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Unanswered questions in headache: so what is photophobia anyway?

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Photophobia is a subjective experience that alters sensory perception of light. Patients often describe photophobia in different ways. For example, some will say “light hurts my eyes” or “light makes my headache worse”, while others will not report associated pain or pain aggravation, but unpleasantness, and state “I cannot stand even low levels of light”. However, regardless of the subjective experience reported, they all manifest a very consistent behavior, they retreat to a dark place or protect their eyes from light. This variability in the subjective experience of photophobic patients is not surprising considering that many different disorders can result in photophobia.

We would like to put out the idea that photophobia involves not only pain pathways, but also limbic system pathways that superimpose an emotional processing of discomfort leading to light avoidance. The interaction of these pathways could provide the drive to seek out darkness. This is especially important in the context of migraine, where photophobia may reflect an allodynic response when even very low levels of light become painful. However, this avoidance can also be protective. Everyone experiences the need to avoid exposure of the eyes to high light intensity. For example, looking directly at the sun is unpleasant and most people will squint or look away to avoid retinal damage. Likewise, the glare of skiing on a sunny day without sunglasses is unpleasant no matter how good the snow is. We suggest that these protective pathways are likely to be the same ones activated by low light in migraine and other pathologies associated with photophobia.

So, how might the brain integrate light with pain and emotional circuits to yield the phenomena of photophobia? In the past few years, we have begun to get glimpses of potential pathways and the direction of needed future research. The cascade begins with light activation of non-image forming melanopsin retinal ganglion cells ^{1–3}. In the landmark study by Nosedá and Burstein, the authors uncovered a convergence of light signals from these retinal ganglion cells with dural nociceptive signals relayed from the trigeminal nerve to the posterior thalamus ¹. Their findings effectively explain how light may aggravate headache in migraine. Likewise, bright light can also activate the trigeminal nerve in the absence of headache. Two intraocular mechanisms have been reported involving either a parasympathetic reflex ⁴ or ocular associational ganglion cells ⁵. In both cases, activation of second-order neurons in the spinal trigeminal nucleus could potentially relay pain signals.

Yet what about the cases where light is perceived more as an annoyance than actual pain? While it could simply be a sub-threshold pain signal, it seems reasonable that light might also activate pathways involved in emotions, such as the amygdala. The amygdala nuclear complex is a principal site for processing fear and anxiety, and importantly, it also relays and modulates nociceptive information. Just as melanopsin retinal ganglion cells project to the posterior thalamus, they also project to the amygdala and other limbic structures ⁶. Indeed, studies by Ahn and colleagues nicely showed that aversive responses to light involved neural activity in the central amygdala, as well as the posterior thalamus, but not the spinal trigeminal nucleus in mouse pups ³.

However, while photophobia has an emotional component, we do not believe that light avoidance in animal models can be explained by anxiety alone ^{2, 7}. Rather, we propose that the two structures (thalamus, amygdala) work in concert, bringing together the sensory and emotional aspects of how light is perceived. There is communication between these areas, and second order neurons project from the spinal trigeminal nucleus to both the posterior thalamus and the amygdala central nucleus ⁸. Hence, light can activate areas of the brain leading to a perception of pain and unpleasantness.

Finally, to return to migraine, how might these pathways become sensitized during a migraine attack so that low light is painful? One contributing mechanism could be enhanced synaptic transmission mediated by the neuropeptide calcitonin gene-related peptide (CGRP) ^{8–10}. The role of CGRP in migraine is now well established ⁹. Intravenous administration of CGRP to migraineurs can provoke a migraine attack, including photophobia, and intracerebroventricular administration of CGRP to mice can elicit light aversive behavior analogous to photophobia ^{7, 11}. In this context, CGRP could act as a neuromodulator to increase glutamatergic signaling, such as seen in amygdala neurons that mediate pain responses ¹². We speculate that this enhanced neurotransmission could be measured using a photic-blink reflex as an objective outcome.

Where might CGRP be acting in photophobia? In the CNS, the peptide and its receptor are widely distributed in both nociceptive and limbic pathways, including the trigeminal system, posterior thalamus, and amygdala nuclei ^{8, 10}. In particular, there are CGRP receptors on neurons responsive to nociceptive trigeminovascular input in the ventroposteromedial thalamus ¹³, an area activated by convergent trigeminal and light signals ¹. In addition, CGRP-containing neurons of the subparafascicular thalamus and other posterior intralaminar thalamic nuclei receive somatosensory and nociceptive stimuli ¹⁴ and CGRP fibers from this region project to the amygdala where they have been suggested to play a role in autonomic and behavioral responses to acoustic and somatosensory stimuli ¹⁵. Perhaps an analogous circuit contributes to photophobia. Future studies using animal models should help unravel the pathways and mechanisms of sensitization in photophobia.

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