Pituitary (AP + PP) and Pineal Glands

- Introduction to hypothalamus, pituitary and pineal function.
- Posterior pituitary hormones (OT, AVP) and their secretion, function and regulation. Countercurrent mechanism and the effect of AVP on collecting ducts. Mechanism of action and control of AVP secretion: osmotic stimulation, baroregulation, additional cellular actions. AVP pathologies: hypothalamic / nephrogenic diabetes insipidus (DI), SIADH, gene mutation in familial DI.
- 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.
- Pineal hormones (melatonin) and their secretion, function and regulation. Melatonin: biosynthesis, N-acetyl transferase 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. Its 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
4. Consequences of adequate or excess secretion:
   a. How those signals are transmitted
   b. How that secretion is controlled
   c. How rapidly the hormone acts
   d. How long it acts
   e. How factors modulate its action
Introduction

Hormones and “story lines”

Components of a hormone response system. Responses produced by hormones generally are sensed by whatever apparatus initiated the secretion and usually decrease further secretion.

Posterior Pituitary Hormones

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

### Chemical characteristics of vasopressin and oxytocin

<table>
<thead>
<tr>
<th></th>
<th>Vasopressin</th>
<th>Oxytocin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecule weight</td>
<td>1364</td>
<td>1307</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>9.5-12 days</td>
<td>9.5-13 days</td>
</tr>
<tr>
<td>Neutrophilic binding protein</td>
<td>Neurophysylin (insulin-stimulated)</td>
<td>Neurophysylin (insulin-stimulated)</td>
</tr>
</tbody>
</table>
Posterior Pituitary Hormones

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

Inputs and outputs to hypothalamic integration centers (⊤) like PVN, SON

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

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

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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
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Positive feedback regulation of oxytocin secretion. (1) Uterine contractions at the onset of parturition apply mild stretch to the cervix. (2) In response to sensory input from the cervix (blue arrows), oxytocin is secreted from the posterior pituitary gland and stimulates (green arrows) further contraction of the uterus, which in turn stimulates secretion of more oxytocin (3), leading to further stretching of the cervix, and even more oxytocin secretion (4), until the fetus is expelled (5).

Milk release
Uterine contraction
Vascular smooth muscle
Anterior pituitary
Maternal behavior
Sexual behavior
Feeding behavior

(Additional information in the reproduction lectures)
Regulation of vasopressin secretion. Increased blood osmolality or decreased blood volume are sensed in the brain or thorax, respectively, and increase vasopressin secretion. Vasopressin, acting principally on the kidney, produces changes that restore osmolality and volume, thereby shutting down further secretion in a negative feedback arrangement. Further details are given in Chapter 9.
Posterior Pituitary Hormones

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

Desmopressin is a synthetic analog of vasopressin

AVP gene also code for its carrier neurophysin
Posterior Pituitary Hormones

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

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

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

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

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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

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AVP and the AgII system

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

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

Plasma and urine osmolality correlated to plasma AVP

Posterior Pituitary Hormones

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

Plasma osmolality, AVP and blood pressure

Plasma osmolality, AVP and thirst
Posterior Pituitary Hormones

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

AVP, blood pressure and water control

<table>
<thead>
<tr>
<th>% blood volume depletion</th>
<th>ADH (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

- AVP, plasma osmolality and plasma volume

Blood volume and plasma osmolality

S ← E
Posterior Pituitary Hormones

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

Blood pressure, ANP, AVP, others

Pathologies of water metabolism
Posterior Pituitary Hormones

- **Hypothalamic connection**
  - 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 a stimulation test but a nephrogenic one will not respond

- **Oxytocin (OT)**
  - excess AVP production results from CNS disease or trauma, drug interactions, or ectopic production by tumors. It cause urine conc. in excess of plasma

- **Vasopressin (AVP, ADH)**
  - 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

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

αMSH and ACTH

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

POMC-mRNA hybridization in rat pituitary
Melanotropin Hormones

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

Melanocortin receptors
- MC-1, pigmentation
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Melanotropin Hormones

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

Alpha MSH on different subtypes of the MC receptor

Alpha MSH on MC-1r and their role on melanosome movement within melanophores
Melanocortin receptors
MC-1, pigmentation
MC-2, adrenal function
MC-3, cardiovascular
MC-4, energy homeostasis
MC-5, exocrine secretion

Melanotropin Hormones

- The POMC precursor

- α-MSH and its receptors

- α-MSH pathologies

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

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

Melanotropin Hormones

- The POMC precursor

- α-MSH and its receptors

- α-MSH pathologies

Alpha MSH on MC-1r and their role on pigmentation
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**
  - POMC, αMSH, ßEND

- **αMSH pathologies**

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

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Melanotropin Hormones

- **The POMC precursor**

- **αMSH and its receptors**

- **αMSH pathologies**

Alpha MSH on MC-4r and their role on energy metabolism
Melanotropin Hormones

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

Acetylated aMSH inhibits feeding (MC-4r)
ßEND stimulates 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

Alpha MSH on MC-4r and their role on energy metabolism

Melanotropin Hormones

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

Energy Balance

Alpha MSH on MC-4r and their role on energy metabolism
Melanotropin Hormones

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

Alpha MSH on MC-4r and their role on cachexia

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Melanotropin Hormones

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

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(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Increased in plasma of CDC III and IV patients, reduced disease progression or death; CDC III and IV patients with higher plasma α-MSH concentrations</td>
<td>41, 45, 46</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Increased in synovial fluid of patients with adult RA</td>
<td>49</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>Increased in patients receiving thrombolytic agents for AMI or unstable angina</td>
<td>50</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Increased in patients with greater disability score</td>
<td>51</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>Increased in patients with detectable plasma endotoxins</td>
<td>52</td>
</tr>
<tr>
<td>Sepsis syndrome</td>
<td>Reduced in plasma during critical phase of sepsis syndrome or septic shock</td>
<td>44</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>Increased in the cerebrospinal fluid of PD patients</td>
<td>53</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>Reduced in the brains of AD patients</td>
<td>54</td>
</tr>
</tbody>
</table>

*Abbreviations: AD, Alzheimer's disease; HIV; MSH, melanocortin-stimulating hormone; PD, Parkinson's disease; RA, rheumatoid arthritis

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

- 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 GABAα-receptors by binding their α subunit)
- antigonadotropic effect, explain light related effects on repro (ME receptors)
- light, eye, scn, scg, pineal, melatonin, ME, DA, GnRH
- 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)