Effects of Apomorphine, a Dopamine Receptor Agonist, on Ocular Refraction and Axial Elongation in a Primate Model of Myopia

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The authors examined the effect of local administration of a dopamine receptor agonist on visual deprivation-induced excessive ocular growth and myopia. Eight rhesus monkeys were monocularly deprived of vision from birth with opaque contact lenses. Four of the monkeys received drops of 1% apomorphine HCl 2–3 times/day in the occluded eye; the four control monkeys received vehicle only. Axial lengths were determined by A-scan ultrasonography at birth and at 5–7 months of age. The authors assessed the axial elongation by comparing the postnatal growth in the axial dimension of the occluded eyes with the postnatal growth in nonoccluded eyes. In three of the four control monkeys, occlusion increased axial growth by an average of 1.3 mm. In contrast, they found that growth of the occluded and nonoccluded eyes of the apomorphine-treated monkeys was equivalent, except in one monkey whose nonoccluded eye did not develop normally and was anomalously small. At 6.5–9.5 months of age, three of four controls had myopic refractive errors (−3 to −7 diopters) in the occluded eyes; three of four of the apomorphine-treated monkeys had hyperopic refractive errors (+1–+3 diopters) in their occluded eyes. The occluded eye of the fourth monkey was only −0.5 diopters myopic. The findings suggest that apomorphine administration retards excessive axial elongation and the concomitant development of myopia associated with visual deprivation in primates. Invest Ophthalmol Vis Sci 32:1674–1677, 1991

Neonatal eye growth and refraction can be influenced by visual experience. In juveniles of species, such as humans, monkeys, tree shrews, and chickens, deprivation of form vision causes excessive axial eye growth and a myopic refractive error.1–5 Moreover, the experimental myopia induced by visual deprivation is accompanied in both chick and monkey by decreased retinal biosynthesis of dopamine.6,7

To test whether levels of retinal dopamine could be relevant to ocular development, we studied the effect of local administration of the dopamine receptor agonist apomorphine on the growth of lid-sutured eyes of neonatal chicks.6 The drug decreased the excessive axial elongation of the lid-sutured chick eye in a dose-dependent manner; at the highest dose, the inhibition was complete. Remarkably, the dopamine agonist effect was abolished by coadministration of a dopamine antagonist, haloperidol, indicating pharmacologic specificity for dopamine receptors.

We have extended our drug studies to visual deprivation myopia in monkeys. Specifically, we examined the effects of topical apomorphine drops on the development of myopia as induced by a monocular opaque extended-wear contact lens in the rhesus monkey.8 A preliminary report of the results has been published in abstract form.9

Materials and Methods

All monkeys came from the colony of the Yerkes Regional Primate Research Center (Atlanta, GA). The right eyes of eight newborn rhesus monkeys (Macaca mulatta) were occluded with opaque extended-wear contact lenses. Lens manufacture and maintenance have been described.10 Lenses were inserted 1–3 days after birth. Lens compliance was monitored at 3–4 hr intervals; missing lenses were replaced immediately. The subjects, born between May and August 1988, were randomly divided into two groups of four monkeys: vehicle control and apomorphine-treated.
Apomorphine HCl was prepared twice daily as a 1% solution in 2.2% glycerol/H₂O. Apomorphine solution was administered topically (2 drops/eye) to the occluded eye of four monkeys; the other four monkeys received vehicle to the occluded eye. Nonoccluded eyes of all animals received vehicle at the same time. Drug treatment began within 1 week of contact lens insertion. Drops were administered twice daily until the monkeys were approximately 4 months of age, after which the treatment was increased to three times/day. There were no indications of systemic toxicity or local discomfort. General health, weight gain, and development were normal.

Axial length was measured by A-scan ultrasonography at birth and at subsequent times, as described previously. Measurements of newborns were made by gentle restraint of the head by hand; after the early postnatal period, animals were anesthetized with ketamine during measurement. Intraocular pressure was measured by applplanation tonometry, and corneal curvature was measured by keratometry. Monkeys with occluder lenses removed were kept in dim red light when possible. Refraction was measured by two observers after 5% homatropine cycloplegia (2 drops repeated × 1 after a 30-min interval) and was reported as the mean of two readings. Cycloplegic refractions were performed at the termination of the study to preclude potential effects of cycloplegia on eye growth. The study adhered to the ARVO Resolution on the Use of Animals in Research.

Results

At birth, the axial lengths of left and right eyes did not differ (right: 13.2 ± 0.2 mm; left: 13.3 ± 0.2 mm; n = 8 monkeys); all were within the normal range for newborn rhesus monkeys. Figure 1 shows the axial growth that took place from birth to 5-7 months of age. For the control group, which received vehicle only, there was a marked difference in axial length between the occluded and nonoccluded eye in three of four monkeys. Occlusion increased ocular elongation by an average of 1.3 mm. The occluded eye of the remaining animal in this group showed slightly less axial growth (0.4 mm) than the fellow nonoccluded eye.

Occluded eyes treated with 1% apomorphine HCl did not experience excessive axial growth. The occluded eyes of the apomorphine-treated monkeys grew less on average than the occluded eyes of the controls (apomorphine: 3.9 ± 0.2 mm; control: 4.9 ± 0.4 mm; n = 4, t = 2.357, P = 0.057). For three of four apomorphine-treated monkeys, growth in the nonoccluded eyes was similar to that in the nonoccluded eyes of the controls. The nonoccluded eye of the fourth monkey in the apomorphine group did not develop normally; it grew considerably less than any other eye of the entire series (gap test P < 0.05, Dixon).

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The increase in axial growth in control eyes occluded by an opaque contact lens derived largely from expansion of the vitreous chamber (Fig. 2), like the myopia that follows lid suture. The axial dimension of the chamber in occluded eyes was significantly larger than that of nonoccluded eyes in the three monkeys that showed excessive ocular growth (paired t = 12.124, P = 0.007). In contrast, no significant dif-
The occluded eye of the fourth monkey in the control group was slightly hyperopic (+1-+3 diopters) in the nonoccluded eye. In contrast, the occluded eyes of three of four apomorphine (+0.85 diopters) in the occluded eye and mildly myopic (-2.0 diopters) in the nonoccluded eye. There was little or no progression of myopia (Fig. 3) as assessed by refractions performed at the end of the study (postnatal age: 6.5-9.5 months; control group mean: 8.0 months; apomorphine group mean: 8.5 months). The three monkeys that showed excessive axial elongation also had myopic refractive errors (ranging from -3 to -7 diopters) in the occluded eyes; there was little or no refractive error in the nonoccluded eye. The remaining monkey in the control group was slightly hyperopic (+0.85 diopters) in the occluded eye and mildly myopic (-2.0 diopters) in the nonoccluded eye. In contrast, the occluded eyes of three of four apomorphine-treated monkeys were hyperopic (+1-+3 diopters), whereas the occluded eye of the fourth monkey was slightly myopic (-0.5 diopters). The increase in postnatal growth in the occluded eyes of control monkeys was associated with the development of myopia (Fig. 3) as assessed by refractions performed at the end of the study (postnatal age: 6.5-9.5 months; control group mean: 8.0 months; apomorphine group mean: 8.5 months). The three monkeys that showed excessive axial elongation also had myopic refractive errors (ranging from -3 to -7 diopters) in the occluded eyes; there was little or no refractive error in the nonoccluded eye. The remaining monkey in the control group was slightly hyperopic (+0.85 diopters) in the occluded eye and mildly myopic (-2.0 diopters) in the nonoccluded eye. In contrast, the occluded eyes of three of four apomorphine-treated monkeys were hyperopic (+1-+3 diopters), whereas the occluded eye of the fourth monkey was slightly myopic (-0.5 diopters). The results of the present pilot study suggest that the dopamine receptor agonist apomorphine, administered as an eye drop, decreases excessive axial elongation of the eye and the development of myopia associated with visual deprivation in infant rhesus monkeys. Studies in juvenile rhesus monkeys show that visual deprivation produced by lid fusion or the use of opaque contact lenses leads to excessive ocular growth in the axial dimension and the development of myopia in most cases. In agreement, we found that ocular occlusion with opaque contact lenses leads to increased axial length and a myopic refractive error (−3 to −7 diopters) in three of four monkeys receiving the vehicle drops. In contrast, the axial growth of occluded eyes treated with apomorphine is not excessive in any instance, corresponding instead to that in vehicle-treated nonoccluded fellow eyes. No significant degree of myopia develops in the occluded eyes of apomorphine-treated monkeys. In contrast, three of the occluded eyes of apomorphine-treated monkeys are hyperopic (+1-+3 diopters). One of the eyes shows minimal myopia (-0.5 diopters) at approximately 8 months of age. These findings agree with the results of similar experiments in form-deprivation myopia in chicks, where apomorphine administered by subconjunctival injection prevented lid suture-induced axial elongation. In that study, apomorphine had no effect on deprivation-induced enlargement of the chick eye in the equatorial dimension, suggesting that axial and equatorial growth may be regulated by distinct mechanisms. The effect of apomorphine on equatorial

**Table 1. Intraocular pressure, keratometry, and ultrasound measurements**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control</th>
<th>Apomorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP (mm Hg)*</td>
<td>Occluded</td>
<td>Nonoccluded</td>
</tr>
<tr>
<td>10.8 ± 0.8</td>
<td>10.8 ± 0.8</td>
<td>10.5 ± 0.9</td>
</tr>
<tr>
<td>Radius of curvature of cornea (diopters)†</td>
<td>51.0 ± 0.5</td>
<td>50.2 ± 0.7</td>
</tr>
<tr>
<td>Anterior chamber depth (mm) †</td>
<td>3.1 ± 0.1</td>
<td>3.2 ± 0.1</td>
</tr>
<tr>
<td>Lens thickness (mm) †</td>
<td>4.3 ± 0.1</td>
<td>4.3 ± 0.1</td>
</tr>
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* Intraocular pressure (IOP) was determined by applanation tonometry under mild ketamine anesthesia when the animal's age ranged from 6-9 months.
† Corneal curvature of the horizontal meridian was determined by keratometry at 7-10 months.
‡ Ultrasound measurements are presented as group means, calculated from the mean of 3-5 determinations/animal (1-5 measurements/determination) made between 3-8 months.

mean spherical equivalent of the occluded eyes of the apomorphine group (+1.55 ± 0.81 diopters, n = 4) was different from that of the vehicle-treated occluded eyes (−3.54 ± 1.76 diopters, n = 4; t = 2.625, P = 0.039). The one nonoccluded eye that did not grow normally was severely hyperopic (+7.5 diopters); all other nonoccluded eyes of the apomorphine group had lower degrees of hyperopia (0.5-4 diopters).

**Discussion**

The results of the present pilot study suggest that the dopamine receptor agonist apomorphine, administered as an eye drop, decreases excessive axial elongation of the eye and the development of myopia associated with visual deprivation in infant rhesus monkeys. Studies in juvenile rhesus monkeys show that visual deprivation produced by lid fusion or the use of opaque contact lenses leads to excessive ocular growth in the axial dimension and the development of myopia in most cases. In agreement, we found that ocular occlusion with opaque contact lenses leads to increased axial length and a myopic refractive error (−3 to −7 diopters) in three of four monkeys receiving the vehicle drops. In contrast, the axial growth of occluded eyes treated with apomorphine is not excessive in any instance, corresponding instead to that in vehicle-treated nonoccluded fellow eyes. No significant degree of myopia develops in the occluded eyes of apomorphine-treated monkeys. In contrast, three of the occluded eyes of apomorphine-treated monkeys are hyperopic (+1-+3 diopters). One of the eyes shows minimal myopia (-0.5 diopters) at approximately 8 months of age. These findings agree with the results of similar experiments in form-deprivation myopia in chicks, where apomorphine administered by subconjunctival injection prevented lid suture-induced axial elongation. In that study, apomorphine had no effect on deprivation-induced enlargement of the chick eye in the equatorial dimension, suggesting that axial and equatorial growth may be regulated by distinct mechanisms. The effect of apomorphine on equatorial

![Fig. 3. Ocular occlusion caused myopia in vehicle-treated, but not in apomorphine-treated eyes. At 7-10 months of age, occluders were removed from the monkeys eyes, cycloplegia was induced with 5% homatropine, and refractive error (expressed as spherical equivalents) was determined by retinoscopy.](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933391/ on 10/17/2017)
growth of the visually deprived monkey eye has not been assessed.

As in lid-sutured monkeys or in chicks visually deprived by lid suture or goggle,3,12 the increase in axial growth of vehicle-treated monkey eyes occluded with contact lenses results almost exclusively from enlargement of the vitreous chamber. Apomorphine treatment to occluded eyes acts by inhibiting excessive vitreous chamber elongation rather than by affecting another component of ocular refraction.

For studies on the pharmacologic regulation of ocular growth, opaque contact lenses have some advantages over lid suture. It is easier to apply eye drops to an eye fitted with a lens than to instill medications behind a sutured lid or into the subconjunctival space. To the extent that a drug accumulates within the contact lens, a reservoir is created to prolong contact time. Lastly, the development of increased axial length in lens-occluded eyes may be faster than in eyes beneath sutured lids.8

In our sample, myopia developed in only three of the four occluded eyes in the control group. Variability of ocular growth and refraction, however, were known to increase with visual deprivation.9 Increased axial length was relatively consistent with the deprivation paradigm used here; in eight of nine monkeys examined (including the four control animals), vehicle-treated or untreated occluded eyes were longer than nonoccluded fellow eyes.8

The site of apomorphine action on ocular growth is unknown. Although receptors for the dopaminergic agonist are in the retina, the intraocular distribution of apomorphine after application as eye drops is not known. The decreased retinal dopaminergic metabolism7 and apomorphine effects in experimental primate myopia parallel findings in the chick.6,13 However, the possibility that apomorphine exerts its effects on an extraretinal site (eg, central nervous system, anterior pituitary) cannot be excluded.

Although caution is warranted, these results in monkeys and chicks are consistent with the hypothesis that retinal dopamine participates in a pathway linking vision with ocular growth control. These results show that eye growth under certain circumstances can be modified. To that end, the apparent activity of apomorphine drops in a primate species suggests that its use, or the use of related dopamine receptor agonists, might be a therapeutic strategy for study in modifying the development of certain human myopias. With the potential for systemic absorption of apomorphine eye drops and the well-known dopaminergic mechanisms in the brain and pituitary gland, more toxicity studies than those reported here are necessary before the use of dopamine-related drugs can be considered in children.

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Key words: visual deprivation, myopia, postnatal ocular growth, apomorphine, dopamine, rhesus monkey

References