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Headache Currents Unanswered Questions in Headache

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Abstract

Photophobia refers to a sensory disturbance provoked by light. However, because it arises distinctly in a broad range of clinical conditions, its definition remains elusive. Many underscore the painful sensory aspects of photophobia, while others emphasize its unpleasant, affective qualities. To add further complexity, recent discoveries in photophobia research have raised disparate and potentially conflicting results. In this installment of an occasional series we asked clinicians and scientists to give their interpretation of what these discoveries tell us about photophobia in the clinic, and vice versa.

Keywords

Migraine; photophobia; pain; aversion; trigeminal; ophthalmology

What are we talking about?

Photophobia is of great diagnostic significance in the clinical evaluation of headache and facial pain, but its definition can be somewhat elusive. The linguistic origins of the term photophobia imply a fear or aversion to light, but the clinical understanding of photophobia often emphasizes the experience of pain¹. That is, even modest ambient illumination can produce an uncomfortable, painful experience that may even exacerbate migraine pain. However, photophobia is heterogeneous²; some patients with migraine will deny that pain is a part of the experience at all, and report only a preference to be in a darkened room. This is also referred to as photophobia.

Drummond used psychophysical methods to quantify the range of these experiences of photophobia in migraine. He operationally defined the concept of a threshold for light-induced migraine pain³. Interestingly, he later showed the reverse interaction between pain and photophobia, that painful stimulation of the forehead could also decrease the threshold of light required to produce visual discomfort in a group of migraineurs⁴.

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However, it is important to appreciate that photophobia is not unique to migraine¹. As highlighted in the clinical perspective by Friedman, a range of refractive and ocular pressure disorders, and even some medications, can cause exquisite light-induced pain.

There's pain and then there's pain

Recent independent work suggests that photophobia associated with ocular disorders and the migraine-related phenomena refer to two biologically distinct pathways.

On the one hand, Bereiter and colleagues performed an elegant series of electrophysiological and pharmacological experiments in anesthetized rat to demonstrate that very bright light can evoke pain-associated signals in trigeminal afferents and trigeminal nucleus arising from within the orbit⁵. They went on to show that bright light evokes responses that appear to be physiologically and pharmacologically related to the autonomic regulation of blood flow within the orbit, and mediated by sympathetic regulation through the posterior hypothalamus⁶.

These findings appear to be consistent with the report of a patient with a corneal abrasion and photophobia, whose functional MRI demonstrated the activation of the trigeminal nucleus and primary somatosensory networks within the brain⁷. These somatosensory responses offer a plausible explanation for how the dysregulation of light within the orbit can trigger vascular autonomic changes and prominent experiences of pain. This close connection between light and primary trigeminal pain among pre-chiasmal disorders could thus be called photo-oculodynia¹.

On the other hand, in recent work by Burstein and colleagues, highlighted here in the commentaries by Nosedá as well as Matynia, photic stimulation of retinal pathways are associated with painful experiences, not through a trigeminal nociceptive pathway but through a purely visual sensory pathway from retinal ganglion cells to the pulvinar nucleus of the thalamus⁸. As detailed by Nosedá, further work in identifying the neurochemical basis of these pain-responsive circuits within the thalamus has implicated a role for the non-image forming light sensors within the retina mediated by melanopsin. To add to complexity, Matynia and colleagues have also identified a non-melanopsin dependent pathway⁹.

This purely visual pathway to pain modulation is exciting in that it offers a neurobiological correlate to Drummond's observed psychophysical interactions between light and pain at even low-light conditions, well below those needed to elicit nociceptive autonomic vascular changes within the orbit. It also offers new insights into the processing of migraine-related pain in the brain. And as indicated by both Nosedá and Friedman, even when migraineurs do not have headache there are neurophysiological changes in visual processing that suggest an overall hypersensitivity, or lack of normal suppression of cortical activity. Friedman suggests the term photoallodynia could be used to describe this interaction between light exposure and the activation of convergent nociceptive pathways.

Light avoidance and aversion

Another interesting perspective of photophobia highlights its behavioral and neurochemical basis, described by Recker and Russo (and detailed in their Invited Review that accompanies this issue). In an elegant series of experiments, mutant mice with enhanced signaling by the neuropeptide calcitonin gene-related peptide (CGRP) were found to have enhanced light avoidance¹⁰. However, because CGRP is also associated with the signaling of pain by peripheral sensory afferents, and nociceptive reflexes were also enhanced in this mouse¹¹, these mutant mice do not offer a clear distinction between the trigeminal sensory and visual sensory aspects of this light-avoidant behavior. Still, they demonstrate the broad role that CGRP plays in the range of sensory and behavior changes associated with migraine, and provide a valuable animal model of the pathophysiology of migraine¹².

In 1927, Crozier and Pincus observed that neonatal rats, even prior to the opening of their eyes, turn away from a localized light source, which he termed negative phototaxis¹³. It is notable that this primitive reflexive behavior occurs at a time when the traditional image-forming photoreceptors are not functional within the retina. More recently, Copenhagen and colleagues showed that this behavior depends critically on retinal ganglion cells expressing the photodetector melanopsin¹⁴.

Further work revealed that these prominent light-avoidant behaviors were not accompanied by the activation of trigeminal pain pathways as noted by Bereiter, nor did it elicit the broadband vocalizations associated with other forms of pain, so thus lacked evidence for overtly nociceptive sensations. However, light did activate ultrasonic vocalizations resembling distress calls, as well as a signal associated with pain-related behaviors in neurons within the central amygdala, a structure whose activity is associated with the negative emotional aspects of pain¹⁵. In other words, behavioral and neurochemical responses to light in neonatal mice suggest a functional distinction between the detection of sensory pain within the trigeminal nucleus and the processing of negatively emotional, aversive experiences within the amygdala.

Does migraine unmask a primitive reflex?

But what could be the significance of these responses in neonatal mice to humans with migraine? One possibility is that photophobia in migraine could represent a transient unmasking of primitive affective and behavioral reflexes that, from an evolutionary viewpoint, could have conferred a behavioral advantage for the newborn. Another possibility is that migrainous photophobia represents the activation of normal light aversion at abnormally low thresholds (i.e. an increase in sensory gain).

Clinical implications

Multiple mechanisms likely account for photophobia in the clinical setting, even for the same patient. This can make it a difficult disorder to define, but on the other hand our present understanding that photophobia engages multiple pathways offers unique opportunities for us to pursue many distinct avenues of treatment for our patients disabled by photophobia¹.

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