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Is myopia a failure of homeostasis?

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ABSTRACT

This review examines the hypothesis that human myopia is primarily a failure of homeostasis (i.e. regulated growth) and also considers the implications this has for research into refractive errors. There is ample evidence for homeostatic mechanisms in early life. During the first few years of life the eye grows toward emmetropia, a process called emmetropization. The key statistical features of this process are a shift of the mean population refraction toward emmetropia and a reduction in variability. Refractive errors result when either this process fails (primary homeostatic failure) or when an eye that becomes emmetropic fails to remain so during subsequent years (secondary homeostatic failure). A failure of homeostasis should increase variability as well as causing a possible shift in mean refraction. Increased variability is indeed seen in both animal models of myopia such as form deprivation and in human populations from the age of 5 or 6 onwards. Considering ametropia as a homeostatic failure also fits with the growing body of evidence that a wide range of factors and events can influence eye growth and refraction from gestation, through infancy, childhood and into adulthood. It is very important to recognize that the refraction of an eye is not a simple trait like eye colour but the consequence of the complex process of eye growth throughout life. To understand how an eye ends up with a specific refraction it is essential to understand all the factors that may promote the attainment and maintenance of emmetropia. Equally important are the factors that may either disrupt early emmetropization or lead to a loss of emmetropia during later development. Therefore, perhaps the most important single implication of a homeostatic view of myopia is that this condition is likely to have a very wide range of causes. This may allow us to identify subgroups of myopia for which specific environmental influences, genes or treatments can be found, effects that might be lost if all myopes are considered to be equivalent.

1. Introduction

The link between myopia and homeostasis has a long heritage. Walter Bradford Canon originally coined the term homeostasis in 1926 (Cannon, 1926). Homeostasis builds upon Claude Bernard's earlier concept of the *milieu intérieur*, which dates back even further to the nineteenth century. The relevance to refraction can also be traced back to before the date that Canon first introduced the term. The concept of 'Emmetropization', whereby the human eye converges toward emmetropia in the years after birth, was first recognized by Straub (1909) and represents the first linkage between the concept of homeostasis and refractive development. Emmetropization was first defined as a statistical phenomenon on the basis that the distribution of refraction in the human population at that time showed a great excess of emmetropia.

Until the advent of animal models of myopia, little progress was made in relation to understanding the mechanisms that might drive this process. In 2004, Josh Wallman and Jonathon Winawer published an extensive review of the myopia literature entitled, 'Homeostasis of Eye Growth and the Question of Myopia' (Wallman and Winawer, 2004). Their review highlighted the wide range of species in which visually guided growth has been found, a finding indicative that the underlying biological mechanisms have been well conserved through evolution. They also described the complex set of control mechanisms have been identified to mediate this process, many of which were discovered by Josh Wallman during his long and distinguished career. Their paper gave renewed prominence to the concept of homeostasis in the regulation of eye growth and, in light of Josh Wallman's great fascination with homeostasis, it is a fitting tribute to revisit the role of this process in the etiology of myopia.

There is now ample evidence that eye growth is regulated in early post-natal life and that optically driven mechanisms contribute to this process. Observations of the recovery of induced myopia in chick, tree shrew and monkey studies demonstrate that such recovery is visually guided (McBrien et al., 1999; Raviola and Wiesel, 1978; Troilo and Wallman, 1991; Wallman and Adams,

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1987). Emmetropization also occurs in animals without any prior manipulation of their refraction (Bradley et al., 1999; Wallman et al., 1981). The process of emmetropization involves a significant reduction in the variability of the refraction as well as shift of the mean population refraction toward emmetropia. The reduction in refractive variability is the hallmark of what would be expected from such active regulation, though it should be noted that passive optical effects might also contribute. While the concept of emmetropization is often given prominence in relation to refractive development, the homeostatic challenge of keeping an eye emmetropic once it has attained accurate focus is also an important aspect of refractive development (Brown et al., 1999). Myopia can result from a failure of emmetropization in infancy as well as a failure of homeostasis to maintain emmetropia later in life.

It is very important to recognize that the refraction of an eye is not a simple trait like eye colour but the consequence of the extensive range of processes that influence eye growth from gestation, through infancy, childhood and into adulthood. In fact myopia (or indeed any refractive error) might be considered to be a surrogate variable for the failure of regulated growth to achieve or maintain emmetropia. This statement can be made on purely logical grounds but a substantial longitudinal study in the UK has demonstrated the influence of both pre-natal and post-natal life course events on myopia development (Rahi et al., 2011). This finding is supported by a range of individual studies that demonstrate the impact on refractive development of individual factors such as: prematurity (Saunders et al., 2002), a range of ocular diseases (Marr et al., 2001; Marr et al., 2003) and even how much time children spend outdoors (Guggenheim et al., 2012; Rose et al., 2008). Genetic factors naturally play a significant role as indicated by high degree of concordance in monozygotic twin studies (Dirani et al., 2008; Hammond et al., 2001). There is also evidence that genetic conditions such as Down's syndrome (trisomy 21) can disrupt the normal pattern of early emmetropization (Al-Bagdady et al., 2011).

To understand how an eye ends up with a specific refraction it is essential to understand all the factors that may promote the attainment and maintenance of emmetropia as well as all the factors that may either disrupt early emmetropization or lead to a loss of emmetropia during later development. Although the number of potential factors that can influence refractive outcome is very large, they can be classified into these two different categories, i.e. regulatory factors, and disruptive factors. The former promote the development and maintenance of emmetropia and the latter serve to promote ametropia. The regulated factors can further be divided in those related to optically guided eye growth of sort seen in animal lens rearing studies and non-optically regulated eye growth such as genetically programed organogenesis and maturation. The unregulated processes may either contribute random variation or a bias away from the ideal state of emmetropia. The final refractive outcome will represent the combination of all these influences. Therefore to fully understand myopia we need to understand the developmental route an eye takes to reach there not just its refraction at any given point.

2. Evidence for regulated and dysregulated growth in animal models

If myopia is indeed primarily the result of dysregulation then we should see the defining characteristic of failed regulation i.e. increased variation or noise. For many decades most experimental studies on refractive development have placed emphasis on the mean refraction and the variability of refraction has been overlooked. The first animal model for myopia involved image deprivation, an intervention that indeed produced a large shift in the mean refractive error in the direction of myopia. What is equally remarkable is the large increase in the variability of refraction as shown in Fig. 1 in which the data from two early pivotal studies in this field have been re-plotted (Raviola and Wiesel, 1985; Wallman et al., 1978).

Fig. 1 shows the narrow distribution of refractions in the control eyes (top panels) and the myopic shift and increased variability in the deprived eyes (lower panels). Even more remarkable is that neither paper makes particular reference to this very dramatic increase in variability, emphasizing instead the change in mean refraction. Such dramatic variability indicates a significant failure of homeostasis as well as a biased error in favor of axial elongation and myopia. A similar pattern can be seen in an early retrospective study of human refraction which compared normal infants with infants with a range of ocular pathology, as shown in Fig. 2 (Rabin et al., 1981). A more recent study on children with a specific form of corneal opacity has demonstrated a very similar pattern of refraction (Meyer et al., 1999). These studies indicate that disruption of visually guided emmetropization by form deprivations leads to a very substantial increase in the variability of refraction – the hallmark of dysregulated growth.

The next major experimental model for myopia involved rearing animals with lenses or contact lenses in front of their eyes. In this paradigm, which was first demonstrated in chicks (Irving et al., 1991; Irving et al., 1992; Schaeffel et al., 1988) and later in a range of species including several primate and proto-primate species (Hung et al., 1995; McBrien et al., 1999; Shaikh et al., 1999; Whatham and Judge, 2001), negatively powered lenses promote myopia and positively powered lenses promote hyperopia. In this situation the induced myopia displays a smaller degree of variation than is seen in deprivation studies. Data from such studies has not typically been presented in histogram form but the published standard deviations demonstrate that, within a range of imposed defocus, compensatory growth can be impressively accurate.

Fig. 3 plots the data from one of the early chick papers (Irving et al., 1992). The top panel shows the resulting intraocular difference in refraction plotted against the lens power in front of the treated eye. Over the range +15 to −10 D, imposed lenses produce very accurate compensation. Outside this range the mean refractive difference deviates from the ideal (dotted line) and the amount of variability increases dramatically. The standard deviations for both the control and treated eyes are shown in the lower panel. This indicates that, over the range for which compensation is accurate, the standard deviation of the treated eye is comparable (though consistently larger) than that of the control eyes. When compensation becomes inaccurate the variability increases dramatically in the manner seen in deprivation studies. In lens rearing studies the generally accurate nature of compensation indicates that the normal homeostatic mechanisms are operating but being driven to an abnormal endpoint by an optical intervention.

Homeostasis is therefore a guiding principal in the two major models of experimental myopia, albeit in different ways. In both paradigms the eyes may be equally myopic but they are myopic for very different reasons and show different statistical features. In the case of deprivation there is a failure of emmetropization characterized by increased variability and a growth bias in favor of axial elongation and myopia. In the case of lens rearing, homeostatic mechanisms are operating but being driven to a different set point by a change in the optical environment (an imposed lens). When the homeostatic mechanisms start to fail in lens rearing and compensation becomes inaccurate, the variability of the refractive outcomes increases dramatically. So in both cases increased variability is a hallmark of homeostatic failure as much as a shift in mean refraction.