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Review Article

Triplex Theory and unconscious vision
Study of the Visual system in Human Embryo

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Abstract

Embryology of the human nervous system is fascinating particularly, early in embryogenesis. If we could follow the evolutionary steps from Billion years ago, we could find out a lot of unknowns easier and earlier. There are interesting work by scientists such as M. Desmond and R. O, Rahilly; Anita Hendrickson... However, There is very little information of the nonvisual photoreception and certainly nothing about the triplex hypothesis and theory of vision in the study of human embryo. In reviewing the literature I could not find report of nonvisual photoreceptors in inner retina except in my papers the triplex hypothesis1993 / theory of vision 2013. in 1981 I noted the Novel nonvisual retinal ganglion cells (NVRGCs) which appear early in embryonic period published in 1993. But, because lack of such study before, my hypothesis was rejected, for no reason, by a few who later published the very same topic without even mentioning my name. That is why I was and I am questioning those authors by several comments, in last two years; these comments on their papers were posted in PLOS One And I appreciate PLOS editors for such clarification , however the authors have not responded as yet. In 1993, based on the original research on serial sections of human embryo in 1981, I proposed that vision may have three components, the rods, cones and a novel photoreceptor cells. I termed the third component nonvisual retinal ganglion cells (NVRGCs). These non visual retinal photoreceptors (Primitive ganglion cells) have a role in proper formation and development of the visual system. After my report subsequent scientists presented exactly the same idea as their own. they only have introduced new terminologies decades later such as: " PACAP: pituitary adenylate cyclase-activating polypeptide, and intrinsic photosensitive retinal ganglion cells (ipRGCs), just to avoid my name and my reports: "nonvisual retinal ganglion cells (photoreceptors) and the Triplex Theory of vision." The evolution of the eye takes more than 600 million or a billion years and I will address it in a separate paper. The vertebrate retina as I noted divided into the inner and the outer retina: 1-The inner retina appear in first four months of intrauterine life consisting of primitive rhabdomeric net, in evolution of chordates which include: Ganglion cells, Amacrine and Horizontal cells. The Ganglion cells's axon transmit the retinal output to the higher visual and nonvisual centers. It is important to know that earliest ganglion cells (As I see in embryos) are non visual because of their connection to nonvisual centers, but later they will participate to the visual centers too. 2-The outer retina consists of ciliary (Rod, Cone and Bipolar cells) with ciliary origin and make synaptic contact onto the rhabdomeric receptors (ganglion cells) in the inner retina. these two different types of cells while are independent but working in proximity to transmit nonvisual and visual information to brain. The purpose of this paper is to confirm my earlier findings and present Blind Sight along with the Triplex Theory of Vision. Arendt 2008 in his studies, almost came to the same conclusion, (If I understand it right). So hereby , I am synthesizing my earlier research with more recent findings to establish the triplex theory of vision and to describe the unconscious vision which is mainly related to early ganglion cells and rhabdomeric system. These will require a lot of genetic (Hox, Pax 6 etc.) and embryologic study.

Keywords: Triplex Theory of Vision, Nonvisual Ganglion cells, Nonvisual pigments, Blind sight, opsin evolution, Proto-eye. "

Introduction

In addition to visual cues, the visual apparatus processes photic information to entrain the circadian rhythm and other non–image-forming functions. Cues about external irradiance are conveyed to many brain

centers, including the Suprachiasmatic nucleus (SCN) of hypothalamus, through pathways that I termed nonvisual fibers 1993.

The circadian clock must be synchronized to the day-night cycles of the real world to regulate time and other tasks and may have influence in image forming network. The diurnal clock influences many physiologic, biologic processes and behaviors. Image-forming photoreceptors are not directly involved in nonvisual functions. Many papers dealing 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) have been published after my 1993 report but, not mentioning my related papers: The Triplex Hypothesis of Vision "THV" 1993 in the Annals of Ophthalmology and The Triplex Theory of Vision IRJBCS Vol (1) 1-5. Various factors play important roles in visual tasks and their development, including genetics, the PAX6 gene, growth factors, 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.

Materials and Methods

In 1981, I conducted research on 100 human and chick embryos at the Complutense University Madrid, Spain, where I discovered nonvisual retinal ganglion cells (NVRGCs), circuit and their net work. I 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 by rivals controversial, and were rejected by many scientists. Richard Young of UCLA, Yushizumi M, and others were among the exceptions and wrote me letters supporting my work. Although tracers or markers were not available at that time for me, I observed novel NVRGCs in the inner neuroblastic layer of the 13.5 mm human embryo and noted that NVRGCs would later be connected with corresponding nonvisual photoreceptors. At that time, I also introduced a net or system of nonvisual circuits in detail, the collaboration of NVRGCs with the visual system, its cellular aspects, pigments, pathways, physiology, immunology, and their pathophysiology (Kashani, 1993).

The focus of the research was the network of nonvisual biological system , which is reminiscent of the visual system of the primitive animals, such as Amphioxus, from 550 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. It is important to note that NVRGCs that develop early are truly nonvisual (rhabdomeric), 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 and instrumentation at that time, I was unable to properly probe these cells and their pigments; however, I predicted that early NVRGCs greatly differ from later ones, according to their location and target tissues (Kashani, 1993). However, the existence of NVRGCs was not widely accepted until three decades later.

With attention to the literature and Nilsson (2005, 2009), evolution, in general, proceed from tasks with small demands on molecular machinery and morphological structures to tasks with gradually more extensive requirements. Regarding the appearance of eye spot and nonvisual photoreceptors, I feel that the evolutionary sequence of early tasks leading to true vision can be reconstructed with some A.A. Kashani,M.D. 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 higher animals and 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 and stacking, along with magnification which provides enough sensitivity to

evolve the first true eyes with spatial vision (Nilsson, 2005, 2009).

Nonvisual Photopigments and The Role of Growth Factors in developing vision.

After "The Triplex Hypothesis of Vision" was published with difficulties and some opposition (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, as a 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 which 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 role and functions. All of these phenomenon are controlled by genes such as Pax 6: Universal Master control genes Hox gene clusters .... with different manifestation in different media but, I believe that monophyletic concept of Charles Darwin 1872 might be correct, I will address this part in separate report.

As I reported in my original paper (1993), growth factors play a role in the development of other parts of the visual system, and their dysfunctions important in pathological processes, which include glaucoma, myopia, sleep disorders, depression, and neurodegenerative diseases, These were never mentioned before. It has been noted that growth and development of a blind twin is retarded and behind than his/her normal counterpart.

In 1993 I reported

The duplex theory of vision is concerned with the light level, 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 uplex theory, visual field, or the dark adaptation curve. I do not know how many photopigments exist and which pigment and what circuit play 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, 2013).

The Duplex Theory of Vision reported by Weale (1961) referring only of two type receptors Rods and Cones (in outer retina) was discovered 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, 2013). Nonvisual photoreceptors, in my opinion, play a role in emmetropia too (Kashani, 2000b).

The NVRGCs are indeed the fourth dimension of vision referring 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 (Kashani 2013). "The Triplex Theory of Vision" and the fourth dimension of vision have now to be a reality that cannot be denied, although some are still challenging 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).

But, No one has worked in human embryo and never was even suggestion of NVRGCs in early human

embryo's inner retina and no one talk in regards of Triplex Hypothesis/Theory of Vision. My work on the inner retina of human embryo was unique and unparalleled.

I must appreciate PLOS for publishing several of my comments recently which are still remained unanswered. Spectral sensitivity and photoactivation in pupillary reaction, 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, 2013; 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 a part of nonvisual circuits, is described in many papers (Kashani, 1993; Moore, Speh, and Card, 1995; Sadun, Johnson, and Schaechter, 1986; SousaPinto 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 called 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 terminologies. As a result of this corroboration, I would like to propose that "The Triplex Hypothesis of Vision" now be replaced by "The Triplex Theory of Vision."

Discussion

Retinal ganglion cells, in my opinion, should, at least be classified into different types which were explained and enumerated in my 1993 paper, including rhabdomeric photoreceptors. The ciliary photoreceptors which appear later. In vertebrates these two types receptors placed side by side. The ciliary photoreceptors usually refer to cones and rods (Arendt et al., 2004; Kashani, 1993, 2010, 2013). NVRGCs and inner retinal cells are primitive and rhabdomeric, with nonvisual pigments and trophic factors wrapped in a membrane (Kashani, 1993, 2010, 2013). I am grateful to the scientists who have confirmed many of my original findings, but wish they had courage to acknowledge my contribution. Unfortunately the main problem is that some scientists forget/ missed /overlooked or they do not want to cite related papers.

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 misleading and cannot describe 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 descriptive and far better (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 is 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 A.A. Kashani,M.D. 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 laminated, and the visual cortex is on 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 after my work 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, still is not widely used only on the political ground and not on scientific basis. They have not even acknowledged my unique research which is again not ethical. my earlier related contribution. However, I appreciate the subsequent work that indirectly confirmed my findings. I appreciate any comments and correction. In addition, I hope they respond to my numerous comments in the Journals such as PLOS One and wikipedia.

Conclusion

What is important now is to conduct further research to explore the ways NVRGCs and their associated pigments may affect the function of nonvisual systems such as circadian rhythm, pupillary light reaction, hormonal activities, mood changes, thermal regulation, and sleep/wakefulness. 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 encountered. 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.

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