

## *Full Length Research Paper*

# **The triplex theory of vision: the fourth dimension**

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### **Abstract**

In 1993, based on my original 1981 research on serial sections of human embryos, I proposed that vision may have three components, rather than just 2—the rods and cones. I termed the third component nonvisual retinal ganglion cells (NVRGCs)(ipRGCs: intrinsically photosensitive retinal ganglion cells NVRGCs: nonvisual retinal ganglion cells, PACAP: pituitary adenylate cyclase-activating polypeptide RHT: retinohypothalamic tract); subsequent researchers identified the same phenomenon, but used a different term, intrinsically photosensitive retinal ganglion cells (ipRGCs). I also reported nonvisual photopigments, one of which, with more recent techniques, has been identified as melanopsin. The purpose of this paper is to synthesize my earlier research with more recent findings to establish the triplex theory of vision and to describe the fourth, *nonvisual*, dimension of vision and its possible future applications for affecting circadian rhythm, pupillary light reaction, hormonal activities, mood changes, thermal regulation, sleep, and other nonvisual functions.

**Keywords:** Triplex theory of vision, nonvisual pigments, melanopsin, ipRGCs, blind sight, cryptochrome.

## **INTRODUCTION**

In addition to visual cues, the visual system also processes photic cues to entrain the circadian rhythm and other non-image-forming functions. Cues about external irradiance are conveyed to many centers, including the main circadian clock, the suprachiasmatic nucleus of the hypothalamus, through pathways that I termed nonvisual fibers with their associated pigments.

The circadian clock must be synchronized to the day-night cycles of the real world to regulate time and other tasks. The diurnal clock influences many physiologic, biochemical, and biologic processes and behaviors. Image-forming photoreceptors are not directly involved in nonvisual functions. Many papers deal with different aspects of this subject (Ecker et al., 2010; Gomez et al., 2009; Hattar et al., 2006; Luan et al., 2011; Provencio et al., 2000). Various factors play important roles in visual tasks and their development, including genetics, the PAX6 gene, and growth factors; the interplay of diurnal, tidal, lunar, and annual rhythmicity; and other cues. As Nilsson (2005, 2009) reported, the phylogenetic tree of photoreceptors, genetics, and opsin-based and ancient cryptochrome-based systems are important in eye development and the evolution of various eye types.

## **Nonvisual Mammalian Photoreceptors**

In 1981, I conducted research on 100 human and chick embryos at the Complutense University in Madrid, Spain, where I discovered nonvisual retinal ganglion cells (NVRGCs) and described them as a third class of mammalian retinal photoreceptors, which constitute approximately 10% of the total retinal ganglion cells in the human embryo (Kashani, 1993). After analyzing serial sections from these human embryos and from chicks, I was the first to note and report the presence of primitive NVRGCs, an observation that prompted me to propose "The Triplex Hypothesis of Vision" (Kashani, 1993).

At that time, my findings were too new and considered controversial, and were rejected by many scientists. Richard Young of UCLA, Yushizumi, and a few others were among the exceptions and wrote me letters that were supportive of my work. Although tracers were not available at that time, I observed novel NVRGCs in the inner neuroblastic layer of the 13 mm human embryo and noted that NVRGCs would later be associated with corresponding nonvisual photoreceptors. At that time, I also introduced a net or system of nonvisual circuits. I presented in detail the collaboration of NVRGCs with the visual system, its cellular aspects, pigments, pathways,

physiology, immunology, and pathophysiology (Kashani, 1993).

### Evolution of Nonvisual Biological Circuits

The focus of the paper was the net of nonvisual biological circuits, which is reminiscent of the visual system of primitive animals, such as *Amphioxus*, from 500 million years ago. Gomez et al. (2009) and Nilsson (2005, 2009) reported that this period encompassed the end of invertebrate dominance and the beginning of the vertebrate period. It is important to note that NVRGCs that develop early are truly nonvisual, since they solely communicate with the nonvisual centers. The types of NVRGCs that develop later are of a different quality, targeting both visual and nonvisual areas. Due to the lack of labeling agents at that time, I was unable to properly probe these cells and their pigments; however, I did predict that early NVRGCs greatly differ from later ganglion cells, according to their location and target tissues (Kashani, 1993). However, the existence of nonvisual NVRGCs was not widely accepted until three decades later.

With attention to the literature and Nilsson (2005, 2009), evolution, in general, proceeded from tasks with small demands on molecular machinery and morphological structures to tasks with gradually more extensive requirements. Regarding the appearance of nonvisual photoreceptors, I feel that the evolutionary sequence of early tasks leading to true vision can be reconstructed with some confidence. This sequence starts with nonvisual photoreception for circadian control in simple animals, followed by directional photoreception for body orientation in more complex animals, which is then replaced by true spatial vision in vertebrates. In terms of structure, this would have corresponded to a sequence from photoreceptor cells without specialized membranes, via directional shading by screening pigment structures, either in the photoreceptor or in an associated cell, leading to the development of membrane folding, which provides enough sensitivity to evolve the first true eyes with spatial vision (Nilsson, 2005, 2009).

### Nonvisual Photopigments

After “The Triplex Hypothesis of Vision” was published (Kashani, 1993), one of the nonvisual photopigments, melanopsin, was identified by Provencio (2000). This is the same substance that I noted and reported in my earlier research, which I named nonvisual pigment, pointing out that different aspects of NVRGCs are mediated by various photopigments and growth factors. Fortunately, three decades later, the results of my original research were indirectly confirmed by others, prompting me to replace the triplex *hypothesis* of vision with “The

Triplex Theory of Vision.” I believe that a variety of pigments appear during evolution and development, each of which has a special function.

### The Role of Growth Factors in Nonvisual Functions

As I reported in my original paper (Kashani, 1993), growth factors play a major role in the development of other parts of the visual system, and their dysfunction is important in pathological processes, which include glaucoma, myopia, sleep disorders, depression, and neurodegenerative diseases. In 1993 I reported:

The duplex theory of vision is concerned with the light level and dual retinal function and refers only to the rod and cone photoreceptor cell systems. There are some visual functions that are not represented by the duplex theory, visual field, or the dark adaptation curve. I do not know how many photopigments exist and which pigment and what circuit plays a role in the photoperiod. Finally, I wonder how the rate of eye growth is regulated. To clarify these concerns, I proposed a new cell type and a third mechanism of vision, which, to my knowledge, has not been described previously (Kashani, 1993).

### The Triplex Theory of Vision

As reported by Weale (1961), the duplex theory of vision, which refers to two types of cells (rods and cones), was proposed by the German anatomist Max Schultze in 1866.

I introduced the third class of photoreceptors in the inner retina, NVRGCs, which form the foundation of “The Triplex Theory of Vision.” The functions of these nonvisual cells can be modified by conventional photoreceptors, other factors, and vice versa (Kashani, 1993, 2002, 2005). Over the years, I have pursued the subject and tried to integrate its functional potential into clinical scenarios (Kashani 2000a, 2000b, 2005, 2009). Nonvisual photoreceptors, in my opinion, also play a role in emmetropia (Kashani, 2000b).

### The Fourth Dimension of Vision

The fourth dimension of vision refers to the function of a variety of centers in the hypothalamus, midbrain, and other related locations in the nervous system, which can be translated as unconscious vision, including blind sight. The NVRGCs play a great role in circadian rhythm, pupillary light reaction, hormonal activities, mood changes, thermal regulation, sleep, and other nonvisual functions. In other words, the fourth dimension is the state of unconscious vision that is beyond our awareness. Without unconscious vision, we are unable to properly control our sleep and wakefulness, deep body

temperature, hormonal activities, and other vegetative functions.

"The Triplex Theory of Vision" and the fourth dimension of vision have now been shown to be a reality that cannot be denied, although some still challenge my theory.

### Scientific Discovery of Nonvisual Elements

Keeler (1924, 1927) of Harvard, who identified blind mice with poor pupillary reaction in 1927, was the first to suggest the possible presence of nonvisual elements in the eye. Foster et al. (1991, 1993) demonstrated circadian photoreception in the rd/rd blind mouse. Pupillary light reaction was attributed to an ocular photopigment (Guler et al., 2008; Lucas et al., 2001).

Spectral sensitivity and photoactivation in pupillary reaction and impairment of pupillary response and optokinetic nystagmus have been well described (Alpern and Campbell, 1962; Bito and Turansky, 1975; Iwakabe et al., 1997; Lau et al., 1992; Yoshimura and Ebihara, 1996). Pupillary light reaction has been attributed to nonvisual photoreceptors, pigments, and a distinct subset of RGCs (Iwakabe et al., 1997; Kashani, 1993; Moore and Lenn, 1972; Moore, Speh, and Card, 1995; Sadun, Johnson, and Schaechter, 1986; Sousa-Pinto and Castro-Correia, 1970).

The retinohypothalamic tract (RHT), which I called nonvisual circuits, is described in many papers (Kashani, 1993; Moore, Speh, and Card, 1995; Sadun, Johnson, and Schaechter, 1986; Sousa-Pinto and Castro-Correia, 1970). The RHT-containing neuropeptide, pituitary adenylate cyclase-activating polypeptide (PACAP), in nonvisual ganglion cells (Sousa-Pinto and Castro-Correia, 1970; Hannibel et al., 1997) is what I identified as "growth factors" at least a decade before, although my report was overlooked at the time.

I communicated my original findings to scientists at the ARVO conference and at other meetings before and after publication in 1993 and acknowledged the responses that I received (Kashani, 1993). Remarkably, some investigators who earlier rejected my hypothesis later published the same idea, using different terminology. As a result of this corroboration, I would like to propose that "The Triplex Hypothesis of Vision" now be presented as "The Triplex Theory of Vision."

### DISCUSSION

Retinal ganglion cells, in my opinion, should be classified into different types, including rhabdomeric and ciliary. In vertebrates, ciliary photoreceptors usually refer to cones and rods (Arendt et al., 2004; Kashani, 1993, 2010). NVRGCs are primitive and rhabdomeric, with nonvisual pigments and trophic factors wrapped in a membrane (Kashani, 1993, 2010). I am grateful to the scientists who

have confirmed many of my original findings, but wish they had acknowledged my contribution.

### Appropriate Terminology

I believe that the term intrinsic photosensitive retinal ganglion cells (ipRGCs) is both redundant and inappropriate. In 1993, two decades earlier, I introduced and reported the more meaningful term nonvisual retinal ganglion cells, or NVRGCs (Kashani, 1993). I also believe that the more recent term, ipRGCs, is not appropriate for describing the nonvisual character of these cells, because ipRGCs, without any pigments, target the same centers and have some nonvisual functions (Guler et al., 2008; Kashani, 1993; Putnam, Butts, and Ferrier, 2008). Therefore, the older term, NVRGCs, is more accurate and more descriptive (Kashani, 1993).

### Controversy over Nonvisual Pathways

In addition, there is a controversy among some of the current publications regarding the pathway of ipRGCs and Y-like RGCs that lead to the dorsal raphe nucleus (Luan et al., 2011). Y-like RGCs are apparently preserved in every mammalian species but, despite the lack of pigment, are nonvisual (Luan et al., 2011), and in contrast with the Hattar et al. (2006) finding of central projection of melanopsin-expressing RGCs (mRGCs) in the mouse. The work of Putnam, Butts, and Ferrier (2008) and Gomez et al. (2009) on the *Amphioxus* genome and the evolution of the chordate karyotype provides valuable insights into pigment appearance and light-sensitive cells, although only a few photoreceptors exist in the neural tubes of animals. Rhodopsin-like sensitivity in extraretinal photoreceptors (Foster, Follett, and Lythgoe, 1985) and opsin in the inner retina (Provencio et al., 2000) are very important findings regarding non-image-forming activities.

The visual RGC axons that develop early, along with NVRGCs, do not innervate their targets in the lateral geniculate nucleus (LGN) until later, since the LGN cells have not yet been born. In the cat, RGC axons arrive at the LGN about midway through the gestational period of 65 days, when the LGN has not yet become laminated, and the visual cortex is an early developmental process (Schatz and Luskin, 1986).

### CORROBORATION OF FINDINGS

The existence of NVRGCs, which are, in reality, the same as mRGCs and ipRGCs, has been demonstrated and accepted by Berson et al. (2002), Ecker et al. (2010), Guler et al. (2008), and Provencio et al. (2000). Despite

this corroboration of my findings, my more accurate and descriptive term, NVRGCs, is not widely used; instead, the term ipRGCs is substituted, without referring to my original paper (Kashani, 1993). As stated earlier, however, I appreciate the subsequent work that has indirectly confirmed my findings.

## CONCLUSION

What is important now is to conduct further research to explore the ways NVRGCs and their associated pigments may affect the dysfunction of nonvisual systems such as circadian rhythm, pupillary light reaction, hormonal activities, mood changes, thermal regulation, and sleep. In addition, there may be some other types of nonvisual photoreceptors in the inner retina and pigments associated with them that have not yet been discovered.

If the capabilities of these cells could be harnessed, or pharmaceutically controlled, perhaps new treatment modalities could be developed for a wide variety of medical problems: hormonal imbalances that affect sexuality, mood, gastrointestinal function, and obesity; sleep disorders, including insomnia, narcolepsy, jet lag, and the circadian rhythm dysfunction of shift workers; body temperature dysregulation; and more.

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