



Faculty of Health and Medical Sciences

# CGRP in Post-Traumatic Headache

Håkan Ashina, MD  
Ph.D. Fellow



Rigshospitalet Glostrup





# Disclosures

- **None**



# What is Post-Traumatic Headache?

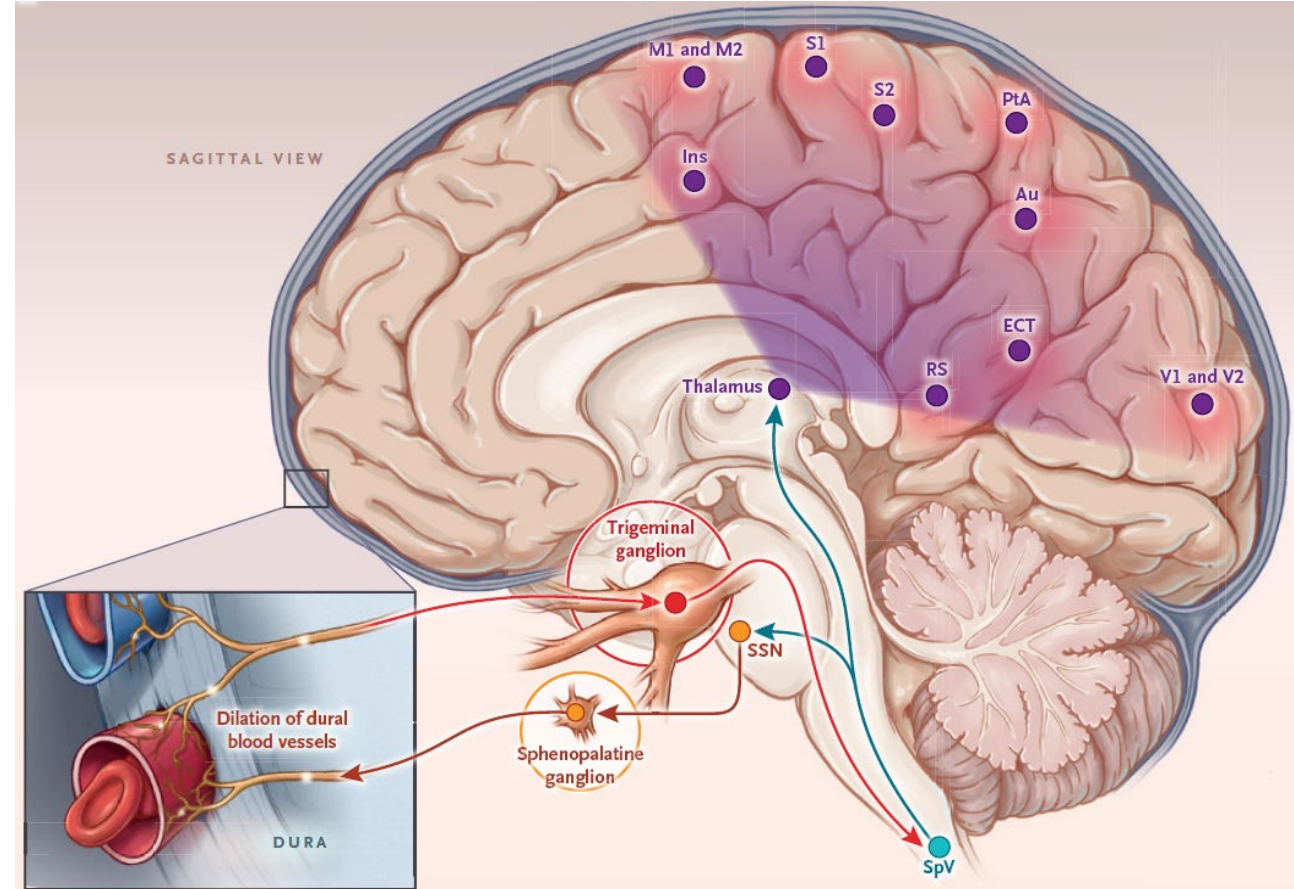
- **Secondary Headache Disorder**
- **Attributed to one of the following:**
  - **Traumatic Brain Injury (TBI)**
  - **Whiplash Injury**
  - **Craniotomy**



# CGRP in Post-Traumatic Headache

## The Trigeminovascular System

- A Common Pathway in Headache Pathogenesis

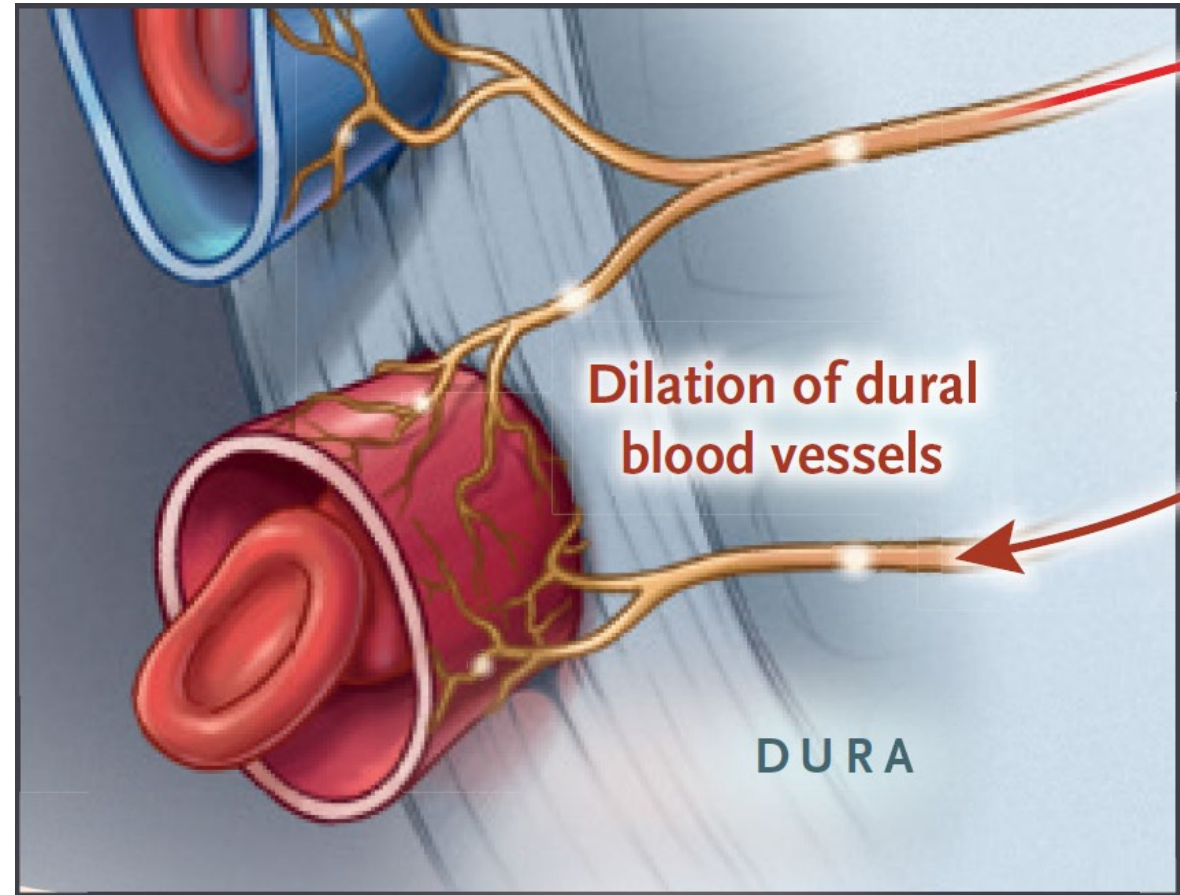




# CGRP in Post-Traumatic Headache

## Axonal Projections from Trigeminal Ganglion Cells

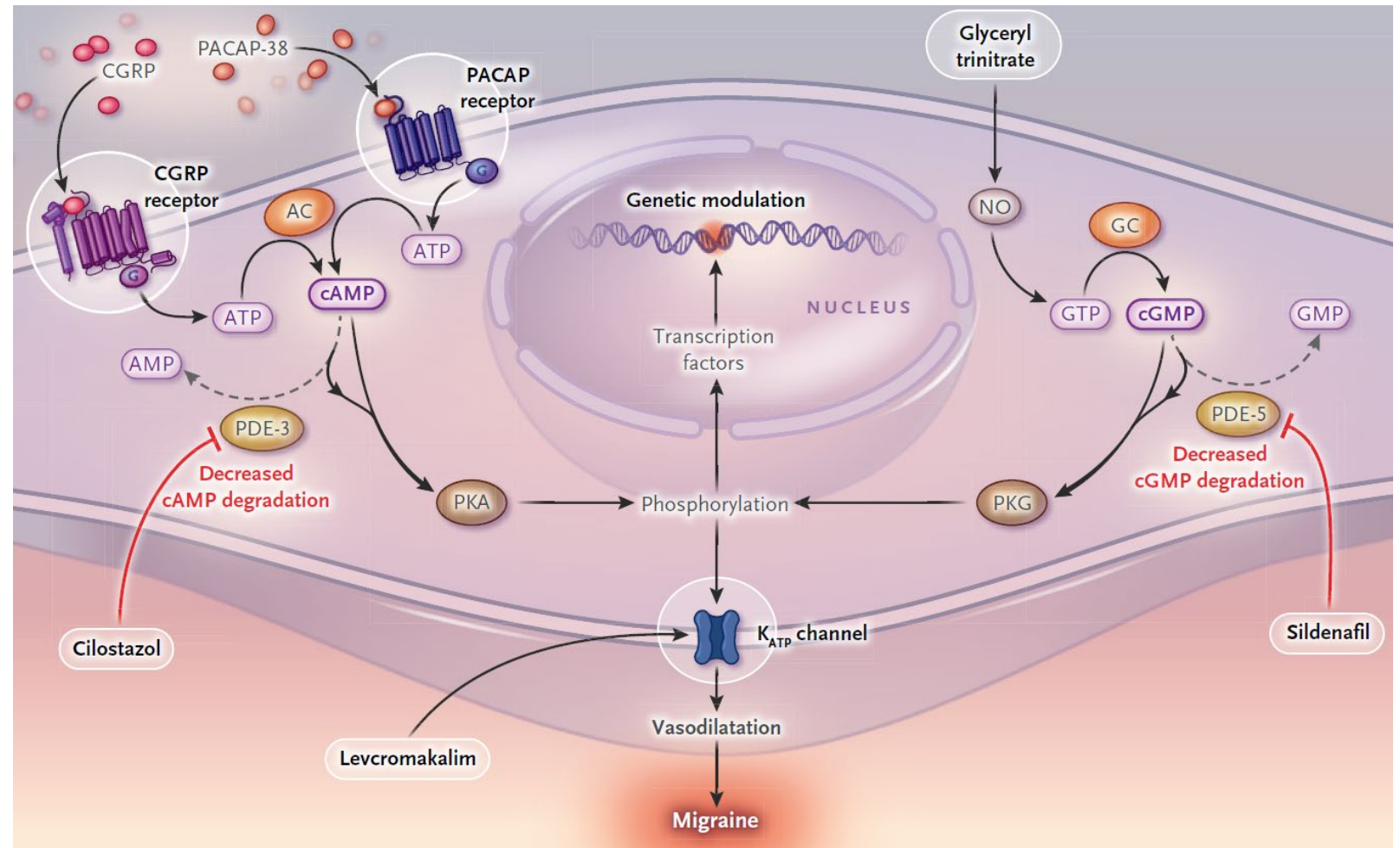
- Innervate Pain-Sensitive Intracranial Structures, e.g. Dura Mater
- Contain Vasoactive Peptides, e.g. CGRP





# Lessons Learned From Migraine

- 1) CGRP binds to its G protein-coupled receptor on VSMCs
- 2)  $\uparrow$ cAMP and activation of PKA
- 4) Opening of  $K_{ATP}$ -channels
- 5) Outflow of potassium and dilation of intracranial arteries
- 6) Chemical and mechanical stimuli
- 7) Activation and sensitization of trigeminal nociceptors





# CGRP in Post-Traumatic Headache

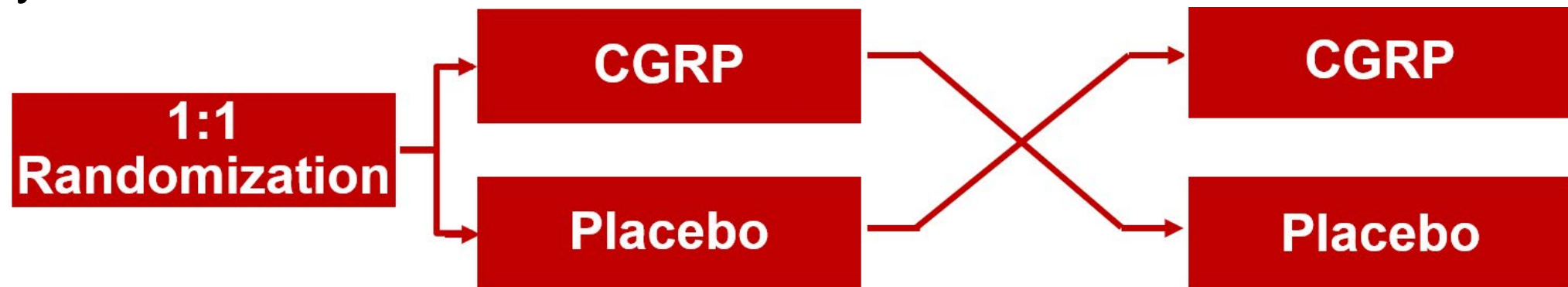
## Background:

- Animal models of PTH have implicated CGRP in modulation of nociceptive transmission in concussed rodents
- Patients with PTH most often experience headaches with migraine-like features
- I.V. infusion of CGRP induces migraine in patients with migraine
- Therapies targeting CGRP signaling have therapeutic benefits in migraine



# CGRP in Post-Traumatic Headache

- **Hypothesis:** I.V. infusion of CGRP induces headache exacerbation with migraine-like features in patients with persistent PTH (and no pre-existing migraine)
- **Design:** A randomized, double-blind, placebo-controlled, 2-way crossover study



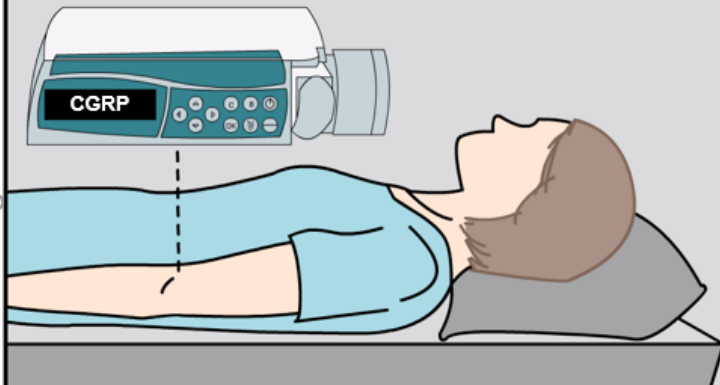




# Hypersensitivity to CGRP in Post-Traumatic Headache

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 2-WAY CROSSOVER TRIAL

Intravenous Infusion with  
CGRP



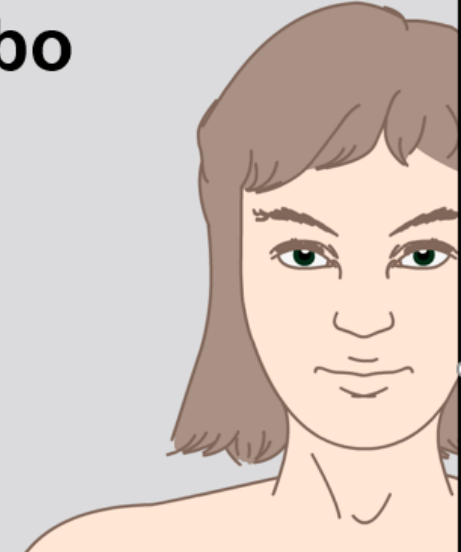
**CGRP**

**N=30**



**Placebo**

**N=30**



Induction Rate of Headache Exacerbation  
with Migraine-Like Features

**70%**

**20%**

**CGRP induces headache exacerbation with migraine-like features  
in patients with PTH**



# CGRP Targeted Therapies in PTH

## Implications:

- CGRP is involved in the pathogenesis of PTH
- CGRP-targeted therapies might address unmet treatment needs in patients with PTH





# Preventive Treatment with Erenumab

- **Hypothesis:** Preventive treatment with erenumab is effective and well-tolerated by patients with persistent PTH
- **Design:** A single-center, non-randomized, single-arm, open-label study
- **Investigational Drug:** Erenumab (monoclonal antibody against the CGRP receptor)



# Key Outcomes

- **Primary Outcome:** The mean change in number of **monthly headache days of moderate to severe intensity** from **baseline** (4-week pretreatment period) to **week 9–12**
- **Exploratory Outcome:** The **proportion of patients** achieving **≥50% reduction** in the mean number of **monthly headache days of moderate to severe intensity** from **baseline** to **week 9–12**



# Efficacy of Erenumab

- Of 100 included patients, **89** completed the 12-week open-label treatment phase
- At baseline, the mean number of headache days of moderate to severe intensity was 15.7 days per month; by week 9 through 12, the number was **reduced by 2.8 days**
- **A  $\geq 50\%$  reduction** in the mean number of headache days of moderate to severe intensity was achieved for **28%** of the 89 patients



# Tolerability of Erenumab

- Of 100 patients, **79 reported at least one AE**, with the most common one being **constipation** (n = 30)
- No serious AEs were reported, although **two patients** experienced AEs (dizziness and worsened headache) that led to **treatment discontinuation**



# CGRP-Targeted Therapy

- Overall, 100 patients received at least one dose of erenumab and were included in the tolerability analyses
- Of these, **79 patients reported at least one AE**, with the most common one being **constipation** (n = 30)
- No serious AEs were reported, although **two patients** experienced AEs (dizziness and worsened headache) that led to **treatment discontinuation**



# Conclusions

- CGRP-targeted therapies (e.g. erenumab) might be effective in prevention of persistent PTH
- RCTs are needed to ascertain the effectiveness of CGRP-targeted therapies for patients with persistent PTH
- For this purpose, it is critical that guidelines for RCTs are developed to establish PTH-specific outcomes and eligibility criteria





**Thank you for your attention**