Citation Key

for more information see: http://open.umich.edu/wiki/CitationPolicy

Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

Public Domain – Government: Works that are produced by the U.S. Government. (17 USC § 105)

Public Domain – Expired: Works that are no longer protected due to an expired copyright **term.**

Public Domain – Self Dedicated: Works that a copyright holder has dedicated to the public domain.

Creative Commons – Zero Waiver

Creative Commons – Attribution License

Creative Commons – Attribution Share Alike License

Creative Commons – Attribution Noncommercial License

Creative Commons – Attribution Noncommercial Share Alike License

GNU – Free Documentation License

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

Public Domain – Ineligible: Works that are ineligible for copyright protection in the U.S. (17 USC § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

Fair Use: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (17 USC § 107) *laws in your jurisdiction may differ

Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we **DO NOT** guarantee that your use of the content is Fair.

To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.

M2 Endocrine Sequence

University of Michigan Medical School

Directors:
Arno K. Kumagai, M.D.
Thomas Giordano, M.D., Ph.D.

University of Michigan Medical School

Winter 2009

General Information

- Syllabus and Lecture notes
- Required Sessions:
  - Patient presentation: Friday, March 6th
  - Endocrine Small Groups: Thurs-Fri, March 5-6th
  - Longitudinal Case
- Endocrine Photo Gallery

Feedback loops and anterior pituitary physiology

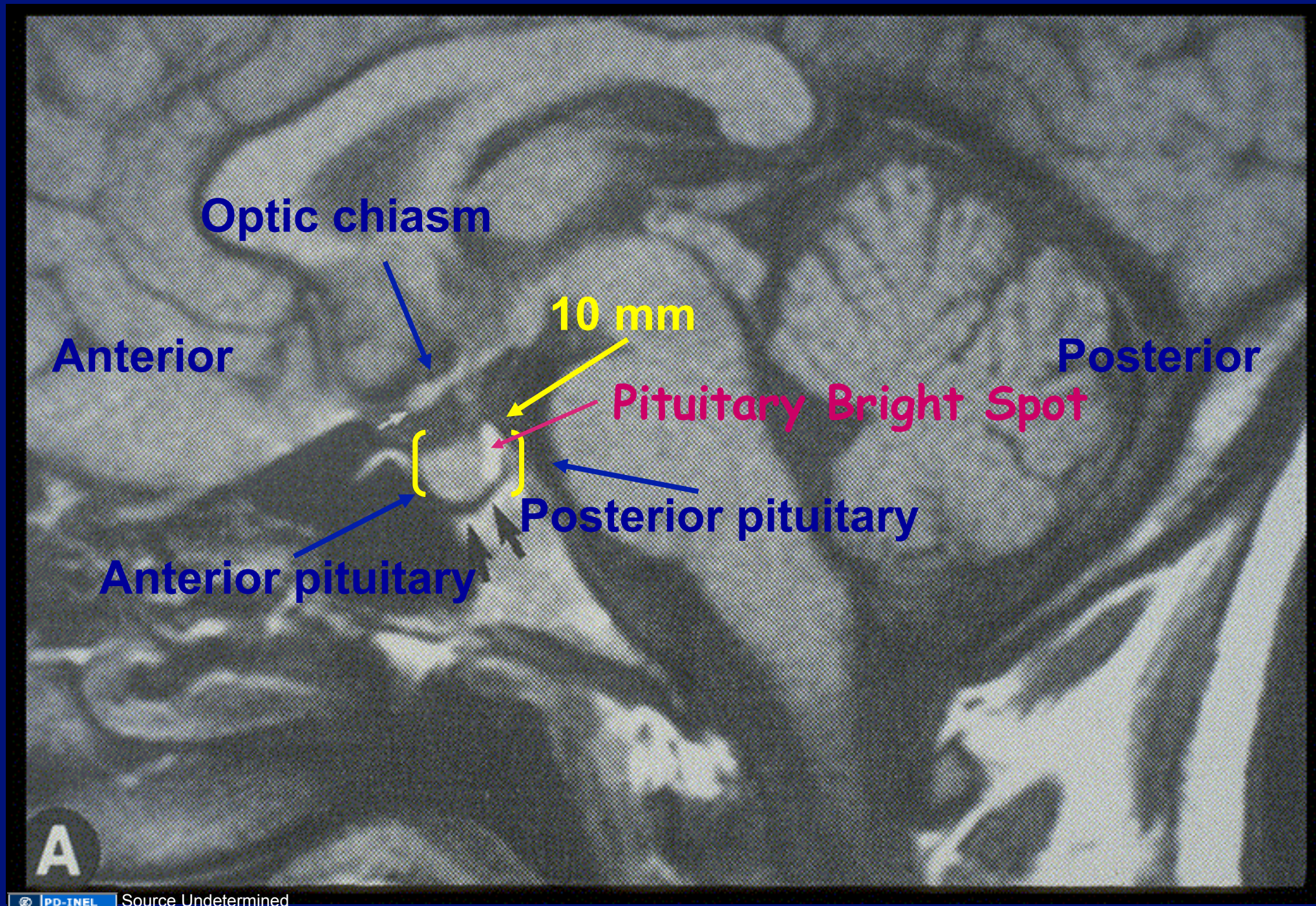
M2- Endocrine Sequence

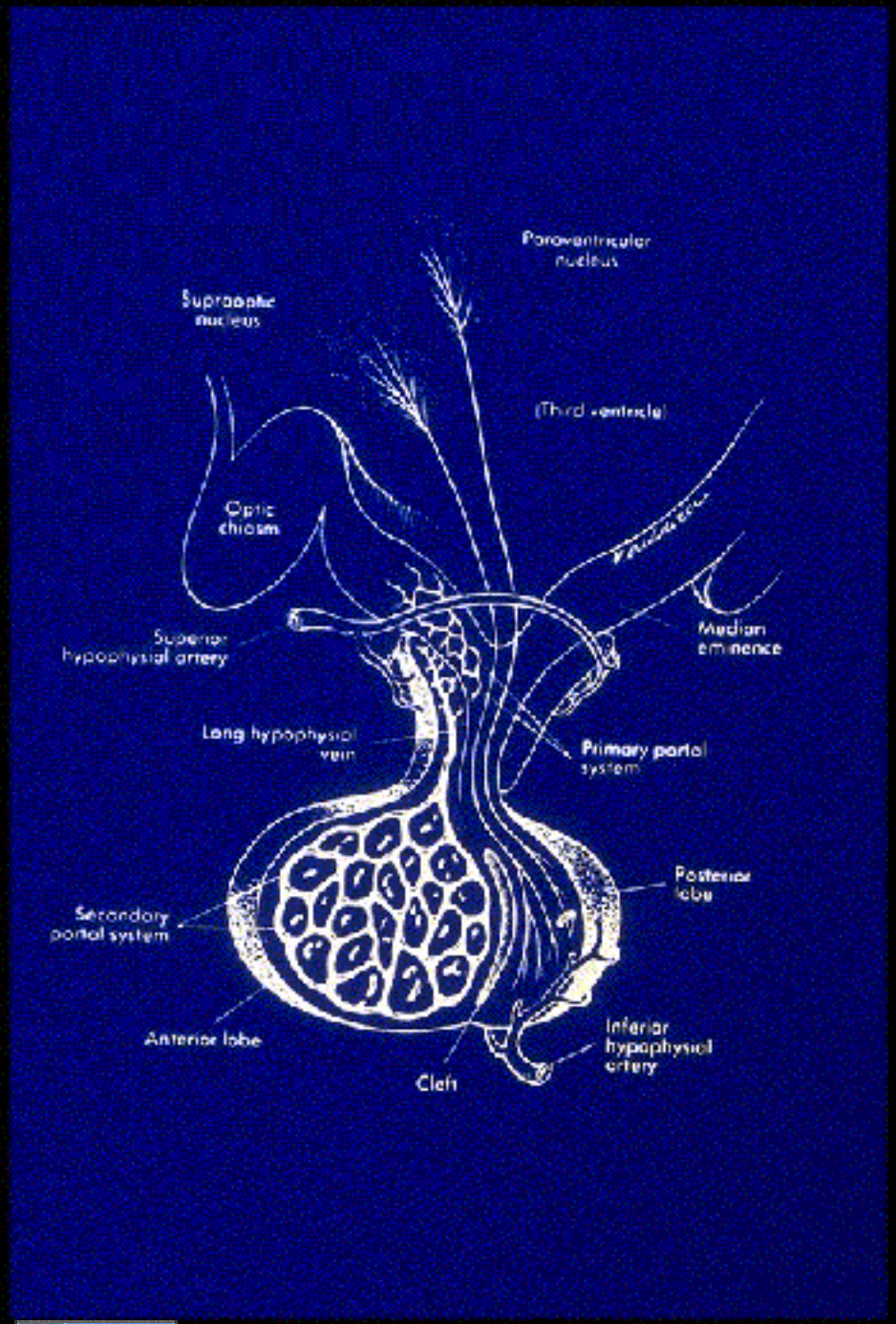
Arno K. Kumagai, M.D.

Division of Metabolism, Endocrinology & Diabetes

Winter 2009

University of Michigan Medical School





Pituitary cell types

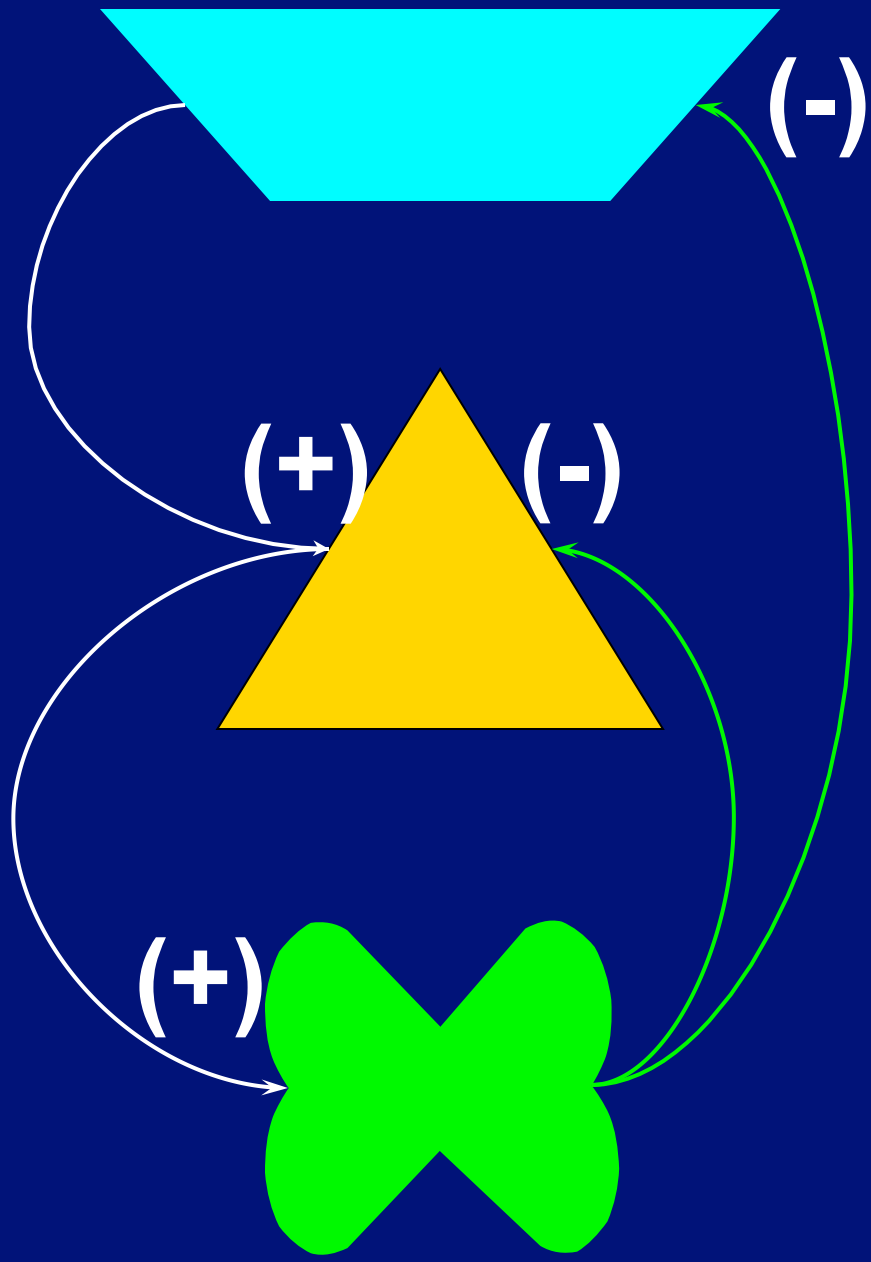
Pituitary cell type	Pituitary hormone	Clinical syndrome associated w/ tumor
Corticotrope	ACTH	Cushing's disease
Somatotrope	GH	Acromegaly
Gonadotrope	FSH and LH	None
Lactotrope	Prl	Prolactinoma
Thyrotrope	TSH	Hyperthyroidism

Hormonal Feedback Loops

You

Your thermostat

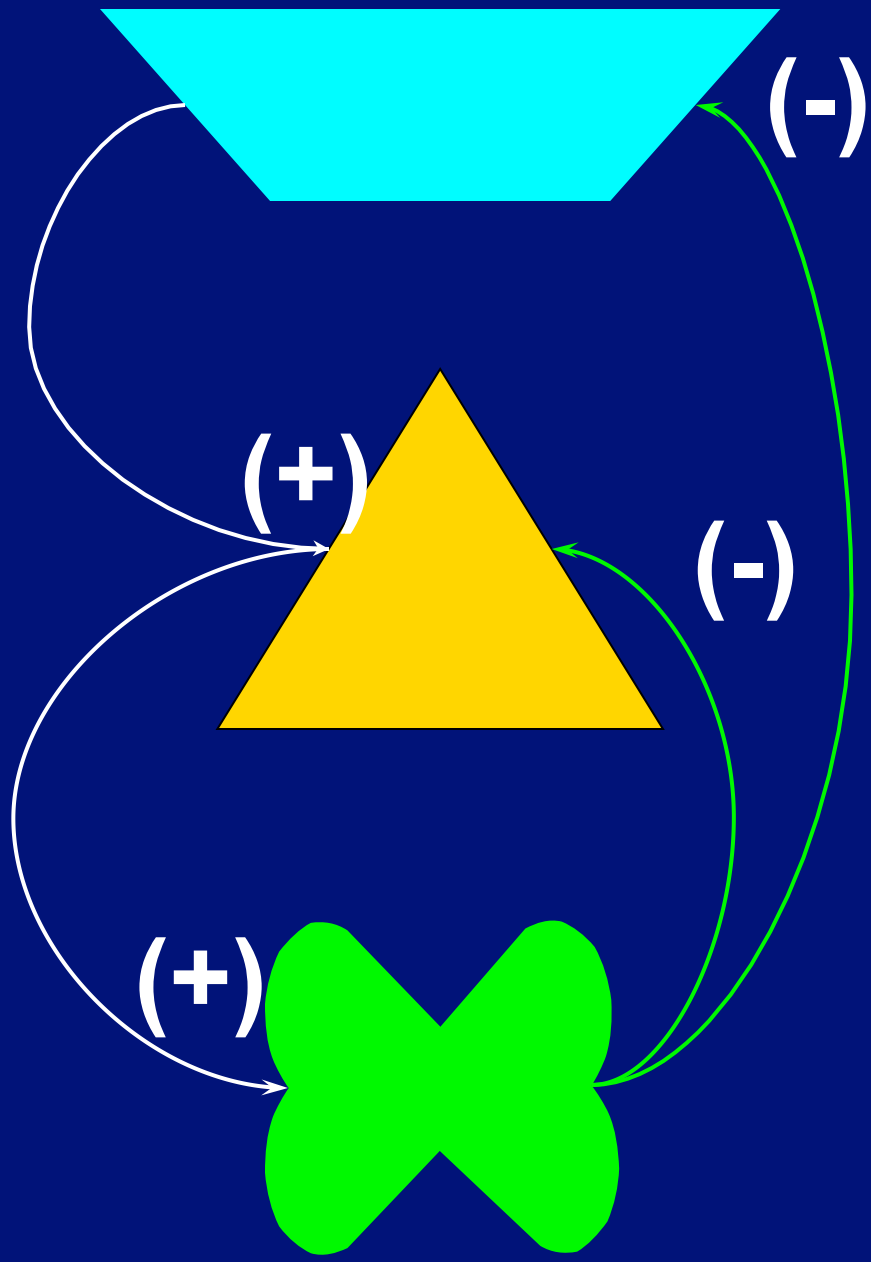
Your furnace



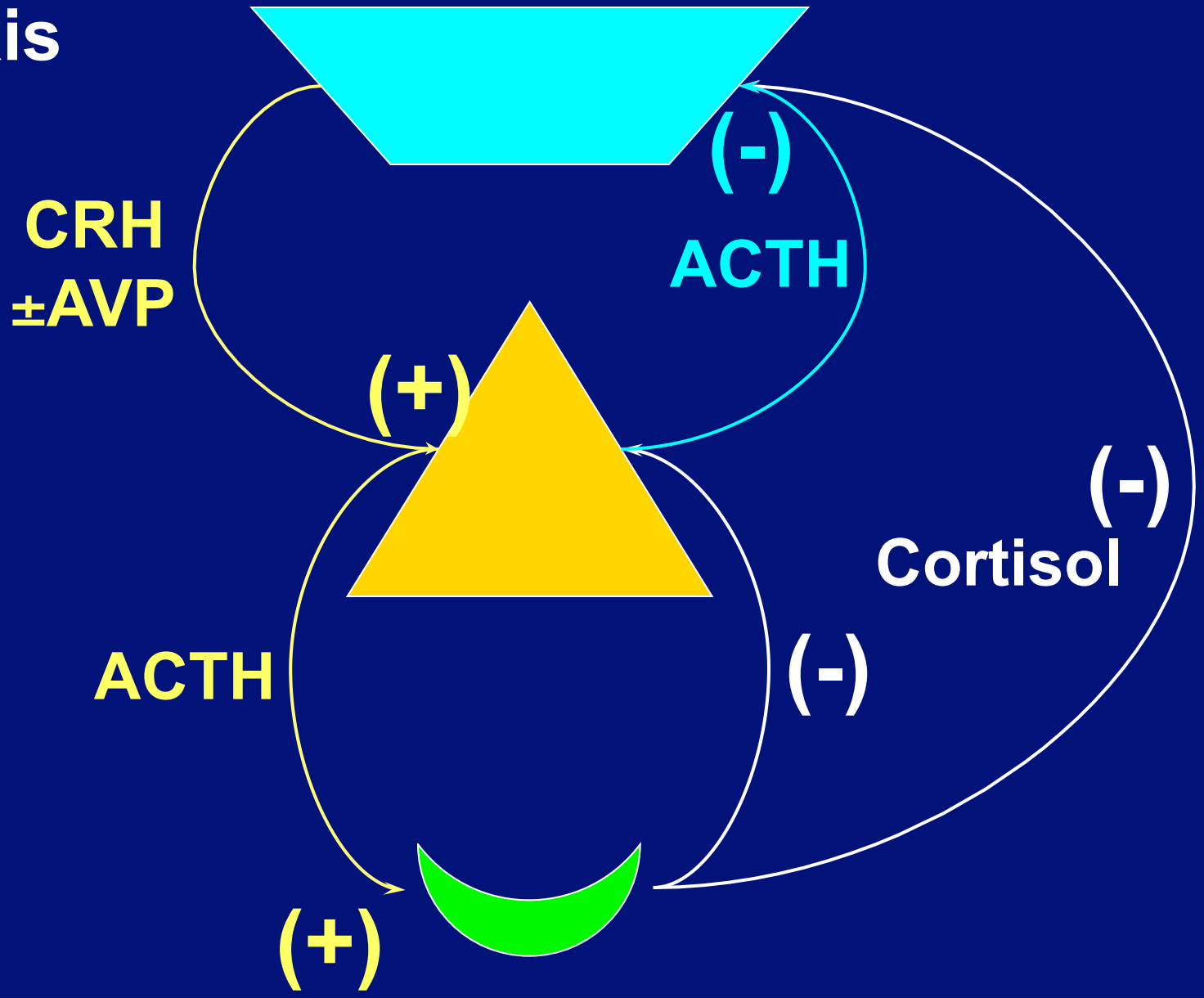
Hypothalamus

Pituitary

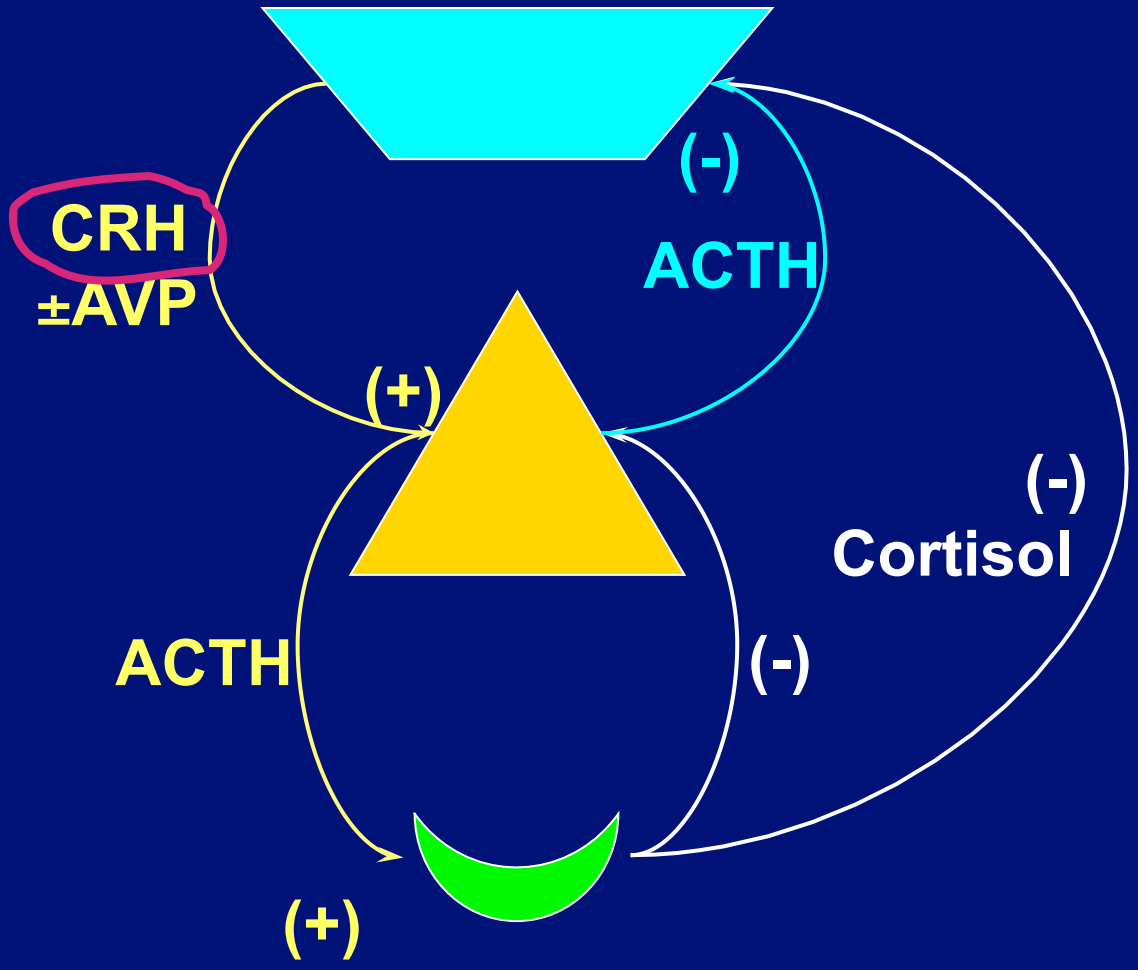
End organ



Adrenal axis



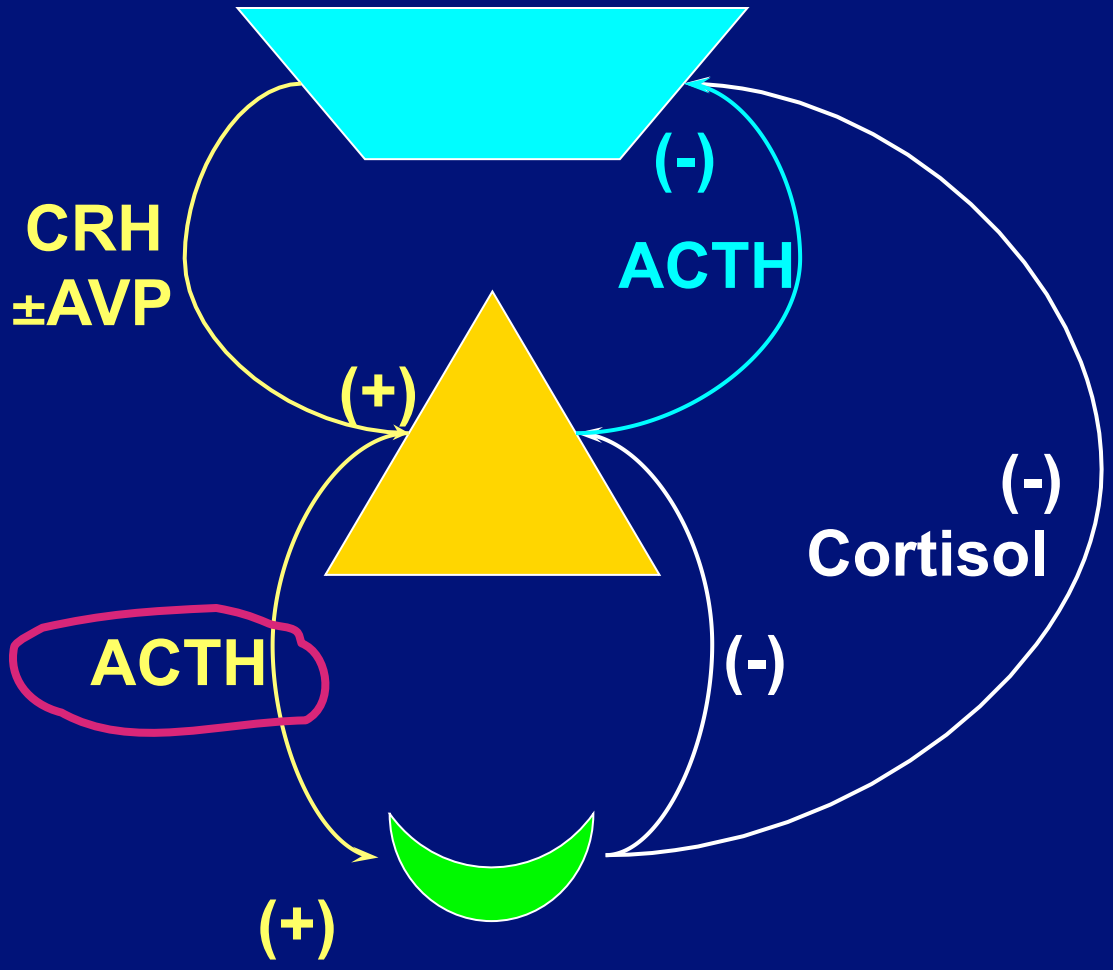
Hypothalamic-Pituitary-Adrenal Axis



CRH = Corticotropin Releasing Hormone

- 41 amino acids long
- Ovine form is more potent than human form
- A trophic factor and a releasing hormone

Hypothalamic-Pituitary-Adrenal Axis

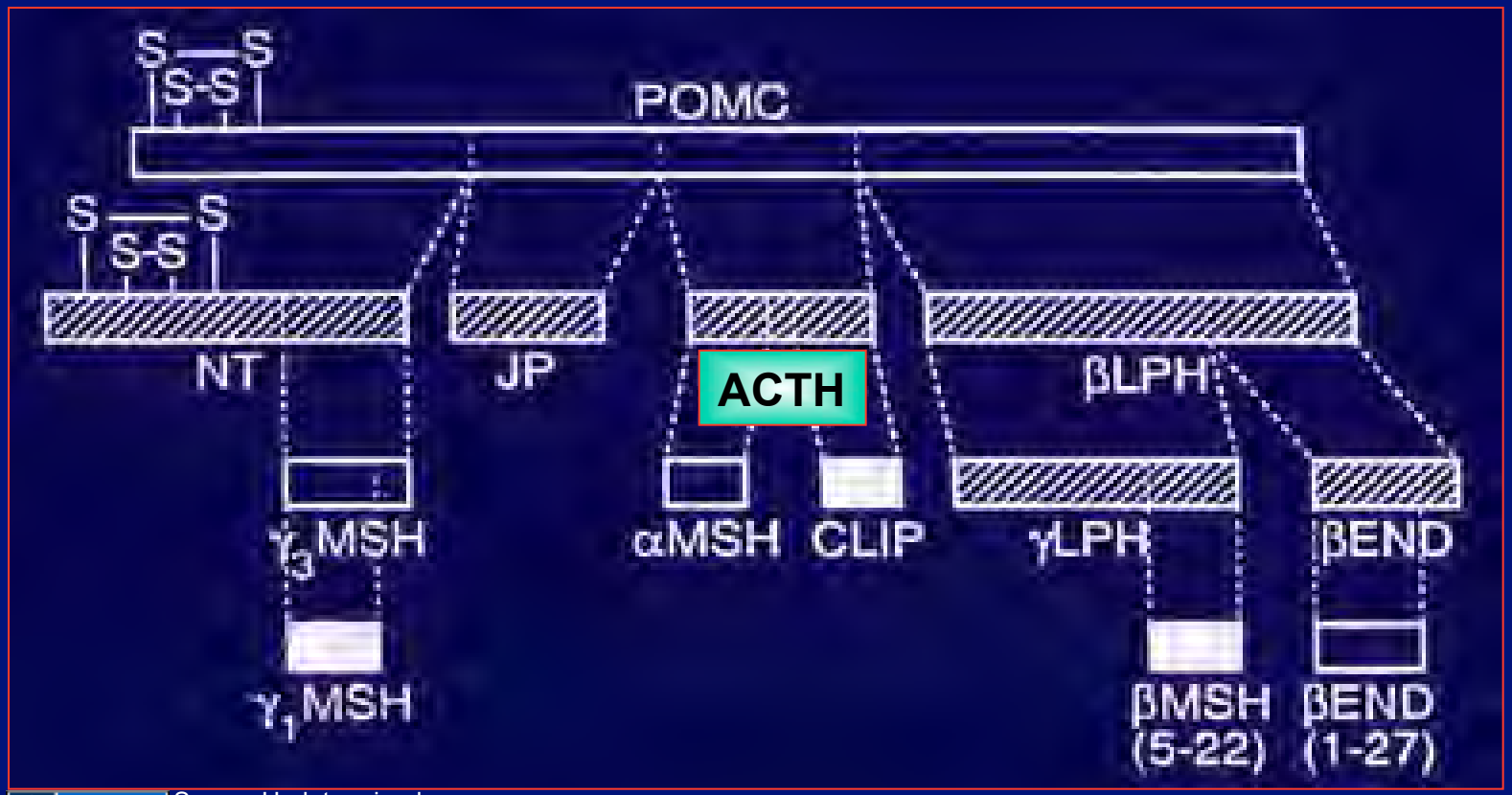


ACTH = Corticotropin

- Derived from a large molecule (POMC)
- 39 amino acids long, first 24 are the same in multiple species
  - ✓ Synthetic ACTH (aa 1-24) used clinically
- 250 μg in the pituitary - about 50 μg secreted daily

Post-translational Processing of POMC in the Normal Pituitary

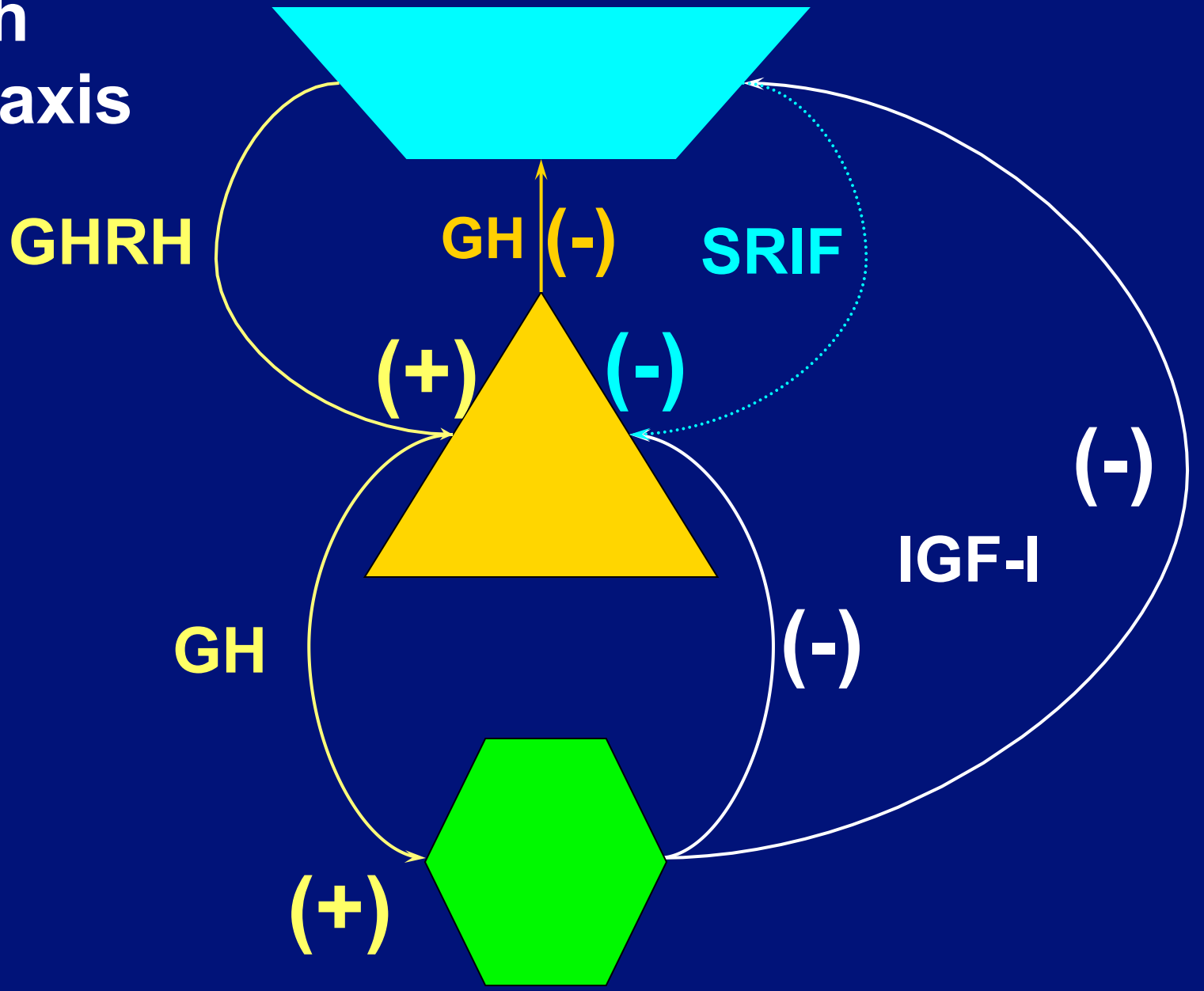
POMC = Pro-opiomelanocortin



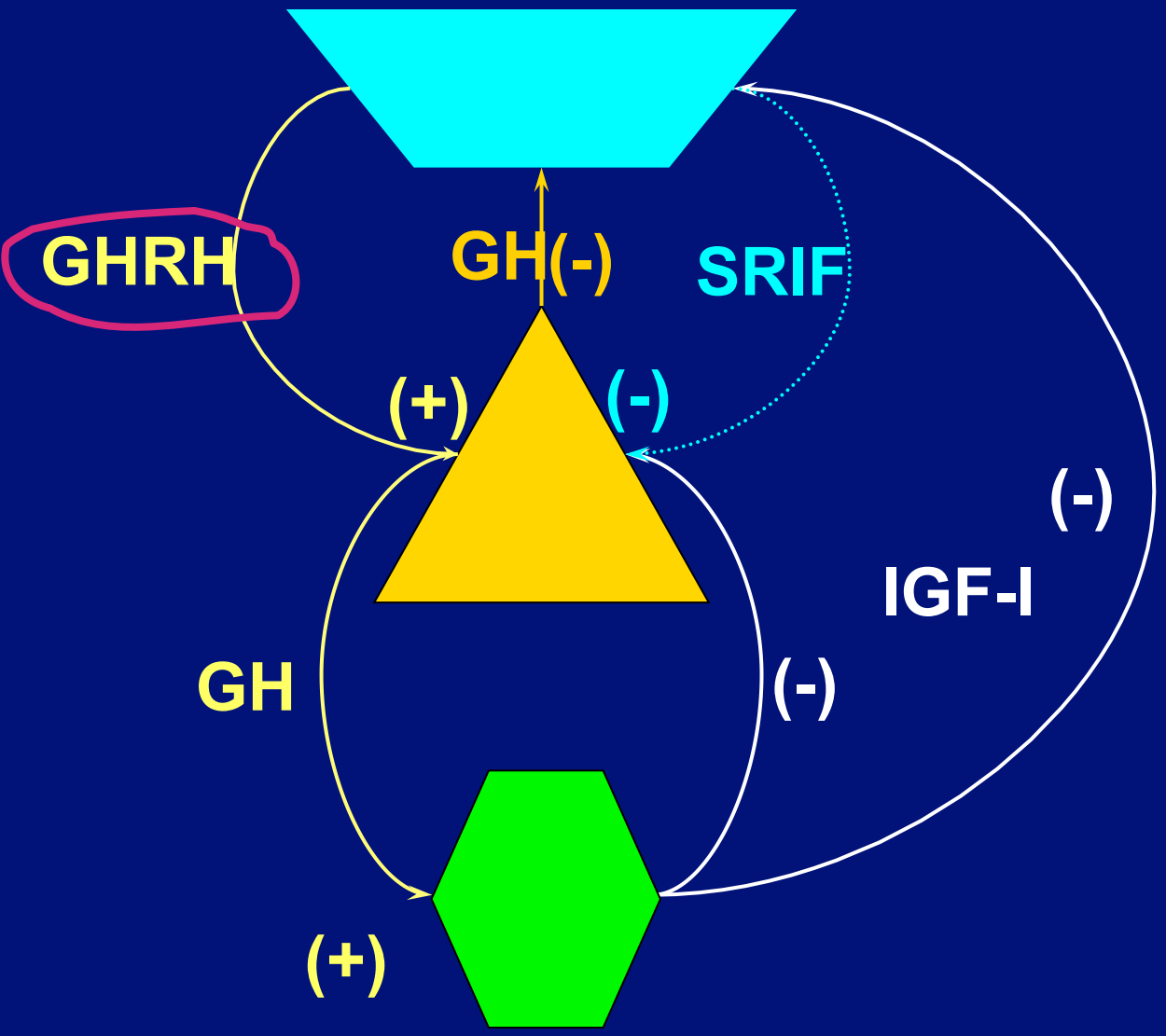
PD-INEL Source Undetermined

MSH = Melanocyte stimulating hormone

Growth hormone axis

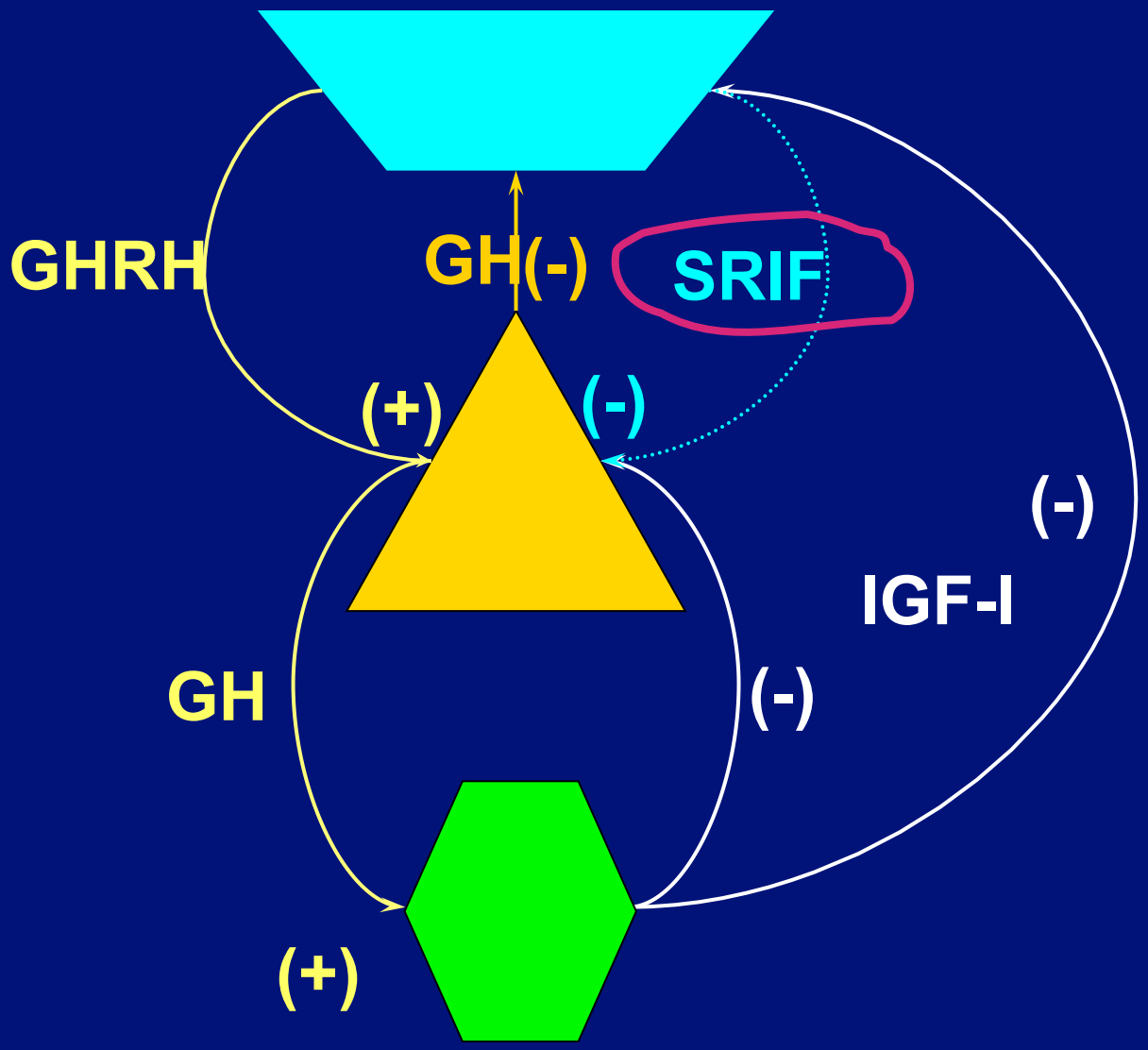


Growth hormone axis



- GH Releasing Hormone (GHRH)
- About 44 amino acids long
- Discovered in pancreatic tumors
- Men over 40 have little response to GHRH

Growth hormone axis



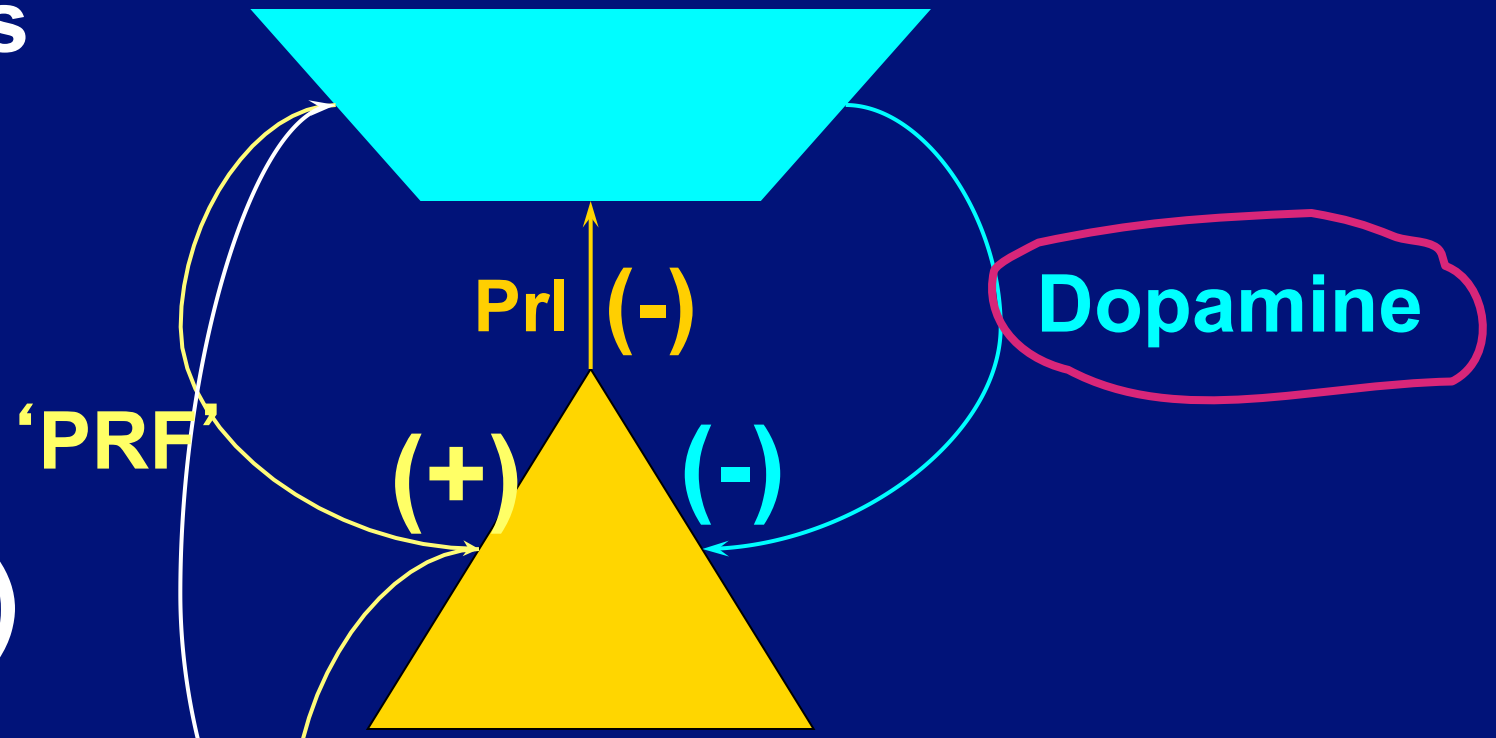
Somatostatin (SRIF)

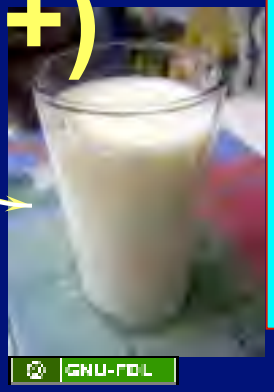
- Inhibits secretion of GH and TSH
- Also inhibits GI hormones and functions
- Octreotide is a clinically useful analogue

Growth hormone - prolactin family

- Significant homology, less so at the protein level (16%)
- **Prl & GH both activate the prolactin receptor**
- Family also includes placental lactogen (PL)

Prolactin axis





Janine Chedid, Wikimedia Commons

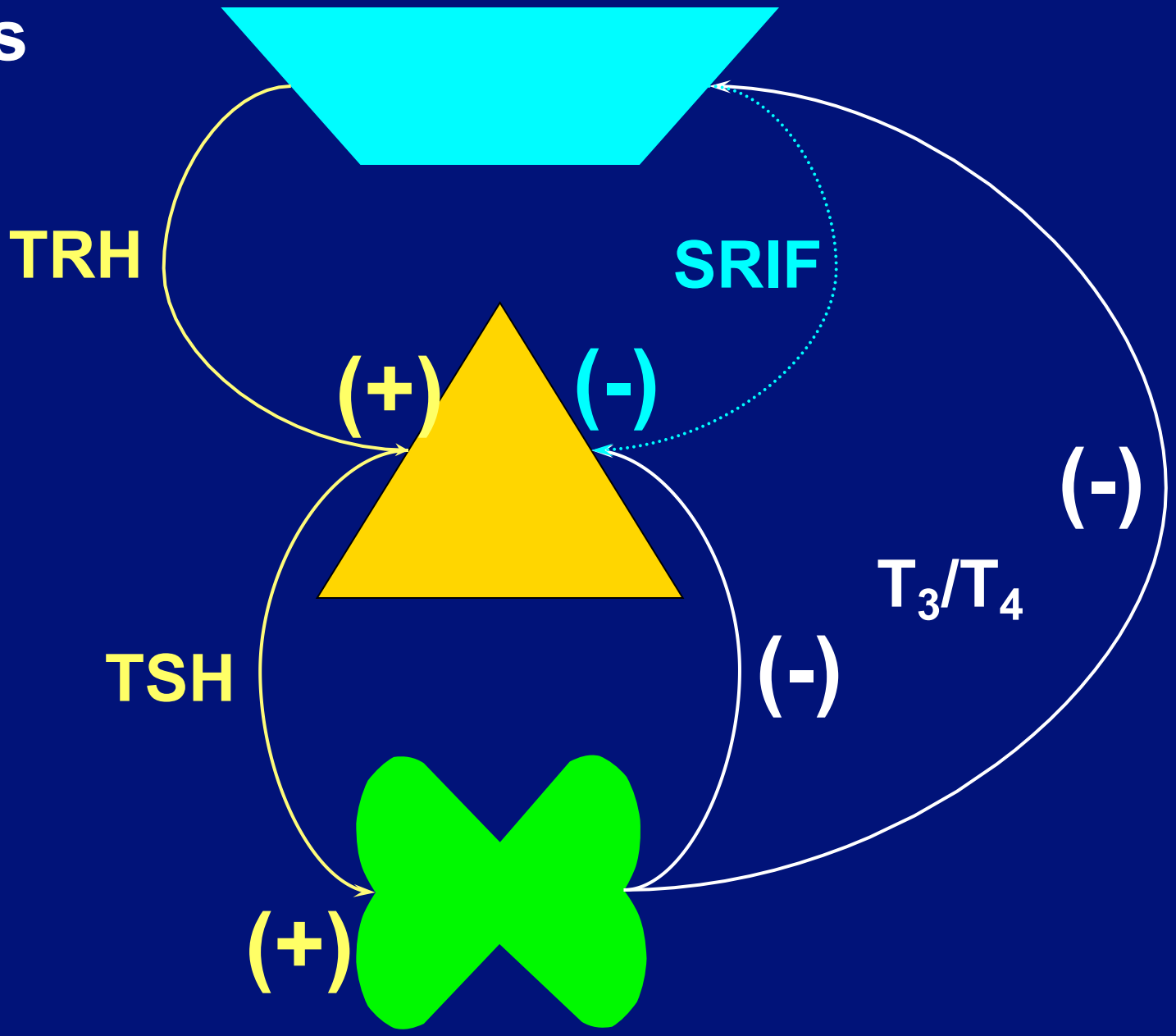
IMPORTANT

Prolactin release is tonically inhibited by DOPAMINE

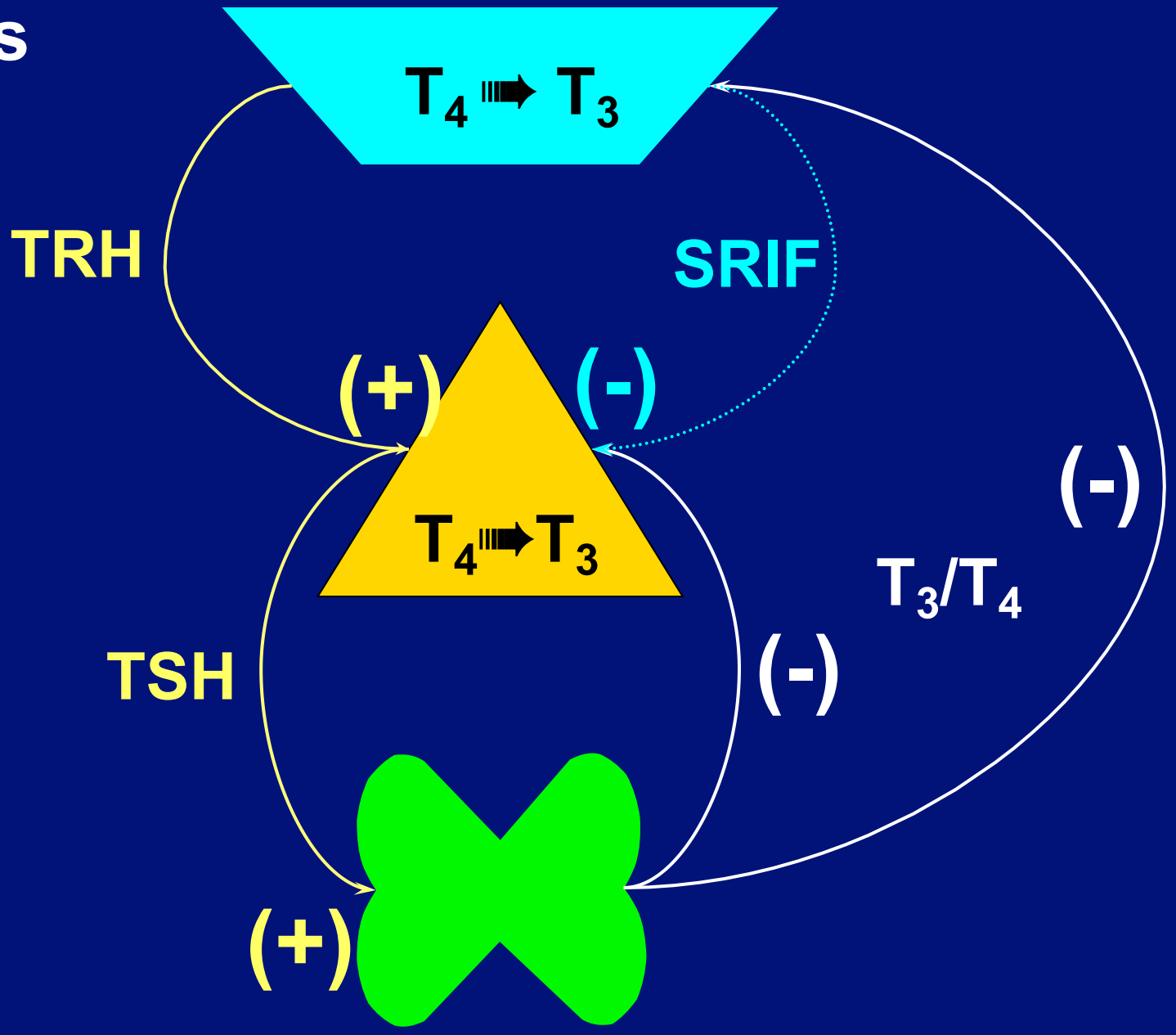
Regulation of prolactin = tonically inhibited

- **Prolactin-inhibiting factors (PIFs)**
  - Dopamine, Dopamine, Dopamine, maybe GABA
  - Bromocriptine is a dopamine agonist
  - Block multiple aspects of lactotrope function
- **Prolactin-releasing factors (PRFs)**
  - TRH - but probably not physiologically important
  - Other candidates: AVP, VIP, Oxytocin, PHI-27

Thyroid axis

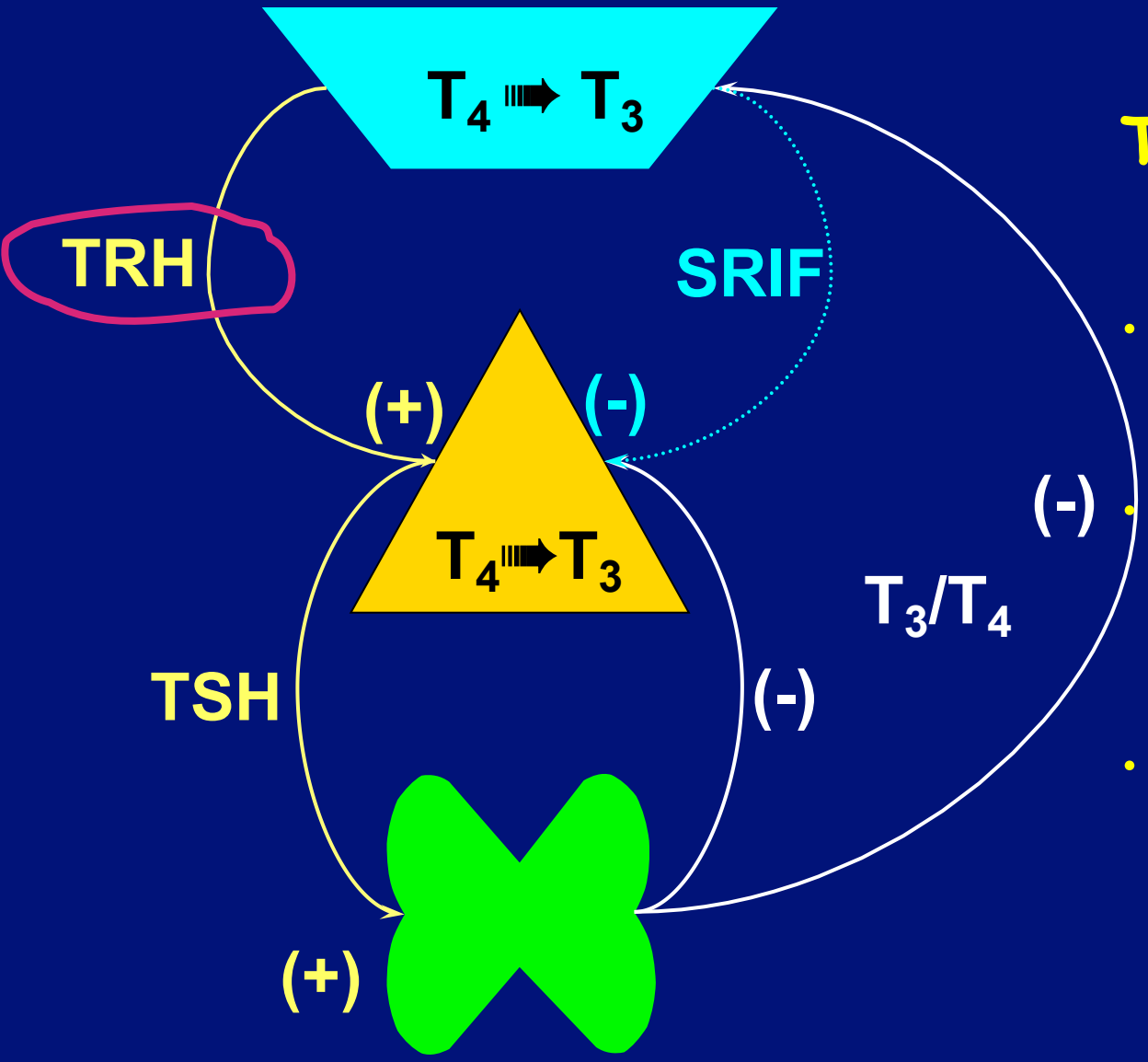


Thyroid axis



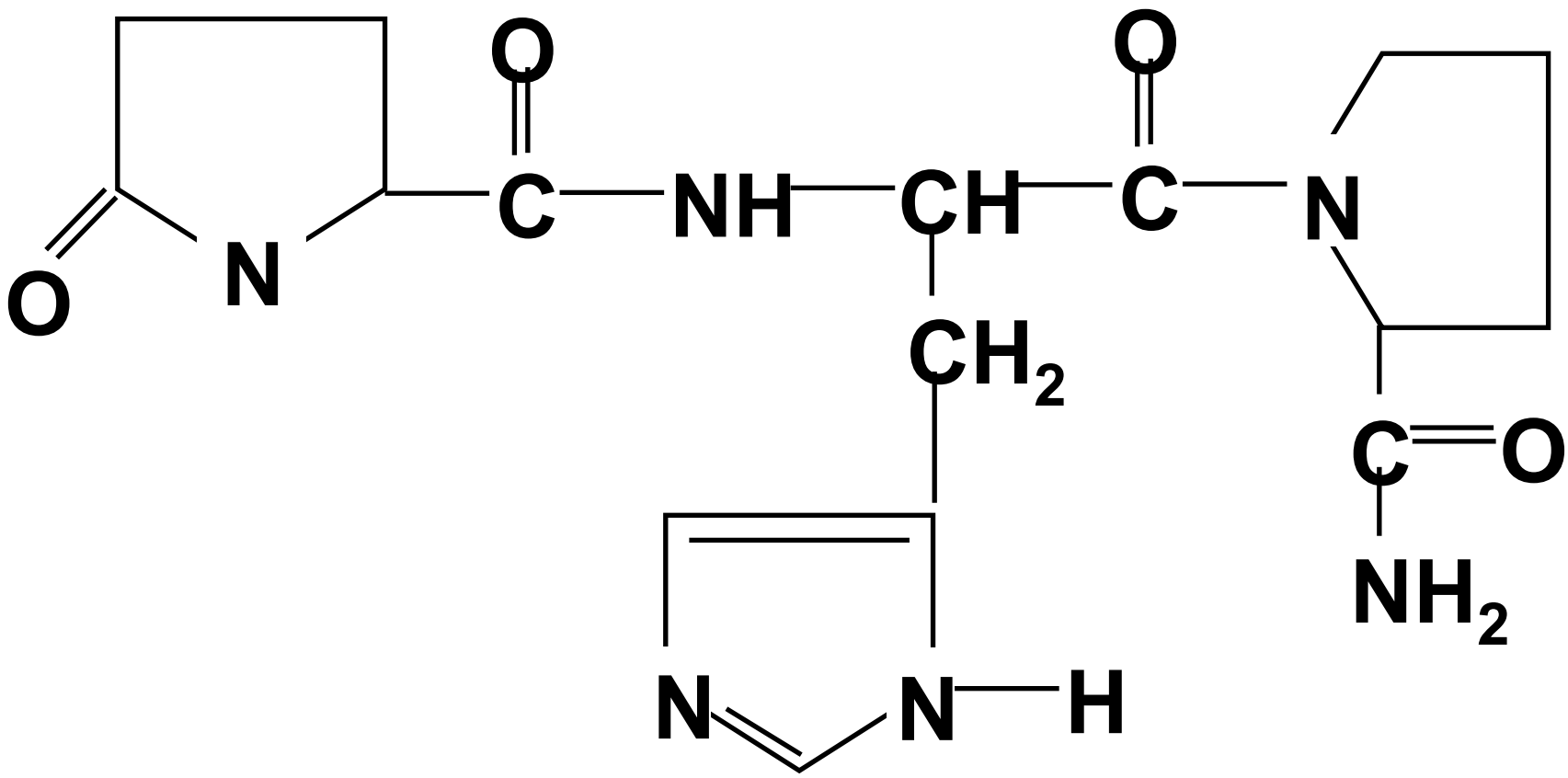
 R. Lash

Hypothalamic-Pituitary-Thyroid Axis

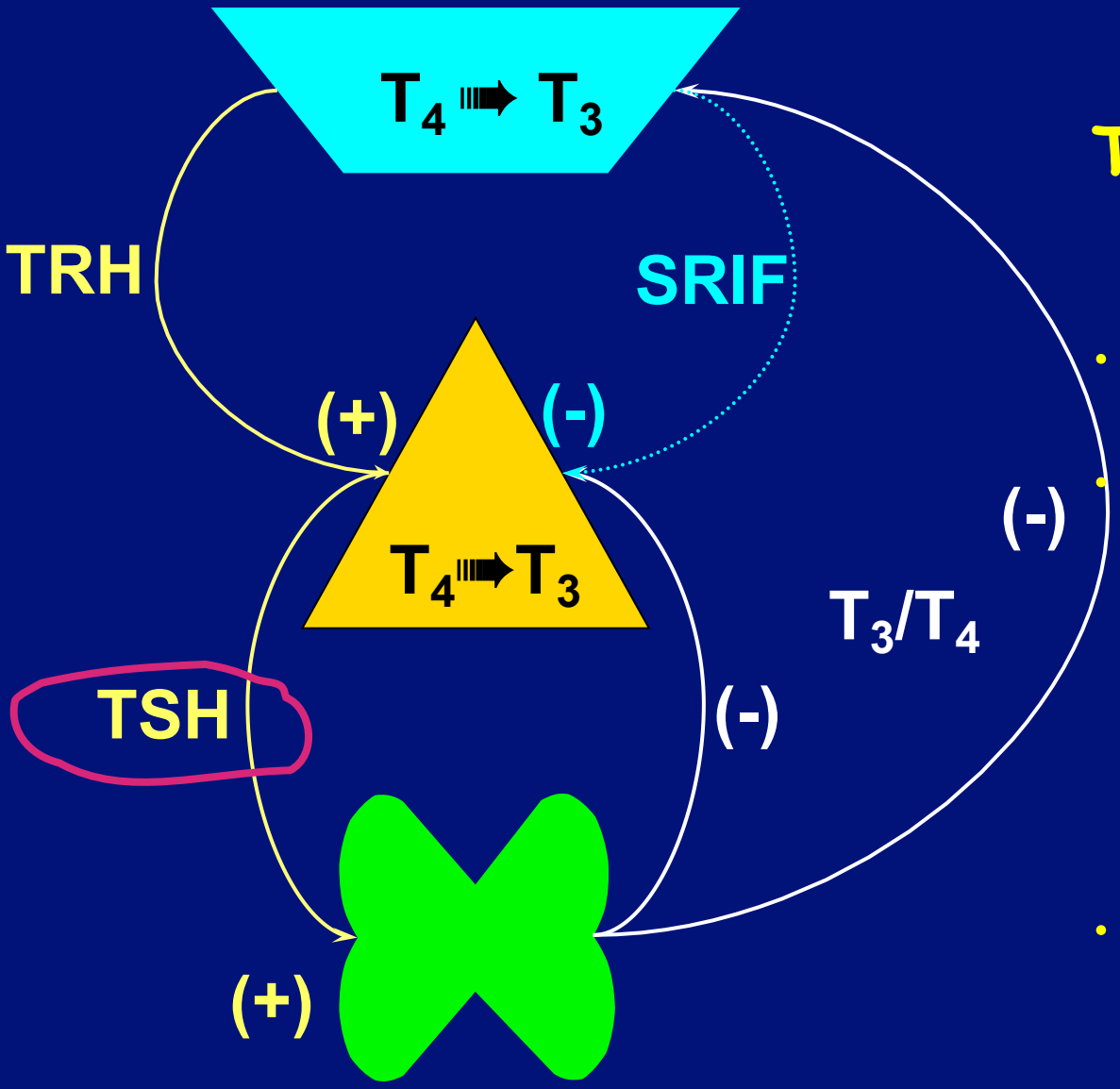


- TRH = Thyrotropin Releasing Hormone
- Tripeptide (3 amino acids)
- Also a potent stimulator of prolactin release
- Synthesized as a prohormone with six copies of the TRH molecule

The TRH Tripeptide



Hypothalamic-Pituitary-Thyroid Axis

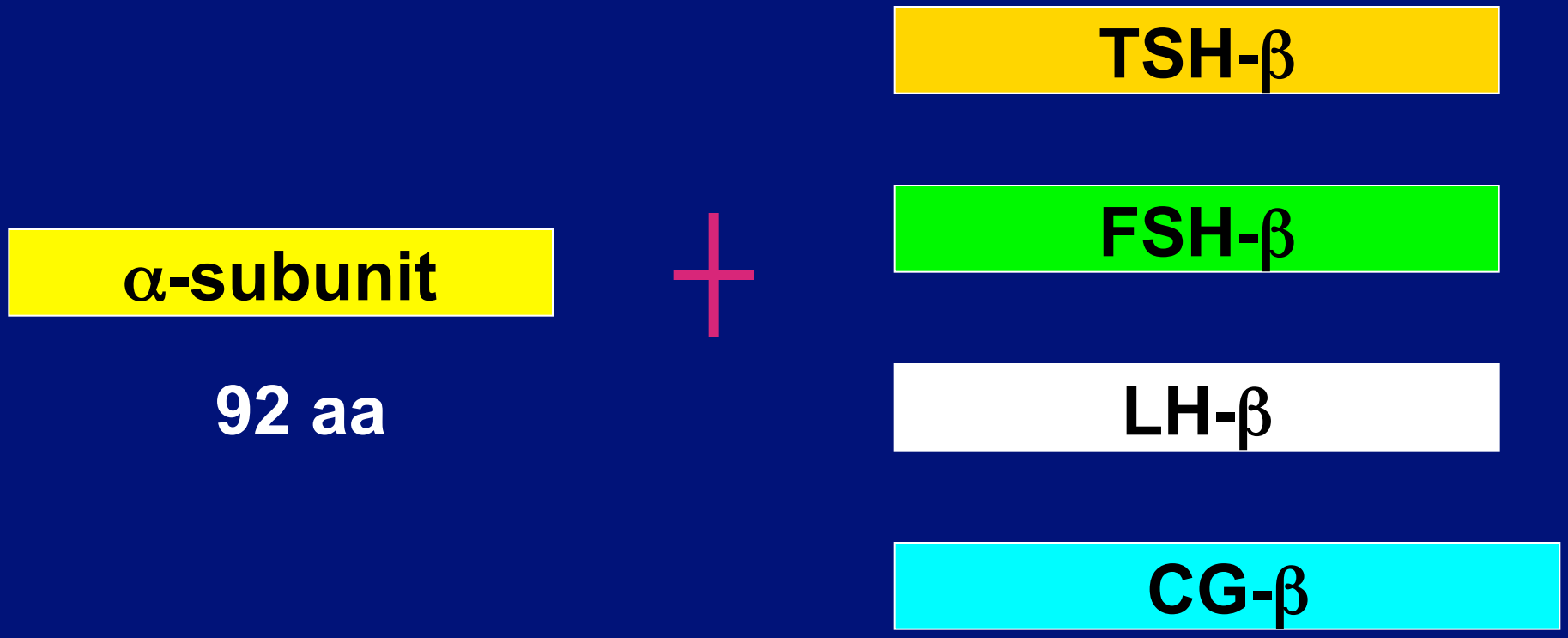


- TSH = Thyroid Stimulating Hormone
- AKA "Thyrotropin"
- Binds to receptors on thyroid to stimulate synthesis and release of thyroid hormones T4 (and some T3).
- Part of a glycoprotein hormone family

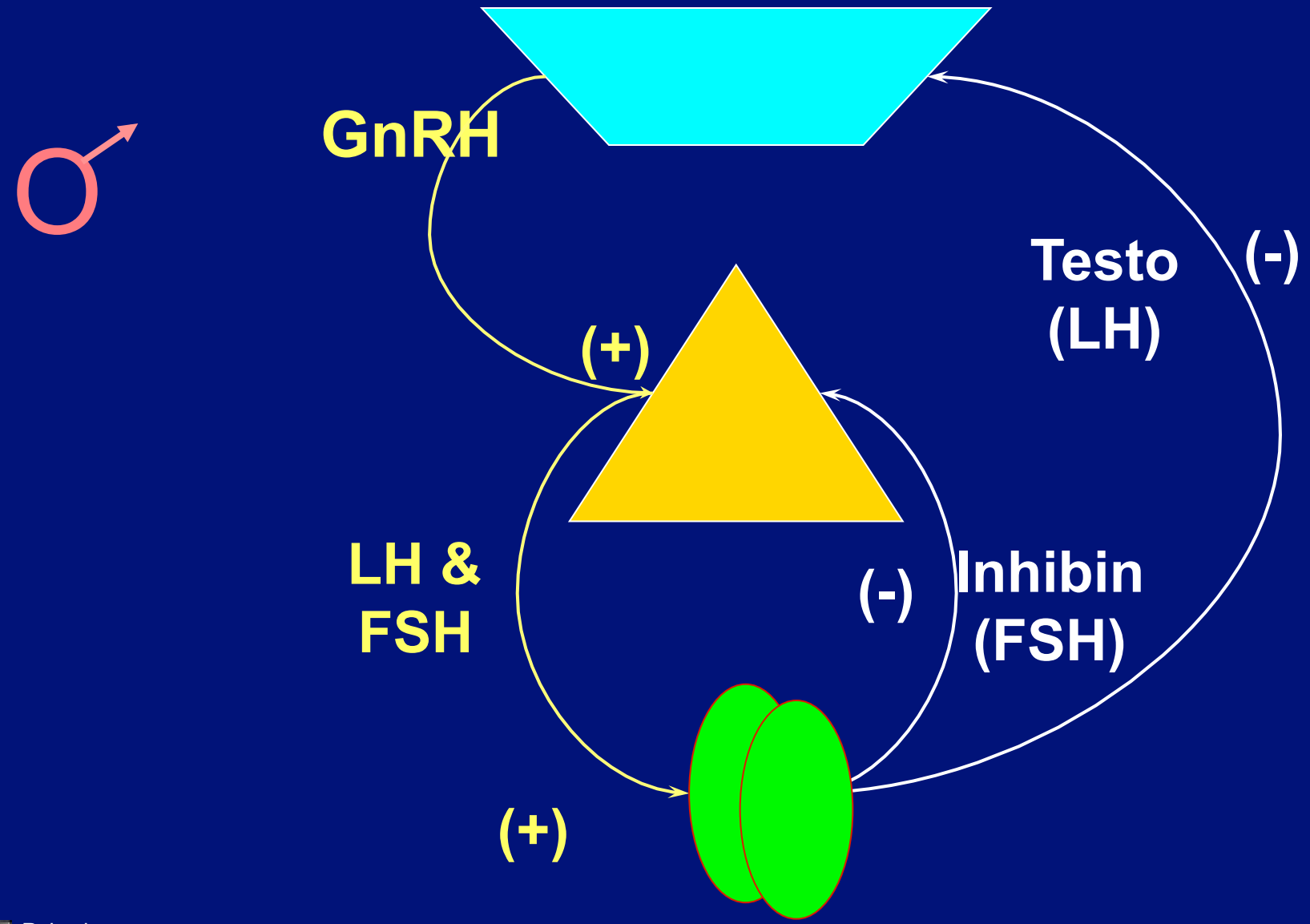
Thyroid stimulating hormone (TSH) is part of a family of glycoprotein hormones

- Composed of noncovalently bound α and β subunits
- Both subunits are glycosylated
- α subunit is common
- β subunits are unique - confer biologic and immunologic specificity

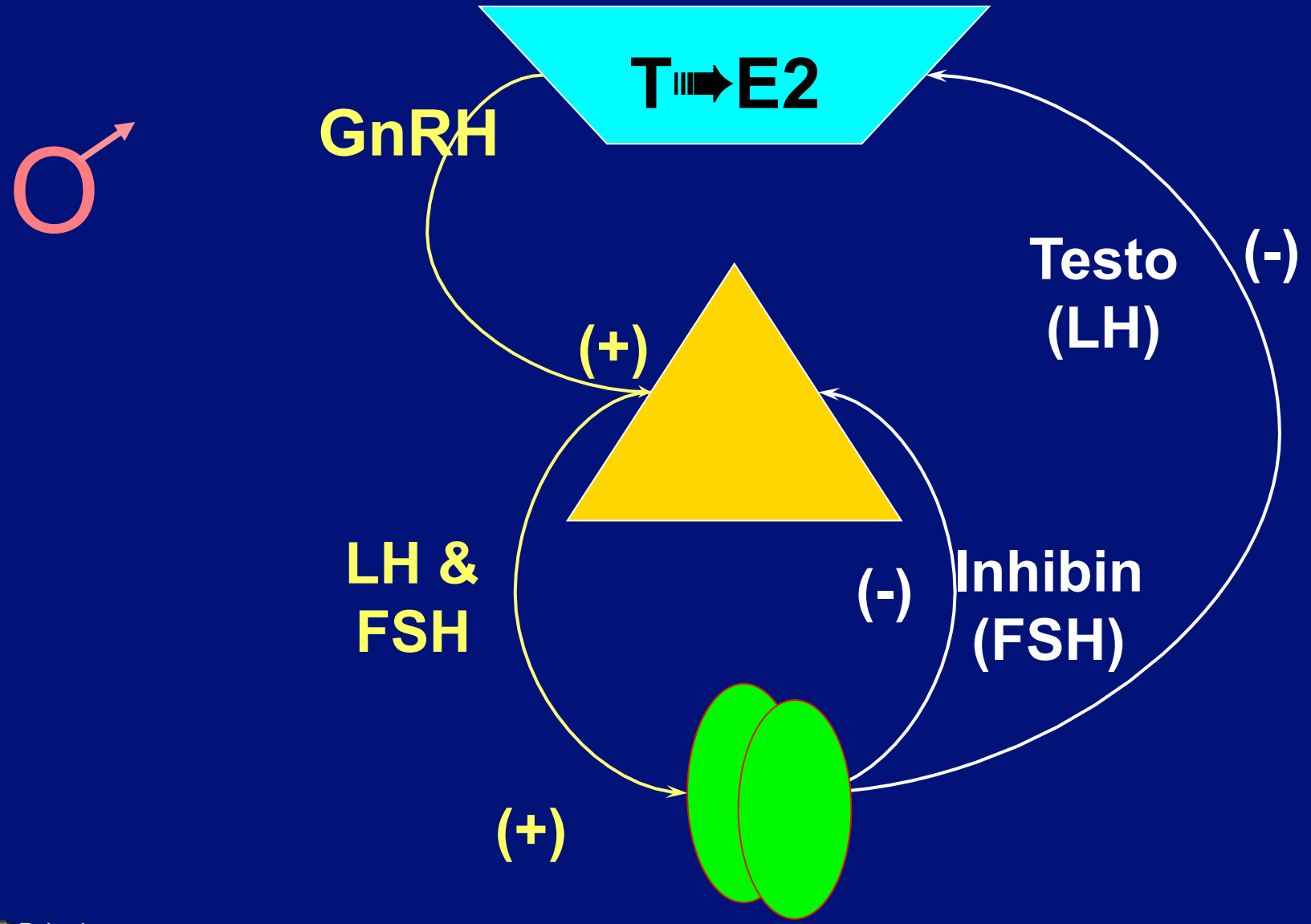
Glycoprotein hormone family



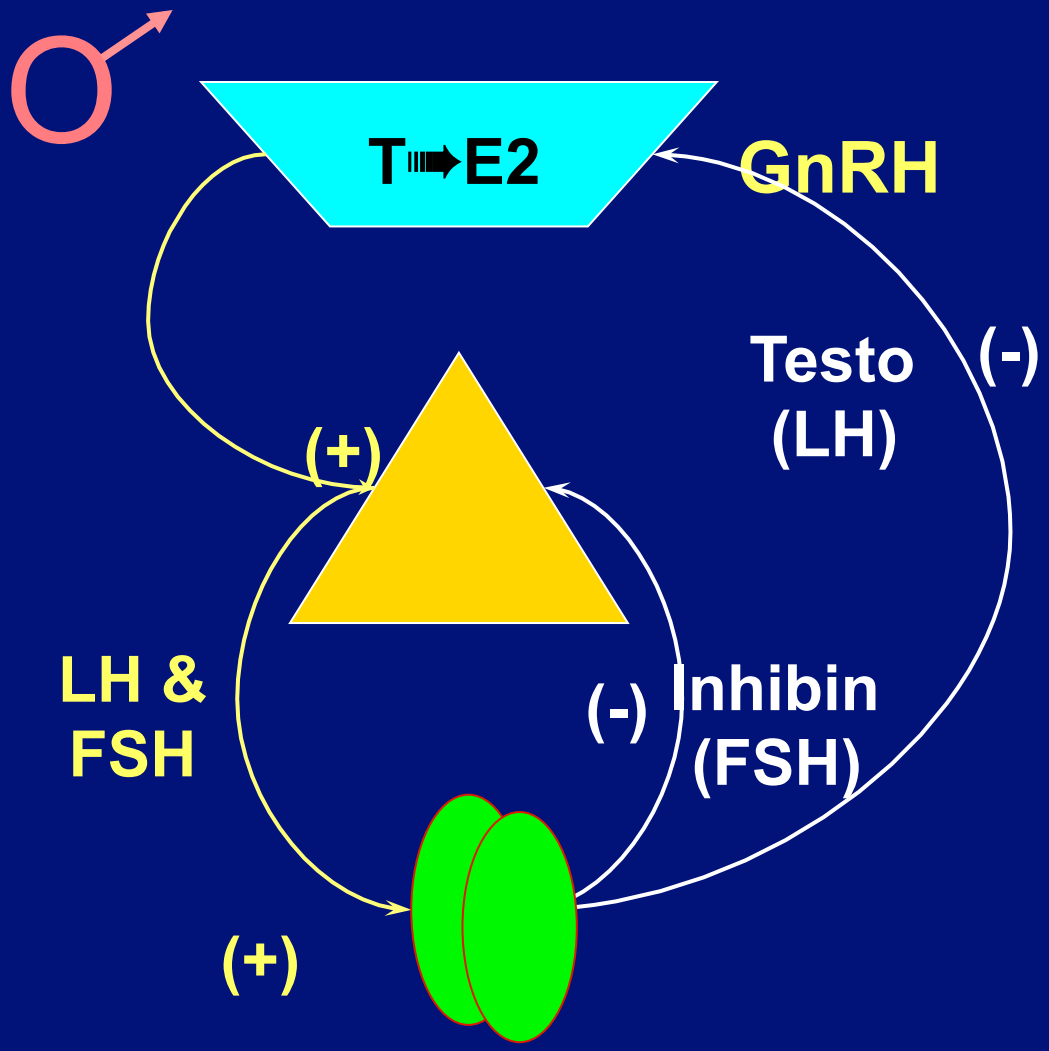
Hypothalamic-Pituitary-Gonadal Axis



Hypothalamic-Pituitary-Gonadal Axis



Hypothalamic-Pituitary-Gonadal Axis



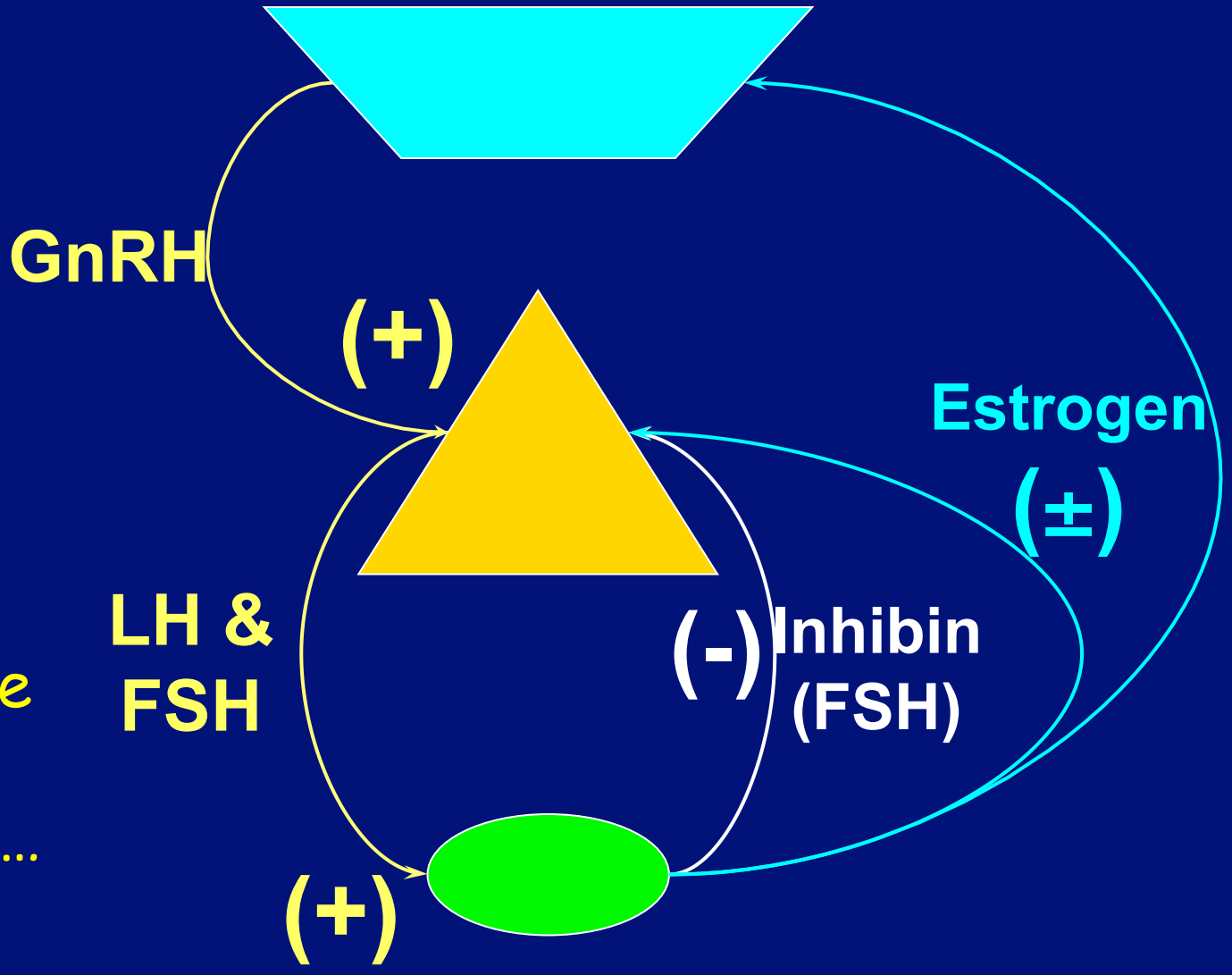
- GnRH = Gonadotropin Releasing Hormone
- 10 amino acids in length
- GnRH ➠ LH & FSH ➠ Sex steroids
- Regulates <u>both</u> LH and FSH

Gonadotropin releasing hormone (GnRH)

- Pulsatility and pulse frequency are critical
- Pulsatile infusion stimulates LH and FSH secretion
- Constant infusion inhibits LH and FSH secretion
- GnRH can be used to induce fertility and suppress gonadal function

Hypothalamic-Pituitary-Gonadal Axis

♀

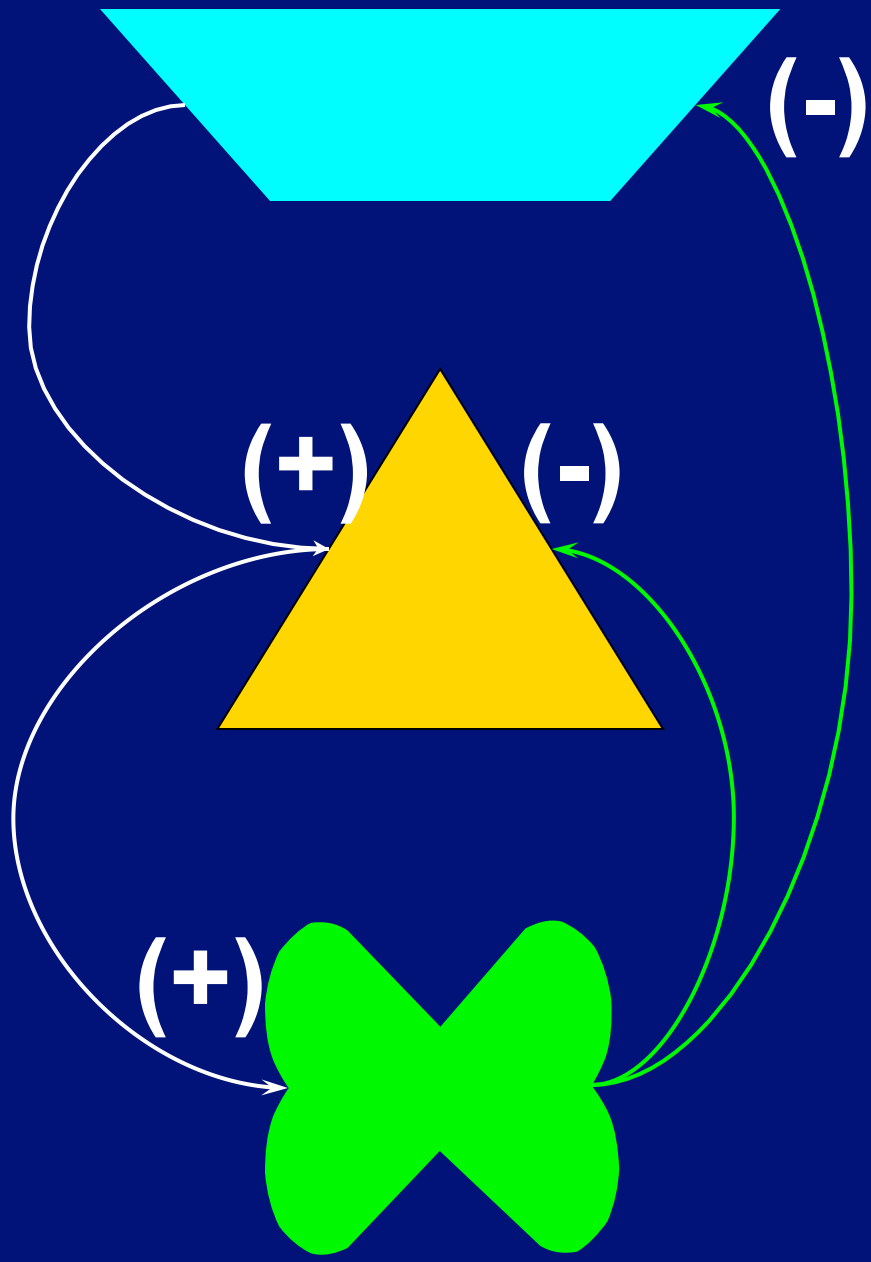


This is where things get complicated…

You

Your stereo

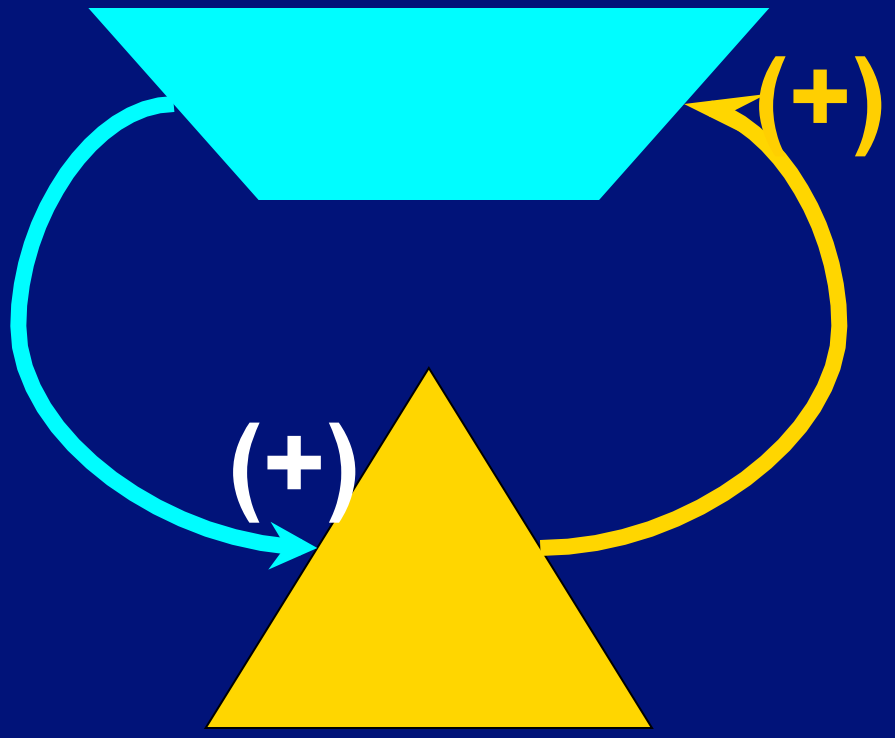
Your roommate



Positive feedback loop

You

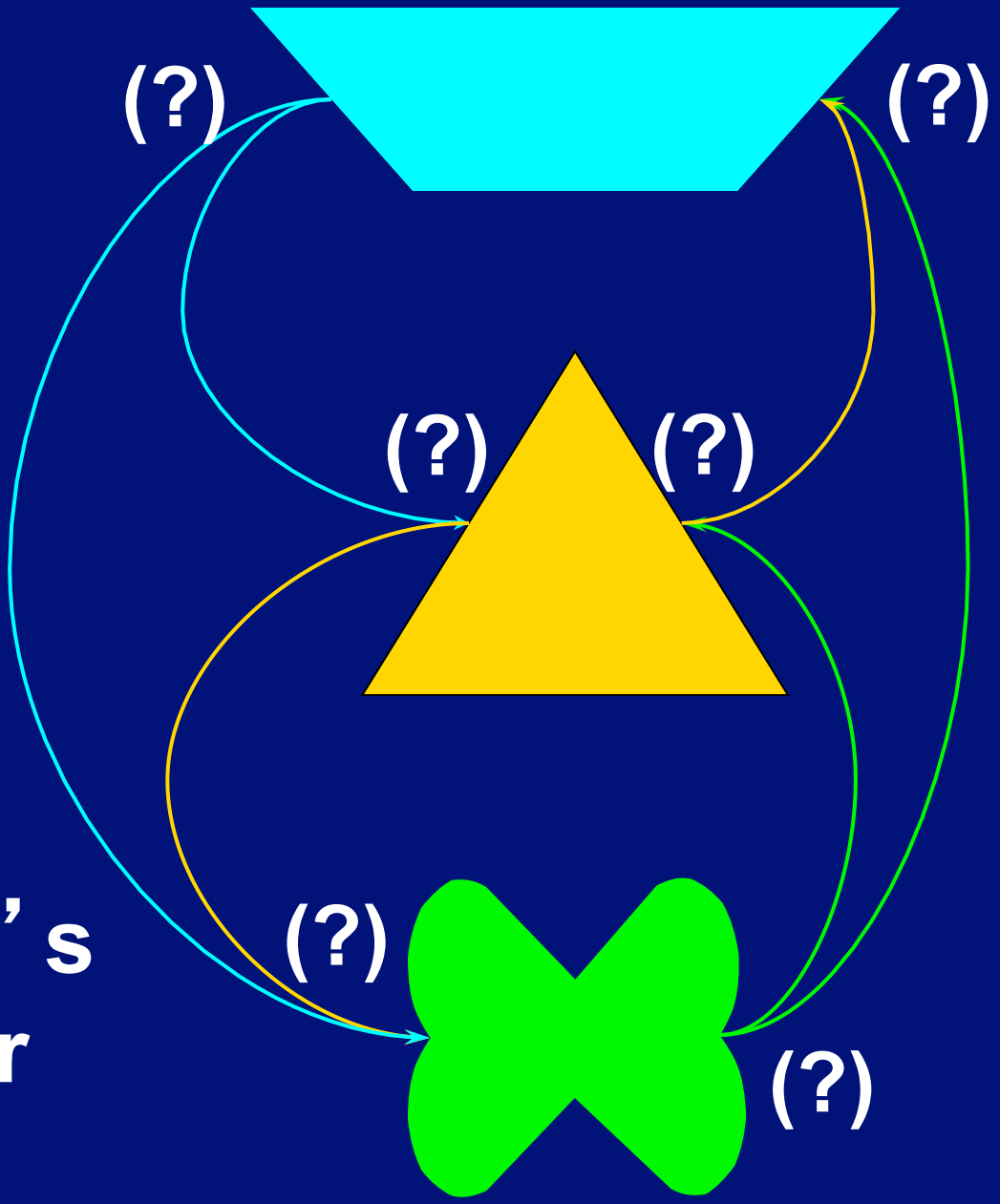
That special someone



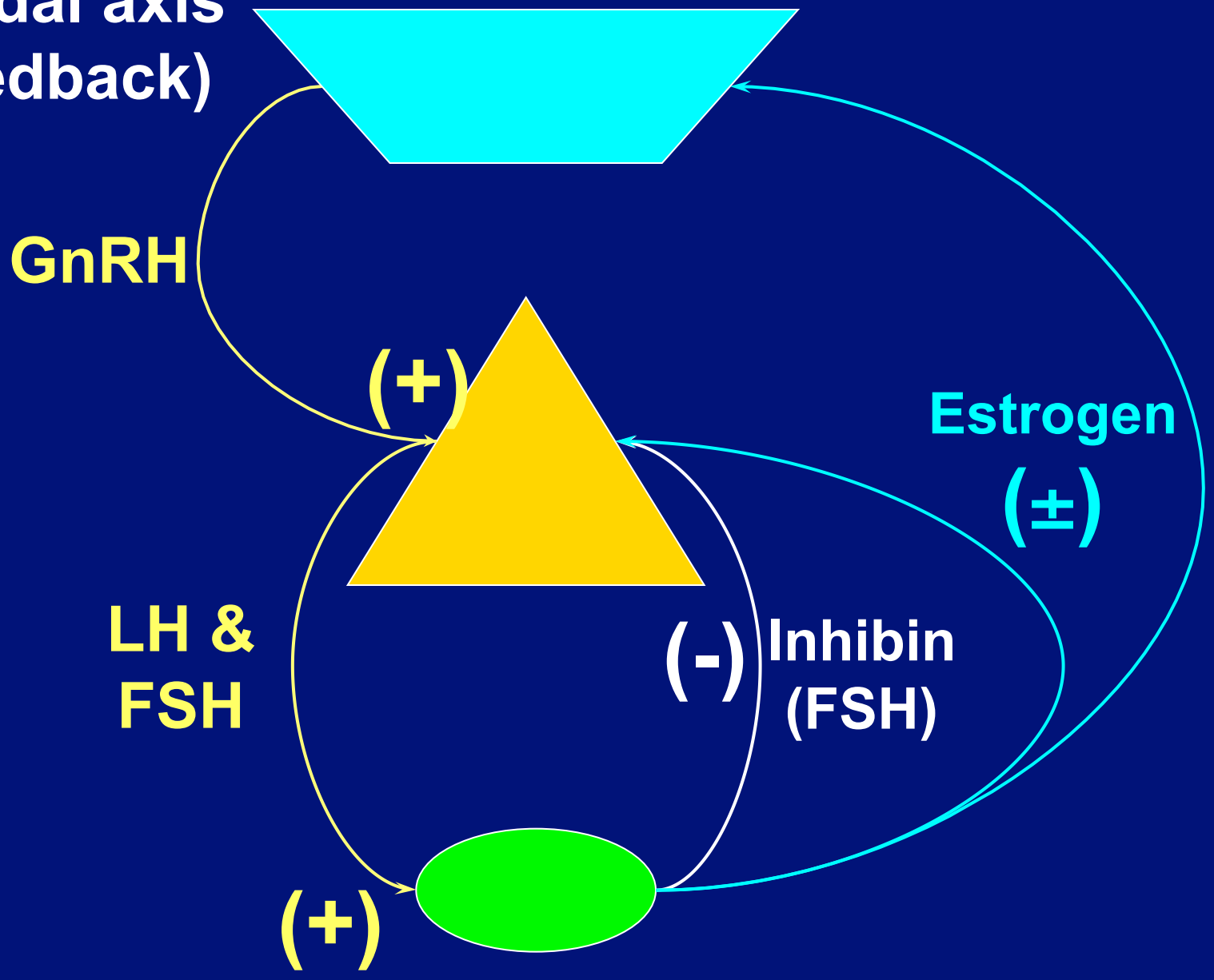
You

That special someone

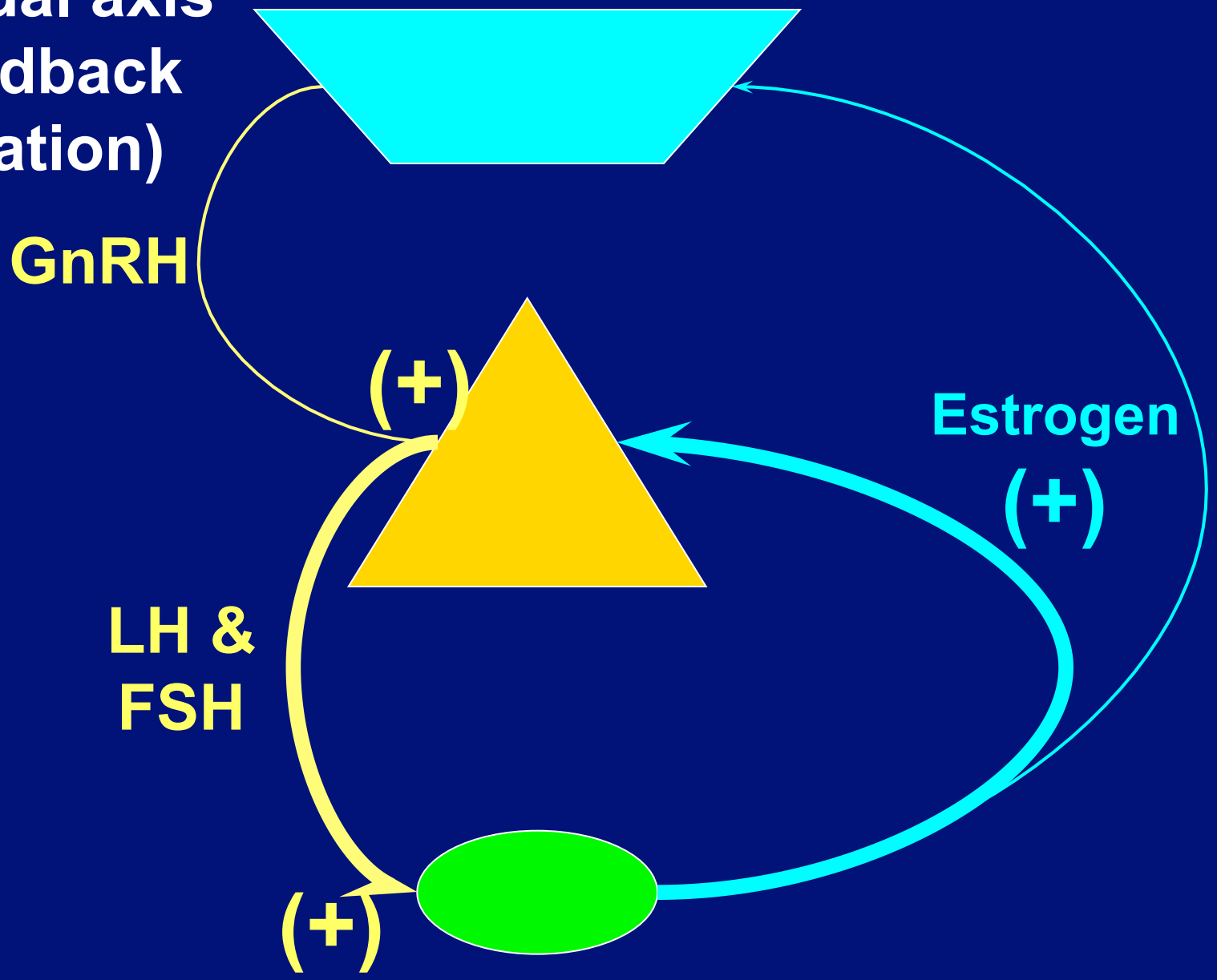
Special someone's significant other



Female gonadal axis (negative feedback)



Female gonadal axis (Positive feedback during ovulation)



Let's review the major players

Hypothalamic releasing factor	Pituitary hormone	Effect of hypothalamic factor
TRH	TSH (and Prl)	Stimulatory
CRH	ACTH	Stimulatory
GHRH	GH	Stimulatory
Somatostatin (SRIF)	GH and TSH	Inhibitory
Dopamine	Prl	Inhibitory
GnRH	FSH and LH	Stimulatory

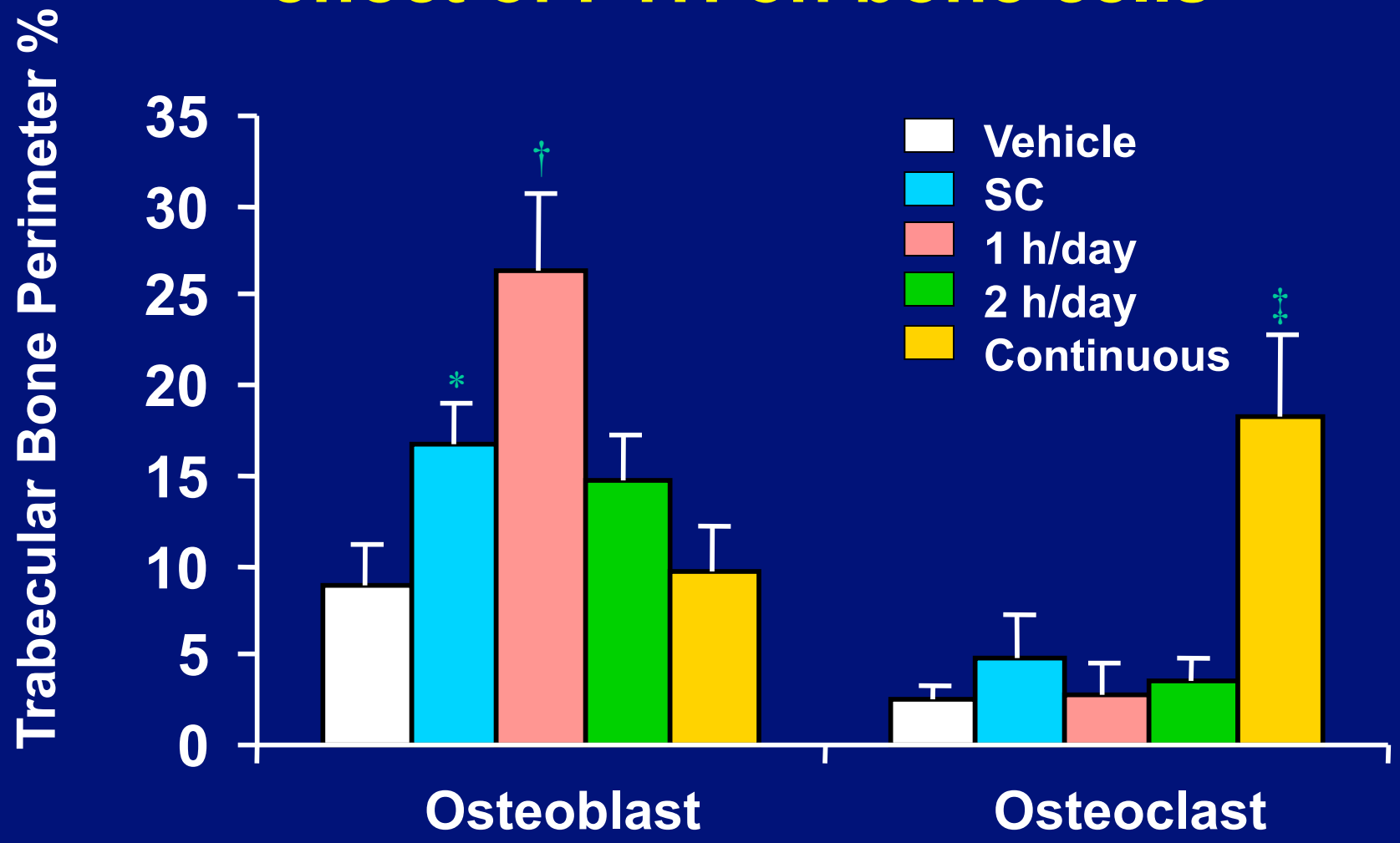
Rhythms in endocrinology

- **Circadian rhythms**
  - Occur over the course of a day, and repeat daily
  - Characteristic of most endocrine functions
  - Examples: Cortisol secretion
- **Ultradian rhythms**
  - Bursts (spikes) of hormone secretion
  - Can be superimposed on circadian rhythms
  - Physiologically important, particularly in reproduction

Pulsatility in the reproductive axis

- **GnRH**
  - Pulsatile infusion at 90 minute intervals can induce ovulation in women with hypothalamic disease
  - Continuous infusion is used to suppress LH/FSH in preparation for in vitro fertilization
- **LH and FSH**
  - Puberty is associated with pulses of greater frequency and amplitude

Frequency of administration determines effect of PTH on bone cells



P<0.05, †P<0.01, ‡P<0.001 vs Vehicle

Dobnig and Turner. Endocrinology 1997;138:4607-4612

Things to remember if you're just waking up

- Generally, hypothalamic hormones stimulate pituitary hormone release
- Prolactin regulation, in contrast, is primarily inhibitory
- The inhibitory hypothalamic factors worth remembering are somatostatin and dopamine

Things to remember if you're just waking up

- Pituitary hormones fall into three groups
  - Glycoprotein hormones (TSH, LH, and FSH)
  - ACTH
  - Growth hormone and prolactin
- Negative feedback is the usual state of affairs, but not the only one
- Hormone activity depends on both the quantity present, and its mode of release

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 6: Source Undetermined
Slide 7: Source Undetermined
Slide 8: Source Undetermined
Slide 10: Robert Lash
Slide 11: Robert Lash
Slide 12: Robert Lash
Slide 13: Robert Lash
Slide 14: Robert Lash
Slide 15: Source Undetermined
Slide 16: Robert Lash
Slide 17: Robert Lash
Slide 18: Robert Lash
Slide 20: Robert Lash; GFDL, Janine Chedid, Wikimedia Commons, http://en.wikipedia.org/wiki/GNU_Free_Documentation_License
Slide 22: Robert Lash
Slide 23: Robert Lash
Slide 24: Robert Lash
Slide 25: Source Undetermined
Slide 26: Robert Lash
Slide 28: Robert Lash
Slide 29: Robert Lash
Slide 30: Robert Lash
Slide 31: Robert Lash
Slide 33: Robert Lash
Slide 34: Robert Lash
Slide 35: Robert Lash
Slide 36: Robert Lash
Slide 37: Robert Lash
Slide 38: Robert Lash
Slide 39: Source Undetermined
Slide 42: Dobnig and Turner. Endocrinology 1997;138:4607-4612