

Non-steroidal hormones and related drugs

Abdu Tuha

Hormones

- Integration of body functions in humans & other higher organisms carried out by
 - The nervous system
 - The immune system
 - The endocrine system
- Endocrine system composed of number of tissues that secrete
 - Endocrine hormones into the circulatory system
 - Disseminated through out the body
 - Regulate function of ***distant tissues*** & maintain homeostasis
- In a separate but related system, exocrine tissues
 - Secrete their products into ducts
 - Then to the outside of the body or to the intestinal tract

Hormones cont.

Classification of hormones

- Based on the site of their biosynthesis
 - Glandular hormones
 - Pituitary gland → growth hormone
 - Pancreas → insulin
 - Tissue hormones formed in tissues
 - Histamine
 - Serotonin
 - Norepinephrine
 - Neurohormones
 - Formed in the nervous tissue
 - Acetylcholine
- Based on their chemical structure
 - Steroid hormones
 - Testosterone
 - Hormones derived from single amino acids
 - Histamine, dopamines, acetylcholine, serotonin, thyroxine, liothyronine
 - Those derived from peptides
 - Growth hormones

Hormones cont.

- Classically endocrine hormones considered
 - To be derived from
 - Amino acids / peptides
 - Sterols
 - And act at sites ***distant*** from their tissue of origin
- Definition based on site of action has begun to blur because some secreted substances act
 - At a distance
 - Classical endocrines
 - Close to the cells that secrete them
 - Paracrines
 - Directly on the cell that secreted them
 - Autocrines
- **Exceptions**
 - Insulin-like growth factor-I (IGF-I)
 - Behaves as an endocrine, paracrine & autocrine

Non steroidal hormones & related drugs

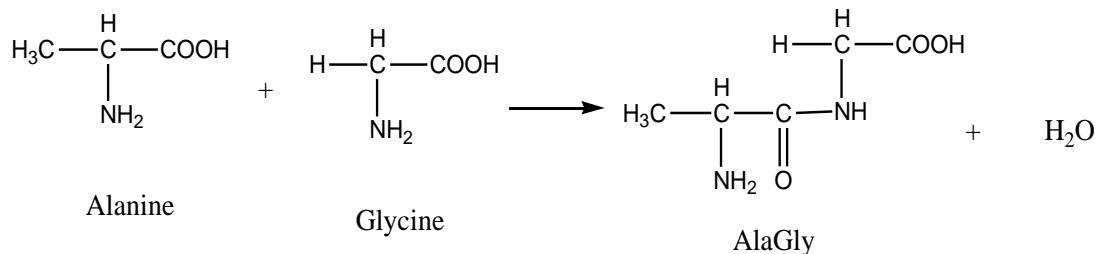
- Poly peptide hormones
 - Are composed of amino acids
 - Differing number & sequence
 - This being determined by genetic information in the DNA
- Peptides classified as
 - Dipeptides (2 AA)
 - Tripeptides (3 AA)
 - Oligopeptides (10-30 AA)
 - Polypeptides (30-50 AA)
 - Proteins (> 50 AA)
 - Glycoproteins (Protein covalently bonded carbohydrate)

Poly peptide hormones_{cont.}

- Proteins, growth factors & peptide hormones
 - Synthesized in the endocrine glands
 - As large precursor molecules (preprohormones)
- Enzymatic cleavage of preprohormones
 - Gives prohormones
 - Further cleavage yields hormones

Chemistry of peptide hormones

- Are biosynthesized from natural amino acids (L- α -amino acids)
- Peptide or amide bond is formed by linkage of
 - α -carboxyl group of one AA &
 - α -amino group of another AA
 - With elimination of H_2O



Amino acids, their 3 & 1 letter abbreviation

<u>Amino acid</u>	<u>3 lett.</u>	<u>1 lett.</u>
• Alanine	Ala	A
• Arginine	Arg	R
• Asparagine	Ans	N
• Aspartic A.	Asp	D
• Cysteine	Cys	C
• Glutamine	Glu	Q
• Glutamic A.	Glu	E
• Glycine	Gly	G
• Histidine	His	H
• Isoleucine	Ile	I

<u>Amino acid</u>	<u>3 lett</u>	<u>1 lett</u>
• Leucine	Leu	L
• Lysine	Lys	K
• Methionine	Met	M
• Phenylalanine	Phe	F
• Proline	Pro	P
• Serine	Ser	S
• Threonine	Thr	T
• Tryptophane	Trp	W
• Tyrosine	Try	Y
• Valine	Val	V

Structure of peptide hormones

- Primary structure
 - Linear/ straight chain structure of amino acids
- Secondary structure
 - Folded/ coiled
 - Stabilized & characterized by regular patterns of hydrogen bonds
- Tertiary structure
 - 3-D structure formed as AAs interact with more distant members of the chain
- Quaternary structure
 - Formation of peptide bond from two or more polypeptide chains
 - Monomers / subunits

Therapeutic uses of polypeptide hormones

- Life time / long term replacement therapy
 - Insulin
- Acute or long term stimulation of endocrine axon terminals
 - Calcitonin – decreases amount of Ca entering the blood from bone
 - Control osteoporosis
- Vasopressin – antidiuretic
- Gonadotropins – stimulate ovarian follicles for ovulation
- Oxytocin – promote uterine contraction
- Anticancer applications
 - Sandostatin, interferons & antibodies
- Thrombolytic therapy
 - Urokinases & streptokinases
- Blood volume replacement
 - Albumin & plasma proteins active immunization
- Active immunization
 - Vaccines
- Passive immunization
 - Immunoglobulins & antioxidants
- Miscellaneous
 - Trypsin & pepsin

I- Hormones of the Hypothalamus

- Synthesized in the hypothalamus
 - Transported to anterior pituitary
 - Via the hypothalamic hypophyseal portal system
- Are usually peptides
 - Control the release of pituitary hormones
- Known hypothalamic hormones include
 - Thyrotropin releasing hormone (TRH)
 - Gonadotropin releasing hormone (GnRH)
 - Somatostatin (somatotropin) releasing – inhibiting hormones (ss)
 - Corticotropin releasing factor (CRF)
 - Growth hormone releasing hormones (GHRH)
 - Lutropin releasing-inhibiting factor (LHIF)
 - Follicle-stimulating factor (FRF)
 - Prolactin releasing hormone (PRF)
 - Melanocyte stimulant hormone releasing factor (MRF)

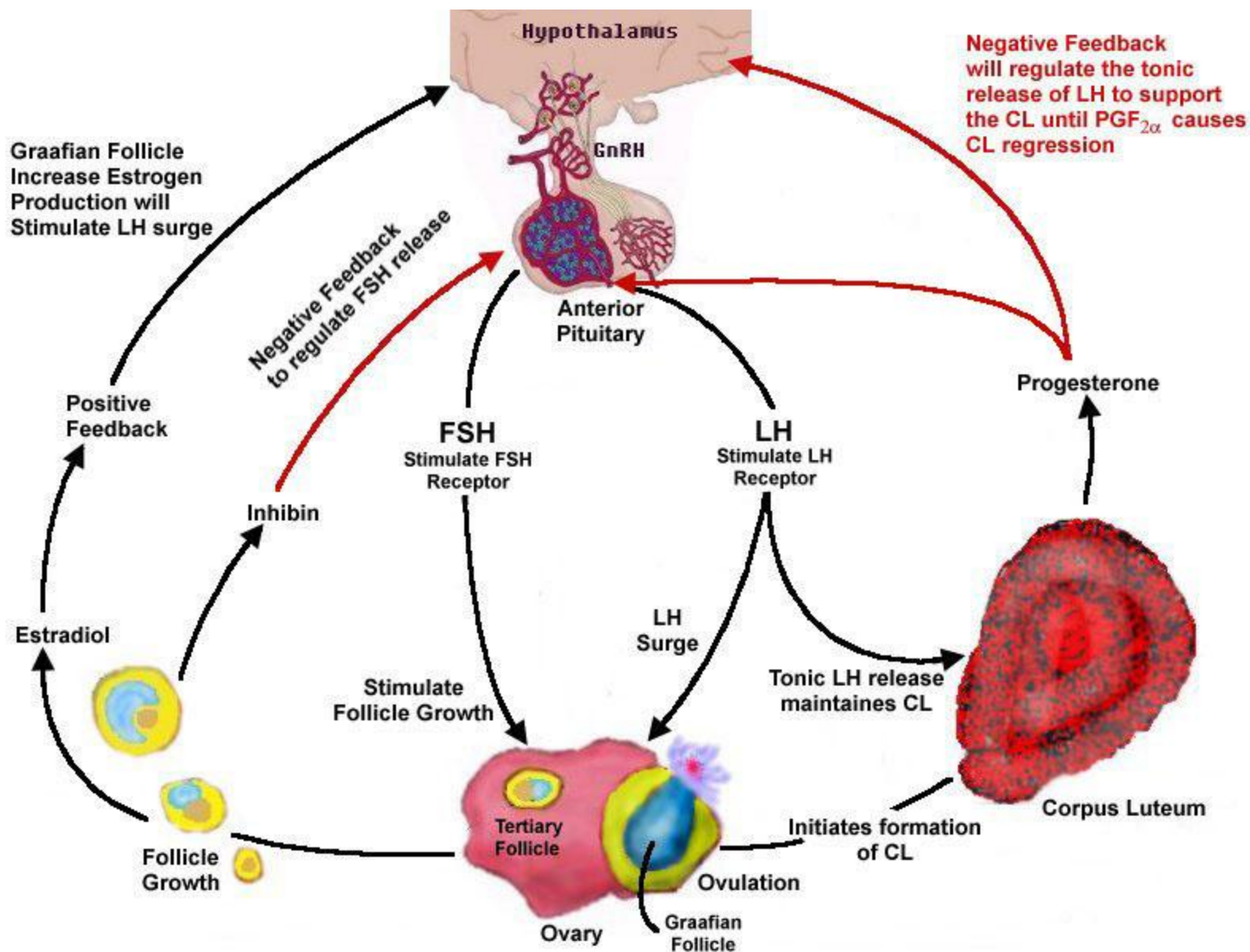
Thyrotropin releasing hormone (TRH)

- Is a tripeptide hormone
 - L-pyroglutamyl-L-histidyl-L-prolindamide
 - pyroGlu-His-pro-NH₂
- Thyroliberin is hypothalamic hormone responsible for the release of thyrotropin (TSH) by pituitary gland
 - TSH acts on the thyroid gland stimulating it to release its hormones
 - Triiodothyronine (T₃)
 - Thyroxine (T₄)
 - It also promotes release prolactin

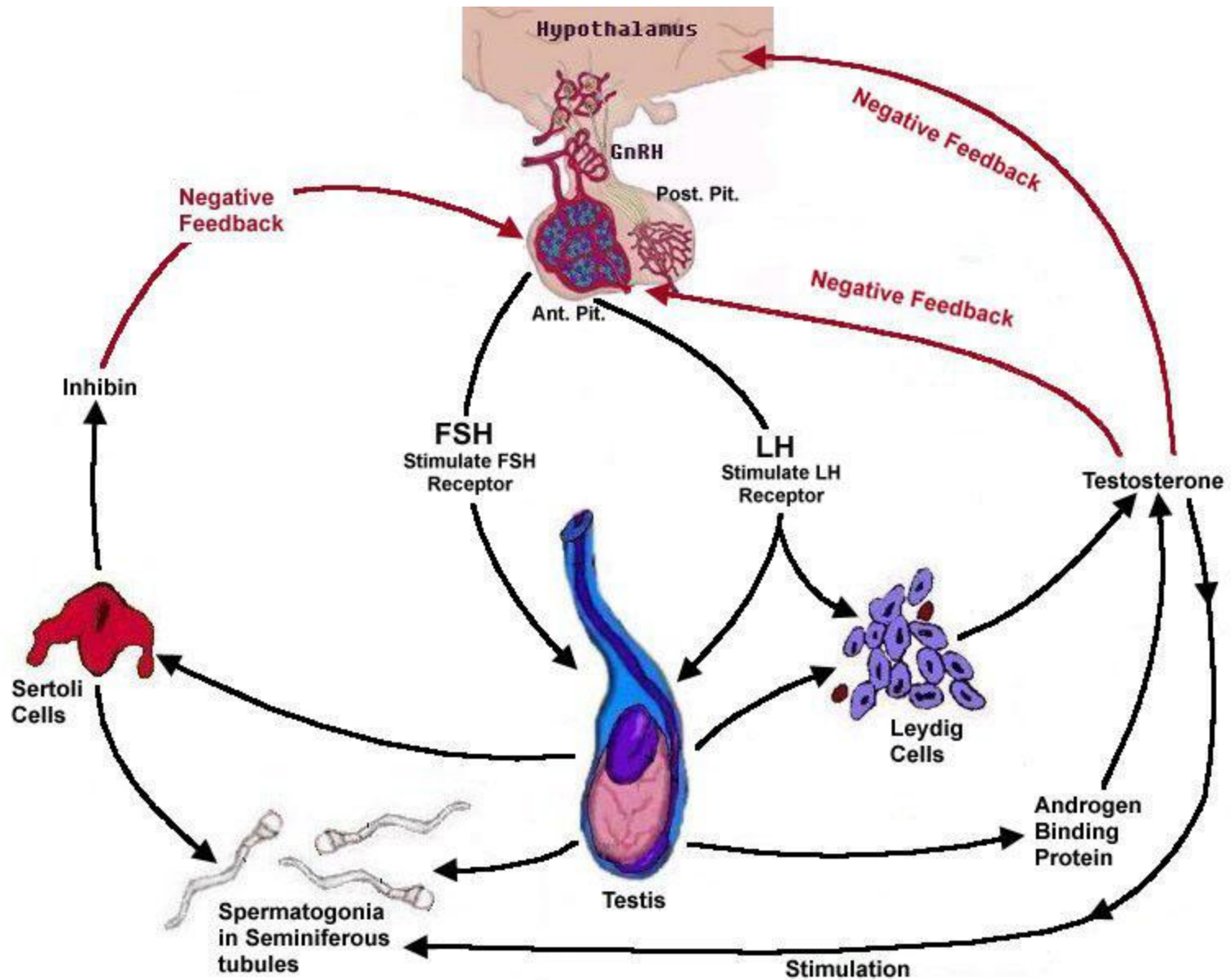
Gonadotrophin releasing hormone (GnRH)

- GnRH controls release of
 - Luteinizing hormone (LH)
 - Follicle stimulating hormone (FSH)
 - From pituitary gland in man & animals
 - Used to treat infertility.
- Chemistry
 - Pyro - ¹Glu - ²His - ³Trp - ⁴Ser - ⁵Tyr - ⁶Gly - ⁷Leu - ⁸Arg - ⁹Pro - ¹⁰Gly-NH₂
 - Gonadoliberin is a linear decapeptide
 - GnRH is a decapeptide with blocked amino and carboxyl termini
 - derived by proteolytic cleavage of a 92-amino-acid precursor peptide

Female feedback Diagram



Male Feedback Diagram



Gonadotrophin releasing hormone (GnRH) cont.

Pyro - ¹Glu - ²His - ³Trp - ⁴Ser - ⁵Tyr - ⁶Gly - ⁷Leu - ⁸Arg - ⁹Pro - ¹⁰Gly-NH₂

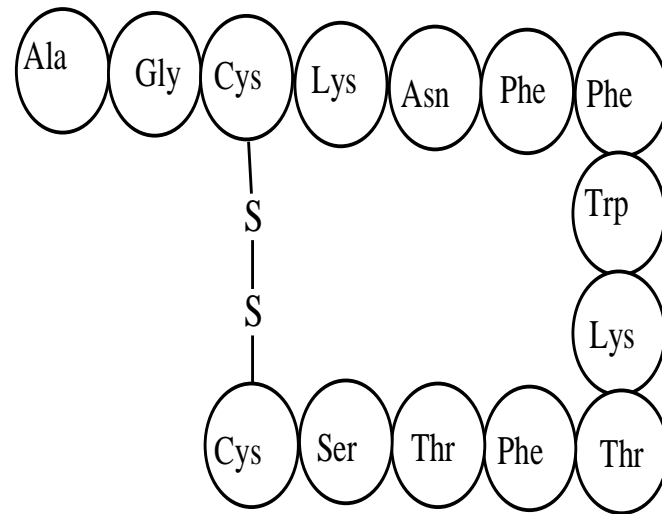
- Structural activity relationship
 - Modification of GnRH molecule may result in super active analogues
 - Potency enhanced to about 100%
 - Increased half life
- Potentiation & ↑ duration of agonistic activity by modification at 6 & 10
 - Omission of Gly (10) & protection of Pro (9) carboxyl group
 - Gives a more active nonapeptide analogue
- Replacement of Gly (6) by D-amino acid shows significant ↑ in activity
 - E.g. D-Ala, D-Lys, D-Leu
- Replacement of Gly (6) with D-isomer of aromatic amino acid ↑ activity several folds
 - E.g. D-Phe or D-Tyr
- Modification of both Gly at 6 & 10 showed ↑ in biological activity & t_{1/2}
- Peptides with less than nine AA moieties did not show agonistic activity
 - Size essential for activity

Structural activity relationship of GnRH cont.

- Analogues with antagonistic activity
 - Useful as contraceptive agents
- Pyro - ¹Glu - ²His - ³Trp - ⁴Ser - ⁵Tyr - ⁶Gly - ⁷Leu - ⁸Arg - ⁹Pro - ¹⁰Gly-NH₂
- Modification of ²His residue leads to
 - Loss of agonist activity through inhibition of GnRH
 - Omission of His (2)
 - Nonapeptide (des-His² GnRH)
 - Omission of ²His & ¹⁰Gly NH₂
 - Octapeptide (des ²His & ¹⁰Gly NH₂)GnRH
 - » Ethyl amide of des-His² GnRH, des ²His & des ¹⁰Gly NH₂ GnRH serve as GnRH inhibitors
 - Replacement of ²His & certain other AA residues
 - D-amino acid
 - » Provides a series of inhibitors

Somatostatins

- Inhibits the release of
 - Growth hormone (GH)
 - Insulin
 - Glucagon
 - Gastrin
 - Pepsin
 - Secretin
 - Vasoactive intestinal peptide
- Is a tetradecapeptide with
 - 3-14 disulfide bond

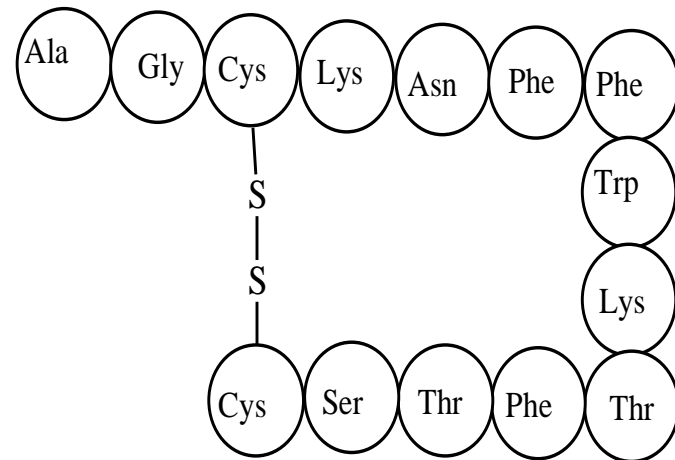


Somatostatin

Somatostatins

SAR

- Replacement of
 - Gly² with Ala
 - Asn⁵ with Ala
 - Enhanced activity
 - Trp⁸ with D-Trp
 - Dramatic potentiation
 - Aromatic residue Phe^{6,7,11} & Trp⁸ by tyrosine
 - Retains activity
- Disulfide bridge essential for activity
- Terminal NH₂ & COOH
 - Not essential for activity
- Ring size not essential
 - Deletion of Lys⁴, Asn⁵ or Ser¹³
 - Retain activity



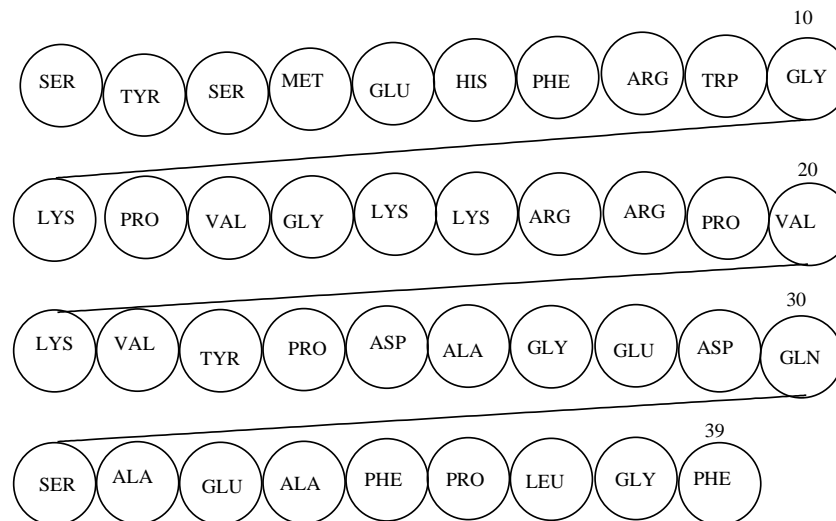
Somatostatin

II- Anterior pituitary hormones (Adenohypophysis)

- Pituitary secretes several polypeptide hormones including
 - Adrenocorticotrophin hormone (ACTH)
 - Lutropin (LH) & Follitropin (FSH)
 - Thyrotropin (TSH)
 - Somatotropin (GH)
 - Prolactin

Anterior pituitary hormones cont.

- Adrenocorticotropin hormone (ACTH)
 - Stimulates adrenal cortex to convert
 - Cholesterol to steroidal hormones
 - Has 39 AA's arranged in single chain



Anterior pituitary hormones cont.

Structural activity relationship

- Sequential removal of AA's from COOH terminal
 - Until residue 20 is deleted
 - No loss in activity
 - A peptide containing 24 aas has full steroidogenic activity without allergenic reactions.
- The five amino terminal residues are essential for activity
- Amidation of the COOH terminal or introduction of D-Ser or β -Ala at NH_2 terminal
 - Avoid enzymatic degradation
 - Increase potency

Follitropin (FSH) & Lutropin (LH)

- Are also called gonadotrophic hormones
- Contain carbohydrate moiety in their molecule
 - Called glycoproteins
- Have a very complex hormonal structure
 - Consist of two subunits
 - α & β subunits
 - α is common to all
 - The β subunit is unique & determine the biological action
 - Major difference occurs at the COOH terminal & in the location of the carbohydrate side chain

Follitropin (FSH) & Lutropin (LH) cont.

- Role of the carbohydrate in glycoproteins
 - Necessary for the protein to fold
 - Attain its proper conformation
 - Protects the protein from proteolytic degradation
 - Transports the protein to its target

Thyrotropin (TSH)

- Stimulates
 - Growth of thyroid gland
 - Secretion of thyroid hormones
- Belongs to the group of glycoproteins
 - The α -subunit is identical to that of LH
 - The β -subunit is a single chain 112 AA's

III- Posterior pituitary hormones (Neurohypophysis)

- Synthesized by the hypothalamus and
 - Transported to the posterior lobe of the pituitary gland
 - Stored in a protein bound form
 - Oxytocin
 - Vasopressin/ Antidiuretic Hormone ADH

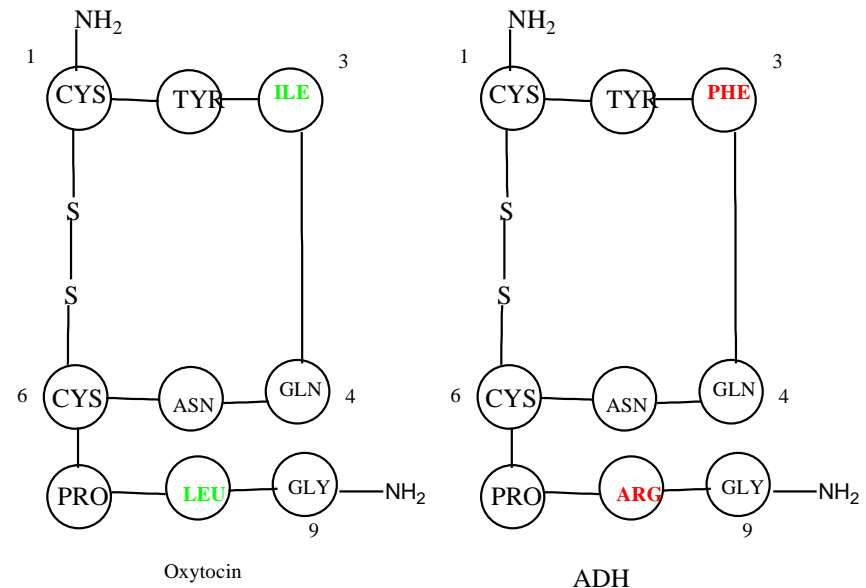
Posterior pituitary hormones_{cont.}

- Oxytocin
 - Induce and maintain labor at term
 - inevitable or incomplete abortion
 - Control hemorrhage and correct uterine hypotonicity
 - Promote milk ejection
- Vasopressin/ ADH
 - Diminishes urine excretion by
 - ↑ permeability of the distal convoluted tubules & collecting ducts to water
 - Also acts as a vasoconstrictor of vascular smooth muscles

Posterior pituitary hormones cont.

Chem. of oxytocin & ADH

- Are nonapeptide hormones
 - With 1,6-disulfide bridge
 - That forms a cyclic hexapeptide structure
 - 20 membered
 - A three peptide side chain
- They differ in two AA's
- SAR
 - Change in size of the ring system &
 - Opening of the ring
 - Loss of activity
 - Replacement of S in sulfur bridge with
 - Methylene groups (carba analogues)
 - Selenium
 - Higher activity
 - Replacement of AA's with their counter enantiomers
 - Enhance activity of hormone
 - Or
 - Antagonize the activity



IV- Pancreatic hormones

(Insulin and oral hypoglycemic agents)

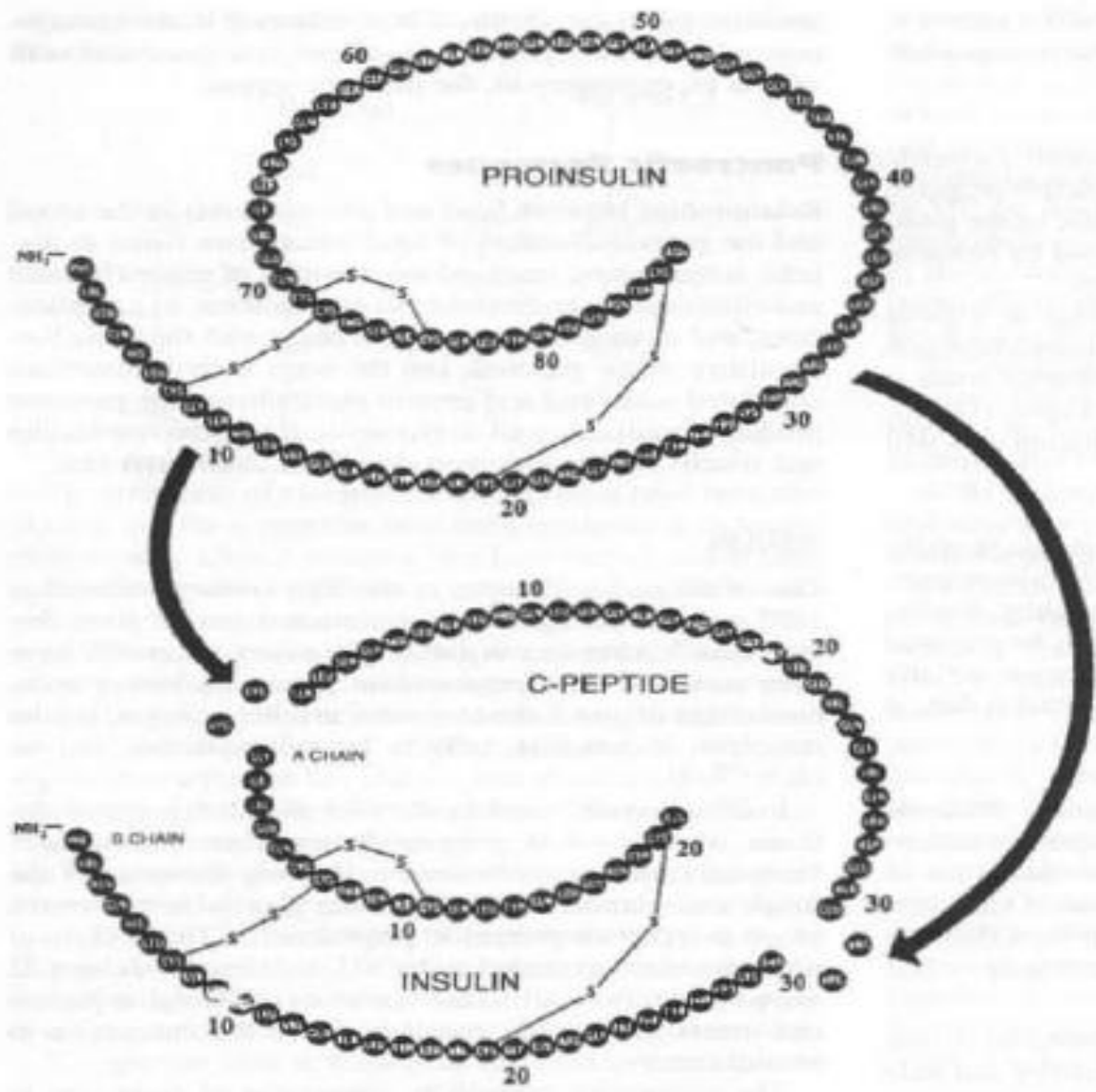
- Pancreas produces
 - From the α -cells of langerhan's
 - Glucagon
 - Has hyperglycemic activity (anti insulin hormone)
 - From β -cells of langerhan's
 - Insulin
 - Hormone elaborating hypoglycemic activity

Insulin

- Is a polypeptide hormone
 - Synthesized from proinsulin
 - A precursor polypeptide with a single chain of 86 AA's
 - Proinsulin has negligible hormonal activity

Chemistry of insulin

- Consists of two peptide chains
 - Chain A
 - Acidic in nature
 - Has 21 AA's
 - Chain B
 - Basic in nature
 - Has 30 AA's
 - Chains A & B linked by two disulfide bridges
 - A₇ to B₇ & A₂₀ to B₁₉
 - A third disulfide bridge in A chain
 - Forming a 20 membered intra-chain ring
 - A₆ to A₁₁
 - Other additional bonds hold chain A & B together
 - Hydrophobic bonds
 - Hydrogen bonds
 - Salt linkages



Insulin cont.

Species variation

- Insulin molecule from different animal spp.
 - Possess same basic frame work
 - With variable AA substitution

• Spp	A ₈	A ₁₀	B ₂₈	B ₂₉	B ₃₀
• Human	Thr	Ile	Pro	Lys	Thr
• Porcine	Thr	Ile	Pro	Lys	Ala
• Lispro	Thr	Ile	Lys	Pro	Thr
• Bovine	Ala	Val	Pro	Lys	Ala

Insulin cont.

Chemical modifications of insulin

- Total synthesis
 - Laborious and difficult task
 - Involves more than 100 steps
 - Done in three steps
 - Synthesis of chain A
 - Synthesis of chain B
 - Linkage of the two through disulfide bonds

Insulin cont.

Semi-synthesis

- Involves coupling of parts of a native hormone
 - With synthetic peptide
- Conversion of porcine insulin ($B_{30} = \text{Ala}$)
 - To human insulin ($B_{30} = \text{Thr}$)
 - By enzymatic removal of sequence B_{23-30}
 - And coupling with synthetic octapeptide of human insulin

Insulin cont.

Recombinant DNA

- An exciting new development
- r-DNA technique successfully applied
 - In commercial production of human insulin
- It involves cloning of human insulin gene in *E. coli*
- Two methods employed in the process
- Earlier method
 - Involved insertion of genes for production of either chain A or B
 - Combining the two chains chemically
 - To produce insulin chemically & structurally identical to the human insulin
- Recent method
 - Insertion of genes for production of proinsulin molecule
 - Into special *E. coli* strain
 - Proinsulin cleaved by enzymes to produce human insulin
 - Lispro insulin obtained by r-DNA technique
 - Identical in structure to human insulin except B₂₈ and B₂₉ that have been inverted

Insulin cont.

Structural activity relationship

- Removal of AA from chain A
 - Causes significant loss of hormonal activity
- Replacement of A₁ glycine with
 - L-alanine → activity reduced by 10-20%
 - D-alanine → remain fully active
- Several AA of chain B are not considered essential
 - B₁₋₆ and B₂₈₋₃₀
 - Can be removed without significant ↓ in activity
- Breakage of disulfide bridges → loss of activity

- Insulin preparations

Rapid acting insulin

- Regular insulin or crystalline zinc insulin
 - Available in solution form; while all others are in form of suspension
 - Dimerization of insulin by complexing with zinc ions
 - Maximum of 4 dimers can be aggregated to larger units of crystalline insulin
 - The only insulin prepⁿ administered iv, im, & sc
- Semilente insulin
 - Has small amount of zinc

Intermediate acting insulin

- Isophane insulin suspension (NPH)
 - Suspension of Zn insulin crystals with balanced amount of protamine sulfate (protein modifier to prolong action)
- Insulin zinc suspension (Lente)
 - 70:30 mixture of ultralente & semilente

Long acting insulin

- Protamine zinc insulin
 - Suspension of protamine, zinc chloride & insulin
- Ultralente insulin
 - Microcrystalline insulin containing ↑ concentration of zinc
- Insulin being a protein can not be administered orally
 - Degraded by proteases and other enzymes

Oral hypoglycemics

- Are drugs taken orally to ↓ blood glucose level
 - In type II (non-insulin dependent) diabetes mellitus
 - Diabetes in which level of insulin is normal or ↑
 - But decreased affinity of receptors to insulin
 - In those who are allergic to insulin
- Classification
 - Sulfonylureas
 - Biguanides
 - Enzyme inhibitors
 - Insulin receptor activators

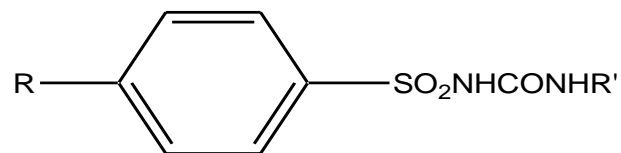
Oral hypoglycemics cont.

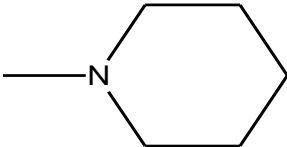
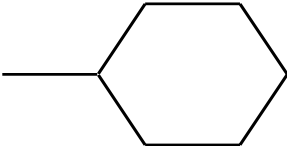
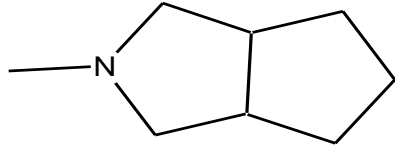
- Benzene sulfonylureas
 - First and second generation sulfonylureas

Mechanism of action

- A. Block K^+ channels \rightarrow depol \rightarrow Ca^{++} channels open \rightarrow insulin (this effect is glucose dependent)
 - ✓ The pattern of insulin secreted by sulfonylureas is similar, but not same, as induced by glucose.
 - B. Release somatostatin (inhibits insulin release, auto off mech.)
 - C. Suppression of gluconeogenesis
- Sulfonyl ureas are weak acids due the delocalization of nitrogen lone electron pair by sulonyl group.
- ✓ strongly plasma protein bound.

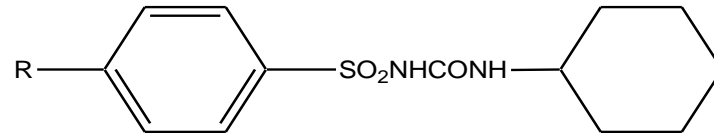
First generation



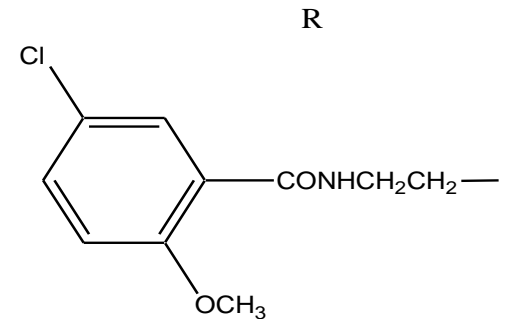
	R	R'
Tolbutamide	CH ₃	n-butyl
Clorpropamide	Cl	n-propyl
Tolazamide	CH ₃	
Acetohexamide	CH ₃ CO	
Gliclazide	CH ₃	

Oral hypoglycemics cont.

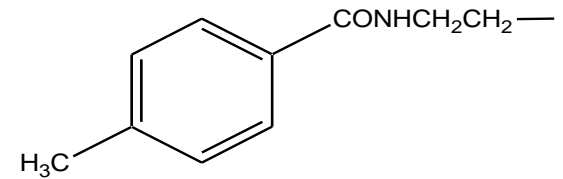
- Second generation



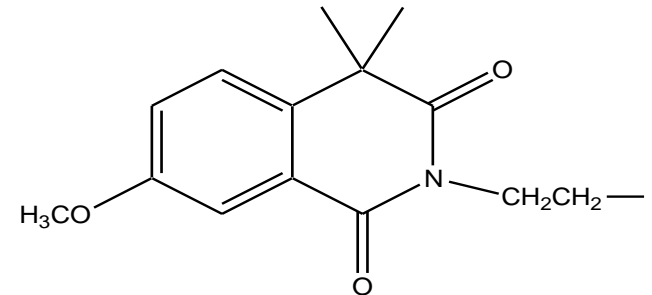
Glibenclamide



Glipizide



Gliquidone

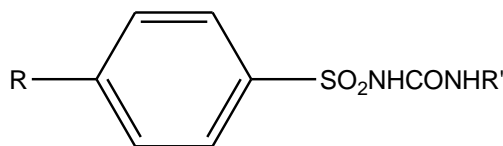


- Chlopropamide has longer duration of action compared to others.
- A valuable adjunct to therapy in diabetic type II DM.

Pharmacokinetics

- are metabolized in liver and excreted via kidney.
 - ✓ What can happen in hepatic/renal insufficiency?
Hypoglycemia b/c metabolized by liver, excreted by kidney,
therefore insufficiency → accumulation → hypoglycemia
- cross the placenta
 - ✓ Hence, they are teratogenic
- Well absorbed orally, food decreases absorption
- Highly protein bound, Rx interactions based on displacement
- sulfonylureas cause a disulfiram reaction by inhibiting
aldehyde dehydrogenase → incr acetaldehyde → flushing, tachy, hyperventilation

Structure activity relationship



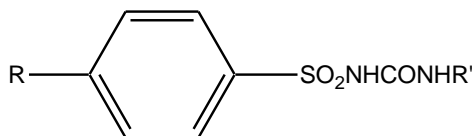
Sulfonylureas

- Benzene ring should contain one substituent
 - Preferably at p-position
- Substituents that enhance hypoglycemic activity are
 - Methyl
 - Amino
 - Acetyl
 - Halogen
 - Methylthio
 - Trifluoro methyl

SAR cont.

Group attached to terminal urea N (R')

- Should have certain size
 - To impart lipophylic properties to the molecule
 - N-methyl derivatives are usually inactive
 - N-ethyl derivatives show low level of activity
 - Optimal activity seen for those containing
 - 3-6 carbons
 - Activity lost for those containing ≥ 12 members
 - Some active compounds contain
 - 5-7 membered ring
 - Heterocyclic ring
 - Tolazamide, gliclazide

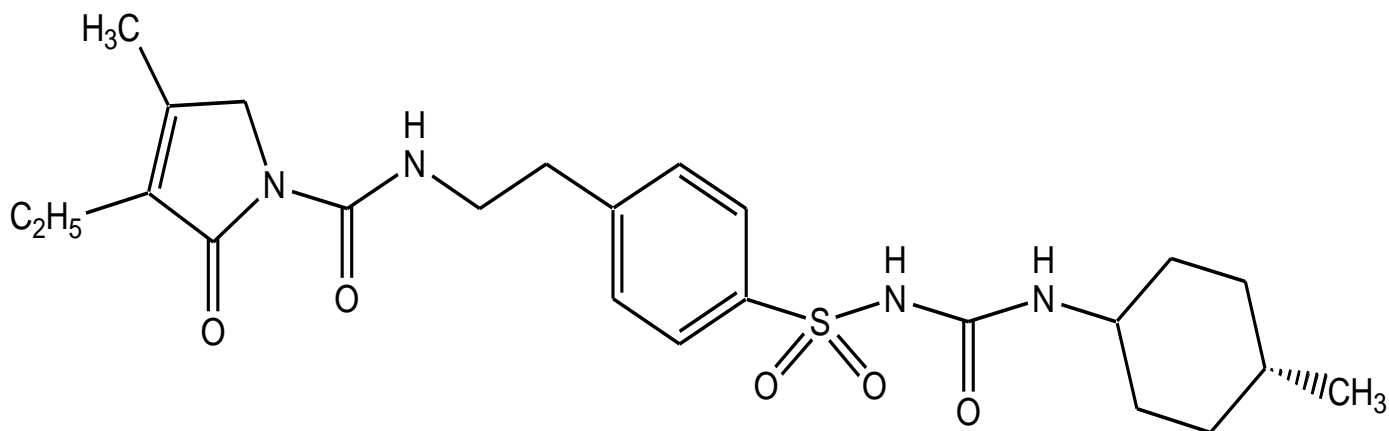


Sulfonylureas

Oral hypoglycemics cont.

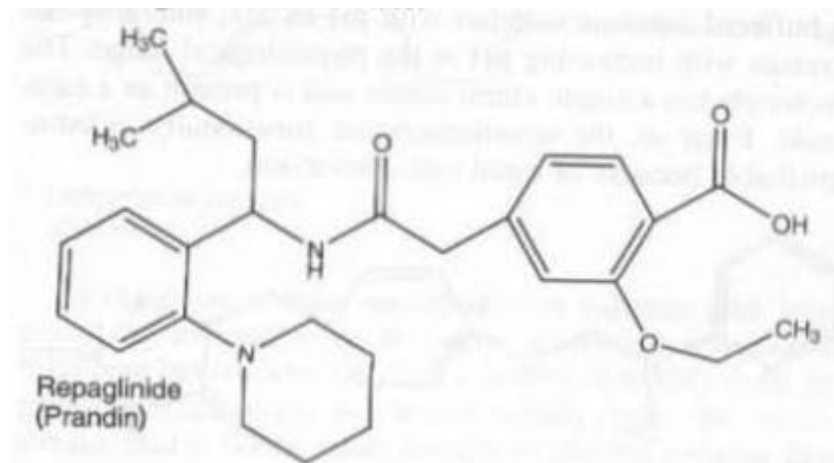
Third generation

- Taken orally once daily and has
 - Rapid onset of action
 - Long duration of action
- Can be taken alone or in combination
- bind to a d/t protein in the putative sulfonylurea receptor.
- Cause translocation of Glut-4 glucose transporter



Glimperide

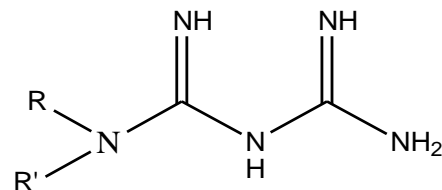
Repaglinide



- more rapid and short duration of action
- Not associated with the prolonged hyperinsulinemia
 - ✓ produces fewer side effects
- Displayed U – shaped conformation
 - ✓ hydrophobic cycles were placed at the end of each branch.
 - ✓ a peptide bond was placed at the bottom of U- shape structured

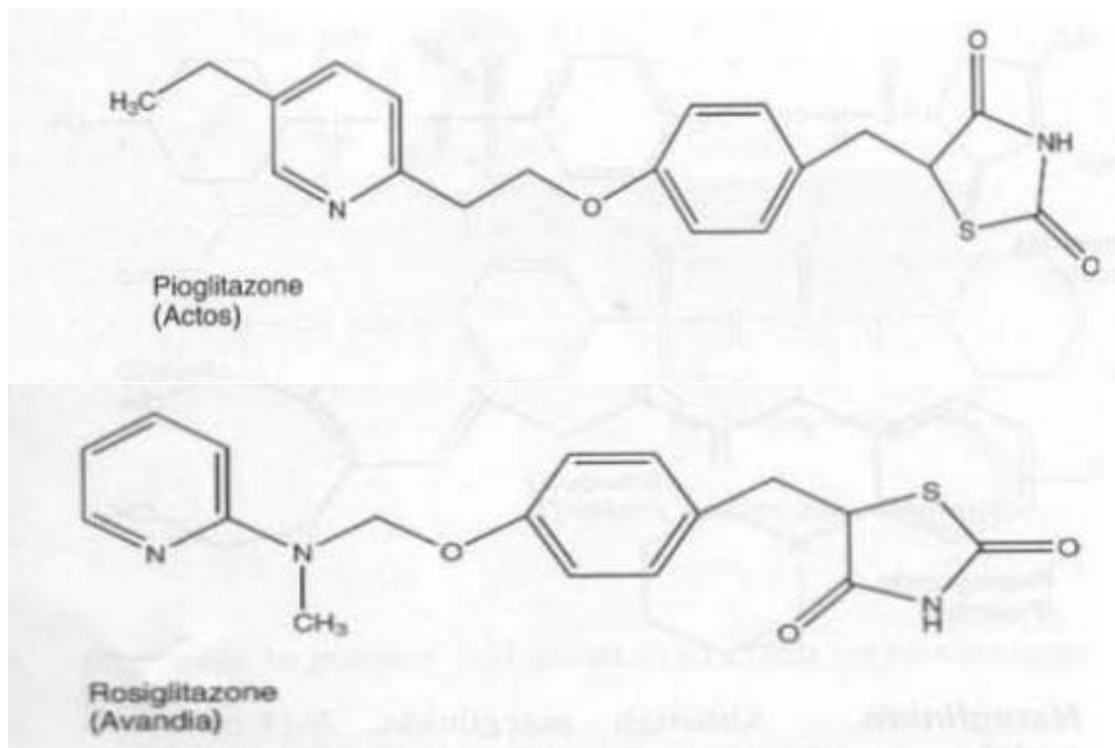
Oral hypoglycemics cont.

- Biguanides
 - Used as adjunct to insulin therapy
 - In contrast to sulfonylureas
 - Biguanides do not stimulate insulin release
 - Hence no effect on blood sugar level of normal person
 - » Might better be called antidiabetic than hypoglycemic



	R	R'
Phenformin	H	PhCH ₂ CH ₂
Metformin	CH ₃	CH ₃
Butformin	H	n-butyl

Insulin receptor activators (Thiazolidediones)



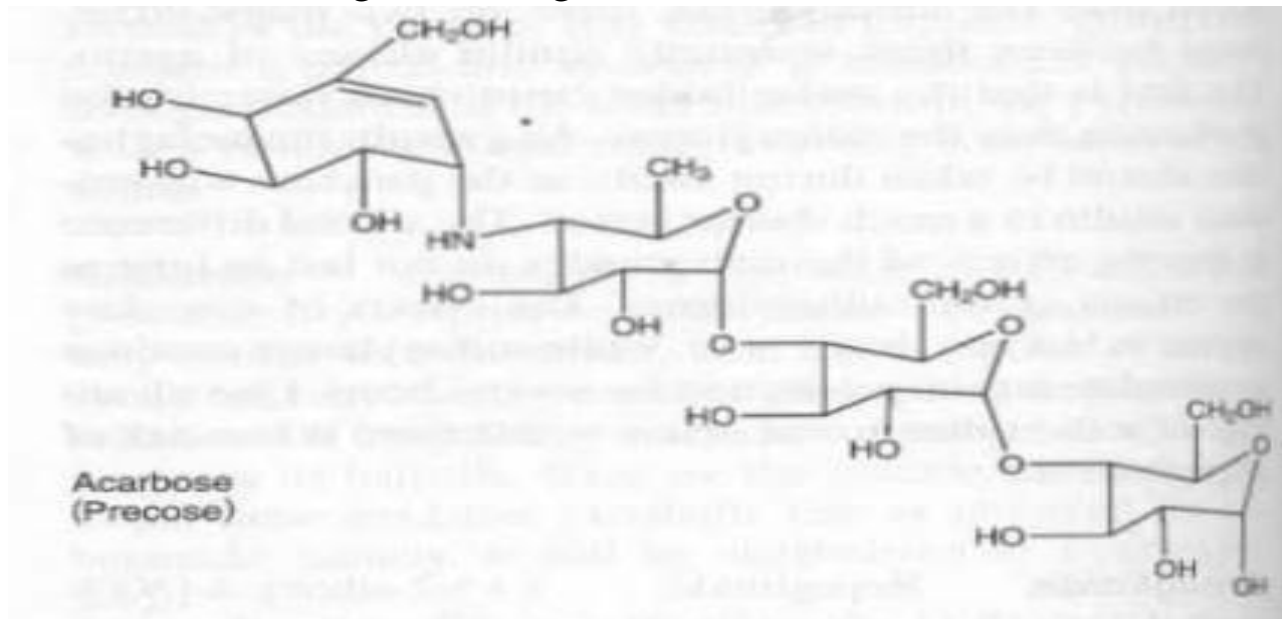
- Used to treat type II diabetics (non insulin dependent diabetes mellitus)
 - Lowers glucose level without affecting insulin secretion
 - Act by increasing insulin sensitivity
 - By up-regulating glucose transporter expression

- Stimulate peroxisome proliferator activated receptor gamma (PPAR γ) , which regulates transcription of genes that code for enzymes in carbohydrate and lipid metabolism
- ✓ Results in:
 - A. Increase glycolysis
 - B. Decrease gluconeogenesis
- Advantage, disadvantage:
- Increase HDL, increase LDL

Oral hypoglycemics cont.

Enzyme inhibitors

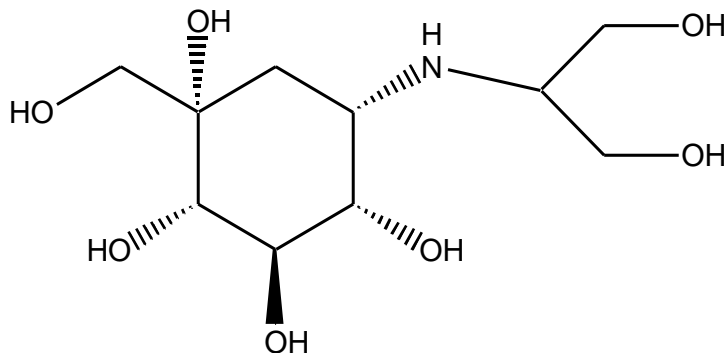
- Acarbose
 - Complex oligosaccharide isolated from *Actinomycete*
 - Delays carbohydrate metabolism in the GIT
 - By inhibiting α -D-glucosidase
 - Lowering blood sugar level



Oral hypoglycemics cont.

Enzyme inhibitors Cont.

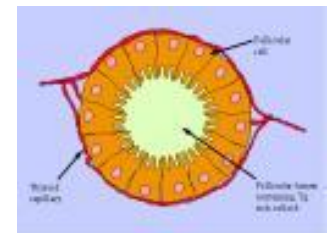
- Voglibiose
 - Orally active α -D-glucosidase inhibitor
 - Used for treatment of postprandial hyperglycemia in diabetic patients
 - Used also to manage other carbohydrate metabolism dependent disorders
 - Obesity
- Is much more potent & with fewer side effects compared to acarbose



Thyroid Hormones and Thyroid Drugs

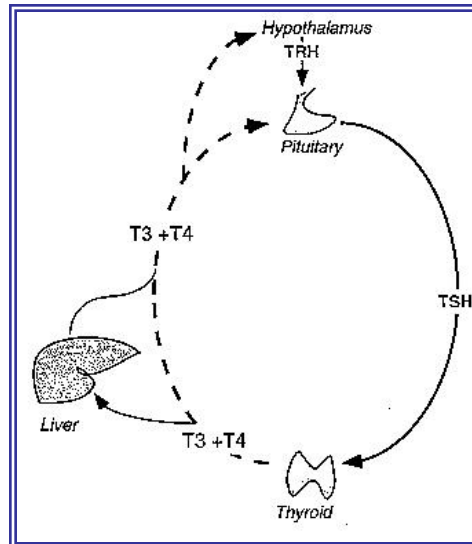
Anatomy and Physiology of the Thyroid Gland

- Member of the Endocrine System
 - Secretes thyroid hormones, thyroxine and calcitonin, which regulate metabolism and growth.
 - Located in neck adjacent to the 5th cervical vertebra (C5).
 - Composed of epithelial cells which specialize in the absorption of iodine and, of course, secretion of thyroid hormones.
 - Follicles surround a protein core, the colloid, where thyroglobulin, a substrate in thyroid hormone synthesis, and thyroid hormones are stored.



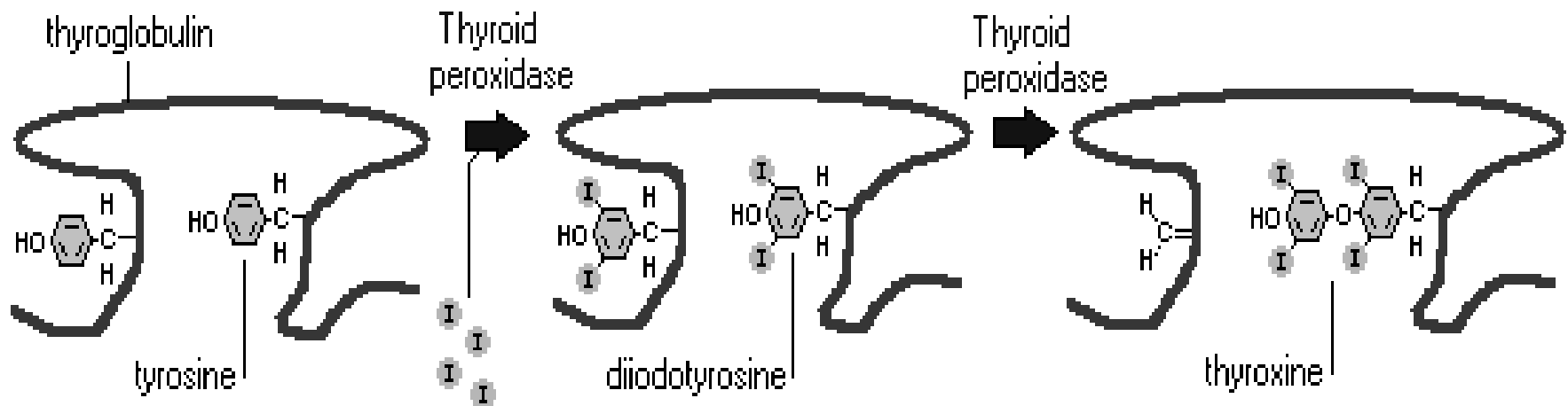
Synthesis of Thyroid Hormones

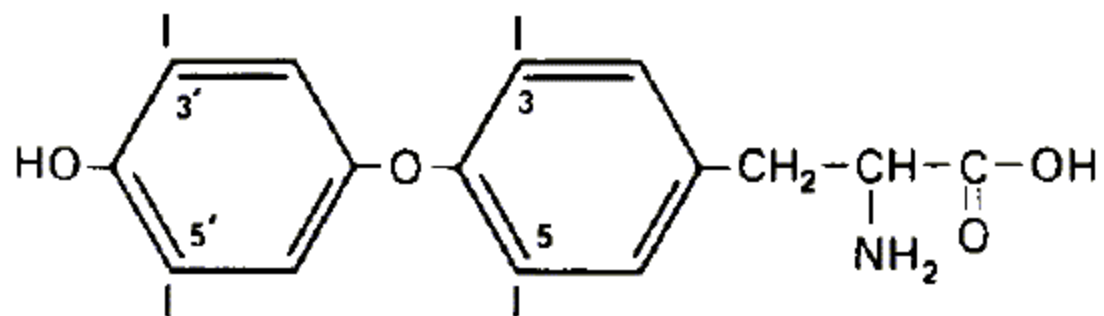
- Regulation:
 - The hypothalamus in the brain secretes thyroid releasing hormone, TRH, that target the pituitary gland which, in turn, secretes thyroid stimulating hormone, TSH. The pituitary gland's sensitivity toward TRH varies with the body's need for thyroid hormones.
 - TSH is absorbed into the thyroid, stimulating the thyroid to absorb iodine and synthesize hormones.
 - Thyroid hormones provide negative feedback for TSH production via a “homeostatic feedback loop.”



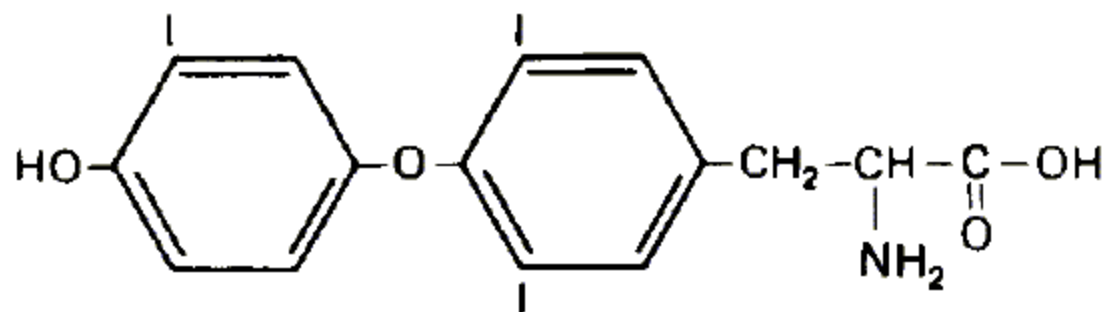
TH Synthesis:

- Active uptake of iodide by follicular cells.
- Thyroid peroxidase (TPO) catalyzes the conversion of iodide (I_2) to iodine (I^-) using H_2O_2 as a cofactor.
- TPO then catalyzes the addition of iodine to the C-3 and C-5 position of a tyrosine residue of thyroglobulin.
- Two iodinated tyrosine rings condense to form thyroxine, or T4, with four iodine substituents.
- Triiodothyronine, or T3, with three iodine substituents, accounts for about 10% of thyroid hormone production.
- Proteolysis of thyroglobulin and release T4 and T3 in to blood.





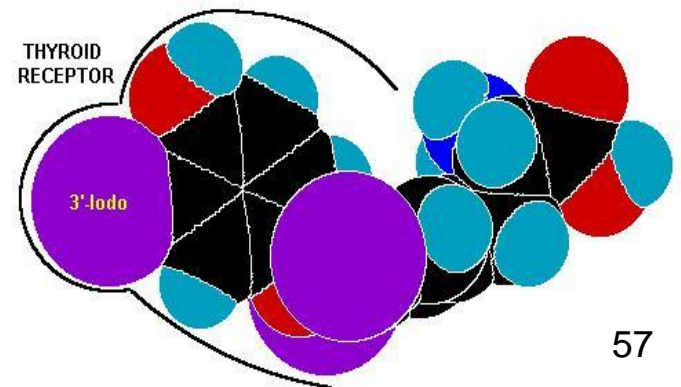
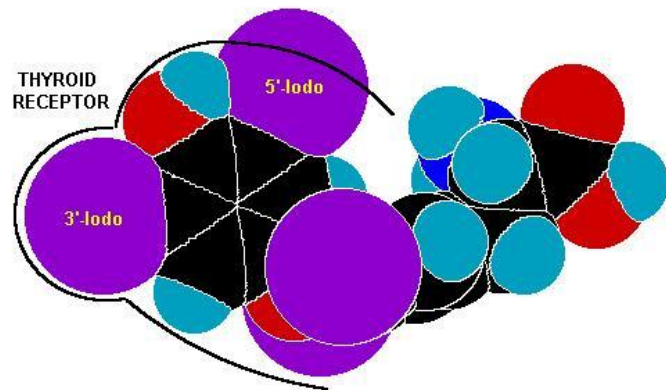
3,5,3',5'-Tetraiodothyronine (thyroxine, T_4)



3,5,3'-Triiodothyronine (T_3)

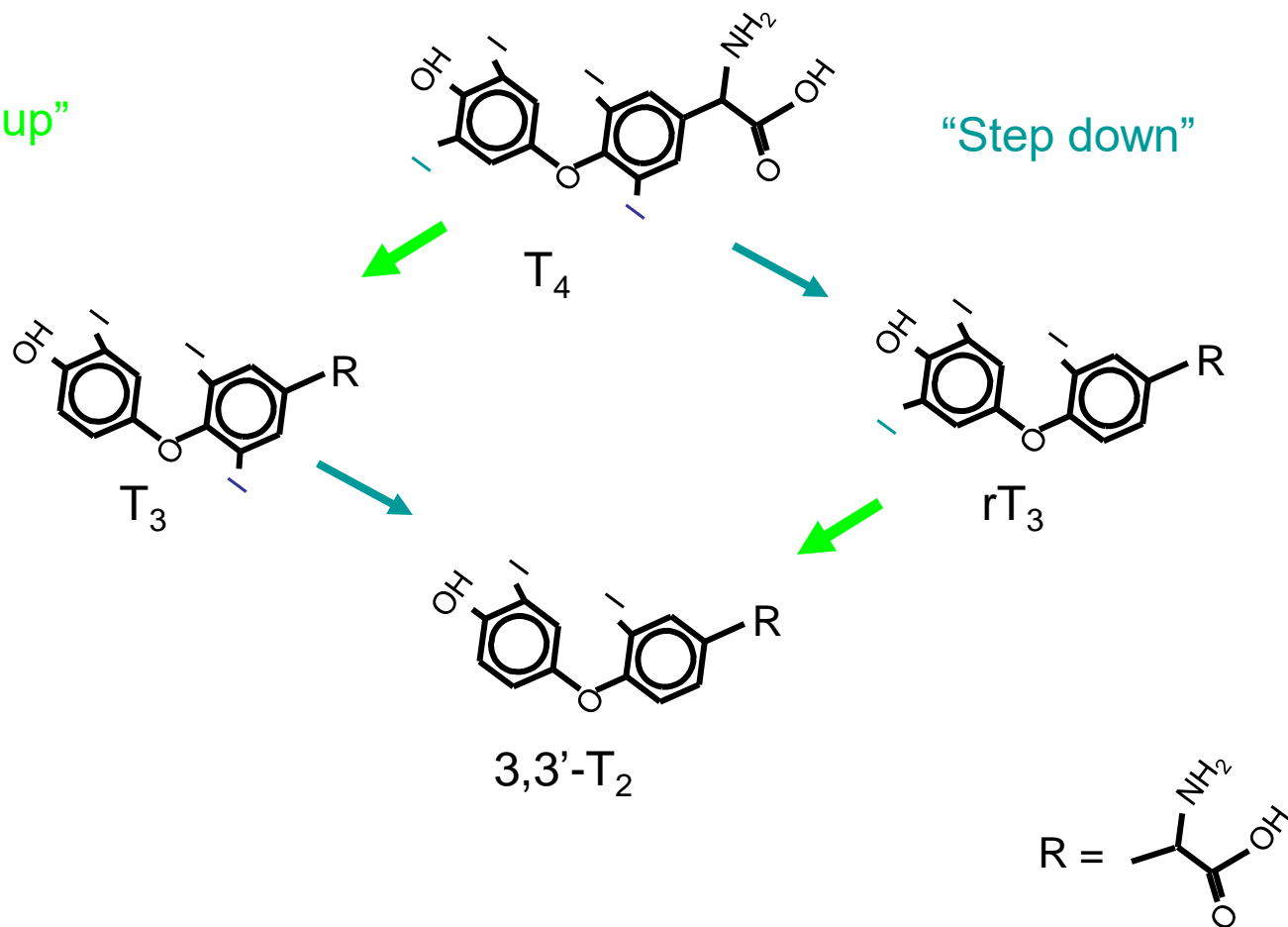
Mechanism of TH Activation in Body

- Hydrophobic molecule transported in the bloodstream with a requisite carrier protein, TBG. Albumin also serves as a TH carrier protein.
- Transported across the cell membrane using a transporter complex. TH enters nucleus.
- The iodine at position 5 on the outer ring serves to sterically hinder the thyroid hormone binding enzyme. T₄ is converted to T₃, the active form.
- Deiodinase, specifically IDI or IDII, cleaves the iodine at position 5 to yield triiodothyronine, T₃.



“Step up”

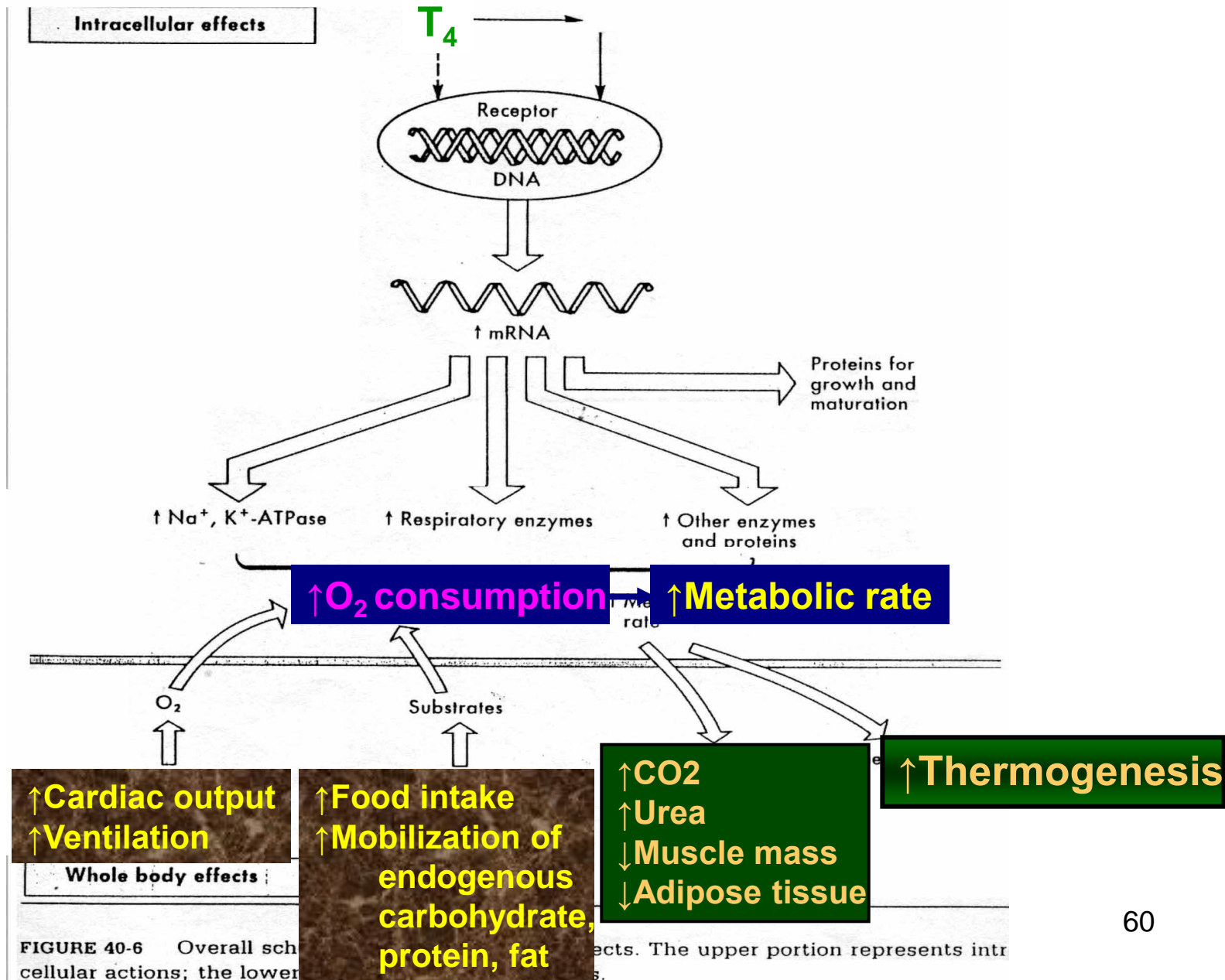
“Step down”



TH effect on metabolism

- TH serves as a nuclear transcription factor, regulating gene expression in targeted cells to increase metabolism.
 - Increase size and number of mitochondria in the cell.
 - Synthesizes cytochromes which feed into the electron transfer chain of cellular respiration, stimulating metabolism through increasing ATP production.
 - Increase ATPase concentration, the enzyme which cleaves a phosphate group from ATP forming ADP and inorganic phosphate.
 - Increased K^+ and Na^+ concentrations in the cell.
- Increase the body's basal metabolic rate, BMR, to maintain electrochemical gradient in cell.
- Stimulate carbohydrate metabolism and lipolysis, or the break down of fats.
- Affects protein synthesis.
- Increase the body's sensitivity to catecholamines, i.e. adrenaline, which is also a derivative of TH.

Overall scheme of thyroid hormone effects



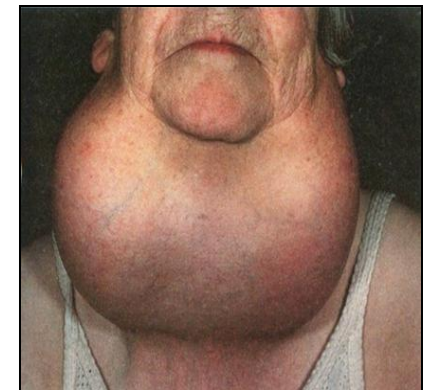
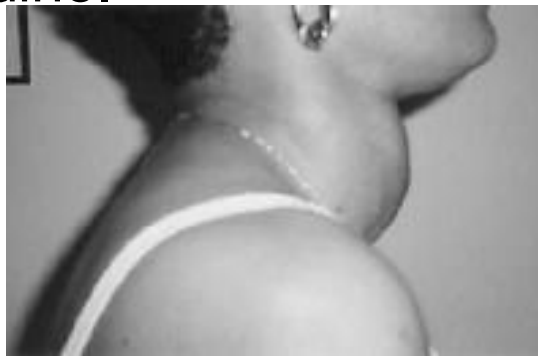
Conditions that Impair Thyroid Function: Hypothyroidism

- Insufficient amount of thyroid hormone synthesized causing lethargy and weight gain, among other symptoms.
- Primary hypothyroidism is typically caused by Hashimoto's Disease, an auto-immune disorder in which the thyroid is destroyed by antibodies.
- Impaired hypothalamus and pituitary function, typically due to a tumor, can inhibit the secretion of THS, causing secondary hypothyroidism.
- A diet insufficient in iodine causes hypothyroidism as well.

Symptoms of Thyroid Dysfunction:

Goiter

- Enlarged thyroid, symptom of hypothyroidism.
- Goiters form for different reasons depending on the cause of hypothyroidism
 - Hashimoto's disease, also known as chronic lymphocytic thyroiditis, causes goiters due to the accumulation of lymphocytes.
 - The decreased amount of thyroid hormones in the body, due to Hashimoto's or other thyroid disorders including infection, signals the increased production of TSH which accumulates in the thyroid causing a characteristic goiter.
 - Goiters form due to an insufficient amount of ingested iodine and serve to increase the surface area of the thyroid and aid in its absorption of iodine.



PRIMARY MYXEDEMA

(DIFFERENTIAL FEATURES)

Hypothyroidism Myxedema

HAIR DRY, BRITTL

LETHARGY, MEMORY IMPAIRMENT,
SLOW CEREBRATION (PSYCHOSES
MAY OCCUR)

EDEMA OF FACE AND EYELIDS

THICK TONGUE
SLOW SPEECH

DEEP COARSE VOICE

SENSATION OF COLDNESS

DIMINISHED PERSPIRATION

HEART ENLARGED,
POOR HEART SOUNDS,
PRECORDIAL PAIN (OCCASIONAL)

HYPERTENSION (FREQUENTLY)

SKIN COARSE, DRY,
SCALING, COLD
(FOLLICULAR KERATOSIS),
YELLOWISH (CAROTENEMIA)

PULSE SLOW

ASCITES

MENORRHAGIA
(AMENORRHEA MAY
OCCUR LATE IN DISEASE)

WEAKNESS

REFLEXES, PROLONGED RECOVERY

HAIR FINER, SOFTER

LOSS OF AXILLARY HAIR

HEART SMALL

HYPOTENSION

SKIN LESS DRY
NOT SCALY

LOSS OF PUBIC HAIR

AMENORRHEA

L. Nutter
M.D.
CHICAGO

Myxoedema --- periorbital swelling



Hypothyroidism --- loss of scalp hair



Hypothyroidism





cretinism

- Infancy onset
- Persists throughout life
- Severe mental retardation

Infantile cretinism

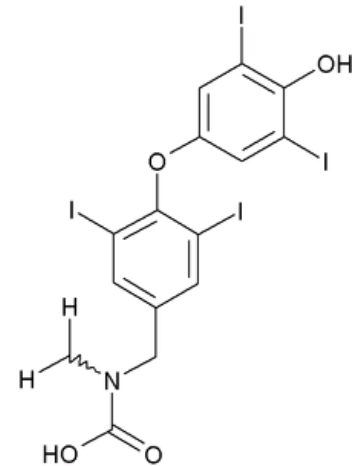


- Megaglossal tongue
- Druppy eyelids
- Lack of genital development
- Severe mental retardation

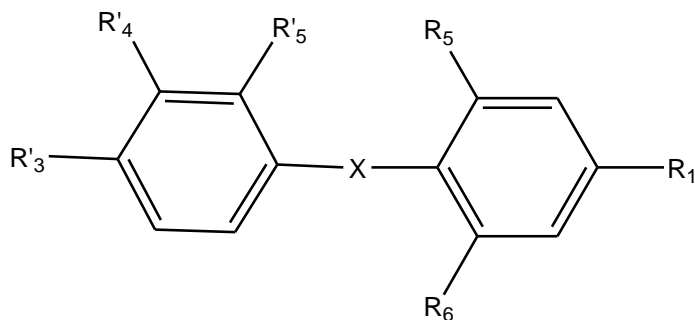


Treatment for Hypothyroidism

- Hormone replacement therapy
- Administered orally with a bioavailability ranging from 48%-80%.
 - Levothyroxine—Synthetic T4
 - Liothyronine—Synthetic T3
 - Liotrix—Combination of synthetic T4 and T3
 - Natural Thyroid Hormones—Thyroid hormones derived from pigs, contains T4 and T3
 - Armour Thyroid
- Dosage specific to individual and is determined by their TSH serum levels. Typically 1.5 μ g T4 per kg body weight.
 - Because thyroid hormones serve to increase heart rate, T4, the inactive form, is typically administered to older patients who have an increased risk for heart attack on account of their age. Synthetic T3 is reserved for younger patients, who do not have a history of heart problems and individuals non-responsive to T4 treatment.
 - Some men are inefficient in the conversion of T4 to T3, making combination drugs like Liotrix and Armour Thyroid ideal treatment options.
- Dosage for individuals suffering from secondary hypothyroidism determined by the amount of free T4 and T3 circulating in their system.
- Administering too high of a dosage leads to hyperthyroid symptoms.



Structural activity relationship



1. Aliphatic side chain

- L- alanine isomers of T3 and T4 are more active than D- alanine derivatives.
- Carboxylate ion and number of atoms connecting it to the ring are important for activity than intact Zwitterionic alanine side chain.
- Activity is maximum with the 2- carbon acetic acid side chain
- Position -1- of the ring is critical position

2. Alanine bearing ring (α - ring)

- Removal of both iodine atoms from the inner ring devoid T4₇₀ like activity.

- Retention of activity is observed on replacement of 3,5 iodine atoms with bromine.
 - Iodine doesn't play a unique role
- 3,5 disubstitution by symmetric ,lipophilic groups , not exceeding the size of iodine is required for activity.

3.Bridging atom

- Replacement of the bridging oxygen atom by sulfur or methylene group produces highly active analogs.
- Attempt to prepare amino and carbonyl bridged analogs have been unsuccessful.

4. Phenolic ring (Outer or β – ring)

- Phenolic ring of the tyronine nucleus is required for hormonal activity.
- Variations in 3' or 3',5' substituents on phenolic ring have dramatic effects on biological activity
- Substitution at 3' position by polar hydroxyl or nitro groups causes decrease in activity.
 - b/c of lowered lipophilicity and intramolecular hydrogen bonding

- Substitution by nonpolar halogen or alkyl group results in an increase in activity in a direct relation to bulk and lipophilicity of substituents.

Eg. $F < Cl < Br$

- Substitution in both 3' and 5' positions by the same halogen produces less active hormones than the corresponding 3'-monosubstituted analogs.
 - Due to the increased in phenolic hydroxyl ionization and results in increase in binding to thyroxine binding globulin.

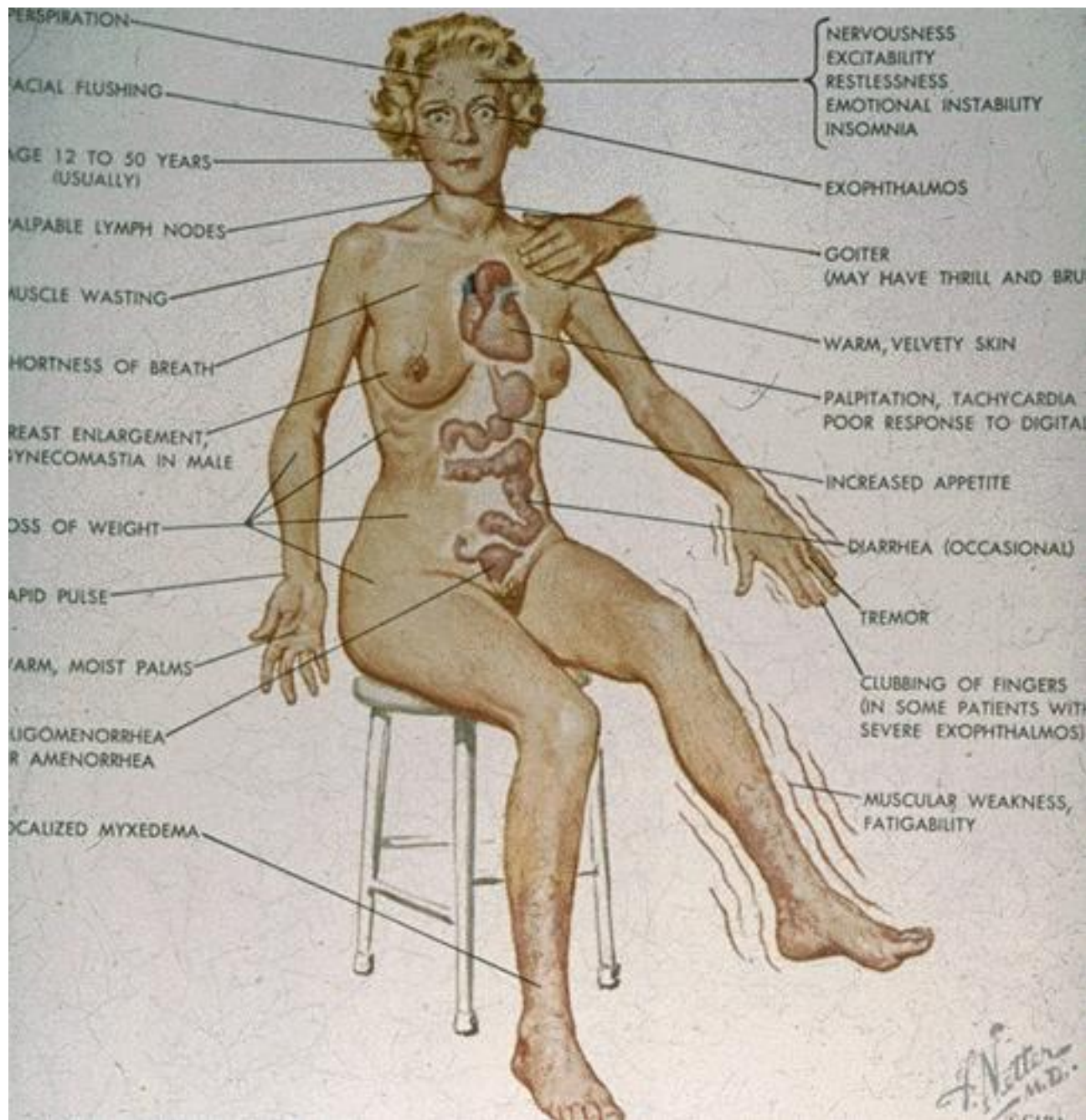
5. Phenolic hydroxyl group

- Weakly ionized phenolic hydroxyl group at the 4' – position is essential for optimum hormonal activity.
- Replacement the 4' – hydroxyl with an amino group results in a substantial decrease in activity (b/c of weak H- bonding ability.)
- 4' – unsubstituted compound is active. 4' –hydroxylation as activating step. However, methylation decreases activity.

Hyperthyroidism

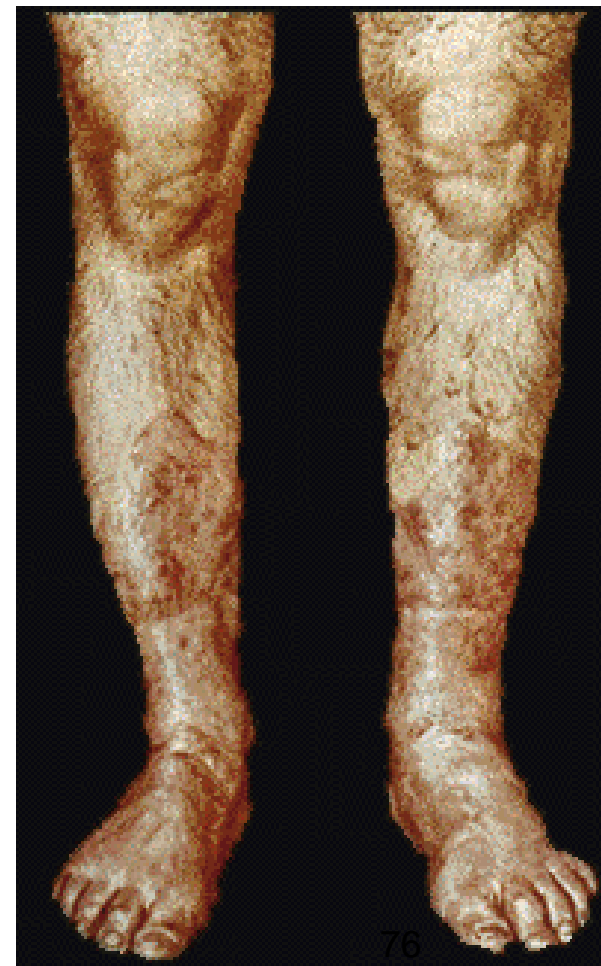
- The over production of thyroid hormones.
- Symptoms include fatigue, weight lose, rapid heart beat, anxiety, swollen eyes, and sensitivity to hot temperatures.
- Causes:
 - Grave's disease, and autoimmune disorder in which antibodies serve as agonists to the THS receptors on the thyroid's surface, causing thyroid growth and activation of hormone synthesis and secretion.
 - Thyroid tumors which cause the uncontrolled synthesis and secretion of thyroid hormones.
 - Thyroiditis, inflammation of the thyroid typically caused by infection.

Graves Disease



Hyperthyroidism

Graves Disease



- Wasting of Temporalis and shoulder
- Myxedema in limbs

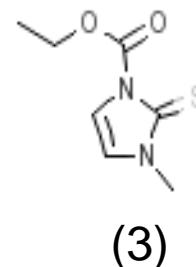
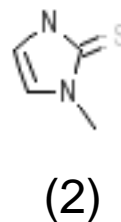
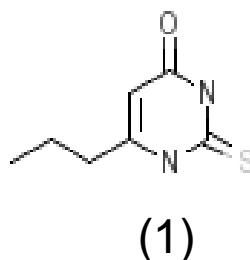
Exophthalmia

- Fat accumulation behind eyes
- High TSH
- Patient previously had a thyroidectomy



Treatment for Hyperthyroidism

- Anti-thyroid drugs—Inhibits thyroid hormone synthesis by irreversibly binding to TPO inhibiting its ability to break down iodine ($I_2 \rightarrow I^-$) and covalently attach it to the tyrosine residue of thyroglobulin.
 - Propylthiouracil (1)
 - Methimazole (2)
 - Carbamazepine—Degraded to methimazole in the body. (3)
- Thyroidectomy
- β -Blockers used in the treatment of thyroiditis to treat symptoms.



- Effective in the long-term treatment of hyperthyroidism.
- 6-8 weeks before maximum effect of the drug achieved. Drug inhibits hormone synthesis, so hormones synthesized prior to drug use will continue to cause hyperthyroid condition.
- Typical side effects include headache, nausea, vomiting, itchy skin and rash, and muscle aches and pains.
- Serious liver damage, decreased red and white blood cell synthesis, as well as decreased platelet production have been reported in a few cases. The drug's interaction with other enzymes responsible for clotting factor synthesis accounts for some of these serious side effects.
- Administering too high a dosage of anti-thyroid drugs can cause hypothyroidism.

Thyroid Treatment: Potential Drug Interactions

- **Drugs that reduce thyroid hormone production**
 - Lithium
 - Iodine-containing medications
 - Amiodarone (Cordarone)
- **Drugs that reduce thyroid hormone absorption**
 - Sucralfate (Carafate)
 - Ferrous sulfate (Slow Fe)
 - Cholestyramine (Questran)
 - Colestipol (Colestid)
 - Aluminum-containing antacids
 - Calcium products
- **Drugs that increase metabolism of thyroxine**
 - Rifampin (Rifadin)
 - Phenobarbital
 - Carbamazepine (Tegretol)
 - Warfarin (Coumadin)
 - Oral hypoglycemic agents
- **Drugs that displace thyroid hormone from protein binding**
 - Furosemide (Lasix)
 - Mefenamic acid (Ponstel)
 - Salicylates