

SLEEP-CIRCADIAN MECHANISMS AND CGRP SIGNALING IN TACS AND HYPNIC HEADACHE: A SYSTEMATIC REVIEW

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Background. Trigeminal autonomic cephalalgias (TACs), particularly cluster headache (CH), are closely linked to sleep, circadian rhythmicity, and hypothalamic regulation. Hypnic headache, although not classified among TACs, is also defined by an exclusive sleep-related occurrence and probable hypothalamic involvement. Calcitonin gene-related peptide (CGRP) has a well-established role in CH pathophysiology and may represent a key mediator connecting trigemino-autonomic activation with sleep–circadian dysregulation. However, the extent to which CGRP interacts with sleep and circadian mechanisms across TACs and hypnic headache remains incompletely defined.

Methods. We conducted a systematic review of PubMed/MEDLINE, Scopus, and Web of Science from inception to April 2026. Search terms combined CGRP, CGRP-targeted therapies, TACs, cluster headache, paroxysmal hemicrania, SUNCT/SUNA, hypnic headache, sleep, insomnia, and circadian rhythm. Original studies, randomized trials, observational studies, case series, case reports, mechanistic studies and neuroimaging studies, reporting data on CGRP, sleep, or circadian outcomes were considered eligible. This systematic review was conducted in accordance with PRISMA 2020 recommendations. Given the heterogeneity of study designs, populations, and outcomes, no quantitative synthesis was performed.

Results. Overall, 18 original studies were included. Evidence for the CGRP–sleep/circadian interface was strongest in CH, where CGRP-mediated trigemino-autonomic activation overlaps with nocturnal attack clustering, circadian and circannual rhythmicity, impaired sleep efficiency, altered melatonin and cortisol rhythms, and posterior hypothalamic activation. CGRP levels increase during CH attacks and decrease after effective acute treatment, supporting its role in attack generation within a temporally regulated hypothalamic–trigeminal network. However, whether CGRP directly modulates sleep or circadian stability remains unknown, as trials of CGRP-targeted therapies have not systematically assessed polysomnography, actigraphy, or circadian biomarkers. For paroxysmal hemicrania and SUNCT/SUNA, evidence was indirect and mainly based on shared hypothalamic and trigemino-autonomic involvement. For hypnic headache, no direct CGRP data were identified.

Conclusions. Current evidence supports a shared sleep-circadian-trigeminal framework linking TACs and hypnic headache, with CGRP acting as a potential downstream mediator. However, its direct role in sleep-circadian regulation remains insufficiently demonstrated. Future studies should systematically integrate objective sleep measures and CGRP assays to clarify whether CGRP contributes only to attack generation or also to sleep-circadian dysregulation in TACs and related sleep-linked headache disorders.