PATHOPHYSIOLOGY AND MECHANISMS OF RADIOPHARMACEUTICAL LOCALIZATION

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20140915 morning meeting

The Pathophysiological basis of Nuclear Medicine 2nd ed. Springer.

The mechanisms of radioisotope localization

1. Isotope dilution — In vivo, MUGA, RBC scan
2. Capillary blockade — MAA lung perfusion
3. Physicochemical adsorption — MDP bone scan
4. Cellular migration and sequestration — WBC scan, denatured RBC spleen scan
5. Membrane transport — Xe-133 ventilation
   - Simple diffusion — HMPAO/ECD brain perfusion scan
     - Diffusion and intracellular metabolism/binding — Tc-99m MIBI
     - Diffusion and mitochondrial binding
     - Diffusion and increased capillary and plasma membrane permeability — Gallium
   - Facilitated diffusion — FDG, IDA derivatives
   - Active transport — Radioiodine, pertecnetate, TlCl, Rb +
   - Phagocytosis — SC
   - Receptor-mediated endocytosis — Gallium
6. Metabolic Substrates and Precursors — FDG
   - Precursors: Radiolabeled Amino Acids — Amino acids
7. Tissue Hypoxia — F-MISO

8. Cell Proliferation Ribonucleic acids, ex: F-18 FLT
9. Specific Receptor Binding
   - Radiolabeled Peptides SST analogues, VIP
   - Steroid Hormone Receptors
   - Adrenergic Presynaptic Receptors and Storage
   - LDL Receptors
   - Radiolabeled Antibodies
10. Imaging Gene Expression

Specific Receptor Binding

- Radiolabeled Peptides
  - SST receptors
  - VIP receptors
- Steroid Hormone Receptors
- Adrenergic Presynaptic Receptors and Storage
- LDL Receptors
- Radiolabeled Antibodies

Specific Receptor Binding—Steroid hormone receptors

- Steroid, cholesterol, adrenocortical hormones
- Application of steroid hormone imaging agents
  - Breast cancer
- ER & PR agents
  - 16α-F-18 fluoro-17β-estradiol (FES): ER
  - 21-F-18 fluoro-16α-ethyl-19-norprogesterone (FENP): PR
  - I-123 cis-11β-methoxy-17α-iodovinylestradiol (Z-[123 I]MIVE): ER, in breast cancer

  → Passive diffusion, bind to steroid receptors in the nucleus

Steroid, cholesterol & adrenocortical hormones

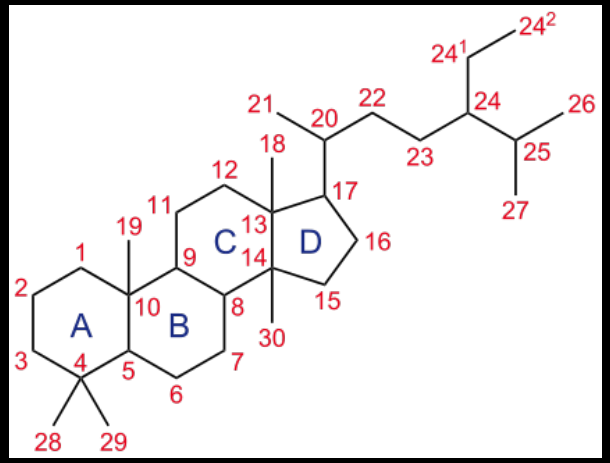
一類化合物
- Steroid
  - An organic compound of a characteristic four cycloalkane rings
    - Cycloalkane 環烷烴
      - Cyclic alkane (通式: $C_nH_{2(n+1-g}$, n: 碳原子個數, g: 環數)
      - Alkane 烷烴
        - A saturated hydrocarbon compound, consisting only of hydrogen and carbon atoms and all bonds are single bonds. (通式: C_nH_{2n+2} ，n: 碳原子個數)
          - Methane 甲烷, Ethane 乙烷, Propane 丙烷, Butane 丁烷, Pentane 戊烷, Hexane 己烷…

直鏈烷與環烷，相對應的命名

Propane 環丙烷, Butane 環丁烷, Pentane環戊烷, Hexane 環己烷

from: Wikipedia, Steroid/ Cycloalkane/ Alkane

Steroid, cholesterol & adrenocortical hormones



- Steroid (cont.)
  - 17 carbon, four cycloalkane: three cyclohexane rings (A, B and C rings) and one cyclopentane ring (the D ring)
  - Examples of steroid:
    - Lipid cholesterol
    - Sex hormones (estradiol, testosterone)
    - Bile acids
    - Drugs (ex: dexamethasone)

from: Wikipedia, Steroid/ Cycloalkane/ Alkane

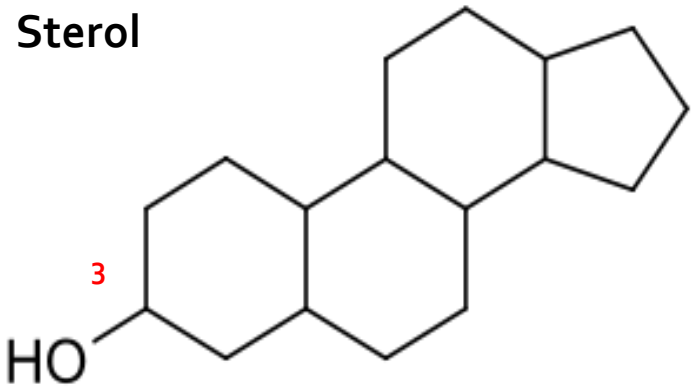
Steroid, cholesterol & adrenocortical hormones

一類化合物
- Sterol (a.k.a. steroid alcohols) 甾醇
  - A subgroup of steroids with an -OH group at the 3-position of the A-ring
  - occur naturally in plants, animals, and fungi, with the most familiar type of animal sterol being cholesterol

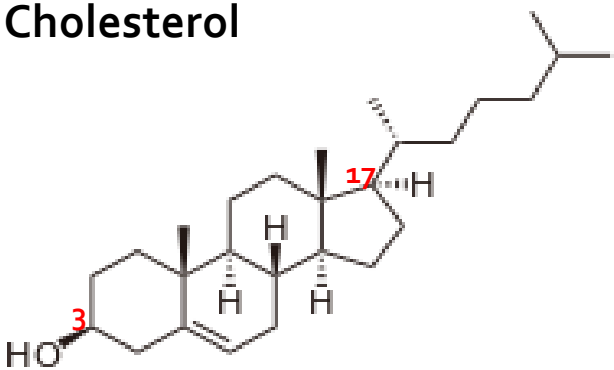
一種化合物
- Cholesterol
  - It is a sterol and is biosynthesized by all animal cells because it is an essential structural component of animal cell membranes that is required to maintain both membrane structural integrity and fluidity
  - C-17: functional group
  - Precursors of sex hormones

from: Wikipedia, choleterol, steroid

Sterol

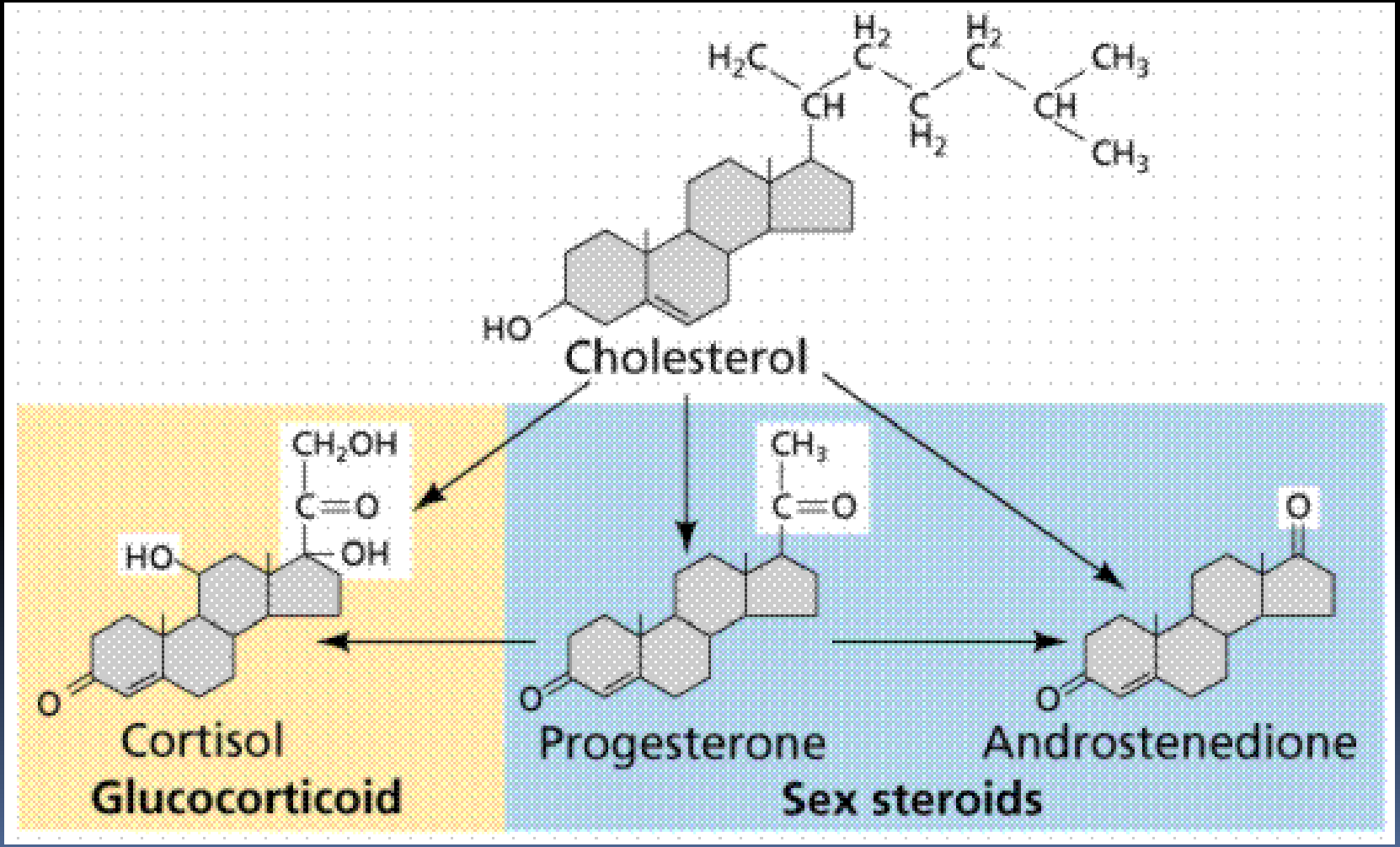


Cholesterol



from: Wikipedia, choleterol, steroid

Relationship between:
Steroid, cholesterol and adrenocortical hormones

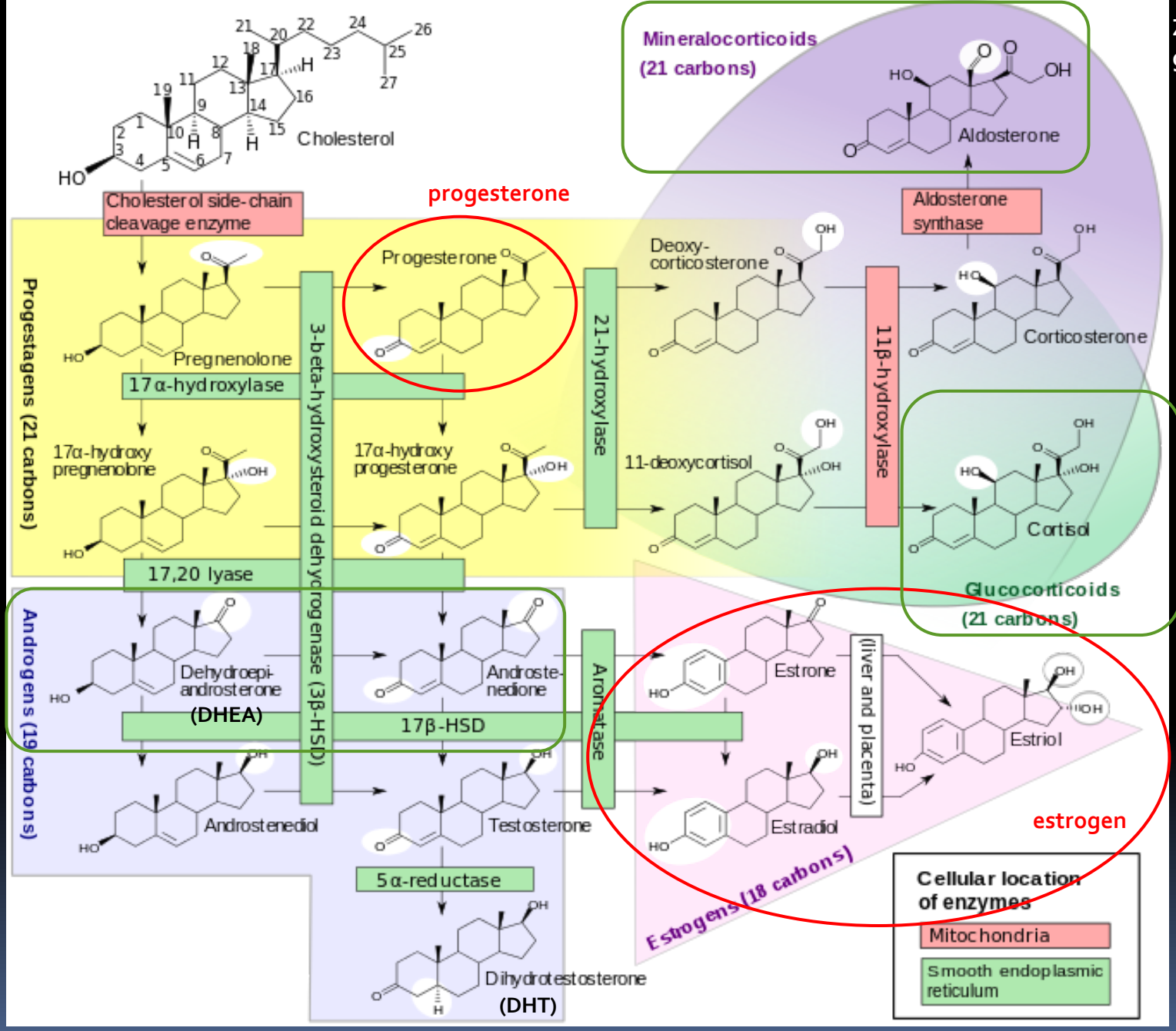


from: Estrella Moutain Community college

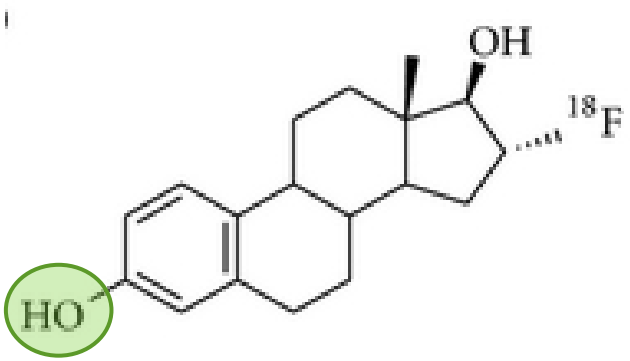
Zona glomerulosa

Zona fasciculata

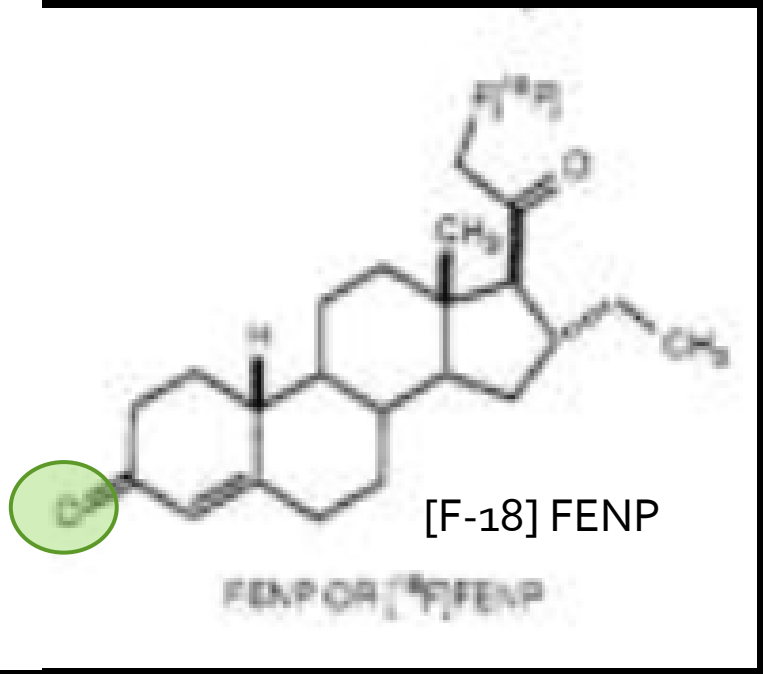
Zona reticularis



From: Wikipedia, steroid



[^{18}F] FES



[F-18] FENP

ER

PR

Z-[123 I]MIVE

ER

SPECT

F-18 FES PET
Potential for detecting ER(+) metastatic foci of breast ca.

Specific Receptor Binding–

Adrenergic presynaptic receptors & storage

脫羧

- APUD: amine precursor uptake and decarboxylation
- a group of cells of common embryonic origin that secrete most of the body's hormones, with the exception of steroids. APUD cells comprise both specialized neurons and other endocrine cells. These cells synthesize structurally related polypeptides and biogenic amines. The acronym APUD derives from the fact that polypeptide production is linked to the uptake of a precursor amino acid and its decarboxylation in the cell to produce an amine.
- Peptide hormones , ex: insulin, ACTH, glucagon and antidiuretic hormone
- Amine hormones ,ex: dopamine, norepinephrine, serotonin and histamine

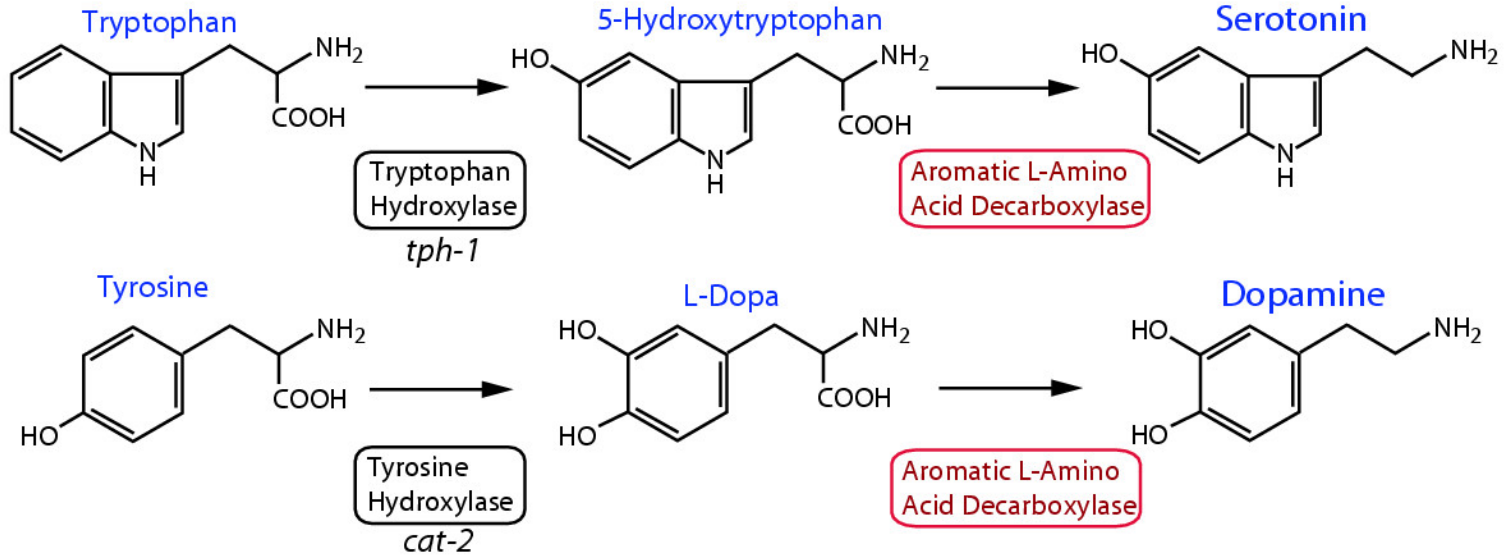
From: Answers.com

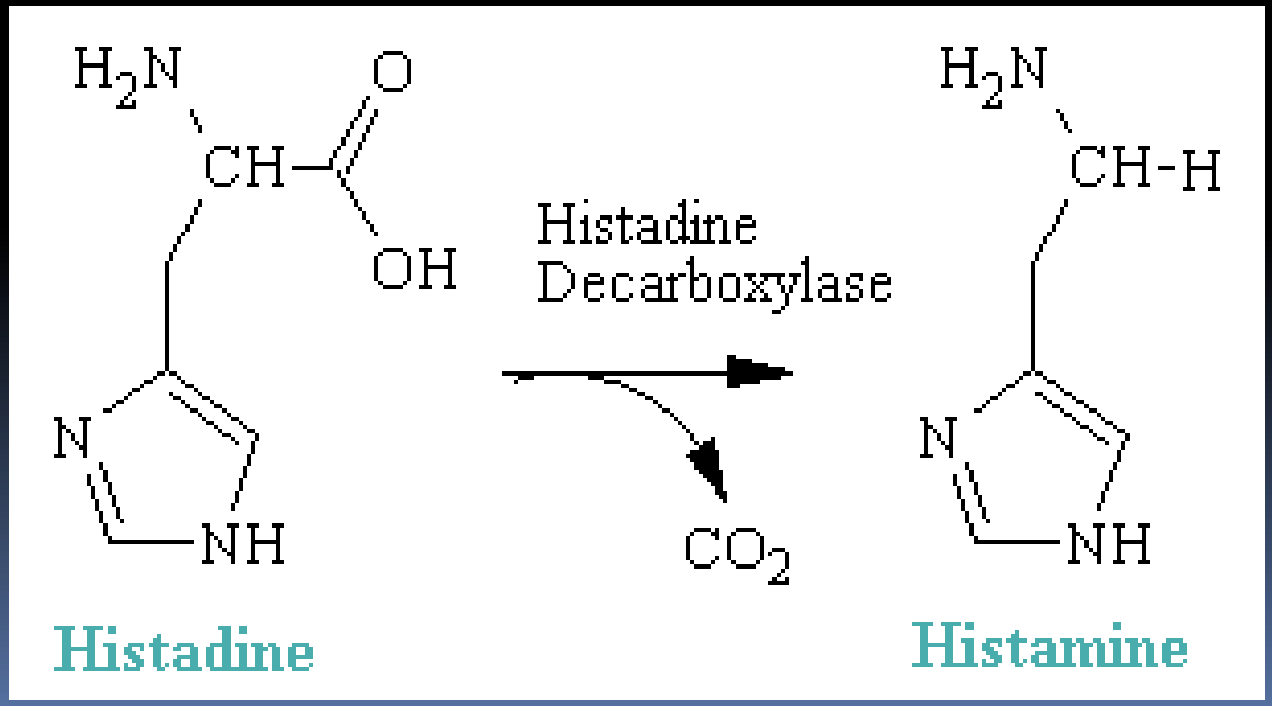
APUD system

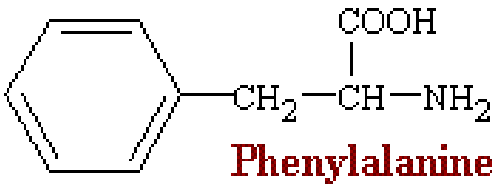
- A morphologic and functional subgroup of the endocrine system, encompassing:
  - C-cells of the thyroid
  - Type-I cells of the carotid body and paraganglia → release noradrenalin
  - Norepinephrine and epinephrine-producing cells of the adrenal medulla
  - Melanoblasts
  - Pineal gland
  - Posterior pituitary cells
- APUD cells take up tryptophan, converting it to 5-HT (serotonin), which is converted to mono-amine oxidase (MAO) 5HIAA
- The term APUD system is little used in the working parlance and has been replaced by neuroendocrine system

From: The Free Dictionary by FARLEX

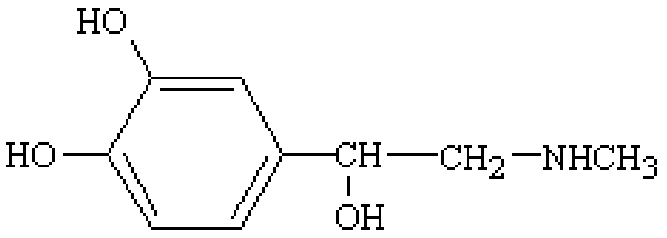
Serotonin & Dopamine Biosynthesis







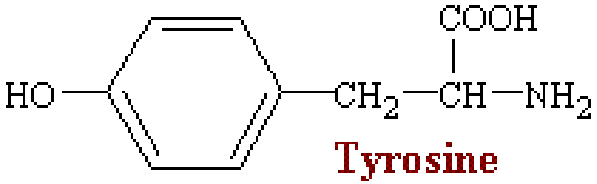
Phenylalanine



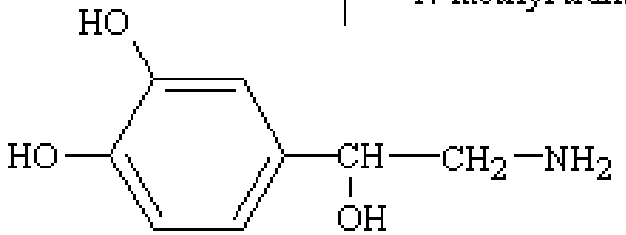
Epinephrine

Phenylalanine hydroxylase

Norepinephrine N-methyl transferase



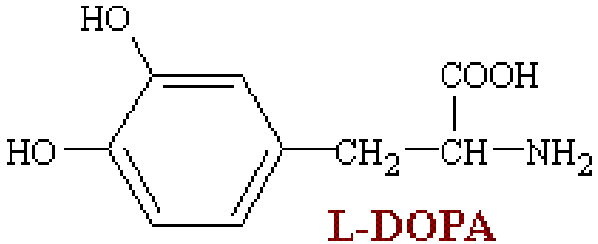
Tyrosine



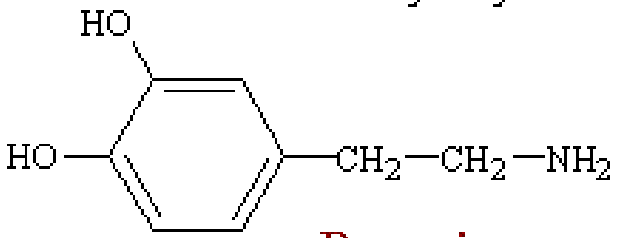
Norepinephrine

Tyrosine Oxidase

Dopamine-B-hydroxylase



L-DOPA



Dopamine

Aromatic L-amino acid Decarboxylase

Specific Receptor Binding—
Adrenergic presynaptic recptors & storage

- I-131 meta-iodobenzyl-guanidine (I-131 MIBG)
  - An analog of noradrenaline
  - accumulate in catecholamine storing chromophil cells of adrenal medulla
  - is believed to be transported into the cell by the reuptake pathways of the adrenergic presynaptic neurons. Within the cells, MIBG is transported into the catecholamine-storing granules by means of the ATPase-dependent proton pump. The major difference bt MIBG and noradrenaline is that MIBG dose not bind to postsynaptic adrenergic receptors
  - Reduced uptake if using: labetalol, CCBs, antipsychotic & sympathomimetic agents

MIBG因為結構類似 norepinephrine，必須緩慢注射以免引起高血壓的危險性。藥物注射後，建議請受檢者在檢查室休息半小時後，無異狀再離開___ CGMH protocol

Specific Receptor Binding—
Adrenergic presynaptic recptors & storage

- I-131 meta-iodobenzyl-guanidine (I-131 MIBG) (cont.)

initially, used in…

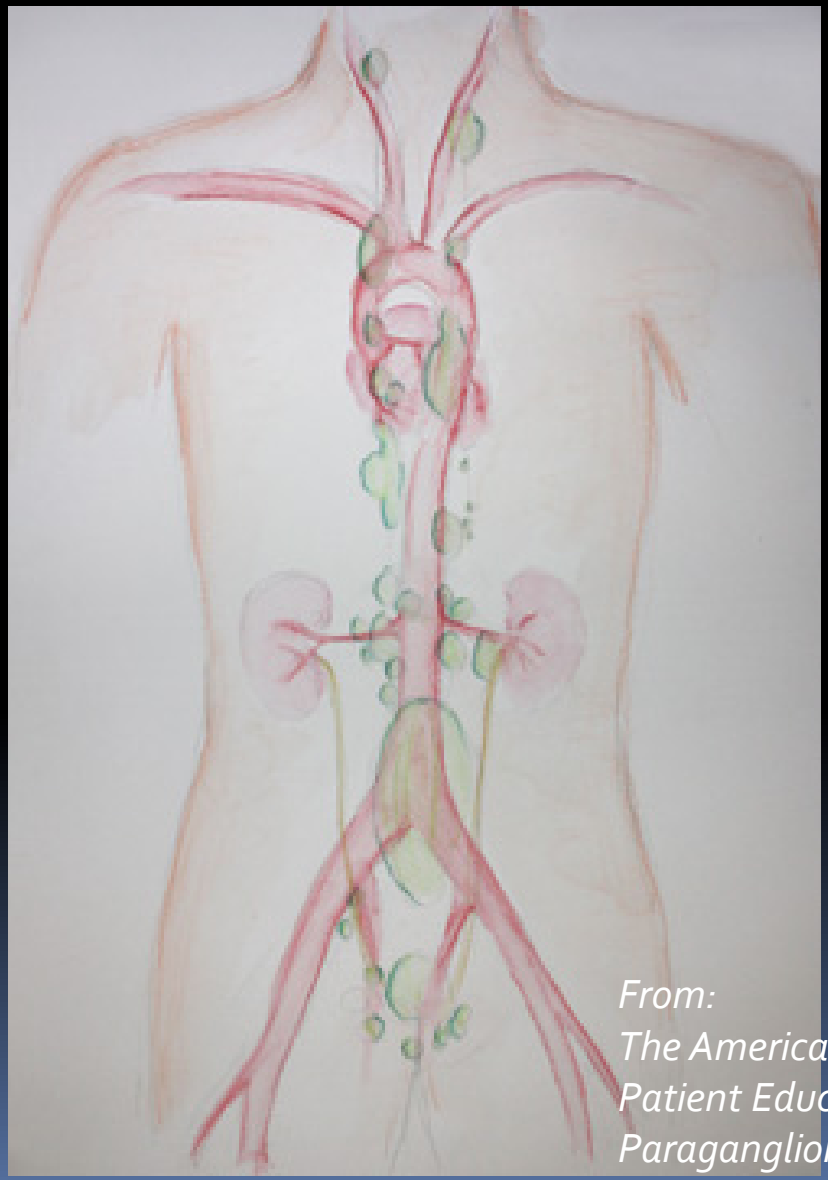
  - Pheochromocytoma… from adrenal medulla
  - Paraganglioma (extra-adrenal pheochromocytoma)… extra-adrenal adrenergic system (special chemoreceptors, chiefly in carotid body, aortic body and may also be located along major arteries)

laterally, used in…

  - Medullary thyroid carcinoma
  - Retinoblastoma
  - Melanoma
  - Bronchial carcinoma

From:
The American Association of Endocrine Surgeons Patient Education Site
Paraganglioma

Possible sites of Paraganglioma



Artwork by
Elizabeth Chabot

From:
The American Association of Endocrine Surgeons
Patient Education Site
Paraganglioma

Specific Receptor Binding–
LDL recptors

- 131 I-6β-iodomethyl-19-norcholesterol (NP-59)
- 131 I-6-iodocholesterol (Iodorin)
- 75 Se-β-iodomethyl-19-norcholesterol (Scintadren)
- Mechanism of uptake:
  - transported by plasma LDL and are accumulated in the adrenal cortex via LDL receptors
  - esterified like cholesterol and stored intracellularly without further metabolism or incorporation into adrenocortical steroid hormones

NP-59 Adrenal Cortical Scintigraphy

- 利用NP-59檢查時有不同的步驟:
  - 當懷疑是庫辛氏症時直接注射NP-59檢查即可，藉著影像表現的不同來判斷是ACTH依賴型或是非依賴型
  - 若懷疑是原發性醛固酮過多症則必須先以dexamethasone(DS)進行抑制ACTH分泌再注射NP-59

- **適應症:**

  1、診斷原發性醛固酮過多症是腺瘤或是腎上腺皮質增生所引起

  2、當CT、MRI、超音波發現腎上腺有腫塊時可以鑑定腫塊的功能及特性

  3、診斷庫辛氏症(Cushing's syndrome)是ACTH依賴型或是非依賴型

  4、診斷女性多毛症或無月經是否因腎上腺雄性素分泌過高引起

From: Green kid

- Thanks your attention.