## ENDOCRINE SYSTEM: FALL2003

MARTIN G. LOW, DEPT. PHYSIOLOGY

**Q:** WHY DO VERTEBRATES HAVE AN ENDOCRINE SYSTEM?

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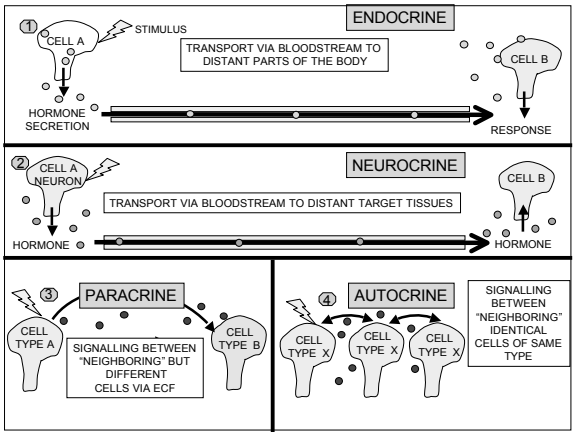
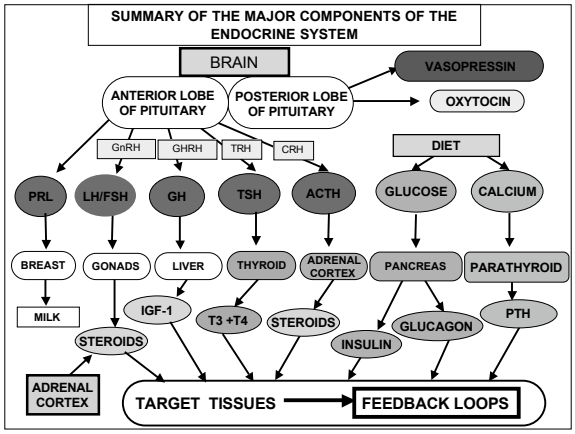
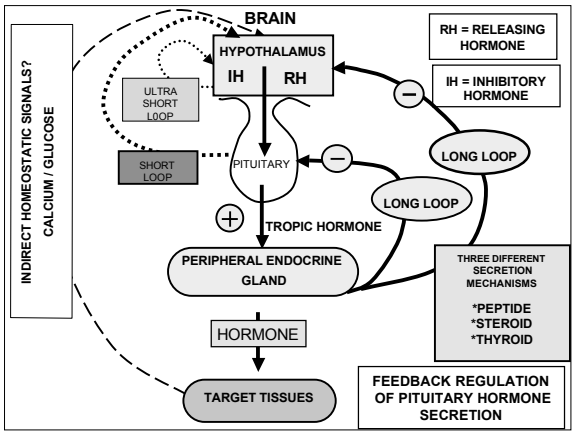
**A:** ALTHOUGH IT ALLOWS EXTREMELY RAPID COMMUNICATION THE "HARD WIRING" OF THE NERVOUS SYSTEM IS TOO "EXPENSIVE", INEFFICIENT (AND UNNECCESARY) FOR THE DELIVERY OF MOLECULAR SIGNALS TO EVERY CELL IN THE BODY.

THE CARDIOVASCULAR SYSTEM, WHICH IS MOSTLY DEVOTED TO TRANSPORTING OXYGEN AND NUTRIENTS, CAN ALSO PROVIDE A HIGHLY EFFICIENT, BUT RELATIVELY SLOW SYSTEM FOR DELIVERING "SOLUBLE" MESSENGER MOLECULES TO ESSENTIALLY EVERY CELL IN THE BODY.

HOWEVER TO ENSURE FIDELITY AND SPECIFICITY OF THE SIGNALLING PROCESS THESE "SOLUBLE MESSENGERS" MUST BE GUIDED TO THE CORRECT DESTINATION BY A "MOLECULAR ADDRESS"






**STRUCTURE & FUNCTION OF MAJOR HORMONES**

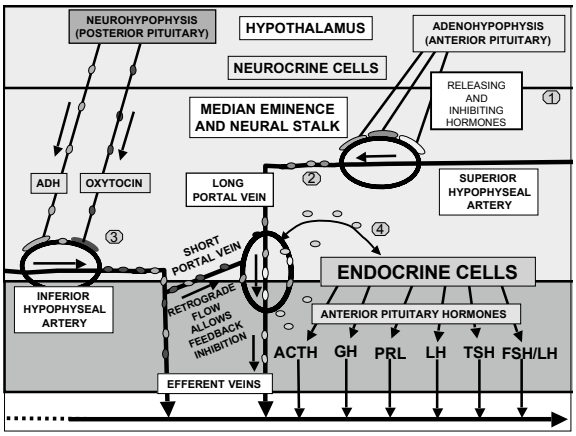
| HORMONE | M.W. | CHEMICAL STRUCTURE | MAJOR FUNCTION |
|---|---|---|---|
| TRIIODOTHYRONINE (T3) | <1000 | IODINATED TYROSINE DERIVATIVES | GROWTH, METABOLISM & DEVELOPMENT |
| THYROXINE (T4) | <1000 | | |
| STEROIDS | <1000 | CHOLESTEROL DERIVATIVES | " |
| ARG-VASOPRESSIN (ADH) | ~1000 | (S-S) LINKED CYCLIC NONAPEPTIDES | ANTI-DIURETIC HORMONE |
| OXYTOCIN | ~1000 | | SUCKLING RESPONSE |
| GLUCAGON | ~3,500 | 29-RESIDUE PEPTIDE | ↑ PLASMA GLUCOSE |
| CALCITONIN | ~ 4,000 | 32-RESIDUE PEPTIDE | ↓ PLASMA Ca |
| ADRENOCORICOTROPHIC HORMONE (ACTH) | 4,500 | 39-RESIDUE PEPTIDE DERIVED FROM 31K POMC PRECURSOR | STIMULATES RELEASE OF CORTICAL STEROIDS |
| INSULIN | 6,000 | 51-RESIDUE PEPTIDE WITH (S-S)-LINKED A AND B CHAINS | ↓ PLASMA GLUCOSE<br>LIPOLYSIS |
| PARATHYROID HORMONE | 9,500 | 84-RESIDUE PEPTIDE | ↑ PLASMA CALCIUM |
| PROLACTIN (PRL) | 23,000 | 198 /191 RESIDUE GLYCOPROTEINS WITH | LACTOGENESIS |
| GROWTH HORMONE (GH) | 22,000 | ~ 80% HOMOLOGY | GROWTH / METABOLISM |
| THYROID-STIMULATING HORMONE (TSH) | 28,000 | GLYCOPROTEINS WITH: | STIMULATES RELEASE OF T3 AND T4 |
| LUTEINZING HORMONE (LH) | 30,000 | COMMON ALPHA SUBUNIT | REGULATION OF SPERMATOGENESIS AND OOGENESIS |
| FOLLICLE-STIMULATING HORMONE (FSH) | 30,000 | AND VARIABLE BETA SUBUNIT | |
| CHORIONIC GONADOTROPHIN (hCG) | 57,000 | LEPTIN: 16kDa 139-RESIDUE PEPTIDE | MAINTENANCE OF CORPUS LUTEUM |

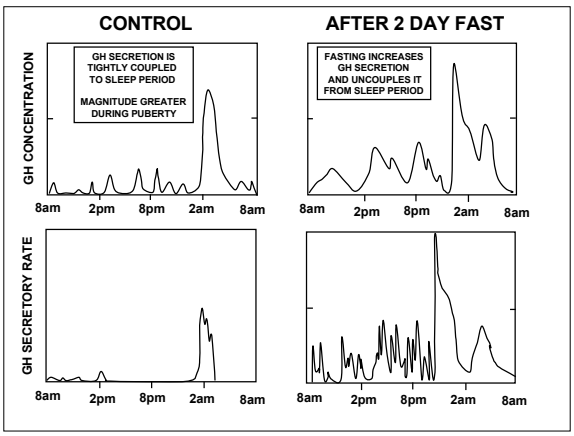
**CELL SURFACE RECEPTORS AND THEIR TRANSDUCERS: GROUP I**

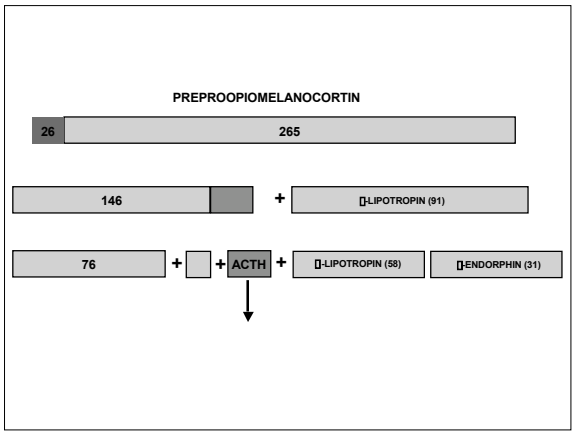
| RECEPTOR / HORMONE | MAJOR TRANSDUCERS |
|---|---|
| _1, _2, _3 - ADRENERGIC | G PROTEIN : CYCLASE |
| _1- ADRENERGIC | G PROTEIN : PLC-_ |
| _2- ADRENERGIC | G PROTEIN : PLC-_ AND CYCLASE ↓ |
| M1- MUSCARINIC | G PROTEIN : PLC-_ |
| D2-DOPAMINERGIC | G PROTEIN : PLC-_ AND CYCLASE ↓ |
| HISTAMINE | G PROTEIN : PLC-_ |
| BRADYKININ | G PROTEIN : PLC-_ |
| ANGIOTENSIN | G PROTEIN : PLC-_ |
| VASOPRESSIN | G PROTEIN : PLC-_ |
| GLUCAGON | G PROTEIN : AND CYCLASE |
| CALCITONIN | G PROTEIN : AND CYCLASE |
| PARATHYROID HORMONE | G PROTEIN : AND CYCLASE |
| PROSTAGLANDIN E2 | G PROTEIN : AND CYCLASE ↓ |
| LEUKOTRIENES | G PROTEIN : PLC-_ |

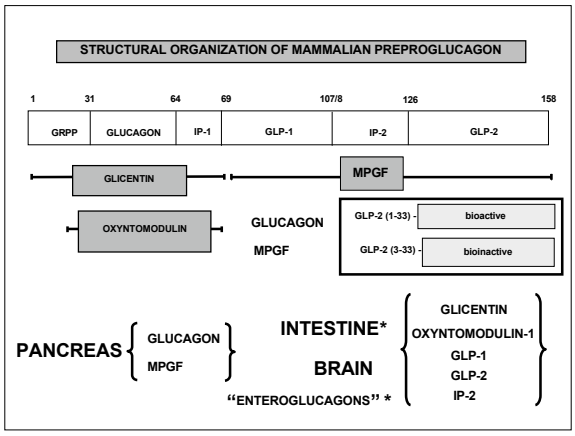
**CELL SURFACE RECEPTORS TRANSDUCERS AND MESSENGERS?: GROUP II**

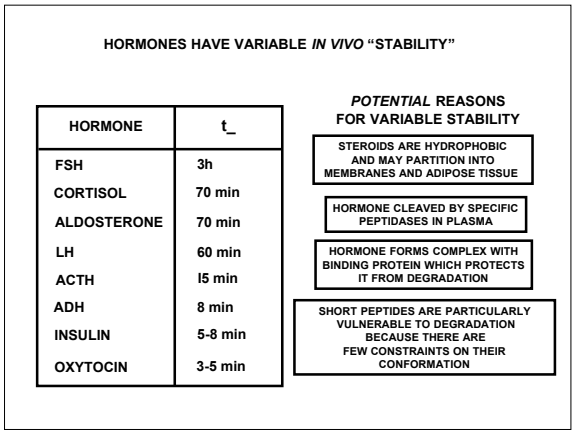
| RECEPTOR / HORMONE | MAJOR TRANSDUCERS |
|---|---|
| THROMBOXANE A2 | G PROTEIN : PLC-_ |
| THYROTROPIN-RELEASING HORMONE (TRH) | G PROTEIN : PLC-_ |
| THYROID-STIMULATING HORMONE (TSH) | G PROTEIN : CYCLASE |
| FOLLICLE-STIMULATING HORMONE (FSH) | G PROTEIN : CYCLASE |
| LUTEINIZING HORMONE (LH) | G PROTEIN : CYCLASE |
| EPIDERMAL GROWTH FACTOR (EGF) | RECEPTOR TYROSINE KINASE: PLC-_ |
| PLATELET-DERIVED GROWTH FACTOR (PDGF) | RECEPTOR TYROSINE KINASE; PLC-_ |
| INSULIN | RECEPTOR TYROSINE KINASE; IRS-1 |
| INSULIN -LIKE GROWTH FACTOR 1 ( IGF-1) | RECEPTOR TYROSINE KINASE; IRS-1 |
| GROWTH HORMONE (GH) | NON-RECEPTOR TYROSINE KINASE; JAK/Stat |
| PROLACTIN (PRL) | NON-RECEPTOR TYROSINE KINASE; JAK/Stat |
| ACTIVIN/INHIBIN (TGF-_ FAMILY) | RECEPTOR Ser/Thr KINASE:Smad |

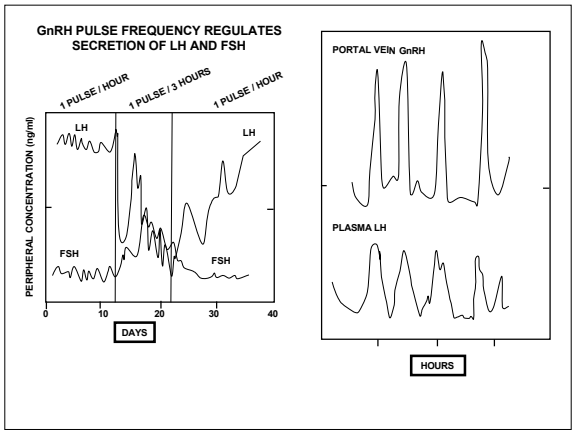


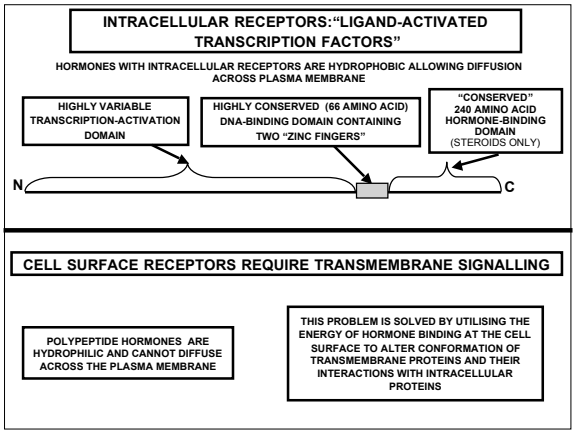



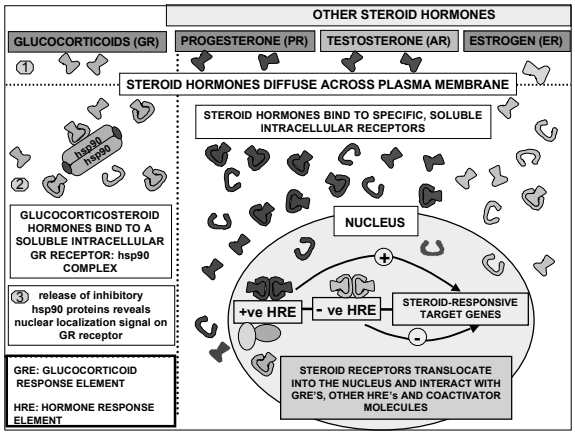

PREPROOPIOMELANOCORTIN
26
265
146
+
-LIPOTROPIN (91)
76
+
+
ACTH
+
-LIPOTROPIN (58)
-ENDORPHIN (31)

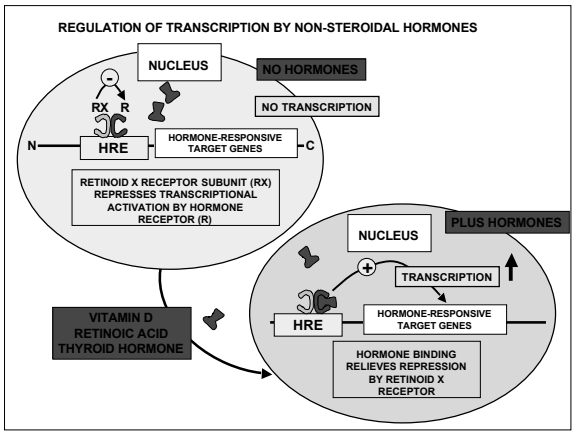

STRUCTURAL ORGANIZATION OF MAMMALIAN PREPROGLUCAGON
1
31
64
69
107/8
126
158
GRPP
GLUCAGON
IP-1
GLP-1
IP-2
GLP-2
GLICENTIN
MPGF
OXYNTOMODULIN
GLUCAGON
MPGF
GLP-2 (1-33)
bioactive
GLP-2 (3-33)
bioinactive
PANCREAS
GLUCAGON
MPGF
INTESTINE*
BRAIN
GLICENTIN
OXYNTOMODULIN-1
GLP-1
GLP-2
IP-2
"ENTEROGLUCAGONS" *

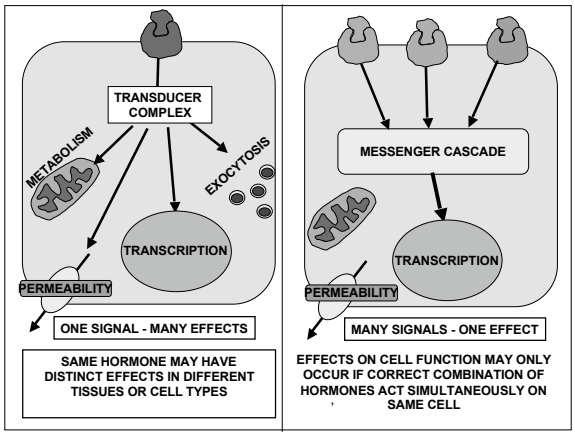

HORMONES HAVE VARIABLE *IN VIVO* "STABILITY"
HORMONE
t_
FSH
3h
CORTISOL
70 min
ALDOSTERONE
70 min
LH
60 min
ACTH
I5 min
ADH
8 min
INSULIN
5-8 min
OXYTOCIN
3-5 min
*POTENTIAL* REASONS FOR VARIABLE STABILITY
STEROIDS ARE HYDROPHOBIC AND MAY PARTITION INTO MEMBRANES AND ADIPOSE TISSUE
HORMONE CLEAVED BY SPECIFIC PEPTIDASES IN PLASMA
HORMONE FORMS COMPLEX WITH BINDING PROTEIN WHICH PROTECTS IT FROM DEGRADATION
SHORT PEPTIDES ARE PARTICULARLY VULNERABLE TO DEGRADATION BECAUSE THERE ARE FEW CONSTRAINTS ON THEIR CONFORMATION

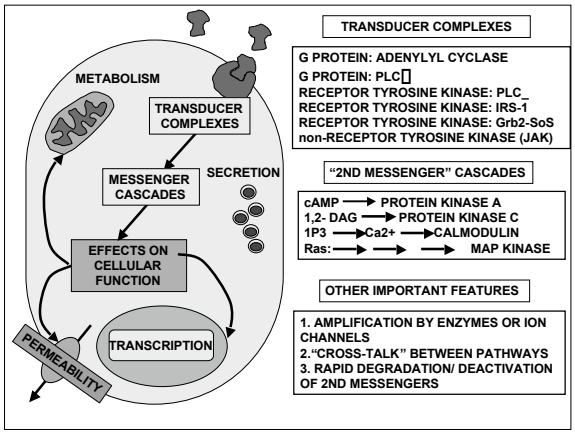

GnRH PULSE FREQUENCY REGULATES SECRETION OF LH AND FSH
1 PULSE / HOUR
1 PULSE / 3 HOURS
1 PULSE / HOUR
LH
LH
FSH
FSH
PERIPHERAL CONCENTRATION (ng/ml)
0
10
20
30
40
DAYS
PORTAL VEIN GnRH
PLASMA LH
HOURS

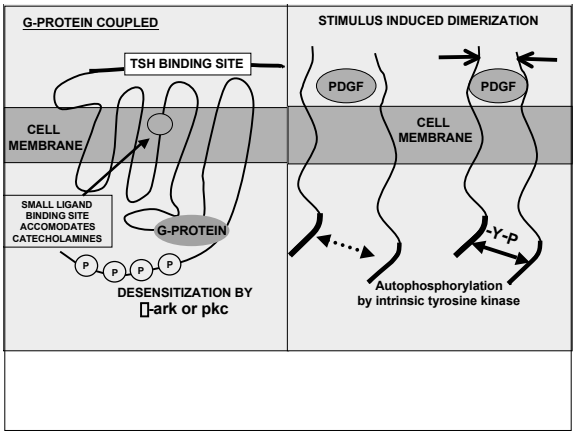

INTRACELLULAR RECEPTORS:"LIGAND-ACTIVATED TRANSCRIPTION FACTORS"
HORMONES WITH INTRACELLULAR RECEPTORS ARE HYDROPHOBIC ALLOWING DIFFUSION ACROSS PLASMA MEMBRANE
HIGHLY VARIABLE TRANSCRIPTION-ACTIVATION DOMAIN
HIGHLY CONSERVED (66 AMINO ACID) DNA-BINDING DOMAIN CONTAINING TWO "ZINC FINGERS"
"CONSERVED" 240 AMINO ACID HORMONE-BINDING DOMAIN (STEROIDS ONLY)
N
C
CELL SURFACE RECEPTORS REQUIRE TRANSMEMBRANE SIGNALLING
POLYPEPTIDE HORMONES ARE HYDROPHILIC AND CANNOT DIFFUSE ACROSS THE PLASMA MEMBRANE
THIS PROBLEM IS SOLVED BY UTILISING THE ENERGY OF HORMONE BINDING AT THE CELL SURFACE TO ALTER CONFORMATION OF TRANSMEMBRANE PROTEINS AND THEIR INTERACTIONS WITH INTRACELLULAR PROTEINS

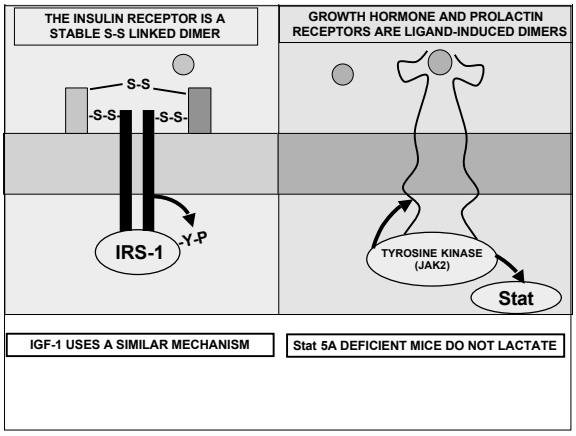

OTHER STEROID HORMONES
GLUCOCORTICOIDS (GR)
PROGESTERONE (PR)
TESTOSTERONE (AR)
ESTROGEN (ER)
1
STEROID HORMONES DIFFUSE ACROSS PLASMA MEMBRANE
STEROID HORMONES BIND TO SPECIFIC, SOLUBLE INTRACELLULAR RECEPTORS
hsp90
hsp90
2
GLUCOCORTICOSTEROID HORMONES BIND TO A SOLUBLE INTRACELLULAR GR RECEPTOR: hsp90 COMPLEX
NUCLEUS
3 release of inhibitory hsp90 proteins reveals nuclear localization signal on GR receptor
+ve HRE
- ve HRE
STEROID-RESPONSIVE TARGET GENES
GRE: GLUCOCORTICOID RESPONSE ELEMENT
HRE: HORMONE RESPONSE ELEMENT
STEROID RECEPTORS TRANSLOCATE INTO THE NUCLEUS AND INTERACT WITH GRE'S, OTHER HRE's AND COACTIVATOR MOLECULES

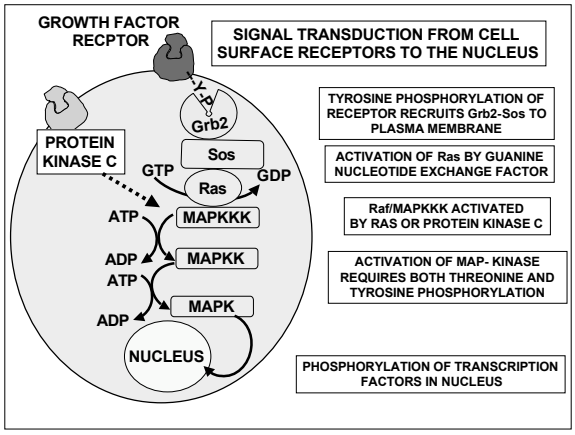

REGULATION OF TRANSCRIPTION BY NON-STEROIDAL HORMONES
NUCLEUS
NO HORMONES
NO TRANSCRIPTION
RX R
N
HRE
HORMONE-RESPONSIVE TARGET GENES
C
RETINOID X RECEPTOR SUBUNIT (RX) REPRESSES TRANSCRIPTIONAL ACTIVATION BY HORMONE RECEPTOR (R)
PLUS HORMONES
NUCLEUS
TRANSCRIPTION
HRE
HORMONE-RESPONSIVE TARGET GENES
VITAMIN D
RETINOIC ACID
THYROID HORMONE
HORMONE BINDING RELIEVES REPRESSION BY RETINOID X RECEPTOR

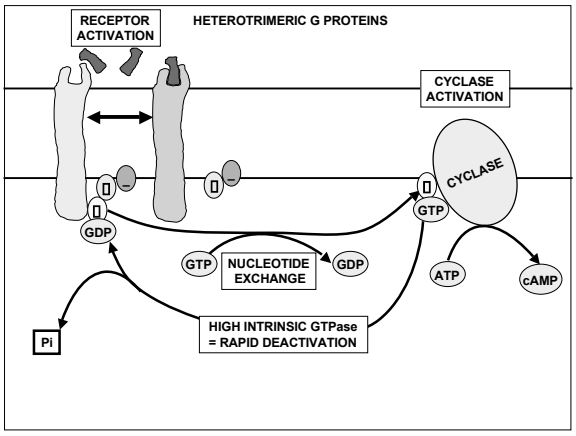

TRANSDUCER COMPLEX
METABOLISM
EXOCYTOSIS
TRANSCRIPTION
PERMEABILITY
ONE SIGNAL - MANY EFFECTS
SAME HORMONE MAY HAVE DISTINCT EFFECTS IN DIFFERENT TISSUES OR CELL TYPES
MESSENGER CASCADE
TRANSCRIPTION
PERMEABILITY
MANY SIGNALS - ONE EFFECT
EFFECTS ON CELL FUNCTION MAY ONLY OCCUR IF CORRECT COMBINATION OF HORMONES ACT SIMULTANEOUSLY ON SAME CELL

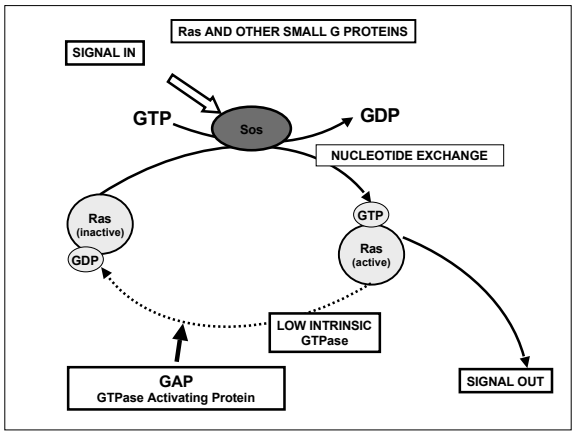

METABOLISM
TRANSDUCER COMPLEXES
MESSENGER CASCADES
SECRETION
EFFECTS ON CELLULAR FUNCTION
TRANSCRIPTION
PERMEABILITY
TRANSDUCER COMPLEXES
G PROTEIN: ADENYLYL CYCLASE
G PROTEIN: PLC
RECEPTOR TYROSINE KINASE: PLC_
RECEPTOR TYROSINE KINASE: IRS-1
RECEPTOR TYROSINE KINASE: Grb2-SoS
non-RECEPTOR TYROSINE KINASE (JAK)
"2ND MESSENGER" CASCADES
cAMP PROTEIN KINASE A
1,2- DAG PROTEIN KINASE C
1P3 Ca2+ CALMODULIN
Ras: MAP KINASE
OTHER IMPORTANT FEATURES
1. AMPLIFICATION BY ENZYMES OR ION CHANNELS
2."CROSS-TALK" BETWEEN PATHWAYS
3. RAPID DEGRADATION/ DEACTIVATION OF 2ND MESSENGERS

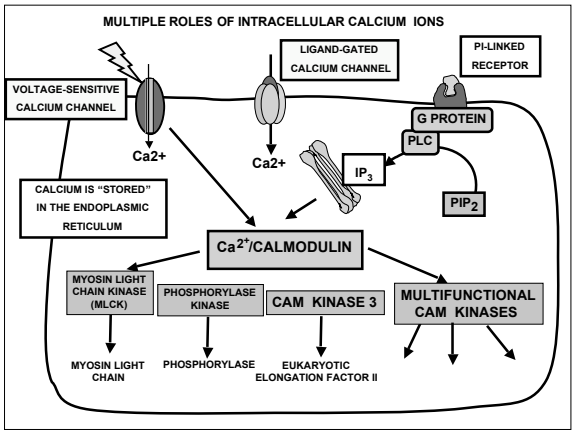

G-PROTEIN COUPLED
STIMULUS INDUCED DIMERIZATION
TSH BINDING SITE
CELL MEMBRANE
SMALL LIGAND BINDING SITE ACCOMODATES CATECHOLAMINES
G-PROTEIN
P
DESENSITIZATION BY -ark or pkc
PDGF
PDGF
CELL MEMBRANE
-Y-P
Autophosphorylation by intrinsic tyrosine kinase

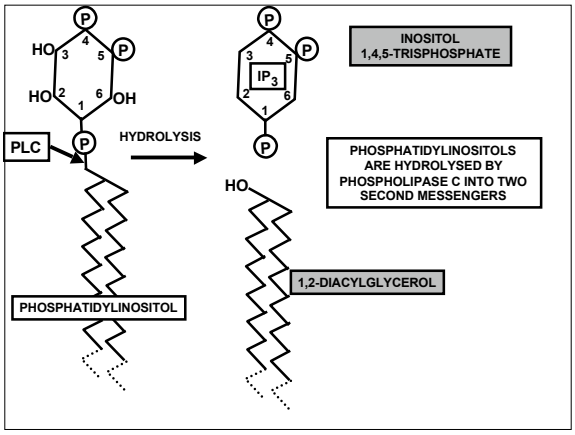

THE INSULIN RECEPTOR IS A STABLE S-S LINKED DIMER
S-S
-S-S-
-S-S-
IRS-1
-Y-P
IGF-1 USES A SIMILAR MECHANISM
GROWTH HORMONE AND PROLACTIN RECEPTORS ARE LIGAND-INDUCED DIMERS
TYROSINE KINASE (JAK2)
Stat
Stat 5A DEFICIENT MICE DO NOT LACTATE

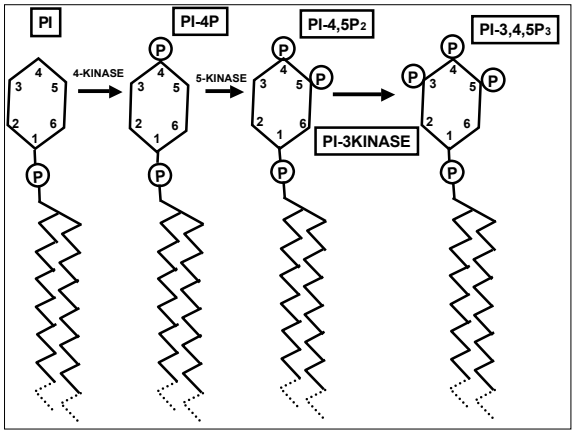

GROWTH FACTOR RECPTOR
SIGNAL TRANSDUCTION FROM CELL SURFACE RECEPTORS TO THE NUCLEUS
Y-P
Grb2
Sos
PROTEIN KINASE C
GTP
Ras
GDP
ATP
MAPKKK
ADP
ATP
MAPKK
MAPK
ADP
NUCLEUS
TYROSINE PHOSPHORYLATION OF RECEPTOR RECRUITS Grb2-Sos TO PLASMA MEMBRANE
ACTIVATION OF Ras BY GUANINE NUCLEOTIDE EXCHANGE FACTOR
Raf/MAPKKK ACTIVATED BY RAS OR PROTEIN KINASE C
ACTIVATION OF MAP- KINASE REQUIRES BOTH THREONINE AND TYROSINE PHOSPHORYLATION
PHOSPHORYLATION OF TRANSCRIPTION FACTORS IN NUCLEUS

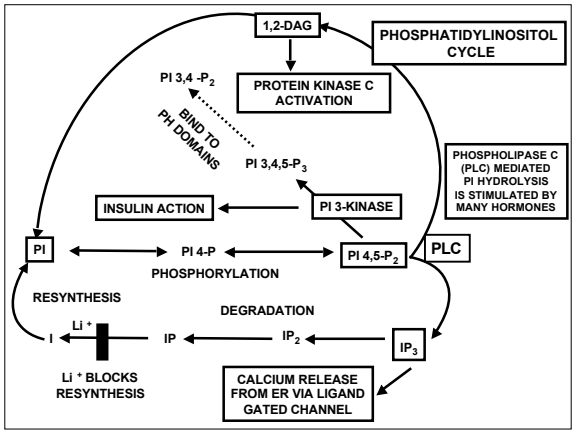

RECEPTOR ACTIVATION
HETEROTRIMERIC G PROTEINS
CYCLASE ACTIVATION
CYCLASE
GTP
GDP
GTP
NUCLEOTIDE EXCHANGE
GDP
ATP
cAMP
Pi
HIGH INTRINSIC GTPase = RAPID DEACTIVATION

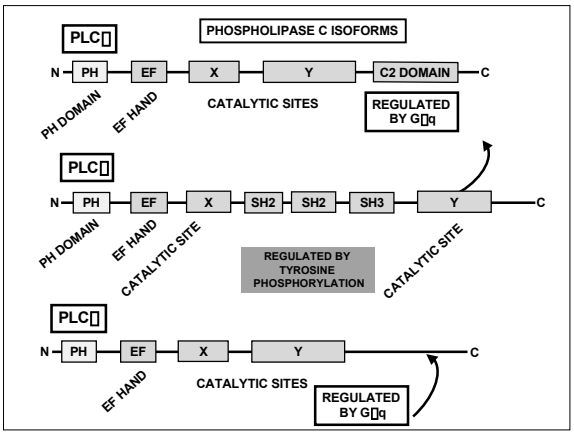

Ras AND OTHER SMALL G PROTEINS
SIGNAL IN
GTP
Sos
GDP
NUCLEOTIDE EXCHANGE
Ras (inactive)
GDP
GTP
Ras (active)
LOW INTRINSIC GTPase
GAP
GTPase Activating Protein
SIGNAL OUT


MULTIPLE ROLES OF INTRACELLULAR CALCIUM IONS
LIGAND-GATED CALCIUM CHANNEL
PI-LINKED RECEPTOR
VOLTAGE-SENSITIVE CALCIUM CHANNEL
G PROTEIN
PLC
Ca2+
Ca2+
IP3
PIP2
CALCIUM IS "STORED" IN THE ENDOPLASMIC RETICULUM
Ca2+/CALMODULIN
MYOSIN LIGHT CHAIN KINASE (MLCK)
PHOSPHORYLASE KINASE
CAM KINASE 3
MULTIFUNCTIONAL CAM KINASES
MYOSIN LIGHT CHAIN
PHOSPHORYLASE
EUKARYOTIC ELONGATION FACTOR II


INOSITOL 1,4,5-TRISPHOSPHATE
HO
OH
IP3
PLC
HYDROLYSIS
PHOSPHATIDYLINOSITOLS ARE HYDROLYSED BY PHOSPHOLIPASE C INTO TWO SECOND MESSENGERS
HO
1,2-DIACYLGLYCEROL
PHOSPHATIDYLINOSITOL


PI
PI-4P
PI-4,5P2
PI-3,4,5P3
4-KINASE
5-KINASE
PI-3KINASE


1,2-DAG
PHOSPHATIDYLINOSITOL CYCLE
PI 3,4 -P2
PROTEIN KINASE C ACTIVATION
BIND TO PH DOMAINS
PI 3,4,5-P3
PHOSPHOLIPASE C (PLC) MEDIATED PI HYDROLYSIS IS STIMULATED BY MANY HORMONES
INSULIN ACTION
PI 3-KINASE
PI
PI 4-P
PI 4,5-P2
PLC
PHOSPHORYLATION
RESYNTHESIS
DEGRADATION
Li +
I
IP
IP2
IP3
Li + BLOCKS RESYNTHESIS
CALCIUM RELEASE FROM ER VIA LIGAND GATED CHANNEL



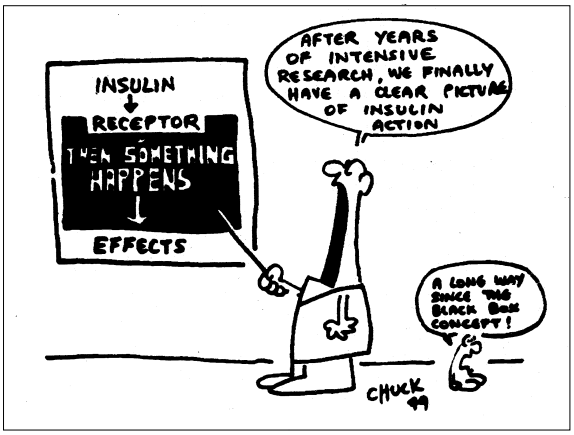

**SEQUENCE MOTIFS INVOLVED IN SIGNAL TRANSDUCTION**

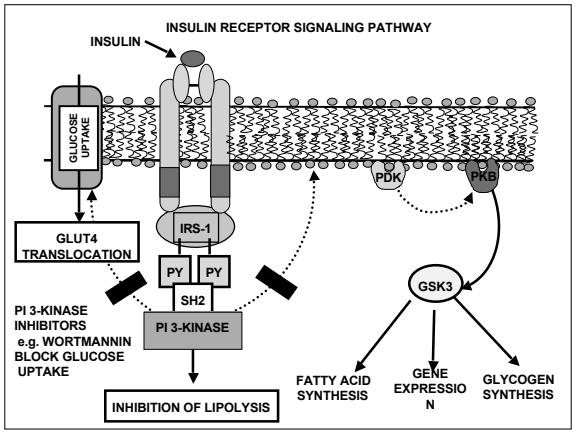
| DOMAIN | NAME | MOTIF RECOGNIZED |
|---|---|---|
| src homology 2 | SH2 | pY-X-X-X |
| "phosphotyrosine-binding" | PTB | - _ -N-P-X-pY- |
| src homology 3 | SH3 | "proline-rich region" |
| Pleckstrin Homology | PH | PI-$P_x$ headgroups |

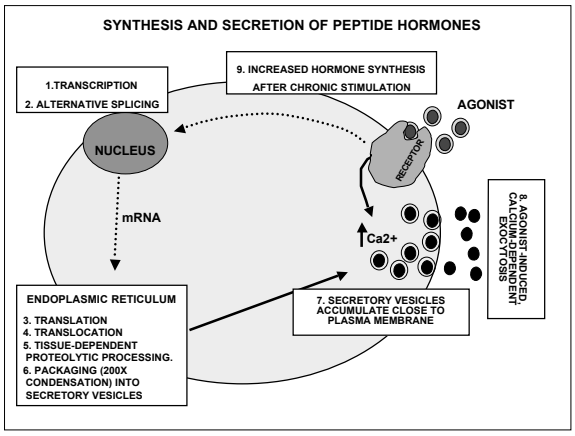
_ =Hydrophobic residue

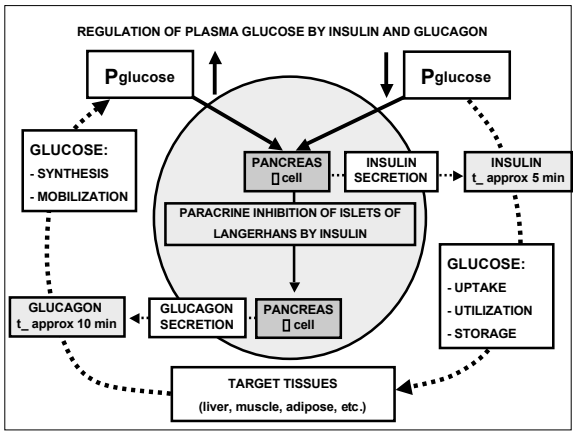
| PROTEIN | ARRANGEMENT OF BINDING DOMAINS AND CATALYTIC SITES |
|---|---|
| *src* kinase | --Myr----SH3----SH3----SH2----Tyr kinase--- |
| Btk | --PH----Pro----SH3----SH2----Tyr kinase---- |
| Shc | --PTB----SH2- ('Collagen-like') |
| Grb-2 | --SH3----SH2----SH3 |
| Shp-2 (*Syp*) | --SH2----SH2----PTPase |
| PLC□ | ? |
| PLC□ | --PH----PLC----PLC-- |
| PLC□ | --PH----PLC----SH2----SH2----SH3----PLC |
| PLC□ | --PH----PLC----PLC |
| PKB | --PH---- Ser/Thr kinase |
| p120Ras-GAP | --SH2----SH3----SH2----PH----GAP |

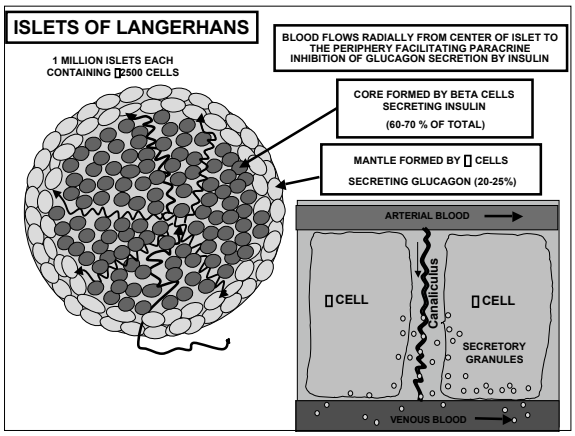
**LECTURE 3**

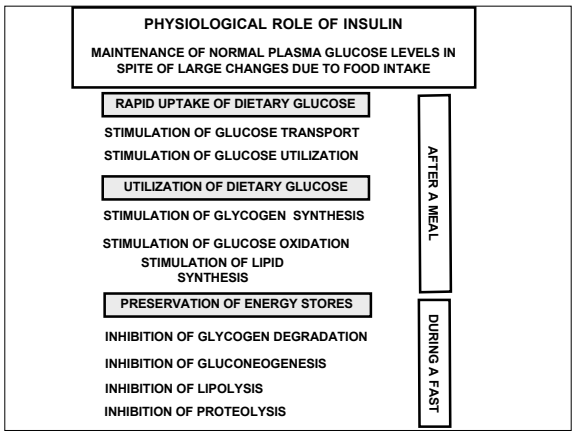


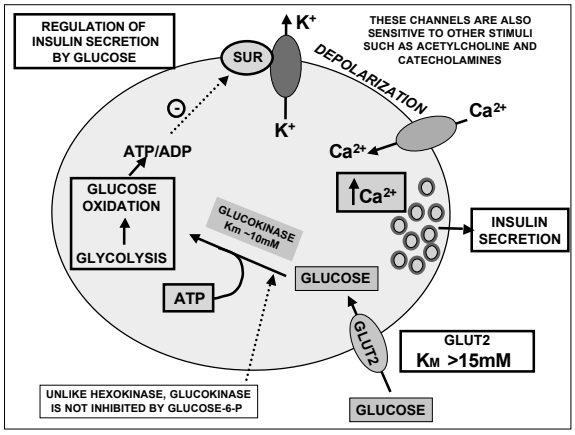



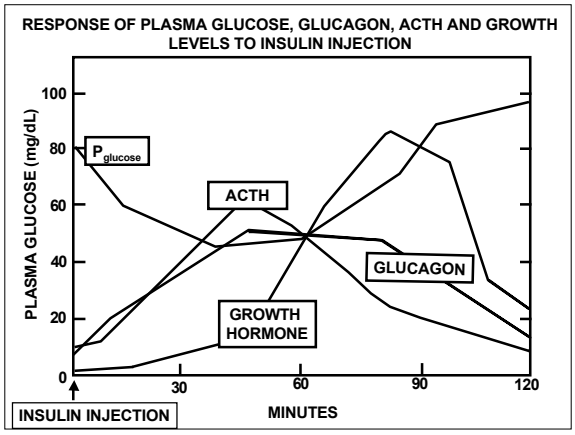

SYNTHESIS AND SECRETION OF PEPTIDE HORMONES
1.TRANSCRIPTION
2. ALTERNATIVE SPLICING
9. INCREASED HORMONE SYNTHESIS AFTER CHRONIC STIMULATION
AGONIST
NUCLEUS
RECEPTOR
mRNA
Ca2+
8. AGONIST-INDUCED CALCIUM-DEPENDENT EXOCYTOSIS
ENDOPLASMIC RETICULUM
3. TRANSLATION
4. TRANSLOCATION
5. TISSUE-DEPENDENT PROTEOLYTIC PROCESSING.
6. PACKAGING (200X CONDENSATION) INTO SECRETORY VESICLES
7. SECRETORY VESICLES ACCUMULATE CLOSE TO PLASMA MEMBRANE

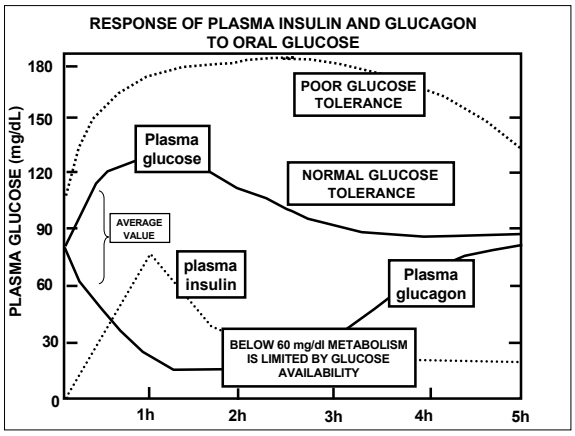

REGULATION OF PLASMA GLUCOSE BY INSULIN AND GLUCAGON
Pglucose
Pglucose
GLUCOSE:
- SYNTHESIS
- MOBILIZATION
PANCREAS cell
INSULIN SECRETION
INSULIN t_ approx 5 min
PARACRINE INHIBITION OF ISLETS OF LANGERHANS BY INSULIN
GLUCOSE:
- UPTAKE
- UTILIZATION
- STORAGE
GLUCAGON t_ approx 10 min
GLUCAGON SECRETION
PANCREAS cell
TARGET TISSUES
(liver, muscle, adipose, etc.)

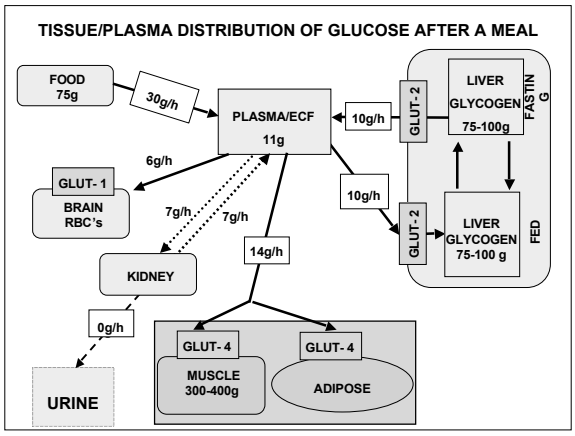

ISLETS OF LANGERHANS
1 MILLION ISLETS EACH CONTAINING 2500 CELLS
BLOOD FLOWS RADIALLY FROM CENTER OF ISLET TO THE PERIPHERY FACILITATING PARACRINE INHIBITION OF GLUCAGON SECRETION BY INSULIN
CORE FORMED BY BETA CELLS SECRETING INSULIN (60-70 % OF TOTAL)
MANTLE FORMED BY CELLS SECRETING GLUCAGON (20-25%)
ARTERIAL BLOOD
CELL
CELL
Canaliculis
SECRETORY GRANULES
VENOUS BLOOD

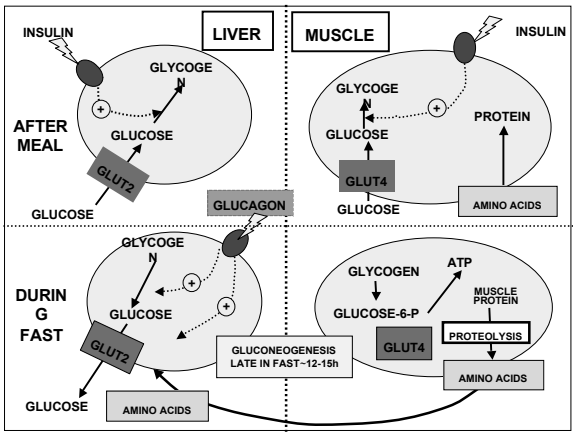

PHYSIOLOGICAL ROLE OF INSULIN
MAINTENANCE OF NORMAL PLASMA GLUCOSE LEVELS IN SPITE OF LARGE CHANGES DUE TO FOOD INTAKE
RAPID UPTAKE OF DIETARY GLUCOSE
STIMULATION OF GLUCOSE TRANSPORT
STIMULATION OF GLUCOSE UTILIZATION
UTILIZATION OF DIETARY GLUCOSE
STIMULATION OF GLYCOGEN SYNTHESIS
STIMULATION OF GLUCOSE OXIDATION
STIMULATION OF LIPID SYNTHESIS
PRESERVATION OF ENERGY STORES
INHIBITION OF GLYCOGEN DEGRADATION
INHIBITION OF GLUCONEOGENESIS
INHIBITION OF LIPOLYSIS
INHIBITION OF PROTEOLYSIS
AFTER A MEAL
DURING A FAST

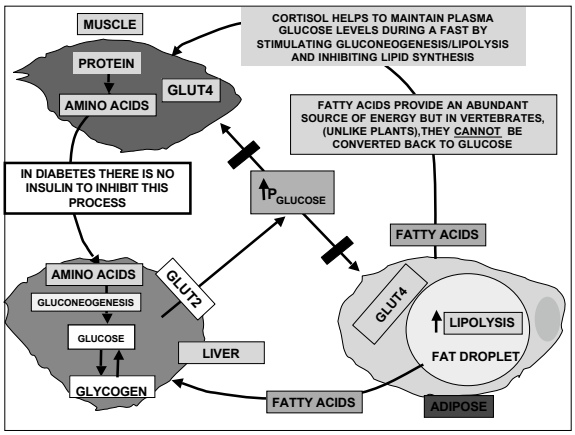

REGULATION OF INSULIN SECRETION BY GLUCOSE
K+
THESE CHANNELS ARE ALSO SENSITIVE TO OTHER STIMULI SUCH AS ACETYLCHOLINE AND CATECHOLAMINES
SUR
DEPOLARIZATION
Ca2+
K+
Ca2+
ATP/ADP
GLUCOSE OXIDATION
GLYCOLYSIS
Ca2+
GLUCOKINASE Km ~10mM
INSULIN SECRETION
ATP
GLUCOSE
GLUT2
GLUT2 KM >15mM
UNLIKE HEXOKINASE, GLUCOKINASE IS NOT INHIBITED BY GLUCOSE-6-P
GLUCOSE

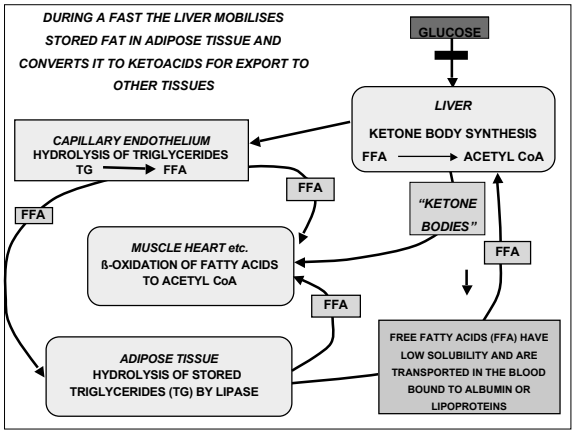

RESPONSE OF PLASMA GLUCOSE, GLUCAGON, ACTH AND GROWTH LEVELS TO INSULIN INJECTION
PLASMA GLUCOSE (mg/dL)
100
80
60
40
20
0
Pglucose
ACTH
GLUCAGON
GROWTH HORMONE
30
60
90
120
INSULIN INJECTION
MINUTES

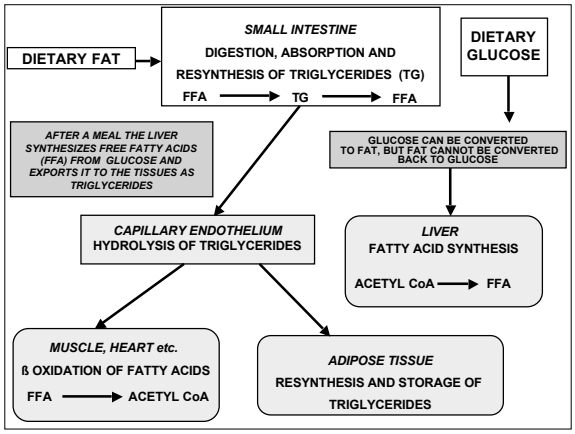

RESPONSE OF PLASMA INSULIN AND GLUCAGON TO ORAL GLUCOSE
PLASMA GLUCOSE (mg/dL)
180
150
120
90
60
30
0
1h
2h
3h
4h
5h
POOR GLUCOSE TOLERANCE
Plasma glucose
NORMAL GLUCOSE TOLERANCE
AVERAGE VALUE
plasma insulin
Plasma glucagon
BELOW 60 mg/dl METABOLISM IS LIMITED BY GLUCOSE AVAILABILITY

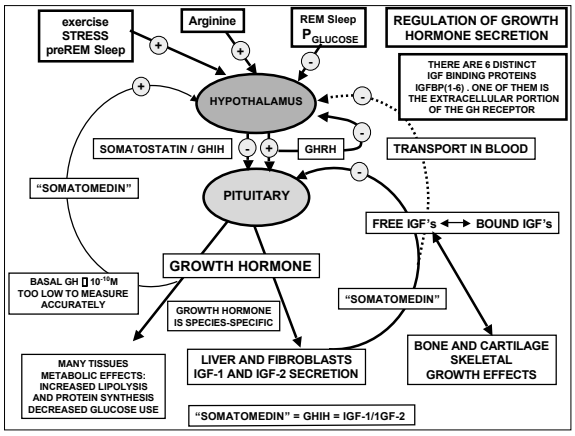

TISSUE/PLASMA DISTRIBUTION OF GLUCOSE AFTER A MEAL
FOOD 75g
30g/h
PLASMA/ECF 11g
10g/h
GLUT- 2
LIVER GLYCOGEN 75-100g
FASTING
6g/h
GLUT- 1
BRAIN RBC's
7g/h
7g/h
10g/h
GLUT- 2
LIVER GLYCOGEN 75-100 g
FED
KIDNEY
14g/h
0g/h
URINE
GLUT- 4
MUSCLE 300-400g
GLUT- 4
ADIPOSE


INSULIN
LIVER
MUSCLE
INSULIN
AFTER MEAL
GLYCOGEN
GLUCOSE
GLUT2
GLUCOSE
GLUCAGON
GLYCOGEN
GLUCOSE
GLUT4
GLUCOSE
PROTEIN
AMINO ACIDS
DURING FAST
GLYCOGEN
GLUCOSE
GLUT2
GLUCONEOGENESIS LATE IN FAST~12-15h
GLUCOSE
AMINO ACIDS
GLYCOGEN
ATP
GLUCOSE-6-P
MUSCLE PROTEIN
PROTEOLYSIS
GLUT4
AMINO ACIDS


MUSCLE
CORTISOL HELPS TO MAINTAIN PLASMA GLUCOSE LEVELS DURING A FAST BY STIMULATING GLUCONEOGENESIS/LIPOLYSIS AND INHIBITING LIPID SYNTHESIS
PROTEIN
AMINO ACIDS
GLUT4
FATTY ACIDS PROVIDE AN ABUNDANT SOURCE OF ENERGY BUT IN VERTEBRATES, (UNLIKE PLANTS),THEY CANNOT BE CONVERTED BACK TO GLUCOSE
IN DIABETES THERE IS NO INSULIN TO INHIBIT THIS PROCESS
↑P GLUCOSE
FATTY ACIDS
AMINO ACIDS
GLUT2
GLUCONEOGENESIS
GLUCOSE
GLYCOGEN
LIVER
GLUT4
LIPOLYSIS
FAT DROPLET
FATTY ACIDS
ADIPOSE

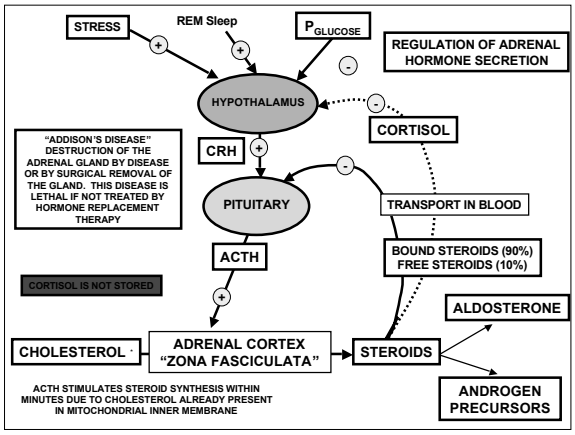

DURING A FAST THE LIVER MOBILISES STORED FAT IN ADIPOSE TISSUE AND CONVERTS IT TO KETOACIDS FOR EXPORT TO OTHER TISSUES
GLUCOSE
LIVER
KETONE BODY SYNTHESIS
FFA → ACETYL CoA
CAPILLARY ENDOTHELIUM
HYDROLYSIS OF TRIGLYCERIDES
TG → FFA
FFA
"KETONE BODIES"
FFA
FFA
MUSCLE HEART etc.
ß-OXIDATION OF FATTY ACIDS TO ACETYL CoA
FFA
ADIPOSE TISSUE
HYDROLYSIS OF STORED TRIGLYCERIDES (TG) BY LIPASE
FREE FATTY ACIDS (FFA) HAVE LOW SOLUBILITY AND ARE TRANSPORTED IN THE BLOOD BOUND TO ALBUMIN OR LIPOPROTEINS


DIETARY FAT
SMALL INTESTINE
DIGESTION, ABSORPTION AND RESYNTHESIS OF TRIGLYCERIDES (TG)
FFA → TG → FFA
DIETARY GLUCOSE
AFTER A MEAL THE LIVER SYNTHESIZES FREE FATTY ACIDS (FFA) FROM GLUCOSE AND EXPORTS IT TO THE TISSUES AS TRIGLYCERIDES
GLUCOSE CAN BE CONVERTED TO FAT, BUT FAT CANNOT BE CONVERTED BACK TO GLUCOSE
CAPILLARY ENDOTHELIUM
HYDROLYSIS OF TRIGLYCERIDES
LIVER
FATTY ACID SYNTHESIS
ACETYL CoA → FFA
MUSCLE, HEART etc.
ß OXIDATION OF FATTY ACIDS
FFA → ACETYL CoA
ADIPOSE TISSUE
RESYNTHESIS AND STORAGE OF TRIGLYCERIDES

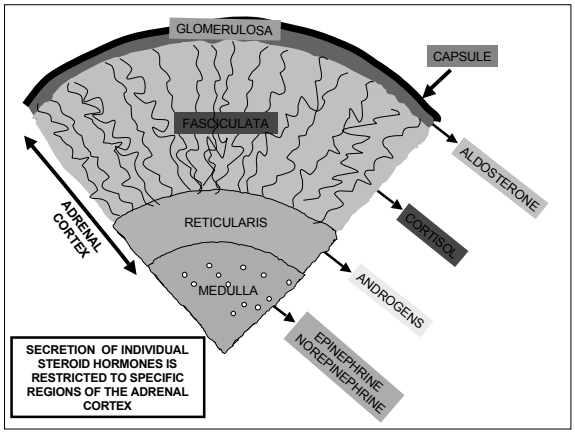


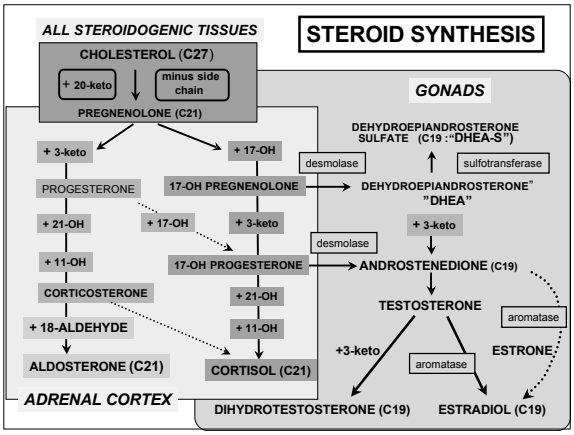

HORMONAL REGULATION OF METABOLISM

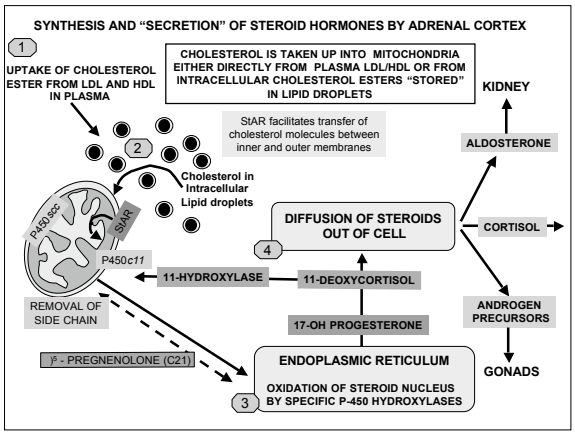
| | LIPOLYSIS | PROTEIN DEGRADATION | GLUCOSE SYNTHESIS | LIVER GLYCOGEN | PLASMA GLUCOSE |
|---|---|---|---|---|---|
| INSULIN | ↓ | ↓ | ↓ | ↑ | ↓ |
| CORTISOL | ↑ | ↑ | ↑ | ↑ | ↑ |
| GLUCAGON | ↑ | .... | ↑ | ↓ | ↑ |
| GROWTH HORMONE | ↑ | ↓ | ↑ | ↓ | ↑ |
| CATECHOLAMINES | ↑ | | ↑ (□-1) | ↓ □ | ↑ □ |
| LEPTIN | ↑ ? | .... | | | ↑ |

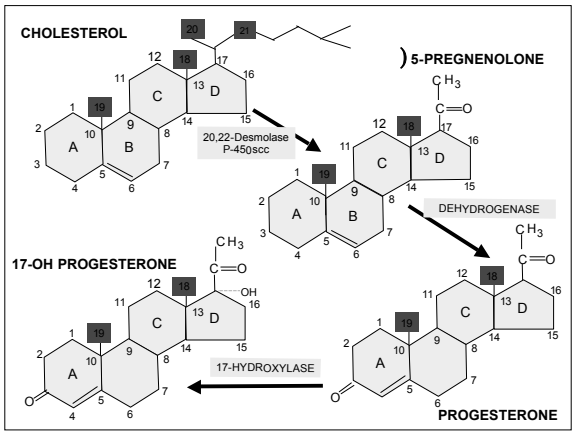


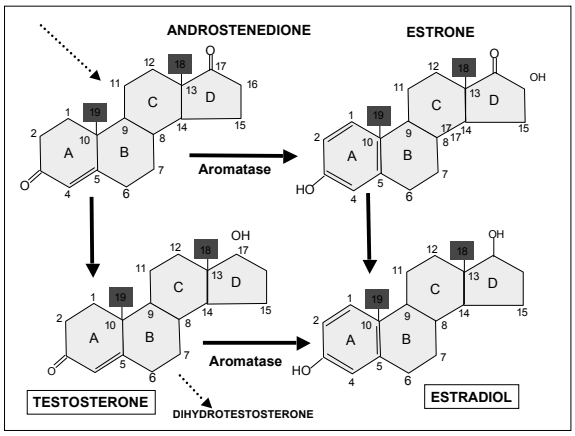

LECTURE 4

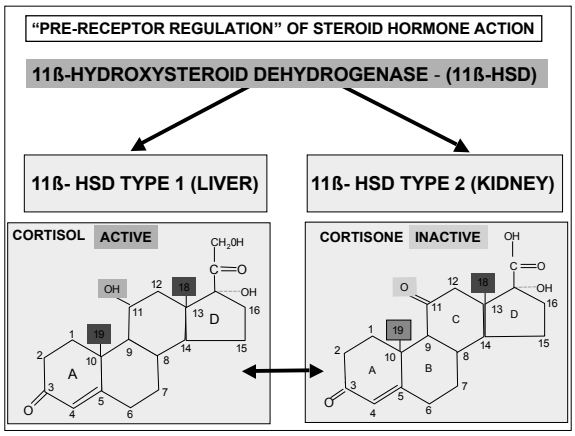


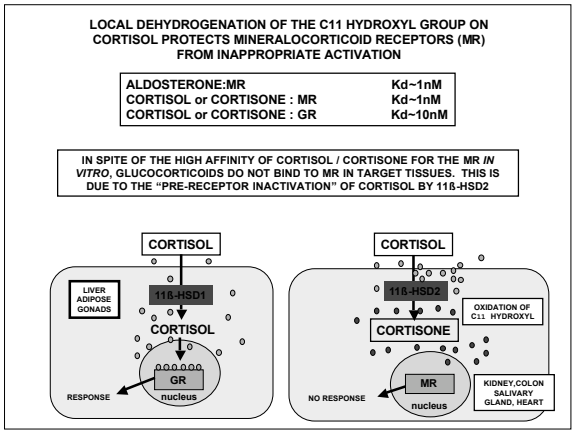





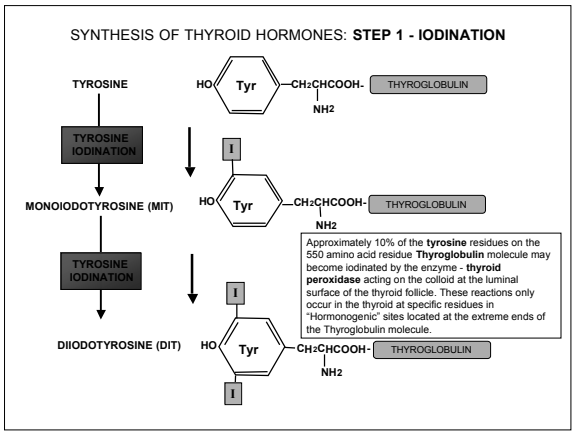



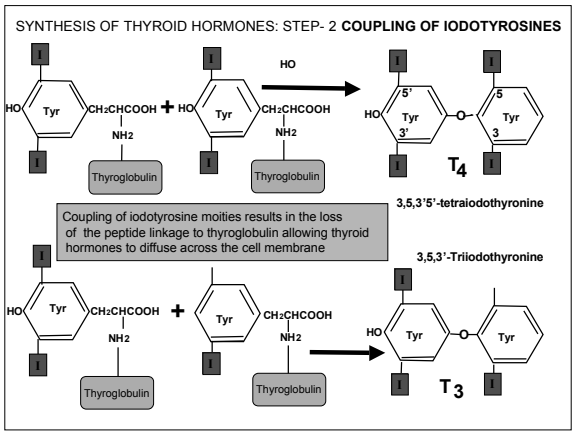



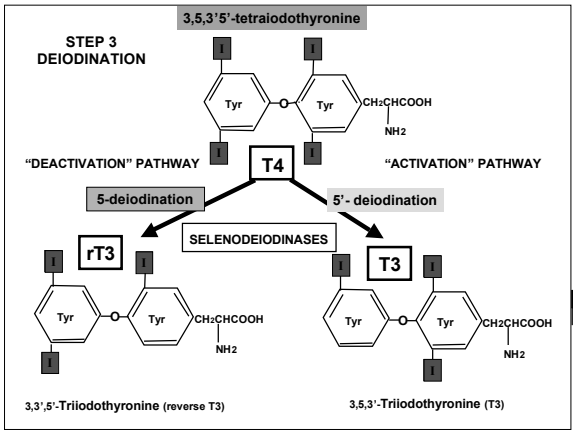



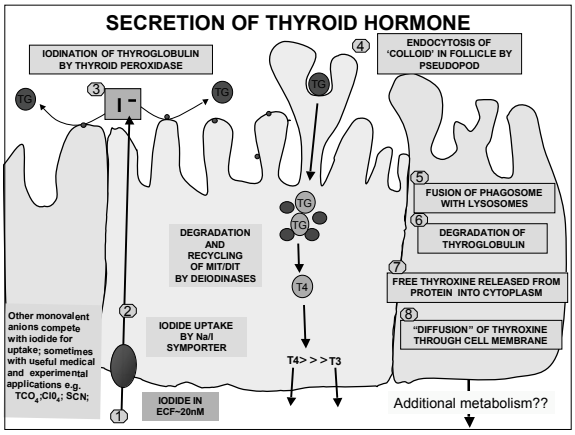

BINDING AFFINITIES OF STEROIDS TO PLASMA PROTEINS

| HORMONE | CORTISOL BINDING PROTEIN (CBP) | SEX HORMONE BINDING GLOBULIN (SHBG) | ALBUMIN |
|---|---|---|---|
| CORTISOL | 76 | 1.6 | 0.003 |
| CORTISONE | 7.8 | 2.7 | 0.005 |
| ESTRADIOL | 0.06 | 680 | 0.06 |
| PREGNENOLONE | 0.18 | 14 | 0.06 |
| PROGESTERONE | 24 | 8.8 | 0.06 |
| 17_ -OH-PROGESTERONE | 55 | 9.9 | 0.4 |
| TESTOSTERONE | 5.3 | 1600 | 0.04 |




**THYROID HORMONES**

| HORMONE | RELATIVE POTENCY | PRODUCTION (µg/day) | PLASMA CONCENTRATION (µg/dL) | BOUND TO PLASMA PROTEINS (%) | $t_{1/2}$ (days) |
|---|---|---|---|---|---|
| $T_4$ | + | 80- 90 | 8 | 99.95 | 6-7 |
| $T_3$ | + + + + | 4-8 (24)* | 0.3 | 99.7 | 1-3 |
| $rT_3$ | - | 2-3 (27) * | 0.04 | 99.8 | 0.1 |

* VALUES IN PARENTHESES INDICATE PERIPHERAL CONVERSION

**EFFECTS OF THYROID HORMONE ON TARGET TISSUES**

MOST EFFECTS OF THYROID HORMONE ARE "PERMISSIVE":
THYROID HORMONE PROMOTES SYNTHESIS OF PROTEINS WHICH ARE THEN REGULATED ACUTELY BY OTHER HORMONES.

**METABOLISM**
THYROID HORMONE INCREASES:
BASAL METABOLIC RATE
BODY TEMPERATURE
CARDIAC OUTPUT/ TACHYCARDIA
MOBILIZATION OF ENERGY STORES

**GROWTH AND DEVELOPMENT**
THYROID HORMONE REQUIRED IN PERINATAL PERIOD FOR:
NEURAL DEVELOPMENT
BONE GROWTH (GH)

**THYROID DISEASES**

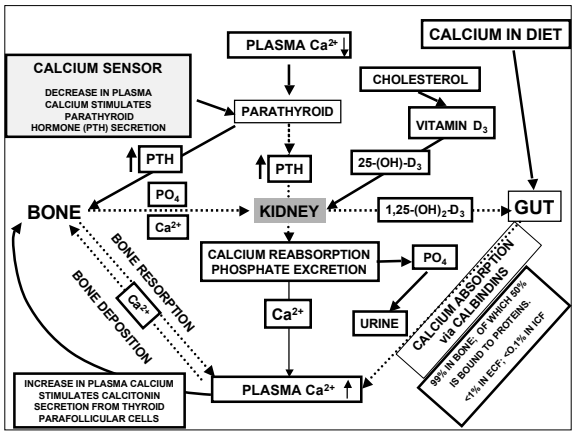
CONGENITAL HYPOTHYROIDISM
DUE TO "METABOLIC" DEFECT IN THYROID HORMONE SYNTHESIS RESULTING IN MENTAL RETARDATION
UNCOMMON IN DEVELOPED COUNTRIES DUE TO EARLY POST- NATAL TESTING

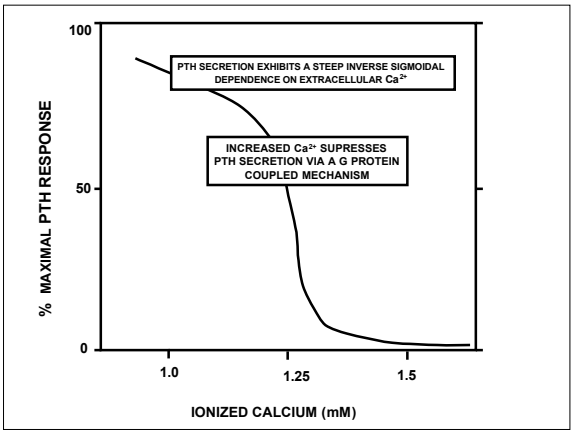
"ENDEMIC" HYPOTHYROIDISM
DUE TO IODIDE DEFICENCY OR GOITROGENS.
READILY PREVENTED BY IODIDE SUPPLEMENTATION OF FOOD

HYPERTHYROIDISM
AUTOIMMUNE "GRAVES DISEASE"
PITUITARY TUMOR
THYROID TUMOR
WEIGHT LOSS

**THYROID DISEASES**

| DISEASE TYPE | THYROID STATUS | SERUM T3 +T4 | SERUM TSH | CAUSE OF DISEASE |
|---|---|---|---|---|
| CONGENITAL | HYPO | LOW | HIGH | DEFECT IN IODIDE TRAP OR THYROID HORMONE SYNTHESIS |
| IODIDE DEFICIENCY | HYPO | LOW | HIGH | DIET: (i) LOW IN IODIDE OR (ii) GOITROGENS PRESENT |
| AUTOIMMUNE: THYROIDITIS | HYPO | LOW | HIGH | DESTRUCTION OF THYROID TISSUE DUE TO INFLAMMATION |
| AUTOIMMUNE: GRAVES DISEASE | HYPER | HIGH | LOW | AUTOANTIBODIES TO THE TSH RECEPTOR PROVIDE CONTINUOUS UNREGULATED STIMULUS |
| THYROID TUMOR | HYPER | HIGH | LOW | UNREGULATED SYNTHESIS AND SECRETION OF T3 AND T4 |
| PITUITARY TUMOR | HYPER | HIGH | HIGH | UNREGULATED SYNTHESIS AND SECRETION OF TSH |




**CALCITONIN IS SECRETED FROM THE THYROID PARAFOLLICULAR CELLS**

**BUT IS CALCITONIN AN IMPORTANT PHYSIOLOGICAL SUBSTANCE?**

**The observation that calcitonin (CT) at supraphysiological doses is hypocalcemic, led to the mistaken conclusion that it was important for calcium homeostasis and this idea has persisted to this day. Despite these findings there is no readily apparent pathology due to CT excess or deficiency and there is no evidence that circulating CT is of substantial benefit to any mammal. ……..**

**Mammalian CT at physiological doses is not essential and very likely the CT gene has survived because of the gene's alternate mRNA pathway to produce calcitonin-gene-related peptide found in neural tissues.**

**HIRSCH,PF and BARUCH H**, ENDOCRINE 2003, 201-208