

## NOVEL THERAPEUTIC TARGETS: THE HYPOTHALAMUS

Andrew Charles, M.D.  
Professor

Director, UCLA Goldberg Migraine Program  
Meyer and Renee Luskin Chair in Migraine and Headache Studies  
David Geffen School of Medicine at UCLA



---

---

---

---

---

---

---

---

## DISCLOSURES

- Amgen –Consultant
- Eli Lilly – Scientific Advisory Board
- eNeura – Medical Advisory Board
- St. Jude Medical – Clinical trial steering committee
- Takeda Pharmaceuticals – Research Grant support

---

---

---

---

---

---

---

---

## FUNCTIONS OF THE HYPOTHALAMUS

- Master controller of the reproductive neuroendocrine axis
- Circadian clock
- Regulation of metabolism, growth appetite
- Regulation of fluid balance

---

---

---

---

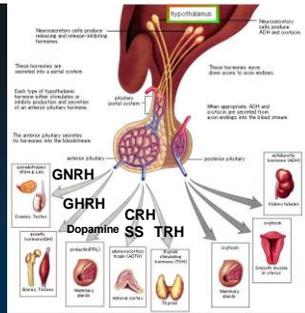
---

---

---

---

## HORMONAL FUNCTIONS OF THE HYPOTHALAMUS




---

---

---

---

---

---

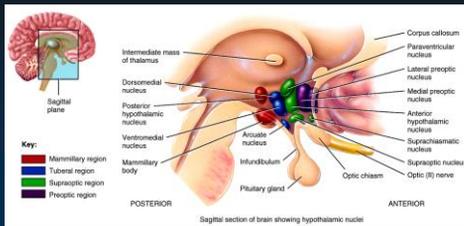
---

---

---

---

## Anatomy of the Hypothalamus




---

---

---

---

---

---

---

---

---

---

## KEY CONCEPTS REGARDING HYPOTHALAMIC FUNCTION

- Significant components of hypothalamic function are **CYCLICAL**.
- Subject to finely tuned feedback loops with multiple neural, sensory, metabolic, and hormonal inputs.

---

---

---

---

---

---

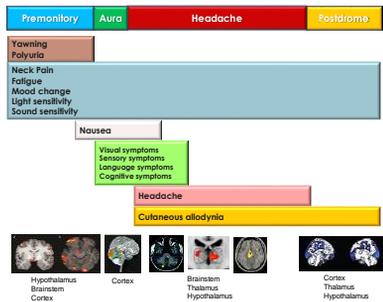
---

---

---

---

**TIMELINE OF A MIGRAINE ATTACK 4-72 hours**




---

---

---

---

---

---

---

---

**Clinical Features Implicating a Role for the Hypothalamus in Headache Disorders**

- Yawning
- Circadian features of migraine and cluster headache
- Effects of the reproductive cycle on migraine
- Polyuria in premonitory phase
- Mood change
- Appetite change

---

---

---

---

---

---

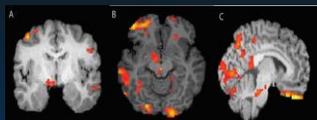
---

---

**PET Studies -Imaging Evidence for a Role of the Hypothalamus in Migraine**



Denuelle et al., Headache, 2007



Maniyar et al., Brain, 2013

---

---

---

---

---

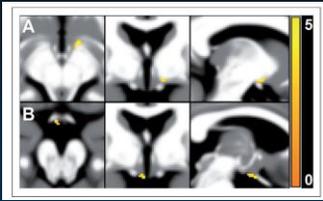
---

---

---



## Increased Hypothalamic Volume in Chronic Cluster



The anterior hypothalamus in cluster headache

Enrico B Arkin<sup>1</sup>, Nicole Schmitz<sup>1</sup>, Gaur G Schoonman<sup>1,2</sup>,  
 Jorine A van Vliet<sup>1,2</sup>, Jonne Haan<sup>1,2</sup>, Mark A van Buchem<sup>1</sup>,  
 Michel D Ferrari<sup>1,2</sup> and Mark C Knudt<sup>1,2</sup>

Cephalgia International Headache Society

2017, Vol. 37(1) 1029-1032

---

---

---

---

---

---

---

---

---

---

## Neuroendocrine Alterations Reported in Migraine Patients

- Altered pituitary and gonadal hormones in both men and women
- Higher neuropeptide Y levels and insulin resistance
- Higher interictal oxytocin levels in chronic migraine

---

---

---

---

---

---

---

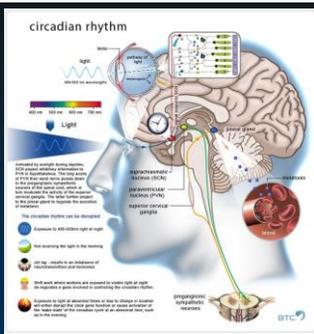
---

---

---

## Circadian Rhythm

<http://www.sleepdisordersresource.com/circadian-rhythm-sleep/circadian-rhythm-sleep/circadian-rhythm-sleep-disorder/>




---

---

---

---

---

---

---

---

---

---

## Adenosine and PACAP- Modulators of both Headache and Circadian Cycle

- Adenosine is believed to be a primary component of the metabolic drive to sleep, possibly by acting on VLPO neurons
- Caffeine, a non-selective adenosine receptor antagonist, has therapeutic benefit for migraine but its mechanism is unknown
- PACAP is present in light sensing retinal ganglion cells and in the retinohypothalamic tract
- In animal models, PACAP can modulate the function of the suprachiasmatic nucleus

---

---

---

---

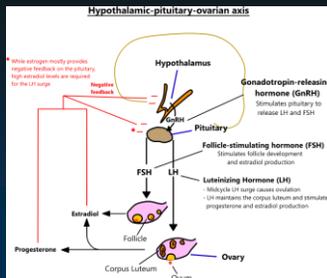
---

---

---

---

## Reproductive Neuroendocrine Axis




---

---

---

---

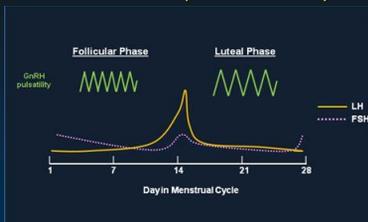
---

---

---

---

## Pulsatile release of GnRH is a reliable "clock" that controls the reproductive cycle



Ehlers, K, Halvorson, L, Glob. libr. women's med., (ISSN: 1756-2228) 2013; DOI 10.3843/GLOWM.10285

---

---

---

---

---

---

---

---

## Energy metabolism and stress response

- Skipped meals a commonly reported migraine trigger.
- Stress (or let-down from stress) is a commonly reported migraine trigger
- Food craving commonly reported in the premonitory phase
- Corticosteroids may have benefit in as acute therapy for migraine and for status migrainosis.

---

---

---

---

---

---

---

---

## Orexin System – Relevance to Migraine

- Orexin receptor antagonists inhibit trigeminal nociception and increase the threshold for cortical spreading depression
- However:
  - Orexin receptor antagonist filorexant did not show efficacy as migraine preventive therapy

---

---

---

---

---

---

---

---

## The Oxytocin System – Relevance to Migraine

- Oxytocin receptors expressed in trigeminal nociceptive pathway
- Intranasal oxytocin studied as an acute and preventive treatment for migraine.
  - Acute treatment did not meet primary endpoint for pain reduction at 2 hours in episodic or chronic migraine
  - Preventive treatment did not meet endpoint for statistically significant reduction in headache days compared with placebo.
    - High placebo response

---

---

---

---

---

---

---

---

## Approaches to Modulation of Hypothalamic Function as Headache Therapies

- Non-pharmacological
  - Sensory inputs – Light, olfaction
  - Diet/energy inputs
  - Sleep
- Hormones or hormone receptor modulators
- Neurochemical mediators of hypothalamic function (e.g. dopamine, adenosine, PACAP)
- Neuromodulation

---

---

---

---

---

---

---

---