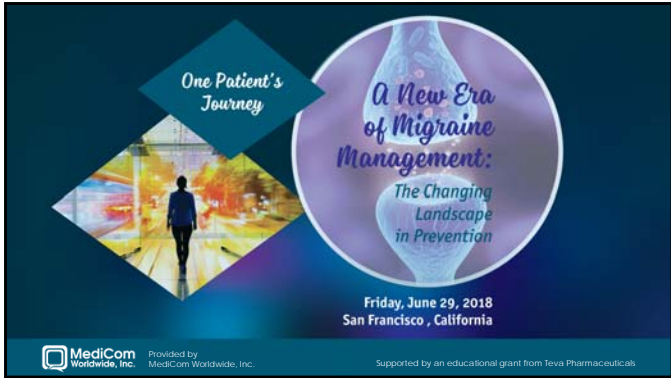


# A New Era of Migraine Management: The Challenging Landscape in Prevention



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### What is a Neuropeptide?

- Small chains of amino acids released by neural cells (neurons or glial cells) to signal to other cells
- Multiple properties that set them apart from classical neurotransmitters



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### Examples of Neuropeptides

- Calcitonin gene-related peptide
- Pituitary adenylate cyclase activating peptide
- Vasoactive intestinal peptide
- Orexins
- Substance P
- Hypothalamic hormones (eg, GnRH, oxytocin)
- Endogenous opioids (endorphins, enkephalins)
- Melanocortin
- Bradykinin

Hökfelt T, et al. Lancet Neurol 2003;2(8):463-472



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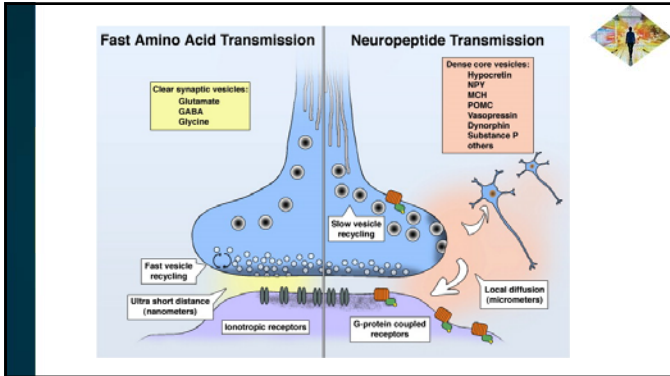
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### Summary

- Compared to neurotransmitters (like glutamate, GABA) neuropeptides:
  - Are produced and packaged differently by cells
  - Take more activation to release
  - Bind more tightly to receptors
  - Have a more sustained effect
  - Can be released away from a synapse
  - Once released can travel to more distant locations
  - Can cause more diffuse effects on glia, vascular cells, endocrine cells, etc.

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### Calcitonin Gene Related Peptide (CGRP)

- 37 amino acid polypeptide
- Alpha-CGRP believed to be primary active form in nervous system
- Beta-CGRP (3 amino acids different from Alpha CGRP) believed to be primarily active form in GI tract
- Activates CGRP receptor and may also activate other types of receptors

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# A New Era of Migraine Management: The Challenging Landscape in Prevention

### Evidence of a Key Role for CGRP in Migraine

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    graph TD
      A[CGRP is Released During a Migraine Attack] --> B[CGRP Levels are Elevated in Chronic Migraine]
      C[CGRP Administration Triggers Migraine] --> D[Antibodies to CGRP or its Receptor Prevent Migraine]
      E[Small Molecule CGRP Antagonists Abort Migraine] --> D
  
```

Goadsby PJ, et al. *Ann Neurol*. 1999;28:183-187. Goadsby PJ, et al. *Brain*. 1994;117(Pt 3):427-434. Hansen JM, et al. *Cephalalgia*. 2010;30(10):1179-1186. Cernuda-Morillon E, et al. *Neurology*. 2013;81(14):1191-1196. Olesen J, et al. *N Engl J Med*. 2004;350:1104-1110. Ho TW, et al. *Neurology*. 2008;70:1304-1312.

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### CGRP Release in Migraine

- CGRP but not neuropeptide Y, VIP, or substance P released during attacks of migraine with and without aura
- Elevated CGRP levels were observed in jugular but not antecubital venous blood on same side as pain
- Greater elevation in CGRP observed in migraine with aura
- CGRP levels normalize upon treatment with sumatriptan
- Serum CGRP levels reported to be chronically elevated in patients with chronic migraine

Goadsby PJ, et al. *Ann Neurol*. 1999;28:183-187. Goadsby PJ, et al. *Ann Neurol*. 1993;33(1):48-56. Cernuda-Morillon E, et al. *Neurology*. 2013;81(14):1191-1196.

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### CGRP Administration Triggers Migraine

Hansen JM, et al. *Cephalalgia*. 2010;30(10):1179-1186. Schytz HW, et al. *Curr Opin Neurol*. 2010;23(3):259-265.

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## Small Molecule CGRP Receptor Antagonists ("Gepants") Abort Migraine



Drug	Pain free at 2 h (%)		Side effects reported	Status in pharmacological trials
	Verum	Placebo		
Olccegepant	44: 2.5 mg	2	20% reported adverse effects	Discontinued development — poor oral bioavailability
Telcagepant	27: 300 mg	10	Transaminitis	Discontinued — hepatotoxic concerns
MK3207	69: 200 mg	39.1	Transaminitis	Discontinued — hepatotoxic concerns
B144370	27.4: 400 mg	8.6	1.4-9.4% reported adverse effects, dose dependent	Phase IIIa complete
BMS-927111	32.9: 150 mg	15.3	1-8% reported adverse effects, dose dependent	Phase IIIa complete

Karsan N, et al. *Curr Opin Neurol*. 2015;28(3):250-254. Voss T, et al. *Cephalalgia*. 2016;36(9):887-898. Marcus R, et al. *Cephalalgia*. 2014;34(2):114-125.

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## What Do Clinical Trials of CGRP-related Therapies Tell Us About Pathophysiology?




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## CGRP Antibody Clinical Trials What Do They Tell Us About Migraine Biology?



- Specificity of antibodies to targets definitively proves primary role for CGRP and CGRP receptor in migraine
- Efficacy of antibodies, which presumably do not cross blood- brain barrier, indicates mechanism of action that is either peripheral, or in brain regions outside of BBB
- Individual patient responses represent an opportunity to markedly increase our understanding of basic mechanisms

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# A New Era of Migraine Management: The Challenging Landscape in Prevention

## CGRP and Receptor Localization Related to Migraine Peripheral and Central Nervous System



- CGRP peptide is localized in neurons and glial cells
- CGRP receptors are localized in neurons, glial cells, dural arteries, and mast cells
- CGRP and its receptors are localized throughout the trigeminal nociceptive pathway, including peripheral afferents, trigeminal ganglion, and trigeminal-cervical complex
- CGRP receptors are localized in multiple brain regions including:
  - Trigeminal nucleus caudalis, dorsolateral pons/midbrain, thalamus, hypothalamus, cortex, cerebellum, amygdala, vestibular nuclei

Karan N, et al. *Curr Opin Neurol*. 2015;28(3):250-254. Kaiser EA, et al. *Neuropeptides*. 2013;47(6):451-461.

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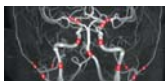
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## The Paradigm Shift from the Vascular Hypothesis of Migraine



Magnetic resonance angiography of intracranial and extracranial arteries in patients with spontaneous migraine without aura: a cross-sectional study



- 19 patients with spontaneous migraine
- *No extracranial artery dilation* during attack
- Slight intracranial artery dilation during attack
- Effective treatment with sumatriptan caused *no intracranial vasoconstriction*

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## If the Vascular Hypothesis of Migraine is not Correct, How Do You Explain the Role of CGRP, Which is a Vasodilator?



- The fundamental tenet of the vascular hypothesis is that the *dilation of blood vessels is responsible for headache*
- While CGRP is indeed a vasodilator, it is also separately involved in pain transmission
- Thus, while CGRP may dilate blood vessels, it is the parallel effect of CGRP on pain transmission that is responsible for headache, and not the dilation of blood vessels

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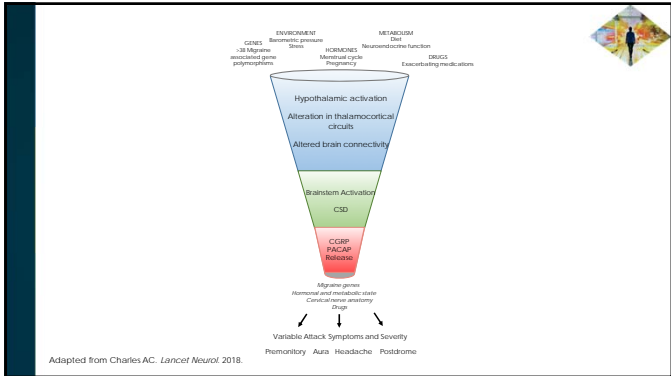
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