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An updated view on the role of dopamine in myopia

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ABSTRACT

A large body of data is available to support the hypothesis that dopamine (DA) is one of the retinal neurotransmitters involved in the signaling cascade that controls eye growth by vision. Initially, reduced retinal DA levels were observed in eyes deprived of sharp vision by either diffusers ("deprivation myopia", DM) or negative lenses ("lens induced myopia", LIM). Simulating high retinal DA levels by intravitreal application of a DA agonist can suppress the development of both DM and LIM. Also more recent studies using knock-out mouse models of DA receptors support the idea of an association between decreased DA levels and DM. There seem to be differences in the magnitude of the effects of DA on DM and LIM, with larger changes in DM but the degrees of image degradation by both treatments need to be matched to support this conclusion. Although a number of studies have shown that the inhibitory effects of dopamine agonists on DM and LIM are mediated through stimulation of the D2-receptor, there is also recent evidence that the balance of D2- and D1-receptor activation is important. Inhibition of D2-receptors can also slow the development of spontaneous myopia in albino guinea pigs. Retinal DA content displays a distinct endogenous diurnal, and partially circadian rhythm. In addition, retinal DA is regulated by a number of visual stimuli like retinal illuminance, spatial frequency content of the image, temporal contrast and, in chicks, by the light input from the pineal organ. A close interaction was found between muscarinergic and dopaminergic systems, and between nitric oxide and dopaminergic pathways, and there is evidence for crosstalk between the different pathways, perhaps multiple binding of the ligands to different receptors. It was shown that DA agonists interact with the immediate early signaling molecule ZENK which triggers the first steps in eye growth regulation. However, since long treatment periods were often needed to induce significant changes in retinal dopamine synthesis and release, the role of dopamine in the early steps is unclear. The wide spatial distribution of dopaminergic amacrine cells in the retina and the observation that changes in dopamine levels can be locally induced by local retinal deprivation is in line with the assumption that dopaminergic mechanisms control both central and peripheral eye growth. The protective effect of outdoor activity on myopia development in children seems to be partly mediated by the stimulatory effect of light on retinal dopamine production and release. However, the dose–response function linking light exposure to dopamine and to the suppression of myopia is not known and requires further studies.

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Animal models have contributed fundamentally to the understanding of the biochemical pathways in the fundus of the eye that link its axial growth to the features of the retinal image. Depriving young animals of sharp vision by eyelid suture (Raviola and Wiesel, 1988) or placing diffusers in front of the eye (Goss and Criswell, 1981; Hodos and Kuenzel, 1984; Wallman and Adams, 1987; Wallman et al., 1978) results in axial elongation and development of deprivation myopia (DM). Removal of the diffusers results in choroidal thickening and inhibition of axial eye growth (Wallman and Adams, 1987; Wallman et al., 1978, 1995). A more specific intervention of axial eye growth involves the use of spectacle lenses which can induce both axial myopia (lens induced myopia, LIM) and hyperopia (lens induced hyperopia, LIH), depending on the sign of imposed defocus (Schaeffel et al., 1988; Sivak et al., 1990). Postnatal eye growth and refractive development appear regulated by local retinal vision-dependent mechanisms in chicks, tree shrews and monkeys (Diether and Schaeffel, 1997; Hodos and Kuenzel, 1984; McBrien et al., 1995; Norton et al., 1994; Norton and Siegwart, 1995; Smith et al., 2009, 2010; Stone et al., 2006; Troilo et al., 1987; Wallman et al., 1987; Wildsoet, 2003; Wildsoet and Wallman, 1995). Local control implies that there are signaling pathways within the eye from retina to sclera. A number of involved messenger molecules have been proposed. Among them, dopamine was the second (Stone et al., 1989) after VIP in 1988

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(Raviola and Wiesel). In particular, the role of the dopaminergic amacrine cell attracted attention (Wallman and Winawer, 2004). Dopamine is released by amacrine cells and/or interplexiform cells, depending on the species (Djamgoz and Wagner, 1992) and plays an important modulatory role in the vertebrate visual system (e.g. Witkovsky, 2004). Spatial tuning of the retina by dopamine has been extensively studied and will be summarized in the next chapter.

1. Multiple control of spatial tuning of the retina by dopamine

Except for the center of the fovea and under photopic conditions, spatial resolution is not limited by the density of the "pixels" in the retina, the photoreceptors, but rather by the amount of convergence of photoreceptor signals which is reflected by the receptive field sizes of the retinal neurons. Although high spatial acuity requires small receptive fields, this may be a disadvantage if the luminance is low and photoreceptor signals become noisy both due to photon noise and due to the noise inherent in the phototransduction cascade. The retina presents multiple mechanisms, at least at three cellular levels, to adjust receptive field sizes dependent on ambient illuminance. A thorough and comprehensive review of the mechanisms was provided by Bloomfield and Völgyi (2009) from which the following descriptions were summarized.

First, cones are electrically coupled by gap junctions, which may reduce their spatial sampling density but definitely also reduce receptor noise. While the primary rod pathway involves a sign-inverting chemical synapse from rod to rod ON bipolar cell, AII amacrine cell and ON ganglion cell (and, with sign inversion, also to OFF Ganglion cell), there is a secondary pathway under mesopic conditions that involves direct electrical coupling of rod to cones, so that cone pathways can be used also by rods. The conductance of the gap junctions between rods and cones is most likely regulated by dopamine through activation of D2/D4 receptors which, in turn, lowers intracellular cAMP and protein kinase A activity, and lowers the conductance of the rod-cone gap junctions. Therefore, at dim light and low dopamine levels, rods and cones are robustly coupled. A third rod pathway includes direct rod coupling to OFF cone bipolar cells but there is no information at present whether this is also controlled by dopamine.

There is extensive coupling also between horizontal cells through gap junctions which produces particularly large receptive fields although an antagonistic center-surround structure is also generated at this level. Horizontal cell coupling is dynamically regulated by retinoic acid, nitric oxide and dopamine (interestingly, all three agents are extensively implicated in myopia development). Dopamine decreases the conductance of the gap junctions by affecting their densities and/or the mean open conductance times through intracellular cAMP, while nitric oxide uses cGMP. Since both dopamine release and nitric oxide production are controlled by light, light adaptation reduces horizontal cell coupling and receptive field sizes, increasing visual acuity at bright light.

Further extensive coupling exists between AII amacrine cells which relay the signal of the rod ON bipolar cell on the ganglion cells (the primary rod pathway). Dopaminergic amacrine cells form dense plexi around AII amacrine cells and control the conductance of AII–AII gap junctions through a cAMP-mediated PKA cascade via release of dopamine. Accordingly, the coupling in the AII network is dependent on the adaptational state of the retina: in the dark, there is little coupling to avoid that single photon events are lost by pooling. Under mesopic conditions, the coupling is increased by a factor of 10, probably to allow for summation of synchronous activity and detection of low contrast at dim light.

Finally, also ganglion cells are electrically coupled but the regulation of the gap junctions is currently not clear. In the case of alpha ganglion cells, coupling is dramatically increased during light adaptation, synchronizing spike activity. Like in horizontal cell networks, this change in coupling seems to be mediated by dopamine acting through D2/D4 receptors although the effect of light is in the opposite direction.

In summary, dopamine has multiple targets in the retina to change receptive field sizes and, accordingly, spatial tuning of the cell responses. It is therefore possible that at least one effect of dopamine on myopia development involves a change of the spatial tuning curves of the retina. It has been shown that receptive field sizes are dynamically regulated also by spatial content of the retinal image (Hosoya et al., 2005). For instance, if the image is low pass filtered by defocus or diffusors in front of the eye, retinal dopamine release will drop, and myopia develops. Conversely, it is possible that dopamine inhibits axial eye growth because it reduces retinal receptive field sizes and simulates a well-focused image with no need for the eye to grow into myopia. Based on these functions, one would assume that it also modulates the input to the feedback-loop controlling axial eye growth.

2. Dopamine and eye growth: early work

In 1989, Stone et al. (1989) reported that visual deprivation in neonatal chicks led to a decreased retinal dopamine content. The finding was confirmed in the same year in rhesus monkeys. In addition, a reduction of tyrosine hydroxylase activity (the rate-limiting enzyme in the synthesis of dopamine) was reported (Iuvone et al., 1989). Later, a decrease in retinal dopamine in eyes deprived of sharp vision was also found in one-year old chicks, tree shrews, and guinea pigs (Dong et al., 2011; McBrien et al., 2001; Papastergiou et al., 1998). A reduction of the primary dopamine metabolite 3,4-Dihydroxyphenylacetic acid (DOPAC) in the vitreous – a robust index of retinal dopamine release (Megaw et al., 2001; Ohngemach et al., 1997) – was also found in chicks treated with negative lenses (Guo et al., 1995; Ohngemach et al., 1997). When only half of the visual field was deprived in chicks by hemifield diffusers, only the deprived areas of the globe started to grow more and it was found that DOPAC levels dropped only in the deprived retinal areas (Ohngemach et al., 1997; Stone et al., 2006). These results were consistent with the hypothesis of an inverse relationship between dopamine release and axial eye growth. Since most of the dopamine measurements were made several days after visual-deprivation had started, they relate to medium-term adaptation, rather than representing an immediate response to changes in visual experience. Megaw et al. (1997) have studied the acute effects of visual deprivation on vitreal DOPAC levels in chicken retina in more detail. They found that deprivation does not reduce the release of dopamine immediately after light onset, at least not during the first 30 min. Later during the light phase the sustained release of dopamine was reduced with diffusers. The authors propose that the observed temporal pattern of dopamine release may reflect adaptional processes that occur in response to low temporal and spatial contrast. Furthermore, Ohngemach et al. (1997) found that vitreal DOPAC content was reduced already after one day of positive or negative lens wear. Retinal dopamine content was not affected at the time, suggesting that release changed more rapidly than retinal content.

In contrast to visual deprivation, after removal of the diffusers, eye growth is sharply inhibited and retinal dopamine levels, as well the level of its metabolite 3,4-Dihydroxyphenylacetic acid (DOPAC) and the DOPAC/dopamine ratio rise rapidly over a period of two days (Pendrak et al., 1997). The extend and time courses of the changes in dopamine synthesis and release led to the suggestion

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