Circadian photoreception in humans:
More than meets the eye

Steven W. Lockley, Ph.D.
Division of Sleep Medicine, Brigham and Women’s Hospital, Boston, MA
Division of Sleep Medicine, Harvard Medical School, Boston, MA

DISCLOSURE: Dr. Lockley has received lecture fees from Takeda Pharmaceuticals North America, consulting fees and conference travel support from Apollo Lighting, and equipment for use in Investigator-initiated and federal research studies from Philips Lighting and ResMed. Dr Lockley has received Investigator-initiated research grants from Apollo Lighting, Philips Lighting, Respironics and Alcon Inc. Dr. Lockley holds a process patent for use of short-wavelength light for resetting the human circadian pacemaker, assigned to Brigham and Women's Hospital.
The ‘body clock’ or circadian pacemaker is situated in suprachiasmatic nucleus (SCN) of hypothalamus.

It controls the timing of most 24-hour behavioral and physiological rhythms including the sleep-wake cycle, alertness and performance rhythms, hormone production, temperature regulation, and metabolism.

‘circadian’ means ‘about a day’
Period of the circadian pacemaker in humans

• Average ~24.2 h (23.6-25.0 h)
• Stable in healthy aging
• Determines direction and extent of daily shift required to entrain to 24 h
  - phase angle of entrainment
  - diurnal preference or ‘owl vs lark’
  - adaptation to jet-lag or shiftwork
• Genetic basis

Czeisler et al. Science 1999
Circadian period is close to but not exactly 24 h and needs to be reset to 24 h every day

**Larks**.........................**Owls**

Mean = 24.2 h

![Histogram of Intrinsic Circadian Periods](image)

75% naturally delay (‘westward’)
- require phase advance each day

25% naturally advance (‘eastward’)
- require phase delay each day

_Czeisler et al. Science 1999_
How important is light in human circadian regulation?

RHT - Retinohypothalamic tract
SCN – Suprachiasmatic nuclei

Adapted from Arendt, 1995
‘Circadian’ Photoreception
Multiple neuroendocrine and neurobehavioral responses

• Light is the most powerful time cue for resetting the circadian pacemaker and ensuring correct synchronization of the internal clock with the environment

• Failure to entrain the circadian pacemaker results in sleep disorders, fatigue, performance problems, hormone and metabolic disorders

• Common examples include the circadian desynchronization caused by shift-work, jet-lag and Advanced- and Delayed Sleep Phase Disorder
‘Circadian’ Photoreception
Multiple neuroendocrine and neurobehavioral responses

• Much like the ear has dual functions for audition and balance, the human eye has a dual role in detecting light for a range of behavioral and physiological responses separate and apart from sight

• These ‘non-visual’ effects of light are mediated by a novel non-rod, non-cone photoreceptor located in the ganglion cell layer of the eye

• These photosensitive ganglion cell contain a novel opsin, melanopsin, to detect light which is maximally sensitive to short-wavelength (blue) visible light ($\lambda_{\text{max}} \sim 480$ nm)
‘Circadian’ Photoreception
Multiple neuroendocrine and neurobehavioral responses

- Circadian entrainment
- Circadian phase shifting

- Enhanced alertness
- Enhanced neurobehavioral performance

- Pineal melatonin suppression
- Cortisol stimulation

- Cardio- and thermoregulation
- Pupillary reflex
- Stimulation of clock gene expression
‘Circadian’ Photoreception
Properties of light affecting circadian photoreception

• Intensity
• Timing
• Pattern
• Light history
• Wavelength
Phase-shifting and melatonin suppressive effects of night-time white light exposure are dose-dependent

Zeitzer et al. J Physiol 2000
Acute enhancement of alertness by 6.5 h of night-time white light exposure is dose-dependent
Action spectra demonstrate short-wavelength sensitivity for non-rod, non-cone photoreceptor system

Melanopsin-containing intrinsically photosensitive retinal ganglion cells

Response of rodless/coneless mice to pupillary reflex to light

$\lambda_{\text{max}} = 484 \text{ nm}$

$\lambda_{\text{max}} \approx 480 \text{ nm}$

A novel opsin termed melanopsin (OPN4) is cloned

Provencio et al., J Neurosci, 2000
Melanopsin distribution in the ganglion cell layer of the mammalian eye

Mouse

Primate

~3000 cells
(0.3% of all GCs)

Provencio et al., J Neurosci 2000

Dacey et al., Nature 2005
Retinal ganglion cells that contain melanopsin have a dense projection to the SCN

Gooley et al., Nat Neurosci, 2001

Hattar et al., Science 2002
Action spectrum for short-duration melatonin suppression response

Brainard et al. J Neurosci 2001
‘Circadian’ Photoreception
What is the evidence for a novel photoreceptor system?

Action spectra for melatonin suppression peak at ~460 nm and do not match known rod and cone photoreceptors

\[ \lambda_{\text{max}} = 464 \text{ nm} \]
\[ R^2 = 0.91 \]

\[ \lambda_{\text{max}} = 446-477 \text{ nm} \]
90 mins exposure

\[ \lambda_{\text{max}} = 459 \text{ nm} \]
30 mins exposure

Brainard et al. J Neurosci 2001
Thapan et al. J Physiol 2001
Lockley et al., J Clin Endocrinol Metab 2003
Short-wavelength sensitivity for resetting the circadian pacemaker

460 nm light is nearly twice as effective at resetting the clock than 555 nm light

460 nm light

-1.67 ± 0.26 h

555 nm light

-2.99 ± 0.18 h*

Note: Photopic lux does not predict
The biological response to the light

* p < 0.0006

Lockley et al., J Clin Endocrinol Metab 2003
Melatonin (pg/ml) vs Clock time (h)

- **2185V**: AUC=96%
- **21B8V**: AUC=86%
- **21B9V**: AUC=65%
- **21B7V**: AUC=71%
- **21C6V**: AUC=69%
- **22A1V**: AUC=1%
Short-wavelength sensitivity for melatonin suppression

460 nm light is twice as effective at suppressing melatonin than 555 nm light

Lockley et al.,
* J Clin Endocrinol Metab 2003

555nm
39.1 ± 34.1 % suppression

460nm
87.7 ± 11.0 % suppression*

* p = 0.0021
Short-wavelength sensitivity for the acute alerting effects of light in sighted subjects

460 nm light is more effective at enhancing alertness and performance than 555 nm light

Lockley et al., Sleep 2006
Short-wavelength sensitivity for direct enhancement of high-alpha and suppression of delta/theta waking EEG activity by light

460 nm light is more effective at enhancing brain activity which indicates a more alert state than 555 nm light.
Short-duration (<1’) blue light preferentially activates the brain

473 nm light increases activity in brain areas associated with alertness, performance and mood during the day compared to 430 nm or 527 nm light.

**Transient effects at light onset**
- **Left Hippocampus**
  - Memory
- **Right Amygdala**
  - Emotion
  - Mood
- **Left thalamus**

**Sustained effects during 35s 2-back task**
- **Left Thalamus**
  - Alertness
  - Cognition
  - Memory
- **Left middle frontal gyrus**
  - Working memory
- **Right and Left brainstem**
  - Arousal
  - Cognition
  - Executive function
  - Locus Coeruleus?
  - NE; arousal

fMRI– Functional Magnetic Resonance Imaging

Vandewalle et al., PLoS One 2007
Summary

‘Circadian’ photoreception in humans

• requires eyes
• minimal light perception is sufficient
• not associated with visual field loss
• functional cones and /or rods not required
• short-wavelength blue-light sensitivity at high intensity

• adaptive multi-photoreceptor system
• responses are light wavelength-, intensity, duration- and history-dependent

• same for day-time exposures?
• same for all ‘non-image forming’ responses?

• photopic lux is an inadequate measure for the non-visual response to light
Light Applications - Clinical

• **Treatment of circadian rhythm sleep disorders**
  - Advanced-, Delayed-, Non-24-hour Sleep Disorders
  - Shift-work Disorder, Jet-lag
  - Sleep timing changes due to adolescence and aging

• **Entrainment to non-24-hour ‘days’**
  - Space flight and bases, Submariners, Antarctica

• **Treatment of affective disorders**
  - Seasonal Affective Disorder (*Glickman et al.*, 2005; *Anderson et al.*, 2009)
  - Alzheimer's Disease (*Riemersma-van der Lek et al.*, *JAMA* 2008)
  - General mood, non-seasonal depression?

• **Improving general sleep patterns**
  - Hospital and institutionalized patients
  - Child and adolescent sleep
Daytime exposure to bright white light improves reaction time and subjective alertness

5 h x 1000 lux  
4 h x 5000 lux

PVT – Psychomotor Vigilance Test  
KSS – Karolinska Sleepiness Scale

Phipps-Nelson et al Sleep 2003  
Rüger et al Am J Physiol 2006
Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality

N=94 workers on 2 floors with (■) and without (□) 17000K lamps for 4 weeks each

Monthly assessment vs Weekly assessment
Light Applications - General

- Non-pharmacological sleepiness countermeasure
- Safe, reversible, short-acting, inexpensive
- High levels of caffeine use illustrate need

  - Offices, schools, colleges, factories, control rooms...
  - Military, security, transport (pilots, captains, truck/car/train drivers)
  - Safety-sensitive occupations (physicians, nurses, nuclear…)
  - Anywhere where enhanced alertness and safety is important

- Challenge is to incorporate these benefits into design
- Lighting design to optimize visual and non-visual effects
- Flexible, ‘smart’ lighting systems with user interaction
Key Questions

• How do we incorporate these findings in real-world applications?
• How do lighting designers model the dual effects of light?
• What more information do designers need?
• How to approach ‘smart lighting’?
• Energy considerations?
• Safety considerations?
• Light pollution, role of darkness?
Acknowledgements

Brigham and Women’s Hospital

- Joshua J. Gooley, Ph.D.
- Joseph T. Hull
- Shantha M.W. Rajaratnam, Ph.D.
- Daniel Aeschbach, Ph.D.
- Erin E. Evans, R.PSG.T.
- Richard E. Kronauer, Ph.D.
- Charles A. Czeisler, Ph.D., M.D.

Thomas Jefferson University

- George C. Brainard, Ph.D.
- John P. Hanifin
- William Coyle
- Robert Levin, Ph.D. (Osram-Sylvania)

Oxford University

- Russell G. Foster, Ph.D.
- Stuart N. Pierson, Ph.D.
- Katharina Wulff, Ph.D.

City University

- Farhan H Zaidi, M.D.
- Merrick Moseley, M.D.

Photon Technologies Inc.

- Ron Kovak, Jon Cooke

Funding Agencies

- SWL: NCCAM (R01 AT002129-02)
- GCB: NINDS (R01 NS36590)
- CAC: Czeisler (R01 MH45130)
- NCRR GCRC (M01-RR02635)
- SWL: Wellcome Trust (060018/B/99/Z)
Treatment of SAD

Anderson JL, Glod CA, Dai J, Cao Re Y, Lockley SW
Light treatment for dementia

Effect of Bright Light and Melatonin on Cognitive and Noncognitive Function in Elderly Residents of Group Care Facilities: A Randomized Controlled Trial

Rixt F. Riemersma-van der Lek; Dick F. Swaab; Jos Twisk; et al.


Van Someren et al Biol Psychiat 1997
What is the impact of circadian desynchrony on physiology and metabolism?

Circadian misalignment and sleep disruption likely underlie increased risk for CV disease, metabolic disorders and diabetes, and cancer in shift-workers.

‘shift-work that involves circadian disruption is probably carcinogenic to humans (Group 2A)’

WHO International Agency for Research on Cancer Monograph Working Group
Straif et al., Lancet Oncol 8, 2007

Circadian oscillators in liver, heart, lung, ovaries, stomach, esophagus, kidneys, bladder…..etc, etc

Dynamic Lighting - supporting the natural rhythm of activity

Philips Lighting Application Center

- Cool light (5500 K)
- Warm light (3000 K)

Lighting level (lux)

- 900
- 800
- 700
- 600
- 500

8:00 10:00 12:00 14:00 16:00 18:00

Good morning  Lunch time  Post-lunch dip  Happy hour

www.dynamiclighting.philips.com
Laminar Organization of the Retina
Circadian photoreception in a ‘totally’ blind man

53 y male
No light perception
Retinitis Pigmentosa
No pupil response in standard penlight exam
Negative visually evoked potentials
Entrained sleep and melatonin rhythms

Zaidi, Hull, Peirson et al., Curr Biol 2007
Circadian photoreception in a ‘totally’ blind man

Melatonin suppression response to bright white light

Zaidi, Hull, Peirson et al., Curr Biol 2007
Spectral sensitivity of circadian photoreception in a ‘totally’ blind man

Melatonin suppression response to 555 nm and 460 nm light

Zaidi, Hull, Peirson et al., Curr Biol 2007
Melatonin suppression

EEG power density (alpha, 8-10 Hz)

Subjective alertness

Reaction time

Lapses of attention

Zaidi, Hull, Peirson et al., Curr Biol 2007
Spectral sensitivity of non-image forming responses in a blind woman

Electroretinogram

Fundoscopy and Ocular coherence tomogram

87 y female
No light perception
Rod-cone dystrophy
No pupil response in standard penlight exam
Negative electroretinogram
Entrained subjective sleep

Zaidi, Hull, Peirson et al., Curr Biol 2007
Spectral sensitivity of non-image forming responses in a blind woman

Action spectrum for pupil constriction response
lens corrected $\lambda_{\text{max}}$ 480nm

Spectral sensitivity for 2AFC test to detect lights on or off

Role for melanopsin in rudimentary vision?

Zaidi, Hull, Peirson et al., Curr Biol 2007
Abolition of rods, cones and melanopsin renders abolishes all visual and non-visual responses to light

Circadian entrainment to LD cycle

No entrainment to LD cycle

No rods, cones or melanopsin

Hattar et al. Nature 2003
Role for multiple photoreceptors in human circadian photoreception?

• Long-duration 555 nm light produces better than expected response for phase shifting and melatonin suppression

• What is the spectral sensitivity of circadian responses in totally blind people without functional rods/cones?

• Are the fluence-response curves for long-duration light exposure univariant in sighted subjects?
Role for multiple photoreceptors in human circadian photoreception?

• Long-duration 555 nm light produces better than expected response for phase shifting and melatonin suppression

• What is the spectral sensitivity of circadian responses in totally blind people without functional rods/cones?
  - Test the hypothesis that 460 nm light would induce a normal melatonin suppression, phase shifting and alerting effect of light and that 555 nm would be ineffective

• Are the fluence-response curves for long-duration light exposure univariant in sighted subjects?
Totally blind people with melatonin suppression response have normal circadian entrainment

Confirms the integrity of the retina-RHT-SCN-pineal pathway


Wehr, 2001
Treatment of SAD

1.43 x 10^{15} \text{photons/cm}^2/\text{s}
1.13 x 10^{14} \text{photons/cm}^2/\text{s}

45 mins daily (6:00-8:00 h) for 3 weeks

Glickman et al Biol Psychiat 2005
Aging

Reduced lens transmission at shorter $\lambda$
Reduced melatonin suppression at shorter $\lambda$

*Fig. 2. Average % melatonin suppression in young (□, n=13) and postmenopausal (○, n=19) women across the four light treatments: (a) $\lambda_{\text{max}}$ 456 nm: 3.8 $\mu$W/cm$^2$ and 9.8 $\mu$W/cm$^2$. (b) $\lambda_{\text{max}}$ 548 nm: 28 $\mu$W/cm$^2$ and 62 $\mu$W/cm$^2$. *$p<0.05$; ***$p<0.001$ compared to the corresponding young group (Tukey HSD post hoc test).*
Circadian rhythm types classified according to disorder

Retinitis Pigmentosa
- NE: 81%
- AE: 19%
- n = 16

Retinal Detachment
- FR: 38%
- NE: 12%
- AE: 50%
- n = 8
Circadian rhythm types classified according to field loss

Central loss only
n = 14

Central loss
NE 79%
UN 14%
AE 7%

Peripheral loss only
n = 11

Peripheral loss
NE 82%
AE 18%

Lockley et al., J Clin Endocrinol Metab 1997
Retinitis Pigmentosa  
\( n = 4 \)

Leber’s Amaurosis  
\( n = 2 \)

Optic nerve Disease  
\( n = 3 \)

Retinal Detachment  
\( n = 6 \)

Retinopathy of Prematurity  
\( n = 6 \)

Congenital Glaucoma  
\( n = 2 \)

Data from Sack et al., 1992; Czeisler et al., 1995; Lockley et al., 1997; Skene et al., 1999

Lockley et al., unpublished; Hull et al., unpublished
### Comparison of rod and cone photoreceptors and intrinsically photosensitive retinal ganglion cells

<table>
<thead>
<tr>
<th></th>
<th>Rods and cones</th>
<th>IpRGCs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Soma location</strong></td>
<td>Outer nuclear layer</td>
<td>Ganglion cell layer (rarely inner nuclear layer)</td>
</tr>
<tr>
<td><strong>Output</strong></td>
<td>Retina (bipolar and horizontal cells)</td>
<td>Brain (e.g. SCN and OPN)</td>
</tr>
<tr>
<td><strong>Light response</strong></td>
<td>Fast hyperpolarizing</td>
<td>Slow depolarizing</td>
</tr>
<tr>
<td><strong>Action potentials</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Role of retinal pigment epithelium</strong></td>
<td>Essential for photopigment regeneration</td>
<td>Apparently unnecessary for photopigment regeneration</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>Moderate (cone) or high (rod)</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Receptive field</strong></td>
<td>Very small</td>
<td>Very large</td>
</tr>
<tr>
<td><strong>Photopigment</strong></td>
<td>Rhodopsin and cone opsin</td>
<td>Melanopsin?</td>
</tr>
<tr>
<td><strong>Photosensitive elements</strong></td>
<td>Outer segment</td>
<td>Soma and dendrites (and axon?)</td>
</tr>
</tbody>
</table>

*Abbreviations: IpRGCs, intrinsically photosensitive retinal ganglion cells; OPN, olivary pretectal nucleus; SCN, suprachiasmatic nucleus*

---

_Berson et al., Trends Neurosci 2003_
Spectral sensitivity of circadian photoreception in a ‘totally’ blind man

Zaidi, Hull, Peirson et al., Curr Biol 2007
Circadian melatonin rhythm is strongly associated with high-alpha EEG activity.
Role for multiple photoreceptors in human circadian photoreception?

- Long-duration 555 nm light produces better than expected response for phase shifting and melatonin suppression

- What is the spectral sensitivity of circadian responses in totally blind people without functional rods/cones?
  - Test the hypothesis that 460 nm light would induce a normal melatonin suppression, phase shifting and alerting effect of light and that 555 nm would be ineffective

- Are the fluence-response curves for long-duration light exposure univariant in sighted subjects?
Phase shift dose-response to light

555 nm

\[ R^2 = 0.53 \]
\[ ED_{50} = 7.29 \times 10^{12} \]

460 nm

\[ R^2 = 0.73 \]
\[ ED_{50} = 3.04 \times 10^{12} \]

---

Gooley et al. unpublished
Phase shift dose-response comparison

555 nm vs. 460 nm

Gooley et al. unpublished
Pupil constriction response in rodless/conless versus OPN4- mice is not the same at all intensities

- **rd/rd cl**
  - No rods or cones
- **mop**
  - No melanopsin

**At low intensities,** animals lacking melanopsin are more sensitive i.e. rod-cone driven

**At high intensities,** animals lacking rods and cones are more sensitive i.e. melanopsin-driven

Lucas et al. Science 2003
Continuous darkness

Light pulse

Pineal melatonin response

Plasma melatonin (pg/ml)

0
5
10
15
20
25
30

22 0 2 4 6 8 10

Plasma melatonin (pg/ml)

0 20 40 60 80 100

22 0 2 4 6 8 10

Tetraplegia

Superior Cervical Ganglion

Paraventricular Nucleus

Pineal Gland

Retina

SCN

Neuroanatomy of the circadian system
Entrainment by light

Neuroanatomy of the circadian system

Pineal melatonin response

Light

Pineal Gland

Paraventricular Nucleus

SCN

Retina

Superior Cervical Ganglion

Plasma melatonin (pg/ml)

0 5 10 15 20 25 30

0 5 10 15 20 25 30

Entrainment by light

22 2 4 6 8 10 12 14 16 18 20
Neuroanatomy of the circadian system
Assessing circadian phase shifts

150 lux 0.5 W/m²

<2 lux 0.005 W/m²

Δφ

Lockley et al., Sleep 2006
Assessing melatonin suppression

Lockley et al., Sleep 2006
Assessing alerting responses

Clock time (h)

KSS = Karolinska Sleepiness Scale
PVT10A = 10-min Auditory Psychomotor Vigilance Task
KDT = Karolinska Drowsiness Test

Lockley et al., Sleep 2006
Disassociation between neuroendocrine and neurobehavioral responses to light

Melatonin suppression and alerting effects do not correlate always

• Day-time exposure improves alertness when melatonin is absent
  (Phipps-Nelson et al 2003; Ruger et al., 2005; Vandewalle et al., 2006)

• 555 nm light in the early night suppresses melatonin without improving alertness (Cajochen et al., 2005)

• Spectral sensitivity for effects of light on day-time alertness may differ from nocturnal melatonin suppression (Revell et al., 2006)

Day-Night differences in responses to light

• Light reduces sleepiness and fatigue at both night and day (Rüger et al., 2006)

• Light increases heart rate and temperature at night but not day (Rüger et al., 2006)
How important is light in human circadian regulation?

What happens if light information to the brain is lost?

RHT - Retinohypothalamic tract
SCN – Suprachiasmatic nuclei

Sleep–wake, temperature and other rhythmic functions

Pineal melatonin rhythm

Reproduction

Adapted from Arendt, 1995
Urinary aMT6s rhythms (48 h/wk) in the visually impaired

Entrained
Normal phase (1:00 - 7:00 h)

Entrained
Abnormal phase (e.g. advanced)

Non-entrained
Non-24-hour rhythm (e.g. 24.7 h)

Lockley et al., J Clin Endocrinol Metab 1997
Normally entrained sleep and melatonin rhythms

Lockley et al., Dialogues Clin Neurosci 2007
Non-24-hour sleep-wake disorder in the blind (n = 9)
Circadian rhythm disorders are associated with severity of blindness

Light perception
or better
n = 30

NE = normally entrained to 24 h; AE = abnormal phase of entrainment;
FR = ‘free-running’, not entrained to 24 h; UN = unclassified

Lockley et al., J Clin Endocrinol Metab 1997; Skene et al., Repr Nutr Develop 1999
Circadian rhythm disorders are associated with severity of blindness

Light perception or better
n = 30

- FR 3%
- UN 7%
- AE 13%
- NE 77%

Totally blind
no eyes
n = 12

- FR 100%

NE = normally entrained to 24 h; AE = abnormal phase of entrainment; FR = ‘free-running’, not entrained to 24 h; UN = unclassified

Lockley et al., J Clin Endocrinol Metab 1997; Skene et al., Repr Nutr Develop 1999
Circadian rhythm disorders are associated with severity of blindness

Light perception or better
n = 30

- FR 3%
- AE 13%
- NE 77%

Totally blind
≥1 intact eyes
n = 25

- UN 4%
- NE 32%
- FR 44%
- AE 20%

Totally blind
no eyes
n = 12

- FR 100%

NE = normally entrained to 24 h; AE = abnormal phase of entrainment; FR = ‘free-running’, not entrained to 24 h; UN = unclassified

Lockley et al., J Clin Endocrinol Metab 1997; Skene et al., Repr Nutr Develop 1999
Neuroanatomy of the circadian system

Adapted from Wehr et al., 2001
Neuroanatomy of the circadian system
Some totally blind people with eyes maintain normal melatonin suppression response to light and have normal circadian entrainment.

Evidence for separation of light detection for visual and non-visual effects of light.
‘Circadian’ Photoreception
What is the evidence for a novel photoreceptor system?

Color-blind people maintain normal melatonin suppression responses to white and green light

Ruberg et al. J Clin Endocrinol Metab 1996
Laminar Organization of the Retina

Slide courtesy of Dr Joshua Gooley
Retinal ganglion cells that project to the SCN are intrinsically photosensitive and require melanopsin.

Berson et al., Science 2002
‘Circadian’ Photoreception
What is the evidence for a novel photoreceptor system?

• Some totally visually blind people with eyes maintain normal melatonin suppression response to light and have normal circadian entrainment.

• Color vision-deficient people maintain normal melatonin suppression to white and green light.

• The spectral sensitivity of ‘non-visual’ responses to light is blue-shifted relative to the photopic or scotopic visual systems and does not match the spectral sensitivity of rod or cone photoreceptors.
‘Circadian’ Photoreception in non-human mammals
What is the evidence for a novel photoreceptor system?

bilateral enucleation abolishes circadian photoreception
but not in mice that are...

• retinally degenerate rodless (rd/rd)
• retinally degenerate slow rodless (rds/rds)
• retinally degenerate transgenic rodless (rdta)
• coneless (cl), rodless/coneless (rd/cl, rdta/cl)
• cryptochrome 2-less (cry2-)
• rodless and/or cryptochrome-less (rd/cry1-/
cry2-)
• rodless / vitamin A-less