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Chapter

Role of Melanin Pigment in Retina and Inner Ear

Donnell J. Creel

Abstract

Melanin pigment is normally present in the outermost layer of the retina of the eye, the inner ear adjacent to capillaries in stria vascularis near hair cells, and vestibular organs. Significant reduction in melanin pigment in mammals is associated with embryonic miswiring and disruption of visual and auditory functions. The consequences for the visual system include abnormal development of the retina and misrouting of optic pathways into the brain impairing visual acuity, eye movement, and stereovision. Lack of melanin pigment in the inner ear is associated with greater susceptibility to noise damage and poorer localization of sound in space.

Keywords: Albinism, melanin pigment, inner ear, retina, optic chiasm, stria vascularis

1. Introduction

The organization of the visual system varies among mammals. Most primates display well-defined retinal foveae, foveal avascular zone, and large numbers of uncrossed optic fibers at the optic chiasm. Mammals with laterally placed eyes, for example, guinea pig, rat, mouse, have little temporal retina producing few uncrossed fibers at optic chiasm. Cats and more so primates with forward-facing eyes have significant temporal retina, with nearly half of optic fibers remaining uncrossed at the chiasm of some primates. Mammals vary in proportion of optic nerve fibers that cross at the chiasm, embryonic development and optic projections terminating in vision centers from suprachiasmatic nuclei to midbrain, to geniculate nuclei, to visual cortex.

Most albino human beings and albino cats lacking retinal pigment have observable nystagmus and many exhibit strabismus. The optic chiasm of albino mammals including human beings and cats shows that almost all retinal ganglion cells cross at the optic chiasm with few uncrossed optic fibers. This misrouting has dramatic effects on organization of the visual system.

In 1965, C.L. Sheridan noticed that retinal ganglion cells originating in temporal retina of albino rats did not function well, hypothesizing that albino rats have fewer uncrossed, non-decussating optic fibers [1]. R.D. Lund anatomically verified that albino rats have fewer non-decussating optic fibers compared to pigmented rats [2]. For several years the abnormality of reduced non-decussating optic fibers at the optic chiasm in albinos was thought to be limited to rats and rabbits [3]. Guillery [4]

reported atypical visual system organization in Siamese cats, but the association with albinism was not identified.

In 1971, Creel initially published the connection between Siamese cats and albinism, and hypothesis that reduced non-decussating optic fibers likely is a "highly general transspecies phenomenon in albino mammals" [5, 6]. Siamese cats, Himalayan mice, rats, and rabbits express a mutation that is a temperature-sensitive pigmentation defect, that is, allowing pigment only on the cold parts of the body. Their retinae lack pigment.

The studies of Siamese cat showed that a single recording site over each visual cortical area reflected differences between pigmented and albino cats [5]. Hence, scalp-recorded visually evoked potentials might detect optic misrouting in human albinos. Testing human albinos using scalp-recorded visually evoked potentials revealed human albinos have reduced non-decussating optic fibers [6, 7]. Animal studies reported that all albino mammals with oculocutaneous, or only ocular albinism, demonstrate reduced uncrossed optic projections [8–10]. Visual system abnormalities in albino mammals include fewer photoreceptors, foveal/area centralis hypoplasia, misrouting of the temporal retinal ganglion cells, variation of geniculate terminations, vascular intrusion into foveal area, abnormal cortical projections, and fewer cones in macular area [11–17].

The animal model close to organization of primate visual system studied the most is the albino cat. Albino cats have observable nystagmus, and many have strabismus. **Figure 1** pictures the optic chiasm of an OCA1 albino cat showing almost all retinal ganglion cells (RGCs) cross at the chiasm. The number of binocular cells is reduced in visual cortical areas 17, 18, and 19 in Siamese cats and albino cats impairing stereovision [19–21].
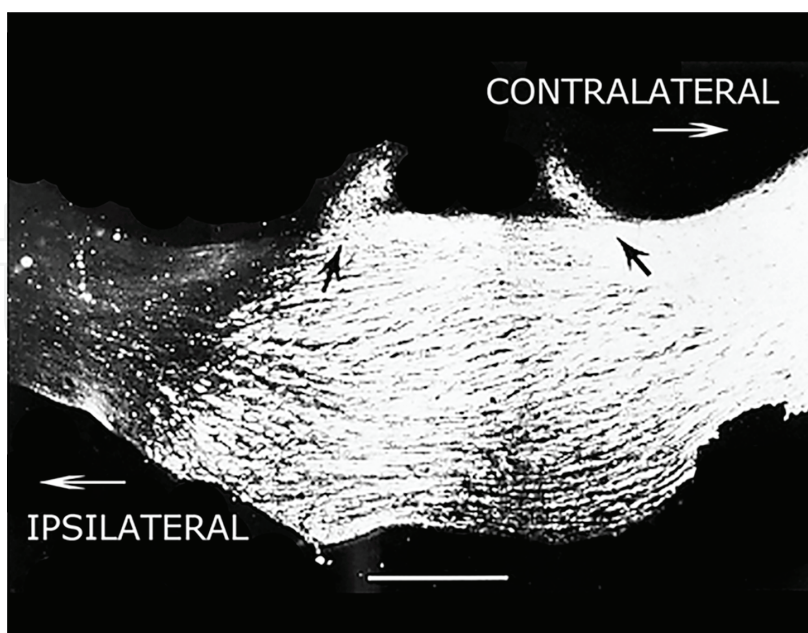

Figure 1.
Dark-field autoradiograph of coronal section through the optic chiasm of a Type 1 albino cat after injection of tritiated leucine into right eye showing difference between contralateral and ipsilateral RGC projections. Almost all RGCs cross at the optic chiasm. Arrows point to projections to suprachiasmatic nuclei. Scale bar 1 mm. From Creel et al. [18].

Phylogenetically older connections are less abnormal in albino mammals as seen in **Figure 1** showing bilateral suprachiasmatic projections appear to be unaffected [18]. Optic projections near chiasm projecting into hypothalamus antecede vertebrates, occurring in early chordates. Chordates have retinal pigment matching vertebrates [22]. Melanopsin retinal ganglion cells are completely crossed or bilaterally projected into suprachiasmatic nuclei above the optic chiasm [23, 24]. These projections are not affected by albinism. The crossed/uncrossed proportion of optic neurons to the suprachiasmatic nuclei in albino cats is like the proportion stated for pigmented cats [25]. The earlier appearing melanopsin pathway is not affected.

Abnormalities associated with hypopigmented retinae vary between species. Most human albinos have poorly formed foveae and little or no vascular sparing of central foveal area of retina [12, 26]. Visually evoked potential studies and functional magnetic resonance imaging reflect the preponderance of crossed optic fibers at the chiasm [15]. Few retinal ganglion cells originating temporal side of fovea in pigmented human beings cross at the optic chiasm. In albino mammals most retinal ganglion cells originating in temporal retina cross at the optic chiasm. **Figure 2** shows approximate differences between the optic chiasm of ocularly pigmented and albino human beings.
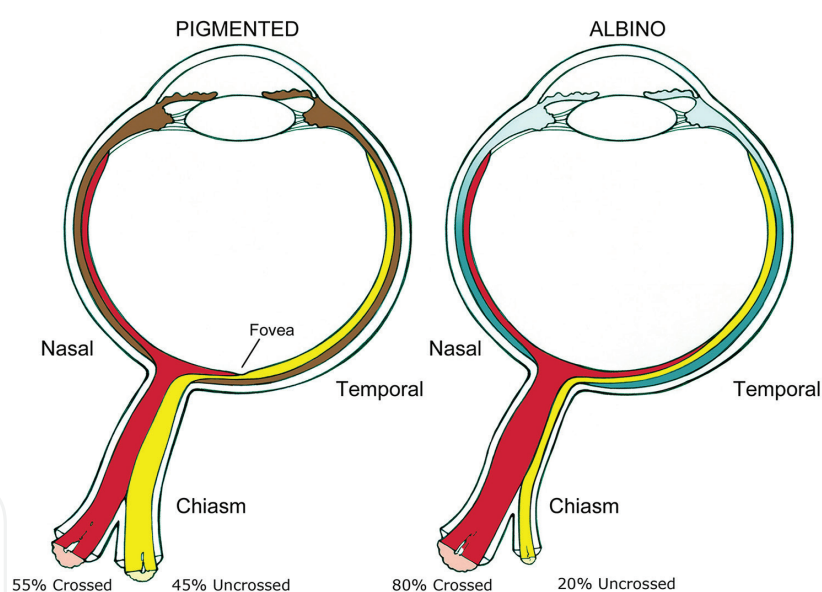

Figure 2.
Schematic of approximate distribution of crossed and uncrossed optic fibers in human beings. From Creel, webvision.med.utah.edu (2014).

Many possibilities are suggested for controlling embryonic retinal ganglion cells coursing through the chiasm. Some conclusions are likely to be correct within the model studied, but not a solution for optic misrouting seen throughout albino mammals. Each species varies. As an example, significant differences between mouse and human embryogenesis specific to chiasm formation are described [27]. Temporal timing of axon arrival at the optic chiasm and path through the chiasm are different between man and mouse. The development of contralateral followed

by ipsilateral optic projections is sequential. There are no absolutes. Variable expression is seen even in littermate animal models [9]. Additionally, exceptions are reported [28, 29].

Due to millions of years of divergent evolution, the micro mechanisms of axon guidance underlying optic neuron decussation and target fate are likely idiosyncratic for each species. Pax2, Pax6, SOX2, and SOX21 seem to participate in development of the visual system. Several conserved loci including ROBO and PAX2/PAX 6 affect guidance in mammals including humans [14, 30–33].

Additionally, intra-genome communication is probably taking place. Visual embryogenesis is possibly affected by contributions from noncoding DNA and conserved noncoding portions of the genome. Noncoding DNA probably modifies expression [32, 33]. Variance within species appears to originate more in noncoding space [34].

Melanin is present in vertebrates and seen in early chordates. Melanin pigment is prevalent in mammalian embryonic development. Melanin pigment's function in the eye is different than in other parts of the body. Melanin pigment is present with melanocytes that are mostly active during early vertebrate embryogenesis. The melanin pigment chemical pathway initiated with tyrosine is expressed similarly from drosophila to primates. The sequence leading to eye formation in the fly is recapitulated in the developing human eye [35, 36]. Phylogeny is recapitulated in the embryonic development of the mammalian visual system.

1.1 Human pigmented vs albino visual system

Figure 3 shows OCT (optical coherence tomography) of the foveal area of a pigmented person (A) and an albino (B). In pigmented retina, the red nerve fiber layer does not cross the fovea. In most human albinos the nerve fiber layer (B) passes over fovea. Poor foveal development and variability among albino foveae are likely due to amount of ocular pigment and genetic background [37]. Albino human beings
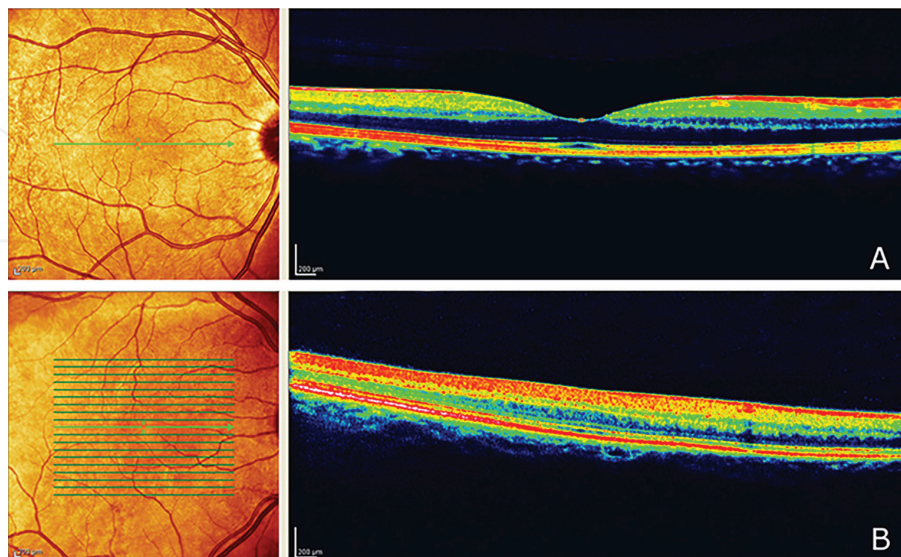

Figure 3.
Ocular coherence tomography (OCT) through the fovea of a normally pigmented (A) and albino (B) human being. Note the absence of foveal pit with the nerve fiber layer (red) continuing over foveal area in albino retina. From Creel, webvision.med.utah.edu (2014).
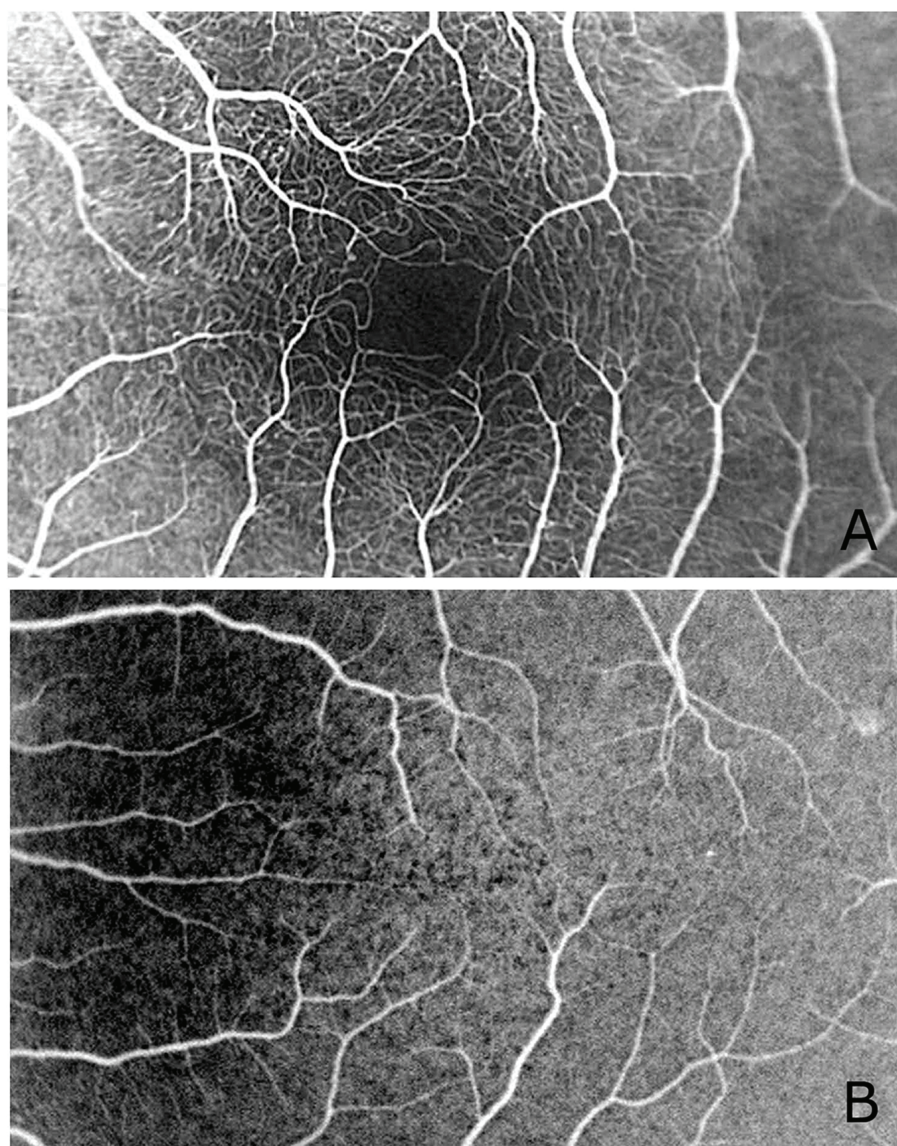
Figure 4.
Angiogram of pigmented human ocular fundus (A) showing vascular sparing of foveal area compared to albino (B) with vascular intrusion into vascular area. From Creel, webvision.med.utah.edu (2014).

manifest a reduction in cone density in the central retina [13]. Ocularly pigmented primates are the only mammals with developed foveae. In most mammals with albinism, the retinal macular area is underdeveloped [38, 39].

In humans with pigmented retinae, retinal blood vessels spare the foveal area. In albino human retinae, blood vessels intrude into foveal area. **Figure 4** compares the central vascular distribution in human pigmented and albino retinae. Pigmented humans exhibit an avascular zone surrounding the fovea. Albinos do not.

1.2 Pigment in inner ear

Vision and hearing evolved together dating back to the PaxB gene, which is a single gene controlling eye and precursors to hearing (mechanoreceptors) in box
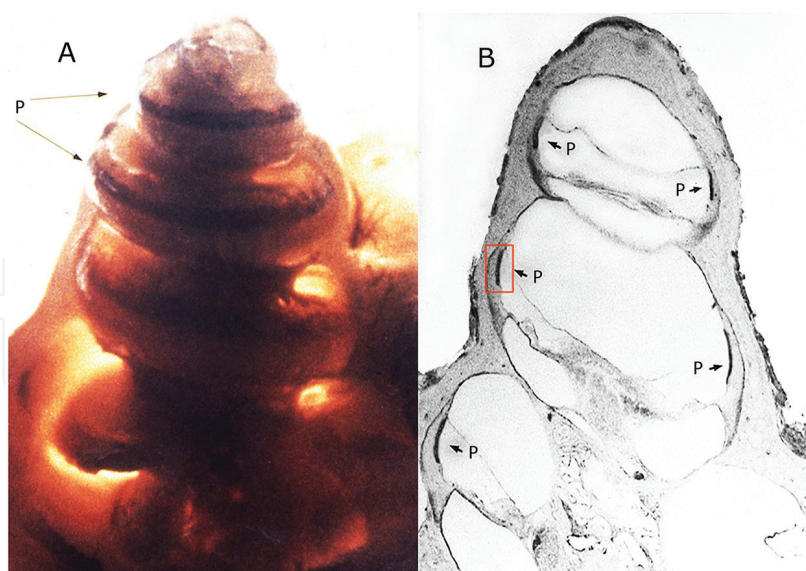
Figure 5.
Decalcified guinea pig cochlea (A) and sagittal section (B) through guinea pig cochlea show melanin pigment in stria vascularis. Red boxed area enlarged in **Figure 6**. *From Creel, webvision.med.utah.edu (2014).*

jellyfish before independent Pax 2 and Pax 6 genes [40]. There are evolutionary connections between eyes and mechanoreceptors of the inner ear to the extent that during evolution, "sensory cells can shift their sensory modalities" [41].

There is normally melanin pigment in the inner ear [42, 43]. **Figure 5A** shows band of melanin pigment (P) in a guinea pig cochlea. **Figure 5B** is a section through a guinea pig cochlea showing melanin pigment (P). **Figure 6** displays a microscopic view of area like that in red box in **Figure 5B**. Red arrows point at capillaries. Melanocytes are adjacent to capillaries in the stria vascularis of inner ear.

Binaural hearing tells eyes where to look [44, 45]. Spatial vision and auditory localization function in a coordinated manner. From diapsids to mammals interaural sound localization circuits are similarly organized. The auditory map in the brain is like the visual space map [46]. Visual and auditory space interact in the brain. When blind individuals localize auditory echoes, fMRIs reveal more brain activity in visual cortex than auditory cortex [47].

Albino mammals are not hearing impaired. The absence of melanin pigment in the inner ear is associated with susceptibility to noise damage [48–50]. Also, prolonged sensitivity to noise measured as a longer temporary threshold shift (TTS) following exposure to loud sounds is documented in albinos [51–53]. In the medial superior olivary nucleus, cell size and dendritic length are decreased in albinos [54]. In albinos component III of auditory brainstem responses is attenuated, which are generated in region of the medial superior olivary nuclei reflecting the reduced neuronal size and dendritic length in albino mammals [54–57].

The brainstem auditory pathways of albino mammals have anomalies like the visual system. Reduced cell size in brainstem olivary nuclei is associated with reduced binaural cell responses in medial superior olive of albino cats [58] resulting in disruption of sound localization, like finding of reduced binocular cells in visual cortex. Moore & Kowalchuk [59] described reduced ipsilateral projections from the cochlear nuclei in hypopigmented ferrets.
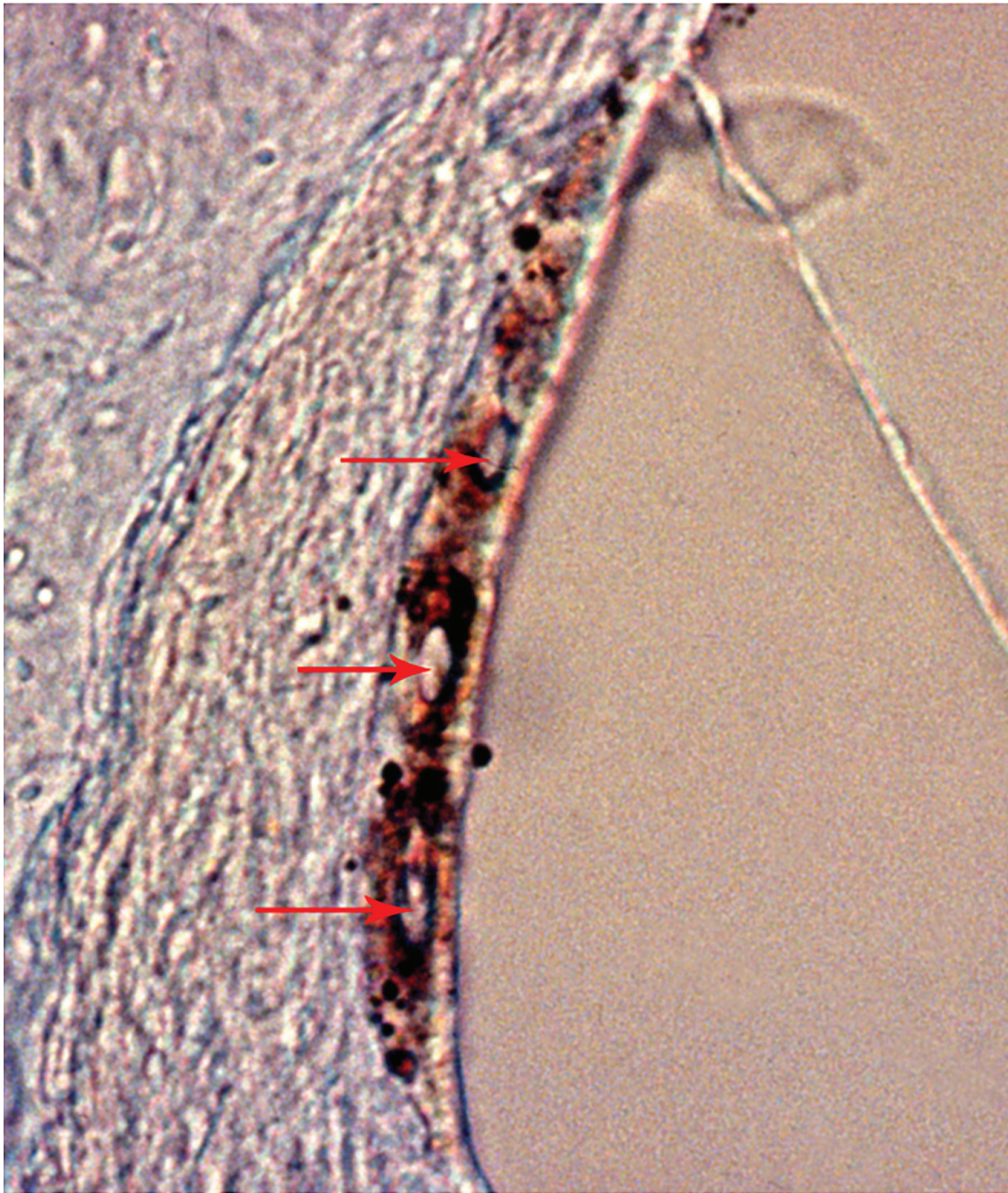
Figure 6.
*Enlargement of red-boxed area in **Figure 5** shows melanin adjacent to capillaries indicated by red arrows. From Creel, webvision.med.utah.edu (2014).*

1.3 Creel theory

The Creel theory proposes that the lack of melanin pigment initiates atavistic expression of visual and auditory embryogenesis. Melanin pigment is an environmental cue. Embryonic progression in albino mammals' visual and auditory systems take a step back initiated by lack of melanin pigment. Abnormalities of chiasmic misrouting in albino mammals is a developmental field defect that is normal in preceding phylogeny [60]. Complete crossing of optic neurons at the chiasm is normal in most vertebrates prior to mammals.

The presence of melanin pigment in the embryonic retina, or possibly genetic coding for melanin pigment, initiates retinal ganglion cell pathway routing. Insufficient coding for retinal pigment launches an earlier, more stable genetic package directing targeting of optic neurons.

Genetic makeup includes preserved earlier evolutionary features. Charles Darwin [61] popularized atavism as the term for reappearance of ancestral characteristics in future generations. Expression of atavistic features, such as complete crossing of optic fibers, is likely due to the flaw in the embryonic environment, in this case, lack of melanin pigment, precipitating formation of an earlier ancestral pathway.

2. Conclusion

Mammals lacking melanin pigment in retina and inner ear have abnormal visual and auditory systems. Mammals preserve the genetic instructions for complete decussation of the retinal ganglion cells at the optic chiasm and presence of melanin pigment adjacent to capillaries in inner ear. Phylogenetically newer genetic directions for formation of a central retinal area, fovea, and vascular sparing of the foveal area are vulnerable. Recent genetic addendums to conserved instructions are at risk if genetic cues, such as sufficient melanin pigmentation, are not present to support variation from ancient instructions. In albino mammals, the genetic instruction for visual pathways defaults to the simpler, more entrenched, platform. The auditory system follows with similar disarray.

Acknowledgements

Author details

Donnell J. Creel
Moran Eye Center, University of Utah School of Medicine, Salt Lake City, UT, USA

*Address all correspondence to: donnell.creel@hsc.utah.edu

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References

[1] Sheridan CL. Interocular transfer of brightness and pattern discriminations in normal and corpus callosum sectioned rats. Journal of Comparative and Physiological Psychology. 1965;**59**:292-294

[2] Lund RC. Uncrossed visual pathways of hooded and albino rats. Science. 1965;**149**:1505-1507

[3] Giolli RA, Guthrie MD. The primary optic projections in the rabbit: An experimental degeneration study. The Journal of Comparative Neurology. 1969;**136**:99-126

[4] Guillery RW. An abnormal retinogeniculate projection in Siamese cats. Brain Research. 1969;**14**:739-741

[5] Creel DJ. Visual system anomaly associated with albinism in the cat. Nature. 1971;**231**:465-466

[6] Creel DJ. Differences of ipsilateral and contralateral visually evoked responses in cats: Strains compared. Journal of Comparative and Physiological Psychology. 1971;**77**:161-165

[7] Creel D, Witkop CJ Jr, King RA. Asymmetric visually evoked potentials in human albinos: Evidence for visual system anomalies. Investigative Ophthalmology & Visual Science. 1974;**13**(6):430-440

[8] Sanderson KJ. Retinogeniculate projections in the rabbits of the albino allelomorphic series1. The Journal of Comparative Neurology. 1975;**159**:15-27

[9] Creel DJ, Giolli RA. Retinogeniculate projections in albino and ocularly hypopigmented rats. The Journal of Comparative Neurology. 1976;**166**:445-455

[10] Guillery RW, Oberdorfer MD, Murphy EH. Abnormal retino-geniculate and geniculo-cortical pathways in several genetically distinct color phases of the mink (Mustela vison). The Journal of Comparative Neurology. 1979;**185**:623-655

[11] Elschnig A. Zur anatomie des menschlichen albinoauges (Translated: On the anatomy of the human albino eye). Graefes Archivfur Ophthalmologie. 1913;**84**:401-419

[12] Fulton AB, Albert DM, Craft JL. Human albinism light microscopy and electron microscopy study. Archives of Ophthalmology. 1978;**96**:305-310

[13] Wilson HR, Mets MB, Nagy SE, Kressel AB. Albino spatial vision as an instance of arrested visual development. Vision Research. 1988;**28**:979-990

[14] Azuma N. Molecular cell biology on morphogenesis of the fovea and evolution of central vision. Nihon Ganka Gakkai Zasshi. 2000;**104**:960-985

[15] McKetton L, Kelly KR, Schneider KA. Abnormal lateral geniculate nucleus and optic chiasm in human albinism. The Journal of Comparative Neurology. 2014;**522**:2680-2687

[16] Bridge H, von dem Hagen EAH, Davies G, et al. Changes in brain morphology in albinism reflect reduced visual acuity. Cortex. 2014;**56**:64-72

[17] Ather S, Proudlock FA, Welton T, et al. Aberrant visual pathway development in albinism: From retina to cortex. Human Brain Mapping. 2019;**40**(3):777-788

[18] Creel D, Hendrickson AE, Leventhal AG. Retinal projections in

tyrosinase-negative albino cats. The Journal of Neuroscience. 1982;**2**:907-911

[19] Di Stefano M, Bedard S, Marzi CA, Lepore F. Lack of binocular activation of cells in area 19 of the Siamese cat. Brain Research. 1984;**303**:391-395

[20] Leventhal AG, Creel DJ. Retinal projections and functional architecture of cortical areas 17 and 18 in the tyrosinase-negative albino cat. The Journal of Neuroscience. 1985;**5**:795-807

[21] Kalberlah C, Distler C, Hoffmann KP. Sensitivity to relative disparity in early visual cortex of pigmented and albino ferrets. Experimental Brain Research. 2009;**192**:379-389

[22] Vopalensky P, Pergner J, Leigertova M, et al. Molecular analysis of the amphioxus frontal eye unravels the evolutionary origin of the retina and pigment cells of the vertebrate eye. Proceedings of the National Academy of Sciences. 2012;**109**:1583-1588

[23] Lucas RJ, Hattar S, Takao M, et al. Diminished pupillary light reflex at high irradiances in melanopsin-knockout mice. Science. 2003;**299**:245-247

[24] Hattar S, Kumar M, Park A, et al. Central projections of melanopsin-expressing retinal ganglion cells in the mouse. The Journal of Comparative Neurology. 2006;**497**:326-349

[25] Hendrickson AE, Wagoner N, Cowan WM. An autoradiographic and electron microscopic study of retino-hypothalamic connections. Zeitschrift für Zellforschung und Mikroskopische Anatomie. 1972;**135**:1-26

[26] McAllister JT, Dubis AM, Tait DM, et al. Arrested development: High-resolution imaging of foveal morphology in albinism. Vision Research. 2010;**50**:810-817

[27] Neveu MM, Jeffery G. Chiasm formation in man is fundamentally different from that in the mouse. Eye. 2007;**21**:1264-1270

[28] van Genderen MM, Riemslag FC, Schuil J, et al. Chiasmal misrouting and foveal hypoplasia without albinism. British Journal of Ophthalmology. 2006;**90**:1098-1102

[29] Poulter JA, Al-Araimi M, Conte I, et al. Recessive mutations in SLC38A8 cause foveal hypoplasia and optic nerve misrouting without albinism. American Journal of Human Genetics. 2013;**93**(6):1143-1150

[30] Kosmik Z. The role of Pax genes in eye evolution. Brain Research Bulletin. 2008;**75**:335-339

[31] Kidd T, Brose K, Mitchell KJ, et al. Roundabout controls axon crossing of the CNS midline and defines a novel subfamily of evolutionarily conserved guidance receptors. Cell. 1998;**92**(2):205-215

[32] Woolfe A, Elgar G. Organization of conserved elements near key developmental regulators in vertebrate genomes. Advances in Genetics. 2008;**61**:307-338

[33] Woolfe A, Goodson M, Goode DK, et al. Highly conserved non-coding sequences are associated with vertebrate development. PLoS Biology. 2004;**3**:e7

[34] Lee JT. Epigenetic regulation by long noncoding RNAs. Science. 2012;**14**:1435-1439

[35] Hanson IM. Mammalian homologues of the Drosophila eye specification genes. Seminars in Cell & Developmental Biology. 2001;**12**(6):475-484

[36] Kumar JP, Moses K. Expression of evolutionarily conserved

eye specification genes during Drosophilaembryogenesis. Development Genes and Evolution. 2001:406-414

[37] Dorey SE, Neveu MM, Burton LC, et al. The clinical features of albinism and their correlation with visual evoked potentials. The British Journal of Ophthalmology. 2003;**87**:767-772

[38] Hendrickson A, Troilo D, Possin D, Springer A. Development of the neural retina and its vasculature in the marmoset Callithrix jacchus. The Journal of Comparative Neurology. 2006;**497**:270-286

[39] Jeffery G. The albino retina: An abnormality that provides insight into normal retinal development. Trends in Neurosciences. 1997;**20**:165-169

[40] Piatigorsky J, Kozmik Z. Cubozoan jellyfish: An Evo/Devo model for eyes and other sensory systems. The International Journal of Developmental Biology. 2004;**48**(8-9):719-729

[41] Fritzsch B, Piatigorsky J, Tessmar-Raible K, et al. Ancestry of photic and mechanic sensation? Science. 2005;**308**:1113-1114

[42] Conlee JW, Parks TN, Schwartz IR, Creel DJ. Comparative anatomy of melanin pigment in the stria vascularis. Evidence for a distinction between melanocytes and intermediate cells in the cat. Acta Oto-Laryngologica. 1989;**107**:48-58

[43] Conlee JW, Gerity LC, Westenberg IS, Creel DJ. Pigment-dependent differences in the stria vascularis of albino and pigmented guinea pigs and rats. Hearing Research. 1994;**72**:108-124

[44] Heffner RS, Heffner HE. Visual factors in sound localization in mammals. The Journal of Comparative Neurology. 1992;**317**:219-232

[45] Feng W, Störmer VS, Martinez A, et al. Sounds activate visual cortex and improve visual discrimination. The Journal of Neuroscience. 2014;**34**(29):9817-9824

[46] Grothe B, Pecka M, McAlpine D. Mechanisms of sound localization in mammals. Physiological Reviews. 2010;**90**:983-1012

[47] Thaler L, Arnott SR, Goodale MA. Neural correlates of natural human echolocation in early and late blind echolocation experts. PLoS One. 2011;**6**:e20162

[48] Mujica-Mota MA, Schermbrucker J, Daniel SJ. Eye color as a risk factor for acquired sensorineural hearing loss: A review. Hearing Research. 2015;**320**:1-10

[49] Meyer zum Gottesberge AM. Physiology and pathophysiology of inner ear melanin. Pigment Cell Research. 1988;**1**(4):238-249

[50] Murillo-Cuesta S, Contreras J, Zurita E, et al. Melanin precursors prevent premature age-related and noise-induced hearing loss in albino mice. Pigment Cell & Melanoma Research. 2010;**23**:72-83

[51] Garber SR, Turner CW, Creel D, Witkop CJ Jr. Auditory system abnormalities in human albinos. Ear and Hearing. 1982;**3**(4):207-210

[52] Conlee JW, Abdul-Baqi KJ, McCandless GA, Creel DJ. Differential susceptibility to noise-induced permanent threshold shift between albino and pigmented guinea pigs. Hearing Research. 1986;**23**:81-91

[53] Barrenäs ML, Lindgren F. The influence of inner ear melanin

on susceptibility to TTS in
humans. Scandanavian Audiology.
1990;**19**(2):97-102

[54] Conlee JW, Parks TN, Creel DJ.
Reduced neuronal size and dendritic
length in the medial superior olivary
nucleus of albino rabbits. Brain Research.
1986;**363**:28-37

[55] Conlee JW, Parks TN, Romero C,
Creel DJ. Auditory brainstem anomalies
in albino cats: II. Neuronal atrophy
in the superior olive. The Journal
of Comparative Neurology.
1984;**225**:141-148

[56] Creel DJ, Garber SR, King RA,
Witkop CJ Jr. Auditory brainstem
anomalies in human albinos. Science.
1980;**209**:1253-1255

[57] Creel D, Conlee JW, Parks TN.
Auditory brainstem anomalies in albino
cats. I. Evoked potential studies. Brain
Research. 1983;**260**:1-9

[58] Yin TCT, Carney LH, Joris PX.
Interaural time sensitivity in the inferior
colliculus of the albino cat. The
Journal of Comparative Neurology.
1990;**295**:438-448

[59] Moore DR, Kowalchuk NE.
Auditory brainstem of the ferret:
Effects of unilateral cochlear lesions
on cochlear nucleus volume and
projections to the inferior colliculus.
The Journal of Comparative Neurology.
1988;**272**:503-515

[60] Opitz JM. 2011 William Allan
Award: Development and Evolution.
American Journal of Human Genetics.
2012;**90**(3):392-404

[61] Darwin C. The Variation of Animals
and Plants under Domestication. Vol. 2.
London: John Murray; 1868