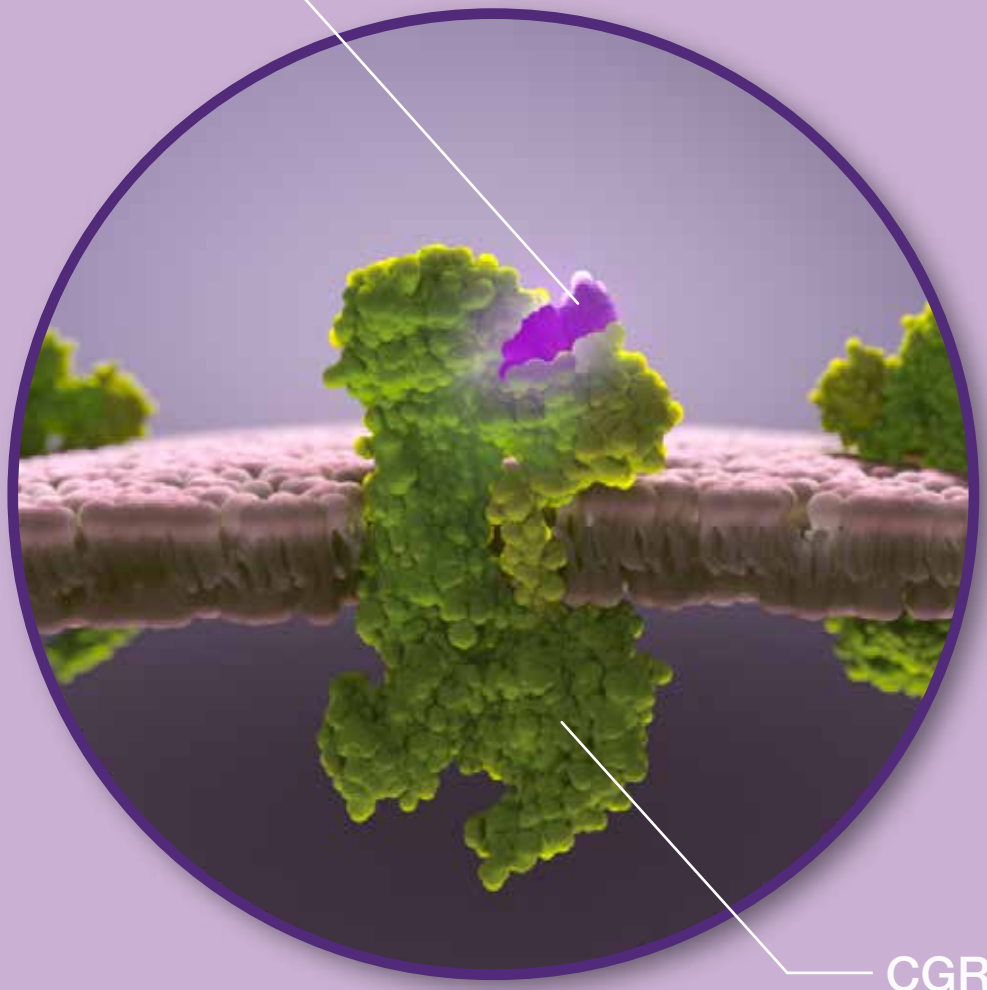
The CGRP Receptor in Migraine



USA-334-053577

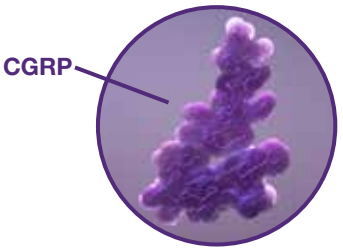
WHAT IS MIGRAINE?

- Migraine is a complex neurological disease associated with recurrent and often debilitating headaches that are accompanied by sensory alterations[1]
- The trigeminovascular system, which relays head pain signals to the brain, plays a key role in migraine pathophysiology and has components in the periphery (ie, outside the BBB) as well as in the CNS (ie, inside the BBB)[1-4]
- Migraine is also associated with changes in neural networks within the CNS, including the cerebral cortex, brainstem, hypothalamus, and thalamus[1]

Migraine may occur as a result of a dysfunctional trigeminovascular system[5]

WHAT IS CGRP?

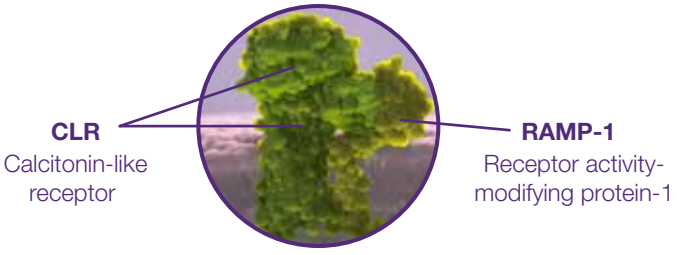
- 37-amino acid, multifunctional neuropeptide[1]
- Produced in central and peripheral neurons[1]
- Known to increase during migraine[3]
- Thought to play a role in migraine pathophysiology[1-3]



WHAT IS THE CGRP RECEPTOR?

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

CGRP-R[1]

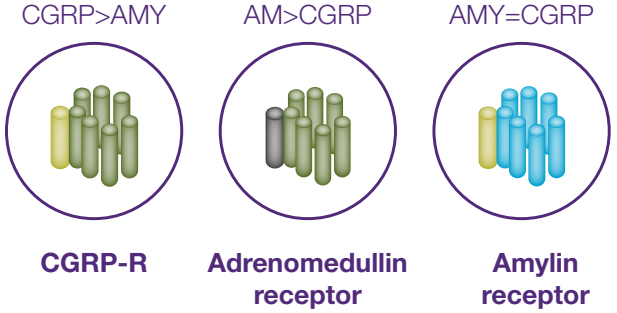


CGRP-Rs are found in key areas for migraine:[2–4]

- Trigeminal ganglion
- Dura vasculature
- Brainstem, eg, TNC
- Brain, eg, thalamus

CGRP binds to the CGRP-R and receptors for two CGRP-related peptides: adrenomedullin and amylin[1,6]

CGRP binding affinity to related receptors[1,6]



Only the CGRP-R has been implicated in migraine pathophysiology[1]

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 (eg, 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]

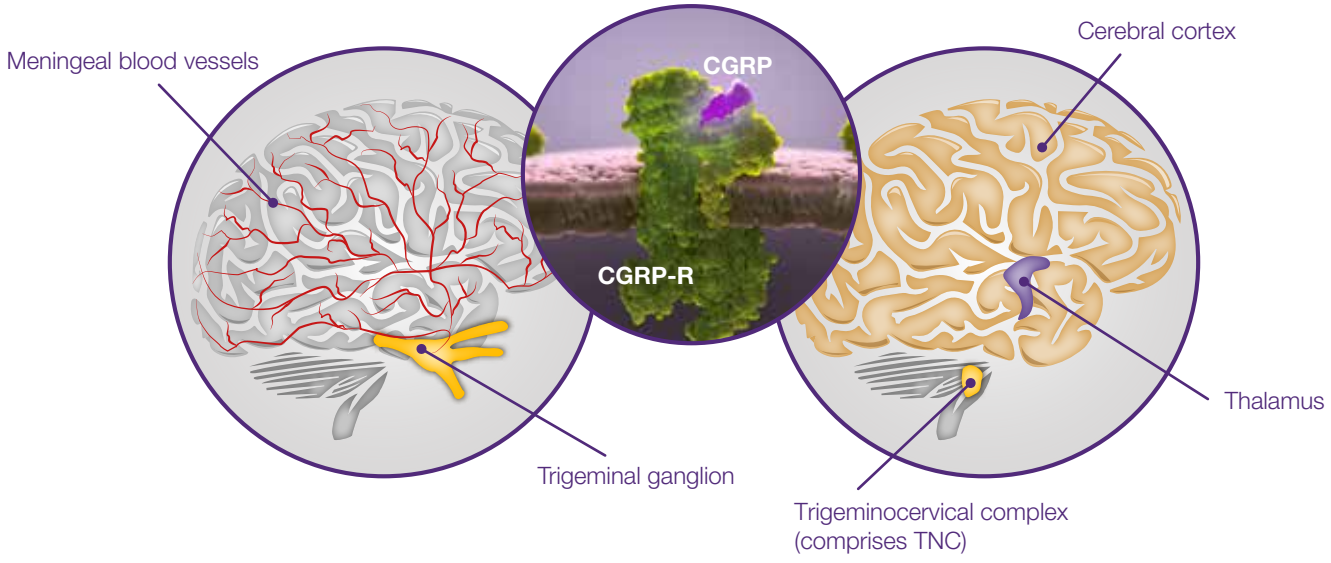
Activation of CGRP-R in the trigeminovascular system plays a critical role in peripheral and central events that ultimately lead to the experience of migraine pain[1,3,7]

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)



CGRP receptors are found in several sites in the trigeminovascular system[3,4]

Summary:

- CGRP is a neuropeptide produced in peripheral and central neurons[1,3]
- CGRP binds to the CGRP-R, located at several sites in the trigeminal pathway[1,3]
- CGRP-R signaling within the trigeminovascular system is a key contributor to migraine pathophysiology[1,3,7,13]
- Research continues to reveal the complex pathophysiology underlying migraine, and the role of CGRP in both the periphery and CNS[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:
1. Russo AF. *Annu Rev Pharmacol Toxicol.* 2015;55:533–552. **2.** Edvinsson L. *Brit J Clin Pharmacol.* 2015; 80:193–199. **3.** Raddant AC and Russo AF. *Expert Rev Mol Med.* 2011;13:e36. **4.** Eftekhari S and Edvinsson L. *Ther Adv Neurol Disord.* 2010;3:369–378. **5.** Noseda R and Burstein R_Pain_2013: 1-A-1, 7-A-3. **6.** Walker CS and Hay DL. *Brit J Clin Pharmacol.* 2013;170:1293–1307. **7.** Silberstein S, et al. *Headache*. 2015;55:1171–1182. **8.** Goadsby PJ, et al. *Ann Neurol.* 1990;28:183–187. **9.** Asghar MS, et al. *Ann Neurol.* 2011;69:635–645. **10.** Lassen LH, et al. *Cephalalgia* 2002;22:54–61. **11.** Hansen JM, et al. *Cephalalgia.* 2011;30:1179–1186. **12.** Karsan N and Goadsby PJ. *Curr Neurol Neurosci Rep*. 2015;15:25. **13.** Russell FA, et al. *Physiol Rev.* 2014; 94:1099–1142.

AMGEN®