CALCITONIN GENE-RELATED PEPTIDE (CGRP) & MIGRAINES

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WHAT IS CGRP?

- Calcitonin Gene-Related Peptide (CGRP) is a neuropeptide that plays a role in the cardiovascular system, neurogenic inflammation and modulating nociceptive input
- CGRP is found throughout the body; CNS, PNS, ENS
- Predominantly found in the trigeminal ganglia

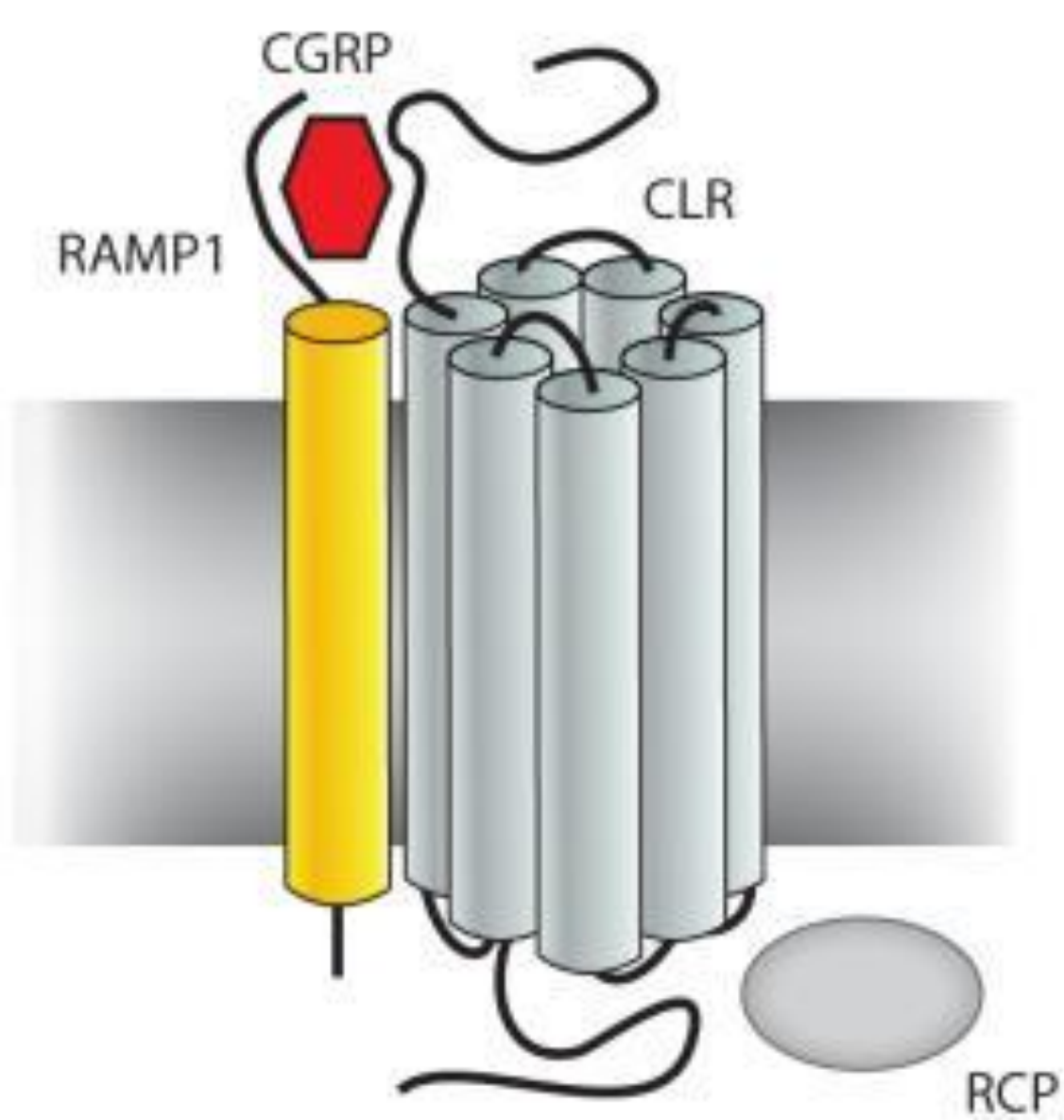
CGRP RECEPTOR

CGRP Receptor Complex includes three subunits:

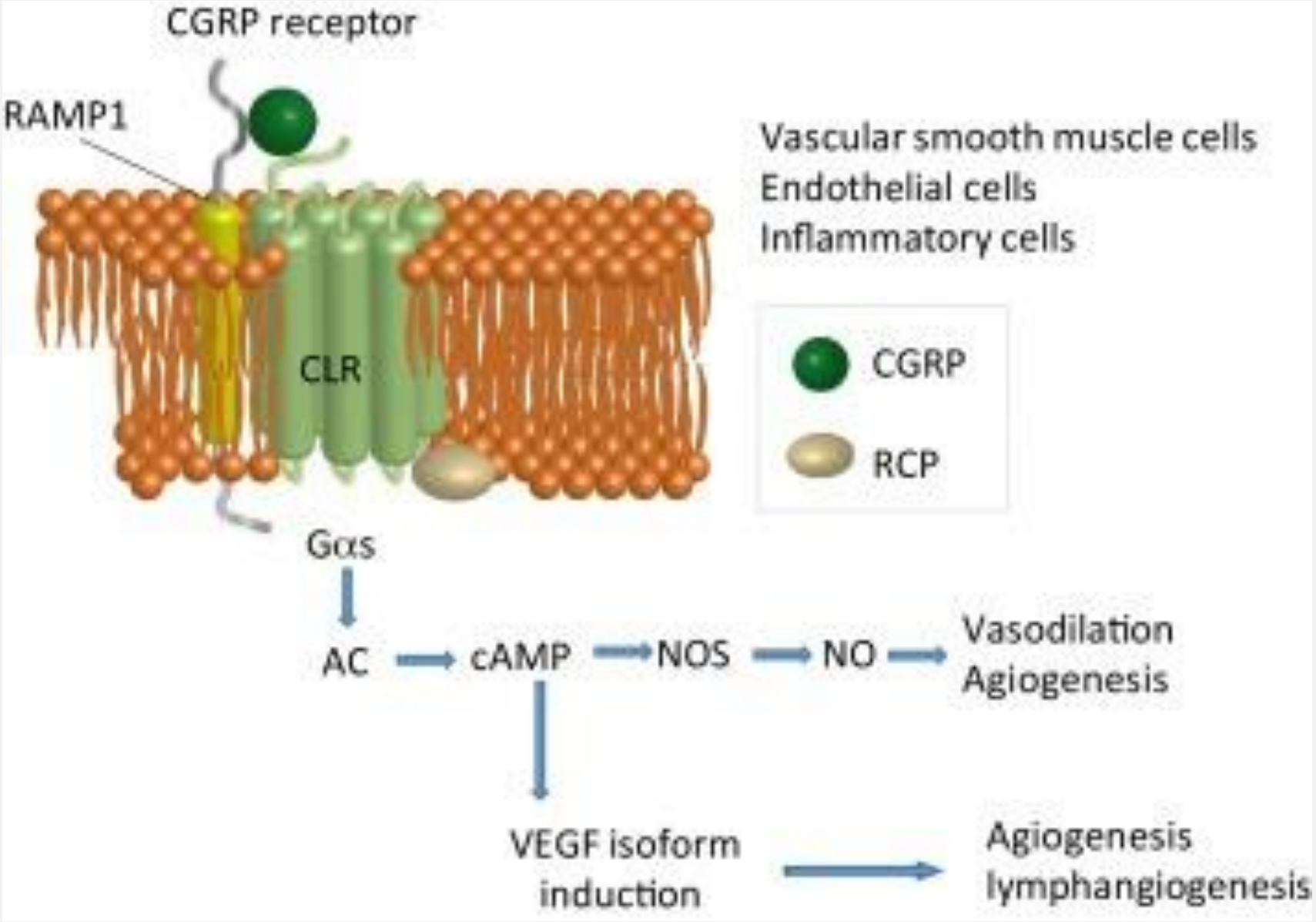
1. Calcitonin-like receptor (CLR) – uses RAMP1 for trafficking

2. Receptor activity-modifying protein 1 (RAMP1) – trafficking to membrane to bind CGRP *rate-limiting subunit

3. Receptor component protein (RCP) – couples Gαs (G-coupled protein)



https://doi.org/10.1146/annurev-pharmtox-010814-124701



https://doi.org/10.1016/j.tips.2018.11.003

CGRP IMPLICATION IN MIGRAINES

- In 1990 it was found that elevated levels of CGRP occurred in jugular outflow during migraine attacks
- Injection of CGRP induces moderate to severe migraines
- Selective CGRP receptor antagonists have been found to effectively treat migraines

TABLE 1. THEORIES OF MIGRAINE PATHOGENESIS		
Theory	**Overview**	**Current evidence**
CGRP theory	Increases in the level of CGRP have been measured in the nerves involved in nociception when migraine attacks occur	CGRP levels rise during a migraine and fall after symptoms resolve. Migraine can be triggered by infusing patients with CGRP Triptans and onabotulinumtoxinA prevent CGRP release and are also effective for aborting and preventing headaches, respectively
Cortical spreading depression (CSD)	Propagated waves of cortical activity, blood flow, metabolism, and MRI signal during migraine attacks mirrored aura	Many patients with migraine do not experience aura and premonitory symptoms such as confusion and yawning occur hours before the aura in different brain areas Some abortive medications stop aura only; others stop only pain
Serotonergic changes	Increased serotonin metabolites in urine collected during migraine suggested changing levels of serotonin could be involved	Triptans that block serotonergic receptors are effective for some people with migraine
Dural neurogenic inflammation	Neurogenic inflammation in dura initiates migraine	Multiple drugs known to block dural protein extravasation in animal models of neurogenic inflammation have failed to yield clinical benefit in clinical migraine trials
Vascular theory	Stimulating dural trigeminal afferents causes headaches, suggesting that intracranial blood vessel dilation initiates headache	Intracranial vessel dilation is not detectable with MRI or MRA during migraine.

https://practicalneurology.com/index.php/articles/2019-may/migraine-preventive-therapies

CGRP ROLE IN MIGRAINES

- CGRP increases sensory responsiveness, especially to pain, leading to migraines
- Afferent sensory neurons innervate blood vessels throughout the body
- Central Nervous System – potent vasodilator independently and with stimulation of NO
- Enteric Nervous System – regulates motility and secretion

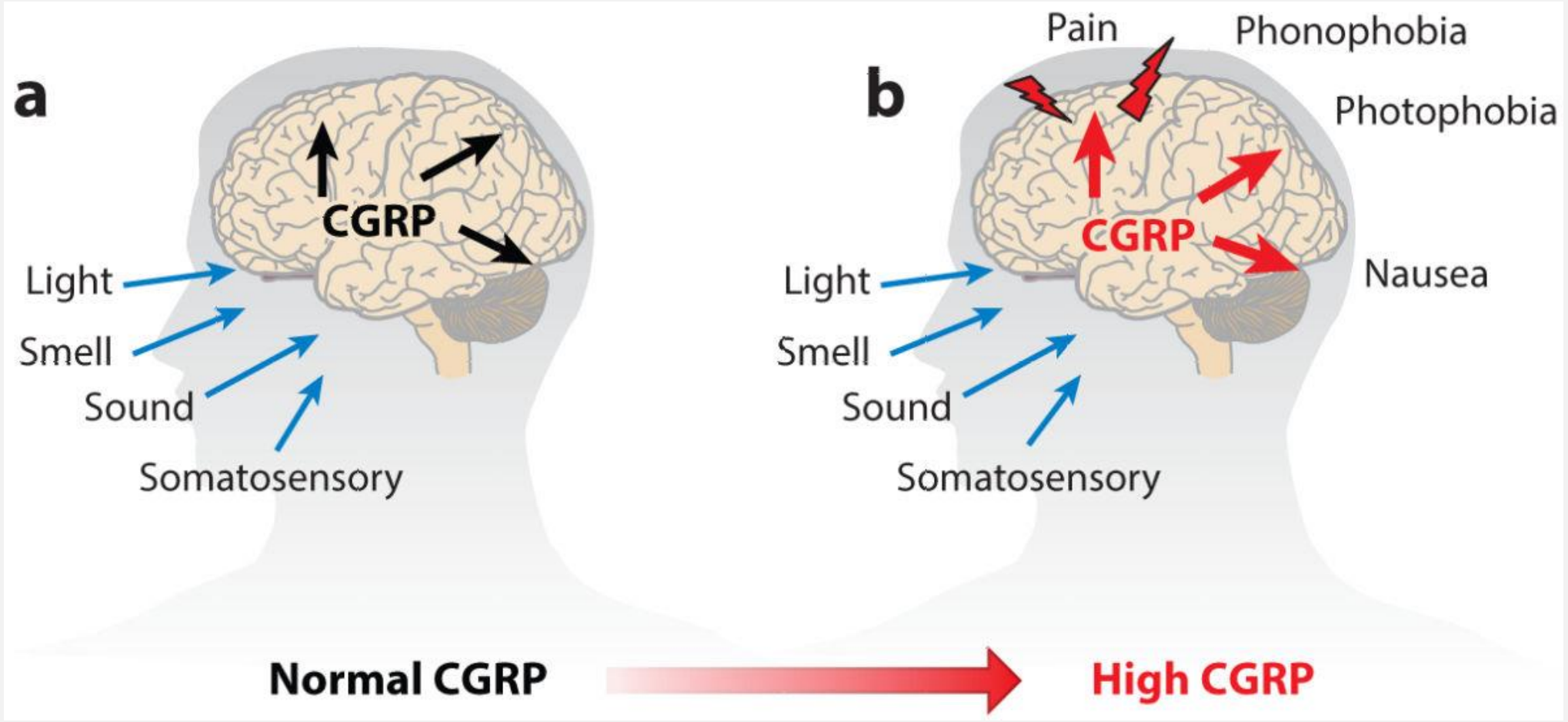
CGRP ROLE IN MIGRAINES

- Neurogenic inflammation with peripheral sensitization of nociceptive neurons
- CGRP can trigger mast cell degranulation, further exacerbating the inflammatory process
- Trigeminal glia contain CGRP receptors causing sensitization via CGRP induced proinflammatory cytokine release
  - Increases $P2X_3$ causing depolarization of trigeminal nerve
  - CGRP induces self release via TNFα via satellite glia

MIGRAINE CRITERIA

- Headache lasting 4-72 hours with 2+ of the following:
  - Pulsating quality
  - Unilateral
  - Moderate to severe intensity
  - Aggravated by activity

- Must have at least 1 of the following:
  - Nausea and/or vomiting
  - Photophobia or phonophobia



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CGRP ANTAGONISTS MOA

- CGRP Antagonist Medications – Mechanism of Action

- Eptinezumab (Vyepti) – inhibits CGRP activity by binding directly to CGRP

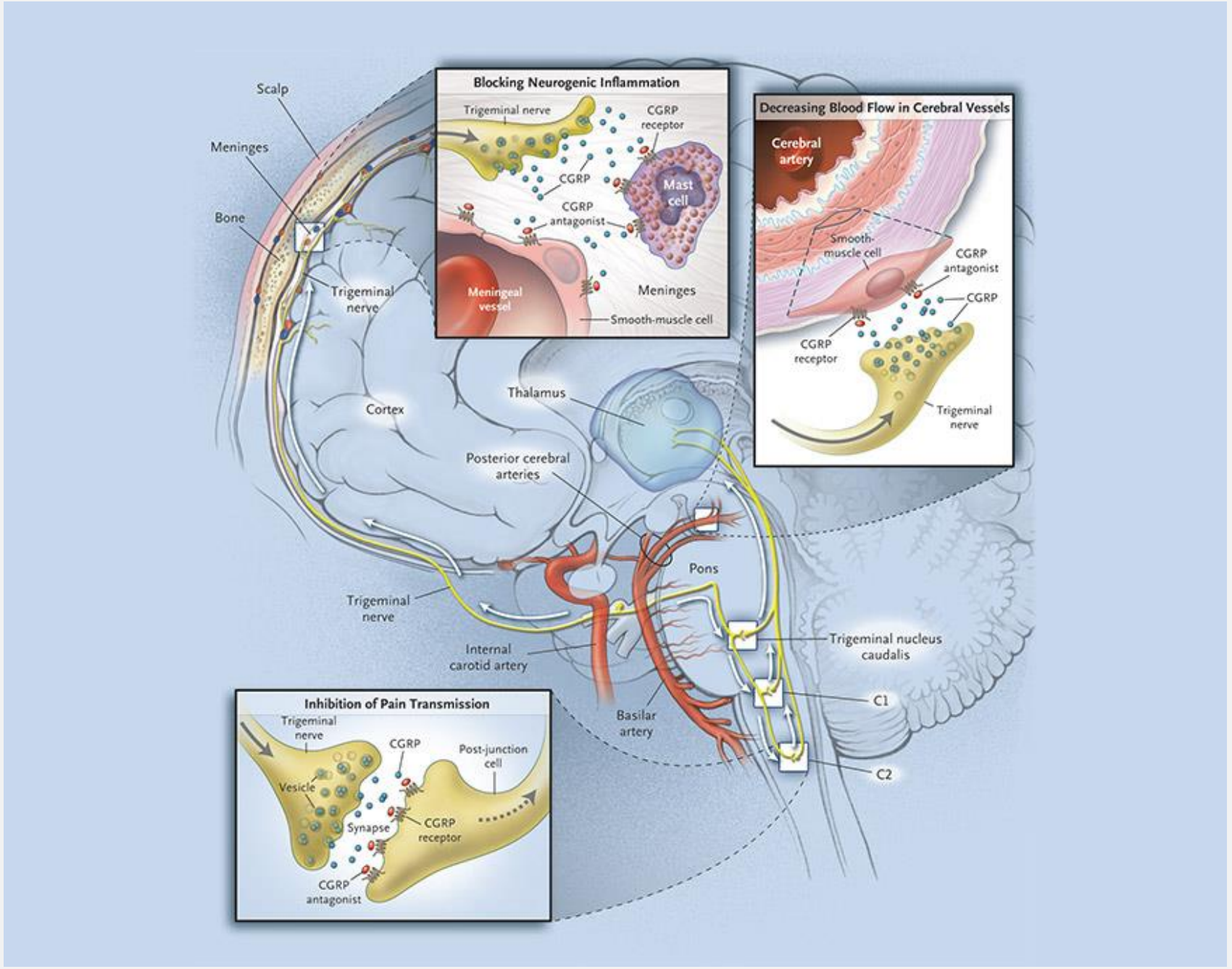
- Erenumab (Amiovig) – binds to CGRP receptor blocking CGRP activity
- Fremanezumab (Ajovy) – inhibits CGRP activity by binding directly to CGRP
- Galcanezumab (Emgality) – inhibits CGRP activity by binding directly to CGRP

CGRP ANTAGONISTS FOR MIGRAINE TREATMENT

- Blocking Neurogenic Inflammation: Binding of CGRP receptor antagonists to CGRP receptors located on mast cells would inhibit inflammation caused by trigeminal nerve release of CGRP onto mast cells within the tough outer covering of the brain, or the meninges.

- Decreasing Artery Dilation: By blocking the CGRP receptors located in smooth muscle cells within vessel walls, CGRP receptor antagonists would inhibit the pathologic dilation of intracranial arteries without the unwanted effect of active vasoconstriction.

- Inhibiting Pain Transmission: Binding of CGRP receptor antagonists to CGRP receptors would suppress the transmission of pain by inhibiting the central relay of pain signals from the trigeminal nerve to the caudal trigeminal nucleus.



https://www.biohavenpharma.com/science-pipeline/resources/cgrps-role-migraine

CGRP ANTAGONISTS FOR MIGRAINE TREATMENT

- Eptinezumab (Vyepti) – IV infusion Q3M (Tmax – 30 minutes)
  - SE: URI, UTI, fatigue, dizziness, nausea/vomiting, joint pain, back pain, dry mouth, EKG changes
- Erenumab (Amiovig) – IM QM (Tmax – 5.5 days)
  - SE: injection site pain, URI, nausea, joint pain, back pain, headache
- Fremanezumab (Ajovy) – IM QM or quarterly (Tmax – 5-7 days)
  - SE: injection site pain, pruritis, URI, UTI, dizziness, back pain, dry mouth, EKG changes, tooth abscess
- Galcanezumab (Emgality) – IM QM (Tmax – 7-13 days)
  - SE: injection site pain, URI, abdominal pain, nausea, dysmenorrhea

THANK YOU

QUESTIONS?

ABBREVIATIONS

- CGRP – Calcitonin Gene-Related Peptide
- CNS – Central Nervous System
- PNS – Peripheral Nervous System
- ENS – Enteric Nervous System
- CLR – Calcitonin-like Receptor
- RAMP1 – Receptor Activity-Modifying Protein 1
- RCP – Receptor Component Protein
- NO – Nitric Oxide
- CSD – Cortical Spreading Depression
- MOA – Mechanism of Action
- TNFα – Tumor Necrosis Factor alpha
- Q3M – every 3 months
- IV – Intravenous
- SE – Side Effects
- URI – Upper Respiratory Tract Infection
- UTI – Urinary Tract Infection
- EKG – Electrocardiogram
- IM – Intramuscular
- QM – every month

REFERENCES

- https://www.biohavenpharma.com/science-pipeline/resources/cgrps-role-migraine
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