced rate of axial elongation under normal visual conditions, but a slower ocular growth rate with form-deprivation [27]. Conversely, inhibition of the ON channel with the L isomer (L α AAA) caused a reduction in axial eye growth of normal eyes, but increased eye growth in form-deprived animals. Similar to chickens, blocking of the ON pathway with D,L-2-amino-4-phosphonobutyric (a selective ON pathway inhibitor) has been shown to cause a significant reduction in axial eye growth of cats [119]. Genetic mutations of neurons or receptor in the ON and OFF pathways in mutant mouse models represent a novel approach to investigating the role of the ON and OFF signaling in refractive development.

5.2.1 *Nyx*^{nob/nob} mice – ON pathway defect model—Pardue et al [48] examined the refractive development and dopamine levels of the *Nyx*^{nob/nob} mouse [120], which carries a null mutation in *Nyx* [121], resulting in a loss of function of the ON pathway [120]. *Nyx* encodes the protein nyctalopin, which is located on the post-synaptic side of the photoreceptor to ON bipolar cell synapse [122]. ON and OFF channels of the visual system are imperative for processing contrast sensitivity information [123, 124], an important prerequisite for a high resolution retinal image.

Under normal unmanipulated visual conditions, the loss of *Nyx* causes only slightly more hyperopic refractions in *Nyx^{nob/nob}* mice compared to WT mice [48]. However, imposing form-deprivation results in a significantly rapid myopic shift in *Nyx^{nob/nob}* mice compared to *Nyx^{wt/wt}* mice (Figure 2). Additionally, during normal visual development, dopamine and DOPAC levels were significantly lower in the *Nyx^{nob/nob}* mice in comparison with the *Nyx^{wt/wt}* mice. These results indicate that low endogenous dopamine levels or blurred visual input secondary to the ON pathway defect may increase the susceptibility to myopia development in the mouse eye.

5.2.2 *Vsx1*−/− mice – OFF pathway defect model—Chakraborty et al (2014) examined the role of OFF pathway signaling in refractive development of the eye using the *Vsx1*−/− mice on a 129S1/Sv background [125], which carry a null mutation in the visual system homeobox 1 gene, *Vsx1* [126]. The detection of *Vsx1* in the mouse retina at postnatal day 5 in the developing bipolar cell region [126], and a reduction in immunolabeling at the axonal termini of various OFF cone bipolar cells (and a few ON bipolar cells) in adult *Vsx1*−/− retinas [125, 127, 128] suggest that *Vsx1* is essential for late terminal differentiation and functioning of OFF cone bipolar cells. However, Chakraborty et al found that a selective impairment of the retinal OFF visual pathway caused by the *Vsx1* mutation does not significantly alter the normal refractive development in *Vsx1*−/− mice compared to the *Vsx1*+/+ mice, potentially due to normal visual transmission through other *Vsx1* independent ON and OFF bipolar cells in the retina [54]. Interestingly, both *Vsx1*+/+ and *Vsx1*−/− mice do not respond to imposed form-deprivation (Figure 2). Furthermore, at 4 weeks of age, 129S1/Sv mice (*Vsx1*+/+) exhibit a significantly elevated retinal dopamine turnover compared to the commonly used C57BL/6J mice, which may prevent against form-deprivation myopia in both 129S1/Sv *Vsx1*−/− and *Vsx1*+/+ mice [54]. Although, these results indicate that OFF pathway signaling may not be critically important for normal refractive development in mice, future studies with mouse mutants that express complete loss of the OFF pathway are required to investigate this further.

5.3 Amacrine and ganglion cell contributions to refractive development

There is also some evidence that the inner retina (especially the amacrine cells and the retinal ganglion cells, RGC) may play some role in refractive development of the eye. While blocking amacrine cell function using cell-specific neurotoxins, such as 6-hydroxy-dopamine (dopaminergic amacrine cells, [129]) and ethylcholine mustard aziridinium ion (cholinergic amacrine cells, [130]), does not alter refractive compensation to imposed defocus in chickens, other neurotoxins, like kainic acid [29, 131] causing a non-specific damage to the inner retina (including amacrine cells) at higher doses, lead to increased ocular growth (mostly in the posterior chamber) under normal conditions, and a reduction in myopic eye growth under form-deprived conditions. These findings warrant further investigation using amacrine cell knock out mutants [132]. Finally, blockade of retinal ganglion cell function does not prevent form-deprivation myopia in both chickens [133] and tree shrews [134], suggesting that the outer retina perhaps plays a major role in defocus detection and signaling for ocular development [25].

5.4 Dopamine modulation of myopia susceptibility in retinal mouse mutants

In addition to acute changes in dopamine with abnormal visual input, results from mutant mice also suggest that basal levels of DA turnover (as indicated by DOPAC/DA ratio) may influence susceptibility to form deprivation myopia. For example, mouse models of retinal degeneration (*rd1*^{-/-} and *rd10*^{-/-}) have decreased DOPAC and DOPAC/DA levels throughout life and increased susceptibility to form deprivation myopia [47]. Since DA is released via ON pathway stimulation [135], mutations in the ON pathway would decrease retinal DA levels. Such is the case in *Nyx*^{wt/wt} mice which have reduced DA and DOPAC levels and increased susceptibility to myopia [48]. Alternatively, mice with high levels of retinal DA and/or DOPAC have reduced susceptibility to myopia, such as *Gnat1*^{-/-} [53] and 129SV *Vsx1*^{+/+} mice [54]. Figure 3 shows the relationship between DOPAC/DA levels at 4 weeks of age and the susceptibility to subsequent form deprivation myopia. These results suggest that DA turnover during early development may “preset” the susceptibility to myopigenic stimulation. Further research is needed to determine how DA alters refractive eye growth so that therapeutic approaches can be developed.

6. Conclusions

In conclusion, the retina plays an important role in regulating visually-driven ocular growth in mammals. The mouse is an extremely useful animal model to examine retinal mechanisms controlling eye growth. Using genetic mouse mutants, genes controlling specific retinal receptors, neurotransmitters and cell types can be selectively probed to examine their role in normal refractive development, as well as under altered visual conditions.

Mutations in different retinal neurons/signaling pathways have differential effects on normal and visually-deprived refractive development of the eye. The refractive phenotypes observed in different retinal mutations may result from the mutation itself, changes in various retinal neurotransmitters associated with the mutation (such as changes in dopamine levels), or a combination of both factors. In mice, although photoreceptors are important for normal refractive development, rod pathways in particular (both functional rods and ON pathway) appear to be extremely critical for both normal refractive development as well as response to visual form deprivation. While cone pathways have previously been implicated in normal ocular refractive development, it requires further investigation using mouse mutants (with mutations in functional cones or OFF cone pathways) to determine if their role is essential.

In rodents, alterations in endogenous retinal dopamine (or DOPAC levels) associated with various mutations are important determinants of susceptibility to form deprivation myopia. It should be noted that this chapter specifically reviewed the changes in retinal dopamine levels, and their potential implications in refractive error development in mice. However, the mammalian retina is a hub for many other neurotransmitters (such as nitric oxide, glucagon, retinoic acid, vasoactive intestinal peptide, etc). Changes in other neurotransmitters with experimental myopia, and their interaction with retinal dopamine during refractive error development are yet to be explored, and beyond the scope of this chapter. Further understanding of how abnormal visual signals from the retina are transmitted downstream

through the RPE and the choroid, causing long-term changes in the sclera are important for designing therapeutic interventions for myopia control.

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Figure 1.

Retinal anatomy and circuitry. During visual processing, the output from the rod and cone photoreceptors in the outer nuclear layer (ONL) are decomposed into a number of different parallel information channels by synapsing in the outer plexiform layer (OPL) to different cells in the inner nuclear layer (INL) (bipolar, amacrine, and horizontal cells). The output from these inner retinal cells are sampled by different retinal ganglion cells in the inner plexiform layer (IPL). Finally, depending on the type of information, specific ganglion cells in the ganglion cell layer (GCL) transmit the signal to higher visual structures in the brain. R, rod; C, cone; RB, rod bipolar cell; CB, cone bipolar cell; H, horizontal cell; A, amacrine cell; AII, AII amacrine cell; DAC, dopaminergic amacrine cell, As, astrocyte; G, ganglion cell; M, microglia. Image modified from <http://webvision.med.utah.edu/book/partvi-development-of-cell-types-and-synaptic-connections-in-the-retina> and <http://webvision.med.utah.edu/book/part-xii-cell-biology-of-retinal-degenerations> with permission, made available through Creative Commons.

Figure 2.

Myopic shift (goggled-opposite eye) across several mutant mouse strains with photoreceptor or ON/OFF retinal pathway defects after 2 weeks of form deprivation. Note that the mutant mice are on different background strains and thus, the WT controls are shown for each strain. *Rd1*^{-/-} mice and *Nyx*^{nob/nob} mice show significantly greater myopic shift than their WT controls. In contrast, *Gnat1*^{-/-} mice with non-functional rods did not show a shift with form deprivation myopia. *Vsx1*^{+/+} mice are on a 129SV background and do not respond to form deprivation. The loss of *Vsx1* did not change the susceptibility to form deprivation myopia.

Figure 3.

Myopic shift after 2 weeks of form deprivation in several different mutant strains with retinal defects plotted against the DOPAC/DA ratio at 4 weeks of age when the form deprivation was initiated. These results suggest that DA turnover at the time of goggling may influence the susceptibility to form deprivation myopia.