Albinism

Albinism: a model of adaptation of the brain in congenital visual disorders

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Preservation of visual field in albinism despite misrouting of the optic nerve

Congenital visual abnormalities can lead to profound differences in the organisation of the visual pathways compared with normal developmental organisation. Knowledge of different cortical organisations is important for understanding the plasticity of the developing brain. Recent advances in functional brain imaging have allowed insights into such functional changes in humans. For example, a large-scale developmental reorganisation of the visual pathway was shown in rod monochromats (achromatopsia, colour blind people who lack cone photoreceptor function). In rod monochromats, the cortical region that normally responds only to cones during functional magnetic resonance imaging activation responded powerfully to rod-initiated signals.¹ Another fascinating example is that the visual cortex can be activated by Braille reading in blind people.² One of the most profound reorganisations of the visual pathway occurs in albinism. In this issue of *British Journal of Ophthalmology*, Hoffmann *et al*³ (see page 509) report on their investigation of visual field function of abnormally wired optic nerve fibres in patients with albinism.

In patients with oculocutaneous and ocular albinism, there is a continuous range of hypopigmentation.⁴ Accordingly, patients have variable degrees of reduction in visual acuity, nystagmus, iris transillumination, hypopigmentation of the retinal pigment epithelium, foveal hypoplasia, optic nerve head anomalies and abnormal crossing of optic nerve fibres. Normally, the decussation between nasal and temporal retinal nerve fibres is located in the vertical meridian of the fovea. In albinism, this line is shifted temporally, causing the contralateral primary visual cortex to receive more input from the retina. Increased crossing of optic nerve fibres in the chiasm is one of the most consistent findings in albinism in all species. In humans, it has been found to be highly specific and asymmetries in visual evoked potentials are very helpful as a diagnostic tool for albinism.⁵ The degree of asymmetries is also variable,⁶ estimated to extend between 2° and 15°.

Anatomical and electrophysiological studies have established that abnormalities of the visual pathway of many different albino mammals extend from the retina to the cortical level. For example, a detailed study in the albino green monkey⁷ has shown no foveal pit in the retina, with a high area of abnormally large ganglion cells in the central retina, increased fibres crossing in the optic tract with regions of the lateral geniculate nucleus and the superior colliculus, normally innervated by ipsilateral afferents, being innervated exclusively by crossed afferents. The laminar pattern of the lateral geniculate nucleus was abnormal, with magnocellular layers more profoundly affected than parvocellular layers. In the primary visual cortex, mapping of the contralateral visual field was normal, whereas the central parts of the temporal retina mapped abnormally in the contralateral visual cortex, forming a monocular map of the central parts of the visual field. The normal map of the contralateral hemifield formed columns alternating with the abnormal map of the ipsilateral hemifield. However, studies indicate that the reorganisation of the cortical topographical representation varies widely in albino animals. Some albino mammals—for example, the Siamese cat or the ferret—have been found to have reordered retinotopic projection with contiguous cortical representation (the “Boston” pattern).^{8,9} However, other studies have shown an absence of any reordering of geniculostriate reorganisation in Siamese cats,¹⁰ called the “Midwestern” pattern. Animals with the Midwestern pattern showed little evidence of activity of cortical cells corresponding to the misrouted fibres. Profound visual field defects have been found—for example, in the misrouted (nasal) retinal areas of albino ferrets.¹¹

In human albinos, functional magnetic resonance imaging studies have shown that the input from the temporal retina is not substantially suppressed and forms a retinotopic mapping that is superimposed on the mapping of the nasal retina in

striate and extrastriate areas.¹² Monocular activation in patients with albinism has shown contralaterally dominated activation of the visual cortex which correlated with the clinical severity of albinism.¹³ The extent to which the increased crossing of optic nerve fibres influences visual perception is unclear. In this issue of *British Journal of Ophthalmology*, Hoffmann *et al*³ aimed to elucidate whether the sensitivity of the abnormally projected temporal retina is normal. They compared temporal and nasal light spot detection sensitivities in the nasal and temporal visual field in 15 patients with albinism. In these patients, sensitivity of the abnormal projecting part of the retina was not reduced. They conclude that in humans, mechanisms of cortical self-organisation make the abnormal crossing fibres available for visual perception. These results, together with functional magnetic resonance imaging investigations mentioned earlier, underline cortical reorganisation and adaptation in human albinism.

However, some earlier investigations showed that visual fields were constricted and had reduced central sensitivity to various degrees in patients with albinism.^{14,15} In a small group of patients with albinism, reduced contrast sensitivity of the temporal visual field has been found. This underlines the fact that some patients with albinism may have reduced visual function in the visual field corresponding to the abnormally crossing fibres.¹⁵ More sophisticated psychophysical tests including motion sensitivity to test the possibility of a more affected magnocellular pathway may show more subtle anomalies in the misrouted retinal fibres. It is also important to investigate a larger number of patients to see whether there are groups with nasal visual field defects or other psychophysical defects more pronounced in the area corresponding to the abnormally crossing fibres. Patient with albinism probably have a spectrum of differences in cortical organisation similar to the Siamese cat. This is supported by a wide range of visual deficits in patients with albinism, which correlate with the cortical reorganisation on functional magnetic resonance imaging data.^{4,13}

The results of Hoffmann *et al*³ in this issue of *British Journal of Ophthalmology* are interesting because they show the developmental plasticity of the visual system establishing compensatory mechanisms to preserve visual function in congenital visual pathway disorders.

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EDITORIAL

Eyes wide s-flt: clearly, avascular fidelity is a vascular endothelial growth factor family affair

Royce Mohan

Soluble vascular endothelial growth factor receptor-1 (s-flt) may be critical for a variety of human corneal angiogenic conditions

Every year, numerous patients successfully receive corneal transplants because this tissue is both immunologically privileged and it has a remarkable resilience to injury induced neovascularisation.¹ The biological explanation of this gift to man and woman in their quest for sustaining life-long vision, enabling corneal transplantation and the more recent corrective vision surgery a reality, has thus far remained an enigma. Notwithstanding, the search for molecules that allow the cornea to preserve its avascular status has rifled through a long list of known antiangiogenic agents, but the testing of experimental mouse models of their deficiencies have all come up without suitable answers.² This negated explanation for a single gene product being responsible for corneal avascularity spawned the next logical idea that biological redundancies in antiangiogenesis could explain the mystical properties of the cornea. Now, contrary to this belief, Ambati *et al.*, looking at eyes from a wide range of mammalian species, have concluded in a recent report that such a formidable antiangiogenic role is, after all, a vascular endothelial growth factor (VEGF) family affair; the bastion of cornea avascularity is soluble VEGF receptor-1 (s-flt).³ In this issue (*see page*

505), Ambati *et al.* provide important proof as to why it is this molecule that needs to be considered critical for a variety of human corneal angiogenic conditions.⁴

The VEGF family, comprised of VEGF-A, -B, -C, -D and placental growth factor, exhibit specific and varied levels of affinity for their receptors, VEGFR1, VEGFR2 and VEGFR3.⁵ Clearly, the requirement for VEGF is so critical to mammalian development that even loss of a single allele of its gene results in embryonic fatality.⁶ Therefore, it is ironic that the principal angiogenic stimulator VEGF-A is present in the avascular cornea. It is this conundrum that set Ambati *et al.* to suggest that not only humans, but other mammals that depend on visual acuity for survival may have adapted mechanisms to counteract VEGF-A in the cornea. Those honed in the yin and yang of the angiogenic balance hypothesis proposed by Judah Folkman⁷ will find vindication that these investigators discovered Nature's choice to select s-flt as the VEGF-A trap in the cornea, no doubt the antagonistic receptor with the highest binding affinity for VEGF-A. Indeed, the K_d for ligand binding of VEGF-A for VEGFR1 is approximately 2–10 pM, which is an order of

magnitude higher than that for VEGFR2.^{8,9} s-FLT is formed by alternative splicing of the pre-RNA and its expression serves as a natural dominant-negative inhibitor of VEGF action because this spliced variant lacks the vital transmembrane and kinase domain found in membrane bound VEGFR1 (mbFlt-1)¹⁰; embraced in this molecular coitus with s-Flt, VEGF-A is thus retained inactive.³

This rationale sounds good for the uninjured cornea where tissue homeostasis levels of VEGF-A are counterbalanced by s-Flt. But what happens when mutations in genes unrelated to vascular development severely compromise corneal epithelial barrier or structural functions causing chronic inflammation to ensue and leading to corneal angiogenesis? To gain support for their hypothesis that it is diminished s-flt levels that make VEGF-A become bioavailable, Ambati *et al.* assessed vascularised corneas of humans suffering from aniridia, a congenital disease caused by mutations in the gene encoding a master eye transcription factor pax-6.^{11,12} Patients with aniridia suffer from multiple eye problems because PAX-6 regulates developmentally controlled pathways that contribute to eye morphogenesis.¹³ This disease is manifested by the smaller size of the globe or “small eye” with differing levels of penetrance of the disorder, most often being characterised by a rudimentary iris. Interestingly, this disease is also naturally found in many other species that present with similar pathogenic anomalies as the human counterpart,¹² with the *Sey* mouse being a popular rodent model that has been relatively well characterised.¹⁴ Thus, when a collection of human aniridia corneas were investigated it was found that s-flt levels were dramatically lowered compared with those from normal human corneas, suggesting that vascularisation of human aniridia may also be regulated by this molecule.

Could these findings have broader impact on other clinical manifestations