The CGRP Receptor in Migraine
WHAT IS MIGRAINE?

- Migraine is a complex neurological disease associated with recurrent and often debilitating headaches that are accompanied by sensory alterations.
- The trigeminovascular system, which relays head pain signals to the brain, plays a key role in migraine pathophysiology and has components in the periphery (i.e., outside the BBB) as well as in the CNS (i.e., inside the BBB).
- Migraine is also associated with changes in neural networks within the CNS, including the cerebral cortex, brainstem, hypothalamus, and thalamus.

Migraine may occur as a result of a dysfunctional trigeminovascular system.

WHAT IS CGRP?

- A 37-amino acid, multifunctional neuropeptide.
- Produced in central and peripheral neurons.
- Known to increase during migraine.
- Thought to play a role in migraine pathophysiology.

WHAT IS THE CGRP RECEPTOR?

The CGRP-R is a membrane bound, G-protein coupled receptor that comprises two subunits: CLR and RAMP-1.

CGRP binds to the CGRP-R and receptors for two CGRP-related peptides: adrenomedullin and amylin.

CGRP binding affinity to related receptors:
- CGRP > AMY
- AM > CGRP
- AMY = CGRP

CGRP-Rs are found in key areas for migraine:
- Trigeminal ganglion
- Dura vasculature
- Brainstem, e.g., TNC
- Brain, e.g., thalamus

Only the CGRP-R has been implicated in migraine pathophysiology.
WHAT IS THE ROLE OF THE CGRP-R IN MIGRAINE?

- Peripheral release of CGRP from trigeminal nerve endings is thought to trigger multiple responses induced by CGRP-R binding, which eventually lead to the sensitization of nociceptor trigeminal neurons\(^1,3\).
- The stimulation of peripheral nociceptive trigeminal neurons is hypothesized to relay the migraine pain signal through the brainstem into the brain, ultimately leading to the experience of migraine pain\(^7\).
- Central effects of CGRP may involve pain transmission through sensitization and activation of central processes (e.g., feedback from a sensitized brain)\(^1\).

Clinical evidence to support the role of CGRP in migraine pathophysiology:

- Elevated levels of peripheral CGRP have been observed following a migraine attack\(^1,8\).
- IV infusion of CGRP was found to induce moderate-to-severe headaches in patients with migraine\(^9-11\).

Activation of CGRP-R in the trigeminovascular system plays a critical role in peripheral and central events that ultimately lead to the experience of migraine pain\(^1,3,7\).

TRIGEMINOVASCULAR SYSTEM\(^1-4,12\)

Peripheral components\(^1-4\)

(outside the BBB)

CGRP-R complex\(^1,4\)

Central components\(^1,3,12\)

(inside the BBB)

Meningeal blood vessels

CGRP

CGRP-R

Trigeminal ganglion

Trigeminocervical complex

(comprises TNC)

Cerebral cortex

Thalamus

CGRP receptors are found in several sites in the trigeminovascular system\(^3,4\).
CGRP is a neuropeptide produced in peripheral and central neurons\textsuperscript{1,3}

CGRP binds to the CGRP-R, located at several sites in the trigeminal pathway\textsuperscript{1,3}

CGRP-R signaling within the trigeminovascular system is a key contributor to migraine pathophysiology\textsuperscript{1,3,7,13}

Research continues to reveal the complex pathophysiology underlying migraine, and the role of CGRP in both the periphery and CNS\textsuperscript{1,3}

**Abbreviations:**

BBB, blood-brain barrier; CGRP, Calcitonin Gene-Related Peptide; CGRP-R, Calcitonin Gene-Related Peptide receptor; CLR, calcitonin-like receptor; CNS, central nervous system; IV, intravenous; RAMP-1, receptor activity-modifying protein; TNC, trigeminal nucleus caudalis.

**References:**