HHS Public Access

Author manuscript

Headache. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Headache. 2015 April ; 55(4): 600–604. doi:10.1111/head.12532.

Photophobia in Primary Headaches

Heather L. Rossi, Ph.D.[1] and **Ana Recober, M.D.**[1]

[1] The Children's Hospital of Philadelphia & University of Pennsylvania, Perelman School of Medicine, Department of Neurology

Abstract

Background—Photophobia is a debilitating feature of many headache disorders.

Overview—Clinical and preclinical research has identified several potential pathways involved in enhanced light sensitivity. Some of these structures include trigeminal afferents in the eye, second order neurons in the trigeminal nucleus caudalis, third order neurons in the posterior thalamus, modulatory neurons in the hypothalamus, and fourth order neurons in the visual and somatosensory cortices. It is unclear to what degree each site plays a role in establishing the different temporal patterns of photophobia across different disorders. Peptides such as calcitonin-gene related peptide and pituitary adenylate cyclase-activating polypeptide may play a role in photophobia at multiple levels of the visual and trigeminal pathways.

Conclusion—While our understanding of photophobia has greatly improved in the last decade, there are still unanswered questions. These answers will help us develop new therapies to provide relief to patients with primary headache disorders.

Keywords

photophobia; light aversion; headache; migraine; cluster headache; preclinical models

Introduction

Photophobia is a common and debilitating symptom often present in headache disorders. Other conditions associated with photophobia include several eye pathologies (corneal lesions, uveitis, iritis, cone dystrophies, etc), essential blepharospasm, meningeal irritation (subarachnoid hemorrhage, meningitis), and traumatic brain injury, especially when secondary to blast injury. It is important to acknowledge that “photophobia” is sometimes used to describe related but distinct phenomena. Etymologically, photophobia means “excessive or irrational fear of light”, which does not convey the clinical definition of this phenomenon. Most commonly, photophobia is used to refer to discomfort or pain induced by light. Commonly in migraine and other primary headache disorders, light evokes or aggravates headache, and some patients experience ocular or periocular pain. This sensitivity to light is abnormal because it occurs at levels of light that most people would not

Correspondence should be addressed to Dr. Ana Recober: Colket Translational Research Building – Rm. 10200 3501 Civic Center Boulevard Philadelphia, PA 19104 Phone: 1-215-590-4384 recobera@email.chop.edu.

Disclosure: Dr. Recober has received an honorarium from Allergan (unrelated to current manuscript) and licensing fees from Alderbio Holdings, LLC (for anti-CGRP antibodies in the treatment of photophobia).

consider bothersome. For example, in a study by Vanagaite *et al.* control subjects did not report discomfort until light intensity reached 23,000 lux (the equivalent of a cloudless, sunny day), and 24% still tolerated this level perfectly well.[1] In contrast, migraineurs reported discomfort in a range of ~500 – 1,000 lux (like an overcast day).[1]

Photophobia is a poorly understood phenomenon. Furthermore, it is unclear what the underlying mechanisms are and which are specifically relevant for headache-related photophobia. A better understanding of the pathogenesis of photophobia will allow us to develop more effective therapies and gain knowledge about several primary headache disorders. In this review, we will discuss recent advances in our understanding of the anatomical substrates of photophobia.

Photophobia in Headache Disorders

The use of experimental light stimulation has provided us with important insight regarding photophobia in headache disorders. Most migraine patients describe low intensity light as "glaring" or "painful" during a migraine attack, making photophobia one of the cardinal diagnostic criteria.[1, 2] However, similar findings have been observed in patients with tension-type[2] and cluster[3] headache. Furthermore, experimental evidence suggests that photophobia is bilateral, even when headache is unilateral in either migraine [1] or cluster headache.[3]

Some differences in the features of photophobia also exist across headache disorders. For tension-type headache, light-induced ratings fell between those of interictal migraineurs and control subjects.[2] The intermediate severity of light sensitivity in tension type headache may indicate that it may be present, but not noticeable to every patient. Cluster headache patients report photophobia ictally and interictally, but only during their cluster period.[3] This suggests that cluster patients experience reversible changes in the neural substrates involved, whereas migraineurs, and perhaps patients with tension type headache, have persistent changes. While light-evoked activation in the brains of migraineurs has been examined using PET[4, 5], the study of light-modulated activity in other headache conditions has lagged behind. Further neuroimaging studies are needed to determine whether the neural substrates involved are the same or different across all of these conditions. This may be challenging for the less prevalent trigeminal autonomic cephalalgias (TACs), but should be feasible for tension-type headache. Given the prevalence and significant burden of tension type headache[6], studies exploring light sensitivity and neural activity in this disorder are warranted.

The trigeminal system has been broadly implicated in generating pain in different headache disorders[6-8], but the causative factors that may sensitize and/or disinhibit the trigeminal pathway may differ across conditions. Several studies have demonstrated that there is an interaction between pain mediated by the trigeminal system and photophobia. In control subjects, painful stimulation of the ophthalmic branch of the trigeminal nerve by intramuscular injection of sodium chloride induced sensitivity to light.[9] Similarly, pain induced by applying ice to the forehead enhanced the degree of photophobia in migraineurs.[10] Conversely, light stimulation significantly reduced trigeminal pressure thresholds in migraine patients, but not in healthy controls.[11] Thus, there seems to be a

bidirectional relationship between trigeminal pain modulating systems and light sensitivity. Such a relationship is supported by recent studies in both humans and animals. Evidence indicates that the light and pain modulating systems can interact at multiple anatomical levels from the eye to the cortex.[12-17] Each of these points of interaction could play a role in photophobia associated with primary headache disorders.

Eye Afferents and Second Order Trigeminal Neurons

An intact visual system is not required for the development of photophobia, as indicated by its occurrence in blind individuals.[12, 16, 18] However, it is unclear how many and which light detecting structures are necessary to produce migrainous photophobia. Although intrinsically photosensitive retinal ganglion cells (ipRGCs) have been implicated[16], light transduction through remaining rods and cones could still contribute to their perception of photophobia in some blind individuals and in fully sighted migraineurs. Several recent studies have demonstrated a direct relationship between light stimulation and trigeminal activity.[13, 17, 19] Importantly, Dolgonos *et al.* showed that light modulates the blink reflex in rats, even after complete transection of the optic nerves.[13] Their findings suggest that the optic nerve may not be required for photophobia to occur, although it may play a role or represent a parallel pathway. Furthermore, the authors propose that associational ganglion cells, which do not send projections through the optic nerve[20], could be interacting with trigeminal nociceptors in the eye to produce the light evoked increase blink responses.[13] In humans, the blink reflex has been used to demonstrate impaired habituation in migraine and cluster[21], and could represent a useful approach to study sensitivity to light in animal models.

Okamoto and colleagues identified two populations of light-responsive neurons within trigeminal nucleus, one at the interpolaris/caudalis border and another within the trigeminal nucleus caudalis/cervical spinal cord transition (TNc/C1), using both immunohistochemical and electrophysiologic techniques.[17, 19, 22] The former population is thought to be implicated in light-evoked lacrimation[22], while the latter is thought to be involved in light-exacerbated pain.[17] They used an elegant design to demonstrate that light-evoked activity in TNc/C1 neurons is dependent on trigeminal afferent drive and activity from the superior salivatory and olivary pretectal nuclei, and could be blocked by intravitreal norepinephrine.[17] Based on these findings, these authors posit that light activates a parasympathetic reflex arch, which increases blood flow in the eye. Trigeminal afferents are then activated either mechanically, by dilated choroid vessels, by neurotransmitters released by postganglionic autonomic nerve terminals, or both.[17, 19] These afferents, in turn activate second order neurons within the TNc/C1, which also receive convergent input from dural afferents[23, 24].

Thalamic Gating

In a landmark study, Burstein's group identified the convergence of dural nociceptive and photic retinal information in the posterior thalamus, revealing another area of interaction between visual and pain pathways that likely contributes to photophobia.[16] Noseda *et al.* demonstrated that third order neurons within the posterior thalamic nuclei were responsive to both light stimulation of the eye and mechanical stimulation of the dura. These third order

neurons may receive direct inputs from retinal ganglion cells[16], and send projections to a wide variety of cortical regions, including, but not limited to, visual cortex, substrates in the "pain matrix", and areas involved in modulating attention[15, 16]. These anatomical connections could explain both the sensitivity to light and the exacerbation of headache by light in migraine and other headache disorders.[14] However, the intraocular mechanisms proposed by Dolgonos *et al.*[13] and Okamoto *et al.*[17] may also contribute to the same phenomena. It is important to note that all of the above studies were performed in healthy rats; additional work with models of trigeminal pain may help clarify the relative contribution of these mechanisms to headache-associated photophobia.

Neuroimaging studies in human subjects also support a role for thalamic gating in photophobia. Maleki *et al.* demonstrated direct input from the optic nerve to the pulvinar using diffusion weighted imaging and probabilistic tractography[25], validating the clinical relevance of similar finding in the posterior thalamus of rodents[16]. A PET study examined thalamic activity in patients with essential blepharospasm and compared patients with or without photophobia to healthy subjects.[26] They found that only the blepharospasm patients with photophobia exhibited hyperactivity in the thalamus, when compared to either the non-photophobic patients or to controls.[26] These results support a role for enhanced thalamic activity in photophobia in humans, although additional imaging of headache patients would more specifically implicate thalamic involvement in headache-associated photophobia.

Hypothalamic Modulation

The hypothalamus has been implicated in the pathophysiology of both migraine and cluster headache. It has been suggested that hypothalamic involvement may explain premonitory symptoms of migraine[27] and could be involved in the onset of migraine following imbalance in homeostatic triggers[28, 29]. Cells in the medial hypothalamus are responsive to light[30], which could have direct implications for photophobia. Recent work has demonstrated that the hypothalamic neurons from the dopaminergic A11/13 group, the ventromedial and tuberomammillary nuclei make direct connections to the posterior thalamic nuclei.[29] The authors propose that such connections could play some role in attacks triggered by homeostatic imbalance. In parallel, Katagiri *et al.* recently demonstrated that disinhibition of the posterior hypothalamus suppresses light-evoked activity of second order trigeminal neurons, suggesting that this region may play some role in negative regulation of light sensitivity and autonomic response to light.[31] The hypothalamic contribution to photophobia provides an intriguing pathway to study the interaction between headache pathophysiology and homeostatic dysfunction, such as that related to obesity or sleep dysregulation.

Cortical Activity: Insights from Neuroimaging of Human Subjects

A number of studies have implicated the visual cortex in the regulation of light sensitivity and photophobia. Bilateral lesions of the ventral occipital cortex abolish protective light avoidance.[32] These patients report complete insensitivity to light (1592 lux), a sense of dimness to their vision, and have difficulty distinguishing night from day. This suggests that the ventral occipital cortex may be particularly relevant for photophobia.[32] Both fMRI[33] and PET[4] studies demonstrated a correlation between the intensity of light stimulus and visual cortex activation in migraine patients interictally and control subjects, with greater cortical

activation in migraineurs. Additionally, Boulloche *et al.* demonstrated that trigeminal pain could enhance this light-evoked activity in migraineurs and reduce the threshold of light intensity necessary to produce significant activity in control subjects.[4] In the absence of concomitant pain stimulation, control subjects only exhibited significantly enhanced activity at the higher light intensity (1800 Cd/m^2), but with pain stimulation they also exhibited significant activity at 600 Cd/m^2. These studies suggest that cortical hyperexcitability, lack of habituation, or both could contribute to photophobia. Although Martin *et al.* argued against habituation deficits as an explanation for their findings, they acknowledged that their stimulation protocol may have been too brief to really evaluate the contribution of habituation.[33] They used a flickering light stimulus, in an on/off design, for a total of 30s of stimulation. Boulloche *et al.* used a continuous stimulus that also lasted 30s and were also not able to rule out a possible contribution of habituation deficits in the migraineurs' response pattern.[4] Boulloche *et al.* also observed significant activity in the posterior parietal cortex, which is associated with attentional modulation and receives input from the locus coeruleus, a pain-modulating nucleus in the brainstem. They hypothesized that pain impaired habituation in control subjects as a result of attentional processing, and that this phenomenon could be involved in migrainous photophobia as well.[4]

PET imaging has also demonstrated changes in visual cortex activity that correlate with migrainous state.[5] Denuelle *et al.* used a low intensity of light to compare light-evoked visual cortex activity in migraineurs during an attack, after headache resolution with sumatriptan, and interictally. This low intensity light evoked cortical activity during the migraine attack phase, but not interictally. After triptan treatment, the level of cortical activation was intermediate. The authors proposed that the trigeminal interaction with visual pathways may explain ictal photophobia, while other brainstem nuclei, such as the locus coeruleus and raphe dorsal nuclei, may be involved in interictal photophobia.[5] The locus coeruleus and raphe dorsal nuclei have been linked to activity within the visual cortex.[34] They are also involved in descending pain modulation, and may contribute to migraine pathophysiology.[35] Additional work will help clarify the role of brainstem modulation in headache-related photophobia.

Contribution of Neuropeptides CGRP and PACAP to Photophobia

While we have recently advanced our understanding of the anatomical substrates that may be involved in headache-related photophobia, the role of molecular signaling pathways within these substrates remains unclear. Neuropeptides that enhance synaptic transmission may play a role in photophobia. Two particular candidates are the calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP), both of which induce migraine attacks in migraineurs.[36-38] These multifunctional peptides are widely distributed in the nervous system and in addition to their vascular actions; they are both implicated in modulating nociception.[39-41] Preclinical studies have linked both of these neuropeptides to photophobia. Intracerebroventricular administration of CGRP in mice elicits light aversive behavior analogous to photophobia.[42-44] Mice lacking PACAP do not develop nitroglycerin-induced light aversion.[45] Both peptides are found in many of the neural substrates discussed above. There are CGRP receptors throughout the brain[46], including neurons in the ventroposteromedial thalamus[47], which contains dural and light

sensitive neurons[16]. PACAP is expressed in the ipRGCs of rats[48], within the trigemino-cervical complex of humans[49], as well as the ventromedial hypothalamus[50]. Future studies using animal models should help clarify the role of these neuropeptides in the generation of headache and photophobia, as well as their most relevant sites of action.

Conclusion

The study of photophobia associated with headache disorders has advanced our understanding of their unique pathophysiology. Preclinical research using a variety of techniques has provided clues as to potential mechanisms involved, although their relative contribution to distinct disorders is not clear. Additional work evaluating light sensitivity and neuronal activity in under studied conditions like tension-type headache, cluster headache and TCAs will provide a frame work for preclinical models. Finally, preclinical models can be used to probe novel therapeutic targets and improve future treatment of headache disorders.

Acknowledgments

The preparation of this manuscript was supported in part by a Career Development Grant from the NINDS/NIH (K-08 NS066087-01)

References

1. Vanagaite J, Pareja J, Støren O, White L, Sand T, Stovner L. Light-induced discomfort and pain in migraine. Cephalalgia. 1997; 17:733–741. [PubMed: 9399002]
2. Drummond PD. A quantitative assessment of photophobia in migraine and tension headache. Headache. 1986; 26:465–469. [PubMed: 3781834]
3. Vingen JV, Pareja J, Stovner L. Quantitative evaluation of photophobia and phonophobia in cluster headache. Cephalalgia. 1998; 18:250–256. [PubMed: 9673803]
4. Boulloche N, Denuelle M, Payoux P, Fabre N, Trotter Y, Géraud G. Photophobia in migraine: an interictal PET study of cortical hyperexcitability and its modulation by pain. J Neurol Neurosurg Psychiatry. 2010; 81:978–984. [PubMed: 20595138]
5. Denuelle M, Boulloche N, Payoux P, Fabre N, Trotter Y, Geraud G. A PET study of photophobia during spontaneous migraine attacks. Neurology. 2011; 76:213–218. [PubMed: 21148120]
6. Bendtsen L, Jensen R. Tension-type headache: the most common, but also the most neglected, headache disorder. Curr Opin Neurol. 2006; 19:305–309. [PubMed: 16702840]
7. Holle D, Obermann M, Katsarava Z. The electrophysiology of cluster headache. Curr Pain Headache Rep. 2009; 13:155–159. [PubMed: 19272282]
8. Vecchia D, Pietrobon D. Migraine: a disorder of brain excitatory–inhibitory balance? Trends Neurosci. 2012; 35:507–520. [PubMed: 22633369]
9. Eckardt LB, McLean JM, Goodell H. Experimental studies on headache: the genesis of pain from the eye. Res Publ-Assoc Res Nerv Ment Dis. 1943; 23:209–227.
10. Drummond PD, Woodhouse A. Painful stimulation of the forehead increases photophobia in migraine sufferers. Cephalalgia. 1993; 13:321–324. [PubMed: 8242724]
11. Kowacs P, Piovesan E, Werneck L, Tatsui CE, Mange MC, Ribas LC, da Silva HP. Influence of intense light stimulation on trigeminal and cervical pain perception thresholds. Cephalalgia. 2001; 21:184–188. [PubMed: 11442552]
12. Amini A, Digre K, Couldwell WT. Photophobia in a blind patient: an alternate visual pathway. J Neurosurg. 2006; 105:765–768. [PubMed: 17121141]

13. Dolgonos S, Ayyala H, Evinger C. Light-induced trigeminal sensitization without central visual pathways: another mechanism for photophobia. Invest Ophthalmol Vis Sci. 2011; 52:7852–7858. [PubMed: 21896840]
14. Noseda R, Burstein R. Advances in understanding the mechanisms of migraine-type photophobia. Curr Opin Neurol. 2011; 24:197–202. [PubMed: 21467933]
15. Noseda R, Jakubowski M, Kainz V, Borsook D, Burstein R. Cortical projections of functionally identified thalamic trigeminovascular neurons: Implications for migraine headache and its associated symptoms. J Neurosci. 2011; 31:14204–14217. [PubMed: 21976505]
16. Noseda R, Kainz V, Jakubowski M, Gooley JJ, Saper CB, Digre K, Burstein F. A neural mechanism for exacerbation of headache by light. Nat Neurosci. 2010; 13:239–245. [PubMed: 20062053]
17. Okamoto K, Tashiro A, Chang Z, Bereiter DA. Bright light activates a trigeminal nociceptive pathway. Pain. 2010; 149:235–242. [PubMed: 20206444]
18. Custer PL, Reistad CE. Enucleation of blind, painful eyes. Ophthal Plast Reconstr Surg. 2000; 16:326–329.
19. Okamoto K, Thompson R, Tashiro A, Chang Z, Bereiter DA. Bright light produces Fos-positive neurons in caudal trigeminal brainstem. Neuroscience. 2009; 160:858–864. [PubMed: 19285114]
20. Sagar SM, Marshall PE. Somatostatin-like immunoreactive material in associational ganglion cells of human retina. Neuroscience. 1988; 27:507–516. [PubMed: 3217002]
21. Perrotta A, Serrao M, Sandrini G, Bogdanova D, Tassorelli C, Bartolo M, Coppola G, Pierlli F, Bappi G. Reduced habituation of trigeminal reflexes in patients with episodic cluster headache during cluster period. Cephalalgia. 2008; 28:950–959. [PubMed: 18624808]
22. Okamoto K, Tashiro A, Thompson R, Nishida Y, Bereiter DA. Trigeminal interpolaris/caudalis transition neurons mediate reflex lacrimation evoked by bright light in the rat. Eur J Neurosci. 2012; 36:3492–3499. [PubMed: 22937868]
23. Burstein R, Yamamura H, Malick A, Strassman AM. Chemical stimulation of the intracranial dura induces enhanced responses to facial stimulation in brainstem trigeminal neurons. J Neurophysiol. 1998; 79:964–982. [PubMed: 9463456]
24. Ebersberger A, Ringkamp M, Reeh PW, Handwerker HO. Recordings from brainstem neurons responding to chemical stimulation of the subarachnoid space. J Neurophysiol. 1997; 77:3122–3133. [PubMed: 9212262]
25. Maleki N, Becerra L, Upadhyay J, Burstein R, Borsook D. Direct optic nerve pulvinar connections defined by diffusion MR tractography in humans: Implications for photophobia. Human Brain Mapp. 2012; 33:75–88.
26. Emoto H, Suzuki Y, Wakakura M, Horie C, Kiyasawa M, Mochizuki M, Kawasaki K, Oda K, Ishiwata K, Ishili K. Photophobia in essential blepharospasm—A positron emission tomographic study. Movement Dis. 2010; 25:433–439. [PubMed: 20014062]
27. Charles A. The evolution of a migraine attack – a review of recent evidence. Headache. 2013; 53:413–419. [PubMed: 23278169]
28. Alstadhaug K. Migraine and the hypothalamus. Cephalalgia. 2009; 29:809–817. [PubMed: 19604254]
29. Kagan R, Kainz V, Burstein R, Noseda R. Hypothalamic and basal ganglia projections to the posterior thalamus: Possible role in modulation of migraine headache and photophobia. Neuroscience. 2013; 248:359–368. [PubMed: 23806720]
30. Brown TM, Wynne J, Piggins HD, Lucas RJ. Multiple hypothalamic cell populations encoding distinct visual information. J Physiol. 2011; 589:1173–1194. [PubMed: 21224225]
31. Katagiri A, Okamoto K, Thompson R, Bereiter DA. Posterior hypothalamic modulation of light-evoked trigeminal neural activity and lacrimation. Neuroscience. 2013; 246:133–141. [PubMed: 23643978]
32. Horiguchi H, Kubo H, Nakadomari S. Lack of photophobia associated with bilateral ventral occipital lesion. Jpn J Ophthalmol. 2011; 55:301–303. [PubMed: 21559913]
33. Martín H, del Río MS, de Silanes CL, Álvarez-Linera J, Hernández JA, Pareja JA. Photoreactivity of the occipital cortex measured by functional magnetic resonance imaging–blood oxygenation

level dependent in migraine patients and healthy volunteers: pathophysiological implications. Headache. 2011; 51:1520–1528. [PubMed: 22082422]

34. Filippov IV, Williams WC, Frolov VA. Very slow potential oscillations in locus coeruleus and dorsal raphe nucleus under different illumination in freely moving rats. Neurosci Lett. 2004; 363:89–93. [PubMed: 15158004]
35. Akerman S, Holland PR, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. Nat Rev Neurosci. 2011; 12:570–584. [PubMed: 21931334]
36. Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. Cephalalgia. 2010; 30:1179–1186. [PubMed: 20855363]
37. Lassen L, Haderslev P, Jacobsen V, Iversen H, Sperling B, Olesen J. CGRP may play a causative role in migraine. Cephalalgia. 2002; 22:54–61. [PubMed: 11993614]
38. Schytz HW, Birk S, Wienecke T, Kruuse C, Olesen J, Ashina M. PACAP38 induces migraine-like attacks in patients with migraine without aura. Brain. 2009; 132:16–25. [PubMed: 19052139]
39. Hashimoto H, Shintani N, Baba A. New Insights into the Central PACAPergic System from the Phenotypes in PACAP- and PACAP Receptor-Knockout Mice. Annals of the New York Academy of Sciences. 2006; 1070:75–89. [PubMed: 16888150]
40. Raddant AC, Russo AF. Calcitonin gene-related peptide in migraine: intersection of peripheral inflammation and central modulation. Expert Rev Mol Med. 2011; 13:e36. doi: 10.1017/S1462399411002067. [PubMed: 22123247]
41. Kaiser EA, Russo AF. CGRP and migraine: Could PACAP play a role too? Neuropeptides. 2013; 47:451–461. [PubMed: 24210136]
42. Kaiser EA, Kuburas A, Recober A, Russo AF. Modulation of CGRP-induced light aversion in wild- type mice by a 5-HT1B/D agonist. J Neurosci. 2012; 32:15439–15449. [PubMed: 23115181]
43. Recober A, Kaiser EA, Kuburas A, Russo AF. Induction of multiple photophobic behaviors in a transgenic mouse sensitized to CGRP. Neuropharmacol. 2010; 58:156–165.
44. Recober A, Kuburas A, Zhang Z, Wemmie JA, Anderson MG, Russo AF. Role of calcitonin gene-related peptide in light-aversive behavior: implications for migraine. J Neurosci. 2009; 29:8798–8804. [PubMed: 19587287]
45. Markovics A, Kormos V, Gaszner B, Lashgarara A, Szoke E, Sandor K, Tuka B, Tajti J, Szolcsanyl J, Pinter E, Hashimoto H, Kun J, Reglodi D, Helyes Z. Pituitary adenylate cyclase-activating polypeptide plays a key role in nitroglycerol-induced trigeminovascular activation in mice. Neurobiol Dis. 2012; 45:633–644. [PubMed: 22033344]
46. Van Rossum D, Hanisch U-K, Quirion R. Neuroanatomical localization, pharmacological characterization and functions of CGRP, related peptides and their receptors. Neurosci Biobehav Rev. 1997; 21:649–678. [PubMed: 9353797]
47. Summ O, Charbit AR, Andreou AP, Goadsby PJ. Modulation of nocioceptive transmission with calcitonin gene-related peptide receptor antagonists in the thalamus. Brain. 2010; 133:2540–2548. [PubMed: 20802202]
48. Engelund A, Fahrenkrug J, Harrison A, Hannibal J. Vesicular glutamate transporter 2 (VGLUT2) is co-stored with PACAP in projections from the rat melanopsin-containing retinal ganglion cells. Cell Tissue Res. 2010; 340:243–255. [PubMed: 20339872]
49. Uddman R, Tajti J, Hou M, Sundler F, Edvinsson L. Neuropeptide expression in the human trigeminal nucleus caudalis and in the cervical spinal cord C1 and C2. Cephalalgia. 2002; 22:112–116. [PubMed: 11972578]
50. Hannibal J, Hindersson P, Ostergaard J, Georg B, Heegaard S, Larsen PJ, Fahrenkrug J. Melanopsin is expressed in PACAP-containing retinal ganglion cells of the human retinohypothalamic tract. Invest Ophthalmol Vis Sci. 2004; 45:4202–4209. [PubMed: 15505076]