Mysterious Myopia: The Retinal Regulation of Eye Growth

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Current Trends in Myopia Prevalence

• NHANES survey: 12-54 year olds
  – Increasing US prevalence
  – 25% in 1971-72 survey
  – 41.6% in 1999-2004 survey
• US Framingham Study
  – 23-34 year olds: 57%
• Swedish 12-13 year olds: 49.7%
• Singapore
  – 7 year olds: 20%
  – Army Conscripts: 79%
• Taiwan: 84% of 18 year olds
Fig 2  Percentage of cases of myopia among school pupils and students between 1913 and 1978 (survey by the Japanese Ministry of Education). ---, Male; ----, female.

Complications of Myopia

• Retinal Disease
  – Retinal Detachment
  – Retinopathy
• Glaucoma: Open-Angle
• Cataract
  – Nuclear and posterior subcapsular cataract
• Complications of Treatment
  – Contact Lens
  – Refractive Surgery
Myopic Retinopathy

normal  myopia
Prevalence of Blindness from Myopia

- Reports affected by variable definitions
- 3-19% of blindness attributable to myopia
- Generally ranks between 1st and 7th leading cause
Myopia: Nature vs. Nuture

Conventional Risk Factors

- Family history
  - Shared genes
  - Shared environment, most notably socioeconomic status
- Educational level
- Intelligence
- Socioeconomic status
- Prematurity
- Nearwork
- Personality traits
- Nutrition
- Body stature, including height/weight

The $R^2$ Enigma –
Modeling analysis yields $R^2 = 0.1 - 0.2$
Form-Deprivation Myopia

- Disruption of visual input: goggle, lid suture
- Myopic refraction and vitreous cavity enlargement
- Species susceptibility
  - chick, cat, tree shrew, squirrel, wallaby, guinea pig, many monkeys
  - man
- Age, responsiveness
  - newborn: robust
  - adolescence: attenuated

from Raviola & Wiesel, NEJM 312:1609, 1985
Full vs. Hemi-Goggles

Treatments used to restrict visual experience to part of the retina. Temporal retina is visually deprived in animal on left, nasal retina in animal on right, and all of retina in center animal.

from Wallman, et al., 1987
Local Visual Deprivations Alter Eye Shape

- **full goggle:** entire retina deprived
- **half goggle:** nasal retina deprived
- **half goggle:** temporal retina deprived

Lens-Induced Image Defocus

emmetropia

minus (−) lens

plus (+) lens

Modified from Miller, Optics and Refraction, 1991
Visual Feedback Mechanisms and Eye Growth Control

- Form-deprivation myopia
- Hemi-goggle effects
- Effects of defocusing spectacle lenses
- Photoperiod effects on the eye
- Recovery from experimental ametropia
- Impaired emmetropization in childhood vision disorders
Vision Dependent Ocular Growth Control: Ocular Localization

• Optic nerve transection
  – Form-deprivation myopia
    • Chicks
    • Monkeys
  – Emmetropization

• Toxins to specific retinal neurons: specific growth effects
  – Kainic acid, quisqualic acid, tunicamycin, formoguanamine, tetrodotoxin
Myopia and Emmetropization: Evidence for Retinal Participation

- Visual experience influences eye growth.
- The growth control mechanism localizes at least partly to the eye.
# Receptor Classes in Emmetropization and/or Myopia

## G-protein coupled receptors
- Cholinergic muscarinic
- Dopamine
- GABA<sub>B</sub>
- Glucagon
- Glutamate: metabotropic (e.g., quisqualate)
- Opioids
- Vasoactive intestinal peptide

## Ligand-gated ion channels
- Cholinergic nicotinic
- GABA<sub>A</sub> and GABA<sub>A0r</sub>
- Glutamate: NMDA & AMPA/kainate
- Glycine

## Protein kinases and transcriptional factors
- Basic fibroblast growth factor
- Transforming growth factor - β family, including bone morphogenetic proteins
- Sonic hedgehog
- Erg-1

## Nuclear receptors
- Retinoic acid

## Gaseous transmitters
- Nitric oxide

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Papers/abstracts from Escaño, Fischer, Fujikado, Megaw, Rohrer, Seko, Stell, Stone, Wells, others
Neurotransmitters and Neuropeptides Implicated in Myopia or Emmetropization

- Dopamine
- Acetylcholine
  - Muscarinic receptors
  - Nicotinic receptors
- Vasoactive Intestinal Peptide
- GABA
- Glucagon
- Nitric Oxide

Retinal Anatomy
Dopamine Amacrine Cells and Myopia


from Stone, et al., *PNAS* 86:704, 1989
Dopamine and Myopia

• Dopamine receptor agonists inhibit form-deprivation myopia in animals.
  – chick
  – monkey
• Retinal dopamine also affected with lens-induced changes of eye growth in chick.
• Dopamine receptor agonists inhibit lens-induced myopia and augment lens-induced hyperopia in chicks.
• Dopaminergic amacrine cells seemingly lie in the pathway regulating refractive development.

Functions for Retinal Dopamine

• State of retinal light:dark adaptation
  – Dopamine influences many relevant functions: melatonin, gap junctions, disc shedding, etc.
  – Dopamine entrains endogenous retinal circadian rhythms to light in birds

• Refractive development
  – Disrupted retinal dopamine rhythms in myopia
  – Drug actions implicate retinal dopamine in refractive development in animals

• Independent or related functions?

• Potential toxicity hinders testing dopamine drugs in children
Partial Coherence Interferometry

- Non-contact, rapid
- Highly precise
  - 95% CI: 7–9μm
- Similar technology to OCT and IOL Master
- Signal normalized to cornea
- No anesthesia needed

**Diurnal Axial Length Changes in Chick**

- **Graph 1:**
  - Title: Distance charge from cornea (mm)
  - X-axis: Time of day (0-6)
  - Y-axis: Distance charge from cornea (0-1.2)
  - Layers: OS, BM, ILM

- **Graph 2:**
  - Title: Open vs. Goggled
  - Comparison: Day vs. Night
  - Units: μm/12 hours
  - Data: Open > Goggled

References:
Diurnal Fluctuations in Ocular Dimensions

- **Laboratory animals**
  - Axial length fluctuations
    - Chick, rabbit and marmoset
  - Choroidal thickness fluctuations
    - Chick and marmoset

Intraocular Pressure (IOP) and Axial Length Fluctuations in Chicks

- On average, axial length and IOP peak at similar times.
- Appropriate compliance of the ocular coats in response to IOP
- Phase differences between the two rhythms in individual eyes
- Autonomic denervations dissociate the two rhythms.
- *IOP fluctuations do not cause axial length fluctuations in chick.*