• Hypothesis •

ipRGCs: possible causation accounts for the higher prevalence of sleep disorders in glaucoma patients

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Received: 2016-12-02 Accepted: 2017-02-06

Abstract

• Sleep accounts for a third of one's lifetime, partial or complete deprivation of sleep could elicit sever disorders of body function. Previous studies have reported the higher prevalence of sleep disorders in glaucoma patients, but the definite mechanism for this phenomenon is unknown. On the other hand, it is well known by us that the intrinsically photosensitive retinal ganglion cells (ipRGCs) serve additional ocular functions, called non-image-forming (NIF) functions, in the regulation of circadian rhythm, melatonin secretion, sleep, mood and others. Specifically, ipRGCs can directly or indirectly innervate the central areas such as suprachiasmatic nucleus (SCN), downstream pineal gland (the origin of melatonin), sleep and wake-inducing centers and mood regulation areas, making NIF functions of ipRGCs relate to sleep. The more interesting thing is that previous research showed glaucoma not only affected visual functions such as the degeneration of classical retinal ganglion cells (RGCs), but also affected ipRGCs. Therefore, we hypothesize that higher prevalence of sleep disorders in glaucoma patients maybe result from the underlying glaucomatous injuries of ipRGCs leading to the abnormalities of diverse NIF functions corresponding to sleep.

• **KEYWORDS:** glaucoma; intrinsically photosensitive retinal ganglion cells; sleep disorders

DOI:10.18240/ijo.2017.07.22

Guo ZZ, Jiang SM, Zeng LP, Tang L, Li N, Xu ZP, Wei X. ipRGCs: possible causation accounts for the higher prevalence of sleep disorders in glaucoma patients. *Int J Ophthalmol* 2017;10(7):1163-1167

INTRODUCTION

Glaucoma, the leading cause of irreversible blindness in the world, is characterized by a degenerative and progressive optic neuropathy that leads to structural and functional changes in the optic nerve and retinal ganglion cells (RGCs)[1]. Previous studies have reported the incidence of sleep disorders, which was characterized by excessive daytime sleepiness, delayed onset of sleep, shortened sleep duration, and increased spontaneous arousals[2-3], was higher in glaucoma patients than that in the control subjects[4-5]. It is well known that many factors contribute to sleep disorders in glaucoma patients, including concerns about the disease, ophthalmic pain, the burden of treatment, and the effects of comorbidities such as depression and anxiety. However, the pathogenic mechanism of these problems has not been fully characterized. Intrinsically photosensitive retinal ganglion cells (ipRGCs), are a distinct subpopulation of RGCs, functioning as a kind of novel photoreceptor which expresses melanopsin[6]. Studies recently show that ipRGCs can affect sleep through direct and indirect pathways. The direct pathway is to influence the onset and homeostasis of sleep by regulating the sleep and wake-inducing centers[7]. The indirect pathways, which contain the ipRGCs projection to suprachiasmatic nucleus (SCN) regulating melatonin secretion[8] and the projection to mood regulation areas[9], could impact many aspects of sleep. Some research suggested ipRGCs damage in glaucoma, along with diverse dysfunctions and a decrease in the number of ipRGCs[10-14]. These studies strongly indicate a connection between the ipRGCs and higher prevalence of sleep disorders in glaucoma patients.

INTRINSICALLY PHOTOSENSITIVE RETINAL GANGLION CELLS

The Characteristics of ipRGCs More than a decade ago, it was reported that there were exclusively cone and rod light sensitive cells which transmit polysynaptic information *via* the optic nerve to the brain. Subsequently, scientists identified the third class of photoreceptor in rodent retina that was named melanopsin-containing RGCs or ipRGCs which exhibit intrinsic photosensitivity[6,15]. More than 95% ipRGCs are localized in the ganglion cell layer, with 5% found in the inner nuclear layer in rodent retina[6]. These distinct light transduction cells, which can detectirradiance of light, are sensitive to the wavelength of around 480 nm[15-16]. The ocular light detecting system is therefore comprised of pathways containing the classic image-forming system involving rods and cones, and the non-visual phototransduction system

involving the retinohypothalamic tract to the SCN, which is the central circadian pacemaker in the anterior hypothalamus. In addition to ipRGCs projection to the SCN, it also innervates other regions throughout the brain, such as the olivary pretectal nucleus[6], which is the relay system for the pupillary light reaction, the ventrolateral preoptic (VLPO) area and lateral hypothalamus (LH)[7], which are important for the regulation of sleep. Furthermore, the areas in relation to mood regulation, involving the medial amygdala and lateral habenula (LHb), as well as their downstream areas (*i.e.* the ventral tegmental area and raphe)[6,9,17-18], are also projected by ipRGCs. Recently, studies reported that the classic and non-classical visual system could influence each other as well[19], which deserves further study. However, the discoveries of more ipRGCs target areas and their related functions have suggested connections between ipRGCs and diseases.

The Relationship Between Sleep and ipRGCs Although the intact physiological mechanism of sleep is unknown, it is thought that there are sleep and wake-inducing systems in the brain, which are mutually inhibiting in the maintenance of sleep homeostasis[20-21]. ipRGCs make direct projection to the VLPO and LH, the former of which expresses inhibitory neurotransmitters γ-aminobutyric acid (GABA) and galanin, and plays a key role in the promotion of sleep[7]. The LH expresses hypocretin, which has excitatory effects on almost every wake-promoting neuronal group of ascending reticular activating systems and enhances the wakeful state through activating wake-inducing systems[22-24]. Also, ipRGCs *via* SCN and downstream neurons indirectly project to the VLPO, LH, and the locus coeruleus (LC), which plays an important function in wake-inducing system[25-26]. ipRGCs perceive ambient light during daytime, and send projection to active the LH and the LC respectively through excitatory neurotransmitters glutamate and orexin[24,27-28]. ipRGCs also *via* interneurons output the GABA-ergic signals to VLPO to inhibit sleep[28]. The overall effect of light during daytime is to maintain wakeful state. And during nighttime, ipRGCs without light input may disinhibit the VLPO and can sustain sleep state[23,28]. These structural and functional connections between ipRGCs and sleep centers provide the basis for deciphering sleep disorders in glaucoma patients.

ipRGCs perceive the environmental zeitgebers and deliver signals *via* retinohypothalamic tract to the SCN, which oscillates with a periodicity that is slightly longer than a solar day[29-30]. The SCN integrates the ambient information perceived by ipRGCs and aligns with the environmental period of precisely 24h to adapt environment, then emits the corrected rhythmic signals to control the rhythm and concentrations of melantonin (MT)[8]. MT, a metabolite of tryptophan in the plasma, has periodic plasma concentrations with the peak concentration at approximately 2:00 a.m.[31-32]. Previous trials suggested short-wavelength light exposure of ipRGCs could elicit phase shift of MT's rhythm[33]. ipRGCs are exposed to blue light with different intensity or duration, which can inordinately inhibit MT secretion[34-35]. Considering that MT has close interaction with sleep[36] and could affect sleep through many aspects: altering neurotransmitters in the cerebrum involving norepinephrine, acetylcholine, and 5-hydroxytryptamine; regulating the rhythm of SCN by binding to MT receptors in the SCN; affecting slow-wave sleep corresponding to MT's effect on body temperature[8,32,37-38]. We could conclude that ipRGCs relaying at SCN can influence sleep by regulating the synthesis and secretion of MT.

In addition to these functions, ipRGCs also innervate to MA, LHb and their downstream areas, which are critical in regulating mood. Accumulating evidence in humans and animals has linked mood disorders to abnormalities of ipRGCs input, and exposure to light at night may alter mood by disrupting circadian rhythm[39-42]. Previous studies have reported that mice exposed to aberrant light directly influenced mood regulation, without disrupting circadian rhythms[43], suggesting that unnatural light exposure can directly affect mood. It is generally accepted that there exists bidirectional relationship between sleep disorders and depression, and an increased incidence of abnormal sleep is associated with mood disorders[44]. So we suggest that mood disorders resulting from abnormalities of ipRGCs can elicit sleep disorders in glaucoma patients.

The ipRGCs Lesions in Glaucoma Previous studies have reported that glaucoma, an ocular disorder characterized by loss of RGCs, could affect the numbers and functions of ipRGCs[10-12,14]. The initial studies using mutant DBA/2J mice reported that glaucomatous RGCs degeneration was not cell type specific, which indicated that ipRGCs might also be damaged in glaucoma[10]. Additional studies reported that melanopsin-containing RGCs were damaged in rats with chronic ocular hypertension[12], and decreased numbers of ipRGCs resulting from chronic ocular hypertension were observed[11,14].

Besides these animal studies, there have been clinical studies focusing on glaucoma and ipRGCs. With the discovery of melanopsin and the characterization of the non-image-forming (NIF) functions system, studies showed that the post-illumination pupil response (PIPR) to blue light could be a specific measure for testing the intrinsic activity of ipRGCs[45-46]. Clinical researches showed that blue light PIPR significantly decreased in glaucomatous patients when compared with age-matched controls[13,47]. And there was a correlated decrease in the PIPR with the increasing severity of glaucomatous neuropathy[47]. The discovery of a positive correlation between blue light PIPR and retinal nerve fiber layer (RNFL) thickness showed that decreased numbers

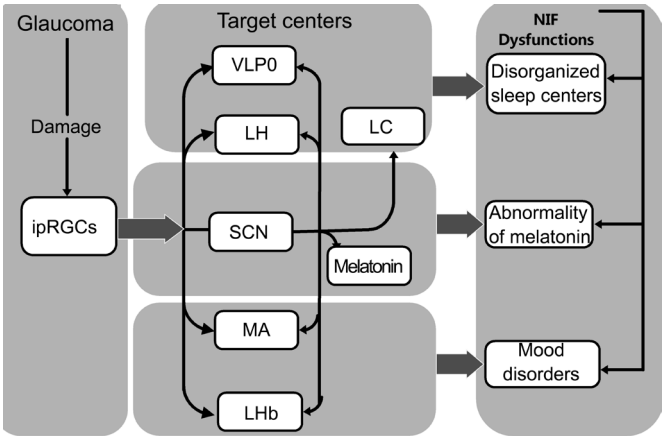

Figure 1 A schematic view of the glaucomatous lesions in ipRGCs leading to various NIF dysfunctions corresponding to sleep.

of ipRGCs was potentially related to the reduced RNFL thickness[48-49]. Some works showed the abnormality of circadian rhythm or light-suppression of MT secretion, may also be caused by disrupted ipRGCs in glaucoma[50-51]. These results suggest that glaucoma could disrupt ipRGCs and leads to various dysfunctions of ipRGCs.

THE HYPOTHESIS

Previous studies have demonstrated the glaucomatous lesions of ipRGCs and the various relationships between ipRGCs and sleep. So we propose the following hypothesis about the mechanism of sleep disorders in glaucoma: the higher prevalence of sleep disorders in glaucoma patients may be caused by the underlying glaucomatous injuries of ipRGCs, leading to diverse NIF dysfunctions corresponding to sleep. Abnormal NIF functions related to sleep involve the disturbance of sleep centers, the abnormality of MT and mood disorders (Figure 1)[52]. Reproduced from reference[52].

DISCUSSION

Glaucoma, a progressive and to date incurable ocular disease, will affect 79.6 million people around the globe and 6 million in China by 2020[53], meanwhile the higher prevalence of sleep disorders in glaucoma worsens the life quality of glaucoma patients. Prior studies attributed the sleep disorders of glaucoma patients to the mental-psychological factors or ocular ache. Nevertheless, the discovery of ipRGCs and NIF functions submits us the implications that ipRGCs lesions in glaucoma leading to the disturbance of sleep centers, the abnormality of MT and mood disorders may be the possible causation accounting for sleep disorders in glaucoma patients. It should be mentioned that sleep disorders in the present article do not include (obstructive) sleep apnea syndrome, which is are search focus between sleep and glaucoma[54] and has it's specific pathomechanism.

Recent discoveries revealed that ipRGCs were not uniform population. Based on morphological and electrophysiological properties, the ipRGCs were identified as at least five subtypes, namely M1-M5[9,55]. Each subtype has specific cell size, melanopsin protein level and central projections[56-58]. Specific central projections provide specific functions for each ipRGCs subtype. So the specific biological properties of each ipRGCs subtype should be taken into account in future experiments as well as in clinical studies. When exploring the correlation between disrupted NIF functions and abnormal structural parameters, the contribution of ipRGCs subtypes also should be allowed for.

In summary, there exists objective fact and data to support our hypothesis, which would be helpful for individual therapy of sleep disorders in glaucoma patients, thus increasing the life quality of glaucoma patients.

ACKNOWLEDGEMENTS

Foundations: Supported by the National Natural Science Foundation of China (No.81200687); the National Major Scientific Equipment Program (No.2012YQ12008005); the Young Scholar for the Doctoral Program of Higher Education of China (No.20120181120014).

Conflicts of Interest: Guo ZZ, None; **Jiang SM,** None; **Zeng LP,** None; **Tang L,** None; **Li N,** None; **Xu ZP,** None; **Wei X,** None.

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