Overview of Neuropeptides: Awakening the Senses?

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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
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

<table>
<thead>
<tr>
<th>Connected to migraine?</th>
<th>Other families</th>
</tr>
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<tbody>
<tr>
<td><strong>CGRP:</strong> CGRP (α, β), calcitonin, amylin, adrenomedullin (AM1,2)</td>
<td>Opioids: enkephalins, dynorphin, endorphins, nociceptin</td>
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<td><strong>Glucagon/secretin:</strong> PACAP, VIP, glucagon, secretin, GHRH, GIP</td>
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<td><strong>Vasopressin/ oxytocin</strong></td>
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<td><strong>F- and Y-amides:</strong> NPY, PYY, NPFF</td>
<td>GRP, neuromedin</td>
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<td><strong>Tensins:</strong> angiotensin, neurotensin, bradykinin</td>
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<td><strong>Family-less:</strong> orexins, MCH, TRH, PTHrP, CART, AGRP, prolactin, diazepam-binding inhibitor peptide, etc</td>
<td>Galanins</td>
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<td>Gonadotropin releasing hormones</td>
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<td>Neuropeptide B/W/S</td>
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[http://www.neuropeptides.nl/tabel%20neuropeptides%20linked.htm](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.

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 =2x 10^6 cubic nm, 2x 10^-18 liter/vesicle
  • 10 mmol/l x 2 x10^-18 l= 20x 10^-18 mmol = 2 x 10^-20 mol/vesicle
  • 2 x 10^-20 mol x 6x10^23 molec/mol= 1.2x 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
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.
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

## Connected to 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?

Slide modified from Peter Goadsby
NPY & Trigeminovascular System

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

Slide from Peter Goadsby

Martins-Oliveira et al., Pain 2016;167:1666
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
Noseda and Burstein, 2013, Pain 154: S44

Li et al., 2016, Cell 167: 60
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

Dhillo 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
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