International Headache Society

IHS Junior Research Grants 2022

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Regulation by triptans and ditans of the proalgesic Schwann cell pathway

Overview

The hypothesis of the project derived from the observation of the pro-migraine role of the neuropeptide calcitonin gene related protein (CGRP) and that drugs that block the CGRP pathway ameliorate migraine pain. However, the cellular and molecular mechanisms underlying CGRP-evoked pain are unknown. We previously reported that CGRP receptor, when engaged by agonist, may undergo internalization in endosomes via clathrin and dynamin mechanisms. A large series of in vivo and in vitro findings consistently indicate that the internalized CGRP/CGRP receptor in Schwann cells increases cAMP levels, protein kinase A activity, and nitric oxide release to induce migraine pain. Here we expanded the study, and hypothesized that antimigraine drugs, such as triptans may at least in part act on Schwann cells to inhibit the proalgesic pathway activated by CGRP.

The project aims at exploring and show that triptans (serotonin 5-HT1B, HT1D receptor agonists) and ditans (serotonin 5-HT1F receptor agonists) exert at least part of their antimigraine action by reducing the increase in intracellular cAMP elicited by the CGRP in Schwann cells surrounding trigeminal nerve fibers. We aim at exploring their activity by in vitro assay in human and murine Schwann cell cultures, and in vivo test, in mice.

Results

We first confirmed the expression, although low levels, of the mRNA of the 5-HT1B, HT1D and HT1F receptor in the human and mouse Schwann cells in culture. We also detected 5-HT1B, HT1D and HT1F protein in cultured human Schwann cells and in the sciatic nerve explanted from mouse by immunofluorescence staining. In addition, we studied the effect of sumatriptan to inhibit the periorbital mechanical allodynia (PMA) induced by the local (periorbital) injection of CGRP in mice. We observed that the local (periorbital) treatment with sumatriptan (0.1, 0.5 and 12 nmol/10ml/site) dose-dependently reduced the PMA induced by CGRP (1.5 nmol/10ml/site). To explore the ability of endogenous CGRP to elicit PMA, we administered capsaicin, which activates TRPV1 channel thus

releasing CGRP and SP from peptidergic nociceptors. Sumatriptan (1 nmol/10ml/site) also reduced PMA induced by periorbital capsaicin (50 pmol/10ml/site). In addition, in vitro studies in primary culture of human Schwann cells revealed that the CGRP (300 nmol) stimulated a prompt increase in cAMP formation in human Schwann cells that was sustained for 300 s. cAMP formation was measured using a virally encoded cAMP cADDis reporter. Sumatriptan (10 and 100 mM) caused an inhibition of CGRP stimulated cAMP formation.

The research was presented during the 22nd International Headache Congress, São Paulo, Brazil, September 2025.

Eduardo Rivera-Mancilla
Erasmus University Medical Center Rotterdam, The Netherlands

Endocannabinoid system and TRP channels as potential therapeutic targets for sexual dimorphism in migraine

Summary

The main objective of my project proposal was to investigate, in a comparative way, the effects produced by selective and non-selective agonists of the cannabinoid receptors in human isolated arteries from both male and female donors, as well as the potential role of TRPV1 channels in endocannabinoid-mediated vascular responses.

To evaluate antimigraine potential, human isolated middle meningeal arteries were used as a proxy for the trigeminovascular system, which represents a predictive vascular model of antimigraine action. Moreover, human isolated coronary arteries were used to assess potential cardiovascular safety. Hence, functional ex vivo studies were performed to investigate the pharmacological mechanisms involved in the vascular effects of the endocannabinoid system, and to compare the functionality of the cannabinoid receptors between males and females. Additionally, modulation of the endocannabinoid system by TRPV1 was analysed. Finally, expression of cannabinoid receptors was examined in artery segments.

Results

The results derived from this project were presented at three conferences:

1. Rivera-Mancilla E, et al. Crosstalk between cannabinoid and vanilloid systems: role of CB receptors in the capsaicin-induced relaxation responses in human coronary arteries. In: 16th European Headache Congress 2022 meeting abstracts. J Headache Pain. 2022;23(Suppl 1):1-2. https://doi.org/10.1186/s10194-022-01527-4
2. Rivera-Mancilla E, et al. Sex-dependent vascular effects of the endocannabinoid system and its regulation by TRPV1 channels. In: Abstracts from the International Headache Congress 14–17 September 2023. Cephalalgia. 2023;43(1_suppl):3-4. https://doi.org/10.1177/03331024231189112
3. Rivera-Mancilla E, et al. Blocking CB receptors as therapy for (neuro)vascular disorders: sex differences in (endo)cannabinoid vascular effects. In: Abstracts from the 18th European Headache Congress (EHC): Rotterdam, The Netherlands. J Headache Pain. 2025;23(Suppl 2):138. doi: 10.1186/s10194-025-02062-8

Invited lectures:

Sex-specific role of TRP channels and cannabinoid receptors in cardiovascular diseases. Internal Medicine Science Days, June 2023. Zeist, The Netherlands.

Additionally, two original articles have been produced. One has been published, and the second is currently in preparation.

1. Rivera-Mancilla E, et al. Functional crosstalk between the vanilloid and endocannabinoid systems in modulating vascular tone: implications for (neuro)vascular disorder therapy. J Headache and Pain. 2025;26(1):203. doi: 10.1186/s10194-025-02085-1

Summary

This research advances scientific understanding in the field of headache, with a particular focus on migraine, by investigating the vascular effects of cannabinoid receptor agonists and the modulatory role of TRPV1 channels. Using human tissues, this study represents a translational approach that bridges experimental pharmacology with potential clinical relevance, providing a solid scientific foundation for future cannabinoid-based interventions in headache medicine.

A key contribution of this project is the identification of sex-specific differences in the function and mechanisms of the endocannabinoid system, an area yet to be fully explored. Recognising these differences is important for developing more personalised treatment strategies that better address the needs of both men and women affected by migraine.

From a clinical perspective, the findings contribute to the ongoing search for novel antimigraine therapies, particularly those targeting the endocannabinoid system, which may offer therapeutic benefits with a lower risk of adverse effects. The consideration of cardiovascular safety further strengthens the potential for these therapies to be both effective and safe.

Overall, this research contributes to current knowledge of headache by elucidating vascular and receptor mechanisms involved in migraine. These insights may help guide future studies and ultimately improve patient outcomes through more targeted and safer treatment options.

Receiving this research grant has been a crucial step in shaping my future career. It has given me the opportunity to deepen my knowledge of headache pharmacology, particularly migraine, through translational research using human tissues. This experience has allowed me to translate laboratory findings into potential clinical applications, which is essential for improving patient outcomes.

The grant has also helped me strengthen my technical skills and build confidence in planning and conducting complex studies. Beyond the laboratory work, it has created opportunities to collaborate with experts in the headache field, expanding my professional network and encouraging a more collaborative research environment.

Most importantly, this funding has provided valuable experience and support that will help me continue development as a researcher and contribute meaningfully to headache research in the future.

The research was presented during the 22nd International Headache Congress, São Paulo, Brazil, September 2025.

Thomas van den Hoek
Leiden University Medical Center, The Netherlands

Home-based EEG for early detection of brain state alterations before the migraine attack

Overview

We propose that increased cortical excitability is a key biosignature of migraine and may signal growing vulnerability to an impending attack. Our prior research has demonstrated that changes in cortical excitability can be detected using EEG in the pre-ictal phase, the period just before a migraine begins. In a small longitudinal study, we found preliminary evidence of altered EEG responses to visual stimuli (using the 'Chirp' paradigm) during this early (pre-symptomatic) phase of the beginning of an attack. Building on these findings, our current project aimed to go beyond laboratory-based EEG recordings. We are testing the feasibility of detecting these excitability changes in a new group of migraine patients using a portable, visual evoked potential EEG (VEP-EEG) system. The ultimate goal was to enable continuous, at-home monitoring that could predict migraine attacks before symptoms start. This would open the door to providing early-warning alerts to patients and initiating timely behavioral or pharmacological intervention, a strategy known as situational prevention. Such proactive measures could reduce migraine severity, frequency, or duration, and significantly improve patients' quality of life.

Results

Findings from the recent study using ambulatory EEG caps in a hospital setting with 16 patients with menstrual-related migraine are submitted as paper *"Assessing pre-ictal features of cortical excitability in migraine by repeated EEG measurements with visual chirp stimulation."* and will be independently published in the thesis of Thomas vd Hoek (see attachment). In addition, new data that includes longitudinal home-based EEG recordings from 15 patients will be presented at the IHS Congress in São Paulo in September 2025 (see Abstract below).

This personal research grant served as pilot for our follow-up project, *Migraine@Home*, which will allow patients to perform VEP-EEG recordings at home towards an attack. Led by a new PhD candidate, Drs. Oosterlee, this project aims to collect high-quality home-based EEG data to validate and extend our earlier findings by identifying early markers of impending migraine attacks on a larger scale.

Finally, this junior research grant has been instrumental in the development of Drs. van den Hoek's academic career, by supporting the completion of his PhD. Drs. van den Hoek is now working as a Neurology resident at Erasmus Medical Center in Rotterdam, The Netherlands.

The research was presented during the 22nd International Headache Congress, São Paulo, Brazil, September 2025.

Abstract submitted to 22nd IHC

Longitudinal EEG Assessment of Cortical Responsivity Before Migraine Attacks: A Study of Visual Chirp Responses

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Objective: Migraine attacks are unpredictable, often disrupting daily life. Previous research suggested that EEG responses to visual chirp stimulation (VEP-EEG) may help detect changes in cortical responsivity during the preictal phase. This study aims to further investigate that hypothesis.

Methods: In this longitudinal, non-interventional study, participants with episodic migraine completed a validated e-headache diary for at least one month. The preictal phase was defined as the 48 hours before an attack. Each participant underwent several EEG recordings in response to 10–40 Hz visual chirp stimulation on separate days at our hospital, continuing until a migraine attack occurred. Changes from baseline in EEG spectral power were compared between interictal and preictal phases across individual stimulation frequencies (10–40 Hz), including driving, harmonic, and overall responses.

Results: Of the 31 patients who participated, 17 had at least one interictal and one preictal measurement which met the criteria for inclusion in the analysis. The mean participant age was 52 ± 15 years; 82% were female, 77% had migraine without aura, and baseline monthly migraine days (MMD) averaged 3.7 ± 2.3. Additionally, 65% of participants were not using prophylactic medication. We observed high variability in EEG responses to chirp stimulation, both between patients and between interictal and preictal measurements. No significant differences were found in EEG spectral power across the individual stimulation frequencies between interictal and preictal recordings for the driving, harmonic, or overall chirp responses ($p = 0.92$, $p = 0.69$, and $p = 0.68$, respectively).

Conclusion: This study did not replicate previous findings of preictal changes in cortical responsivity in migraine. We recommend increasing the sample size and number of recording days, potentially by adapting the protocol to a home-based setup.