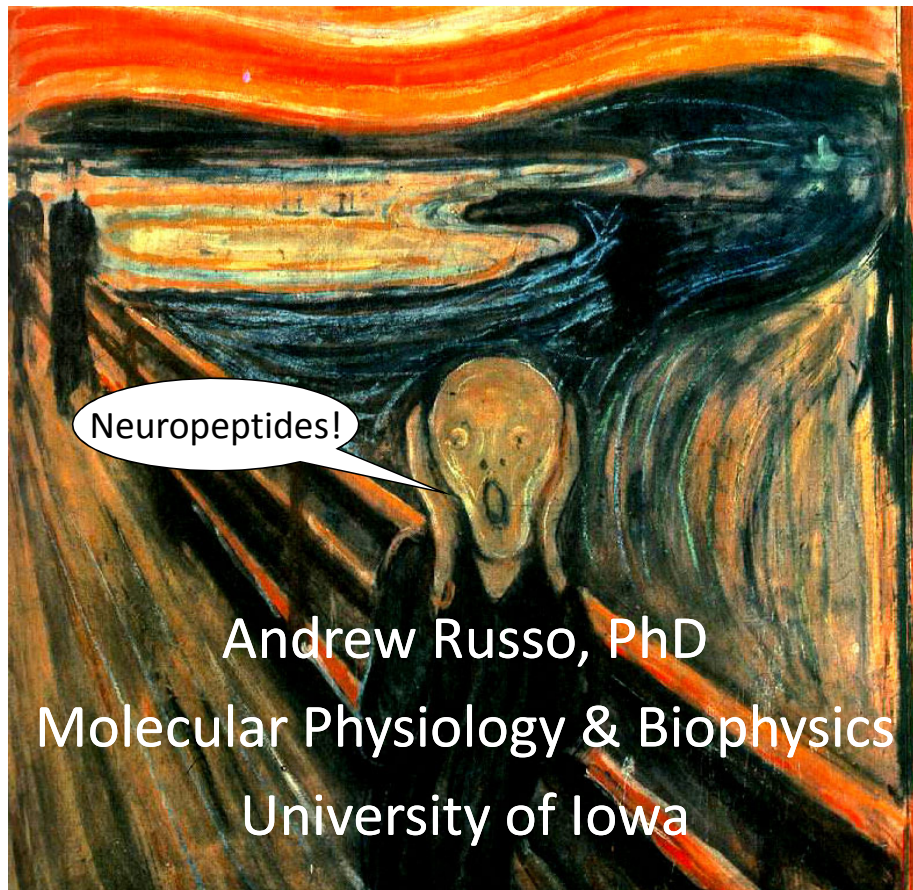


Overview of Neuropeptides: Awakening the Senses?



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Disclosures

Funding:

NIH, DoD, VAMC, Alder
Biopharma

Consultant:

Pharmnovo
Alder Biopharma
Eli Lilly
LeClairRyan; Medacorp;
Sudler NY; DDB Remedy

Objectives

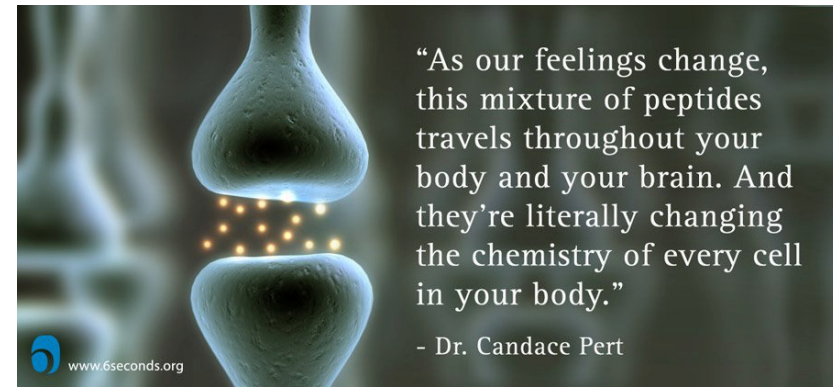


- To appreciate the diversity of neuropeptides in the body.
- To recognize that neuropeptides act by modulating synaptic transmission in the CNS.
- To appreciate that neuropeptides also act in peripheral tissues to alter cellular activities.

What are Neuropeptides?

*“**Neuropeptides** are small protein-like molecules (peptides) used by neurons to communicate with each other” (Wikipedia)*

- Distinction between *neuropeptide* and *peptide hormone* is solely based on synthesis in neuron
 - Both are synthesized, modified, and degraded by same sets of enzymes and both can act nearby and at a distance
 - Nearly all neuropeptides also found as peptide hormones
- So, while we use the term *neuropeptide*, remember ...
 - neuropeptides are not just in the nervous system – they act both in and out of the CNS



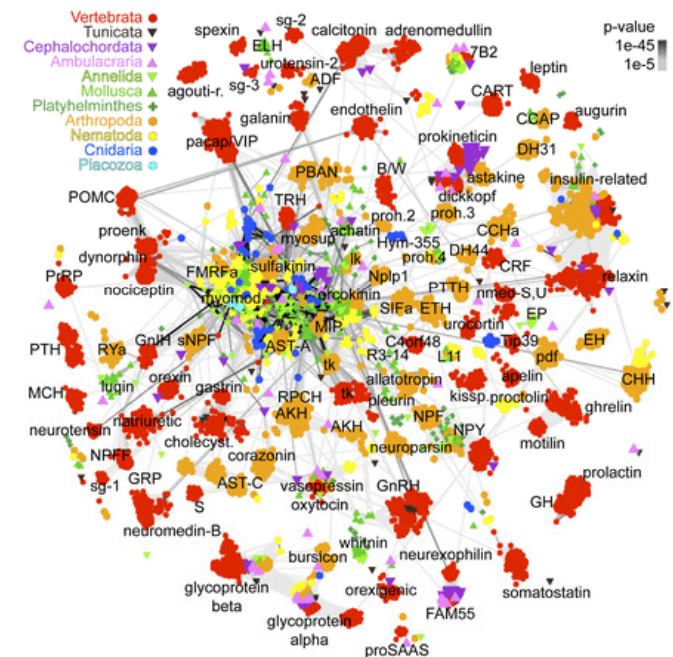
Candace Pert 1946-2013
<http://www.6seconds.org/wp-content/uploads/2007/01/synapse-widened-pert.jpg>

Diversity of Neuropeptides

- > 100 known neuropeptides in human brain

www.neuropeptides.nl/tabel%20neuropeptides%20linked.htm

- > 1000 total peptides in Homo sapiens
 - based on genome homologies of neuropeptides, peptide hormones, cytokines, growth factors, antimicrobial peptides, toxins & venom peptides, antifreeze proteins. www.peptides.be/?p=home
- Evolutionary conservation of peptides and receptors



Global view of the evolution and diversity of metazoan neuropeptide signaling
Jekely, 2014 PNAS 110, 8702
<http://www.pnas.org/content/110/21/8702.full>

Diverse Neuropeptide Families

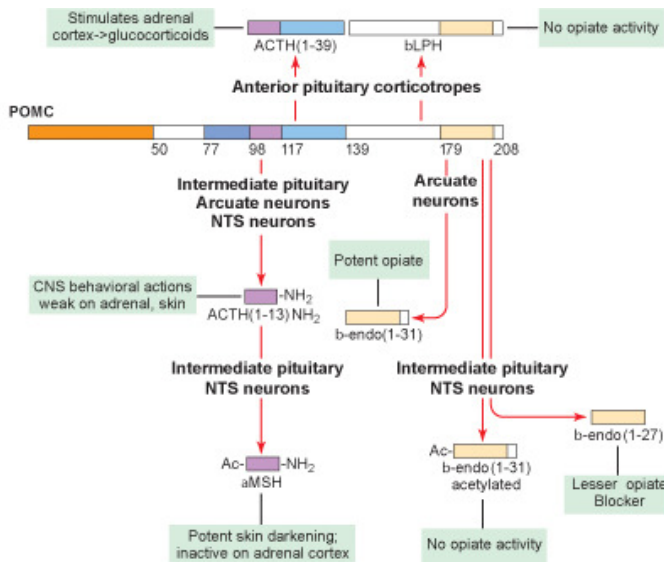
Connected to migraine?	Other families
CGRP: CGRP (α , β), calcitonin, amylin, adrenomedullin (AM1,2)	Opioids: enkephalins, dynorphin, endorphins, nociceptin
	Somatostatin/cortistatin
Glucagon/secretin: PACAP, VIP, glucagon, secretin, GHRH, GIP	Natriuretic factors: ANF, BNF, CNP
	GRP, neuromedins
Vasopressin/ oxytocin	Endothelins
	CCK/gastrin
F- and Y-amides: NPY, PPY, NPFF	Insulins: insulin, IGFs, relaxins
	Motilin/ghrelin
Tachykinins: Sub P, neurokinin A, neuropeptide K, neuropeptide gamma	Galanins
	Gonadotropin releasing hormones
Tensins: angiotensin, neurotensin, bradykinin	Neuropeptide B/W/S
	Neurexophilins
CRH-related: CRH, urocortin, urotensin	Cerebellins
	Granins: chromogranins, secretogranins
Adipose neuropeptides: leptin, adiponectin, resistins	
Family-less: orexins, MCH, TRH, PTHrP, CART, AGRP, prolactin, diazepam-binding inhibitor peptide, etc	
	http://www.neuropeptides.nl/tabel%20neuropeptides%20linked.htm

Common Features of Neuropeptides

1. Modulate target cells
 - CNS= enhance/dampen synaptic activity
 - Peripheral tissues= neurohormones, many targets, many functions
2. All are signal transducers that act at cell-surface receptors
 - Nearly all act at G protein coupled receptors
 - Consistent with neuropeptides inducing a slower and modulatory response compared to neurotransmitters
3. All processed from precursors
 - Synthesis to degradation shared features

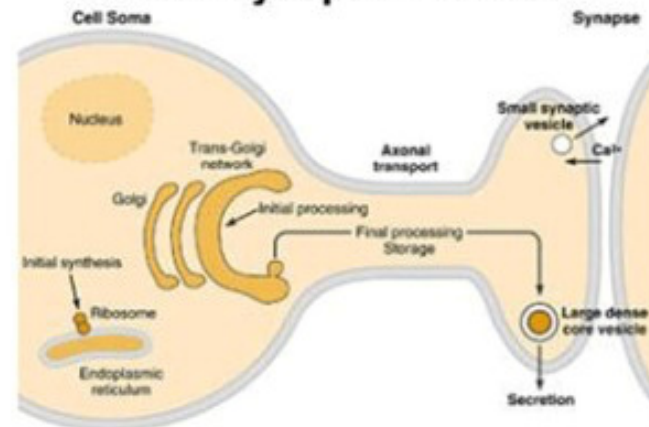
Common Features: Synthesis & Release

Processing of precursors



Pro-peptides are proteolytically cleaved and often modified by C-terminal amidation.

Large Dense Core Vesicles vs. Small Synaptic Vesicles



From dense core vesicles at synapses, cell bodies, varicosities along axon. At synapses often co-released with a neurotransmitter.

Dick Mains & Betty Eipper lab
<http://neuropeptidelab.uchc.edu>

How many neuropeptides in a vesicle?

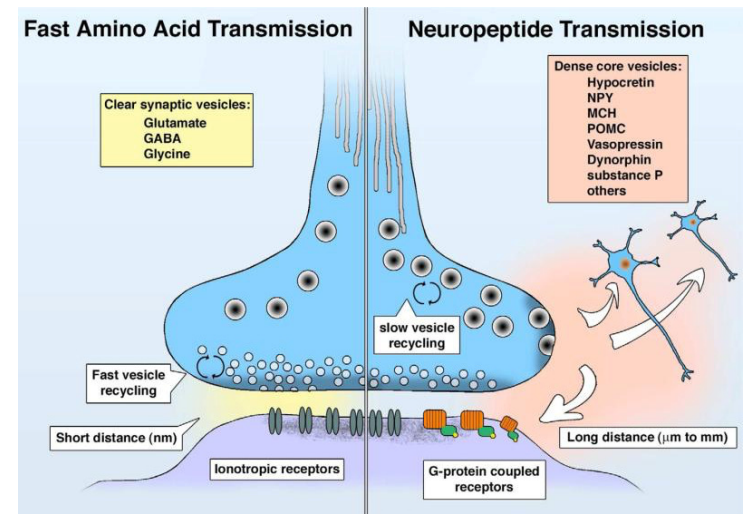
- How many neuropeptides can dance on the head of a pin (or in a secretory vesicle)?
- About 100,000 peptides in a large dense core vesicle
 - Calculated from: (3-10 mM, Mains + Eipper, 1999, Basic Neurochemistry, 6th ed; 60 mM for oxytocin, vasopressin in posterior pit, Nordmann + Morris, 1984, PNAS 81:180-84)
 - 100-200 nm diameter, vol = 2×10^6 cubic nm, 2×10^{-18} liter/vesicle
 - 10 mmol/l $\times 2 \times 10^{-18}$ l = 20×10^{-18} mmol = 2×10^{-20} mol/vesicle
 - 2×10^{-20} mol $\times 6 \times 10^{23}$ molec/mol = 1.2×10^4 molec/vesicle (~100,000 peptides/ vesicle)
- Tens to hundreds of vesicles released at synapse, cell bodies, varicosities in time scale of msec (chromaffin cells have 20,000 dense core vesicles, Plattner, JCB, 1997)
- So millions of neuropeptides are released in a short burst from a single cell



"I don't dance on the head of a pin unless I'm really drunk."

Common Features: Diffusion & Degradation

- Neuropeptides diffuse from point of release (volume transmission)
 - Nonsynaptic dispersion in extracellular fluid and CSF
 - Slowly removed from extracellular space, which contributes to relatively long lasting effects
 - No reuptake system
 - Can be active at relatively large distances at relatively low concentrations
 - High receptor affinities (compared to neurotransmitters)
- Inactivation occurs by extracellular proteases
 - This can also create different bioactive peptides



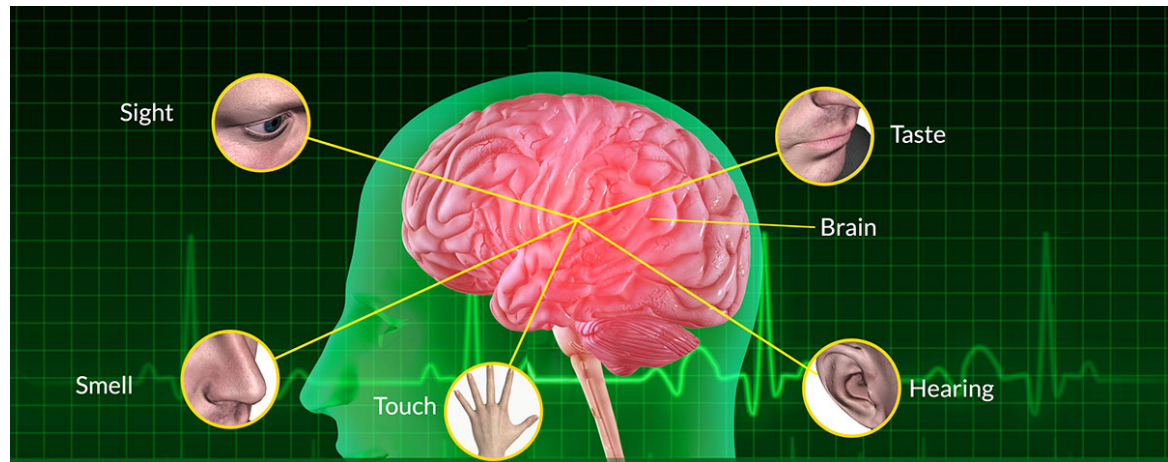
Van den Pol (2012)
Neuron 76: 98–115

Neuropeptides & Sensory Perception?

- Neuromodulation in the brain coupled with altered peripheral signals



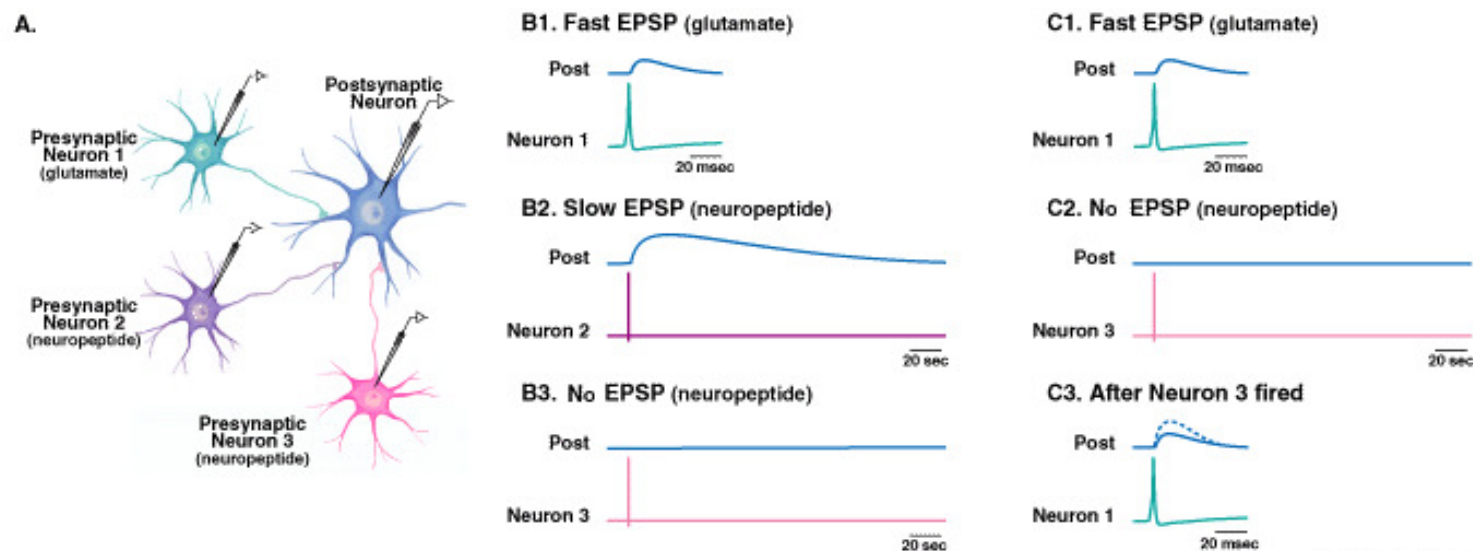
<http://www.luminousself.com/awakening-the-luminous-self.html>



<http://www.epainassist.com/brain/sensory-processing-disorder-spd>

Within the Brain: Neuromodulation

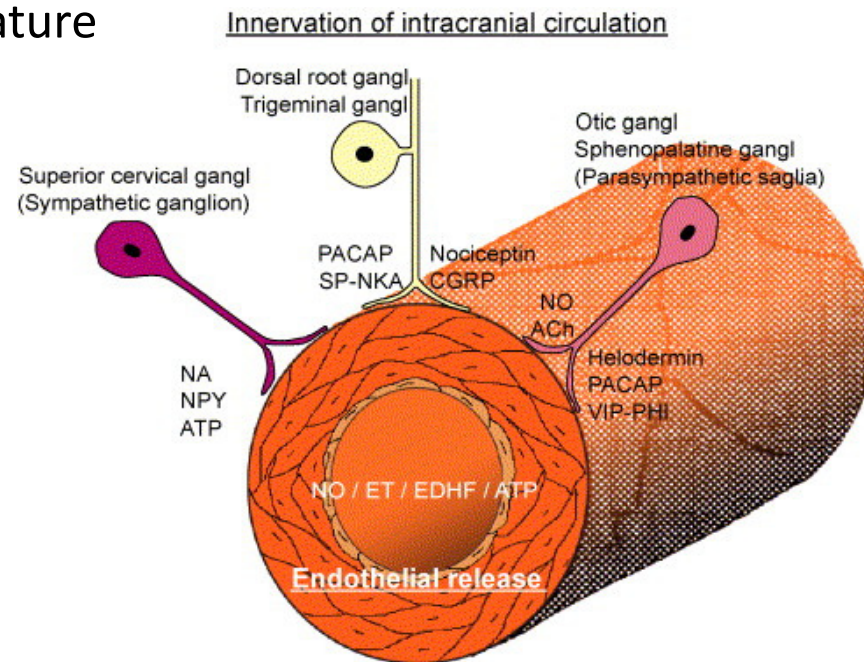
- Generally modulate activity of co-released neurotransmitters to either increase or decrease strength of synaptic signaling
 - Influence many functions, e.g. analgesia, reward, food intake, metabolism, reproduction, social behaviors, learning and memory.



<http://neuroscience.uth.tmc.edu/s1/chapter14.html>

Within the Periphery: Alter Cellular Activities

- Can function similar to peptide hormones and act on various target tissues to modulate nearly all bodily functions
 - At the vasculature



Edvinsson and Uddman,
Brain Research Reviews
48(3):438-56 2005

Neuropeptide Families & Migraine

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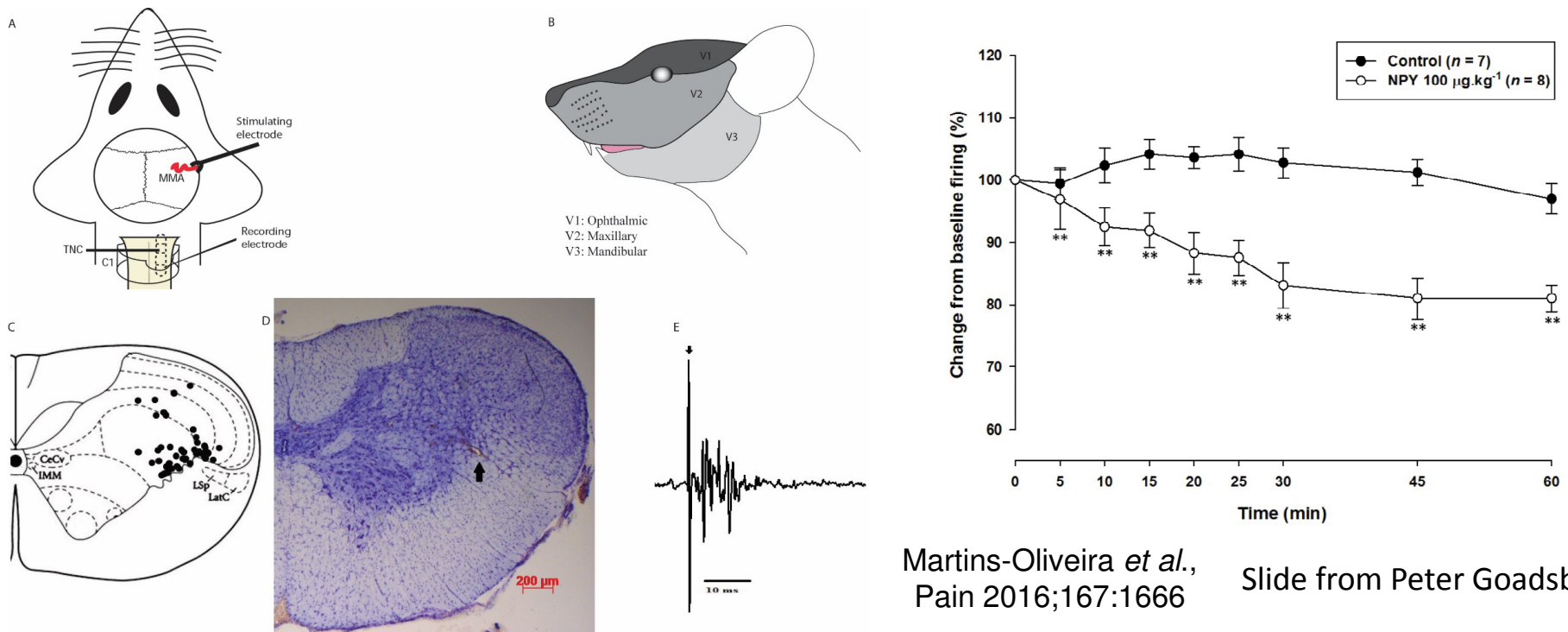
NPY: Premonitory Phase

Feeding Peptides & Migraine

- NPY Roles
 - Pain
 - Appetite control
 - Synchronization of circadian rhythm
- NPY brain location
 - Hypothalamic nuclei
 - Basal ganglia
 - Limbic system
- NPY receptors (G protein coupled Y receptors)
 - Six sub-types
 - Not all in humans (1-5)
- **In migraine**
 - Could neuropeptide Y mechanisms link altered appetite and nociceptive processing?

NPY & Trigeminovascular System

- Anesthetized rat; durovascular stimulation
- Recording from second order trigeminocervical neurons
- NPY dose-dependently inhibits nociceptive trigeminovascular transmission

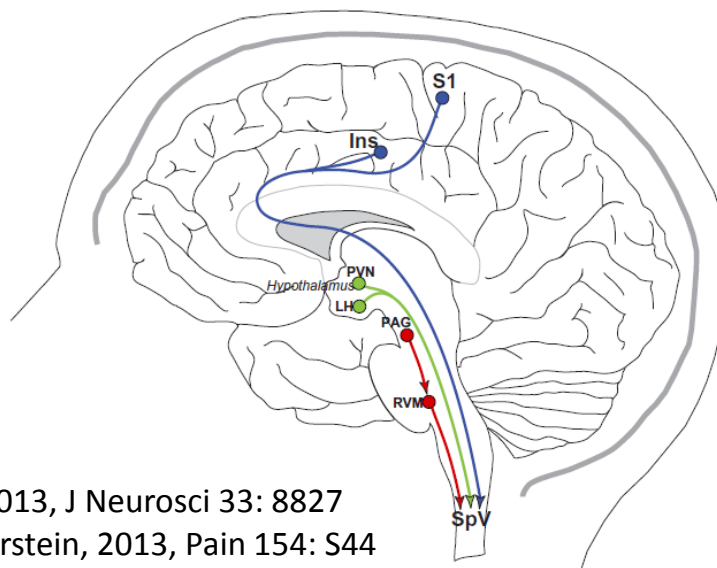


Martins-Oliveira *et al.*,
Pain 2016;167:1666

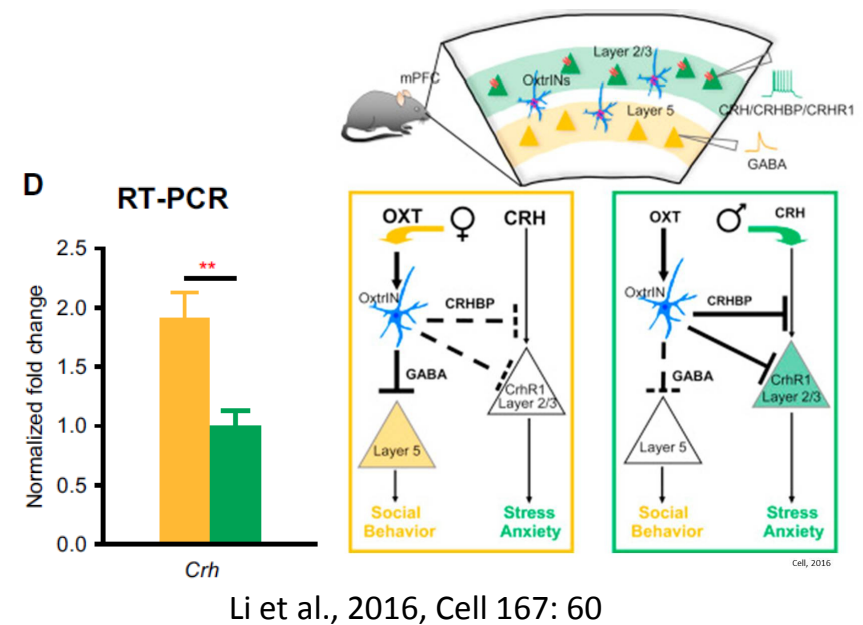
Slide from Peter Goadsby

CRH & Migraine?

- CRH is a stress hormone released by the PVH, which sends projections to spinal trigeminal nucleus
- Sexual dimorphism. CRH levels in PVH are twice as high in female & actions are inhibited by oxytocin in males, but not females

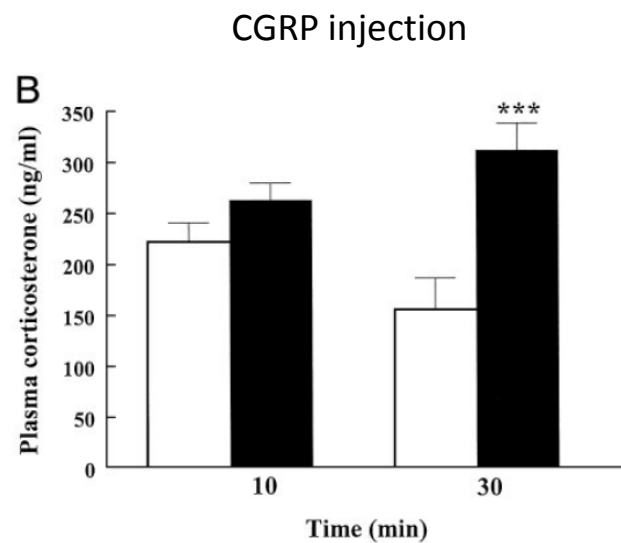


Robert et al., 2013, J Neurosci 33: 8827
Nosedá and Burstein, 2013, Pain 154: S44

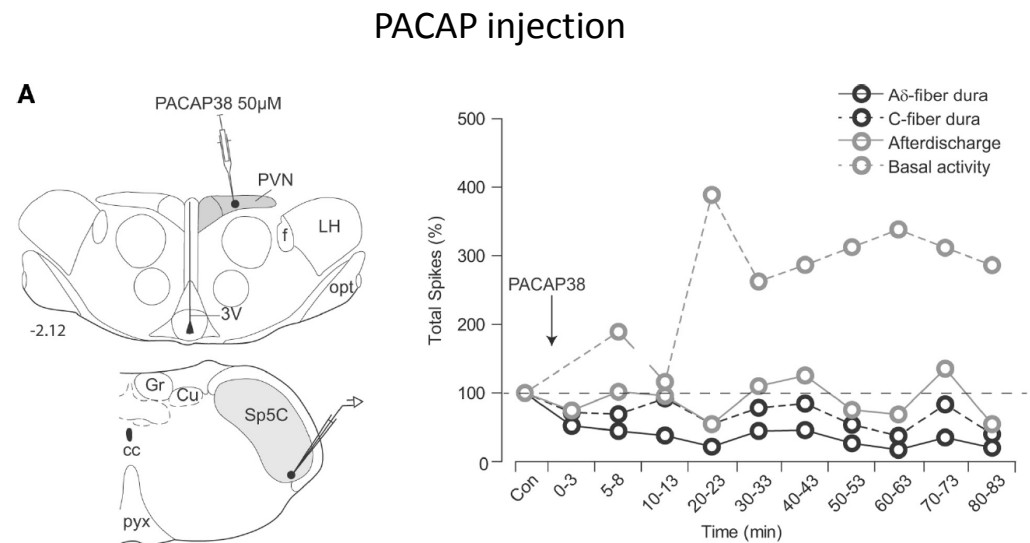


CRH links with CGRP and PACAP

- CGRP injection in PVH induces CRH-dependent release of ACTH, corticosterone
- PACAP injection in PVH activates spinal trigeminal nucleus



Dhillon et al., 2003, Endocrinology 144:1420



Robert et al., 2013, J Neurosci 33: 8827

Conclusion

- Given the evidence for CGRP and the emerging evidence for other peptides...
- It seems likely that altered neuropeptide actions may be a general theme underlying the heightened sensory state of migraine



<http://io9.gizmodo.com/5752351/zapping-the-brain-sparks-bright-ideas>

Acknowledgments

Adisa Kuburas

Brandon Rea

Bianca Mason

Levi Sowers

Anne-Sophie Wattiez

Connor Castonguay

Bennett Robertson

Former members

Paul Durham

Ana Recober

Eric Kaiser



Collaborators:

- Randy Kardon (U Iowa)
- Pieter Poolman (U Iowa)
- Leon Garcia-Martinez (Alder)
- Minyan Wang (Xi'an Jiaton-Liverpool Univ)
- Mark Chapleau (U Iowa)

