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)

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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
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<th>Theory</th>
<th>Overview</th>
<th>Current evidence</th>
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<td>CGRP theory</td>
<td>Increases in the level of CGRP have been measured in the nerves involved in nociception when migraine attacks occur</td>
<td>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.</td>
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<td>Cortical spreading depression (CSD)</td>
<td>Propagated waves of cortical activity, blood flow, metabolism, and MRI signal during migraine attacks mirrored aura</td>
<td>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.</td>
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<td>Serotonergic changes</td>
<td>Increased serotonin metabolites in urine collected during migraine suggested changing levels of serotonin could be involved</td>
<td>Triptans that block serotonergic receptors are effective for some people with migraine.</td>
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<td>Dural neurogenic inflammation</td>
<td>Neurogenic inflammation in dura initiates migraine</td>
<td>Multiple drugs known to block dural protein extravasation in animal models of neurogenic inflammation have failed to yield clinical benefit in clinical migraine trials.</td>
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<td>Vascular theory</td>
<td>Stimulating dural trigeminal afferents causes headaches, suggesting that intracranial blood vessel dilation initiates headache</td>
<td>Intracranial vessel dilation is not detectable with MRI or MRA during migraine.</td>
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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 P2X3 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
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.
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

CGRP ANTAGONISTS FOR MIGRAINE TREATMENT
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


