# An Introduction to Endocrinology

*DEPARTMENT OF ZOOLOGY*

# What is endocrinology?

**Endocrinology =**

**Intercellular Chemical Communication**

**Endocrinology is about communication systems & information transfer.**

# What are endocrine systems for?

## Endocrine Functions

- Maintain Internal Homeostasis
- Support Cell Growth
- Coordinate Development
- Coordinate Reproduction
- Facilitate Responses to External Stimuli

# What are the elements of an endocrine system?

- ***Sender*** **= Sending Cell**
- ***Signal*** **= Hormone**
- ***Nondestructive Medium*** **= Serum & Hormone Binders**
- ***Selective Receiver*** **= Receptor Protein**
- ***Transducer*** **= Transducer Proteins & 2º Messengers**
- ***Amplifier*** **= Transducer/Effector Enzymes**
- ***Effector*** **= Effector Proteins**
- ***Response*** **= Cellular Response (2º Hormones)**

# What is a hormone?

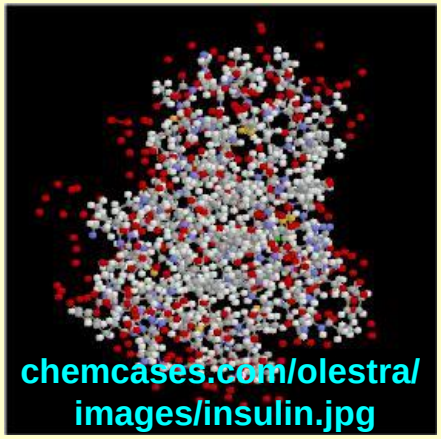
A molecule that functions as a message within an organism; its only function is to convey information.

Because of this function, physical descriptions of a chemical thought to be a hormone are not adequate to indicate the molecule's physiological role. A molecule is a hormone only when described in the context of its role in a biological communication system. Definition of a hormone requires testing of that molecule in a biological response system, running a bioassay.

Ultimately, the existence of endocrinology is dependent on the existence & use of bioassays. (This is also true for pharmacology & toxicology.)

# What kinds of hormone are there?

## Known Hormonal Classes



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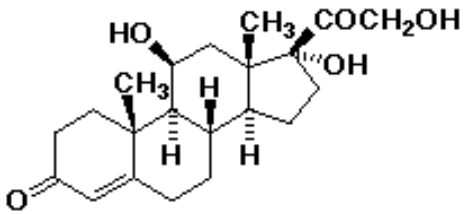
- **Proteins & peptides**

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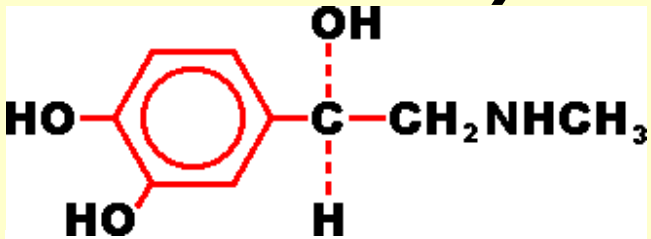
- **Lipids (steroids, eicosanoids)**
- **Amino acid derived (thyronines, neurotransmitters)**

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- **Gases (NO, CO)**

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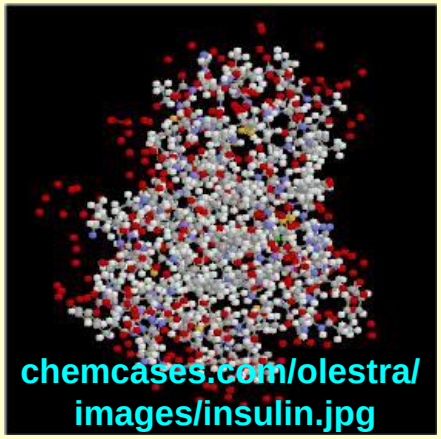

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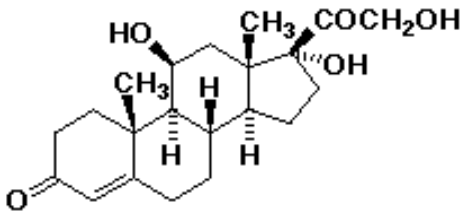


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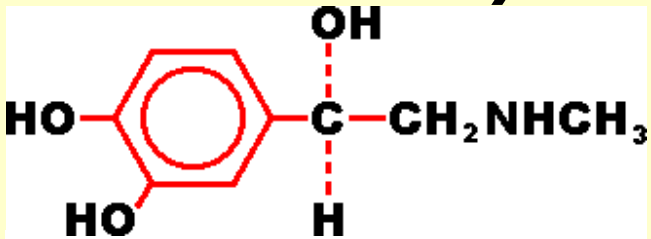


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- **Gases (NO, CO)**

# What is a hormone receptor?

**Hormone Receptors are cellular proteins that bind with high affinity to hormones & are altered in shape & function by binding; they exist in limited numbers.**

**Binding to hormone is noncovalent & reversible.**

**Hormone binding will alter binding to other cellular proteins & may activate any receptor protein enzyme actions.**

# What are the main types of receptors?

## Membrane Receptors

**Imbedded in target cell membrane; integral proteins/ glycoproteins; penetrate through membrane**

**For protein & charged hormones (peptides or neurotransmitters)**

**3 major groups: Serpentine = 7 transmembrane domains, Growth factor/cytokine = 1 transmembrane domain, Ion channels**

## Nuclear Receptors

**Nuclear proteins that act in pairs & bind to specific Hormone Recognition Elements (HREs) = sequences on the DNA in the promoter regions of target genes**

**For small, hydrophobic molecules (steroids, thyroid hormones)**

# What are transducers?

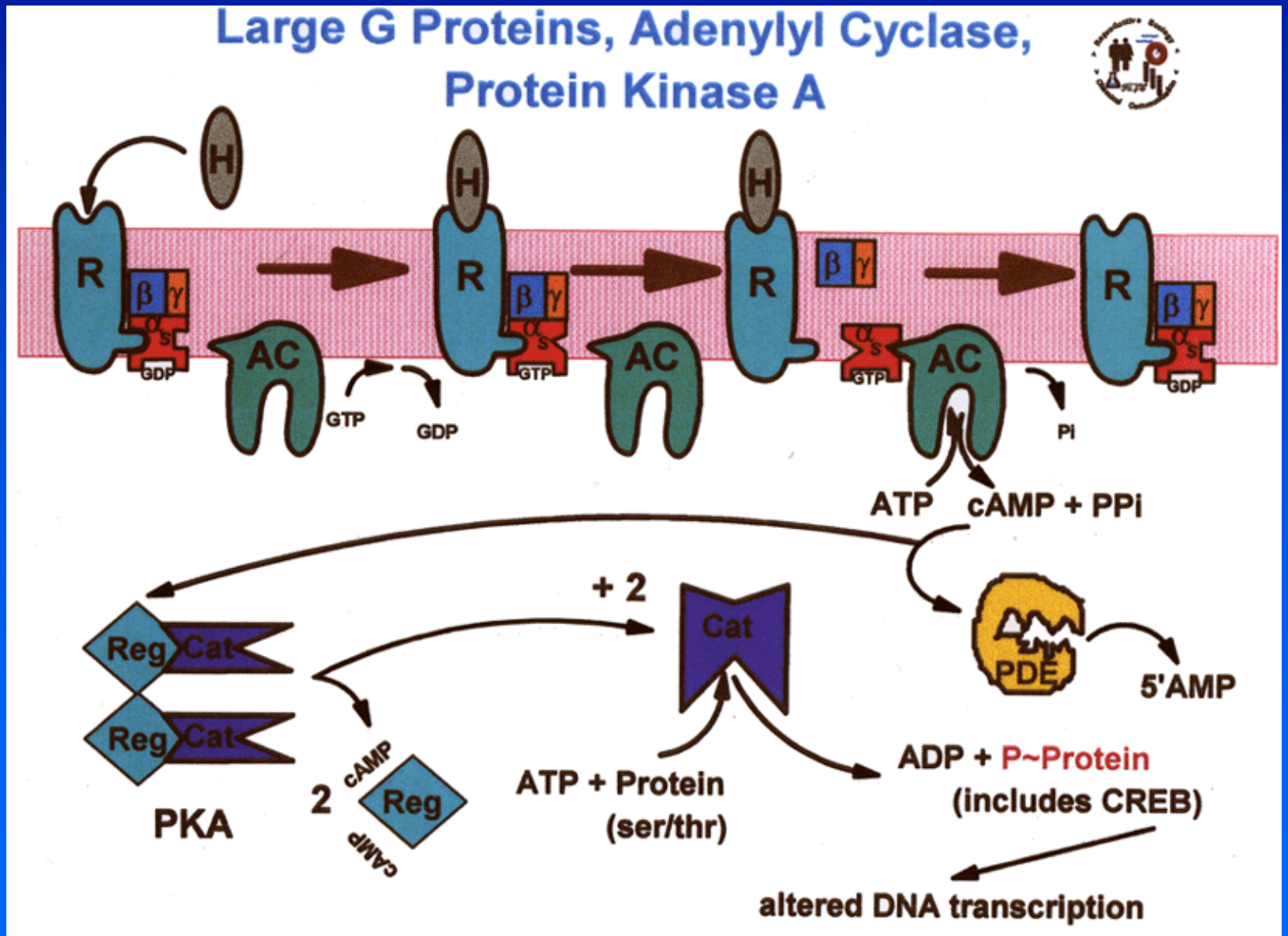
**Transducers are proteins that convert the information in hormonal signals into chemical signals understood by cellular machinery.**

**They change their shape & activity when they interact directly with protein-hormone complexes.**

**Usually enzymes or nucleotide binding proteins, they produce 2$^{nd}$ messengers, or change the activity of other proteins by covalently modifying them (adding or removing phosphate, lipid groups, acetate, or methyl groups), or they interact with other proteins that do these things.**

**They begin amplifying the energy content of the original hormone signals.**

# How many kinds of transducers are there?



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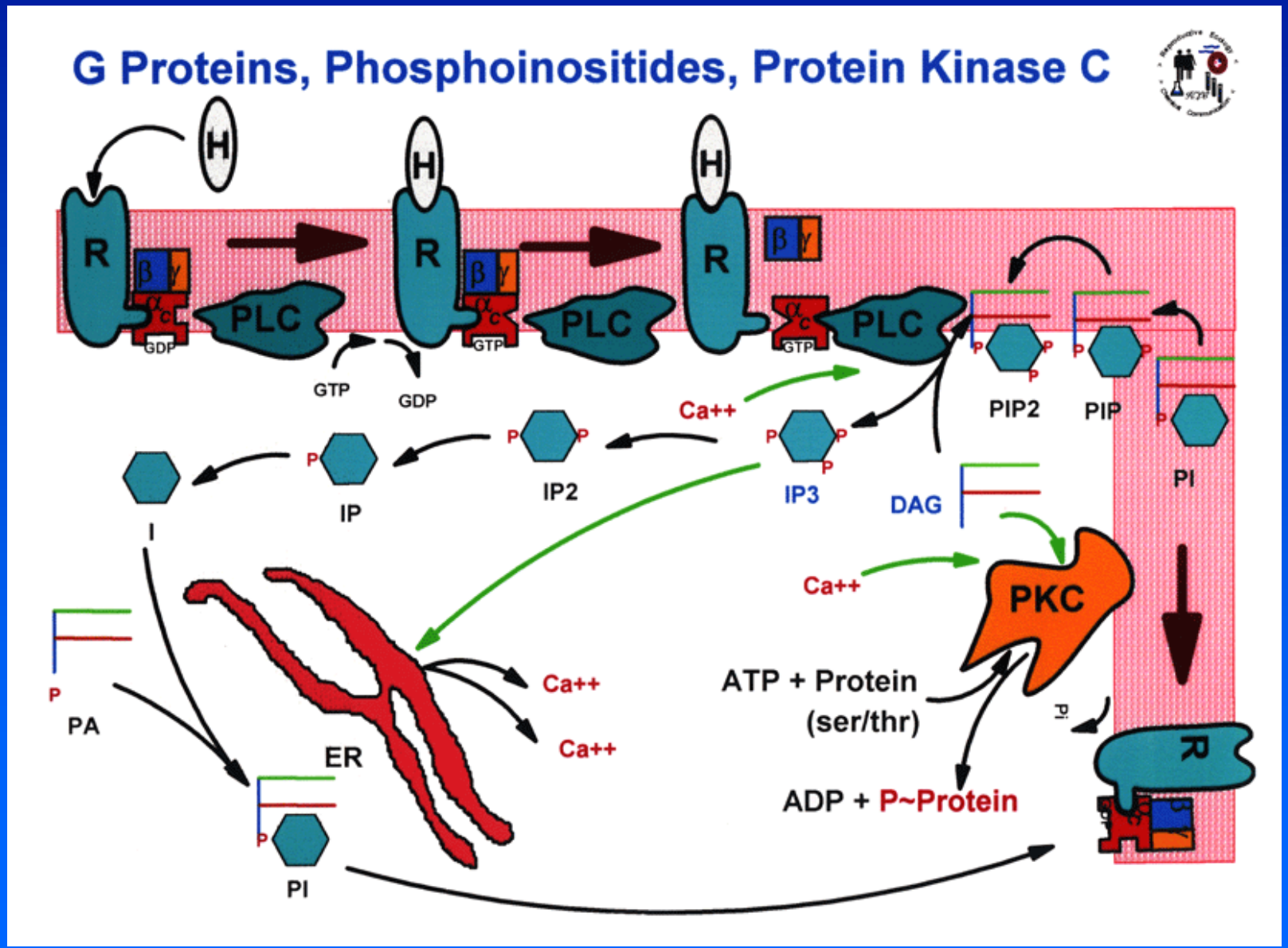

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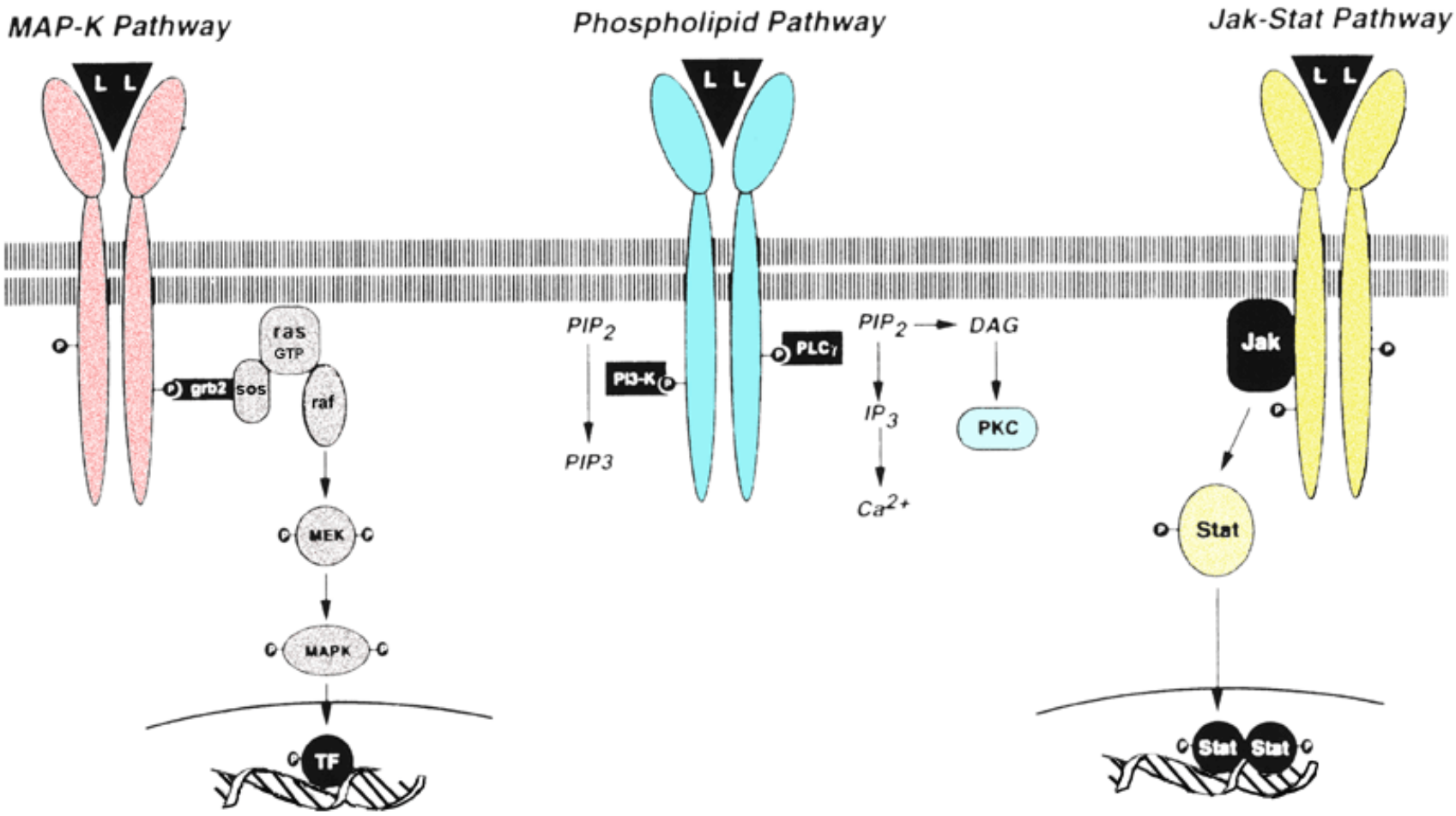


Modified from Mayo, Receptors: Molecular mediators of hormone action, In, Conn & Melmed, ed., *Endocrinology: Basic and Clinical Principles,* Humana Press: Totowa, NJ, 1997.

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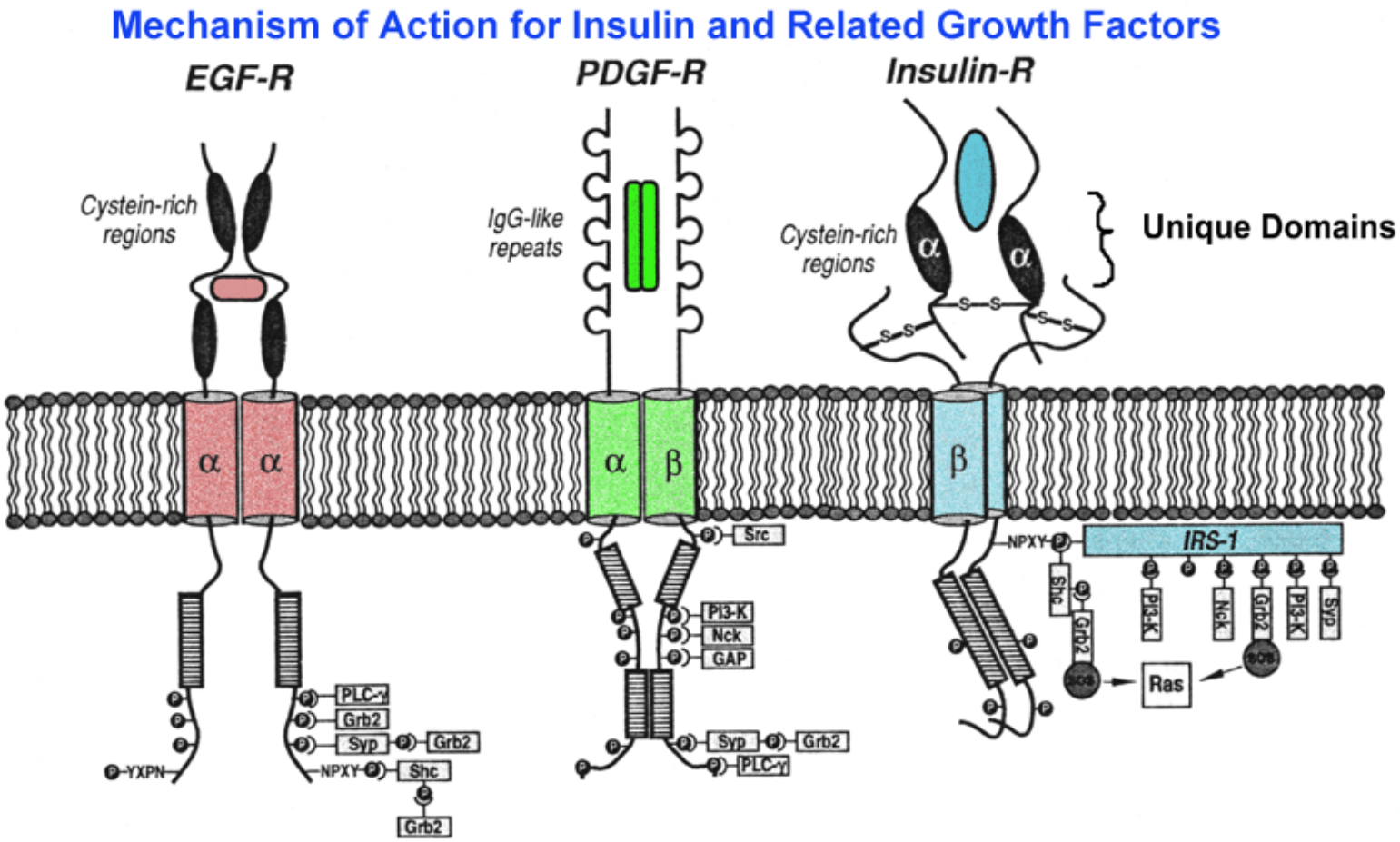
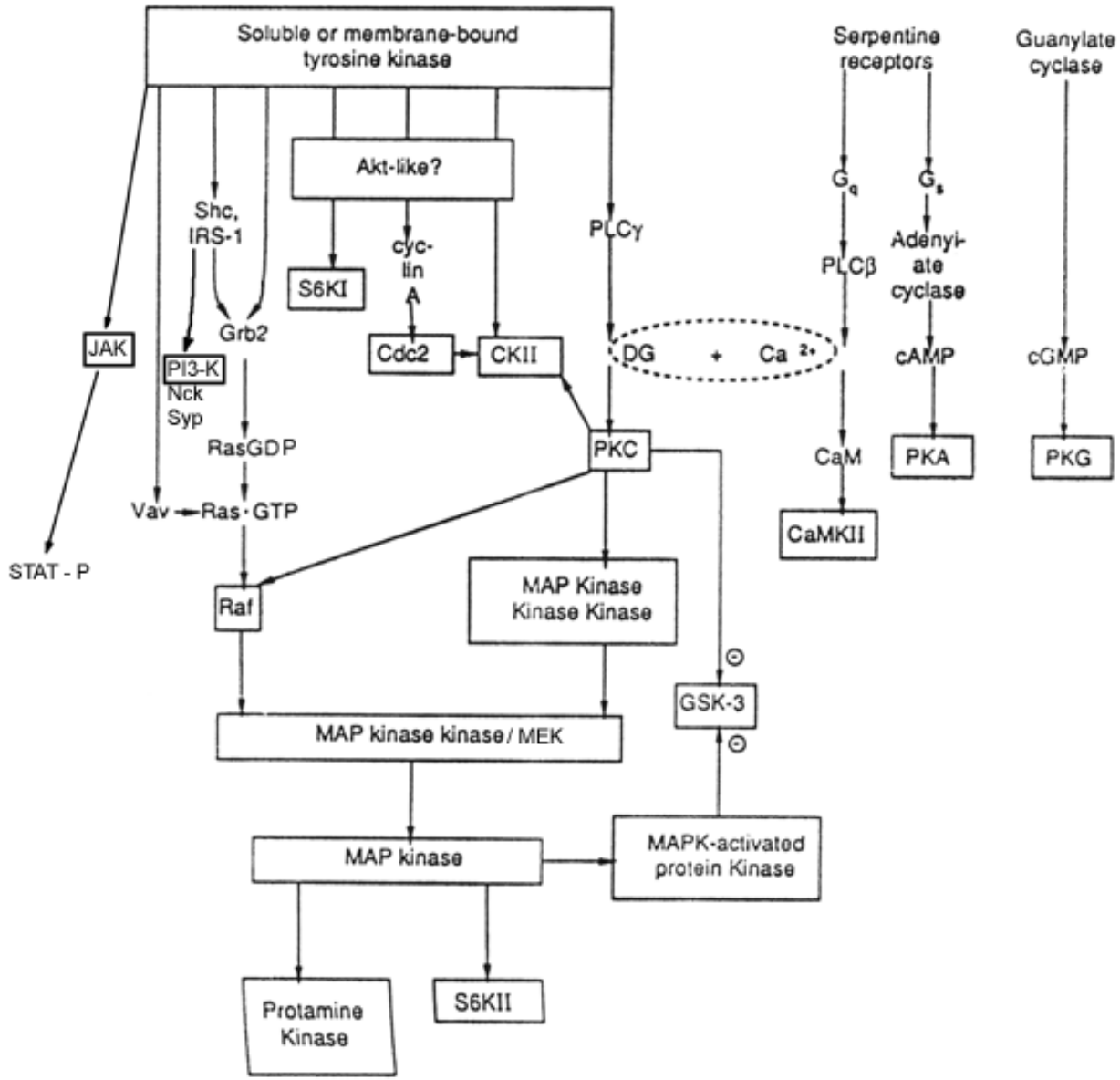



Activated EGF receptor forms a homodimer but can also form heterodimers with other related receptors. PDGF receptor can form hetero - or homodimers. Insulin receptor is synthesized as a disulfide - linked heterodimer which aggregates upon stimulation. SH2 domains and PTB domains allow formation of networks of adapter and effector proteins. However, insulin receptor uses the docking protein IRS - 1 to anchor the effector proteins that initiate its multipronged, pleiotropic response. (Modified from Mayo, Receptors: Molecular mediators of hormone action, in Conn & Melmed, ed., *Endocrinology: Basic and Clinical Principles,* Humana Press: Totowa, NJ, 1997.)

# Some Membrane Receptor Transduction Networks




**Kinases (boxed) act as amplifiers in these cascades, interconnections are common and phosphorylations of both cytoplasmic proteins and nuclear transcription factors drive early and late hormonal responses, respectively. (Modified from Bolander, Molecular Endocrinology, 2nd Ed., Academic Press:San Diego, CA, 1994.)**

# What are effectors?

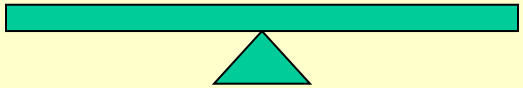
**Effectors are the enzymes & other proteins that convert the transduced hormonal signal into biochemical changes that generate the cellular response to hormone binding.**

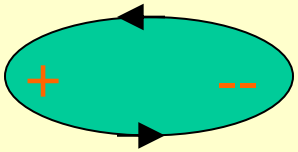
**Usually amplify the signal further & allow cellular work to be done: cell motion, growth, division, altered metabolism, secretion, depolarization, etc.**

# What are feedback systems?

## Feedbacks Generate Control Loops

**Negative**

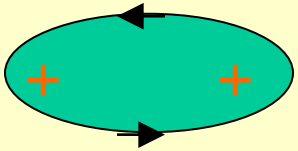





**These maintain hormonal balance & are linked to homeostatic processes.**

**If the multiplicative effect of the links in a control loop is negative, the entire control loop is negative.**

**Positive**




**These cause physiologic changes in the system.**

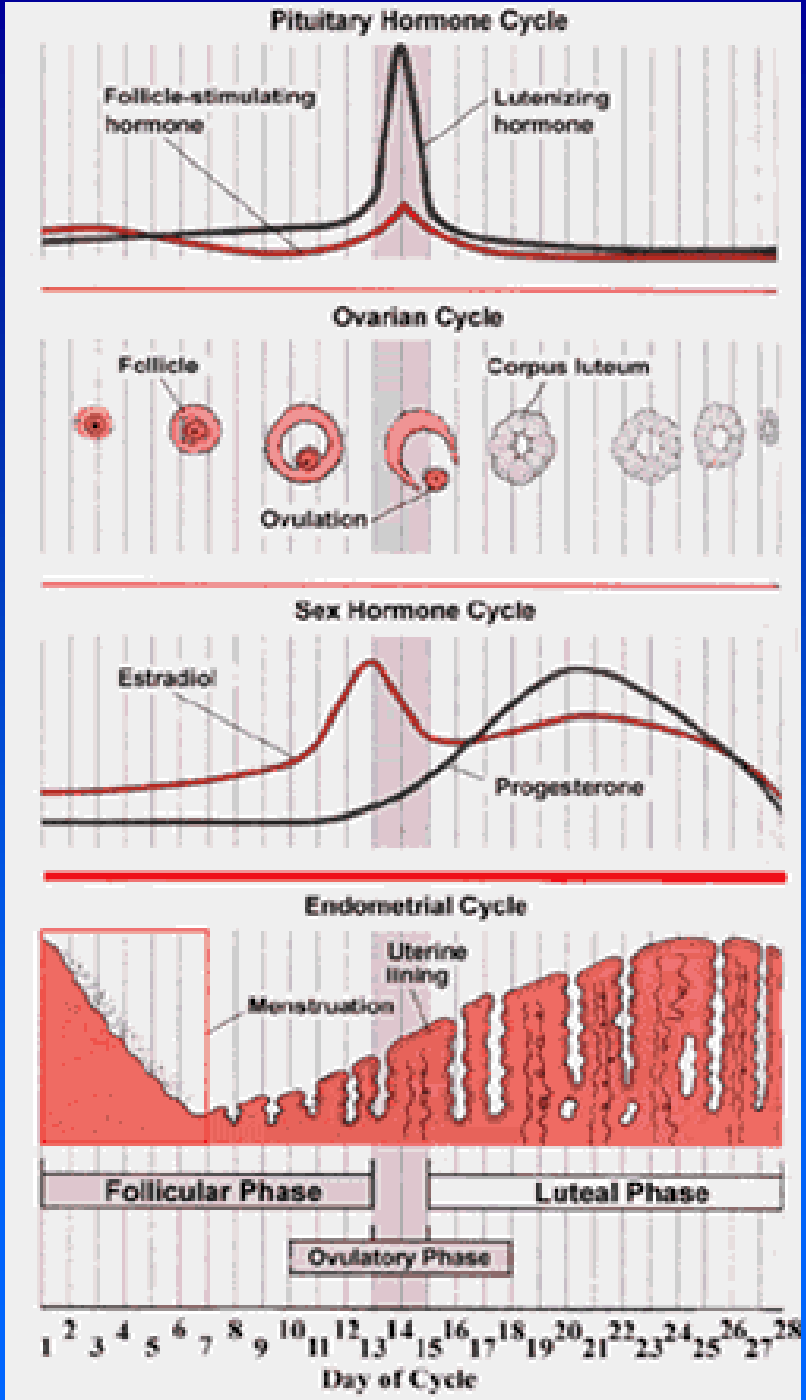
**If the multiplicative effect of the links in a control loop is positive, the entire control loop is positive.**

# How dynamic are these systems?

**Hormone, receptor, transducer & effector levels vary with time. Some change over short terms, others over long terms.**

**Levels also vary with developmental stage, gender, & health status.**

# How dynamic are these systems?

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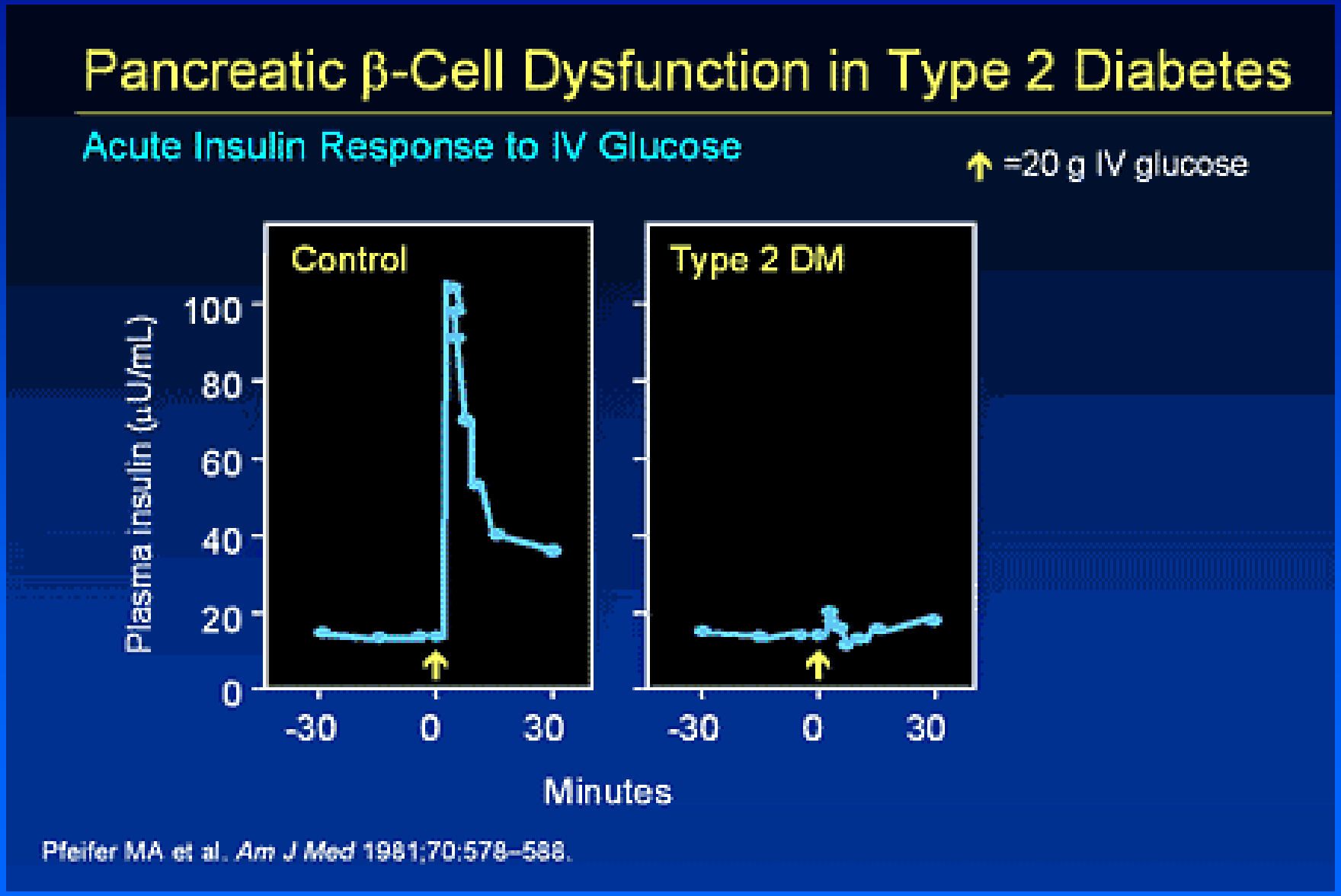

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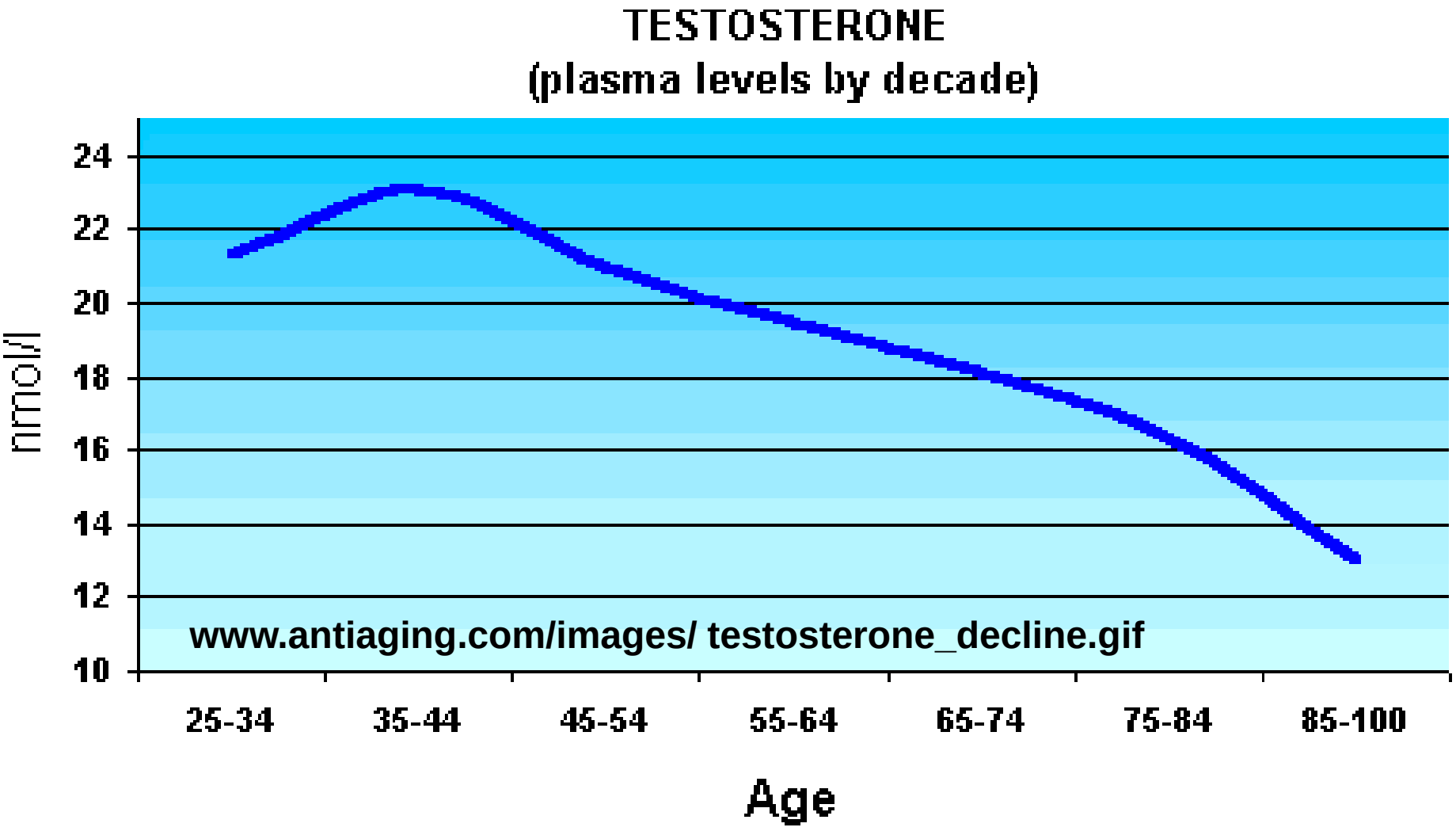


# Can single cells make or sense more than one hormone at a time?

**Yes, cells can make multiple hormones, even of differing chemical classes, & they can sense multiple signals -- & integrate them -- all at once.**

**Examples:**

**Ovarian granulosa cells make inhibin (protein), estradiol (steroid), & androstenedione (steroid) during the follicular phase of the ovarian cycle. At the same time they respond to FSH & growth factors (proteins), estradiol (steroid), & thyroxine (amino acid derivative), along with other hormones.**

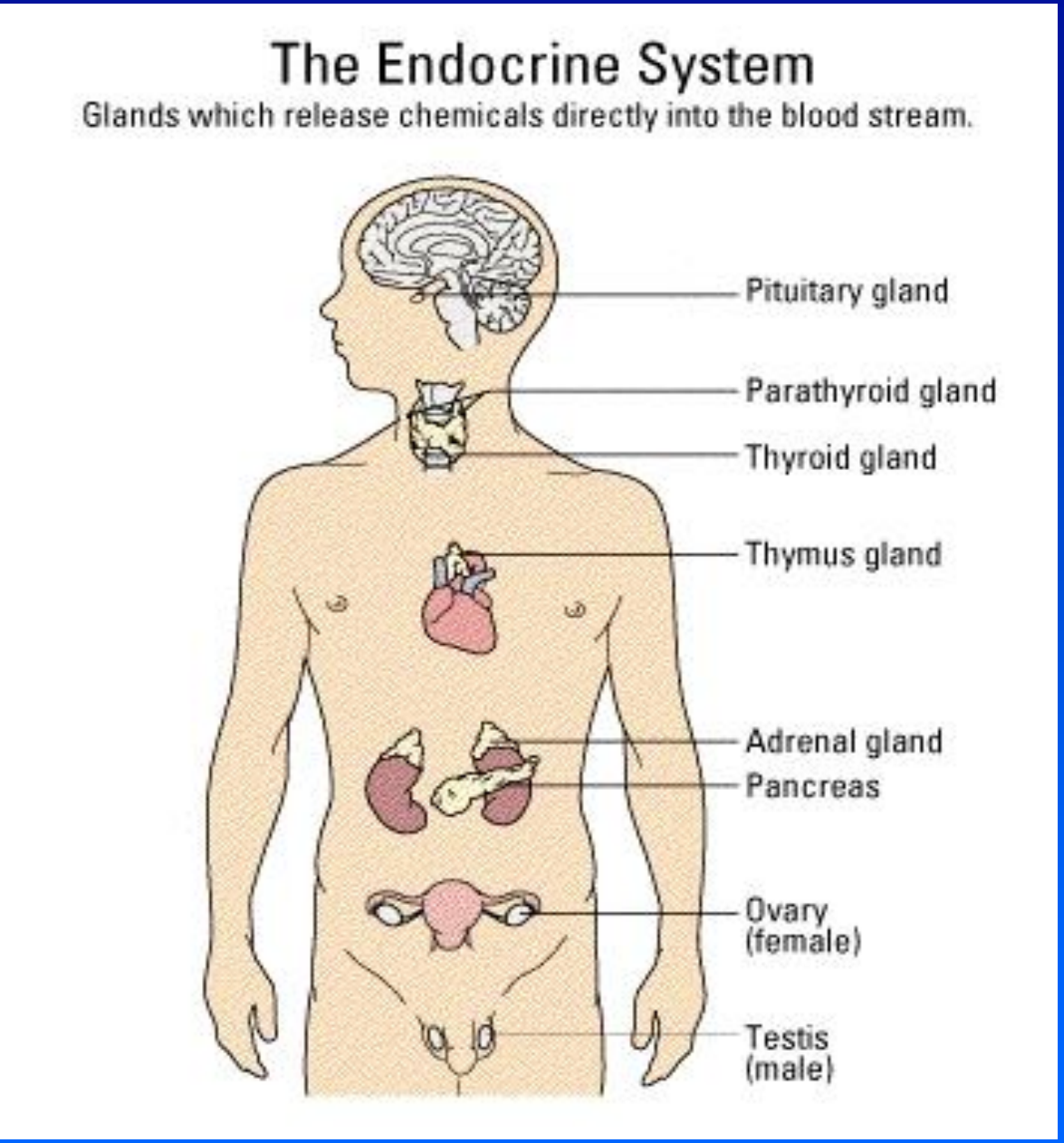
**Anterior pituitary gonadotropes respond to LHRH (peptide) & inhibin (protein), estradiol, testosterone, progesterone, & glucocorticoids (steroids) while they make both FSH & LH (proteins).**

# How do hormone levels vary?

Hormone levels rise & fall due to **synthesis** of hormone & due to **degradation** & clearance of hormone. Target cell binding accounts for only a small fraction of removal of hormone from circulation.

In addition to hormone levels changing, **target cell receptor, transducer, & effector levels can also change** with age, sex, & physiological or developmental state. These also vary among cell types giving rise to tissue differences in hormone sensitivity.

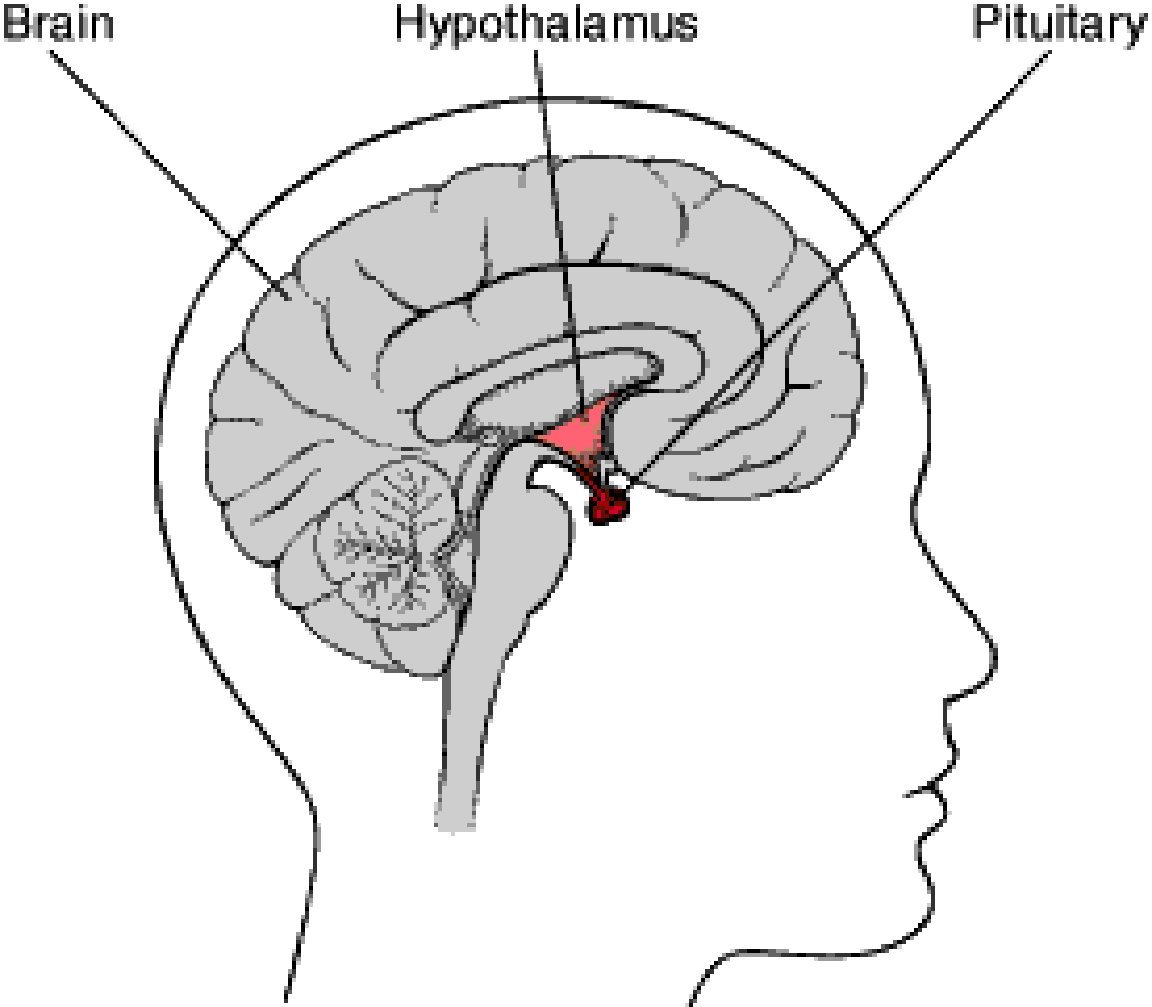
# What is the classical endocrine system?




**We now know that nearly every tissue secretes chemical signals that act as hormones, heart, immune cells, stomach, intestines, bone cells, liver, skin, glial cells, etc.**

www.cushings-help.com/ images/endocrine.jpg

# Structural Relationships: Hypothalamus & Pituitary

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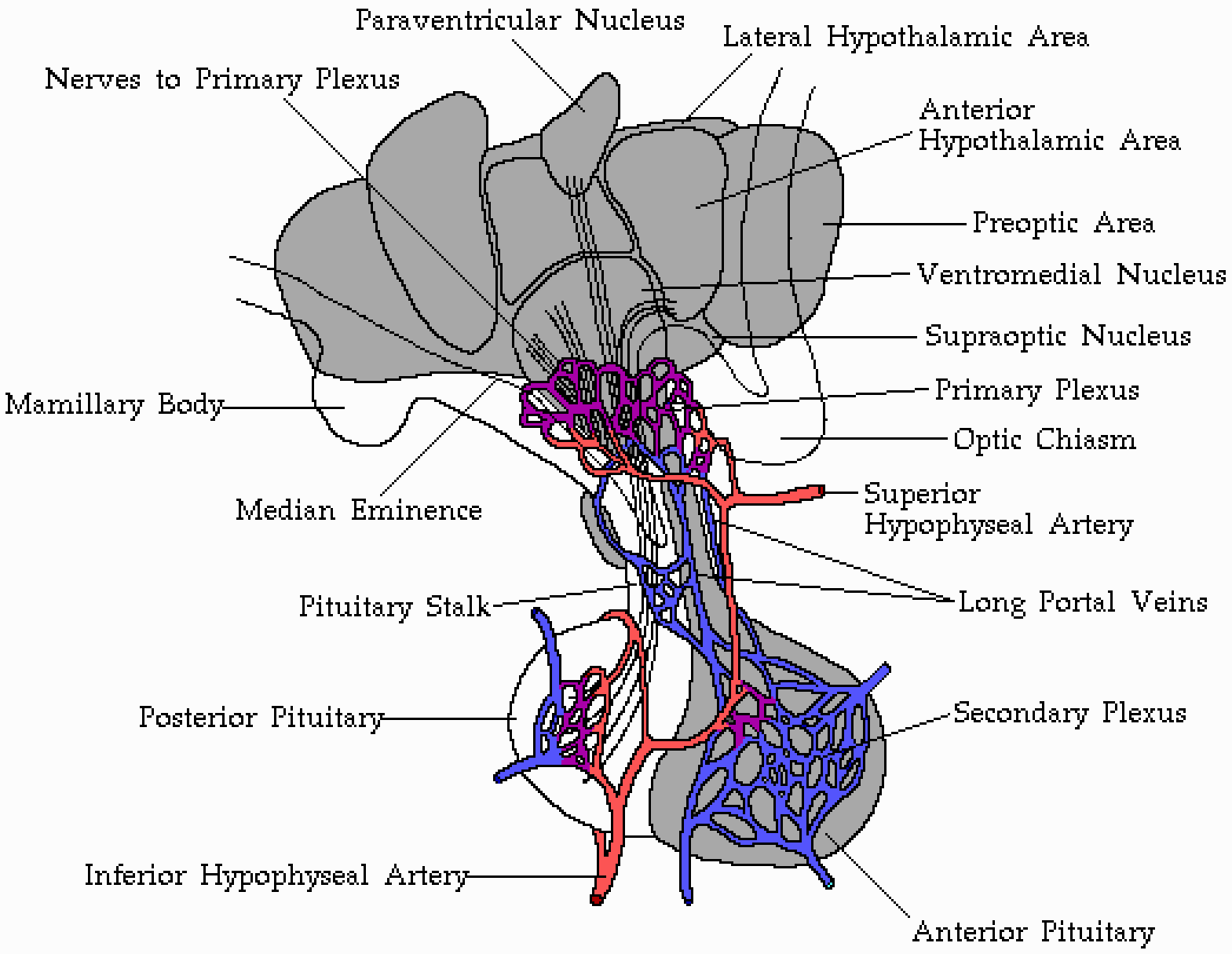
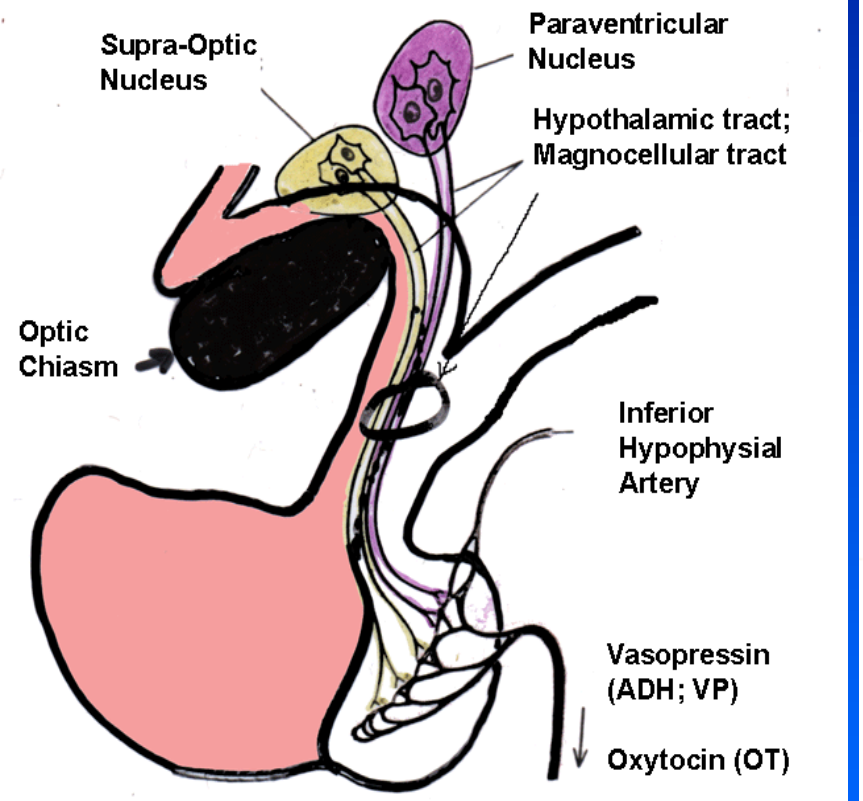



www.cushings-help.com/ anterior-pituitary.gif

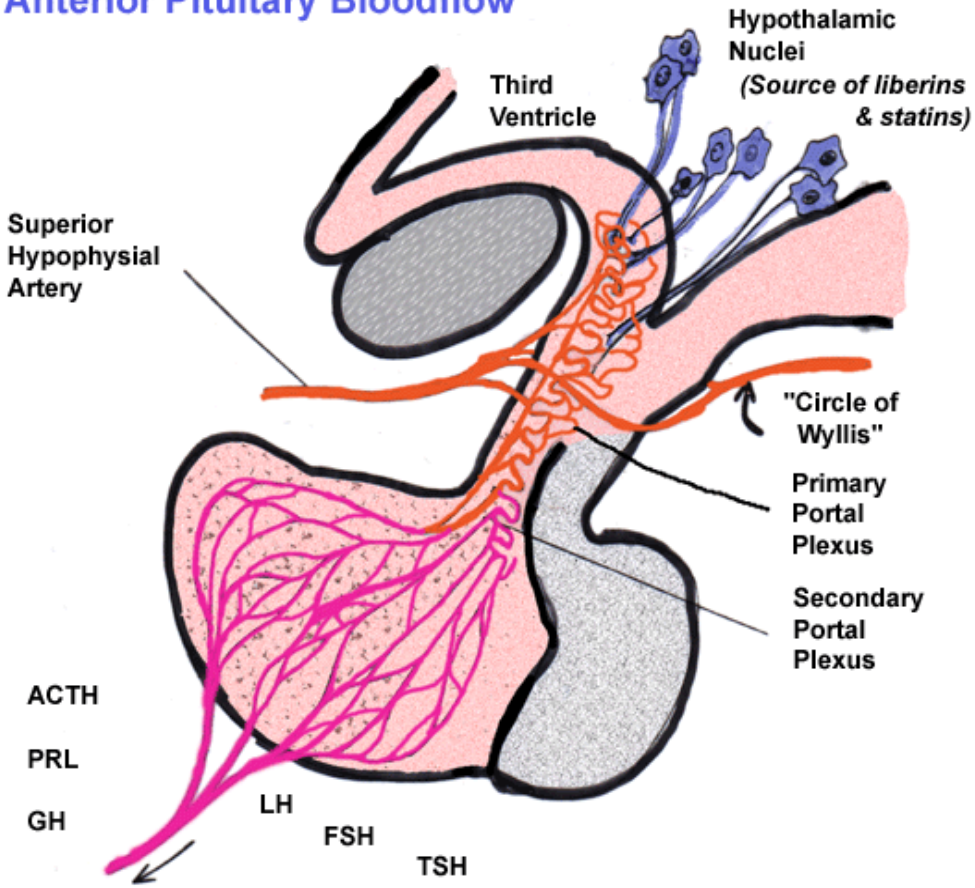
# Structural Relationships: Hypothalamus & Pituitary

Modified from R. Guillemin & R. Burgus (1972)
The hormones of the hypothalamus, *Sci Am 227*:24-33.




Neuroendocrine Products of the Neurohypophysis

## Anterior Pituitary Bloodflow




The primary portal plexus, a "priviledged" or "leaky" portion of the brain vasculature, provides a port of entry for the neuroendocrine secretions of the cells of many hypothalamic nuclei. These are carried by pulsing capillary bloodflow to the cells of the adenohypophysis (anterior pituitary) where they bind and modulate the synthesis and secretion of the six anterior pituitary hormones. Note that the products of the anterior, posterior, and intermediate (where it exists) lobes may diffuse back to the hypothalamus during the nadir of capillary blood flow.

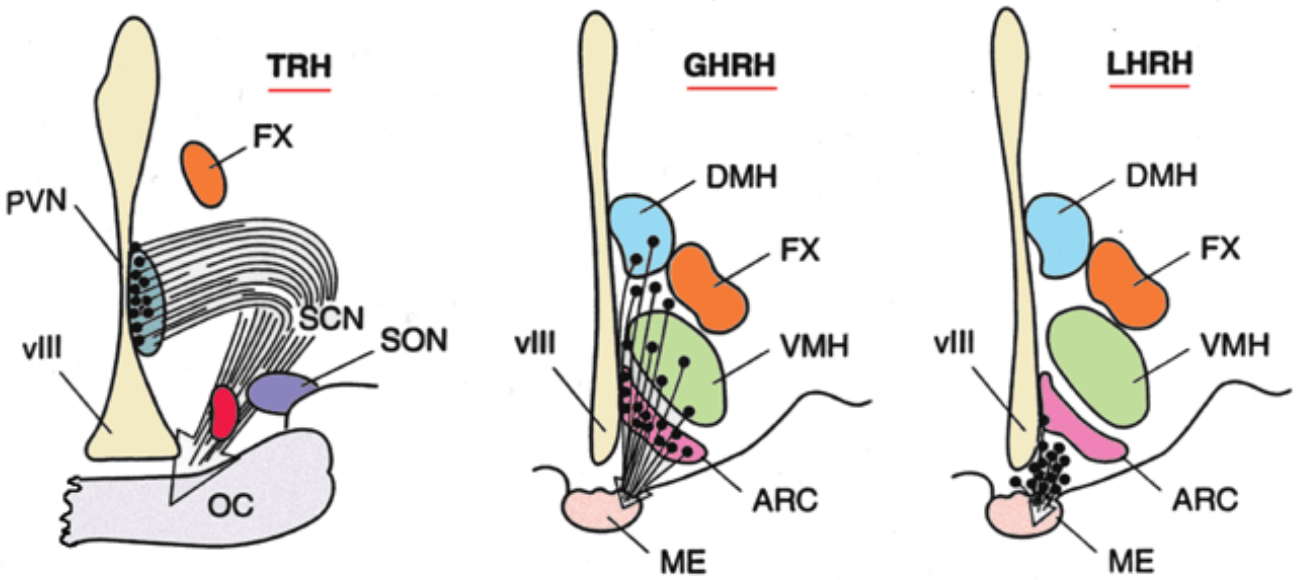
Modified from R. Guillemin & R. Burgus (1972)
The hormones of the hypothalamus, *Sci Am 227*:24-33.

# What are the regulatory products of the hypothalamus?

| *Hormone* | *Acronym* | *Hypophysial Cell Type* | *Hypothalamic Regulator(s)* | *Hormonal Function(s)* |
|---|---|---|---|---|
| **Corticotropin, Adrenocorticotropin** | **ACTH** | **Corticotrope** | **+Corticotropin Releasing Hormone, Corticoliberin (CRH); + Interleukin 1 ; - Glucocortical Steroids (via CRH); + Vasopressin; + PACAP** | **Stimulates glucocorticoid production by adrenal fasiculata & reticularis** |
| **Thyrotropin, Thyroid Stimulating Hormone** | **TSH** | **Thyrotrope** | **-Thyroxine ($T_4$); +Thyroid Releasing Hormone, Thyroliberin (TRH); -Somatostatin (SS)** | **Stimulates thyroxine production by thyroid** |
| **Prolactin, Mammotropin, Luteotropin** | **PRL** | **Lactotrope; Mammotrope** | **-Dopamine; + TRH; - SS; + Estrogens; + Oxytocin** | **Stimulates milk synthesis by secretory epithelium of breast; supports corpus luteum function** |
| **Somatotropin, Growth Hormone** | **GH** | **Somatotrope** | **+ Growth Hormone Releasing Hormone, Somatoliberin (GHRH); - SS; + PACAP** | **Stimulates somatic growth, supports intermediary metabolism** |
| **Follitropin, Follicle Stimulating Hormone** | **FSH** | **Gonadotrope** | **+ Gonadotropin Releasing Hormone, Luteinizing Hormone Releasing Hormone, Gonadoliberin (GnRH, LHRH); - Inhibin; - Sex steroids (via LHRH)** | **Supports growth of ovarian follicles & estradiol production; Supports Sertoli cell function & spermatogenesis** |
| **Lutropin, Luteinizing Hormone** | **LH** | **Gonadotrope** | **+ GnRH (LHRH); - Sex steroids (via LHRH in & ); + Estradiol in near midcycle** | **Supports late follicular development, ovulation, & corpus luteum function (especially progesterone synthesis); Supports testosterone synthesis, Leydig cell** |
| **Melanotropin, Melanocyte Stimulating Hormone** | **MSH** | **Melanotrope** | **+ CRH** | **Supports dispersal & synthesis of pigment in melanocytes; may alter adrenal response to ACTH** |

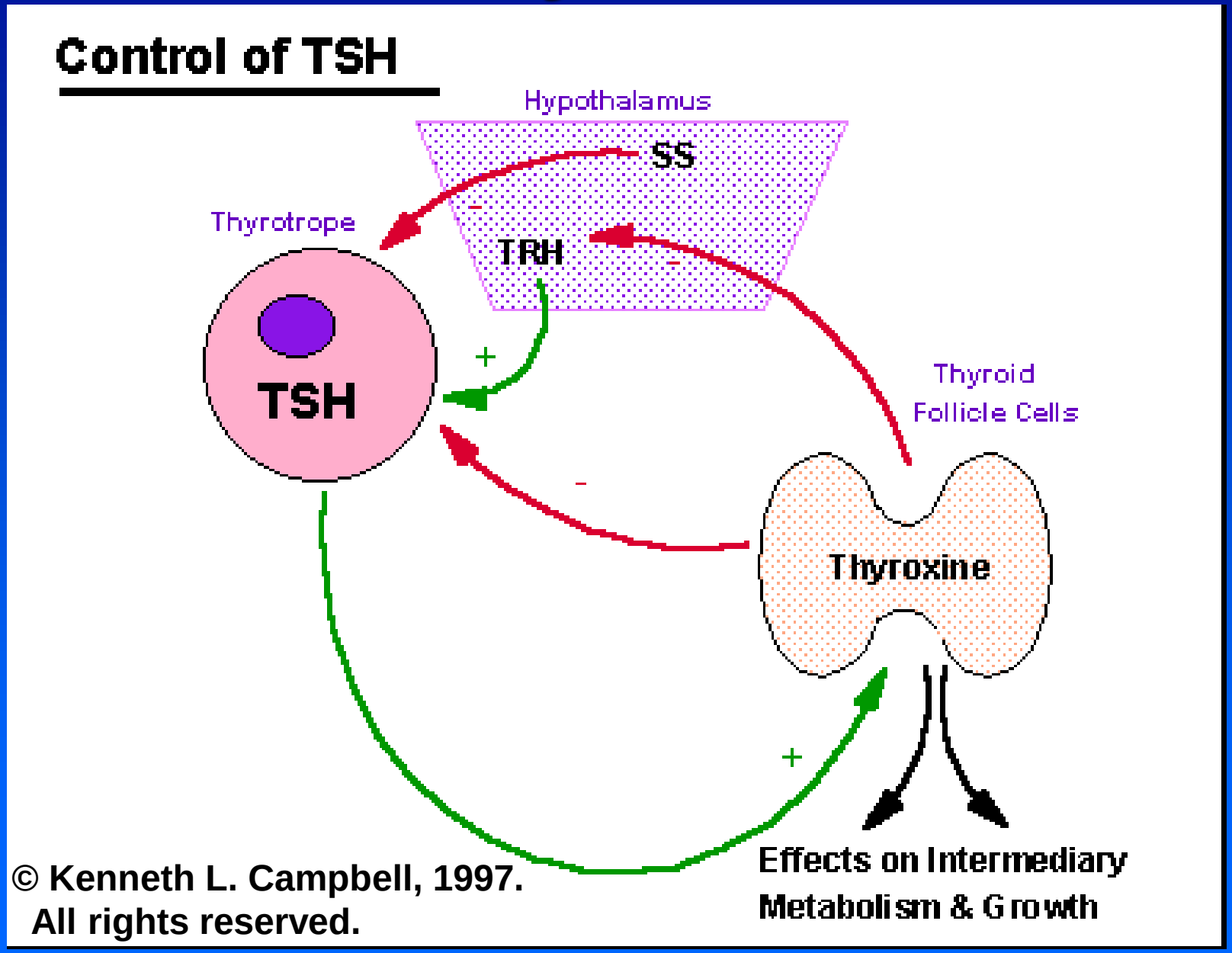
# Where do these come from?

## Sources of Three Hypothalamic Hormones

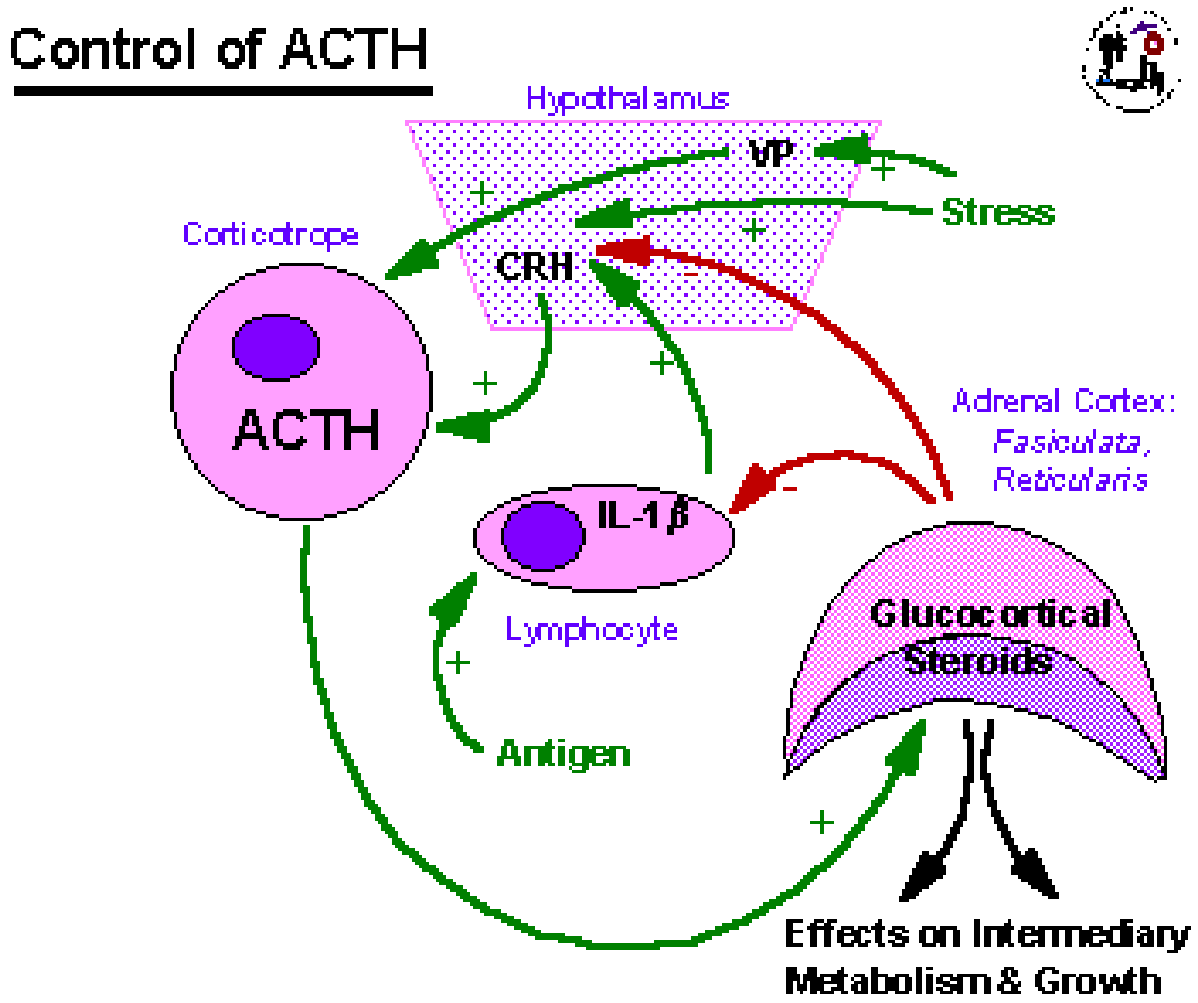



Hypothalamic localization of the neurons that secrete thyrotropin-releasing hormone (TRH), growth hormone-releasing hormone (GHRH), and luteinizing hormone-releasing hormone (LHRH) based on human and animal studies. The neurons (solid dots) are shown in a coronal section through the plane of the densest cell bodies. The projection pathway of axons toward the median eminence is depicted by the solid lines forming an arrow. Arcuate nucleus, ARC; dorsomedial hypothalamic nucleus, DMH; fornix, FX; median eminence, ME; optic chiasm, OC; paraventricular nucleus, PVN; suprachiasmatic nucleus, SCN; supraoptic nucleus, SON; third ventricle, vIII; ventromedial hypothalamic nucleus, VMH. (Modified from Riskind and Martin, in De Groot, ed, *Endocrinology, 2nd ed, Vol. 1*, Saunders: Philadelphia, PA, 1989.)

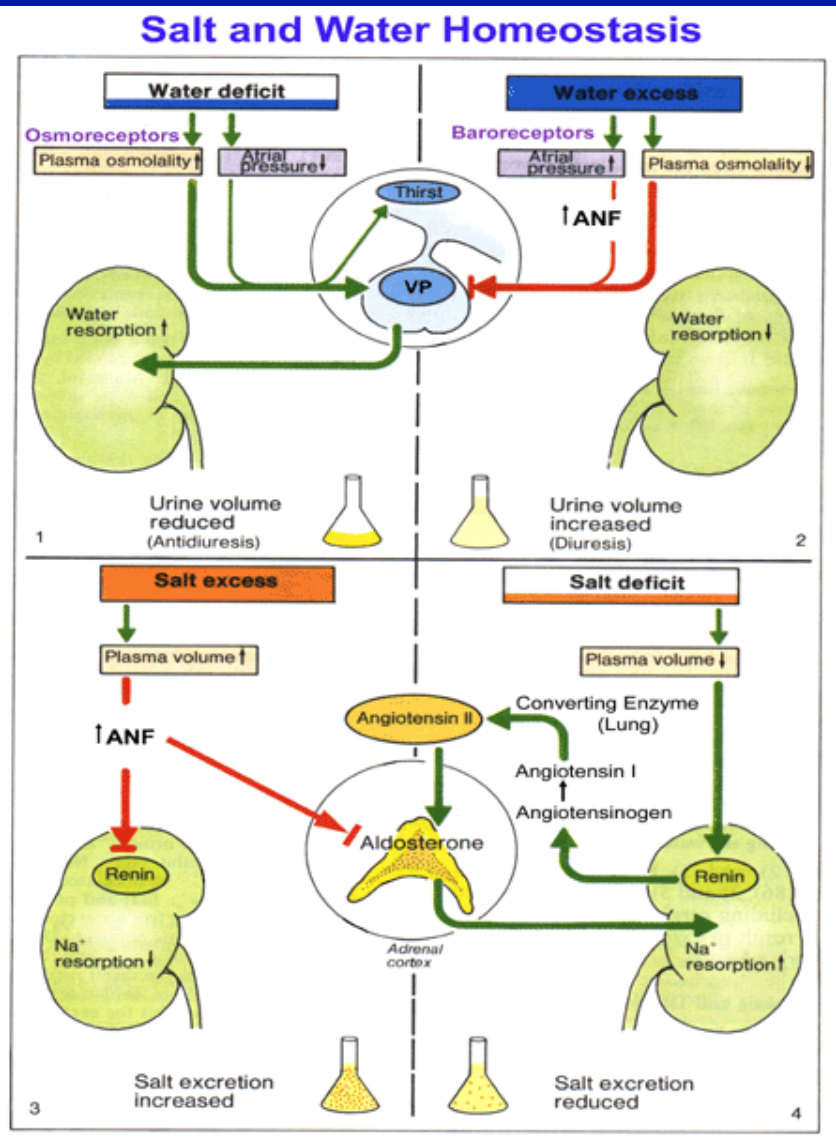
# How is the thyroid controlled?



# How is the adrenal cortex controlled?

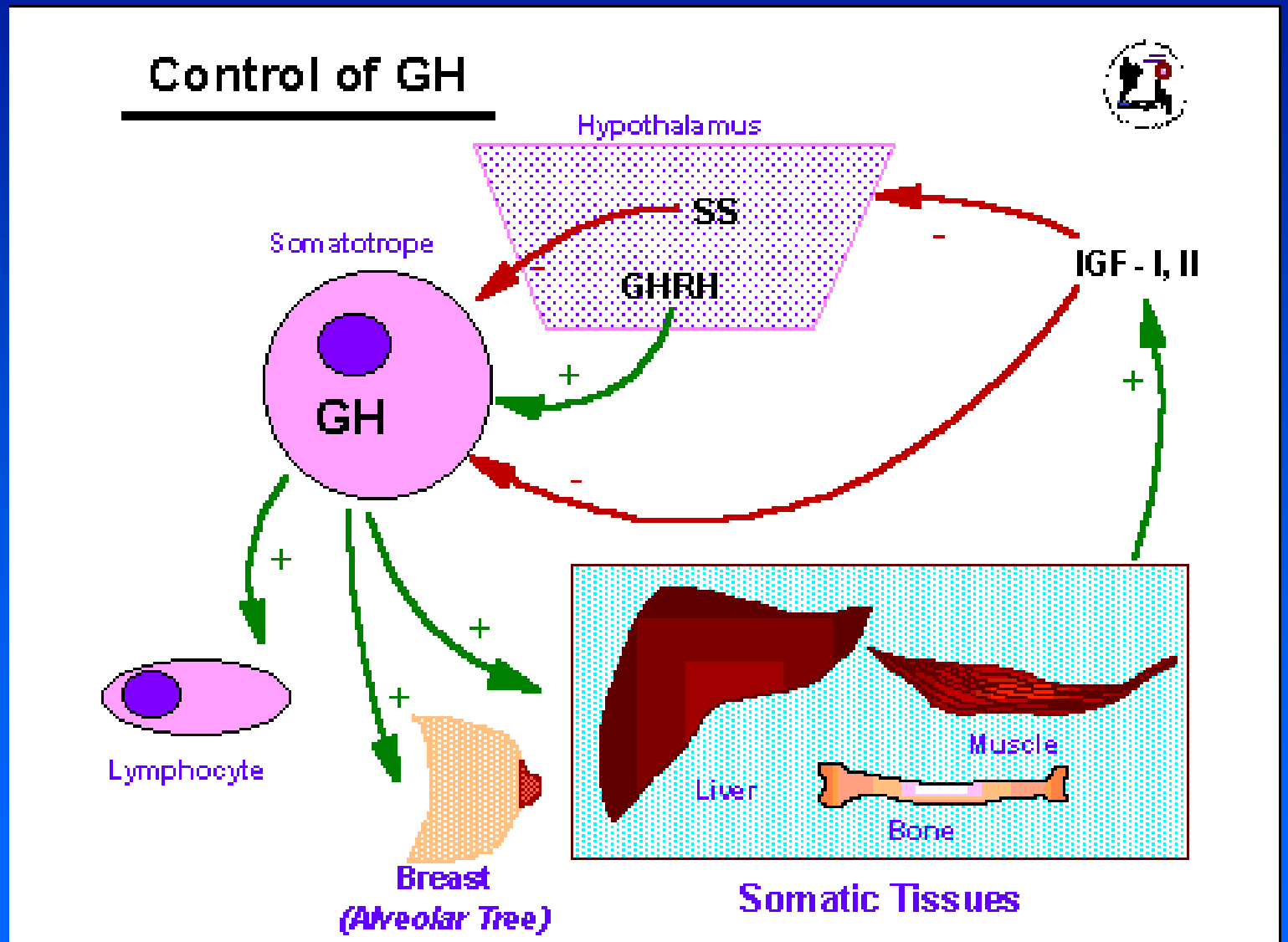


# The adrenal/stress axis & blood pressure

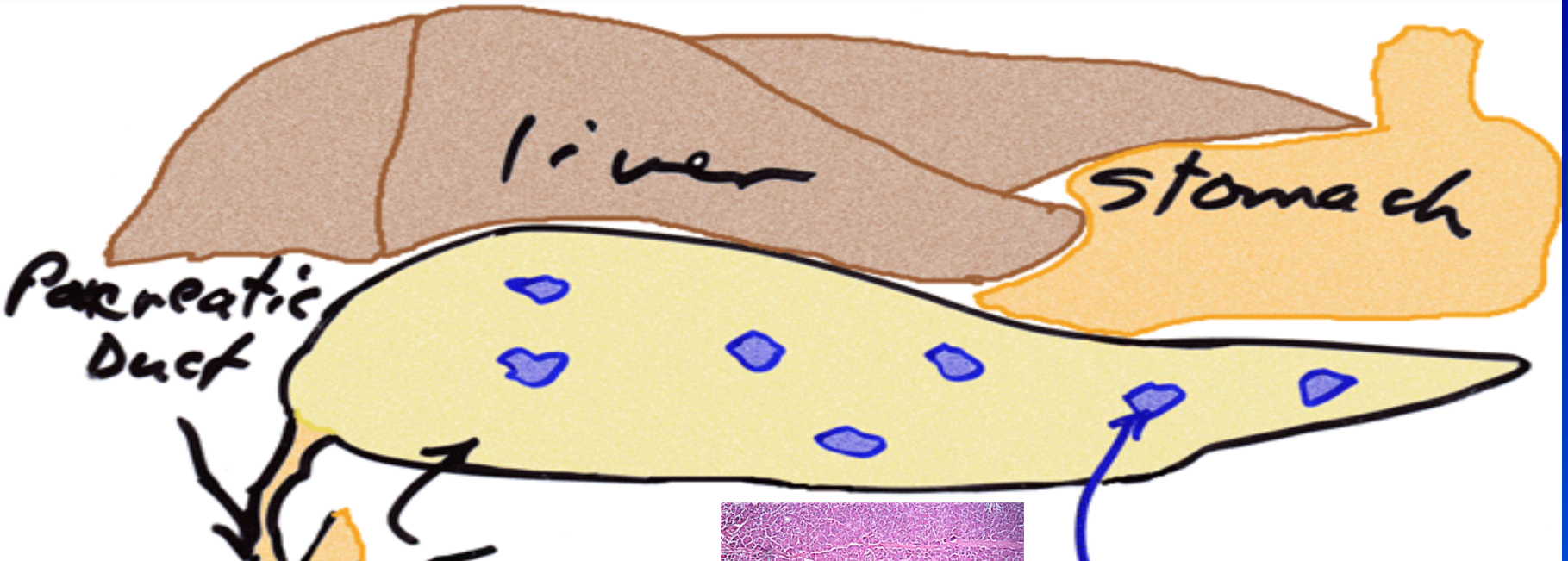



(Modified from Despopoulous & Silbernagl, *Color Atlas of Physiology, 3rd Ed*, Thieme inc.: New York, 1986.)

# How is growth hormone controlled?

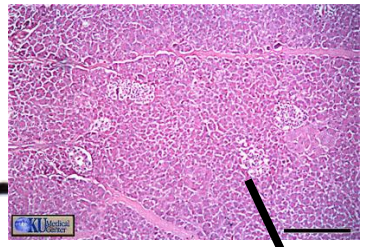


# Schematic Gross Anatomy of the Pancreas



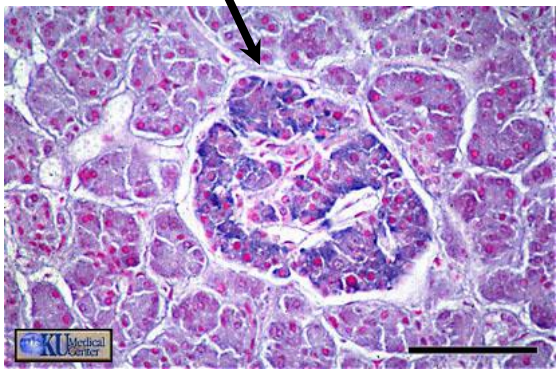

Exocrine Pancreas (majority of tissue)

— zymogens (Digestive enzyme precursors)

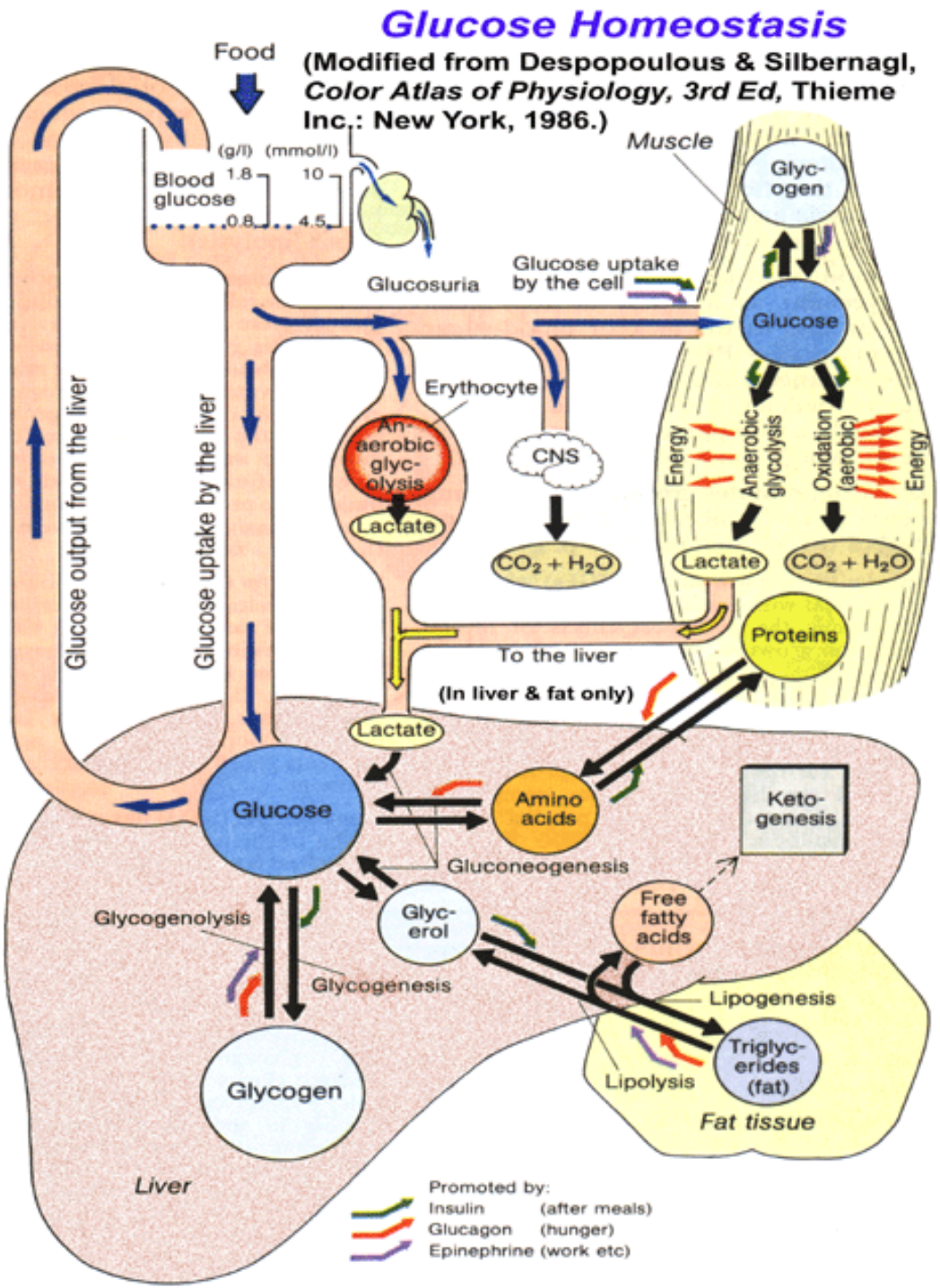


Islets of Langerhans

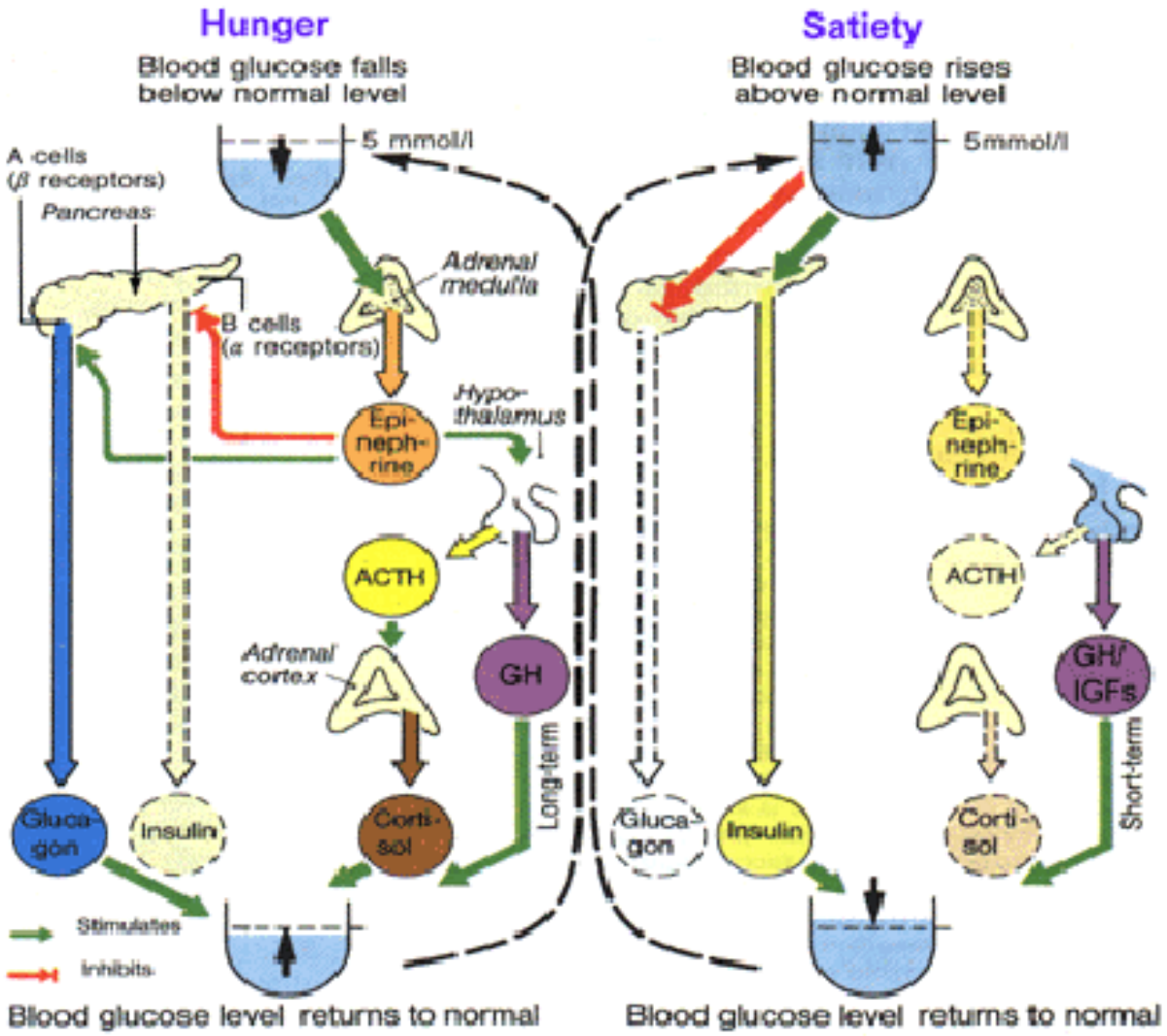
4 cell types



After meals glucose from liver is mainly stored as glycogen in liver & muscle & as fat in fat cells. When more energy is needed between meals, glycogen, fat & protein (last) are broken down & liver uses the parts to make glucose. Hormones (insulin, glucagon, adrenalin, cortisol) signal the change from storage to synthesis.

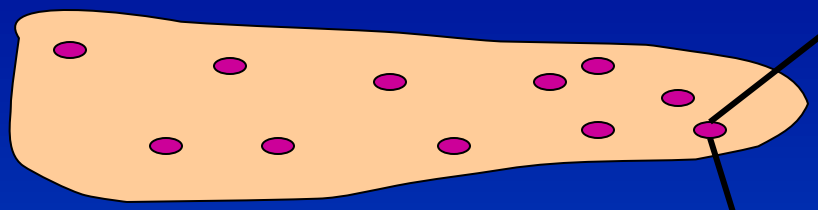


# Hormonal Control of Glucose Homeostasis



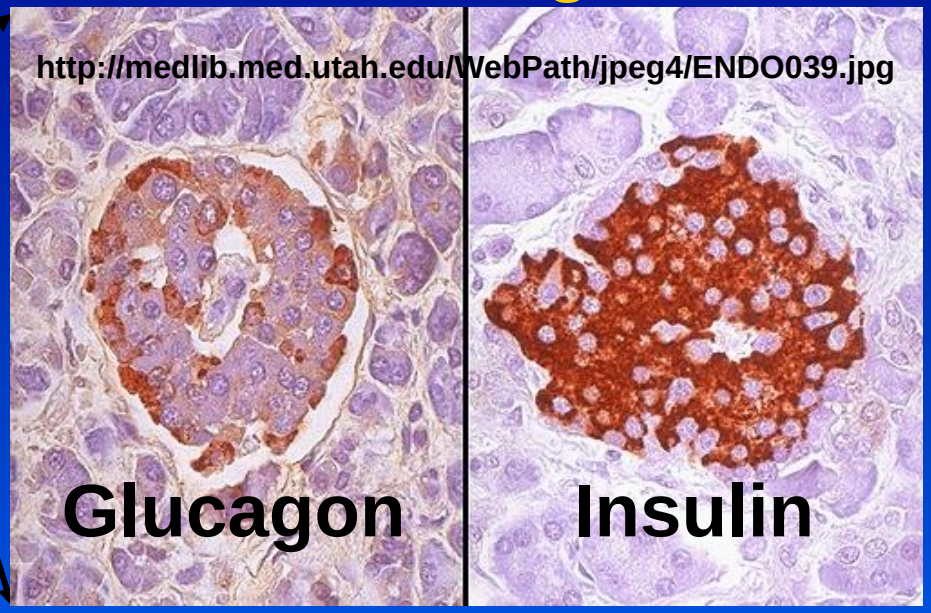

(Modified from Despopoulos & Silbernagl, *Color Atlas of Physiology, 3rd Ed,* Thieme Inc.: New York, 1986.)

# Hormones Control the Glucose Balance



Pancreas

## Islets of Langerhans



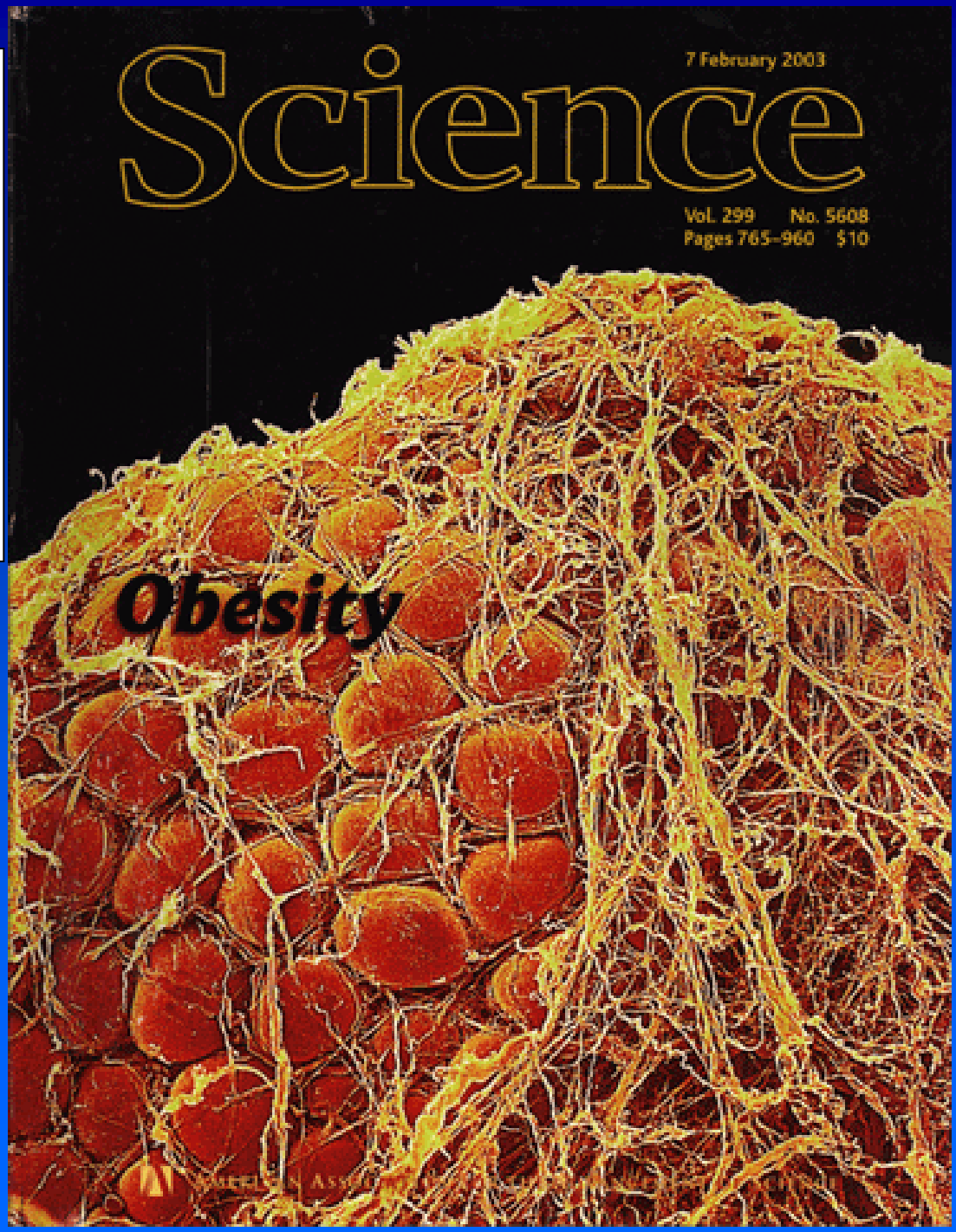

**Insulin** acts on body cells to allow them to take in circulating glucose. **Insulin** levels rise when glucose rises.

**Glucagon** acts on liver to stimulate glucose production & release, & on fat to cause fat breakdown. **Glucagon** rises when glucose falls.

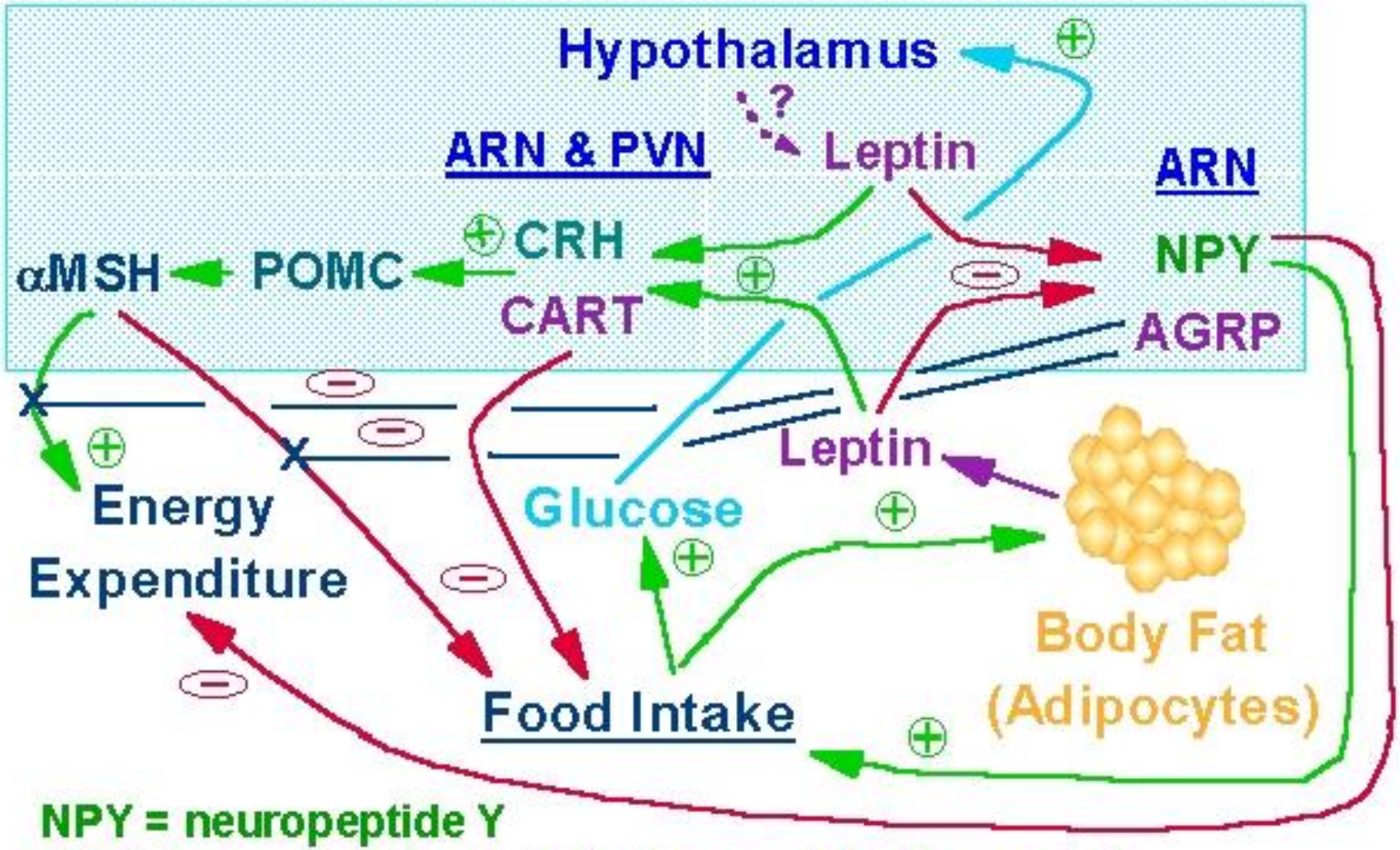
**Adrenaline, cortisol, & growth hormone** also make blood glucose rise. But **insulin-like-growth factor I** acts like insulin.

# Body Mass Homeostasis: Our New Understanding


www.garvan.org.au/library / images/jpg/adipocytes.jpg



# Controls on Food Intake

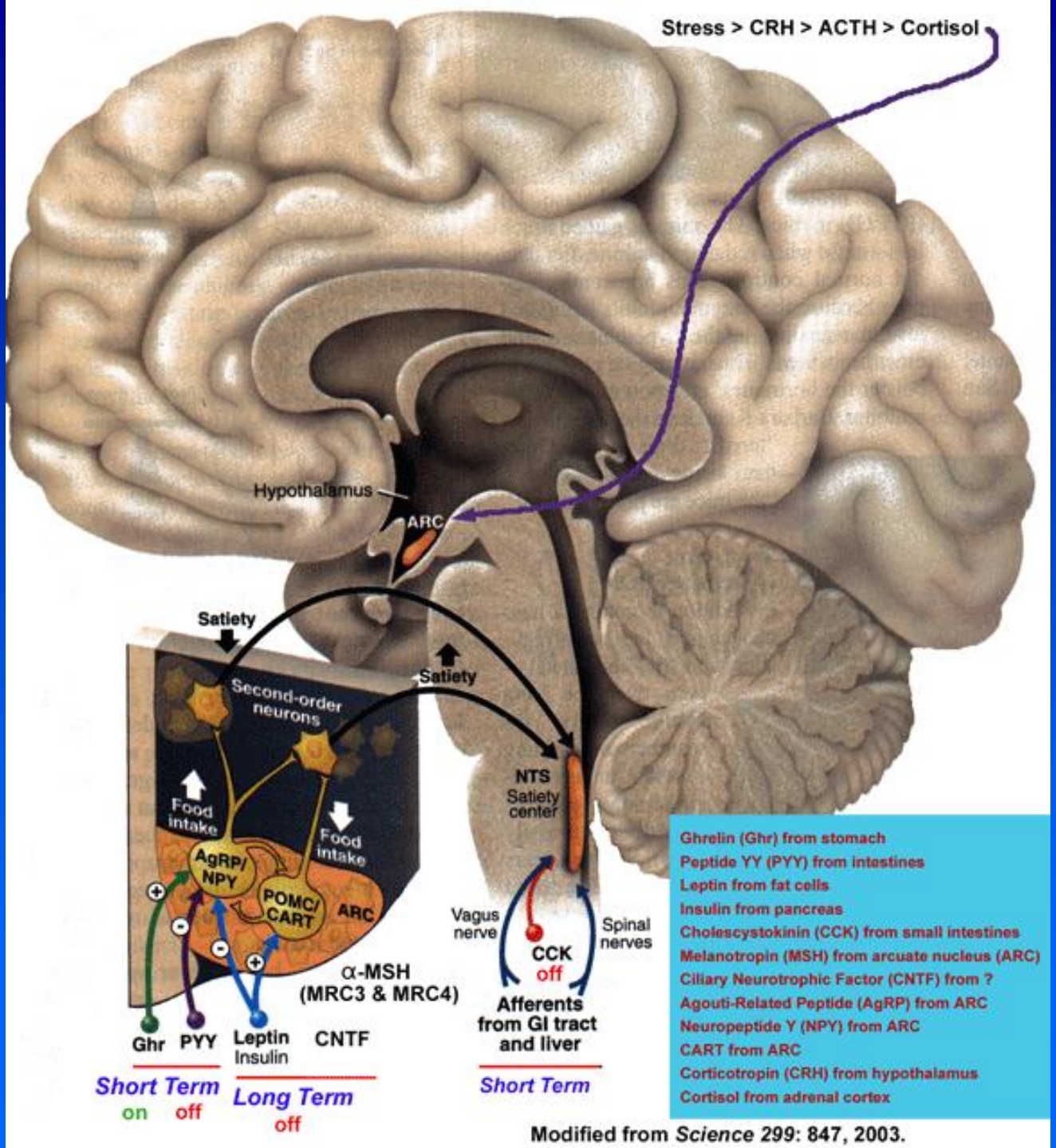



NPY = neuropeptide Y

CART = cocaine & amphetamine - related transcript

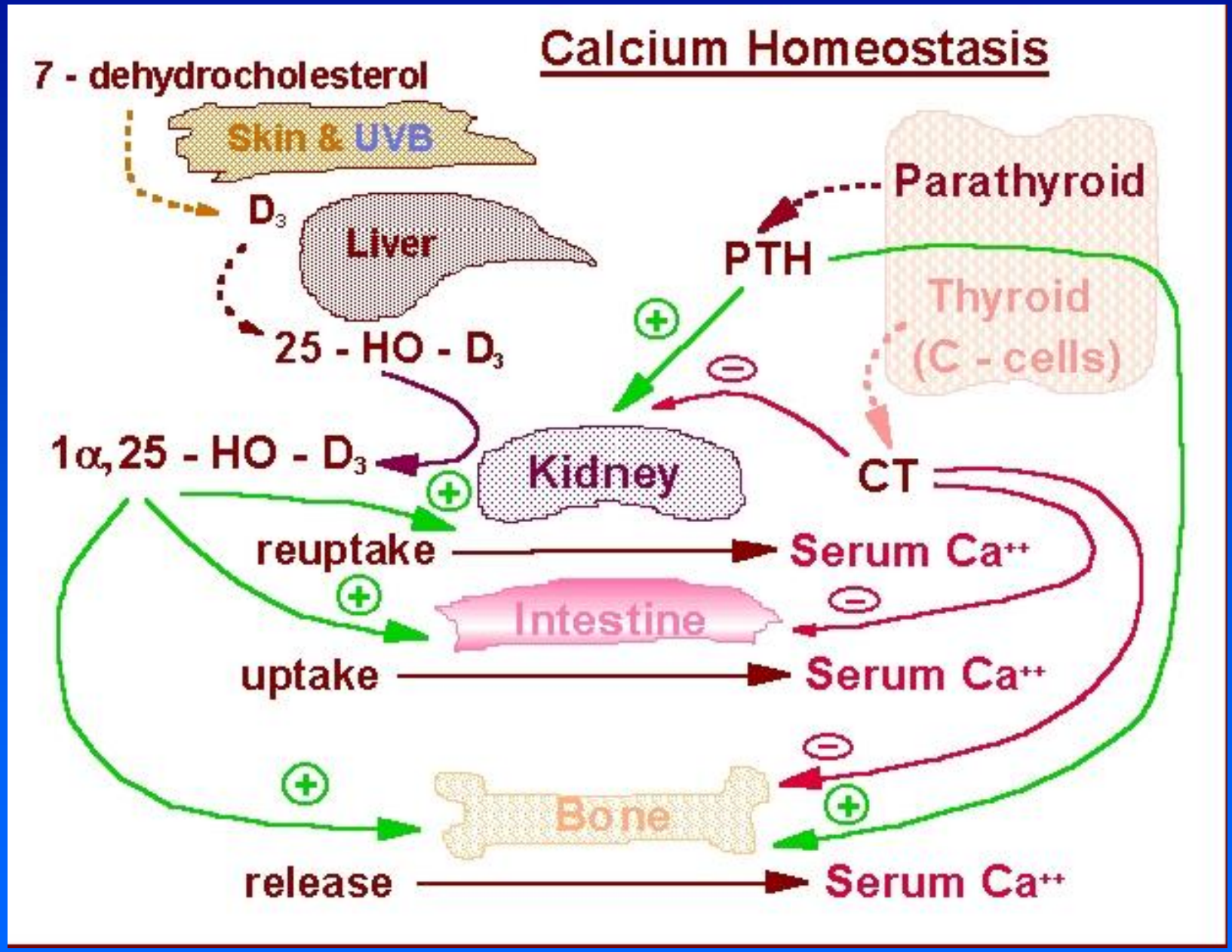
AGRP = agouti - gene related peptide,
endogenous αMSH antagonist

# A Little More About the Central Players

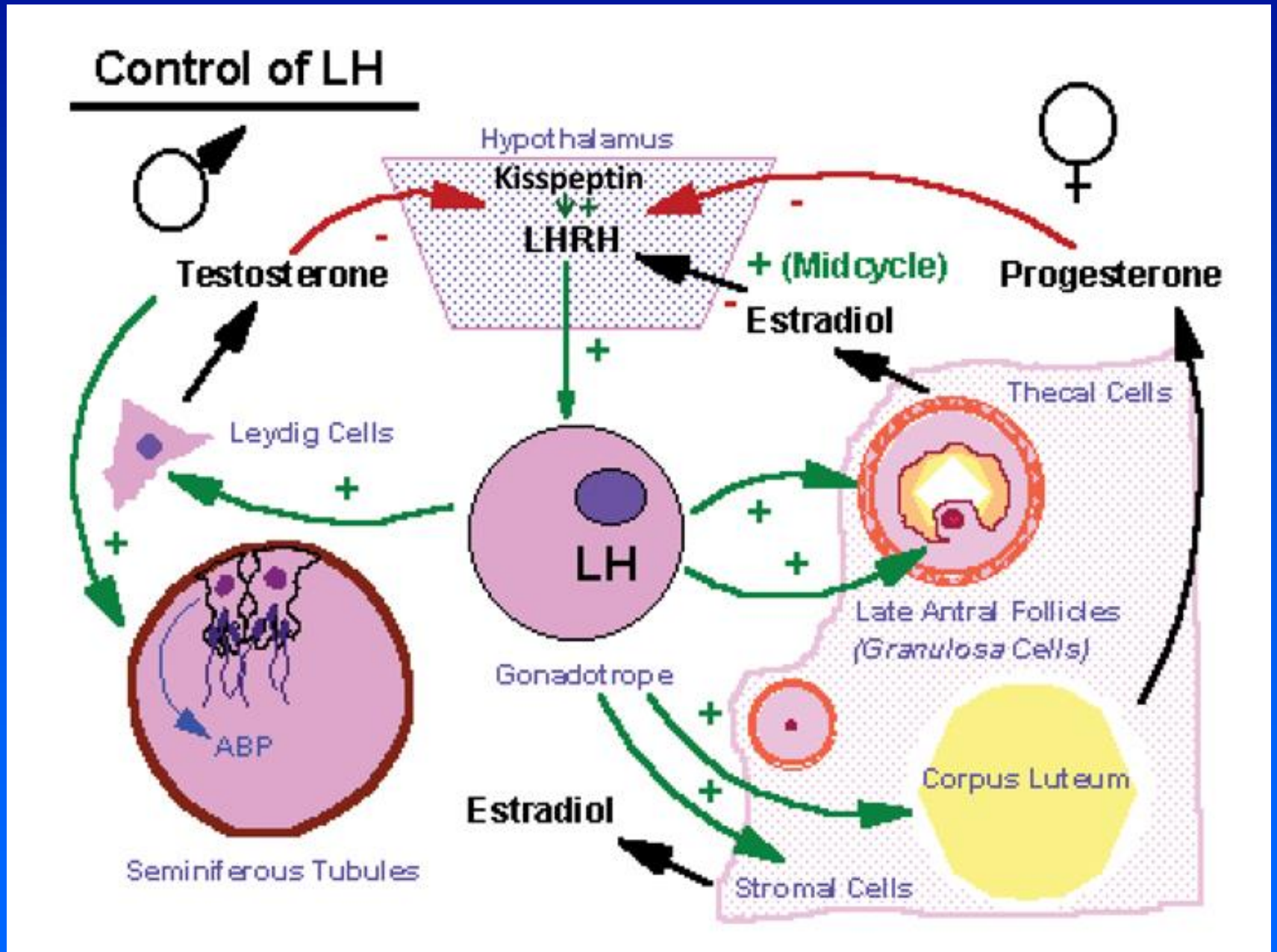



Modified from *Science 299*: 847, 2003.

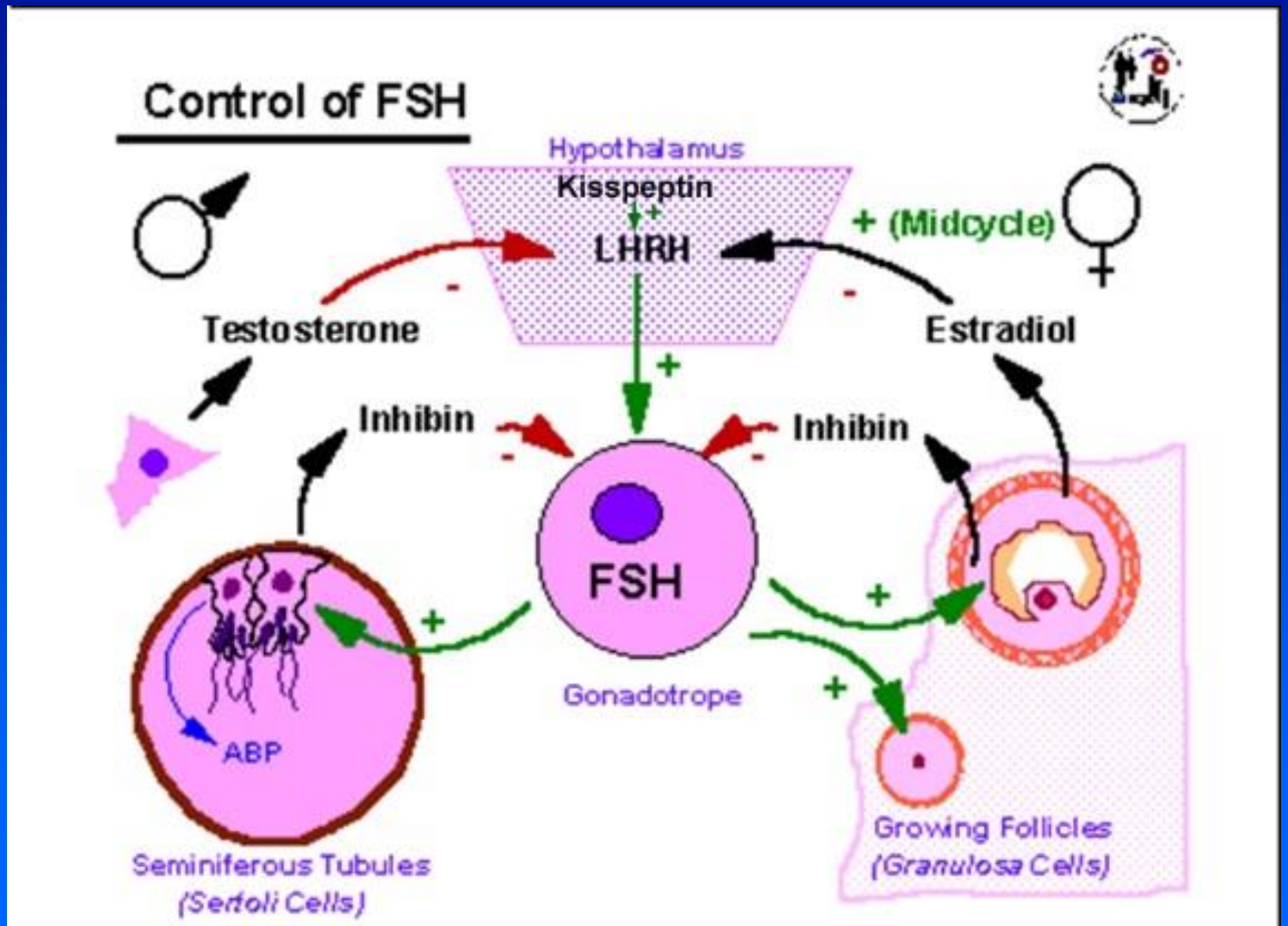
# Calcium Homeostasis



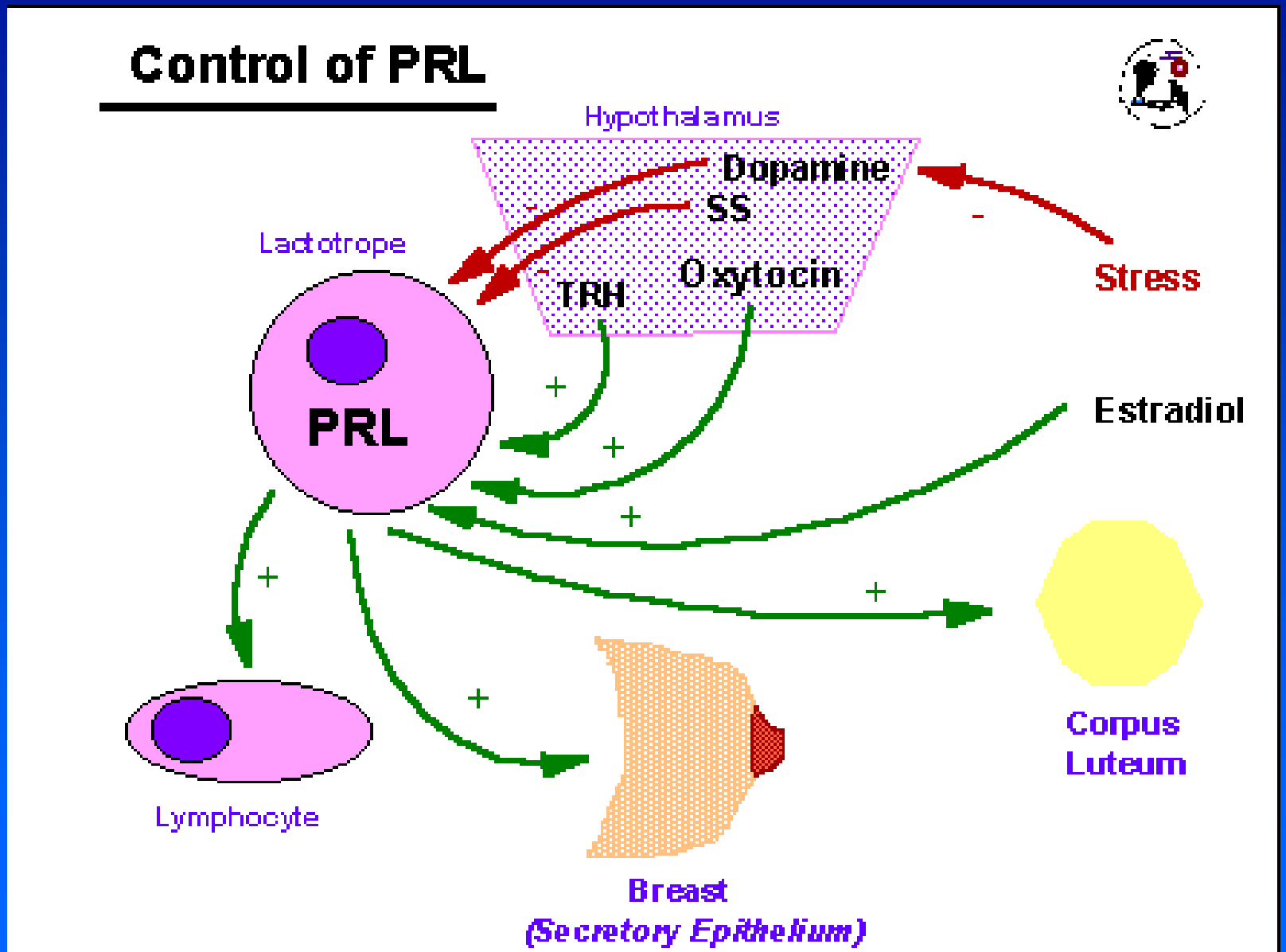
# How are the gonads controlled? LH



# How are the gonads controlled? FSH



# How is prolactin controlled?



# What questions remain open?

## Examples:

- Molecular discovery
- Exploration of molecular interactions
- Definition of the genetics of endocrine molecules & their interactions
- Description of dynamics & kinetics of cellular interactions
- Impacts of environmental variables on molecular or cellular interactions
- Impacts of toxicants on molecular or cellular interactions
- Discovery & exploration of chemical modifiers of the endocrine system

# What specializations are involved?

Genomics, Proteomics, Transgenics, Pharmacology, Toxicology, Clinical & Veterinary Medicine, Nursing, Diagnostics, Forensics, Epidemiology, Statistics, Biomedical Engineering, Informatics, Basic Endocrine Research

# Conclusions:

**Communication among cells & organisms & between organisms & their environment is absolutely central to life & reproduction. While many of the basics of endocrine communication are known, we are continually surprised by new findings that revise our existing knowledge. Many, of the details of endocrine molecular biology, genetics, cell biology, & development remain to be defined. As one of the most dynamic & central of the biomedical sciences for practitioners, paramedical professions, & basic scientists, endocrinology will continue to be a vital science for many years to come.**