Hypothalamus and Posterior Pituitary

- Hypothalamus and posterior pituitary hormones, secretion, function and regulation of OT and VP: Countercurrent mechanism and the effect of AVP on collecting ducts. Mechanism of action and control of AVP secretion: osmotic stimulation, baroregulation, other cellular actions. AVP pathologies: hypothalamic / nephrogenic diabetes insipidus (DI), SIADH, gene mutation in familial DI.

- Overview of neurohormones to be expanded in later lectures: Anterior pituitary melanotropic hormones (ßEND, MSH) and their secretion, function and regulation. MSH effects on pigmentation and food intake, species variability, regulation, rhythms, receptors, mechanism of action. ßEND central and peripheral effects, action mechanism.

- Overview of neurohormones to be expanded in later lectures: Pineal hormones (melatonin) and their secretion, function and regulation. Melatonin: biosynthesis, N-acetyltransferase activity and rhythms, light - dark cycle, physiological functions, sleep, behavioral rhythmicity, reproduction, thermoregulation.

Introduction

Hormones and “story lines”

For each hormone, the student should know
1. Its cell of origin
2. In chemical nature, including
   a. Distinctive features of its chemical composition
   b. Biosynthesis
   c. Whether it circulates free or bound to plasma proteins
   d. How it is degraded and removed from the body
3. Its principal physiological actions
   a. At the whole body level
   b. At the tissue level
   c. At the cellular level
   d. At the molecular level
   e. Consequences of inadequate or excessive secretion
4. What signals or perturbations in the internal or external environment evoke or suppress its secretion
   a. How those signals are transmitted
   b. How that secretion is controlled
   c. What factors modulate the secretory response
   d. How rapidly the hormone acts
   e. How long it acts
   f. What factors modulate its action
Introduction

Hormones and “story lines”

Posterior Pituitary Hormones

- Hypothalamic connection
- Oxytocin (OT)
- Vasopressin (AVP, ADH)
- AVP, blood pressure and water control

<table>
<thead>
<tr>
<th>Chemical characteristics of vasopressin and oxytocin</th>
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<tbody>
<tr>
<td>Agonists: vasopressin</td>
<td>Oxytocin</td>
</tr>
<tr>
<td>Agonists: AVP</td>
<td>Oxytocin</td>
</tr>
<tr>
<td>PVN, SON, hypophyseal tract</td>
<td></td>
</tr>
<tr>
<td>Posterior pituitary</td>
<td>AVP = ADH</td>
</tr>
<tr>
<td>OT</td>
<td></td>
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<tr>
<td>Venous outflow</td>
<td>Arterial inflow</td>
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<tr>
<td>Paraventricular nucleus</td>
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<tr>
<td>Supraoptic nucleus</td>
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<tr>
<td>Cell bodies of neurons that produce posterior pituitary hormones</td>
<td></td>
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</tbody>
</table>
Posterior Pituitary Hormones

- Hypothalamic connection
- Oxytocin (OT)
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Inputs and outputs to hypothalamic integration centers (Σ) like PVN, SON

Peripheral info reaches brain integration centers through nervous system
Posterior Pituitary Hormones

- Hypothalamic connection

- Oxytocin (OT)

- Vasopressin (AVP, ADH)

- AVP, blood pressure and water control

Peripheral afferent information also reaches brain integration centers through the vascular system (e.g., to osmo-receptors)

Hypothalamic connection

Oxytocin (OT)

Vasopressin (AVP, ADH)

AVP, blood pressure and water control

AVP / OT are nonapeptides with disulfide bond between cystine residues 1 - 6. Precursors, encoded by distinct but structurally related genes, are processed on route to PP.
Posterior Pituitary Hormones

- **Hypothalamic connection**
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- **AVP, blood pressure and water control**

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Posterior Pituitary Hormones

- **Hypothalamic connection**
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Milk release
Uterine contraction
Vascular smooth muscle
Anterior pituitary
Maternal behavior
Sexual behavior
Feeding behavior

(additional information in the reproduction lectures)
Posterior Pituitary Hormones

- Hypothalamic connection

  - Oxytocin (OT)

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  - AVP, blood pressure and water control

Milk release
Uterine contraction
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Maternal behavior
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(Additional information in the reproduction lectures)

Desmopressin is a synthetic analog of vasopresin
Posterior Pituitary Hormones

- Hypothalamic connection
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AVP main effect is antidiuresis but the “driving force” is the kidney medullary countercurrent mechanism
Posterior Pituitary Hormones

- Hypothalamic connection
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AVP main effect is antidiuresis but the “driving force” is the kidney medullary countercurrent mechanism

- kidney, nephron, medulla
- counter-current mechanism
- descending, ascending loop of Henle
- gradient, diuretics AVP / ADH effect
- AQP (1-4)
Posterior Pituitary Hormones

- Hypothalamic connection
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ADH receptors have 7-tm domains characteristic of GPCR: V1a (hepatic) and V1b (AP) act through IP3 to mobilize Ca; the V2r (kidney) coupled to AC (V2r, Gs, AC, cAMP, PKA, AQP2) has 48% homology with OTr; V3 is expressed in AP
Posterior Pituitary Hormones

- Hypothalamic connection
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Plasma and urine osmolality correlated to plasma AVP

AVP and the AngII system
Posterior Pituitary Hormones

- Hypothalamic connection
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Plasma osmolality, AVP and blood pressure

Plasma osmolality, AVP and blood pressure

Blood volume and plasma osmolality

Hypothalamic connection

Oxytocin (OT)

Vasopressin (AVP, ADH)

AVP, blood pressure and water control
Posterior Pituitary Hormones

- Hypothalamic connection
- Oxytocin (OT)
- Vasopressin (AVP, ADH)

- AVP, blood pressure and water control

AVP, plasma osmolality and plasma volume

Posterior Pituitary Hormones

- Hypothalamic connection
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- Vasopressin (AVP, ADH)

- AVP, blood pressure and water control

Blood pressure, ANP, AVP, others
Posterior Pituitary Hormones

- Hypothalamic connection
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Causes of polyurea and polydipsia

| Hypothalamus | Posterior Pituitary
|--------------|-------------------|
| Primary stimulation of thirst osmoreceptor | Osmotically active
| Primary polypysmia | Vasopressin

Pathologies of water metabolism

- diabetes insipidus is usually caused by destruction or dysfunction of AVP neurons and is treated with AVP analog doses binding V2 but not V1 receptors. A neurogenic origin state will respond to stimulation test but a nephrogenic one will not respond

- excess AVP production results from CNS disease or trauma, drug interactions, or ectopic production by tumors. It cause urine concentration in excess of plasma concentration
  For example, the Syndrome of Inappropriate AntiDiuretic Hormone (SIADH) secretion is caused by excess AVP secretion with still normal renal and adrenal function in spite of hyponatremia, continued renal Na excretion, absence of clinical evidence of volume depletion or edema, and inappropriately high urine osmolality
**Posterior Pituitary Hormones**

- Hypothalamic connection
- Oxytocin (OT)
- Vasopressin (AVP, ADH)
- AVP, blood pressure and water control

Gene mutation in familial diabetes insipidus

Pathologies of water metabolism

**Melanotropin Hormones**

- The POMC precursor
- αMSH and its receptors
- αMSH pathologies

POMC, MSH, βEND, ACTH
Melanotropin Hormones

- The POMC precursor
- αMSH and its receptors
- αMSH pathologies

POMC-mRNA hybridization in rat pituitary

Melanocortin receptors
MC-1, pigmentation
MC-2, adrenal function
MC-3, cardiovascular
MC-4, energy homeostasis
MC-5, exocrine secretion

Alpha MSH and ACTH
Melanotropin Hormones

- The POMC precursor
- αMSH and its receptors
- αMSH pathologies

Melanocortin receptors
- MC-1, pigmentation
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Melanosome movement within melanophores

Alpha MSH on different subtypes of the MC receptor

Alpha MSH on MC-1r and their role on melanosome movement within melanophores
Melanotropin Hormones

- The POMC precursor

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Alpha MSH on MC-1r and their role on activation of melanocyte tyrosinase and melanin synthesis

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Alpha MSH on MC-1r and their role on activation of melanocyte tyrosinase and melanin synthesis
Melanotropin Hormones

• The POMC precursor
  - disperse melanin within melanophore cells (dark)
  - delays extinction of learned-avoidance / food motivated behaviors, antipyretic, anti-inflammatory
  - species variability regarding pars intermedia
  - inhibited by MSH-IF (DA?) and MCH (17aa)
  - expression of its receptor (MC1-R) occurs only in melanocytes. Another receptor (MC3-R, 43% homology) is in hypothalamus and limbic system
  - Melatonin antagonizes MSH on melanocytes
  - blood MSH is higher during day time while melatonin is higher at night time

• αMSH and its receptors
  - Melanocortin receptors MC-1, pigmentation
  - MC-2, adrenal function
  - MC-3, cardiovascular
  - MC-4, energy homeostasis
  - MC-5, exocrine secretion

• αMSH pathologies
  - POMC,aMSH, ßEND
  - AGRP,NPY
  - Leptin
  - Inhibitory inputs to feeding and energy storage
  - (+) stimulatory inputs to feeding and energy storage

Alpha MSH on MC-1r and their role on pigmentation

Alpha MSH on MC-4r and their role on energy metabolism (additional info in food intake lect)
Melanotropin Hormones

• The POMC precursor

• aMSH and its receptors

• aMSH pathologies

Alpha MSH on MC-4r and their role on energy metabolism (additional info in food intake lect)

Melanocortin receptors
MC-1, pigmentation
MC-2, adrenal function
MC-3, cardiovascular
MC-4, energy homeostasis
MC-5, exocrine secretion

Acetylated aMSH inhibits feeding (MC-4r)
ßEND inhibits feeding (μ receptor)
leptin receptors in arc-POMC neurons lower POMC synthesis
AGRP, an antagonist of MC-4 receptors is made in arc NPY neurons

Melanotropin Hormones

• The POMC precursor

• aMSH and its receptors

• aMSH pathologies

Alpha MSH on MC-4r and their role on energy metabolism (additional info in food intake lect)
Melanotropin Hormones

• The POMC precursor

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Melanocortin receptors
MC-1, pigmentation
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MC-4, energy homeostasis
MC-5, exocrine secretion

Alpha MSH on MC-4r and their role on cachexia (additional info in food intake lect)

Table 2. Plasma concentrations of α-MSH in human disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Plasma α-MSH and relation with disease severity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Increased in plasma of CDC III and IV patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced disease progression or death in CDC III</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>and IV patients with greater plasma α-MSH</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>concentrations</td>
<td></td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>Increased in synovial fluid of patients with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>adult and juvenile RA</td>
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<tr>
<td>Acute myocardial</td>
<td>Increased in patients receiving thrombolytic</td>
<td></td>
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<tr>
<td>infarction</td>
<td>agents for AMI or unstable angina</td>
<td></td>
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<tr>
<td>Multiple sclerosis</td>
<td>Increased in patients with greater disability</td>
<td></td>
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<td></td>
<td>scene</td>
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<tr>
<td>Haemodialysis</td>
<td>Increased in patients with detectable plasma</td>
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<td></td>
<td>endotoxins</td>
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<tr>
<td>Sepsis syndrome</td>
<td>Reduced in plasma during critical phase of</td>
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<tr>
<td></td>
<td>sepsis syndrome or septic shock</td>
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<tr>
<td>Parkinson’s disease</td>
<td>Increased in the cerebrospinal fluid of PD</td>
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<tr>
<td></td>
<td>patients</td>
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<tr>
<td>Alzheimer’s disease</td>
<td>Reduced in the brains of AD patients</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: AD, Alzheimer’s disease; AMI, acute myocardial infarction; CDC, Centers for Disease Control; α-MSH, α-melanocyte-stimulating hormone; PD, Parkinson’s disease; RA, rheumatoid arthritis

Alpha MSH and their role on human disorders
Pineal Hormones (melanotonin)

- inhibits MSH and melanocytes directly thus lightening skin color
- also produced in pineal are AVP, TRH, GnRH, T3, CRH, indoles, and β-carbolynes (anxiogenic, block GABAa-receptors by binding their α subunit)
- antgonadotropic effect, explain light related effects on repro (ME receptors)
- light, eye, scn, scg, pineal, melatonin, ME, DA, LHRH
- derived from tryptophan through its conversion to 5HT
- the daily rhythm of melatonin secretion is caused by the daily NAT rhythm
- pineal level of 5HT precursor is low at night, when melatonin synthesis is high
- HIOMT is sensitive to long-term changes in photoperiod (seasonality role)
- photo-transducer / receptor (birds/reptiles), thermoregulation in cold blooded
- circadian rhythms, perch-hopping activity in sparrows, running activity in rats, therapy for jet-lag in humans, over the counter drug (??)
- psychological depression (SAD), light therapy
- reproduction, puberty, testis in rams
- secretion to CSF (??), neurohormones
- pineal recess as bi-directional info road for CNS and melatonin targets (pars tuberalis, ME, scn, retina, AP, gonads)

Additional info on melatonin in the lecture on biological rhythms