USA-334-83499

The CGRP Receptor:
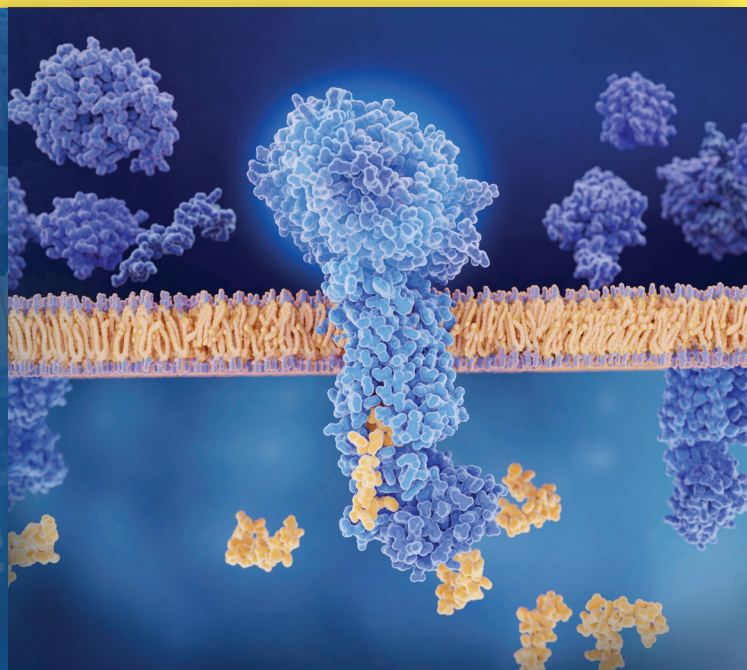## WHAT NEUROLOGISTS NEED TO KNOW

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Introduction

New insights into the role of calcitonin gene-related peptide (CGRP) in migraine pathophysiology have contributed to our evolving understanding of this disease.[1-3] CGRP, a member of the calcitonin family of peptides, which also consists of amylin (AMY), adrenomedullin (ADM), and calcitonin (CT),[4] is a 37-amino-acid neuropeptide produced in central and peripheral neurons.[1,2,5] The interaction of CGRP with its receptor (CGRP-R) is thought to play a key role in migraine pathophysiology through activation of the trigeminovascular system.[1,2,5] Other members of the calcitonin family may mediate physiologic functions such as glycemic, gastrointestinal, and bone regulation,[6-11] but their role in migraine pathophysiology has not been clearly demonstrated.[1,12,13]

Overview of the CGRP-R

The CGRP-R is a member of the calcitonin family of receptors, which are transmembrane-bound G-protein-coupled receptors that share subunits in different configurations.[1,4,14] Other members include the receptors for AMY (AMY1-R, AMY2-R, and AMY3-R) and ADM (ADM1-R and ADM2-R; **Figure 1**).[4,14]
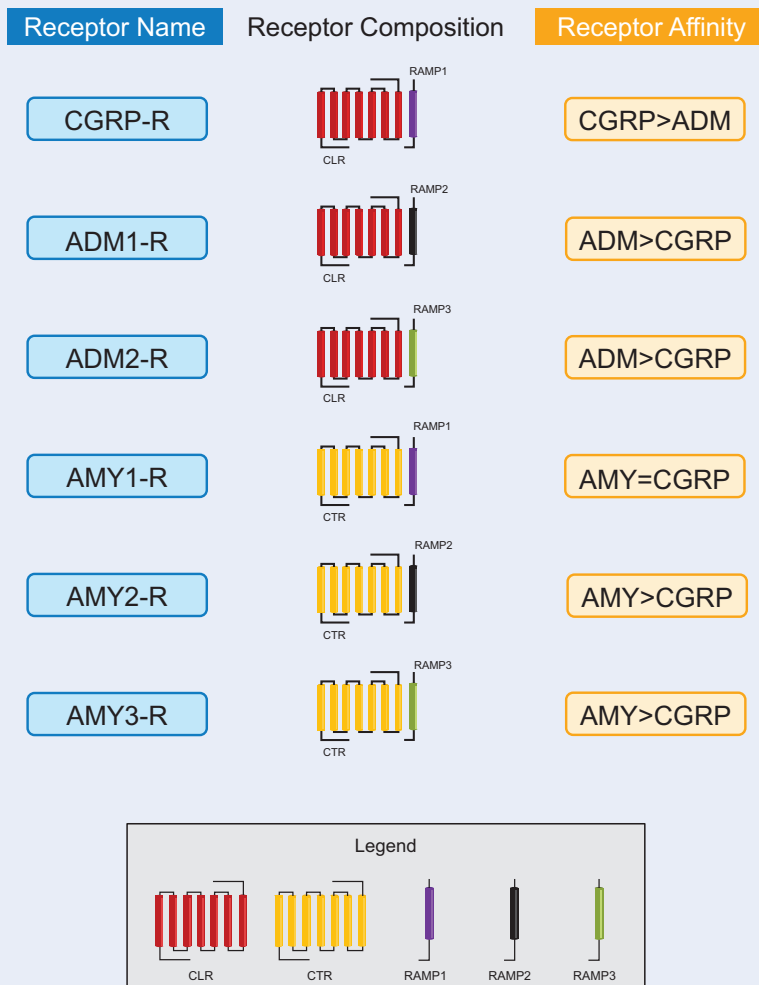
The CGRP-R comprises two main subunits: calcitonin receptor-like receptor (CLR), a G-protein-coupled receptor that is inactive on its own,[4,15-17] and receptor-activity-modifying protein 1 (RAMP1), which is responsible for receptor trafficking (**Figure 2**)[1,4,15,16,18,19] and determines the species specificity of the receptor (**Figures 1 and 2**).[14,16,19] Creation of a functional CGRP-R requires coexpression of both CLR and RAMP1 and formation of a heterodimer, which translocates from the endoplasmic reticulum to the cell membrane (**Figure 2**).[15-17,19]

Activation of G-protein-coupled receptors involves a cyclical model, whereby receptors can be recycled back to the cell surface.[20,21] Ligand binding leads to transient receptor activation and induces a cellular response via second messenger signaling.[20,21] Receptors are then inactivated and internalized via endocytosis before being trafficked to either recycling or degradative pathways.[15,20-22]

Localization of CGRP and CGRP-Rs

CGRP and CGRP-Rs are expressed in trigeminovascular system regions involved in migraine pathophysiology (**Figure 3**).[2,5,16,18,23,24] In humans, CGRP is abundantly expressed in trigeminal ganglia (35%-50% of neurons)[1,18,24,25] and within the central nervous system (CNS).[1,18,24,25] Other sites of expression supported by human data include cranial meninges, perivascular nerves, respiratory tract, kera-

FIGURE 1. The CGRP-R Is a Member of the Calcitonin Family of Receptors.[14]

Receptor Name	Receptor Composition	Receptor Affinity
CGRP-R	CLR / RAMP1	CGRP>ADM
ADM1-R	CLR / RAMP2	ADM>CGRP
ADM2-R	CLR / RAMP3	ADM>CGRP
AMY1-R	CTR / RAMP1	AMY=CGRP
AMY2-R	CTR / RAMP2	AMY>CGRP
AMY3-R	CTR / RAMP3	AMY>CGRP

Legend

CLR   CTR   RAMP1   RAMP2   RAMP3

Abbreviations: ADM, adrenomedullin; AMY, amylin; CGRP, calcitonin gene-related peptide; CGRP-R, calcitonin gene-related peptide receptor; CLR, calcitonin receptor-like receptor; CTR, calcitonin receptor; RAMP, receptor-activity-modifying protein.

CGRP Signaling in Migraine

Following nerve stimulation, CGRP is released from its storage vesicles through the process of calcium-dependent exocytosis.[18] CGRP–CGRP-R signaling regulates trigeminal neuron sensitization and neurotransmitter release, key events that underlie migraine pathophysiology.[1,18]

The signaling pathways may involve multiple processes in the CNS, including vasodilation, neurogenic inflammation, cortical spreading depression, central sensitization, hypothalamic dysfunction, and descending control of brainstem structures.[1,5,35-38] Consistent with the widespread expression of CGRP-Rs outside the CNS, the signaling pathway also involves the peripheral nervous system.[1,5,35,39] Notably, peripheral nociceptive trigeminal neurons are involved in the relay of the migraine pain signal through the brainstem to the rest of the brain, ultimately leading to the experience of migraine pain.[35,36,39]

CGRP-R: Role in Migraine

In humans, expression of AMY or AMY1-R has been demonstrated in trigeminal ganglia, CNS, gastric mucosa, blood vessels, and the pancreas (**Figure 3**).[4,40-43] Unlike AMY, which is an important glucoregulatory hormone,[41,44] CGRP has established roles in key physiologic processes relevant to migraine, such as nociception, sensory modulation, and vasodilation (**Figure 3**).[1,18,35]

Convergent evidence from clinical studies corroborates the involvement of CGRP in migraine.[3,45,46] Plasma CGRP levels increase significantly during migraine attacks[45,46] and return to normal following relief of migraine pain.[45] In migraine patients, infusion of CGRP can also induce migraine-like attacks.[3] While CGRP may also bind to other receptors in the calcitonin family (for example, *in vitro* data suggest it has high affinity for both the CGRP-R and AMY1-R), its affinity for these other receptors is less.[1,4,14]

tinocytes, and the digestive system (liver, pancreas, and gastric mucosa; **Figure 3**).[15,18,26-32]

CGRP-Rs are located both inside and outside the blood–brain barrier, at several sites involved in modulating trigeminal pathway nociceptive signaling.[5,16,18,24] In humans, they are expressed in a subset of trigeminal neurons and glia, cranial meninges, respiratory tract, gastric mucosa, blood vessels (including the vascular smooth muscle cells), keratinocytes, and within several regions of the brain (including the pituitary gland; **Figure 3**).[14,18,24-26,30,31,33,34]
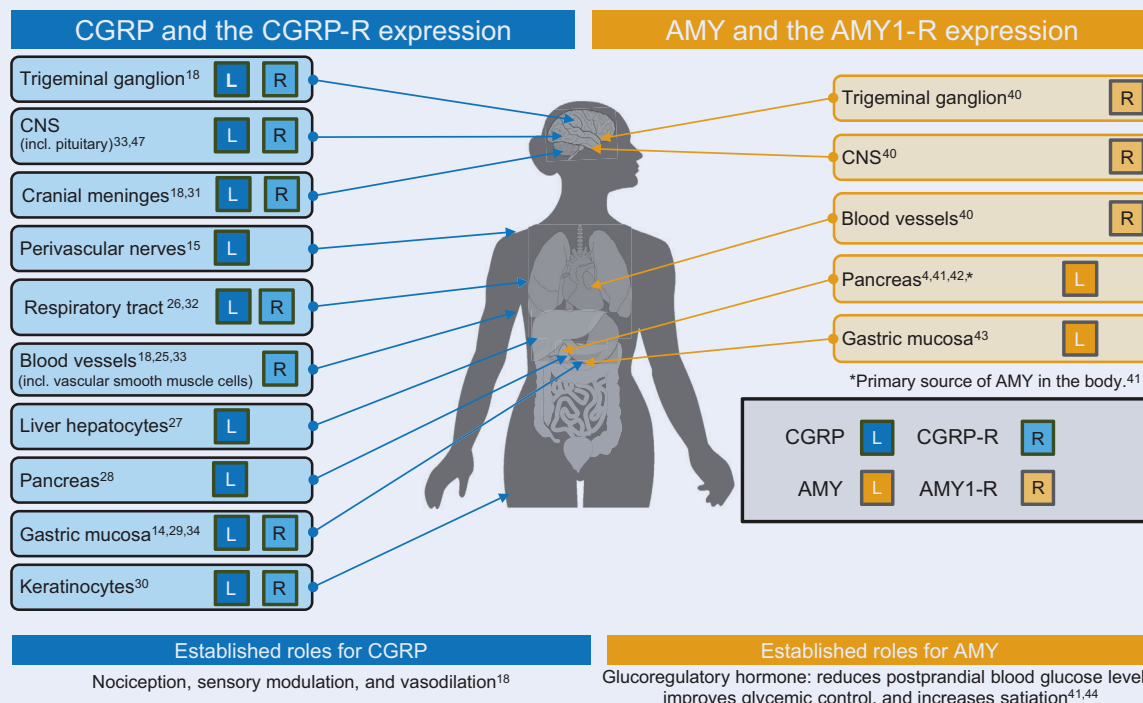
FIGURE 2. Coexpression of CLR With RAMP1 Forms a Functional CGRP Receptor.[19]
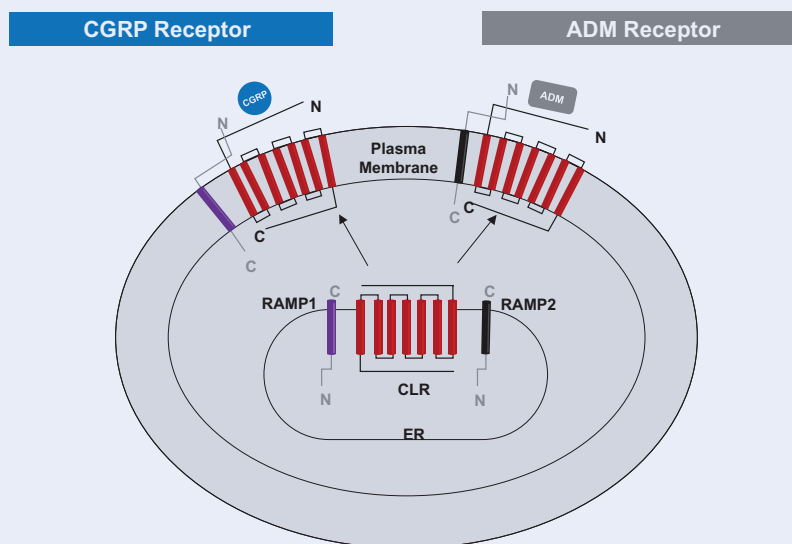
Abbreviations: ADM, adrenomedullin; CGRP, calcitonin gene-related peptide; CLR, calcitonin receptor-like receptor; ER, endoplasmic reticulum; RAMP, receptor-activity-modifying protein.

FIGURE 3. CGRP, AMY, and Their Receptors Are Expressed in Various Tissues and Have Established Roles in Some Key Physiologic Processes.[4,14,15,18,25-34,40-44,47]

CGRP and the CGRP-R expression

- Trigeminal ganglion[18] — L R
- CNS (incl. pituitary)[33,47] — L R
- Cranial meninges[18,31] — L R
- Perivascular nerves[15] — L
- Respiratory tract[26,32] — L R
- Blood vessels[18,25,33] (incl. vascular smooth muscle cells) — R
- Liver hepatocytes[27] — L
- Pancreas[28] — L
- Gastric mucosa[14,29,34] — L R
- Keratinocytes[30] — L R

AMY and the AMY1-R expression

- Trigeminal ganglion[40] — R
- CNS[40] — R
- Blood vessels[40] — R
- Pancreas[4,41,42,*] — L
- Gastric mucosa[43] — L

*Primary source of AMY in the body.[41]

CGRP — L   CGRP-R — R
AMY — L   AMY1-R — R

Established roles for CGRP
Nociception, sensory modulation, and vasodilation[18]

Established roles for AMY
Glucoregulatory hormone: reduces postprandial blood glucose levels, improves glycemic control, and increases satiation[41,44]

Expression data are based on a variety of methodologies, including histology, protein, and mRNA analyses in human tissue.[18,25,27] The roles presented here as 'established' are based on evidence from multiple studies and/or trials.[18,41,44]

Abbreviations: AMY, amylin; AMY1-R, amylin type 1 receptor; CGRP, calcitonin gene-related peptide; CGRP-R, calcitonin gene-related peptide receptor; CNS, central nervous system; L, ligand; mRNA, messenger RNA; R, receptor.

Conclusions

CGRP and the CGRP-R are abundantly expressed at several sites within the trigeminal pathway involved in modulating trigeminal nociceptive signaling[2,5] and mediate key events in the pathophysiology of migraine, such as nociception, sensory modulation, and vasodilation.[1,18,35] CGRP and CGRP-R are known to play a key role in migraine pathophysiology.[1,14,35]

REFERENCES

1. Russo AF. *Annu Rev Pharmacol Toxicol*. 2015;55:533-552.
2. Raddant AC, Russo AF. *Expert Rev Mol Med*. 2011;13:1-18.
3. Lassen LH, et al. *Cephalalgia*. 2002;22:54-61.
4. Hay DL, et al. *Br J Pharmacol*. 2018;175:3-17.
5. Edvinsson L. *Br J Clin Pharmacol*. 2015;80:193-199.
6. Poyner DR, et al. *Pharmacol Rev*. 2002;54:233-246.
7. Hieronymus L, Griffin S. *Diabetes Educ*. 2015;41:47S-56S.
8. Pittner RA, et al. *J Cell Biochem*. 1994;55S:19-28.
9. Cornish J, et al. *Am J Physiol*. 1997;273:E1113-E1120.
10. Martínez A, et al. *Endocrinology*. 1996;137:2626-2632.
11. Martínez V, et al. *Endocrinology*. 1997;138:3749-3755.
12. Wattiez A-S, et al. *Expert Opin Ther Targets*. 2020;24:91-100.
13. Petersen KA et al. *Cephalalgia*. 2009;29:23-30.
14. Walker CS, Hay DL. *Br J Pharmacol*. 2013;170:1293-1307.
15. Russell FA, et al. *Physiol Rev*. 2014;94:1099-1142.
16. Lennerz JK, et al. *J Comp Neurol*. 2008;507:1277-1299.
17. Hilairet S, et al. *J Biol Chem*. 2001;276:42182-42190.
18. Edvinsson L, et al. *Nat Rev Neurol*. 2018;14:388-350.
19. Cooray SN, et al. *Mol Cell Endocrinol*. 2009;300:17-24.
20. Pavlos NJ, Friedman PA. *Trends Endocrinol Metab*. 2017;28:213-226.
21. Lane JR, et al. *ACS Chem Neurosci*. 2013;4:527-534.
22. Bond RA, et al. *Front Pharmacol*. 2019;10:124.
23. Goadsby PJ, et al. *Physiol Rev*. 2017;97:553-622.
24. Eftekhari S, Edvinsson L. *Ther Adv Neurol Disord.* 2010;3:369-378.
25. Miller S, et al. *Neuroscience*. 2016;328:165-183.
26. Dakhama A, et al. *Curr Opin Pharmacol*. 2004;4:215-220.
27. Bracq S, et al. *FEBS Lett*. 1994;351:63-66.
28. Al-Salam S, et al. *Neuro Endocrinol Lett*. 2009;30:506-510.
29. Mönnikes H, et al. *Digestion*. 2005;71:111-123.
30. Hou Q, et al. *Pain*. 2011;152:2036-2051.
31. Eftekhari S, et al. *J Pain*. 2013;14:1289-1303.
32. Martling C-R, et al. *Regulatory Peptides*. 1988;20:125-139.
33. Wimalawansa SJ. *Endocr Rev*. 1996;17:533-585.
34. Cottrell GS, et al. *Peptides*. 2012;35:202-211.
35. Bigal ME, et al. *Headache*. 2013;53:1230-1244.
36. Noseda R, Burstein R. *Pain*. 2013;154(suppl 1):S44-S53.
37. Pozo-Rosich P, et al. *Cephalalgia*. 2015;35:1298-1307.
38. Li XF, et al. *Endocrinology*. 2004;145:1556-1563.
39. Silberstein S, et al. *Headache*. 2015;55:1171-1182.
40. Walker CS, et al. *Ann Clin Transl Neurol*. 2015;2:595-608.
41. Hay DL, et al. *Pharmacol Rev*. 2015;67:564-600.
42. Westermark P, et al. *Biochem Biophys Res Commun*. 1986;140:827-831.
43. D'Este L, et al. *Arch Histol Cytol*. 1995;58:537-547.
44. Mietlicki-Baase EG. *Physiol Behav.* 2016;162:130-140.
45. Goadsby PJ, Edvinsson L. *Ann Neurol*. 1993;33:48-56.
46. Goadsby PJ, et al. *Ann Neurol*. 1990;28:183-187.
47. Petermann JB, et al. *J Biol Chem*. 1987;262:542-545.