**Catecholamines**

- Introduction to the adrenal medulla and to the stress response: neural and endocrine components
- Catecholamines: synthesis, secretion, receptors, mechanism of action, general hormonal effects
- Sympathoadrenal roles: intermediary metabolism, thermogenesis, CV, respiratory, link to stress
- Pheochromocytoma as main endocrine pathology: a possible role for medullary peptides

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**Today’s lecture**

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

**Adrenal medulla and its “story lines”**
Introduction

- Adrenal medulla

- Catecholamines

- Sympathoadrenal effects

- Pathologies

- a “fight or flight” array of responses (also known as the stress response) involve the sympathetic nervous system and the adrenal

- stimuli: emotional stress, cold, heat, burns, pH changes, exercise, anoxia, asphyxia, hypotension, hypoglycemia

- responses: increase heart/respiration rate, blood flow to heart, brain, skeletal muscle, liver, glycogenolysis, lipolysis

- secretion: Epi, cortisol, insulin, ACTH, glucagon, renin, melatonin

The sympatho-adrenal system as a faster neuronal and a relatively slower endocrine component
Introduction

- Adrenal medulla
- Catecholamines
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- Pathologies

The sympatho-adrenal system as a faster neuronal and a relatively slower endocrine component

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Both sympathetic and parasympathetic branches of the ANS are involved in the stress response
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Both sympathetic and parasympathetic branches of the ANS are involved in the stress response
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The main integrator of the sympatho-adrenal system is located in the hypothalamus (PVN).
The catecholamines are biogenic amines that serve as neurotransmitters and as hormones.

Catecholamine biosynthesis

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Catecholamine biosynthesis

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TOH is the rate limiting enzyme. It is regulated by CAs feedback inhibition.

- CAs are stored in granules and are released (exocytosis) through stimulus-secretion coupling requiring Ca.
- CAs are catabolized by COMT & MAO (reuptake, degradation, VMA, drugs).

- Cholinergic receptors: nicotinic (curare, “brazilian darts”) and muscarinic (atropine, “belladona”)
- Adrenergic receptors: alpha (NE>E>ISO) and beta (ISO>E>NE) are 7tm/G
- Dopamine receptors: D1 and D2, mainly restricted to brain. Prl control.

The catecholamines are biogenic amines that serve as neurotransmitters and as hormones.
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Catecholamine release

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Vasculature of the adrenal gland enters in the cortex and exit from the medulla
Catecholamine release

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Biosynthetic sequence for epinephrine E and norepinephrine N in adrenal medullary cells. TH = tyrosine hydroxylase; AAD = aromatic L-amino acid decarboxylase (also called DOPA decarboxylase); DBH = dopamine beta-hydroxylase; PNMT = phenylethanolamine-N-methyltransferase.

Catecholamine release

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Relation between arterial input and venous drainage NE levels
Catecholamine degradation occurs predominantly through re-uptake and MAO.
Catecholamine degradation

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Catecholamine degradation occurs predominantly through re-uptake and MAO

Stress and catecholamines

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To visualize the stress response imagine the gazelle running away from the lion
Stress and catecholamines

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Typical responses after stimulation of adrenal medulla

- Adipose tissue: Increased lipolysis
- Liver: Increased glycogenolysis
- Skeletal muscle: Increased twitch

Somebody has to pay the energy bill for the gazelle running away from the lion.

Or you may visualize the gazelle reading this table while running away from the lion.
Stress and catecholamines

- Adrenal medulla: Epi, NE, Ach, DA, glucagon, Gs (β1, β2), Gq (α1)
- Catecholamines: adrenoreceptors are upregulated in absence of stimulation and downregulated under continuous stimulation (e.g., denervation supersensitivity vs continuous isoproterenol)
- Sympathoadrenal effects: adrenoreceptor responses to CAs are affected by gonadal steroids (e.g., uterine contraction due to CAs in E2 vs P4 milieu)
- Pathologies: cortisol is permissive for cAMP metabolic and pressor effects, T3 & sympathoadrenal activity

Stress and catecholamines

- Adrenal medulla: NE released by sympathetic neurons provide localized ANS control, whereas Epi from adrenal is a humoral messenger that provides reinforcement
- Catecholamines: ANS effectors have β, or βplus Ach receptors
- Sympathoadrenal effects: smooth muscle: contract β, relax α, except gut / heart
- Pathologies: generally, βr stimulate and αr inhibit cell secretion

The gazelle’s body know how to follows the adrenoreceptor “almost” rules
Stress and catecholamines

- **Adrenal medulla**
  - both postganglionic sympathetic neurons and adrenal chromaffin cells are directly innervated by cholinergic neurons
  - under stress, adrenal chromaffin enzymes are regulated by both neuronal and endocrine paths
  - TH and DBH are regulated mainly by neuronal transynaptic stimulation, whereas PNMT is mainly under glucocorticoid control (adrenal denervation prevents increases in TH and DBH in response to stress, whereas PNMT still rises)
  - decreases in PNMT and DBH after hypophysectomy can be restored by ACTH or glucocorticoid
  - TOH is raised by ACTH but not glucocorticoids

- **Catecholamines**

- **Sympathoadrenal effects**

- **Pathologies**

The gazelle strongly suggests you remember the above comments

Adrenoreceptors

- **Adrenal medulla**

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- **Sympathoadrenal effects**

- **Pathologies**

Adrenoreceptors are seven transmembrane domain receptors (GPCR)
Adrenoreceptors

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Adrenoreceptors are seven transmembrane domain receptors (GPCR)

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Adrenoreceptors are seven transmembrane domain receptors (GPCR)
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Example of a silent receptor

The Epi receptors is an adrenoreceptor (GPCR) linked to AC
Adrenoreceptors

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Examples of alpha and beta receptors and of their agonist / antagonists

Adrenoreceptors

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All alpha and beta receptors and of their agonist / antagonists interact with a GPCR
Signal transduction

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Most GPCR of the sympathoadrenal system are linked to AC and/or PLC
Regulation of hormone secretion

- Kidney, Juxtaglomerular apparatus
  - Renin
  - Angiotensin
- Pancreatic islets
  - Alpha cells
    - Glucagon
  - Beta cells
    - Insulin
  - Delta cells
    - Somatostatin
- Non-a, b, k cells
  - Pancreatic polypeptide
- Thymus
  - Follicles
    - Thyrotoxins
  - C cells
    - Calcitonin
- Parathyroid
  - Parathyroid hormone
- Gastric antrum and duodenum
  - Gastrin
- Adrenal cortex
  - Zona fasciculata
    - Adrenocortical
  - Zona glomerulosa
- Ovary and placenta
  - Granulosa cells or corpus luteum
    - Progesterone
  - Theca cells
    - Androgens
- Testes
  - Testosterone
- Pituitary
  - Melanin
- Heart, Atrial
  - Atrial natriuretic factor

Regulation of circulation

- Adrenal medulla
  - Baroreceptors
    - Venous
  - Brainstem Sympathetic Centers
    - NTS
  - Arterial Baroreceptors
  - Sympathetic Ganglia
    - Sympathetic Nerves
    - Heart Arterioles
    - Venae Cavae

Baroreceptors provide feedback info to the sympathoadrenal CV central control
Regulation of circulation

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**Regulation of circulation**

The sympathoadrenal CV central control is involved in blood pressure homeostasis

- **Adrenal medulla**
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- **Pathologies**

The sympathoadrenal CV central control is involved in blood pressure homeostasis

- Epi increases both the force and the rate of the heartbeat through stimulation of β-receptors
- particular distribution of vascular smooth muscle adrenoreceptors provides a mechanism for shunting of blood to various compartments during stress
- decreased blood flow to the kidneys reduces glucose clearance from circulation, which might explain the prolonged hyperglycemia induced by CAs
- spleen capsule contraction, induced by Cas through a β-receptor, increases circulating levels of erythrocytes (increase oxygen uptake from lungs)
- Epi enhances blood platelets adhesiveness and reduces clotting time by its action on platelets α receptors
Regulation of fuel mobilization

• Adrenal medulla

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• Pathologies

The sympathoadrenal system is involved in the hormonal control of fuel mobilization.

Effect of insulin-induced hypoglycemia on epinephrine (Epi) & norepinephrine (Nepi).

Changes in blood concentrations of epinephrine and norepinephrine in response to hypoglycemia. Insulin, which produces hypoglycemia, was injected at the time indicated by the arrow.

Effect of insulin-induced hypoglycemia on epinephrine (Epi) & norepinephrine (Nepi).
Regulation of fuel mobilization

- Adrenal medulla
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The hyperglycemic effect of epinephrine is controlled by several organs & processes

- under stress glycemia should be elevated for energy source by brain, heart, skeletal muscle
- Epi stimulates hepatic glycogenolysis (β receptor)
- glycogen, lactic acid, liver (gluconeogenesis)
- Cas inhibit insulin/stimulate glucagon (β recep.)
- hypoglycemia stimulates adrenal Epi secretion by a CNS glucoreceptor (can be blocked by anesthetic in the hypothalamus)
- Epi stimulates lipolysis by stimulating hormone sensitive - lipase and triglyceride - lipase
- FFA as energy source (glucose-sparing action)
- Epi lowers muscle proteolysis and aa release which might be of physiological importance to stress short-term response (β receptor)

The sympathoadrenal CV central control is involved in blood pressure homeostasis
Regulation respiration / thermogenesis

- **Adrenal medulla**
  - bronchial smooth muscle is relaxed in response to catecholamines, through a β-receptor effect
  - relaxation of bronchial smooth muscle dilates bronchial passageways so that increased amounts of air containing oxygen are made available to the blood under conditions of increased exertion

- **Catecholamines**
  - sympathetic system is critical for thermogenesis responses to cold exposure and dietary intake. Fasting suppresses and overfeeding stimulates the sympathetic system
  - thermogenesis associated with muscular activity is a by-product of shivering thermogenesis. Piloerection is controlled by the sympathetic nervous system
  - CAs-induced thermogenesis is mediated by β-r. In BAT there is an increase in sympathetic activity in response to both cold exposure and to overfeeding

- **Sympathoadrenal effects**
  - The sympathoadrenal system is involved in respiration and thermogenesis

- **Pathologies**
  - Pheochromocytomas are tumors that arise from the adrenal medulla
  - Pheochromocytoma & neuroblastoma are in medulla or along the sympathetic chain.
  - I-MIBG scan of a left adrenal pheochromocytoma with superimposed renal outlines
  - Unenhanced computerized tomography scan showing a large left pheochromocytoma with a fluid level (arrow)
Sympathoadrenal pathophysiology

- **Adrenal medulla**
- **Catecholamines**
- **Sympathoadrenal effects**

**Pathologies**

- Pheochromocytomas are tumors that arise from the adrenal medulla.

Pheochromocytomas and neuroblastomas are usually found in adrenal medulla or along the sympathetic chain. They cause severe hypertension, increased basal metabolic rate, rised oxygen consumption, weight loss, psychosis, tremulousness, and increased respiratory rate. TOH inhibitors (aMT) are used as treatment.

- alpha receptor stimulation results in fat storage and ß stimulation causes cellular catabolic metabolism. Individuals with android fat distribution have higher risk for diabetes, hypertension, stroke, ischemic heart disease and early death, than those with a gynecoid distribution.

- ß-blockers are important in hypertension, ischemic heart disease, and arrhythmias.

The sympathoadrenal system is involved in respiration and thermogenesis.