HHS Public Access

Author manuscript

Expert Rev Ophthalmol. Author manuscript; available in PMC 2017 August 25.

Published in final edited form as:

Expert Rev Ophthalmol. 2016 ; 11(5): 321–324. doi:10.1080/17469899.2016.1222905.

What can photophobia tell us about dry eye?

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Keywords

Dry eye; photophobia; neuropathic ocular pain

1. Photophobia and dry eye (DE)

Photophobia, or an abnormal experience of pain to light, is a frequent complaint in patients with sensations of ocular dryness. This editorial will review potential pathways of photophobia and discuss the possibility that its presence is suggestive of central sensitization as a component of DE. Potential approaches to the treatment of central sensitization in DE and ways to address photophobia will also be discussed.

2. Frequency and morbidity of DE symptoms

Dry eye (DE) is a prevalent condition, with approximately 15% of various populations over 50 years old reporting symptoms of visual disturbances and/or sensations of dryness. [1] Alongside these traditional complaints, patients may also report other ocular sensations using descriptors such as “aching” (56%) and “hot burning” (53%) to describe their eye pain.[2] In a population of 236 veterans with mild or greater DE symptoms (dry eye

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Declaration of interest

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questionnaire 5 score≥6), we found that, 75% reported pain sensitivity to light (photophobia); 39% of whom rated the sensitivity to be of moderate or greater severity (≥4 on scale of 0–10). In a similar manner, 64% reported pain sensitivity to wind; 32% of whom rated the sensitivity to be of moderate or greater severity. It is no surprise then, that DE symptoms, including pain complaints, affect the quality of life of millions of Americans.[1] A study utilizing the Impact of DE on Everyday Life (IDEEL) questionnaire, found that DE symptoms correlated with difficulties in physical and mental functioning.[3] Utility assessment revealed that patients with severe DE symptoms have utility scores in the same range of conditions as class III/IV angina.[4]

3. What can we learn from the co-existence of photophobia in patients with other DE symptoms?

As above, we have found that the majority of patients with symptoms of ocular dryness report some degree of photophobia. However, photophobia is not unique to DE but can be found in a wide number of conditions including intraocular inflammation, iris abnormalities, retinal degenerations, migraines, blepharospasm and other neurologic pathology. Interestingly, photophobia has also been reported in blind patients.[5] Implied by such variation in causation is a multiplicity of diverse pathways converging on a common pain response.

4. Pathways of photophobia

The trigeminal nerve and its nuclei (the nucleus caudalis in particular[6]) arise as obvious unifying culprits that can tie in photophobia and DE. The V1 distribution of the trigeminal nerve supplies nociceptive innervation to the ocular and orbital structures as well as the meninges. The primary afferents throughout V1 converge onto the trigeminal nucleus caudalis which then conveys sensory information into the central nervous system, projecting nociceptive sensation through the parabrachial and thalamic nuclei and on to the cortex and subcortical centers involved in the experience of pain.[7] Light activates the trigeminal system as can be seen with increased firing and c-fos positive neurons in the trigeminal nucleus caudalis in a rat model.[6]

While the thalamic nuclei mediate the transmission of the sensory component of the painful experience to noxious stimuli or to light in photophobia, pathways involving the parabrachial nuclei mediate the affective/motivational/behavioral components involved in the manifestations of photophobia and DE.[8–10] This explains the multidimensional nature of the painful experience in patients with DE and/or photophobia, conditions not infrequently accompanied by high levels of emotional distress[11], as well as the aversive behaviors of patients who protect their eyes with sun glasses, avoid intense light, avoid exposure to wind, and exhibit preferences for dark rooms and isolation.

More than one diverse circuit has been identified in humans and/or animal model that tie in light with the trigeminal – thalamic – cortical pathway.[7]

1. As light is the primary stimulus for photophobia, the classical pathways of light perception are involved. These pathways include rods, cones (as primary light sensors), bipolar and amacrine cells, retinal ganglion cells and then the optic nerve, thalamic geniculate nucleus and occipital cortex. Yet, some afferent fibers instead of continuing to the lateral geniculate nucleus (as they do for visual input), project to the olivary pretectal nucleus, which activates downstream the superior salivatory nucleus (SSN), and the pterygopalatine ganglion. This parasympathetic activation causes activation and sensitization of ocular trigeminal afferents via mechanisms that include uveal vasodilation and release of neuro-inflammatory mediators (e.g. calcitonin gene-related peptide, vasoactive intestinal peptide and nitric oxide). Trigeminal afferents from the eye (heavily expressed in ocular blood vessels) may then convey pain signals to nucleus caudalis, thalamus and higher brain centers involved in pain perception, and via the parabrachial nucleus to areas driving the affective/aversive and behavioral manifestations of photophobia.[7]

   So, light, via the aforementioned pathways, may produce increased activation of the nucleus caudalis and generate subsequent perception of its input as painful. Interestingly, other cranio-facial pain conditions also involve active parasympathetic pathways, namely trigeminal autonomic cephalalgias (e.g. cluster headaches). Functional imaging suggests that these syndromes activate a normal human trigeminal-parasympathetic reflex with clinical signs of cranial sympathetic dysfunction being secondary.[7]

   The contents of the orbit also receive sympathetic innervation, via the short ciliary nerves to the blood vessels, and via the long ciliary nerves to the pupil. Sympathetic efferents have been also shown to reach the cornea[12], and this may be relevant to pain states, too. This is implied from the notion that stimulation of the superior cervical sympathetic ganglion can cause pain in humans[13], while its blockade produces analgesia in patients with intractable facial pain who have failed trigeminal section.[13]

2. Other circuits originate from light sensing but not image –forming pathways, and this may explain the fact that even blind patients may experience photophobia.[5] These originate from intrinsically-photosensitive retinal ganglion cells (IPRGCs), with melanopsin rather than rhodopsin as photo-pigment. Melanopsin responds maximally to light at a wavelength of 480 nm. In humans, only a minority (0.2–0.8%) of ganglion cells are intrinsically photosensitive.[14]

   These neurons respond to light (but in a non-image forming manner) and via the optic nerve project also to the olivary pretectal nuclei, but also to thalamic nuclei bypassing the nucleus caudalis. Therefore, thalamic nuclei receive convergent nociceptive input from ocular primary afferents and from other trigeminal neurons via the nucleus caudalis, as well as direct input from the IPRGC projecting neurons. As a result of this convergence, they may get sensitized, and may convey pain-like signaling in response to light to higher brain centers involved in pain perception.[7]

3. Finally, intrinsically photosensitive ganglion-like cells that contain melanopsin are also present in mammalian iris.[15] So, light sensed by these afferents may activate trigeminal blink reflex even after transection of the optic nerve that contains the pathways from the image–forming and non-image forming cells

5. How does this pathway tie in with DE?

DE starts at the ocular surface with findings that include changes in tear composition, tear instability, hyperosmolarity, and inflammation. Corneal nociceptors are sensitive to such changes as their terminal endings are in close contact with the tear film [16]. For example, ocular surface abnormalities such as hyperosmolarity and inflammation have been found to sensitize cold and polymodal afferent receptors, respectively.[17] It is well known that prolonged and intense nociceptive input generates a state of increased excitability and synaptic potentiation in central nociceptive pathways.[18] This phenomenon has complex electrophysiologic, molecular and genetic determinants and clinically manifests as enhanced spontaneous pain, as increased responsiveness to painful stimuli (hyperalgesia), as perception of non-painful stimuli as painful (allodynia), as distortion of the normal sensory experience, and as a variety of several other unpleasant sensations. Central sensitization has been implicated as a significant factor in generating and maintaining other chronic cranio-facial pain states, via increased brain excitability and decreased descending inhibitory to pain signaling.[19] Thus, the finding of photophobia in patients with “typical” DE symptoms may suggest that central sensitization underlies at least a portion of their symptoms.

Activation of glia as part of a neuroinflammatory response, triggered by an interplay of noxious injury, genetic and molecular mechanisms, also significantly contributes to alteration of the processing of sensory signals by the central nervous system so that they are perceived as painful.[20] This is also the case in the trigeminal sensory system.[21] Because by central sensitization, any focal noxious process can evolve into widespread hypersensitivity to non-painful and painful stimuli[22], input of light signaling may generate perception and behaviors suggestive of pain (i.e. photophobia or “allodynia to light”).

6. How does this affect DE treatment?

We have found that patients with photophobia have a more chronic disease course and report more severe symptoms than their counterparts with DE symptoms but without photophobia. [23] In addition, in a cross-sectional study, patients with photophobia were more likely to report that their ocular pain was not completely relieved by artificial tears (hypromellose 0.4%).[24] Despite the limitations of our studies[23,24], taken together, these data suggest that patients with photophobia may have a chronic disease course that is more resistant to topical therapies. In these patients, a multimodal approach may be beneficial including treating tear abnormalities and ocular surface damage with ocular surface protection and anti-inflammatory agents, and modulating somatosensory dysfunction. More research is needed, however, to understand which drugs, through which route, are best suited to modulate corneal somatosensory function.

Outside the eye, the management of neuropathic pain depends on pain severity, underlying pathophysiology, and systemic comorbidities. Typically, first line therapies for neuropathic pain are the alpha 2 delta ligand antiepileptics (gabapentin, pregabalin), followed by serotonin–norepinephrine reuptake inhibitors (duloxetine, venlafaxine) as second-line agents and tricyclic antidepressants (nortriptyline, amitriptyline) as third-line agents due to their side effects. Combination therapies (antiepileptics and antidepressants) are also used in cases where monotherapy provides only partial relief. In addition, depending on pain severity and upon failure of other treatments, some opioids (tramadol, buprenorphine) can be used in selected patients, together with the therapies above. Topical agents (diclofenac, lidocaine and capsaicin) are also used even as first-line therapies or as parts of multimodal therapies or in specific conditions such as in the treatment of post-herpetic neuralgia.[25–27]

More aggressive measures (eg, nerve blocks, peripheral and/or central stimulation) are used in patients who have failed conservative therapy or if there are specific indications, such as for neuropathic pain localized in the area of innervation of a specific nerve and related to neuropathy of that nerve. Sympathetic blocks of the superior cervical ganglion, for example, have already been shown to attenuate ocular pain and photophobia.[28] In addition, delivering all these therapies in a multidisciplinary approach (cognitive, behavioral, and physical therapy) is important.

Taking into consideration the affective and aversive manifestations of photophobia, that generate maladaptive behaviors and emotional distress, cognitive behavioral or other appropriate therapy aiming at behavioral modifications should be considered as an integral part of any comprehensive therapeutic approach. For example, in the context of avoidance maladaptive behaviors, addressing photophobia in DE may require some additional considerations. First, the use of sunglasses indoors should be strongly discouraged.[14] Wearing dark glasses indoors causes dark-adaption and only makes light sensitivity worse. Instead, tinted lenses, such as FL-41 (which blocks light at 480 nm; the wavelength at which IPRGCs are maximally sensitive) have been shown to improve light sensitivity in a variety of clinical situations, including migraine and blepharospasm.[14]

With many agents available to treat neuropathic pain, research is needed to understand which of these approaches will be beneficial in addressing DE symptoms in those patients who continue to have persistent symptoms despite using currently approved therapies.

Acknowledgments

Funding

This paper was supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Clinical Sciences Research EPID-006-15S (Dr. Galor), NIH Center Core Grant P30EY014801, Research to Prevent Blindness Unrestricted Grant, and NIH NIDCR R01 DE022903 (Dr. Levitt). In addition, we would like to note that the contents of this study do not represent the views of the Department of Veterans Affairs or the United States Government.

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