Author Response: Concerning Manuscript “Bright Light Suppresses Form-Deprivation Myopia Development With Activation of Dopamine D1 Receptor Signaling in the ON Pathway in Retina”

We thank Zhu et al.\textsuperscript{1} for their interest in our recent publication entitled “Bright Light Suppresses Form-Deprivation Myopia Development With Activation of Dopamine D1 Receptor Signaling in the ON Pathway in Retina.”\textsuperscript{2} We appreciate the comments and the opportunity to respond to this letter from IOVS, and we would like to clarify some points raised in the letter.

Regarding the choice of time points (i.e., 2 days) for c-fos-D1R colocalization analysis, we select this time point for two reasons. (1) To understand myopia pathogenesis, we are particularly interested in the early changes during the initiation period, which is more related to the etiology of myopia. Thus, we chose to evaluate the biological changes after 2 days of form deprivation. (2) We selected c-fos as the biomarker for identifying the cells that are activated by light because light can induce c-fos expression in 0.5 to 1 hour.\textsuperscript{3,4} c-fos is an immediately early gene, and the induction of c-fos likely subsides after 4-week treatment. We do not intend to suggest that the change we uncovered at 2 days of form deprivation (light stimulation) reflects the cellular changes after 4-week treatment. We argued that cellular activation in the retina as indicated by c-fos likely contributes to the initiation progress of myopia and possibly also to progression of myopia during 4-week periods. With regard to the ocular biometry after 2 days of form deprivation, it is impossible to detect any significant changes in biometry after such a short period. Thus, we elected to not measure biometry at this time point.

Compared with the chicken (the animal model widely used for myopia research) and humans, mice are nocturnal animals and are more sensitive to light-induced retinal damage. A luminance at 10,000 to 40,000 Lux (which is used in human studies) will cause retina damage in mice,\textsuperscript{5} resulting in uninterpretable results. Therefore, the luminance levels (100 to 200 and 1500 to 3300 Lux for normal light [NL] and bright light [BL] luminance, respectively) we selected were generally lower than that of the studies using chicken as a myopia model. However, the light stimulation nonetheless produced the expected anti-myopia effect under these light conditions.

Many studies have reported findings that some dopamine (DA) drugs and atropine selectively modulate eye growth induced by diffusers or lenses but have no effect on eye growth with normal vision.\textsuperscript{6} This selectivity of drug actions may be due to the difference in the DA system between myopia development (a pathologic situation) and refractive development (a physical situation), which may include the changes in DA diurnal pattern or the retinal DA level.\textsuperscript{7–12} In the mentioned reference 6, the D1R antagonist promoted excessive eye growth and spontaneous myopia development in albino guinea pigs, which have low retinal DA. In reference 7, the defocus may have altered the activation of retinal DA system. This selectivity of drug actions indicates that we can pharmacologically target an abnormal refractory shift without affecting normal eye growth, a critical concern in drug development for developing children.

Form deprivation affected retinal visual inputs including the received light intensity, spatial visual inputs, etc., which may in turn affect different visual pathways involved in DA releasing and signaling. The altered DA system may act on the DA receptors in specific visual pathways and influence these pathway functions to modulate visually driven eye growth. We also find that form deprivation (FD) decreased the expression of c-fos in NL but did not alter that in BL (Chen S, et al., unpublished data, 2017), which indicates the light intensity may have different effects on the retinal visual pathway between normal vision and FD. Further investigations are needed to clarify the FD-induced changes in the retinal visual pathway.

The etiology of myopia is complicated. DA and light both exert multiple and delicate effects on the retina. This published study focused on the effect of D1R in light-induced myopia inhibition. The effects of D2R and the interaction between D1R and D2R receptors in development of myopia is our ongoing study. Much additional work is needed to understand the intricate relationship among light, DA, and myopia.

References

9. Iuvone PM, Tigges M, Fernandes A, Tigges J. Dopamine synthesis and metabolism in rhesus monkey retina: develop-


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