Glaucoma is the second leading cause of blindness in the world and is typically a slowly progressing neurodegenerative disease. It is characterized by a gradual loss of retinal ganglion cells (RGCs), which leads to vision loss. The most common form of glaucoma, occurring in 70 to 90% of patients, is primary open angle glaucoma (POAG). A compelling epidemiological feature of POAG is that its incidence shows a striking sex-related difference. Women have a significantly lower incidence of POAG, as compared to men, until the age of 80 years. This sex-related difference has been linked to the extent of lifetime estrogen exposure. Indeed, there is a strong association between increased estrogen exposure and a reduced POAG risk. Conversely, studies have shown that a decreased exposure (i.e. early loss of estrogens), due to late onset of menstrual cycles, oral contraceptive use, early menopause, early surgical removal of the ovaries, and a shorter duration between menarche to menoapause, confers an increased risk of POAG.

We hypothesize that an early estrogen deficiency accelerates the aging of the optic nerve and predisposes to glaucomatous damage. We further hypothesize that estrogen administration will remove these risks and serve as a novel preventive treatment for glaucoma, and in particular, POAG. To begin to test this hypothesis, we examined whether estrogen deprivation promotes the development of glaucoma.

**DESIGN & METHODS**

We obtained breeding pairs of C57BL/6J - aromatase knockout (ArKO) heterozygous mice (Dr. Nabil J. Alkayed; Oregon Health & Science University, Portland, OR) to generate ArKO mice and their wildtype (WT) controls. The ArKO mice harbor a targeted disruption of exon IX in the cyp19 gene and possess no aromatase activity. Aromatase catalyzes the conversion of androstenedione to estrone and 17β-estradiol. In the absence of aromatase, the synthesis of estrogens is completely diminished by the conversion of androstenedione to estrone and the conversion of testosterone to estradiol. In the absence of aromatase, the synthesis of estrogens is completely eliminated. All mice were genotyped at least twice to confirm their genetic background. At 12 and 24 weeks of age, we measured in a masked fashion the IOP (n = 6 consecutive IOP measurements/value, 3 values/eye/day, 2 consecutive days) in the left and right eyes of conscious mice (n = 8/group/sex). Animals were then sacrificed and retinas were processed for the analysis and quantitation of RGCs. Unpaired t-tests were used for statistical analyses.

**RESULT**

The IOP levels in both 12- and 24-week old female ArKO mice were significantly (p < 0.0001) higher than those of age- and sex-matched WT controls. The mean increase in IOP levels in 12-week-old females was significant (p < 0.05, 12-week, † one-tailed T-test) versus controls. In contrast, estrogen deficiency did not lead to an increased IOP in male mice. There was, however, a significant reduction in RGC counts in the 12- (p < 0.05), but not 24-, week-old male ArKO mice, as compared to their age- and sex-matched WT controls.

**DIAGRAM**

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