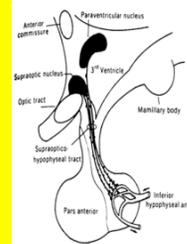


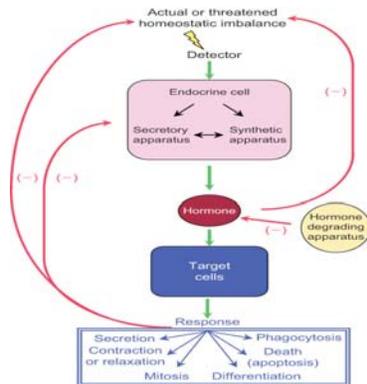
Pituitary (AP + PP) and Pineal Glands



- 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 (β END, MSH) and their secretion, function and regulation. MSH effects on pigmentation and food intake, species variability, regulation, rhythms, receptors, mechanism of action. β END 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"



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

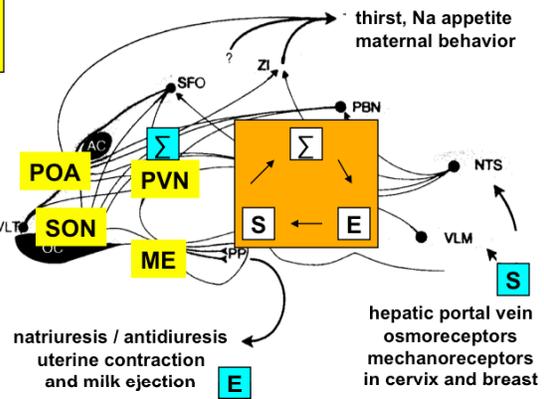
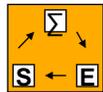
For each hormone, the student should know

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
 - e. Consequences of inadequate or excess 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

Posterior Pituitary Hormones

- Hypothalamic connection**

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

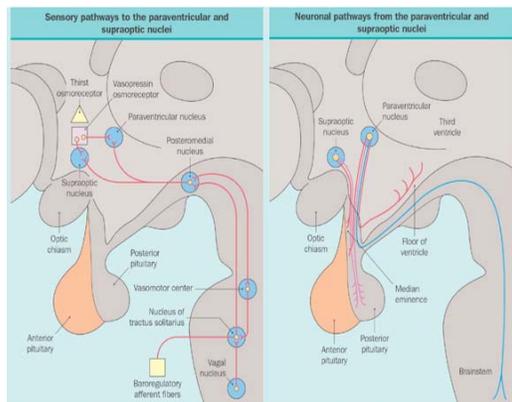
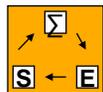


Inputs and outputs to hypothalamic integration centers (Σ) like PVN, SON

Posterior Pituitary Hormones

- Hypothalamic connection**

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

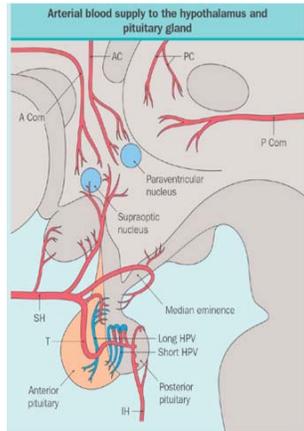
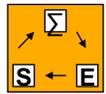


Peripheral info reaches brain integration centers through nervous system

Posterior Pituitary Hormones

Hypothalamic connection

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

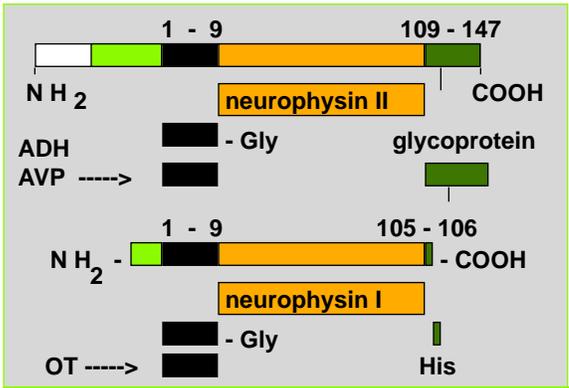
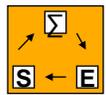


peripheral afferent information also reaches brain integration centers through the vascular system (e.g. to osmoreceptors)

Posterior Pituitary Hormones

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

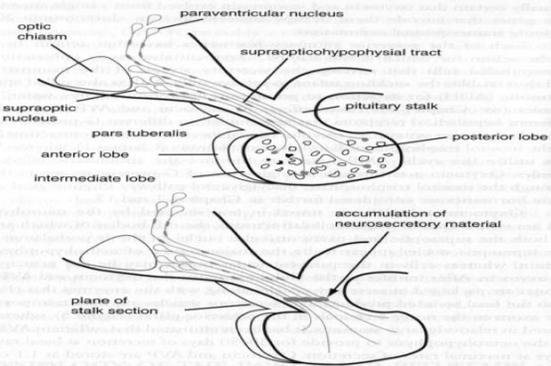
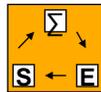
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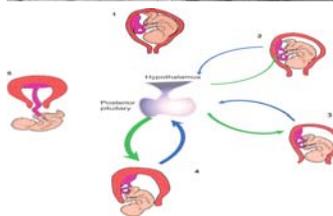
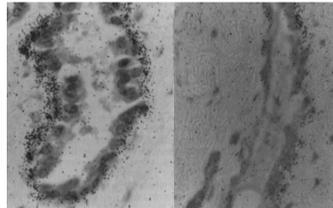
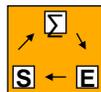
Posterior Pituitary Hormones

- Hypothalamic connection

- Oxytocin (OT)

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- AVP, blood pressure and water control



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

(additional information in the reproduction lectures)

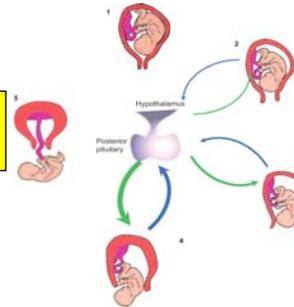
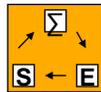
Posterior Pituitary Hormones

- Hypothalamic connection

- Oxytocin (OT)

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- AVP, blood pressure and water control



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
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- Vascular smooth muscle
- Anterior pituitary
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- Sexual behavior
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(additional information in the reproduction lectures)

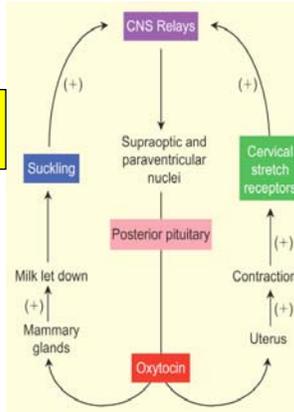
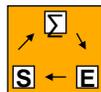
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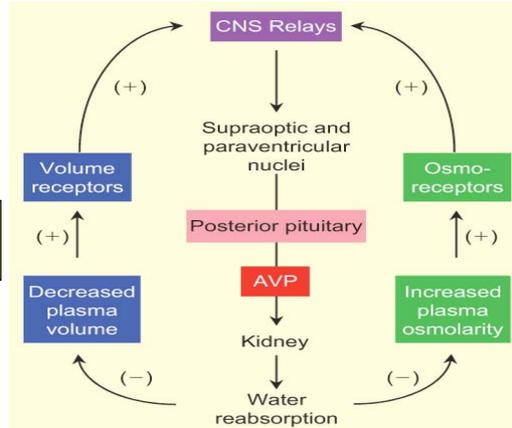
Posterior Pituitary Hormones

- Hypothalamic connection

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- AVP, blood pressure and water control



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.

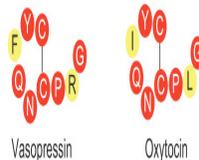
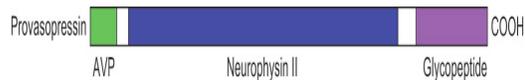
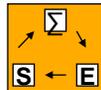
Posterior Pituitary Hormones

- Hypothalamic connection

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Structures of the hormones of the neurohypophysis and their prohormone precursors. Because final processing of the prohormones takes place in the secretory granules, the neurophysins and the glycopeptide fragment are cosecreted with oxytocin or vasopressin, but have no known physiological actions. Amino acid sequences of oxytocin and vasopressin are shown in the single letter code: C = cysteine, Y = tyrosine, F = phenylalanine, I = isoleucine, Q = glutamine, N = asparagine, P = proline, R = arginine, L = leucine, G = glycine.

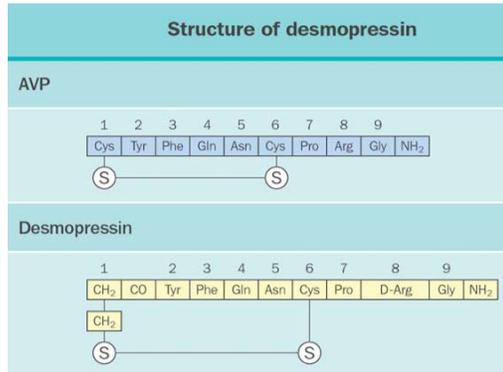
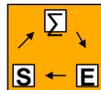
Posterior Pituitary Hormones

- Hypothalamic connection

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- Vasopressin (AVP, ADH)

- AVP, blood pressure and water control



Desmopressin is a synthetic analog of vasopressin

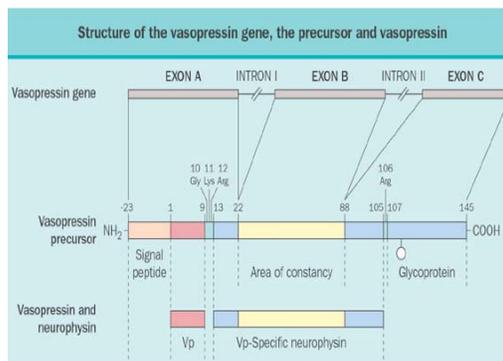
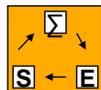
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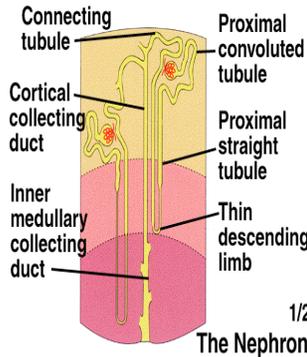
- AVP, blood pressure and water control



AVP gene also code for its carrier neurophysin

Posterior Pituitary Hormones

- Hypothalamic connection
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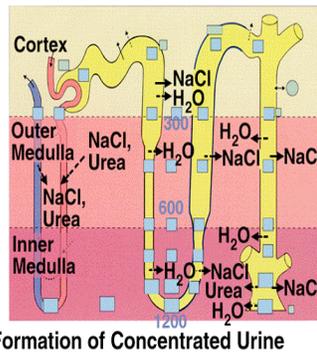
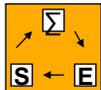


- kidney, nephron, medulla
- counter-current mechanism
- descending, ascending loop of Henle
- gradient, diuretics AVP / ADH effect
- AQP (1-4)

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

Posterior Pituitary Hormones

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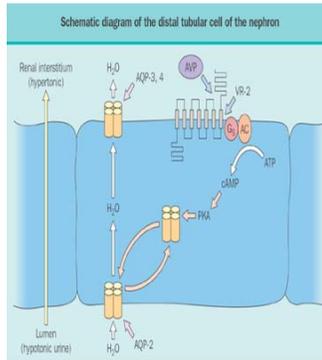
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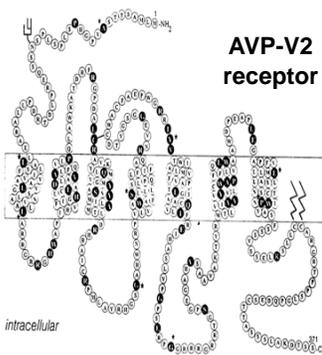
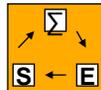
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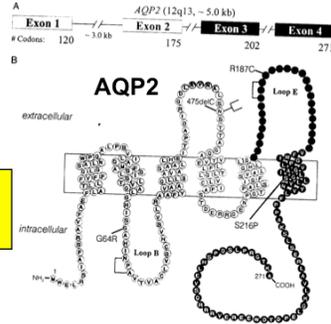
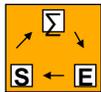
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ADH receptors have 7- tm domains characteristic of GPCR: V1a (hepatic) and V1b (AP) act through IP3 to mobilize Ca; the V2r (kidney) coupled to AC (V2r, Gs, AC, cAMP, PKA, AQP2) has 48% homology with OTR; V3 is expressed in AP

Posterior Pituitary Hormones

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

Vasopressin (AVP, ADH)



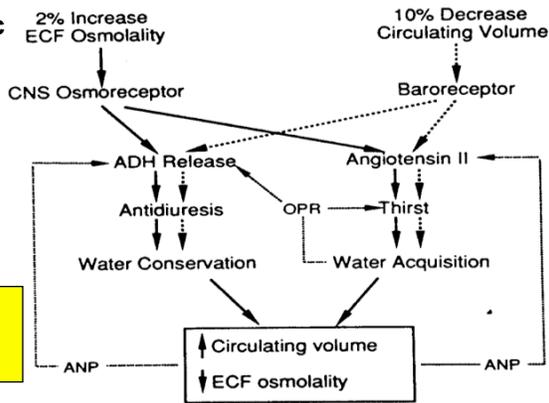
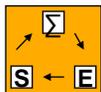
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AVP, blood pressure and water control

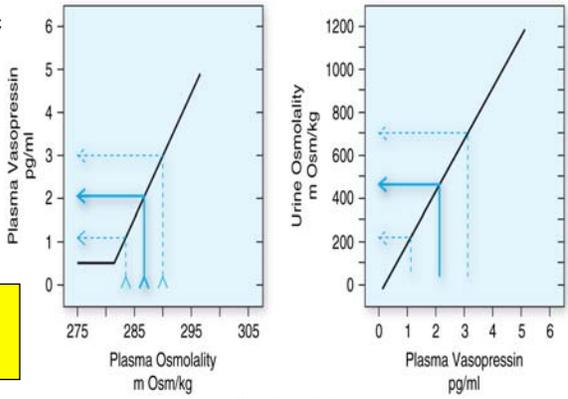


AVP and the AgII system

Posterior Pituitary Hormones

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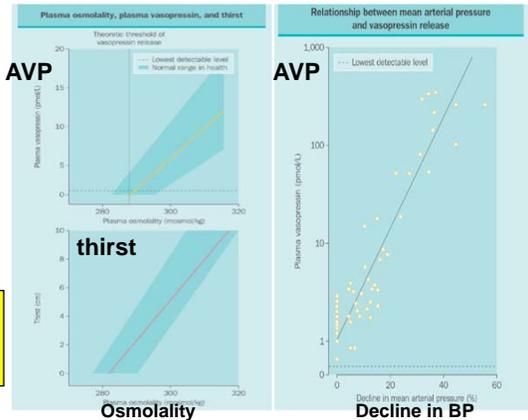
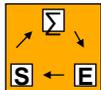
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Plasma and urine osmolality correlated to plasma AVP

Posterior Pituitary Hormones

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• AVP, blood pressure and water control

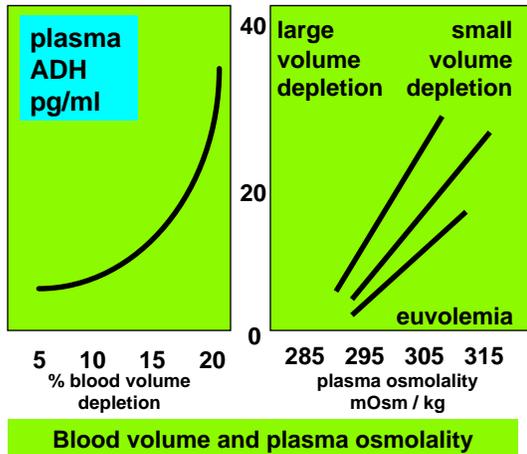


Plasma osmolality, AVP and blood pressure

Posterior Pituitary Hormones

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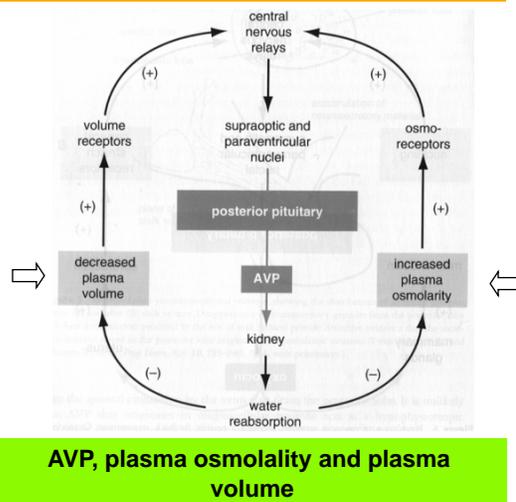
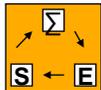
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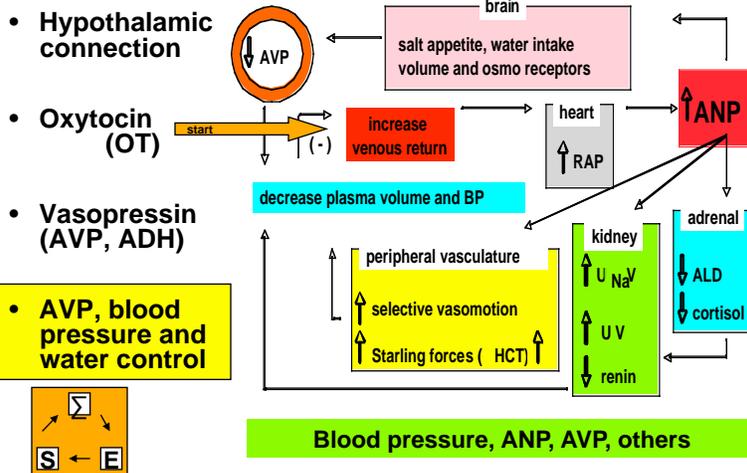
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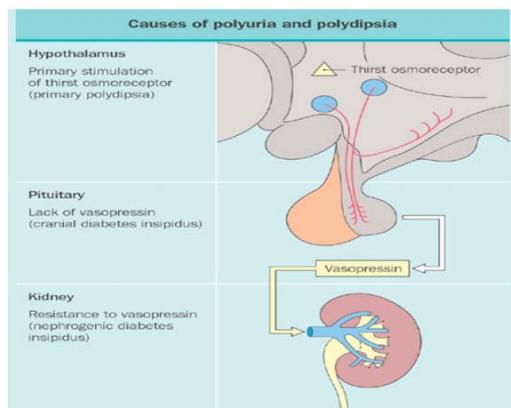
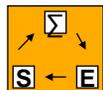
Posterior Pituitary Hormones



Posterior Pituitary Hormones

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AVP, blood pressure and water control



Pathologies of water metabolism

Posterior Pituitary Hormones

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- Oxytocin (OT)
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- AVP, blood pressure and water control



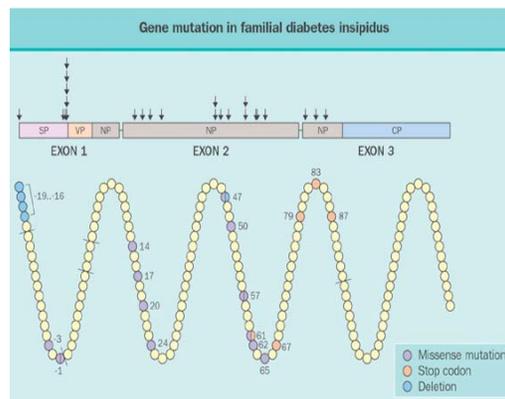
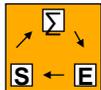
- diabetes insipidus is usually caused by destruction or dysfunction of AVP neurons and is treated with AVP analog doses binding V2 but not V1 receptors. A neurogenic origin state will respond to a stimulation test but a nephrogenic one will not respond
- excess AVP production results from CNS disease or trauma, drug interactions, or ectopic production by tumors. It cause urine conc.. in excess of plasma
- 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

Posterior Pituitary Hormones

- Hypothalamic connection
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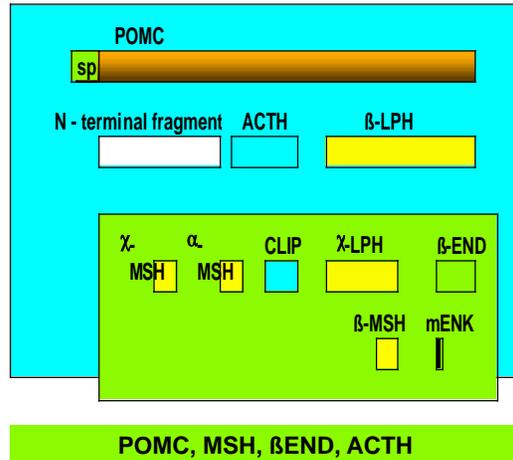
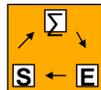
Pathologies of water metabolism

Melanotropin Hormones

- The POMC precursor

- αMSH and its receptors

- αMSH pathologies

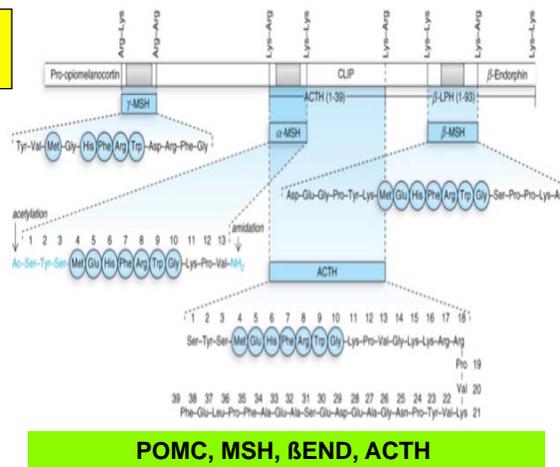
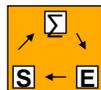


Melanotropin Hormones

- The POMC precursor

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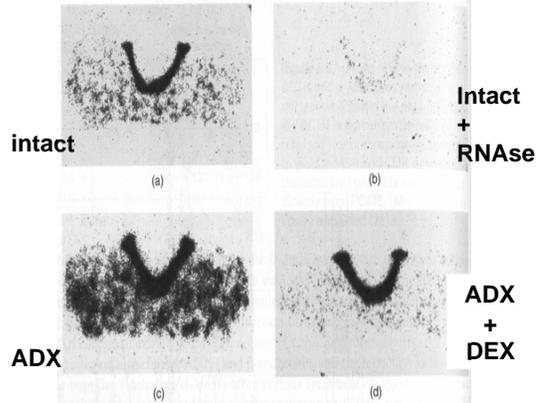
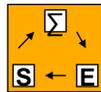


Melanotropin Hormones

- The POMC precursor

- αMSH and its receptors

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POMC-mRNA hybridization in rat pituitary

Melanotropin Hormones

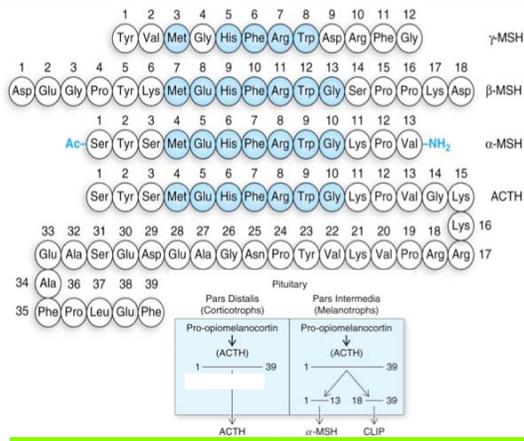
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Melanocortin receptors

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



Alpha MSH and ACTH

Melanotropin Hormones

- The POMC precursor

- **αMSH and its receptors**

- **αMSH pathologies**

Melanocortin receptors

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

TABLE 8.1 Melanocortin Ligands, Receptors, Responses

Ligand	MSH	ACTH	MC*	MC*	MC*
Receptor					
Receptor Subtype	MC1	MC2	MC3	MC4	MC5
Expression	Skin Melanocytes	Adrenal Cortex	Brain	Brain	Exocrine Glands
Response	¹ Melanogenesis	² Steroidogenesis	³ Cardio-vascular?	⁴ Weight Homeostasis	⁵ Secretion

*Melanocortin (MC): Natural Ligand Unknown.

¹Tyrosinase activation and melanin production.

²Cortisol production in the zone fasciculata.

³Variable effects on blood pressure; by modifying sympathetic outflow?

⁴Melanocortins induce satiety (reduce food intake); energy homeostasis.

⁵Lacrimal gland secretion; sebum production/pheromone production.

Alpha MSH on different subtypes of the MC receptor

Melanotropin Hormones

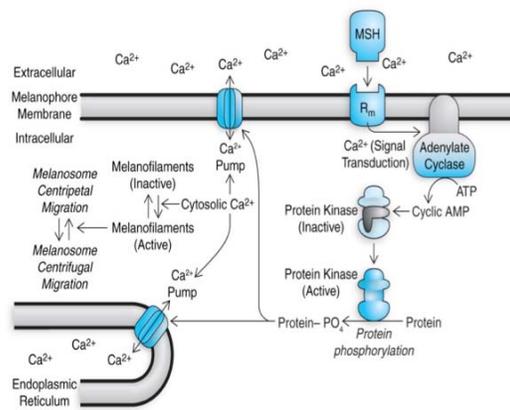
- The POMC precursor

- **αMSH and its receptors**

- **αMSH 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 melanosome movement within melanophores

Melanotropin Hormones

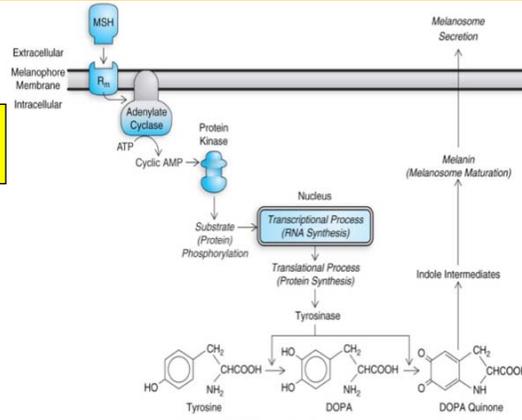
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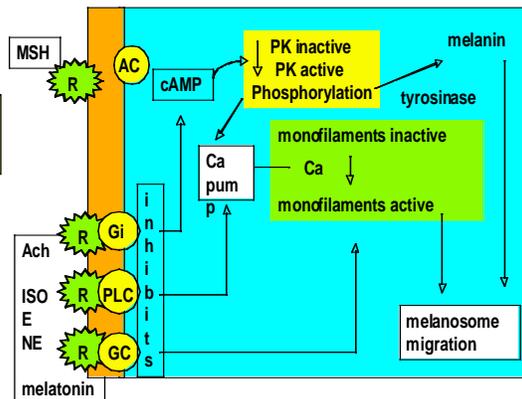
Alpha MSH on MC-1r and their role on activation of melanocyte tyrosinase and melanin synthesis

Melanotropin Hormones

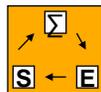
- The POMC precursor

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- aMSH pathologies



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



Melanotropin Hormones

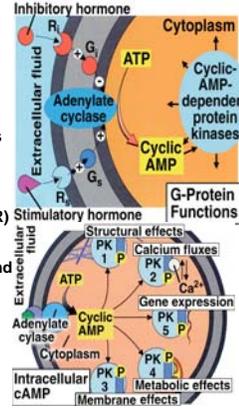
- The POMC precursor

- **aMSH and its receptors**

- **aMSH pathologies**



- 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



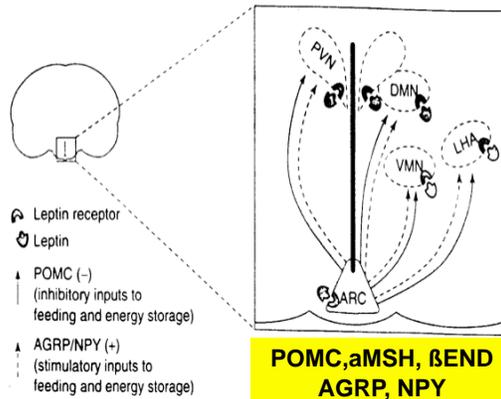
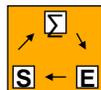
Alpha MSH on MC-1r and their role on pigmentation

Melanotropin Hormones

- The POMC precursor

- **aMSH and its receptors**

- **aMSH pathologies**



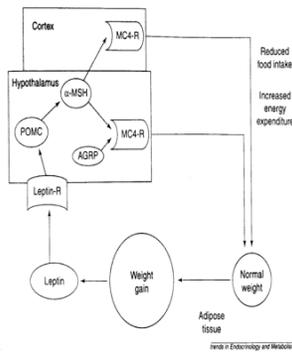
Alpha MSH on MC-4r and their role on energy metabolism

Melanotropin Hormones

- The POMC precursor

- α MSH and its receptors

- α MSH pathologies

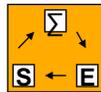


acetylated α MSH inhibits feeding (MC-4r)

β END 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



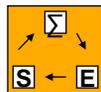
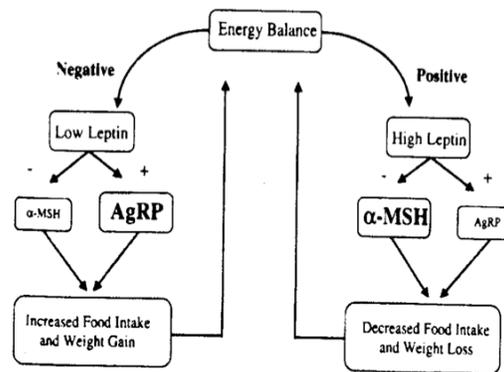
Alpha MSH on MC-4r and their role on energy metabolism

Melanotropin Hormones

- The POMC precursor

- α MSH and its receptors

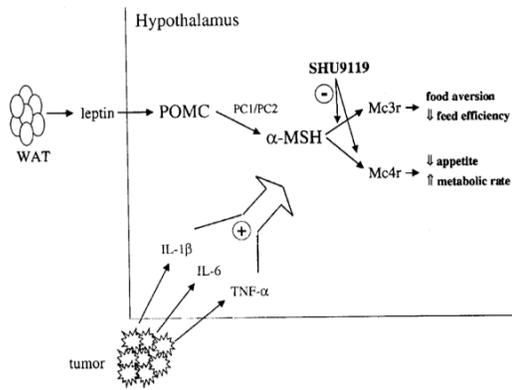
- α MSH pathologies



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

Melanotropin Hormones

- The POMC precursor
- α MSH and its receptors
- α MSH pathologies



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

Melanotropin Hormones

- The POMC precursor
- α MSH and its receptors
- α MSH pathologies



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

Disease	Plasma α -MSH and relation with disease severity	Refs
HIV	Increased in plasma of CDC III and IV patients	11, 45
	Reduced disease progression or death in CDC III and IV patients with greater plasma α -MSH concentrations	46
Rheumatoid arthritis	Increased in synovial fluid of patients with adult and juvenile RA	49
Acute myocardial infarction	Increased in patients receiving thrombolytic agents for AMI or unstable angina	50
Multiple sclerosis	Increased in patients with greater disability score	51
Haemodialysis	Increased in patients with detectable plasma endotoxin	52
Sepsis syndrome	Reduced in plasma during critical phase of sepsis syndrome or septic shock	48
Parkinson's disease	Increased in the cerebrospinal fluid of PD patients	53
Alzheimer's disease	Reduced in the brains of AD patients	54

*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 (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 GABA_A-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)