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# Suppression of Melatonin Secretion in Totally Visually Blind People by Ocular Exposure to White Light

## *Clinical Characteristics*

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***Purpose:*** Although most totally visually blind individuals exhibit nonentrained circadian rhythms due to an inability of light to entrain the circadian pacemaker, a small proportion retain photic circadian entrainment, melatonin suppression, and other nonimage-forming responses to light. It is thought that these responses to light persist because of the survival of melanospin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs), which project primarily to the circadian pacemaker and are functionally distinct from the rod and cone photoreceptors that mediate vision. We aimed to assess the integrity of nonimage-forming photoreception in totally visually blind patients with a range of ocular disorders.

***Design:*** Within-subject, dark-controlled design.

***Participants:*** A total of 18 totally visually blind individuals (7 females; mean age ± standard deviation = 49.8±11.0 years) with various causes of blindness, including 3 bilaterally enucleated controls.

***Methods:*** Melatonin concentrations were compared during exposure to a 6.5-hour bright white light (~7000 lux) with melatonin concentrations measured 24 hours earlier at the corresponding clock times under dim-light (4 lux) conditions.

***Main Outcome Measures:*** Area under the curve (AUC) for melatonin concentration.

***Results:*** Melatonin concentrations were significantly suppressed (defined as ≥33% suppression) during the bright-light condition compared with the dim-light condition in 5 of 15 participants with eyes (retinitis pigmentosa, n = 2; retinopathy of prematurity [ROP], n = 2; bilateral retinal detachments, n = 1). Melatonin concentrations remained unchanged in response to light in the remaining 10 participants with eyes (ROP, n = 3; optic neuritis/neuropathy, n = 2; retinopathy unknown, n = 2; congenital glaucoma, n = 1; congenital rubella syndrome, n = 1; measles retinopathy, n = 1) and in all 3 bilaterally enucleated participants.

***Conclusions:*** These data confirm that light-induced suppression of melatonin remains functionally intact in a minority of totally visually blind individuals with eyes. None of the bilaterally enucleated individuals or those with phthisis bulbi was responsive to light; of the remainder, half were responsive to light. Although inner retinal damage is associated with a high likelihood that nonimage-forming photoreception is absent, the impact of outer retinal damage is more ambiguous, and therefore the assessment of the presence, attenuation, or absence of nonimage-forming light responses in totally blind patients requires careful individual confirmation and cannot simply be assumed from the type of blindness. *Ophthalmology 2018;■:1–12 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Appropriately timed ocular exposure to light inhibits pineal melatonin secretion in humans.[1–3] This response is mediated exclusively by the eyes via the suprachiasmatic nuclei (SCN), the site of the circadian pacemaker, which receives photic input from the retina via the retinohypothalamic tract (RHT).[4,5] Efferents from the SCN project to the pineal via the superior cervical ganglion and are required for both the synthesis and light-induced suppression of melatonin. Photic transmission via the RHT-SCN-pineal pathway originates from a subset (~0.5%) of intrinsically photosensitive retinal ganglion cells (ipRGCs) containing the photopigment melanopsin.[6,7] These ipRGCs are distributed widely across the retina and project to the ventromedial region of the hypothalamic SCN.[8–13]

The functional integrity of the retina-RHT-SCN-pineal pathway in visually blind humans can be determined by assessing whether ocular light exposure (LE) can suppress melatonin secretion.[14–16] Bilateral lesions of the neural



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pathway between the retina and the SCN, for example, via severing the optic nerve or enucleation, abolish light-induced suppression of melatonin production or photic entrainment of the circadian clock.[17] Consequently, the majority of totally visually blind people (those without conscious light perception) cannot maintain circadian entrainment to the 24-hour light-dark cycle and exhibit non−24-hour sleep-wake rhythm disorder.[18–21]

Classic rod and cone photoreceptors can contribute, but are not required, to mediate melatonin suppression or other "nonimage-forming" responses to light such as circadian phase resetting.[22,23] The specificity of this nonvisual pathway is underscored by observations that a small fraction of totally visually blind individuals can maintain melatonin suppression and circadian entrainment to light in the absence of light perception and negative neuro-ophthalmologic tests,[14,16] confirming that the retina-SCN-pineal axis is functionally intact. In addition, wavelength-dependent melatonin suppression has been demonstrated in a blind individual,[24] with substantial suppression during 460 nm blue LE, and no suppression at 555 nm, consistent with a melanopsin-mediated, and not photopic, response. Similar blue-light sensitivity has been shown for pupillary reflex,[25] unconscious "visual" perception[24,26] and activation of brain areas associated with alertness and mood[26] in such totally visually blind but circadian photoreception intact blind patients.

Given the rarity of totally visually blind patients who retain melatonin suppression, circadian entrainment or pupillary responses to light (only 7 such patients reported in the literature to date; subject codes are from Brigham and Women's Hospital); Czeisler et al in 1995[14] (n = 3; nos. 1053, 1155, and 1459); Klerman et al in 2002[16] (n = 1; no. 1492); Zaidi et al in 2007[24] (n = 2; no. 22CS and female); Vandewalle et al in 2013[26] (n = 1, nos. 2811, 1492, and 22CS), we aimed to examine the prevalence of a positive melatonin suppression response in a larger cohort and examine the relationship between the cause of blindness and retention of functional nonimage-forming responses to ocular LE.

## Methods

### Study Participants

Case histories, ophthalmological examinations, and a melatonin suppression test were performed in 18 healthy, blind patients, including 15 with at least 1 natural eye present (8 male, 7 female) and 3 bilaterally enucleated male patients (Table 1). The test was performed within a broader research study of circadian rhythms in the blind, including assessment of circadian entrainment using field-based techniques.[19] All but 5 of the participants had confirmed non−24-hour rhythms in urinary 6-sulphatoxymelatonin (aMT6s) (24.10−24.79 hours). The other 5 individuals had confirmed 24-hour rhythms in aMT6s (1492, 22CS, 23CM, 2740, 2811). Four of the 18 participants tested were assessed for melatonin suppression on 2 or more occasions (1451, 1492, 22CS, 23CM). Some results have been reported previously in 4 participants (1451, 1492, 22CS, 2811; participant 1451 [with eyes present] was reported as participant no. 9 in Czeisler et al in 1995,[14] as 1451 in Klerman et al in 1998,[15] and as participant no. 2 in Klerman et al in 2002[16]; participant 1492 was reported as participant no. 5 in Klerman et al in 2002,[16] and participant no. 3 in Vandewalle et al in 2013[26]; participant 22CS was reported as the single blind male participant in experiment no. 1 in Zaidi et al in 2007,[24] as the single blind male participant in Gooley et al in 2012,[25] and as participant no. 2 in Vandewalle et al in 2013[26]; participant 2811 was reported as participant no. 1 in Vandewalle et al in 2013[26]). Only the results from the most recent melatonin suppression assessment are included in this report.

Participants were recruited from the community via newspaper, newsletter, and radio advertisements placed through numerous institutions, associations, and groups for visually impaired and blind persons across North America. Each participant provided written informed consent before participating in both the screening procedures and inpatient protocol, and each participant was provided a copy of the text of the research study consent form in Braille, computer text, or audio CD format as requested. Institutional Review Board approval was obtained for all study procedures by the Partners Human Research Committee. The experiment was performed in accordance with the Declaration of Helsinki.

Participants were required to be ambulatory, to be taking no prescription medications, and to have no major health, psychologic, or neurologic disorders other than complete blindness and sleep disruption associated with their blindness.[27,28] Participants were healthy based on a comprehensive physical and psychologic examination, blood and urine tests, and electrocardiogram. Urine toxicology (i.e., for caffeine, nicotine, narcotics) tests confirmed that all participants were drug-free during screening and on admission to the inpatient study.

Participants completed the Sleep Disorders Questionnaire.[29] All were negative for risk of sleep apnea; 2 participants (23BP, 26Q5) met the criteria for narcolepsy risk; 2 (22A6, 26Q5) for sleep disruption associated with psychiatric disorders; and 7 (22J2, 27A8, 23BP, 2347, 27Q2, 26Q5, 2306) for nocturnal myoclonus, interpreted as general sleep interruption.[29] Participants reported no history of working night shifts or long-distance travel across 1 or more time zones in the last 3 years before their screening.

### Ophthalmologic Testing

On initial screening, participants reported having no conscious light perception. Participants were studied regardless of the cause of blindness (with the exception of cortical blindness), age and rapidity of vision loss, presence or absence of eyes, or self-reported sleep disturbances. An ophthalmologic assessment was performed in all blind participants with eyes before or after the inpatient study. As part of the eye examination, the following descriptions were noted for each eye: history of vision loss, description of appearance of globe/optics, ocular motility, a fundoscopic examination, and pupil reflex to light was examined with a slit lamp with the brightest light of an indirect ophthalmoscope. Visual evoked potential results were available in 9 of the 15 intact blind participants using a flash stimulus (hand-held stroboscopic lamp) at 2 per second. Electroencephalography was recorded from Fz-Oz, Pz-Oz, Fz-O1, and Fz-O2. Each eye was tested individually in a darkened room during 2 separate trials by covering 1 eye during ocular exposure to the strobe flash stimulus. Sensitivity was 3 uv/cm, and the average peak-to-peak ambient noise level was 2 uv. For the 3 participants who were bilaterally enucleated, cause and history of blindness were obtained by self-report, and a physician confirmed the absence of eyes during the screening physical examination.

### Inpatient Protocols

The protocol consisted of assessing melatonin concentrations under dim light conditions during a constant routine (CR) protocol and under bright light conditions during a LE protocol (Fig 1). The CR