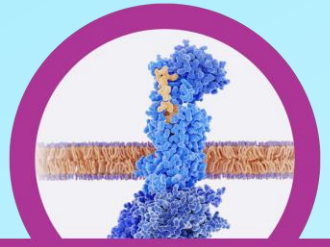
Clinical and Physiologic Evidence Supports the Role of CGRP in Migraine Pathophysiology

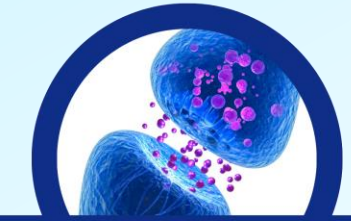


Plasma CGRP levels increase during a migraine attack and return to normal after using a triptan.[1,2]

CGRP infusion can induce migraine-like headaches in people who have migraines.[3]

CGRP is elevated in saliva and tears during an acute migraine attack.[4,5]

CGRP receptors are found in the trigeminal ganglion, cerebral and meningeal vasculature, trigeminal nucleus caudalis, and thalamus.[6-8]

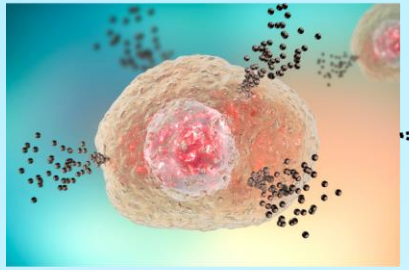


CGRP receptors are found on neurons, vascular smooth muscle, glia, and mast cells.[6-9]

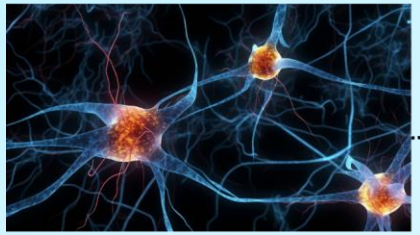
CGRP, calcitonin gene-related peptide. 1. Goadsby PJ, et al. *Ann Neurol.* 1990;28:183-7; 2. Goadsby PJ, et al. *Ann Neurol.* 1993;33:48-56; 3. Lassen LH, et al. *Cephalalgia.* 2002;22:54-61; 4. Cady RK, et al. *Headaches.* 2009;49:1258-66; 5. Kamm K. *Front Neurol.* 2022;13:930383; 6. Raddant AC, et al. *Expert Rev Mol Med.* 2011;13:e36; 7. Edvinsson L. *Br J Clin Pharmacol.* 2015;80:193-9; 8. Edvinsson L. *Revue Neurologique*. 2021;177(7):785-90; 9. Miller S et al. *Neuroscience.* 2016;328:165-83.

CGRP Receptors Are Localized on Cells and in Areas Associated With Migraine Pathophysiology

Smooth muscle cells



Mast cells

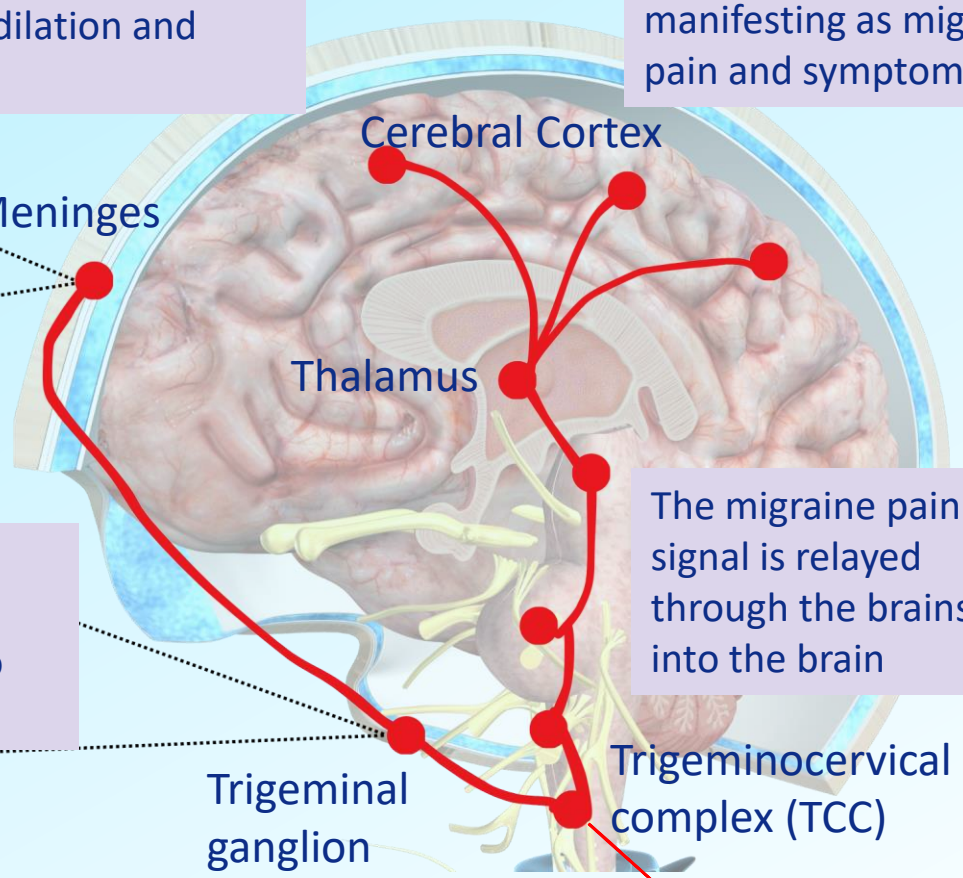


Neurons and glial cells

CGRP binds to receptors on smooth muscle and mast cells and causes meningeal and cerebral blood vessel vasodilation and inflammation

CGRP release in the trigeminovascular system triggers events that lead to migraine pain

Cortical areas process input from TCC manifesting as migraine pain and symptoms



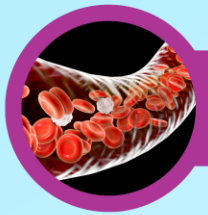
The migraine pain signal is relayed through the brainstem into the brain

Dodick DW. *Headache*.2018:58:4-16; Illustration adapted from The Role of CGRP in Migraine. (n.d.). Science of migraine.com. Accessed December 16, 2023. https://www.scienceofmigraine.com/pathophysiology/cgrp

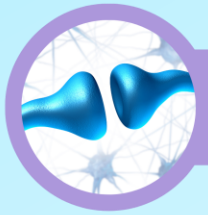
CGRP-CGRP-R Signaling in Migraine Pathophysiology May Involve Multiple Central and Peripheral Nervous System Processes

Research has yet to determine which, if any, of these processes may be causal. The relationship may be correlative or unrelated.

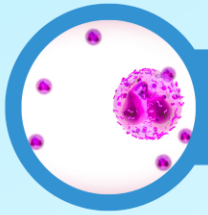
Peripheral



Vasodilation[1-3]



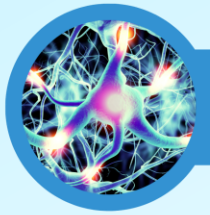
Nociceptor Sensitization[1-3]



Neurogenic inflammation [1-3]

Central

Cortical-spreading depression[1,3]



Trigeminal sensory activation[3]

Central sensitization[3]

Hypothalamic dysfunction activating meningeal nociceptors and lowering pain thresholds[4]

1. Raddant AC, et al. *Expert Rev Mol Med.* 2011;13:e36; 2. Edvinsson L. *Br J Clin Pharmacol.* 2015;80:193-9; 3. Russo AF, et al. *Annu Rev Pharmacol Toxicol.* 2015;55:533-52; 4. Burstein R, et al. *J Neurosci.* 2015;35:6619-29.

Pharmacologic Support for the Role of CGRP in Migraine Pathophysiology

Triptans[1]
- Inhibit CGRP release induced by trigeminal activation
- Constrict CGRP-dilated vessels
- Normalize CGRP levels
- Increase serotonin release

Selective serotonin (5-HT_{1F}) agonist (ditans)[2]
- Inhibits CGRP release

Anti-CGRP monoclonal antibodies[2,3]
- Block CGRP actions
- Prevent sustained trigeminal nerve firing

Onabotulinumtoxin A[3]
- Inhibits CGRP release
- Downregulates receptors on nociceptive neurons

Small-molecule CGRP receptor antagonists (gepants)[1]
- Inhibit CGRP binding
- Block pain amplification and perpetuation processes

Ergots[2]
- Activate 5-HT_{1D} receptors on intracranial blood vessels
- Increase 5-HT_{1D} receptor expression on trigeminal sensory nerve ending
- Constrict CGRP-dilated vessels
- Inhibit CGRP release

1. Altamura C, et al. *Neurol Sci.* 2022;43(9):5697-708; 2. Tanaka M, et al. *Expert Opin Pharmacother.* 2021;22(10):1221-5; 3. Ailani J, et al. *Headache.* 2022;62:106-8.