



The development of eye shape and the origin of lower field myopia in the guinea pig eye

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ABSTRACT

In a variety of species, the refractive state of the eye differs in different parts of the visual field (VF) with greater myopia in the region that views the ground (“lower field myopia”). We studied the refraction and eye shape of the normal guinea pig eye to determine what feature(s) underlie this visual adaptation. Guinea pigs ($n = 67$) were either newborn or raised under incandescent light until 14, 37 or 45 days of age (20, 44, 20 and 11 eyes respectively). Refractive error was measured on-axis and 30° off-axis in the superior (SVF), inferior (IVF), temporal (TVF) and nasal (NVF) visual fields. Eye shape was analyzed from images of frozen hemisections in both the horizontal and vertical mid plane in 14 day animals, and in the vertical plane at 0, 14 and 45 days of age. Axial distances in vitro were correlated with in vivo high frequency ultrasound ($r^2 = 0.90$). In the horizontal plane, asymmetry was caused by a $\pm 6^\circ$ conical zone surrounding the optic nerve (12° off-axis in NVF), suggesting significant myopia in this zone. At 30°, there was no asymmetry in eye length, but the NVF was +1.7 D more myopic due to asymmetry in corneal power. In the vertical plane at 30°, the IVF was more myopic than the SVF by -3.8 D at 0 days, -5.9 D at 14 days and -6.0 D at 37 days. It resulted from vertical asymmetry in the distance of the retina from the lens center, which was longest in the mid IVF. This non-linear ramp retina was present at birth. In older animals, the peak of the ramp shifted more centrally, and the eye developed longer lengths in the extreme upper periphery (SVF) which may have been caused by the low position of the room ceiling. The vertical asymmetry in eye shape was mirrored by changes in choroid thickness, suggesting a mechanism by which eye shape was refined by vision during development. In early life, ocular growth in the vertical plane was 1.7 times higher in the center relative to the periphery, a pattern that reversed in the following month. Since emmetropization was achieved over this period, local visual cues related to clear vision may provide a switch to change ocular growth from a central to a peripheral emphasis.

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1. Introduction

In many species, the eye does not have a single refractive error but rather it varies in different parts of the eye. Commonly, the inferior visual field is more myopic when compared with the remaining visual fields (“lower field myopia”) (pigeons: Catania, 1964; Fitzke et al., 1985, turtles: Henze, Schaeffel, & Ott, 2004, chicks, quails and cranes: Hodos & Erichsen, 1990; Millodot & Blough, 1971; Nye, 1973, chicks, frogs and toads: Schaeffel et al., 1994). In humans, the lower visual field has also been reported to be slightly more myopic than the upper (Seidemann et al., 2002). This variation could arise from differences in the distance of the retina from the nodal point in different parts of the visual field and/or from variation in optical power at different peripheral eccentricities. The former was termed a ramp retina (Walls, 1942) and originally

proposed to substitute for accommodation in horses and stingrays (Sivak, 1976; Sivak & Allen, 1975), but has subsequently been shown to be unlikely in horses (Harman et al., 1999). In animals with small eyes that live close to the ground, it is plausible that this refractive variation is a local adaptation to the distance of the ground and sky in the inferior and superior visual fields respectively (Hodos & Erichsen, 1990). Raptors, which catch their prey from the air, do not show lower field myopia (Murphy, Howland, & Howland, 1995). It is possible that this adaptation occurs during development. It is well established that myopia can arise from visual disruption of the emmetropization process, in which the refractive errors present at birth normally dissipate as the eye grows. For example, in birds, fish, primates and mammals, if the eye receives blurred input (from hyperopic defocus) or is deprived of form vision early during development, the rate of ocular elongation accelerates and myopia develops (Wallman & Winawer, 2004).

In the present study, our aim was to study lower field myopia in the guinea pig eye: a relatively unspecialized typical small

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mammalian eye. The guinea pig retina is avascular (Chase, 1982) and has a relatively high percentage of cones (Peichl & Gonzalez-Soriano, 1994) with a rod/cone ratio similar to primates and dichromatic color vision (green and blue cones) (Jacobs & Deegan, 1994). It also has a modest visual streak characterized by increased ganglion cell density in the horizontal plane and extending into a peak density zone located in temporal retina 4–5 mm from the optic disk (Do-Nascimento et al., 1991).

Our first aim was to measure the refractive error variation in different sectors of the young guinea pig eye. Second, we aimed to determine the origin of any variation in refractive state by measuring optical parameters and eye shape in both horizontal and vertical meridians. To study eye shape in these small eyes and to maximize resolution, we optimized a technique based on high-resolution imaging of frozen hemisections. The internal ocular distances measured on the optical axis using this *in vitro* freezing method were validated against the same measures obtained with high-resolution ultrasound recorded *in vivo*. Third, we studied the development of refractive error and eye shape as the animals aged to determine if lower field myopia was present in the guinea pig eye at birth or whether it developed during emmetropization as the eye grew. Finally, developmental myopia in humans and animals is characterized by myopia in the central visual field and relative hyperopia in the periphery and a relatively prolate eye shape (Mutti et al., 2000; Smith, 2011; Verkicharla et al., 2012). Since the guinea pig is a useful animal model of myopia (Howlett & McFadden, 2006, 2009; Liu et al., 2007; Lu et al., 2006; McFadden, Howlett, & Mertz, 2004; Qu et al., 2010), we also compared the natural rate of change in central and peripheral eye shape.

2. Methods

2.1. Animals

Pigmented guinea pigs (*Cavia porcellus*, $n = 67$) sourced from the University of Newcastle, were reared and housed with their mothers, in opaque plastic boxes (65 × 45 × 20 cm) with wire mesh lids. Lighting was provided by incandescent bulbs above each box (3 × 40 W, 500 lux at each box center) evenly distributed through an opaque Perspex barrier set 200 mm above the boxes. Lights were on a 12 h day/12 h night cycle. All procedures were approved under Australian animal ethics legislative requirements and adhered to the EU Directive 2010/63/EU for animal experiments.

2.2. Procedures

First, ocular characteristics were measured in young guinea pigs 14 days old, as this age corresponds to just after the initial period of maximum ocular growth and is typically used in studies of myopia (Howlett & McFadden, 2006, 2007, 2009). Ocular characteristics included mapping the variation in refractive error in different sectors of the visual field, *in vivo* measures of corneal power and ocular distances on-axis, and horizontal and vertical eye shape from frozen sections (Table 1, Group 1). These measures allowed detailed comparison of horizontal and vertical asymmetries in the eye. Second, to validate measuring eye shape in frozen hemisections, we compared *in vivo* measures (from ultrasound) and *in vitro* measures (from frozen hemisection) in these same 14 day old animals. In a separate group of animals (Table 1, Group 2), we also studied the effect of freezing dissected (untensioned) crystalline lenses, to separate the pure effect of freezing from differences in lens tonus which may occur between our *in vivo* and *in vitro* measures of tensioned lenses. Third, we studied the development of lower field myopia and eye shape in the vertical plane by comparing refractive error and eye shape in vertical

mid-sections taken from eyes of newborn (0 days of age within 12 h of birth), young (14 days old) or older animals (37 and 45 days of age) (Table 1, Group 3). The older age corresponds to after emmetropization is achieved, which takes approximately 30 days (Howlett & McFadden, 2007).

The measures taken in each group of animals is shown in Table 1. The order of measures was: (1) corneal power measured in hand-held awake animals using infrared keratometry; (2) eyes were then cycloplegic (1–2 drops of 1% cyclopentolate), and 1.25 h later on- and off-axis refractions were measured using retinoscopy; (3) animals were then anesthetized with 1.5% isoflurane in oxygen and ocular length and component axial distances ascertained with high frequency ultrasound (Group 1 only); and (4) finally, within 30 min of finishing the previous procedure, animals were again anesthetized with isoflurane in oxygen, euthanized with 130 mg/kg of pentobarbitone sodium into the heart, and eyes were enucleated within 1 min of death. Eye shape measures were subsequently made from frozen hemisections. Details of each of these methods follow.

2.3. Measurement of refractive error

Eyes were refracted using white light retinoscopy in five positions: the central (C) visual field (on-axis), and in the temporal (T), nasal (N), inferior (I), and superior (S) visual fields (VF) (off-axis). The four off-axis locations were taken at ±30° from the central pupil axis with reference to the long axis of the eye (N, T) and at right angles to this axis (S, I) (Fig. 1A). These eccentricities corresponded to approximately the edge of the lens core visible in the pupil. The 30° angles were found by first locating the optic axis, and then moving the retinoscope by 30° using an attached string based protractor system. Both horizontal and vertical meridians were recorded at each of the five locations, and the mean of these two meridians is reported as the mean spherical equivalent.

2.4. Ultrasound measurement of axial dimensions

Axial dimensions were obtained in anesthetized animals to enable comparison with measures taken from frozen sections in enucleated eyes (see below). The method used high frequency ultrasound (20 MHz) (Panametrics Model 176599), with a 100 MHz a/d sampling board (Sonix 8100). Peaks were selected for the front of the cornea, the front of the crystalline lens, the back of the crystalline lens, the vitreal–retinal, retinal–choroidal and choroidal–scleral interfaces, and the back of the sclera as previously described (Howlett & McFadden, 2006; McFadden, Howlett, & Mertz, 2004). The distance from the anterior cornea surface to the anterior lens surface was defined as the anterior chamber depth (AC). Axial length was defined as the distance from the front of the cornea to the back of the retina, which corresponds to eye length at 90° in the frozen sections (see below).

2.5. Determination of eye shape

Both enucleated eyes were placed into phosphate buffered saline on ice with left or right order randomly selected. Using a freezing microtome with open stage access (Ziess, HM 430), one eye was carefully aligned initially using the position of the long ciliary artery to minimize eye tilt (Fig. 1B), embedded in colored freezing medium (OCT, Tissue Tek®) and frozen at –30 °C over a 45 s period. Eyes were sectioned in 60 μm steps in either the horizontal or vertical plane (Table 1), adjusted for tilt once the iris was reached, and magnified digital images (250 pixel/mm, 10 MP Nikon D80 with Nikkor AF-S DX 55–300 mm lens) collected of the cut surface (Fig. 2A and B) illuminated with multiple halogen lamps (4 × Oriol® 50 W 12 V).

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