▪ Headache Medicine 2026, Supplement ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

ID: 314

Physiological mechanisms of the retinohypothalamic pathway in photophobia and the impact of intrinsically photosensitive retinal ganglion cells in migraine: a systematic review

João Gabriel Dantas, Eduardo Santana Fernandes Filho, Maria Eduarda Silva Guimarães, Alberto de Faria Santana, Clarissa da Paixão Barboza Salgado, Ana Ariel Santos Aragão, José Roberto Menezes Neto, João Bosco da Costa Filho, Rayan Oliveira Falcão, Ana Luiza Conceição Carvalho, Giulia Carolinne Santos Gonçalves, Humberto Fábio Nunes de Oliveira Filho, Renan Guedes de Brito, Yasmin Gabriele Ferreira Santos, Bruna Mendonça Doria de Jesus

Tiradentes University, Aracaju, Sergipe, Brazil

Eduardo Santana Fernandes Filho
eduardo.sfernandes@souunit.com.br

Introduction

Photophobia is the second most debilitating symptom of migraine. Intrinsically photosensitive retinal ganglion cells (ipRGCs), which express melanopsin, mediate this sensitivity by integrating intrinsic signals with those from cones and projecting them to dura-sensitive neurons in the posterior thalamus. The retinohypothalamic pathway, comprising ipRGC projections to the hypothalamus and thalamus, represents a critical circuit in the pathophysiology of migraine-associated photophobia.

Objective

This study aims to describe the physiological mechanisms through which the retinohypothalamic pathway modulates photophobia in migraine, identifying signal integration and specific neural alterations in these patients.

Methods

A systematic review was conducted across the PubMed, MEDLINE, and Scopus databases using the descriptors: "intrinsically photosensitive retinal ganglion cells", "ipRGCs", "melanopsin", "photophobia", "migraine", and "retinohypothalamic pathway". Experimental studies, clinical trials, and reviews (2013–2023) assessing ipRGC mechanisms in migraine photophobia in humans or animal models with a clear methodology were included.

Results

Migraine patients exhibit a selective amplification of integrated ipRGC signals for visual discomfort, without alterations in the summation of melanopsin and cones within the retina. Photophobia occurs via the retino-thalamo-cortical pathway, with the contribution of melanopsin being 1.5 times greater than cone luminance. Migraineurs presented reduced photophobia thresholds and greater amplitude in the post-illumination pupil response (PIPR). Functional near-infrared spectroscopy (fNIRS) data revealed hemodynamic alterations in the primary visual cortex of migraine sufferers that were dependent on ipRGC stimulus intensity, a phenomenon not observed in controls. Reflexive eye closure proved to be coupled with photic pulses; patients with aura manifested higher electromyographic activity and blinking rates. Anatomical mapping identified projections from the hypothalamus and basal ganglia to the posterior thalamus, regions harboring trigeminovascular neurons associated with allodynia and photophobia.

Conclusion

Photophobia in migraine results from a post-retinal alteration in the processing of ipRGC signals, generating a selective amplification for visual discomfort. Hypersensitivity of the melanopsin system is indicated by increased and prolonged post-illumination pupil responses. Visual-nociceptive interactions occur within the retina, midbrain, thalamus, hypothalamus, and visual cortex, mediated by Calcitonin Gene-Related Peptide (CGRP) and Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP). The sensitization of third-order thalamic neurons, which project to the somatosensory and visual cortices, explains why light exacerbates headache. Hypothalamic projections to the posterior thalamus modulate trigeminovascular neurons, linking attacks to disrupted sleep, fasting, and stress.

Keywords:
Migraine
Photophobia
Central sensitization
Pathophysiology

© Copyright 2025