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Dopamine Signaling and Myopia Development: What Are the Key Challenges

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Abstract

In the face of an “epidemic” increase in myopia over the last decades and myopia prevalence predicted to reach 2.5 billion people by the end of this decade, there is an urgent need to develop effective and safe therapeutic interventions to slow down this “myopia booming” and prevent myopia-related complications and vision loss. Dopamine (DA) is an important neurotransmitter in the retina and mediates diverse functions including development, visual signaling, and refractive development. Inspired by the convergence of epidemiological and animal studies in support of the inverse relationship between outdoor activity and risk of developing myopia and by the close biological relationship between light exposure and dopamine release/signaling, we felt it is timely and important to critically review the role of DA in myopia development. This review will revisit several key points of evidence for and against DA mediating light control of myopia: 1) the causal role of extracellular retinal DA levels, 2) the mechanism and action of dopamine D1 and D2 receptors and 3) the roles of cellular/circuit retinal pathways. We examine the experiments that show causation by altering DA, DA receptors and visual pathways using pharmacological, transgenic, or visual environment approaches. Furthermore, we critically evaluate the safety issues of a DA-based treatment strategy and some approaches to address these issues. The review identifies the key questions and challenges in translating basic knowledge on DA signaling and myopia from animal studies into effective pharmacological treatments for myopia in children.

Keywords

myopia; dopamine; D2 receptor; D1 receptor; apomorphine

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1. Introduction

Over the last decades, we are witnessing an “epidemic” increase in myopia: 90%–95% of teenagers and young adults are myopic in China and Seoul; and about half of the young adults in the United States and Europe are also affected by myopia. It is projected that myopia will affect one-third of the world’s population — 2.5 billion people by the end of this decade (Dolgin, 2015). Thus, there is an urgent need to develop effective and safe therapeutic interventions to slow down this “myopia booming”.

As reported at the 15th International Myopia Conference (IMC 2015, Wenzhou, China) and in the literature, there is a convergence of epidemiological and animal studies in support of the inverse relationship between bright light exposure and risk of developing myopia (for example, (Jones et al., 2007; Rose et al., 2008)). There is a critical need to understand the biological mechanism for this relationship in order to recommend the most effective interventions. Dopamine (DA) is an important neurotransmitter in the retina that mediates diverse functions including development, visual signaling, and refractive development (Witkovsky, 2004).

Since the first publication for a link between DA and the control of eye growth in 1989 (Stone et al., 1989), a growing body of work (with total ~100 publications so far) has led to the DA hypothesis (i.e. the release of DA in the retina to antagonize myopia development) as the leading hypothesis of myopia control (Stone et al., 1989). Furthermore, the light hypothesis, i.e. light-stimulated DA antagonizes myopia development (Rose et al., 2008) has been supported by a number of studies that show outdoor activity and/or bright light inhibits myopia, potentially through DA-mediated mechanisms (Ashby et al., 2009; Chen et al., 2017; Cohen et al., 2011; Cohen et al., 2012; Li et al., 2014; Morgan et al., 2012; Smith et al., 2012; Wang et al., 2015; Wu et al., 2013). The evidence from pharmacological and genetic studies has provided more details regarding how light or visual input controls retinal DA signaling and contributes to refractive development (for a recent review, see (Feldkaemper and Schaeffel, 2013)).

There is increasing recognition of the urgent need for effective pharmacological treatments that are deeply rooted in mechanistic understanding of the biological effect of DA and other neuromodulators. Extensive studies have investigated DA pharmacological effects on myopia from mammals and non-mammal models of myopia, supporting the critical role of DA in mediating control of myopia development. However, DA pharmocology studies of myopia development are limited by their partial specificity that likely contribute to some discrepancies of pharmacology in these various species used in myopia research. Furthermore, since DA receptors are expressed in various cell types and different vision pathways, DA receptors in these various sites may produce distinct/different effects on myopia development. In this review we seek to identify several key conceptual questions and challenges, with particular focus and insights from mouse model of myopia and related genetic and other molecular approaches. Though the disadvantages of the mouse model is also conspicuous because of its small eye size and the differences in ocular anatomy when compared to human, for example, the poor visual acuity and the lack of accommodation and fovea in mouse eye, this focus allows us to overcome these intrinsic limitations of DA

pharmacology with the availability of different types of transgenic mice with targeted manipulation of vision pathways or DA signaling proteins. After reviewing the multiple lines of the evidence for the role of DA in mediating light control of myopia and the associated cellular and receptor mechanisms, we review the experiments in which DA, DA receptors and vision pathways have been altered using pharmacological, genetic, or visual environment approaches to show causation. Furthermore, we critically evaluate the safety issues of a DA-based treatment strategy and some approaches to address these issues. By revisiting several key conceptual questions with the evidence for and against these key points, we identify the key challenges ahead in order to create ground-breaking knowledge on myopia development and treatment.

2. Effects of altered DA levels on myopic eye growth

2.1 DA synthesis, release and metabolism

Retinal DA is synthesized in and released by subtypes of amacrine and interplexiform cells (e.g., (Dowling and Ehinger, 1978a, b; Frederick et al., 1982)). Dopamine is synthesized from the amino acid tyrosine in two steps: (1) L-tyrosine is converted to 3,4-dihydroxy-L-phenylalanine (L-DOPA) by tyrosine hydroxylase (TH); and (2) conversion of L-DOPA to DA by DOPA decarboxylase. Tyrosine hydroxylation is the rate-limiting and highly-regulated step in the synthesis of DA. Newly synthesized DA is transported into synaptic vesicles by the vesicular monoamine transporter VMAT2. Light stimulates the synthesis and release of DA, with a concomitant activation of TH that maintains steady-state stores of DA under conditions of enhanced neuronal activity (Iuvone et al., 1978; Kramer, 1971). When released, DA acts on postsynaptic and presynaptic receptors. DA also diffuses away from the synapse to act on extrasynaptic DA receptors by a process referred to as volume transmission (Bjelke et al., 1996). DA released at synapses is transported back into the DA neurons by the specific dopamine transporter (DAT) (Mitsuma et al., 1998). Inside the cell it may be repackaged in synaptic vesicles or metabolized by monoamine oxidase to form 3,4-dihydroxyphenylacetic acid (DOPAC), the primary metabolite of DA in the retina (Cohen et al., 1983). Under most conditions, changes in the level of DOPAC in the retina and vitreous are thought to reflect DA release and turnover (Megaw et al., 2001; Ohngemach et al., 1997). DOPAC may be further metabolized extra-neuronally to homovanillic acid (HVA) by catechol-O-methyltransferase (Meiser et al., 2013).

2.2 Studies implicating a role for DA in myopia

Data from several experiments across different species suggest that DA acts as a “stop” signal in refractive eye growth (Feldkaemper and Schaeffel, 2013). This is based on HPLC results of retinal or vitreal DA and/or DOPAC that show reduced levels in response to form deprivation in primates, chickens, and guinea pigs, (Dong et al., 2011b; Iuvone et al., 1989; McBrien and Gentle, 2001; Papastergiou et al., 1998; Stone et al., 1989) or negative lens defocus in chickens (Guo et al., 1995; Ohngemach et al., 1997). With partial form deprivation, retinal DOPAC is decreased locally only in the half of the retina that has been deprived (Ohngemach et al., 1997; Stone et al., 2006) and returns to normal after removal of the diffusers in chickens (Pendrak et al., 1997). Retinal DA levels after form deprivation myopia (FDM) are apparently not altered in wild-type mice (Chakraborty et al., 2015b; Park

et al., 2014; Wu et al., 2015), indicating a unique emmetropization process or subtle change of DA in mice. Nonetheless, most studies from multiple species support an association between retinal DA alteration and myopia.

2.3 Effects of altered DA levels on myopic eye growth

If DA levels and/or signaling are decreased during myopic eye growth, then increasing DA level or DA receptor activity would be predicted to prevent myopia. The first step in proving this hypothesis is to increase the overall availability of DA by injecting DA directly into the eye or using L-DOPA to increase DA synthesis. Such experiments have shown that increasing DA levels prevents FDM in guinea pigs (Mao et al., 2010), rabbits (Gao et al., 2006) and mice (Landis et al., 2016). Another approach is to increase DA signaling with a non-selective DA receptor agonists, such as apomorphine (APO) and 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide (ADTN). A large number of studies show that treating with APO prevents FDM in several species, including chicken (Rohrer et al., 1993; Schmid and Wildsoet, 2004; Stone et al., 1989), guinea pig (Dong et al., 2011b), monkey (Iuvone et al., 1991) and mice (Yan et al., 2015b). Similarly, ADTN inhibits FDM in chicken (Ashby et al., 2007; McCarthy et al., 2007). Notably, the inhibitory effect of APO on refraction is robust and consistent for FDM, but less consistent for negative lens-induced myopia (Dong et al., 2011b; Schmid and Wildsoet, 2004). Furthermore, treating mice with daily injections of APO inhibits FD, while continuous infusion of APO with a mini-pump produced no effect (Yan et al., 2015b). This may be due to differences in drug concentrations and their affinities for the different DA receptors, or downregulation of DA receptors resulting from continuous occupation with minipump infusion. Additionally, APO and exogenous L-DOPA have no effect on refractive development when visual input is normal (Dong et al., 2011a; Mao et al., 2010; Rohrer et al., 1993; Yan et al., 2015a). Together these studies suggest that DA receptor activation is needed for normal refractive eye growth under challenging/abnormal visual conditions (FD or lens defocus) and that increasing DA levels in the eye can prevent myopic growth signals.

If DA receptor activation is needed for normal visually-driven eye growth, then decreased levels of DA would be predicted to cause myopia in eyes with normal visual input and potentially increase the susceptibility to FD or lens defocus. Pharmacologically, DA can be reduced using 6-hydroxydopamine (6-OHDA) which is toxic to dopaminergic neurons or reserpine which depletes catecholamines from sympathetic nerve endings. However, pharmacological depletion of DA has produced less consistent results, likely due to the complex actions of these pharmacological actions. Contradictory to the hypothesis, treatment with 6-OHDA and reserpine prevents (rather than facilitates) development of FDM in chickens by reducing axial eye growth (Li et al., 1992; Schaeffel et al., 1995). Interestingly, 6-OHDA has no effect in lens-induced myopia in chickens (Schaeffel et al., 1994) or fish (Kroger et al., 1999), suggesting potentially different roles for DA with these different types of visual disruptions (Schaeffel et al., 1995). This apparently paradoxical effect might be due to the non-selective depletion of catecholamines with 6-OHDA, including DA as well as norepinephrine (Jiang et al., 2014a). There are also examples of decreased DA due to genetic defects. For example, in albino guinea pigs with defective tyrosine metabolism (Hansson et al., 1980), serum DOPA levels are markedly reduced,

which may lead to spontaneous myopia and the altered response to FDM (Jiang et al., 2011; Jiang et al., 2014b). Additionally, administration of 6-OHDA in wild-type mice results in relative myopic refractive errors under normal visual conditions and enhanced FDM response (Wu et al., 2016). A recent report shows that retinal-specific TH knockout mice show spontaneous myopia with shorter axial lengths and a normal response to FD (Bergen et al., 2016), even though retinal DA levels are unaltered with FD (Bergen et al., 2016). These results suggest that modulation of visually-driven eye growth is not simply due to the level of retinal DA.

2.4 Altering DA signaling with light stimulation

Light stimulation is known to increase the release of dopamine in a linear fashion over four log units of light intensity (Cohen et al., 2012; Proll et al., 1982). Inspired by recent epidemiological studies showing the inverse relationship between the outdoor activity and development of myopia, an area of intense interest is the protective effect of bright light on myopia development, possibly via dopamine signaling (Karouta and Ashby, 2015). Children that spend more time outside have delayed myopia onset (Guggenheim et al., 2012; Rose et al., 2008; Sherwin et al., 2012). This is due to bright light, not activity or other factors (Read et al., 2014; Rose et al., 2008). Further evidence of the protective effects of bright light have been shown in a number of experiments with animal models. Using chickens (Ashby et al., 2009; Ashby and Schaeffel, 2010; Ashby et al., 2014; Backhouse et al., 2013; Lan et al., 2014), primates (Smith et al., 2012), and tree shrews (Norton and Siegwart, 2013), bright light has been reported to decrease the myopic shift induced by FD or lens defocus (Ashby and Schaeffel, 2010). These protective effects have been attributed to increased retinal DA levels and DA receptor activation as the DA D_2-like receptor antagonist, spiperone blocks the protective effects of bright light (Ashby and Schaeffel, 2010). The release of DA is regulated by light intensity and image contrast, both of which are detected by photoreceptors and have been implicated in myopia development. Thus, exposure to bright light may be an environmental intervention to control myopia development by increasing DA levels in the retina. Meanwhile, APO and D2R agonist quinpirole inhibited ocular growth induced by negative lens with transient increases in choroid thickness which is similar to the effect of daily brief periods of unrestricted vision (Nickla et al., 2010). These results indicate that DA may mediate the myopia inhibition effect of visual stimulus like bright light or unrestricted vision. The retinal DA may induce choroidal thickening and ocular growth inhibition by triggerring the release of other transmitters like nitric oxide (NO) from either the retina or choroid (Nickla et al., 2009; Nickla and Wildsoet, 2004; Sekaran et al., 2005).

Importantly, two randomized, control trials reported that extending outdoor exposure time led to significant declines from 23% to 50% in the onset of myopia incidence. However, these studies also revealed modest inhibition of myopia progression from 0.06 to 0.13 D/year in elementary school children by extending outdoor expsoure time (He et al., 2015; Wu et al., 2013). Another meta-analysis included 7 cross-sectional studies reported a 2% reduced odds of myopia per additional hour of time spent outdoors per week (Sherwin et al., 2012). Furthermore, the animal studies showing that bright light reduced myopia were done under standard laboratory conditions with non-fluctuating luminance and chromaticity that does not mimic the real-world, natural environment as the luminance in the natural

environment varied considerably based on time of day and cloud cover, as does chromaticity, contributing to variable effects of outdoor exposure of light on the development of FDM in chicks (Ashby et al., 2009; Stone et al., 2016). These observations suggest that a pharmacological approach to the treatment of myopia may be more efficacious than an environmental intervention.

3. Role of D_1-like and D_2-like receptors in myopia development

3.1 DA receptors

DA receptors are G-protein coupled receptors (Table 1). Consistent with volume transmission of DA, DA receptors are found on almost all neuronal classes within the retina. The retina expresses 4 of the 5 DA receptor subtypes: D_1R, D_2R, D_4R, and D_5R (Table 1; (Jackson et al., 2009)). D_1 and D_5 receptors stimulate the synthesis of the intracellular second messenger cyclic AMP, while D_2 and D_4 receptors inhibit its formation (Beaulieu and Gainetdinov, 2011). DA receptors have been associated with other intracellular signaling pathways as well. The next step in evaluating the involvement of DA signaling in refractive eye growth is to determine which DA receptors are involved. Using pharmacological manipulations, the influence of the activation or inhibition of specific DA receptors have been tested on refractive development under normal, FD or lens defocused conditions. One caveat of these pharmacological approaches is that they don't target specific DA receptor subtypes, but instead they act on the families of DA receptors (D_1-like and D_2-like), which makes it difficult to make definitive conclusions about how DA signals visually-driven eye growth.

3.2 Effects of D_2-like receptor agonists and antagonists on myopia

Of the studies reported in the literature, most have focused on: (1) examining the effects of D_1-like and D_2-like receptor agonists on development of myopia (e.g., (Stone et al., 1989)); (2) use of antagonists to manipulate the effects of a DA agonist on development of myopia (APO; (Rohrer et al., 1993; Stone et al., 1989)); or the ability of DA antagonists to prevent the effect brief periods of normal vision, which inhibit development of FDM (McCarthy et al., 2007; Nickla and Totonelly, 2011; Schmid et al., 2013). In general, these studies show that activation of D_2-like receptors by subconjunctival or intravitreal agonist injection mimics the protective effect of periods of unobstructed vision on FDM (McCarthy et al., 2007; Nickla and Totonelly, 2011; Schmid et al., 2013), while intravitreal injection of D_2-like antagonists inhibits the protective effect of periods of unobstructed vision on FDM (Rohrer et al., 1993; Stone et al., 1989). Furthermore, co-administration of APO and a D_2R antagonist abolishes the inhibitory effect of APO on myopia (Rohrer et al., 1993). It is interesting to note that D_2R antagonists are not sufficient to induce myopia (Huang et al., 2014) but they facilitate myopia development induced by FDM (Schaeffel et al., 1995; Stone et al., 1989). On the other hand, systemic injection of D_2 antagonists produced different effects than intravitreal injection of the drugs, indicating possible systemic effects or different DA concentrations that may contribute to this discrepancy (Huang et al., 2014). Further supporting this possibility that DA concentrations are important, D_2R agonists have been found to inhibit FDM at low doses and enhance FDM at high doses (Zhou, unpublished data; Table 2). Also, like systemic injection of D_2R antagonists, global genetic deletion of

D_2Rs in mice inhibits FDM development (Huang et al., 2014), indicating a possible developmental compensation effect of D2Rs (Table 2). It will be important to determine in future studies if D_2R knockout mice have altered DA levels and/or altered spatial frequency resolution that would influence their response to FD.

D4R is a D2-like receptor with a highly enriched expression pattern in retina. D4R agonists systemically injected into C57BL/6 mice for 4 weeks had no effect on normal refractive development, but increased the response to form deprivation (Zhou, unpublished data). In contrast, D_4R antagonists produced a hyperopic trend in C57BL/6 mice under normal visual conditions and inhibited FDM (Zhou, unpublished data). In future work, it is important to determine whether the D_4R recapitulate/contribute to the D2R-like drug effects.

3.3 Contribution of D_1-like receptors on myopia

The role of D_1R in development of myopia is less clear. Effects of D1-like antagonists have been contradictory. Some studies show D1-like antagonists to either have no effect on the protective effects of normal vision (McCarthy et al., 2007; Nickla and Totonelly, 2011) or on the protective effects of APO on FDM (Rohrer et al., 1993). Other studies have shown D1-like antagonists to abolish the ameliorating effects of periods of unobstructed vision on lens-induced myopia (Nickla et al., 2010) and to block the development of FDM in chickens (Schaeffel et al., 1995). Preliminary studies in C57BL/6 mice indicate that D1R-like agonists inhibit FDM while D1R-like antagonists enhance FDM (Zhou et al., 2014). Further studies are needed to address these apparent paradoxical protective effects of D1R agonists and antagonists and determine the exact role of D1R signaling cascades in control of visual growth and myopia development.

3.4 Working hypothesis for DA receptor contributions on myopia development

Collectively, these results suggest that D2-like (D2 and D4) receptors may play a larger role in DA signaling control of refractive eye growth than D1-like receptors in chicks. Based on the results from mouse models, a working hypothesis of homeostatic control of myopia has been proposed in which activation of D1-like receptors leads to hyperopia and activation of D2-like receptors leads to myopia (Figure 1).

Dopamine is involved in both FDM and LIM, as both suppress the metabolism and release of DA in chicken (Guo et al., 1995; Papastergiou et al., 1998; Stone et al., 1989), and the axial elongation in FDM and LIM can both be blocked by DA agonists (Feldkaemper and Schaeffel, 2013). However, the DA drugs have also been shown to modulate refractive eye growth differently depending on the type of myopia that is being induced. For example, In guinea pigs, FD (but not negative len wearing) decreased DA, DOPAC and DOPAC/DA ratios with myopia development (Dong et al., 2011b). This difference may be attributed to the different mechanism or to the unmatched blurriness or the temporal course between FD and negative defocus. Pharmacological studies further support differential mechanisms between FDM and LIM: APO inhibits FD, but not hyperopic defocus in guinea pigs (Dong et al., 2011b). 6-OHDA blocks FDM in chickens, but has no effect on LIM (Schaeffel et al., 1995). To further support this notion, Nickla & Totonelly (Nickla and Totonelly, 2011) have shown that D_2-like antagonists inhibit the protective effects of brief periods of unrestricted

vision on FDM, but not on negative lens-induced myopia. These results suggest that DA may have a greater contribution to inhibition of myopia induced by FD versus lens defocus.

Notably, some discrepancies on the DA pharmacological effects on myopia have been reported. For examples, both DA activation (the non-specific DA receptor agonist apomorphine) and DA depletion with 6-OHDA and reserpine) have been shown to suppress myopia development in chickens (Stone, R. A et al., 1989; Schaeffel et al. 1995; Diether and Schaeffel, 1999). Also, D1 receptor agonists can have no effect in chickens or suppressive effects in guinea pigs (McCarthy, C. S et al., 2007;Nickla et al, 2010; Jiang et al 2012;). Similarly, D2 receptor antagonists can reverse apomorphine-induced suppression of myopia (Cottrial et al, 2001; Rohrer et al, 1993) or have no effect on myopia development (Arumugam and McBrien, 2010; McCarthy et al., 2007, Cottriall et al., 2001). These mixed results may reflect the complexity and intrinsic limitation of DA pharmacology. However, even if difference exist in the mechanisms by which DA inhibits myopia, the fact that DA impacts refractive development in both mammalian and non-mammalian species emphasizes the evolutionary conservation of this neuromodulator's role in refractive development.

In addition to the species differences, there are several possible explanations for these inconsistencies: including i) the difficulty in assessing the exact drug concentrations in retina and sclera after intra-vitreal injection versus systemic administration of dopamine agonists and antagonists; ii) lack of the comparative studies on the cellular distribution of D1 and D2 receptor in retina (versus sclera) among various species during ontogeny and myopia development. iii) based in part on recent finding from mouse model of myopia, we suggest that differential activation of dopamine receptors in distinct vision pathways (despite similar expression levels) and neural circuits (Chen et al., 2017), may also contribute to different functional outcomes. Coupled with cellular biomarkers and molecular approaches, insights from mouse genetic manipulation would provide complementary and fresh view for some of the long-held views on myopia development.

4. DA signaling and visual pathway interactions in myopia

4.1 Signaling of dopaminergic neurons in the retina

While DA levels and DA receptors play key roles in modulating visual function and refractive development, the action site of dopamine signaling in retina to control myopia is largely undefined. DA signaling is regulated by visual input and several retinal circuits provide input into the dopaminergic amacrine cells and interplexiform cells that synthesize and release DA (Dowling and Ehinger, 1978a, b; Frederick et al., 1982). These retinal dopaminergic amacrines have cell bodies at the border of the inner nuclear layer (INL) and inner plexiform layer (IPL), and long, ramifying dendrites and axons in sublamina 1 of the IPL. DA neurons in species like fish and new world monkeys have processes that ascend through the INL to the outer plexiform layer; hence the term 'interplexiform cell' (Ehinger and Falck, 1969). Processes of dopaminergic amacrines in the IPL intercalate with dendrites of intrinsically photosensitive retinal ganglion cells (ipRGCs) (Prigge et al., 2016b) and form rings around AII amacrine cells (Debertin et al., 2015). The retinal DA neurons receive excitatory input via ectopic synapses with ON bipolar cells in the OFF sublamina of the IPL (Dumitrescu et al., 2009a). They also receive inhibitory input from GABAergic and

glycinergic amacrine cells (Qiao et al., 2016). Dopamine signaling may interact with the visual pathways by two possible mechanisms to modulate visually-driven eye growth: a) dopamine may act on the DA receptors in specific visual pathways and influence the pathways' functions or b) visual pathway activity may influence myopia development by altering DA release and signaling. By acting on DA receptors expressed in different visual pathways, dopamine may modulate ON pathways (Farshi et al., 2016; Smith et al., 2015), OFF pathways (Maguire and Werblin, 1994; Yang et al., 2013), rod pathways (Herrmann et al., 2011) and retinal gap junctions (Bu et al., 2014; Kothmann et al., 2009; Zhang et al., 2011a), contributing to control of myopia development (Chakraborty et al., 2014; Chakraborty et al., 2015c; Park et al., 2014). Alternatively, visual inputs such as bright light and flickering light, stimulate ON pathway and ipRGC and alter dopamine synthesis and release (Contini et al., 2010; Dumitrescu et al., 2009b; Prigge et al., 2016a).

4.2 Primary or secondary effects of DA pharmacological treatments on myopia

The rate-limiting enzyme for DA synthesis, TH, is detected in dopaminergic amacrine cells, but D1-like and D2-like DA receptors are widely distributed at various cell types (including photoreceptors and retinal pigment epithelium cells for D2-like receptors, and bipolar, horizontal, amacrine and ganglion cells for D1-like receptor) (Witkovsky, 2004). It is not clear which visual pathways are specifically affected by DA pharmacological treatment. Consequently, it is unknown if the pharmacological treatments described above directly alter refractive eye growth mechanisms or if they produce secondary effects by altering visual function and/or retinal pathways that are important for myopic eye growth. Recent evidence shows that DA receptors are involved in specific aspects of visual function: D1Rs are important for spatial frequency thresholds and D4Rs are specific to contrast sensitivity thresholds and light adaptation (Jackson et al., 2012). Future studies are critically needed to define the specific visual input whereby DA signaling exerts its actions to control myopia development. For instance, experiments using retina- and cell-type-specific knockout mice or models with over-expression of D1Rs and D2Rs are needed to verify whether the effect of DA is local or systemic, and to define the cellular basis of DA action.

4.3 Retinal pathway defects alter myopia development and DA levels

It has been well-established that photic activation of retinal neurons and/or retinal circuits leads to changes in retinal dopamine release. Activation of rods, cones and ipRGCs excite dopaminergic amacrine cells, which in turn increases retinal dopamine content and turnover (Qiao et al., 2016; Zhang et al., 2008). DA is also released in response to ON bipolar cell stimulation (Boatright et al., 1994; Boelen et al., 1998; Dumitrescu et al., 2009b). Genetic-targeting of these retinal pathways in mouse models results in changes in DA and DOPAC levels, as well as refractive development and the response to FD. For instance, mice with ON pathway mutations have reduced retinal DA and DOPAC levels, developed greater myopic refractions in normal visual environment, and became more susceptible to FDM (Chakraborty et al., 2015b; Pardue et al., 2008). The exaggerated response to FDM may be due to the lower DA and DOPAC or the loss of ON pathway stimulation of another signaling pathway necessary for the response to FD. In addition, mice with mutations that cause photoreceptor degeneration have reduced DA and DOPAC and normal to hyperopic

refractions during normal development with increased susceptibility to FD (Park et al., 2013). In contrast, mice with inactive rod photoreceptors also have reduced retinal DOPAC levels and DOPAC/DA ratios, but they do not have a normal pattern of refractive development across age compared to wild-type controls and do not respond to FD (Park et al., 2014). ipRGCs are a subclass of retinal ganglion cells (RGCs) that function as classical RGCs with input from the photoreceptor-driven bipolar cells, or by directly responding to light (Schmidt and Kofuji, 2011). ipRGCs control the pupillary light response and suprachiasmatic nucleus (SCN), where they entrain the biological circadian clock (Schmidt and Kofuji, 2011). In addition, ipRGCs influence retinal processes (Barnard et al., 2006) through retrograde signaling, in part through dopamine signaling (Prigge et al., 2016a; Zhang et al., 2008); but see (Cameron et al., 2009). Recent evidence also suggests that ipRGCs are involved in refractive development and FDM. Mice with targeted disruption of the Opn4 gene, which encodes melanopsin (the photopigment protein in ipRGCs), have altered refractive development and increased susceptibility to FD, implicating the involvement of ipRCSs in development of myopia (Chakraborty et al., 2015a). These findings indicate that visual stimulation through multiple pathways may alter DA signaling and DA receptors to modify refractive development. In fact, a comparison of the DA turnover in several different mouse models with retinal pathway defects shows that lower DOPAC/DA ratios at the age of FD induction results in greater susceptibility to FDM (Figure 2; (Chakraborty et al., 2015b)). These results suggest that reducing DA levels through altered visual signaling may not result in spontaneous myopia, but can alter the susceptibility to myopia. This raises an important question: do children at risk for myopia development have low DA turnover that doesn’t alter retinal function, but affects refractive development?

5. DA signaling and myopia: therapeutic strategies and clinical implications

Given the critical need for effective and safe pharmacological treatments to prevent myopia progression, one of the key questions is whether there is sufficient preclinical and clinical data on the efficacy and safety of DA-based strategies for prevention and treatment of myopia. As described above, increasing preclinical data supports the ability of DA agonists (particularly APO and D2R agonists) to inhibit FDM. It is important to note DA agonists (such as APO) can induce selective inhibition of FDM without affecting normal visual growth in mice (Yan et al., 2015b). Additionally, the effects of L-DOPA on amblyopic vision in three clinical trials were reported (Leguire et al., 1992; Leguire et al., 1993a; Leguire et al., 1993b). Some early studies (Leguire et al., 1993a; Leguire et al., 1993b), but not others (Leguire et al., 1998), showed that L-DOPA can enhance the effect of dominant eye occlusion in treatment of amblyopia. However, a recent study with well-designed controls by the Pediatric Eye Disease Investigator Group supported by the National Eye Institute found no enhancement by L-DOPA of the effect of dominant eye occlusion therapy (Pediatric Eye Disease Investigator et al., 2015). Additional studies with L-DOPA in large numbers of children with myopia are required to demonstrate its effectiveness for prevention and treatment of myopia.

5.1 Potential negative side effects of dopaminergic therapies

From the perspective of developing DA based therapeutic strategies, what are the potential toxicological ramifications of treating children with dopaminergic agents? DA is the major neurotransmitter in the brain and retina and is also an important physiological regulator of cardiovascular, endocrine and immunological functions. In the developing brain, over-activation of the DA system has been shown to produce schizophrenia-like behavioral changes (Angrist, 1994). Consistent with these preclinical studies, some mild side effects were noted in a L-DOPA clinical trial in a small number of myopic children, including nausea, headache, fatigue, mood changes, emesis, dizziness, dry mouth, decreased appetite, and night mares; the use of carbidopa, a peripheral dopa decarboxylase inhibitor, in combination with L-DOPA reduced the side effects (Angrist, 1994; Repka et al., 2010). Moreover, in developing children treated with stimulants for attention deficit disorder (ADD)/attention deficit hyperactivity disorders (ADHD) that work by increasing extracellular dopamine levels in the brain (including Ritalin, Adderall, and Dexedrine), common side effects include feeling restless and jittery, difficulty sleeping, loss of appetite, headaches, upset stomach, irritability, mood swings, depression, dizziness, racing heartbeat, and tics (Jeffers et al., 2013; Salardini et al., 2016). The American Heart Association recommends that all individuals, including children, have a cardiac evaluation prior to starting a stimulant (Thomas et al., 2011). Moreover, the long-term impact of ADD/ADHD medication on the youthful, developing brain is not yet known. These studies indicate that more research and potentially novel pharmacological targeting is needed to avoid the negative side effects of systemic activation of DA signaling.

5.2 DA receptor agonists as a treatment option for myopia

A DA receptor agonist may provide a therapeutic option with less side effects. DA receptor agonists are currently FDA-approved to treat various diseases, including Parkinson’s disease, restless leg syndrome and diabetes mellitus. However, the use of DA agonists during critical periods of development may be detrimental. DA receptors have profound effects on glucose metabolism (Lopez Vicchi et al., 2016). Recent studies show that the dopamine D2R agonist bromocriptine, and the D1R agonist SKF38393 produce improvements in obesity, hyperglycemia (improved glucose metabolism) and hyperinsulinemia in obese (ob/ob) mice (Cincotta et al., 1997).eye growth may be associated with the energy consumption and vitreal glucose level (Feldkaemper et al 2000, IOVS). D2R knockout mice develop features of Parkinson disease (Tinsley et al., 2009), prolactinoma (Cristina et al., 2006), chronic pituitary hyperplasia (Cristina et al., 2006) and a moderate decrease in MSH content (Kelly et al., 1997). Thus, extensive studies on possible side effects of DA on visual and systemic functions are necessary before DA agonists could be considered as an anti-myopic drug in children.

5.3 Local delivery of DA therapies to the eye

From a therapeutic perspective, local administration of APO and DA by eye drops may achieve therapeutic effects on myopia, with reduced systemic side effects. Using animal models, we need to study the effect of local application of DA agonists (with a wide range of doses) on refractive errors and retinal functions. Furthermore, given the wide-spread effects

of DA in eye, brain and throughout the body, it is not sufficient to demonstrate only an anti-myopia effect of DA treatment. We also need to determine any potential effects on growth (endocrinology), psychiatric behaviors, blood pressure, etc. To our knowledge, only one study has examined the effects of APO eye drops; this study showed that local application reduced the development of deprivation-induced myopia in infant rhesus monkeys (Iuvone et al., 1991). While only a single dose was tested, the approach showed promise and there were no indications of systemic toxicity, or alterations in weight gain, general health, or development. Further studies are also needed to identify myopia-specific DA signaling for therapeutic intervention by characterizing DA signaling systems during FDM (receptor numbers, affinity, DA autoreceptor, sensitivity to DA drugs, cell-types, interaction with other neuromodulators, and the developmental time window).

6. Challenges in understanding the role of DA signaling in myopia

DA has been proposed as a stop signal for myopia eye growth for over 25 years, and recently emerged as a likely target for myopia therapy. It is clear from many studies that DA has an anti-myopigenic effect. However, the exact mechanism of action and the potential interaction with retinal pathways has remained elusive. Several key questions in the role of DA signaling in development of myopia remain to be addressed:

6.1 Does DA signaling represent a “stop” signal for control of axial eye growth or an adaptive or compensatory response as a result of refractive changes?

A related question is *whether DA signaling in the retina affects initiation versus progression of myopia development*. Recent epidemiological studies indicate that outdoor activity (with increasing light exposure) affects mainly the onset of myopia but not the progression of myopia development in children, indicating a possible effect of DA signaling on initiation of myopia (Guo et al., 2013; He et al., 2015; Jin et al., 2015). Data from mouse models with retinal pathway defects that result in decreased dopamine turnover and increased myopia susceptibility would also support the hypothesis that DA release alters myopia induction (Figure 2). Evidence in support of DA as an adaptive response includes the relatively slow response of DA to changes in visual input. In chicken retina, visual deprivation did not reduce vitreal DOPAC level immediately (within 30 minute) but reduced sustained DA release during the light phase (Megaw et al., 1997). Thus, DA release may be an adaptive response to low temporal and spatial contrast. Clarification of this question with direct measurement of the extracellular DA concentration is critical to our understanding of the role of DA in myopia development.

6.2 Is visually-driven myopia a fundamentally different process from the normal (developmental) growth of eye/vision?

In the retinal-specific TH knockout mice with selective depletion of DA in the retina from birth, animals develop spontaneous myopia but do not show an altered response to FD (Bergen et al., 2016). Furthermore, APO inhibits deprivation myopia in mice, but had no effect on axial growth of eyes with normal vision (Yan et al., 2015b). Thus, myopia that arises with normal visual input may be different than that induced with FD. Myopia development with excessive growth may differ from normal developmental growth due to

upregulation of DA receptor numbers or an increase in DA receptor affinity for exogenous DA. Further studies are needed to better characterize DA signaling systems during FDM to identify “myopia-specific” DA signaling for therapeutic intervention.

6.3 Does DA exert homeostatic regulation of visual growth by distinct effects of D1-like and D2-like receptors?

The homeostatic regulation of visual growth by DA receptor subtypes is not clear. Non-specific DA receptor agonists (L-DOPA and APO) produce more consistent and effective inhibition of myopia development than D1-like and D2-like DA agonists, suggesting that the interaction between DA D1-like and D2-like receptors might be important. Furthermore, bi-phasic effects have been reported for APO and the D2-like agonist quinpirole on control of myopia: high doses of APO inhibit FDM, while low doses promote FDM in guinea pigs (Jiang et al., 2014b); in contrast, quinpirole inhibits myopia at low doses and promotes myopia at high doses in C57 mice (Zhou, unpublished data); while both effects are abolished in D_2R KO mice (Zhou, unpublished data). This suggests that two distinct elements of DA receptor actions may exist with opposite effects under varying DA concentrations (Figure 1). Perhaps the DA receptors located on different retinal pathways serve as an auto-control mechanism to prevent the overactivation of specific DA receptor (D2-like?) from promoting over-growth of the eye.

6.4 How does retinal pathway transmission interact with DA signaling to control myopia development?

While studies with mutant mouse models have uncovered the critical role of ON, OFF, rod photoreceptor and ipRGC pathways on modulation of myopia development (Chakraborty et al., 2015a; Chakraborty et al., 2014; Pardue et al., 2008; Park et al., 2014), it is critical to determine whether specific retinal pathways control myopic development by a direct effect on ocular growth or by altering DA signaling and indirectly modifying visually-driven eye development. Pharmacological studies have also established the role of DA drugs (mainly APO and D2R agonists) in control of myopia development. However, the retinal pathway basis (i.e. the ON, OFF and ipRGC pathways and their down-stream signaling) of DA actions are largely undefined. New methods or techniques such as cell-type specific retinal gene knockdown or chemical genetics (such as DREADD) and optogenetics, coupled with DA pharmacology, are needed to dissect out the retinal pathway mechanism of DA actions in control of myopia.

7. Tackling key challenges in myopia studies with new technologies

To unravel these key questions in the role of DA signaling in development of myopia, new technologies and experimental approaches are critically needed.

7.1 Two-photon image and caging

The application of two-photon photorelease of caged dopamine with two-photon calcium imaging in defined cells of the living retina (Newkirk et al., 2013, 2015) may allow us to evaluate the differential effects of DA in different retinal neurons, and provide novel insight into the role of DA signaling in retinal adaptation, and thereby myopia development.

7.2 Cell-specific and retina-specific knockout mice

Transgenic methods to knock out specific types of retinal neurons or visual signaling pathways have already uncovered potential links between retinal signaling and DA in myopia development (Chakraborty and Pardue, 2015). However, more studies are needed to fully elucidate the contributions of DA signaling to visually-driven eye growth and myopia in these mutant mice. In addition, using techniques like Cre-lox recombination, transgenic mice targeting DA related proteins only in the retina have been developed (Bergen et al., 2016) which avoids the toxicity and other side effects of systemic knock-out models (Morgan et al., 2015). Further mouse models using inducible cre promoters could provide a method to induce loss of key DA proteins during the critical period of refractive development without deleting the gene from early retinal and visual development.

7.3 Genetic labeling of D1R- and D2R-containing cells

Transgenic mice harboring D1 (such as BAC-Drd1a-tdTomato) and D2 (such as BAC-Drd2a-EGFP) receptors linked with fluorescence protein allows for the genetic labeling and visualization of D1R and D2R receptors in the retina. The release of DA and excitability of dopaminergic amacrine cells can be evaluated by patch clamp recordings after induction of myopia or in response to different myopia-related visual stimuli. By coupling with c-Fos immunohistochemistry, this approach provides an unique resource to identify the activation of specific subpopulations of retinal cells containing D1Rs or D2Rs in response to light exposure (see Figure 3).

7.4 Optogenetics and DREADD

The recent development of optogenetics and DREAD (Designer Receptor Exclusively Activated by Designer Drugs) (Armbruster et al., 2007; Urban and Roth, 2015) offers unparalleled spatiotemporal resolution by allowing the manipulation of defined neural circuits in a physiologically relevant (milliseconds in optogenetics to second to minutes in DREADD) timescale in a reversible manner (Boyden et al., 2005; Cardin et al., 2010; Yizhar et al., 2011; Zhang et al., 2007). By selectively introducing adeno-associated virus (AAV) targeted expression of light-gated ion channels or pumps (Zhang et al., 2011b) or modified cholinergic hM3Dq (M3, excitatory) or hM4Di (M4, inhibitory) receptors into genetically defined populations of neurons (such as specific retinal neurons), light stimulation (optogenetics) or injection of clozapine-N-oxide (CNO) can selectively stimulate or inhibit cells in defined cell types and visual circuits. Using optogenetics or DREADD, we can further establish the critical role of specific retinal cells and retinal pathways (as identified in retinal pathway knockout studies) in controlling normal visually-driven eye growth and modulating myopic development.

8. Future Directions

The cause of the growing prevalence of myopia is unclear, but it now affects nearly a quarter of the world population (Holden et al., 2016). If current trends continue, it is estimated that by 2050 myopia will affect ~50% of the world population, 4.76 billion people, with almost a billion people suffering from high myopia (Holden et al., 2016). It is a critical time to develop effective therapy (such as DA-based strategies) for managing and preventing

myopia-related complications and vision loss. It is also an exciting time in myopia research as new insights into the mechanisms of visually-driven eye growth and myopia may be revealed with use of new mammalian models of myopia that can be genetically manipulated, the creation of several new genetic tools to target DA related proteins (such as cell-specific and retina-specific DA receptor knockouts mice), and the recent development of optogenetic and chemical genetic approaches to manipulate defined retinal pathways in intact animals. To develop effective DA-based pharmacological treatments to prevent progressive myopia, future studies are critically needed to address key mechanistic questions that will deepen our biological understanding of the role of DA signaling in myopia development. Furthermore, as myopia is a complex disorder involving genetic and environmental factors, future studies are also warranted to address the role of DA signaling in genetic (myopia-related genes and locus) and environmental (light) interactions in myopia devellopment. Importantly, further studies on possible side effects of DA on visual and systemic functions are essential to clarify the possible unwanted side effects of DA agonists as an anti-myopic drug in children. Lastly, future studies to better characterize DA signaling and pharmacology in humans, particularly in developing children, are essential to translate basic knowledge on DA signaling and myopia into effective pharmacological treatments for myopia prevention in children.

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Article highlights

- Retinal DA, released in response to light, is a stop signal for homeostatic control of myopic eye growth
- DA exerts homeostatic control of eye growth by distinct actions of DA receptors
- DA signaling modulates specific retinal pathways to modify visual functions
- Studies on the unwanted effects of DA agents on visual and systemic functions are needed

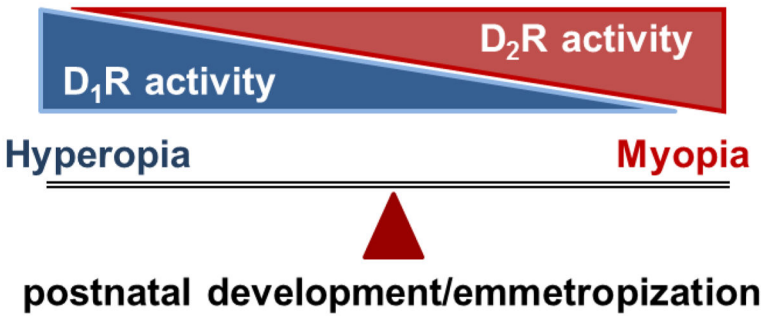

Figure 1. A working hypothesis: Homeostatic control of myopia by opposing effects of D1-like and D2-like receptors in mouse eye

Based on genetic and pharmacological results from mouse models of myopia, we postulate that D1-like and D2-like receptor activation in distinct cell types exert homeostatic control of the emmetropization process. The balance of D1-like and D2-like receptor activation in the eye modulates refractive eye development, such that over activation of D1-like receptors leads to hyperopia while over activation of D2-like receptors leads to myopia.

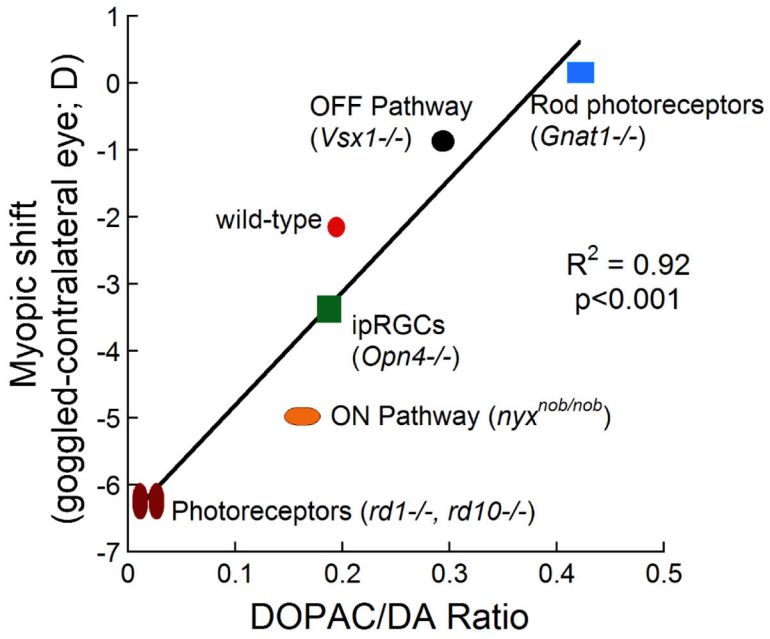

Figure 2. Retinal pathway defects alter dopamine signaling and susceptibility to FDM

Several mouse models were tested that had mutations targeting retinal neurons or pathways. Comparing the myopic shift after two weeks of FD with the DOPAC/DA ratio, an indication of DA turnover, showed a strong correlation ($R^2 = 0.92$, $p<0.001$). These results suggest that the level of DA turnover at the start of FD induction may alter the susceptibility to myopia, with lower DA activity predicting greater myopic shifts. (Modified from (Chakraborty and Pardue, 2015)).

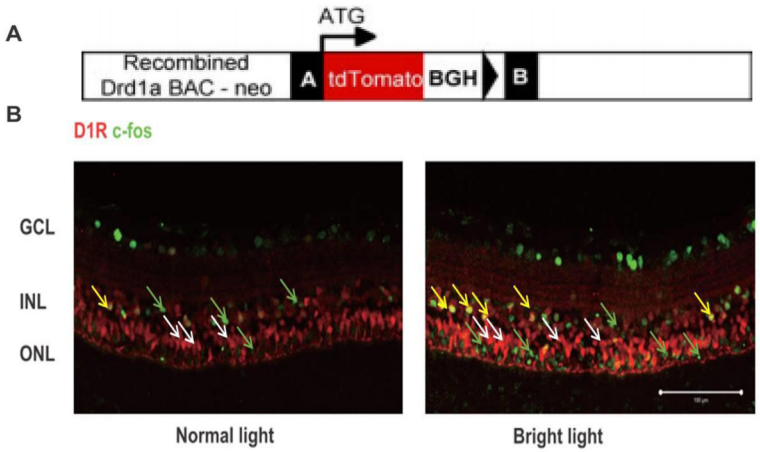

Figure 3. Identification of light-triggered D1R activation in specific subpopulations of D1R-containing cells in the retina using the BAC-Drd1a-tdTomato transgenic mice

The BAC-Drd1a-tdTomato transgenic mice (genetic structure shown in A, available from the Jackson Laboratory, Bar Harbor, USA) coupled with c-fos immunohistochemistry allows for the identification of specific retinal subpopulations of D1R-containing cells in response to normal and bright light exposure. Bright light significantly increased c-fos expression in specific subpopulations of D1R-containing cells including horizontal and bipolar cells in retina. B left: the c-fos expression in D1R + retinal neurons in normal light (100–200 lux); B right: the c-fos expression in bright light (2500–5000 lux). White arrows indicate the D1R+ neurons; green arrows indicated c-fos expression; yellow arrows indicated the activated D1R + neurons (marked by c-fos).

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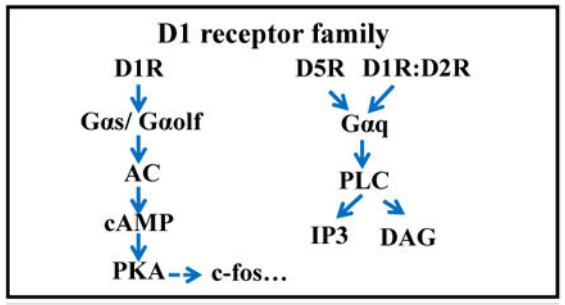
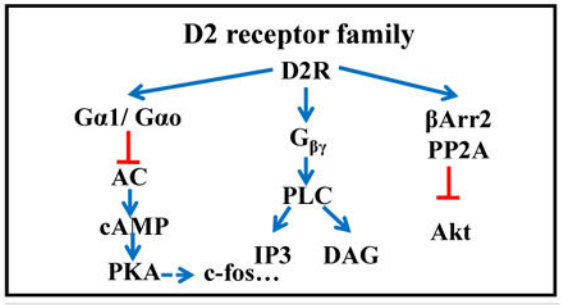
Table 1

Dopamine receptor biology in retina: signaling, distribution and pharmacology

The two main families of dopamine receptors are listed with their receptor subtypes and various agonists and antagonists. RP: photoreceptor; BC: bipolar cell; HC: horizontal cell; AC: amacrine cell; RGC: retinal ganglion cell; RPE: retinal pigment epithelium.





		D1	D5	D2	D3	D4
Retinal distribution		**Type-specific BCs, HCs, a set of ACs, RGCs**	**RPE**	**PR Dopaminergic ACs**	**none**	**PR (mouse)**
Agonist Ki value (nM)	Dopamine	0.9–2340	<0.9–261	2.8–474	4–27	28–450
	Apomorphine	0.7–680	122–168	0.7–24	20–32	4
	SKF-38393	1–150	0.5–100	150-9560	5000	1000–1300
	PD-168077	>10000	n/a	2820-3740	2810	8.7–25
Antagonist Ki value (nM)	Haloperidol	27–203	33-151	0.6–1.2	2.74-7.8	2.3–5.1
	Spiperone	99–350	135-4500	0.06–0.37	0.32–0.71	0.05–4
	SCH-23390	0.11–0.35	0.11-0.54	270–1100	314–800	3000–3560
	Sulpiride	20400–45000	11000–77270	2.5–7.1	8–206	21–1000
	L-745870	n/a	n/a	960	2300	0.43

Table 2

Modulation of myopia development by genetic and pharmacological manipulation of dopamine receptor signaling: focus on mouse models.

	Normal Eye	FDM	Reference
D1R KO	Not available	Not available	
D2R KO	No effects	Inhibition	Huang et al., 2014
APO (daily injection)	No effects	Inhibition	Yan et al., 2015
APO (continuous infusion)	No effects	No effects	Yan et al., 2015
D1R agonist (SKF-38393)	No effects	Inhibition	Zhou et al., ARVO 2014
D1R antagonist (SCH-23390)	No effects	Enhancement	Zhou et al., ARVO, 2014
D2R agonist (Quinpirole)	No effects	Inhibiting (low doses), Enhancement (high doses)	Zhou, unpublished data
D2R antagonist (sulpiride)	No effects	Inhibition	Huang et al., 2014
D4R agonist (PD-168077)	No effects	Enhancement	Zhou, unpublished data
D4R antagonist (L-745870)	Hyperopic trend	Inhibition	Zhou, unpublished data
6-OHDA	Myopic shift	Enhancement	Wu et al., 2016