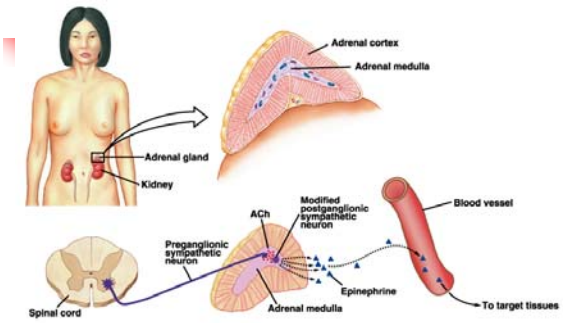
Catecholamines

Adrenal medulla

- The "other" part of adrenal gland
- Neural origin
- Functionally and developmentally part of the sympathetic nervous system, a modified sympathetic ganglion
- Not essential for life
  - mainly reinforces the actions of the sympathetic nervous system

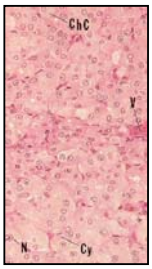


Adrenal medulla

- Cells in cords with reticular fiber network
- Many capillaries
- Large spherical nuclei
- Cytoplasmic granules containing epinephrine or norepinephrine

Histology

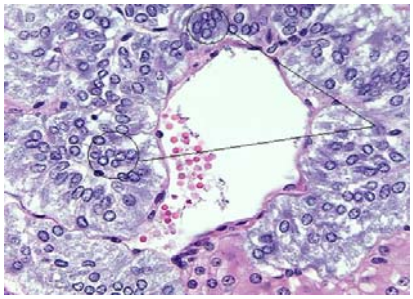
- Pheochromocytes (= chromaffin cells; axonless secretory cells)
  - Name is derived from the observation that their granules turn dark (*pheo-*) when stained with chromic acid
- Epinephrine-producing cells: numerous, weak chromate staining, small, less dense granules
- Norepinephrine-producing cells: fewer, strong staining, large dense granules
- True sympathetic ganglion cells (only a few)



Chromaffin cells

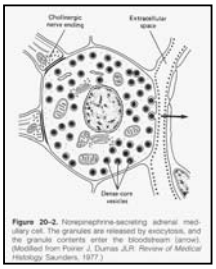
- Receive synaptic input from other neuronal cells
  - Depolarize and generate action potentials in response to sympathetic stimulation
  - Release the stored secretory material in response to depolarization
- Also found in association with:
  - Carotid bodies
  - Liver
  - Heart
  - Kidney
  - Gonads

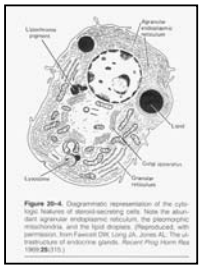
Chromaffin cells



Chromaffin Cells

Catecholamine and steroid producing cells

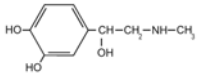




Adrenal medulla – hormones

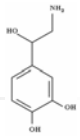
- Catecholamines - the main secretory products of the medulla
  - epinephrine (E; a.k.a. adrenaline) 80%
  - norepinephrine (NE; a.k.a. noradrenaline) (the dominant form at birth)
  - dopamine (DA)
- Endogenous opioids (met-enkephalin)
- NPY, vasopressin
- Adrenomedullin: 52 a.a peptide, related to calcitonin first found in a. medulla, but it is widely distributed among various tissues

Epinephrine (E)



- 1901 – first extracted from adrenal gland of animals
- 1904 – first synthesized by Friedrich Stoltz
- Short-term stress hormone
- Fight-or-Flight response – prepares the body for strenuous activity

Norepinephrine (NE)



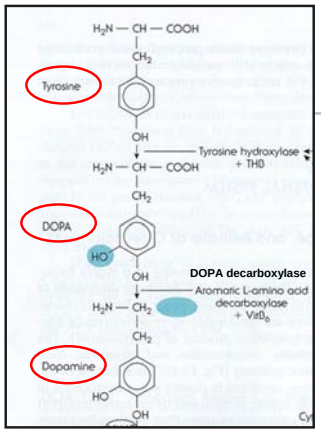
- First synthesized in 1904
  - In 1946 – recognized as a secretory product of the adrenal medulla and a major neurotransmitter of the postganglionic sympathetic nerves
- Local neurotransmitter in the peripheral nerves
- Acts locally and reaches general circulation only when intense activation of the sympathetic nervous system occurs

Synthesis

- The synthsesis of catecholamines in the CNS, sympathetic postganglionic neurons and chromaffin tissue is identical

Precursors of catecholamines

- Phenylalanine – essential amino acid
  - Must be obtained from diet
  - Phenylalanine hydroxylase – enzyme that catalyzes the reaction of phenyalanine to tyrosine
    - Found in liver and nerves
    - Phenylketonuria – deficiency of the enzyme found in 1 out of 200 humans
- Tyrosine – amino acid
  - Not essential because most people can synthesize this from phenylalanine



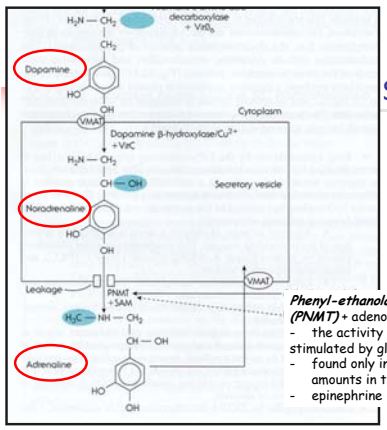
Synthesis

regulated by preggl. neurons and intracellular catecholamine levels:

- acute ↑ in the activity of preexisting enzyme by PKA, PKC and CaM-kinases
- long-term stimulation by upregulating TH expression
- catecholamines suppress TH activity

Tyrosine hydroxylase

- Present in adrenal medulla, brain, and all sympathetically innervated tissues
- Rate-limiting enzyme
- Activated by phosphorylation
- Converts tyrosine into 3,4-dihydroxyphenylalanine (DOPA)



Synthesis

Phenyl-ethanolamine-N-methyltransferase (PNMT) + adenosyl methionine

- the activity and expression of the enzyme stimulated by glucocorticoids,
- found only in the a. medulla, minute amounts in the brain
- epinephrine inhibits PNMT

Storage

- in vesicles
- vesicles contain
  - catecholamines bound to ATP and chromogranin A (49-kD protein)
  - Dopamine β-hydroxylase
- active transport processes keep high concentrations of catecholamines inside the vesicles

Regulated secretion

- In response to sympathetic preganglionic activation → release of acetylcholine → depolarization of chromaffin cells → exocytosis of all the vesicle contents → plasma chromogranin A levels are good indicators of adrenal medulla secretory activity

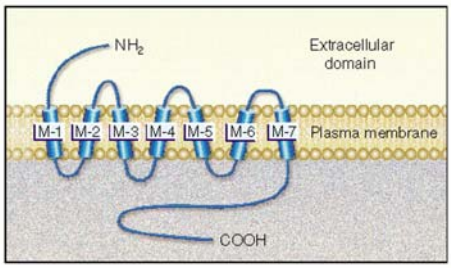
Transport in blood

- Even though E is the primary product of the a. medulla, in the circulation the NE/E ratio is 9:1
- half-life ~ 2 min
- significant amounts bound to albumin

Metabolism of catecholamines

- Synaptic cleft:
  - reuptake into the axon terminals
  - reenter secretory vesicles
  - degraded by MAO
- Degradation by the target cells: by COMT
- Degradation by the liver: by COMT and/or MAO
- Direct filtration into urine (2-10%)

Catecholamine receptors



Catecholamine receptors

- At least 9 catecholamine receptor subtypes
- G protein coupled
- The receptor subtype in a specific tissue determines the effect of catecholamines on that tissue

Catecholamine receptors

- One organ → several receptor subtypes → divergent (often opposite) effects
- The overall effects of catecholamines on a given organ is determined by the balance between the activity levels of the various receptor subtypes

Did you know?

- Catecholamines cannot cross the BBB
- Maternal catecholamines cannot cross the placenta but catecholamines from fetal adrenal medulla are required for cardiovascular response to hypoxia

Adrenergic receptors

Receptor	Effectively Binds	Effect of Ligand Binding	Found in	
Alpha 1	Epinephrine Norepinephrine	Increased free calcium	Most sympathetic target tissues	NE>E
Alpha 2	Epinephrine Norepinephrine	Decreased cyclic AMP	Gastrointestinal tract and pancreas	NE>E
Beta 1	Epinephrine Norepinephrine	Increased cyclic AMP	Heart, muscle kidney	NE=E
Beta 2	Epinephrine	Increased cyclic AMP	Certain blood vessels and smooth muscle of some organs.	E>NE

Biological actions of epinephrine

- Arousal
  - Pupillary dilation
  - Sweating
  - Bronchial dilation
  - Tachycardia
  - Inhibition of smooth muscles in GI tract
  - Relaxation of uterine muscles

Carbohydrate metabolism

- Hyperglycemia (α and β receptor)
  - glycogenolysis↑↑ (in liver and skeletal muscle) → plasma glucose↑↑
  - gluconeogenesis↑↑ → plasma glucose↑↑
  - insulin secretion↓↓ → plasma glucose ↑↑
    - α-receptors inhibit β cell insulin secretion
    - β-receptors stimulate α cell glucagon secretion

Fat metabolism

- Catecholamines cause lipolysis (β receptor)
- The products are used as energy sources
  - Lipolysis ↑ → plasma FFA↑↑ → FFA serves as energy source and source for glucose formation
- A reduced production of NE results in obesity

Protein metabolism

- Protein degradation↓, plasma a.a. levels↓
  - E acting on β-adrenoreceptors decreases the release of amino acids from muscle via proteolysis inhibition
- This increases the energy available

Basal metabolic rate

- Increased → body temperature ↑↑

Cardiovascular effects

- E causes an increase in cardiac output via β-adrenoreceptors
- ↑ Heart rate
- ↑ Vasoconstriction
- Organs shunt blood to important areas when their β -adrenoreceptors are stimulated
- Major organs have α-receptors
- Hematocrit increases when the spleen capsule is contracted α -receptors
- Decreased clotting time by acting on platelet α -receptors

Respiratory effects

- Catecholamines cause bronchodilation
- Only α -adrenoreceptors are present

Medical uses of epinephrine

- α-agonist: isoproterenol used to dilate bronchi for treatment of asthma
- β-antagonist: propranolol used to ↓ cardiac output for treatment of hypertension
- Used as a stimulant in cardiac arrest
- Used as a vasoconstrictor in shock
- Treatment for anaphylaxis – serious and rapid allergic reactions
- Used to lower intra-ocular pressure in treatment of glaucoma

Dopamine receptors

- 5 major receptors, several receptor subtypes
- all G protein-coupled
  - D1: cAMP↑
  - D5: cAMP↑
  - D2: cAMP↓
  - D3: cAMP↓
  - D4: cAMP↓

Dopamine effects

- Primary prolactin-inhibitory hormone
- Role in movement
  - Critical to the way brain controls movement
  - Crucial part of the basal ganglia motor loop
  - ↓ DA in nigrostriatal pathway causes Parkinson's disease
    - Lose the ability to execute smooth and controlled movements

Did you know?

- D4 is upregulated 6-fold in the brain of schizophrenics
- Disruption in Dopaminergic pathway linked to psychosis and schizophrenia
- Antipsychotic drugs - Phenothiazines - D receptor antagonists
- Cocaine and amphetamines (↑ DA levels) can lead to psychosis

Disorders of catecholamines

- Low levels have no discernable pathologic effect
  - Adrenal catecholamines non-essential for life
- High levels lead to hypertension
  - Usually caused by a tumor called pheochromocytoma
  - Can be detected by measuring plasma hormone levels or by testing the urine for the metabolites VMA and metanephrines
  - Clonadine supression test
  - Chromogranin A test

Pheochromocytomas

- Tumors arising from chromaffin cells in the sympathetic nervous system
  - Release E or NE (or both)
  - May release DA
  - May produce a wide variety of peptides (ADH, somatostatin, ACTH, β-endorphin, lipotropin, etc.)
  - Produce 500X normal epinephrine in plasma

Pheochromocytoma

- Can be found anywhere chromaffin cells are found
  - Sympathetic ganglia
  - Nerve plexus
  - Nerves
  - 95% found in abdomen
    - 85% found in adrenal medulla
    - In or around kidney
    - Bladder wall
  - Heart

Pheochromocytoma

- Sudden releases of hormone causing sudden "attack"
- Symptoms reflect effects of excess NE and E
  - Hypertension
  - Tachycardia
  - Sweating
  - Tremors
  - Palpitations
  - Nervousness
  - Weight loss
  - Hyperglycemia

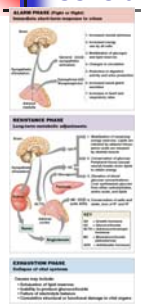
Did you know?

- Ratio of E/NE:
  - Humans: 10:1
  - Cats: Equal
  - Whales: 90-100% NE
- The E/NE ratio also changes with age
  - No E early in development
  - By one year of age there are equal amounts of NE and E
  - E/NE ratio increases thereafter

Did you know?

- NE levels were greater (28% day, 75% night) in older men who had less stage 4 and REM sleep and more wakefulness at night
  - The aging effect on sleep might be associated with increased sympathetic nervous system activity

General adaptation syndrome (GAS)



- Also called stress response
- How bodies respond to stress-causing factors
- Is divided into 3 phases:
  - alarm phase
  - resistance phase
  - exhaustion phase

Alarm Phase

- Is an immediate response to stress
- Is directed by autonomic nervous system
- Energy reserves mobilized (glucose)
- "Fight or flight" responses
- Dominant hormone is epinephrine

7 Characteristics of Alarm Phase

1. Increased mental alertness
2. Increased energy consumption
3. Mobilization of energy reserves (glycogen and lipids)
4. Circulation changes:
   - increased blood flow to skeletal muscles
   - decreased blood flow to skin, kidneys, and digestive organs

7 Characteristics of Alarm Phase

5. Drastic reduction in digestion and urine production
6. Increased sweat gland secretion
7. Increases in blood pressure, heart rate, and respiratory rate

Resistance Phase

- Entered if stress lasts longer than few hours
- Dominant hormones are glucocorticoids
- Energy demands remain high
- Glycogen reserves nearly exhausted after several hours of stress

Effects of Resistance Phase

1. Mobilize remaining lipid and protein reserves
2. Conserve glucose for neural tissues
3. Elevate and stabilize blood glucose concentrations
4. Conserve salts, water, and loss of K^+, H^+

Exhaustion Phase

- Begins when homeostatic regulation breaks down
- Failure of one or more organ systems will prove fatal
- Mineral imbalance

But…a little stress goes a long way

JCI Feb 2007

- The integrated stress response prevents demyelination by protecting oligodendrocytes against immune-mediated damage.
- A little stress is good: IFN-gamma, demyelination, and multiple sclerosis.