

Neurobiology of Photophobia

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Background: Photophobia is commonly associated with migraine, meningitis, concussion, and a variety of ocular diseases. Advances in our ability to trace multiple brain pathways through which light information is processed have paved the way to a better understanding of the neurobiology of photophobia and the complexity of the symptoms triggered by light.

Purpose: The purpose of this review is to summarize recent anatomical and physiological studies on the neurobiology of photophobia with emphasis on migraine.

Recent Findings: Observations made in blind and seeing migraine patients, and in a variety of animal models, have led to the discovery of a novel retino-thalamo-cortical pathway that carries photic signal from melanopsinergic and nonmelanopsinergic retinal ganglion cells (RGCs) to thalamic neurons. Activity of these neurons is driven by migraine and their axonal projections convey signals about headache and light to multiple cortical areas involved in the generation of common migraine symptoms. Novel projections of RGCs into previously unidentified hypothalamic neurons that regulate parasympathetic and sympathetic functions have also been discovered. Finally, recent work has led to a novel understanding of color preference in migraine-type photophobia and of the roles played by the retina, thalamus, and cortex.

Summary: The findings provide a neural substrate for understanding the complexity of aversion to light in

patients with migraine and neuro-ophthalmologic other disorders.

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Photophobia is commonly associated with anterior segment disorders of the eye such as uveitis, cyclitis, iritis, and blepharitis (1). Intracranial pathologies such as migraine, meningitis, subdural hemorrhage, and intracranial tumors are also associated with photophobia (2–5). There are at least 3 distinct definitions of photophobia in the literature: 1: abnormal sensitivity to light (1); 2: ocular discomfort, also termed photo-oculodynia, (6); 3: exacerbation of headache by light (7–9); and 4: our recent proposal to define photophobia more broadly: general aversion to light (10).

Neural pathways that mediate aversion to light differ greatly from neural pathways that mediate exacerbation of headache by light in migraineurs or from neural pathways that mediate ocular discomfort. To alter visual perception during migraine, it is reasonable to propose that a flow of nociceptive signals along the trigeminovascular pathway converges on visual pathways that terminate in the visual cortex. Conversely, to alter the perception of headache during exposure to light, it is reasonable to propose that a flow of photic signals converge on nociceptive trigeminovascular pathways that terminate in cortical areas is involved in the processing of pain perception. To induce ocular discomfort or pain in the eye by light, it is likely that light indirectly activates intraocular trigeminal nociceptors; these, in turn, activate second-order nociceptive neurons in the spinal trigeminal nucleus. To induce general aversion to light, it is reasonable to propose that light alters the activity of neural pathways that regulate affect and autonomic functions.

NEURAL PATHWAYS THAT MEDIATE EXACERBATION OF HEADACHE BY LIGHT

Because the headache phase of migraine depends on flow of nociceptive signals that originate in meningeal nociceptors

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and are conveyed to the cortex through central trigemino-vascular neurons in the spinal trigeminal nucleus and thalamus, it is reasonable to assume that the intensification of headache by light involves a cross-talk between brain pathways that process vision and those responsible for the classical pain of migraine headache. The first site in which such cross-talk may occur was identified in 2010. Using sophisticated anatomical, electrophysiological, and immunohistological techniques, Nosedá et al (7) showed in animals that 1: light enhances the activity of thalamic trigemino-vascular neurons in a manner that resembles the way light activates melanopsinergic retinal ganglion cells (RGCs); 2: a subset of dura-sensitive thalamic neurons, located mainly in the posterior most area of the thalamus, receives monosynaptic input from axons of melanopsinergic and nonmelanopsinergic RGC that travel from the eye to the brain along the optic nerve; and 3: the axons of these dura-sensitive thalamic neurons, whose activity is enhanced by light, project to primary and secondary somatosensory cortices and the insula. These structures constitute the so-called pain matrix (7). The unraveling of a pathway that carries photic signals to cortical areas where the perception of headache and its intensity are generated (Fig. 1) defines a mechanism for the exacerbation of migraine headache by light.

Critical confirmation of the role of the posterior thalamus in the exacerbation of migraine headache by light was provided in an earlier study. In that investigation, sophisticated neuroimaging and in vivo electrophysiology techniques were used to demonstrate that the posterior thalamic nuclei contain large number of neurons that initially become active during migraine in patients (i.e., in the pulvinar). These neurons (i.e., in the posterior and lateral posterior nuclei) also activate in response to stimulation of the dura in animals and become sensitized (11)—to the extent that their sensitization can mediate the whole-body allodynia of migraine (12). Additional support for the existence in humans of a direct retinopulvinar projection has been provided in another study in which diffusion weighted imaging and probabilistic tractography were used to map connectivity of direct pathways from the optic nerve to the pulvinar (13).

NEURONAL PATHWAYS THAT MEDIATE COMMON MIGRAINE-ASSOCIATED SYMPTOMS

The massive projections of axons of dura- and light-sensitive thalamic neurons into visual, auditory, and olfactory

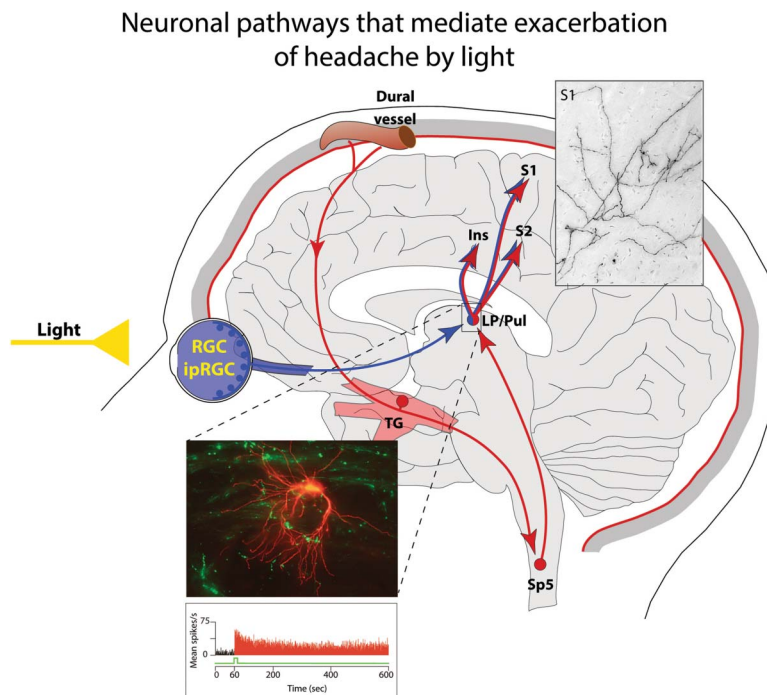


FIG. 1. Neuronal pathways that mediate exacerbation of headache by light. Proposed mechanism for exacerbation of migraine headache by light through the convergence of the photic signals from the retina and nociceptive signals from the meninges on the same thalamic neurons that project to the somatosensory cortices. Red depicts the trigemino-vascular pathway. Blue depicts visual pathway from the retina to the posterior thalamus. Inserts show distribution of trigemino-vascular axons in the somatosensory cortex (top right), monosynaptic connections between axons of RGC and dendrites of thalamic trigemino-vascular neurons (bottom left) and light effect on activation pattern of a thalamic trigemino-vascular neuron (bottom left). RGC, retinal ganglion cells; ipRGC, intrinsically photosensitive retinal ganglion cells; TG, trigeminal ganglion; Sp5, spinal trigeminal nucleus; LP, lateral posterior nucleus; Pul, pulvinar; S1, primary somatosensory cortex; S2, secondary somatosensory cortex. Adapted from (7,14,49,50).

cortices, as well as to the motor, retrosplenial, and parietal association cortices (7,14), define distinct neuroanatomical pathways through which exposure to light during migraine can bombard these cortices with overwhelming number of signals capable of altering the normal functioning of these cortical areas. These signals, in turn, can give rise to a variety of symptoms that appear in association with the migraine experience (Fig. 2). Symptoms include compromised cognitive functions and transient decline in short-term memory, partially attributed to altered function of the retrosplenial cortex (15); impaired motor coordination, partially attributed to the altered function of the motor cortex (16); transient decline in ability to maintain attention, partially attributed to altered functions of the parietal association cortex (17); abnormal perception of light, color, and visual images, attributed mainly to altered processing in primary and secondary visual cortices (18,19); and enhanced sensitivity to sound and smell, attributed to abnormal processing of auditory and olfactory stimuli by the auditory and olfactory cortices (20–22).

NEURONAL PATHWAYS THAT MEDIATE COLOR PREFERENCE IN MIGRAINE PATIENTS

We originally reported that a “non-image forming” pathway, which originates in melanopsinergic RGC, can explain the preferential sensitivity to blue light in blind migraine

patients, who, despite losing the ability to form images due to degeneration of cones and rods (23) can still detect light (7). These findings suggested that blue light could be fundamental to migraine-type photophobia, and that the exacerbation of the headache by light could be minimized by devices (sunglasses and contact lens) that block the blue light (24–27). However, a recent, carefully designed, psychophysical study conducted in migraine patients with normal eyesight (28) revealed that, during the ictal phase, white, blue, amber, and red light exacerbates migraine headache almost equally and significantly more than green light (Fig. 3A–B). Using electroretinography (ERG) and visual evoked potential recordings in patients, and multiunit recording of dura- and light-sensitive thalamic neurons in rats, this same study showed that green light activates cone-driven retinal pathways to a lesser extent than white, blue, and red (Fig. 3C–D). It also demonstrated that thalamic neurons are most responsive to blue and least responsive to green (Fig. 3E–F), and that cortical responses to blue, amber, and red lights are significantly larger than those generated by green light (Fig. 3G–H). These findings define a novel concept in migraine-type photophobia whereby color selectivity, and its effects on the severity of migraine-type photophobia seem to originate in cone-driven retinal pathways. These are fine-tuned and preserved in relay thalamic neurons outside the main visual pathway and are eventually converted into perception by the visual

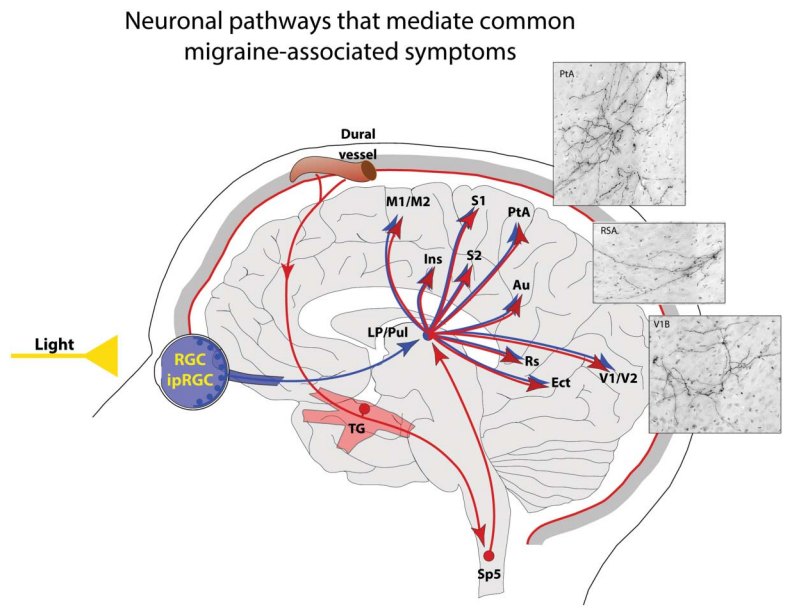


FIG. 2. Neuronal pathways that mediate common migraine-associated symptoms. Proposed mechanism for initiation or exacerbation of common migraine-associated symptoms by light during migraine through convergence of nociceptive signals from the meninges on thalamic neurons that project to the motor (M), parietal association (PtA), auditory (Au), retrosplenium (RS), olfactory (ECT), and visual (V) cortices. Inserts (top right) show distribution of trigeminovascular axons in the parietal association, retrosplenium, and visual cortices. Red depicts the trigeminovascular pathway. Blue depicts visual pathway from the retina to the visual cortex. RGC, retinal ganglion cells; ipRGC, intrinsically photosensitive retinal ganglion cells; TG, trigeminal ganglion; Sp5, spinal trigeminal nucleus; LP, lateral posterior nucleus; Pul, pulvinar; S1, primary somatosensory cortex; S2, secondary somatosensory cortex. Adapted from (7,14,49,50).

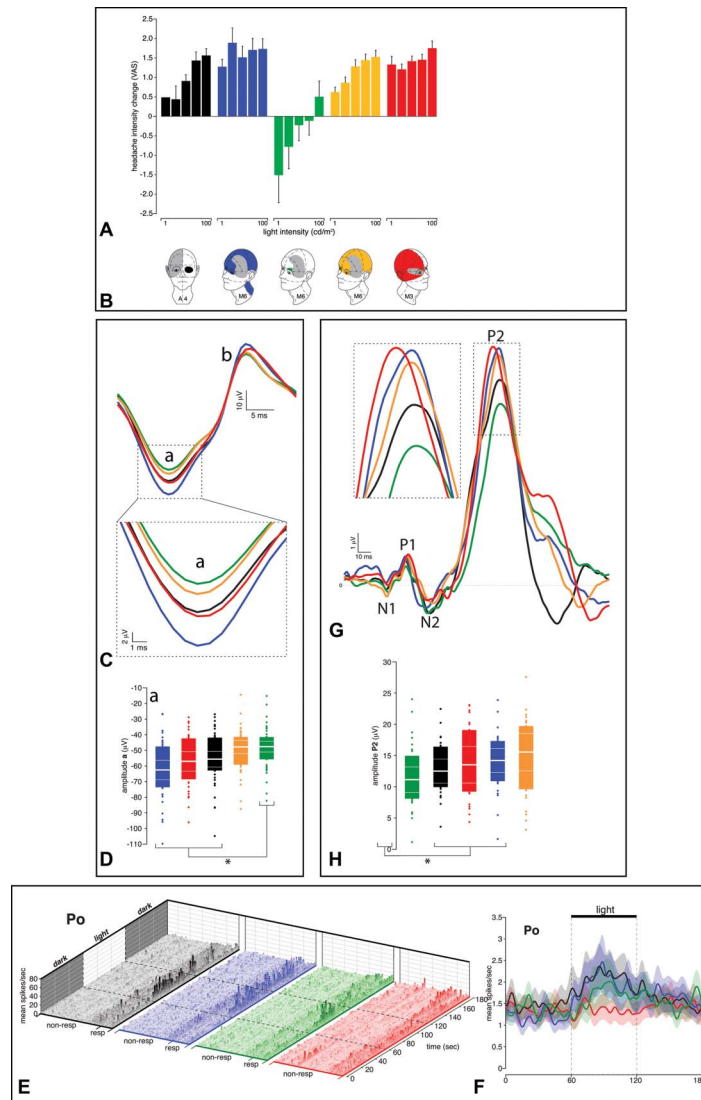


FIG. 3. Proposed mechanism for color preference in migraine-type photophobia. **A–B.** Effects of color on pain rating and headache location. **C.** Chromatic ERGs recorded in 43 migraine patients. Shown in the figure are superimposed means of standard light-adapted 30-Hz flickering ERG waveforms averaged (\pm SEM) across patients in response to each color of light. These light-adapted flickering ERG waveforms illustrate that blue, red, and white lights generated significantly larger a-wave amplitudes as compared to green light (enlarged view in inset) ($P < 0.0001$). **D.** Box plot illustrating median, 95% CI, interquartile range, and observations below and above the 25th and 75th percentile, respectively. Asterisks depict the significantly greater a-wave amplitude induced by blue, red, and white lights compared with green. **E.** 3D bar graphs illustrating firing frequency (i.e., raw data expressed in mean spikes/second, bin size = 1 second) of 37 posterior hypothalamus neurons to 44, 59, 58, and 59 cycles (dark-light-dark, 1 minute each) of photic retinal stimulation with white, blue, green, and red lights, respectively. Neurons, whose activity in the light increased by >2 SD over baseline (i.e., in the dark), are marked as responders (resp) and shown on the right side of each collection of color-selective bar graphs. The data were collected using sophisticated 3-tetrode in vivo multiunit recording technique. **F.** Differential responses of trigeminovascular and non-trigeminovascular thalamic neurons to photic stimulation with white, blue, green, and red lights. **G.** Chromatic visual evoked potentials (VEPs) recorded in 28 migraine patients. Shown in the figure are superimposed means of standard flash VEP waveforms averaged (\pm SEM) across patients in response to 1,792 flashes (64 flashes per patient, 1 second interstimulus interval) of each color of light. The superimposed means of these flash VEPs demonstrate that blue, red, and amber generated significantly larger P2 amplitude (enlarged view in inset) as compared to green ($P < 0.02$). By contrast, no differences were found in the amplitudes of the N2 waves. **H.** Box plot illustrating median (thick horizontal white line), 95% CI (thin dotted horizontal lines), interquartile range (25th–75th percentile; lower and upper box boundaries), and observations below and above the 25th and 75th percentile, respectively (individual dots). Asterisk depicts the significantly smaller P2-wave amplitude induced by the green light compared with red, blue, and amber. CI, confidence interval. Adapted from (28).

Neuronal pathways that mediate color preference in migraine-type photophobia

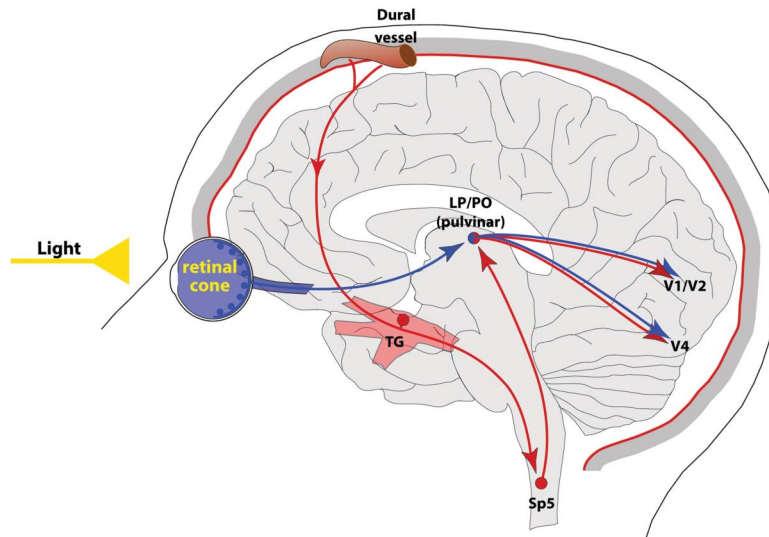


FIG. 4. Neuronal pathways that mediate color preference in migraine-type photophobia. Such pathways involve sequential activation of cone photoreceptors, postcone retinal pathways, cone-opponent RGCs, relay posterior thalamic neurons (located in the pulvinar, lateral posterior, and posterior nuclei), and double-opponent neurons in V1, V2, and V4. RGC, retinal ganglion cells; ipRGC, intrinsically photosensitive retinal ganglion cells; TG, trigeminal ganglion; Sp5, spinal trigeminal nucleus; LP, lateral posterior nucleus; Pul, pulvinar; S1, primary somatosensory cortex; S2, secondary somatosensory cortex. Adapted from (49,50).

cortex (Fig. 4). This interpretation is based on strong data that support the view that color processing involves cone but not rod photoreceptors, RGCs, relay neurons in the lateral geniculate nucleus (LGN), the primary (V1), secondary (V2) visual cortices, and parts of the inferior temporal lobe (V4). To perceive color correctly, the brain needs to receive (and compare) signals that originate in 2 different classes of cones located in the same area of the retina. Signals originating in different classes of cones (i.e., red-green and blue-yellow) activate cone-opponent RGCs whose axons project to the LGN and relay LGN cells whose axons terminate in the visual cortex. Signals arriving in V1 from different classes of cone-opponent cells activate double-opponent neurons (19,29) whose role is to establish the neural basis of color contrast, color constancy, poor spatial resolution of color vision, and overall color encoding (30–35). In V1, color-encoding cells, which are clustered within blobs (36,37), project to distinct stripes in V2, that in turn convey color signals to the inferior and posterior inferior temporal cortex. This is where the human brain can generate the perception of millions of different colors (29). Supporting the proposal that V1, V2, and the inferior temporal cortex are involved in the generation of color selectivity among migraine patients is studies showing different or simply greater patterns of activation signal in the LGN (38), visual cortex (38–43), and temporal lobes (44,45) of migraine patients as compared to control subjects.

NEURONAL PATHWAYS THAT MEDIATE GENERAL AVERSION TO LIGHT

Although most migraine patients report that light exacerbates their headache, a significant number of patients report that, during migraine, exposure to light is unpleasant. In a recent psychophysical study (10), we defined more completely what patients mean or feel when they say that exposure to light is “unpleasant.” In that study, patients with migraine were exposed to different colors of lights (blue, green, amber, and red) during and in the absence of migraine. The perception, sensation, or emotions that each of the colors triggered were functionally grouped as 1: hypothalamic-mediated autonomic responses, 2: hypothalamic-mediated nonautonomic responses, 3: affective negative responses, and 4: affective positive responses. Their description of hypothalamic-mediated autonomic responses included a myriad of symptoms, such as the perception of chest tightness, throat tightness, shortness of breath, fast breathing, faster than usual heart rate, light headedness, dizziness, nausea, vomiting, dry mouth, salivation, rhinorrhea, stuffy sinuses, and lacrimation. Description of experiences we assigned to nonautonomic hypothalamic functions included thirst and hunger (regulation of feeding) and feelings of being drowsy, tired, sleepy, and fatigued. Some patients described actual yawning and difficulties with regulation of sleep. Descriptions of negative emotions most frequently included words such as intense, irritable, angry, nervous, hopeless,

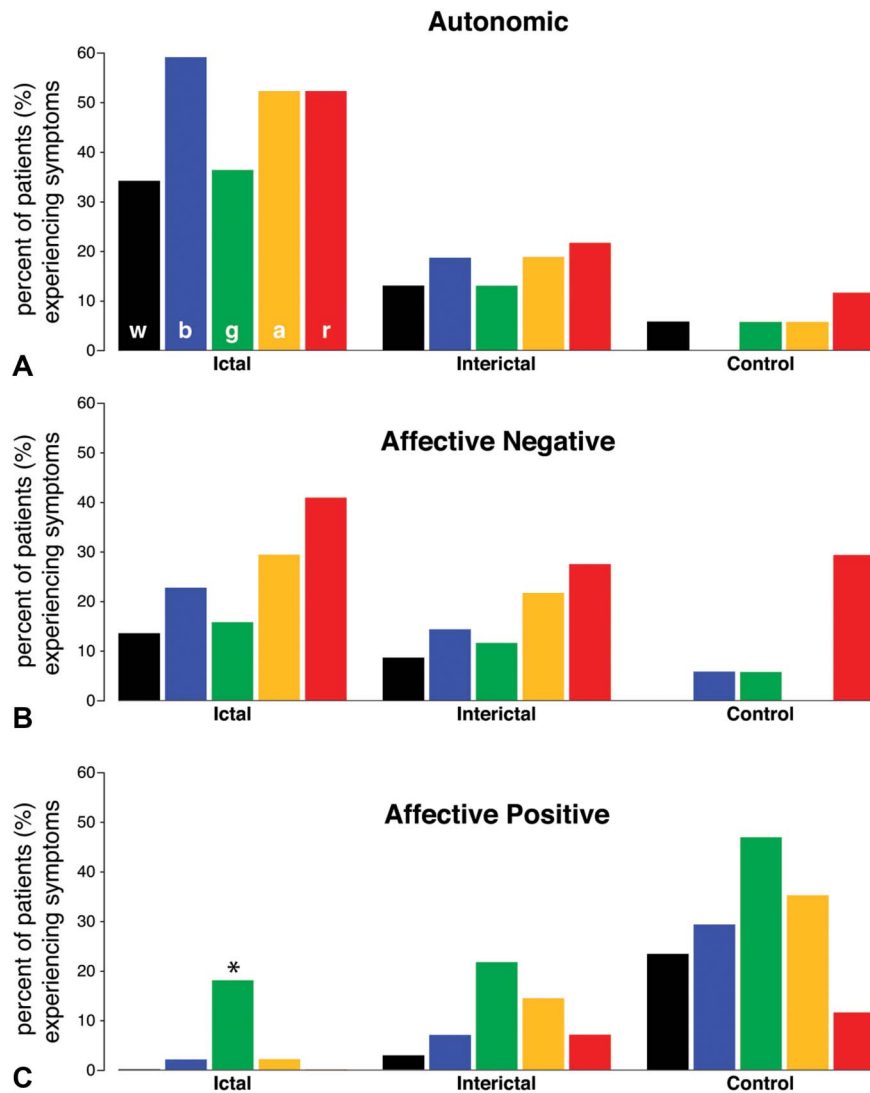


FIG. 5. Aversion to light. **A.** Proportion of migraine patients and control subjects experiencing autonomic responses to white, blue, green, amber, and red lights. **B.** Proportion of migraine patients and control subjects experiencing negative emotions in response to white, blue, green, amber, and red lights. **C.** Proportion of migraine patients and control subjects experiencing positive emotions in response to white, blue, green, amber, and red lights. Adapted from (10).

needy, agitated, sad, scared, cranky, upset, depressed, disappointed, jittery, worried, stressed, anxious, panic, and fear. Some individuals experienced actual crying. Positive emotions were expressed most frequently with words such as happy, relaxing, soothing, and calming. The results of that study demonstrated that 1: light triggers more changes in hypothalamic-mediated autonomic functions and negative emotions during rather than in absence of migraine or in control subjects (Fig. 5A), 2: that color is more likely to trigger negative effects in migraineurs than in control subjects (Fig. 5B), and 3: that the association between color and positive emotions is stronger in control subjects than in migraineurs (Fig. 5C). These findings expand the definition of photophobia beyond that of the commonly used criteria of “headache (intensity) worsened by light” to the extent that it

explains why migraine patients avoid light even when it does not seem to worsen their head pain.

Preclinical neuroanatomical investigations that followed the psychophysical study described above showed that axons of RGCs converge on hypothalamic neurons containing dopamine, histamine, orexin, melanin-concentrating hormone, oxytocin, and vasopressin (Fig. 6A). These neurons, in turn, project directly to preganglionic parasympathetic neurons in the brainstem superior salivatory nucleus (Fig. 6B) and sympathetic preganglionic neurons in the intermediate lateral nucleus of the thoracic spinal cord (Fig. 6C). We termed these novel connections as the retinohypothalamic–parasympathetic and retinohypothalamic–sympathetic pathways, defining a new anatomical substrate for future studies on alterations of hypothalamic-mediated (autonomic and nonautonomic) functions by light. These are present both in migraineurs and

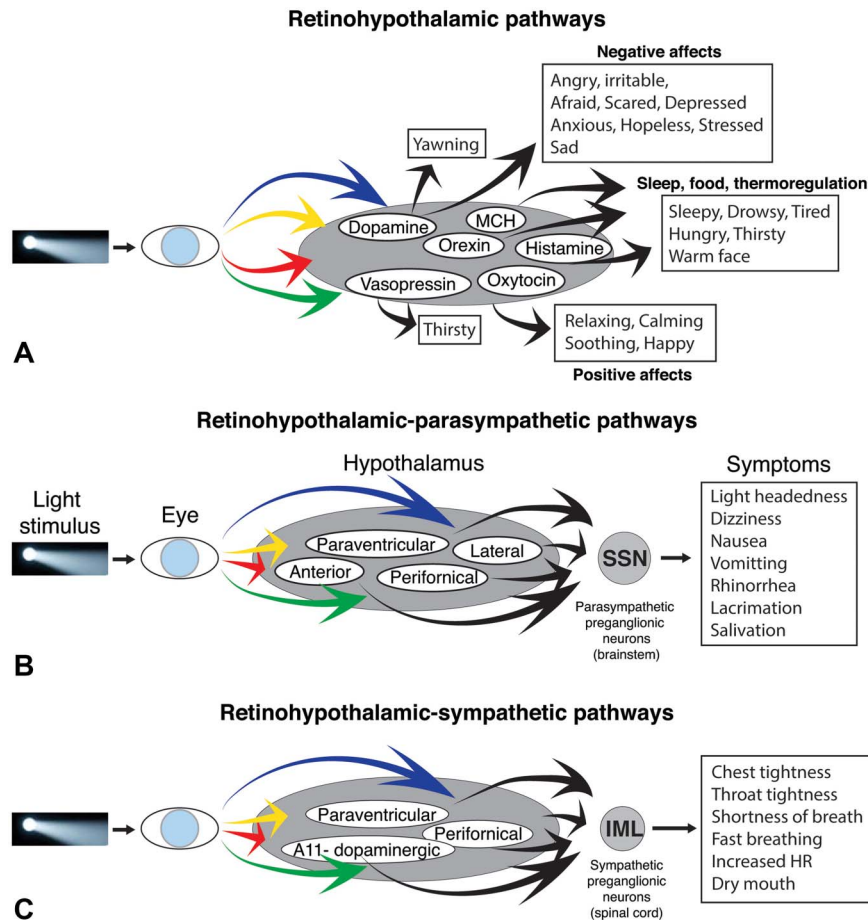


FIG. 6. Neuronal pathways that mediate general aversion to light. Proposed pathways for modulation of autonomic responses, hypothalamic functions, and emotions by light. **A.** Pathways for inductions of symptoms mediated by dopamine, orexin, histamine, melanin concentrating hormone, oxytocin, and vasopressin. **B.** Pathways for induction of symptoms associated with activation of the parasympathetic system. **C.** Pathways for induction of symptoms associated with activation of the sympathetic system. Adapted from (10).

nonmigraineurs. Because the induction of all hypothalamic-mediated responses is not generally influenced by the color of light, it is likely that the retinohypothalamic interactions observed in the study are independent of color processing by the visual cortex. This scenario differs greatly from the one described above, showing that the perception of headache intensity is color-specific and most likely depends on sensory processing by the retino-thalamo-cortical pathway (28) and on its origin in retinal cones (Fig. 4).

In summary, although the rat studies define novel frameworks for conceptualizing how light triggers the symptoms described by patients, the human studies suggest that the aversive nature of light is more complex than simply an association with headache intensification.

PHOTOPHOBIA AND THE UNIQUE EFFECTS OF GREEN LIGHT

The clinical studies described above demonstrated that the a-wave amplitude generated by a narrow band (530 nm) of

green light (as captured in the ERG studies) is smaller than the a-wave amplitude generated by narrow bands of blue, red, and white lights. They also demonstrate that the P2 amplitude generated by green light (as captured in the visual evoked potential studies) is smaller than the P2 amplitudes generated by blue, amber, and red lights, and that green light is least likely to exacerbate migraine headache or give rise to negative emotions and unpleasant hypothalamic-mediated autonomic responses. In fact, instead of exacerbating migraine, low-intensity 530-nm green light seems capable of decreasing headache intensity and increasing positive emotions (described by migraineurs in the study using words such as happy, relaxing, soothing, and calming). Although the neurobiology of the soothing effects of green light are largely unknown and likely to involve a complex psychobiology (46–48), it is reasonable to suggest that by triggering the smallest activation signals in the retina, thalamus, and cortex, green light may be able to reduce the migraine-driven cortical hyperexcitability and hypothalamic hypersensitivity to physiological and emotional deviation from homeostasis.

SUMMARY

- The discovery of a novel retino-thalamo-cortical pathway that carries photic signal from melanopsinergic and non-melanopsinergic RGCs to thalamic trigeminovascular neurons (i.e., those involved in migraine headache) that project to multiple cortical areas provides a neural substrate for exacerbation of headache by light, distortion of visual, auditory and olfactory perception by migraine, and the transient decline in cognitive functions.
- Visually-impaired migraine patients perceive blue light as most painful. This finding is attributed to activation of intrinsically photosensitive RGCs.
- Migraine patients who are not blind perceive blue and red light as most painful and green light as least painful. This color preference depends on signals that originate in retinal cone and postcone pathways.
- The discovery of novel projections of RGCs into distinct groups of hypothalamic neurons that regulate parasympathetic and sympathetic functions provide a neural substrate for understanding light's ability to alter autonomic function.
- The discovery of novel projections of RGCs into hypothalamic nuclei containing dopaminergic, histaminergic, orexinergic, oxytocinergic, and vasopressinergic neurons pave a way for understanding light's ability to trigger positive and negative emotions.
- In the context of migraine, the aversive nature of light is more complex than its association with headache intensification.

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