

The Endocrine System: Overview and Some Issues to Consider in Endocrine Disruption

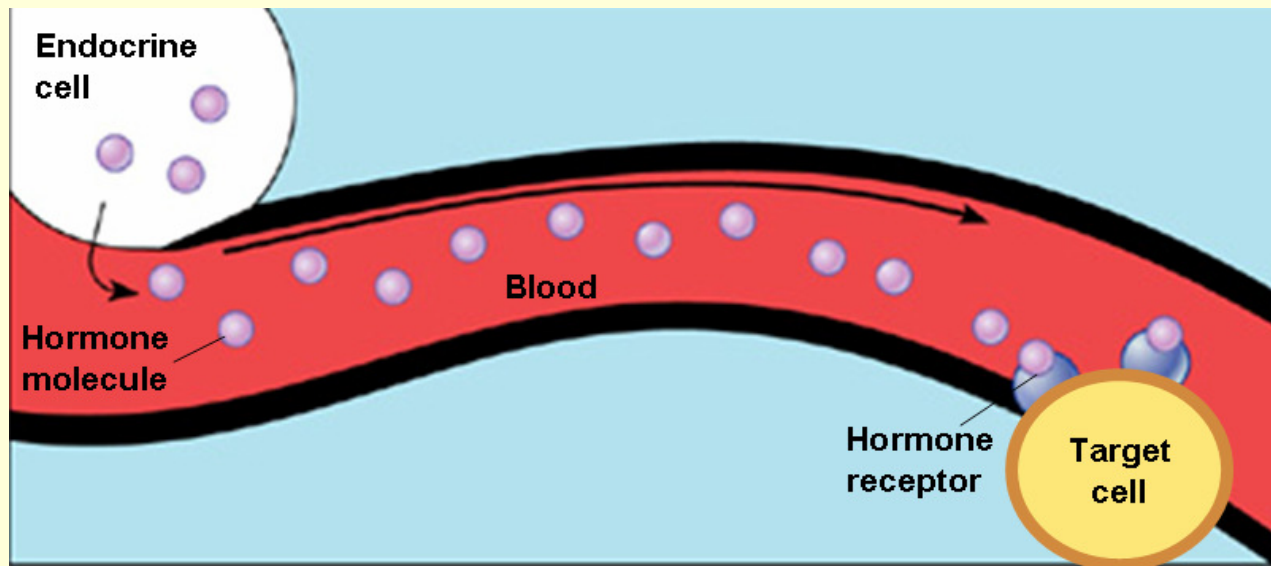
**Raphael J. Witorsch, Ph.D.
Professor of Physiology and Biophysics
School of Medicine
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia**

witorsch@hsc.vcu.edu

Overview of Endocrine System

Hormone

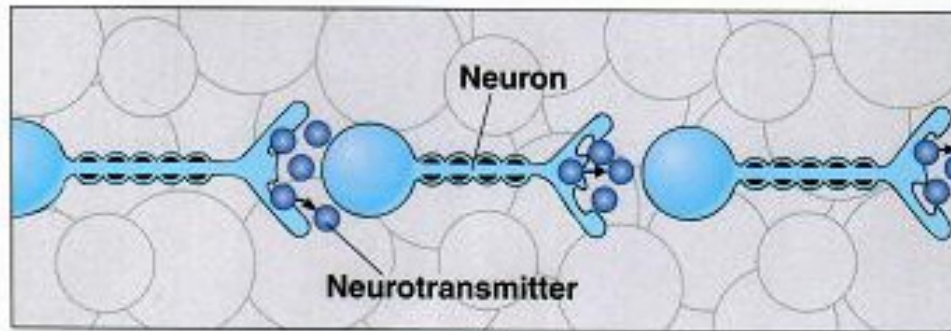
- Derived from Greek term to “excite” or “arouse”.
- A substance made by an *endocrine* cell to be secreted into the circulation to produce an effect at a distant site.



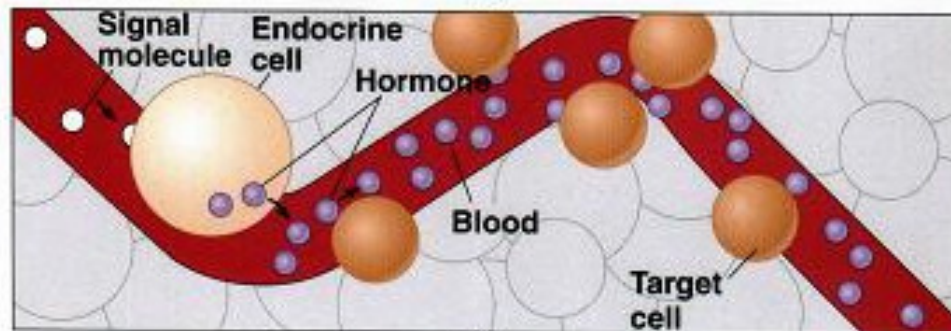
(c) 2003 Brooks/Cole - Thomson Learning

Human Physiology, 4th Edition
Rhoades and Pflanzler
Thomson/Brooks/Cole Publishers

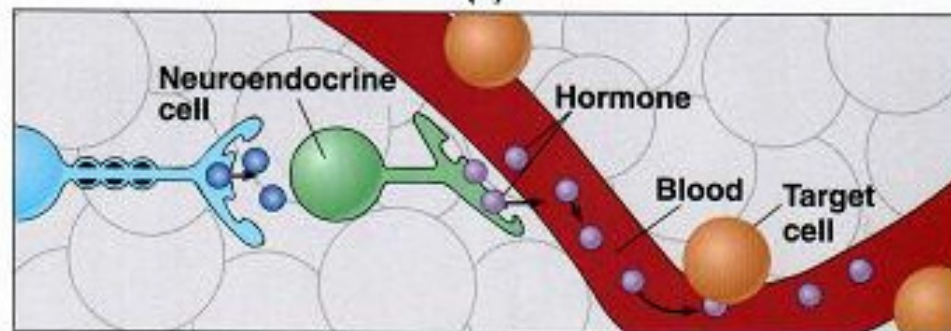
Neural, Endocrine and Neuroendocrine Modes of Communication



(a)

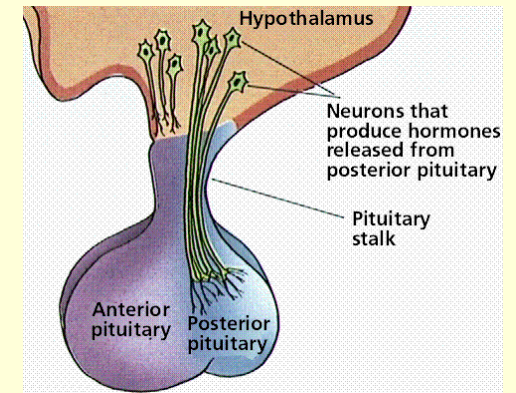
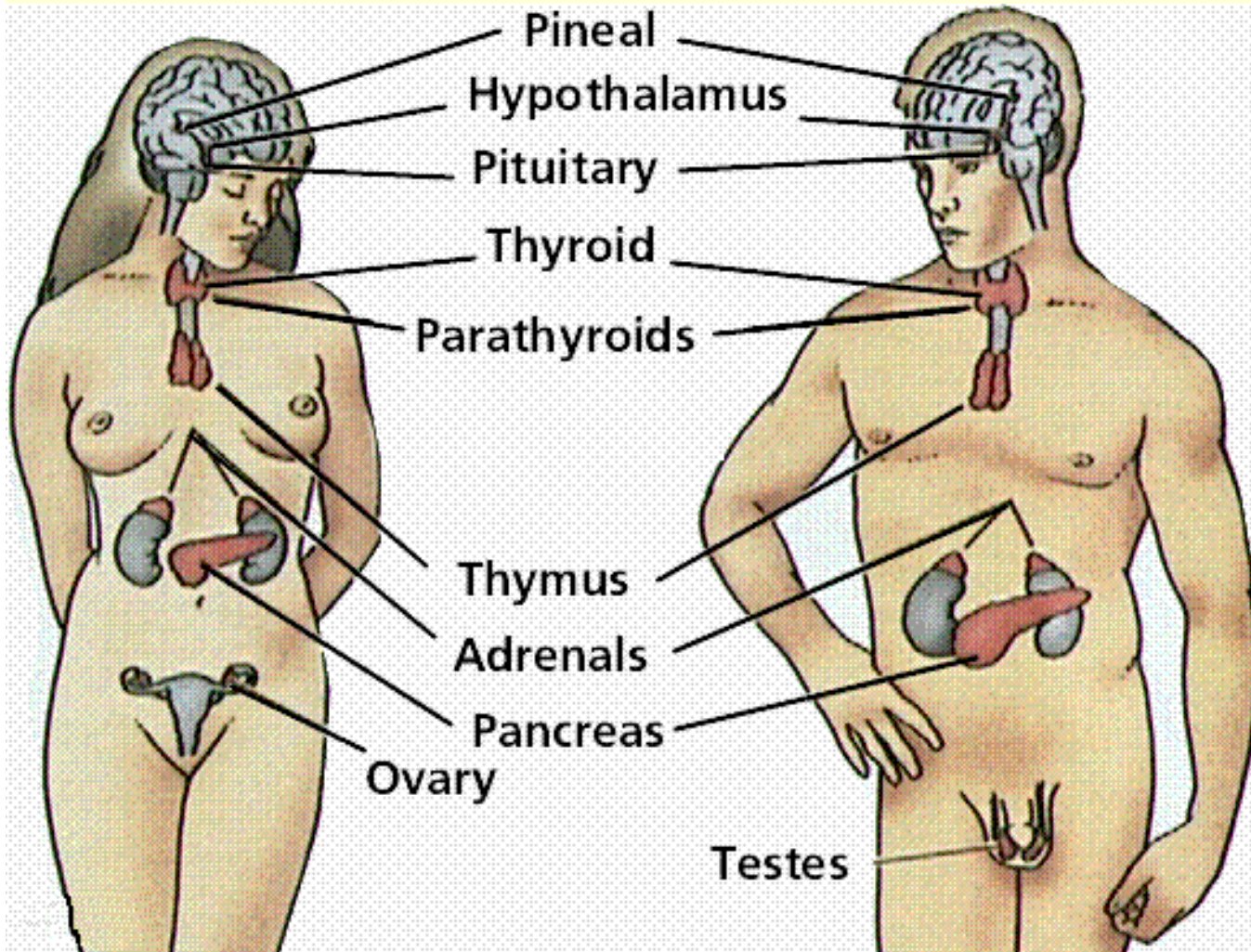


(b)



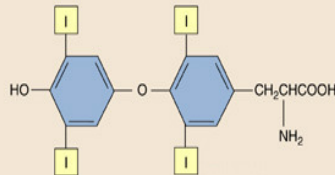
(c)

Endocrine Glands



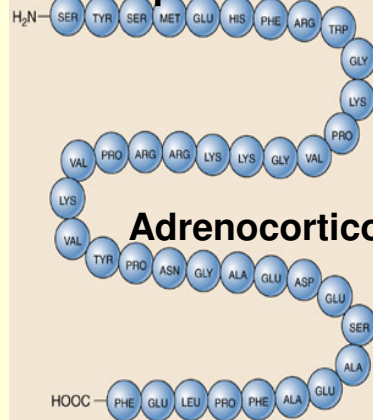
Chemical Classes of Hormones

Amino acid derivative



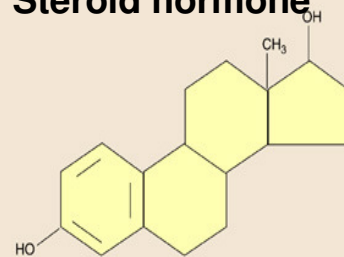
Thyroxine

Peptide hormone



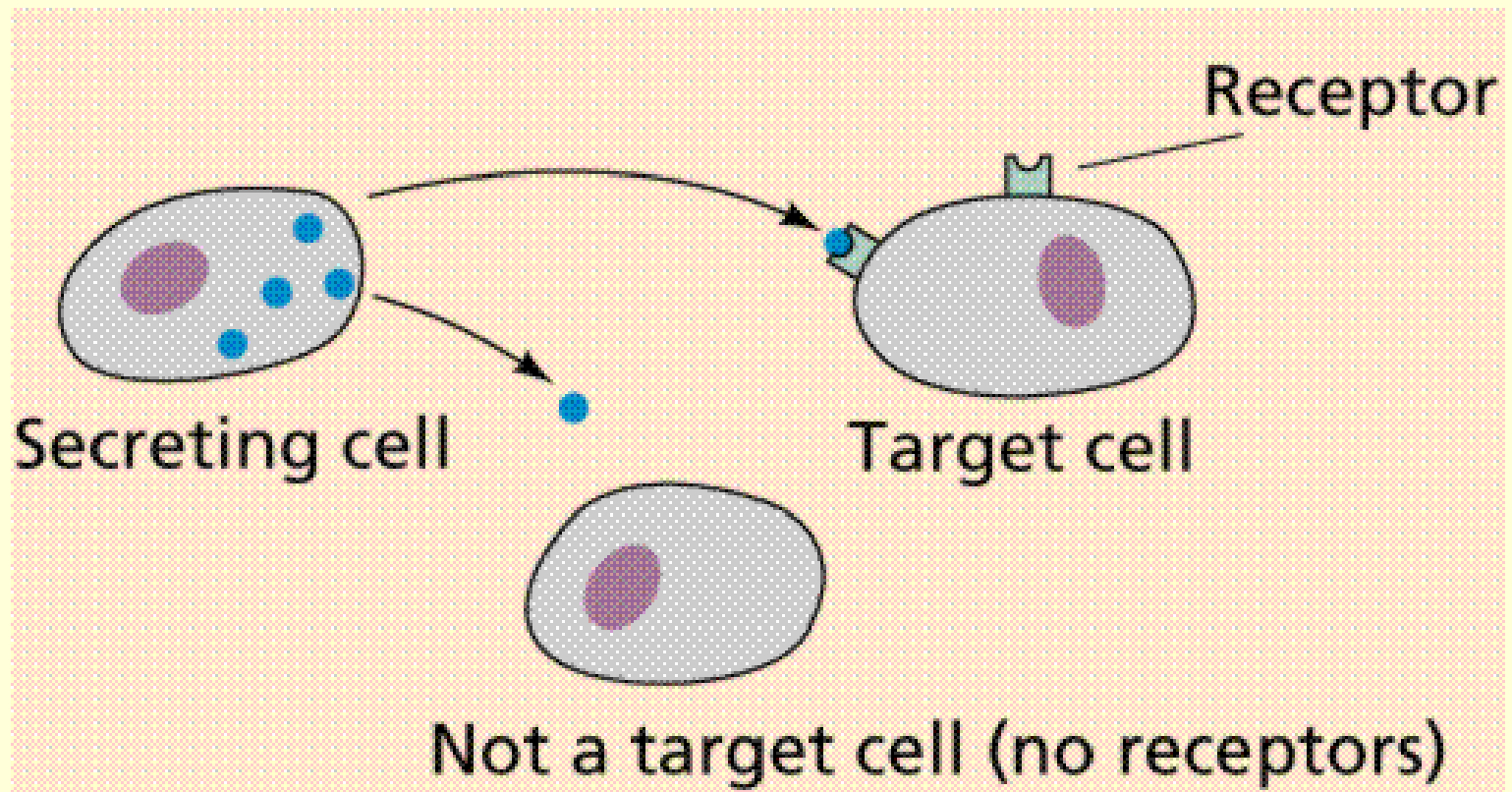
Adrenocorticotrophic hormone (ACTH)

Steroid hormone

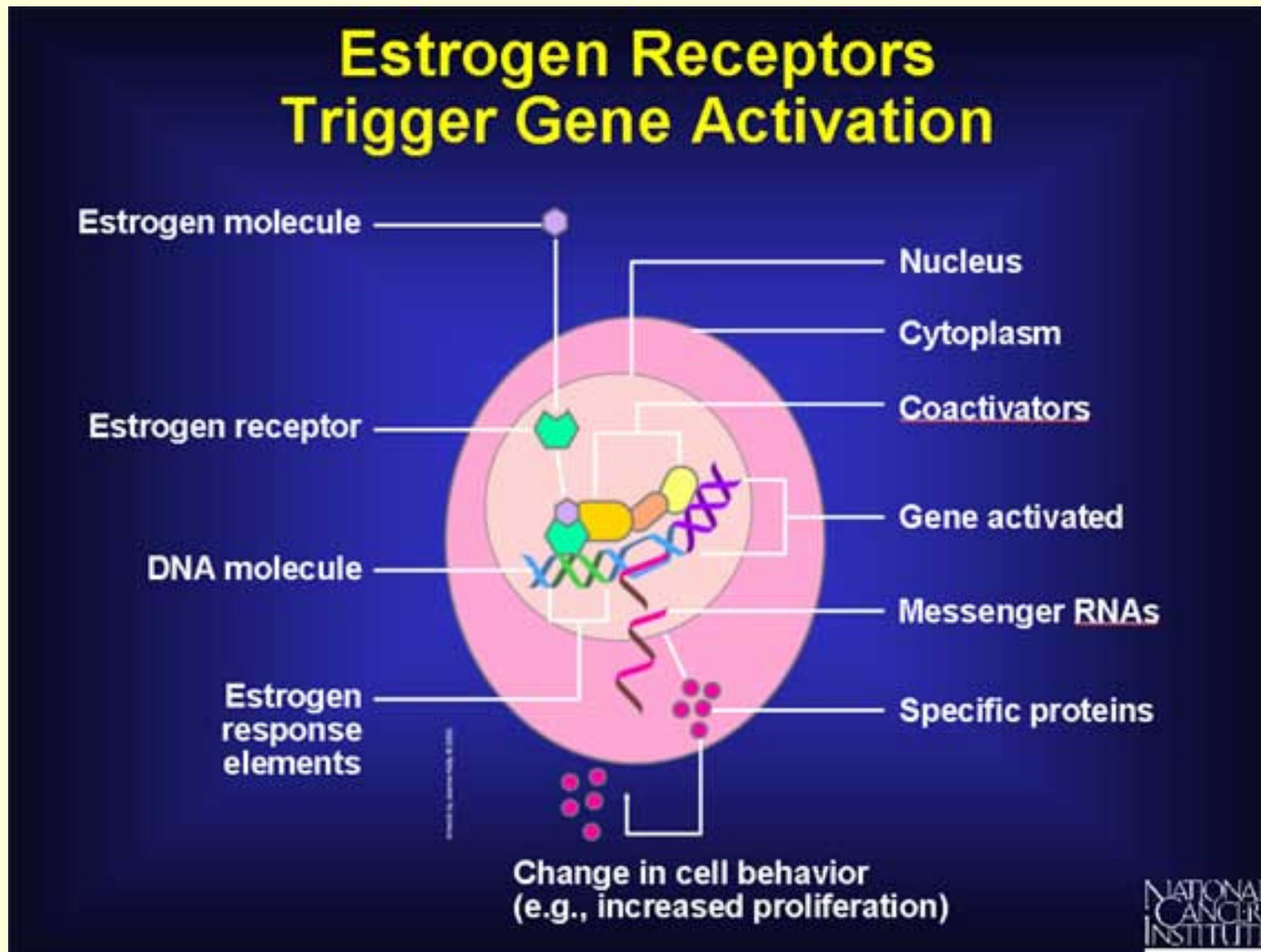


Estradiol

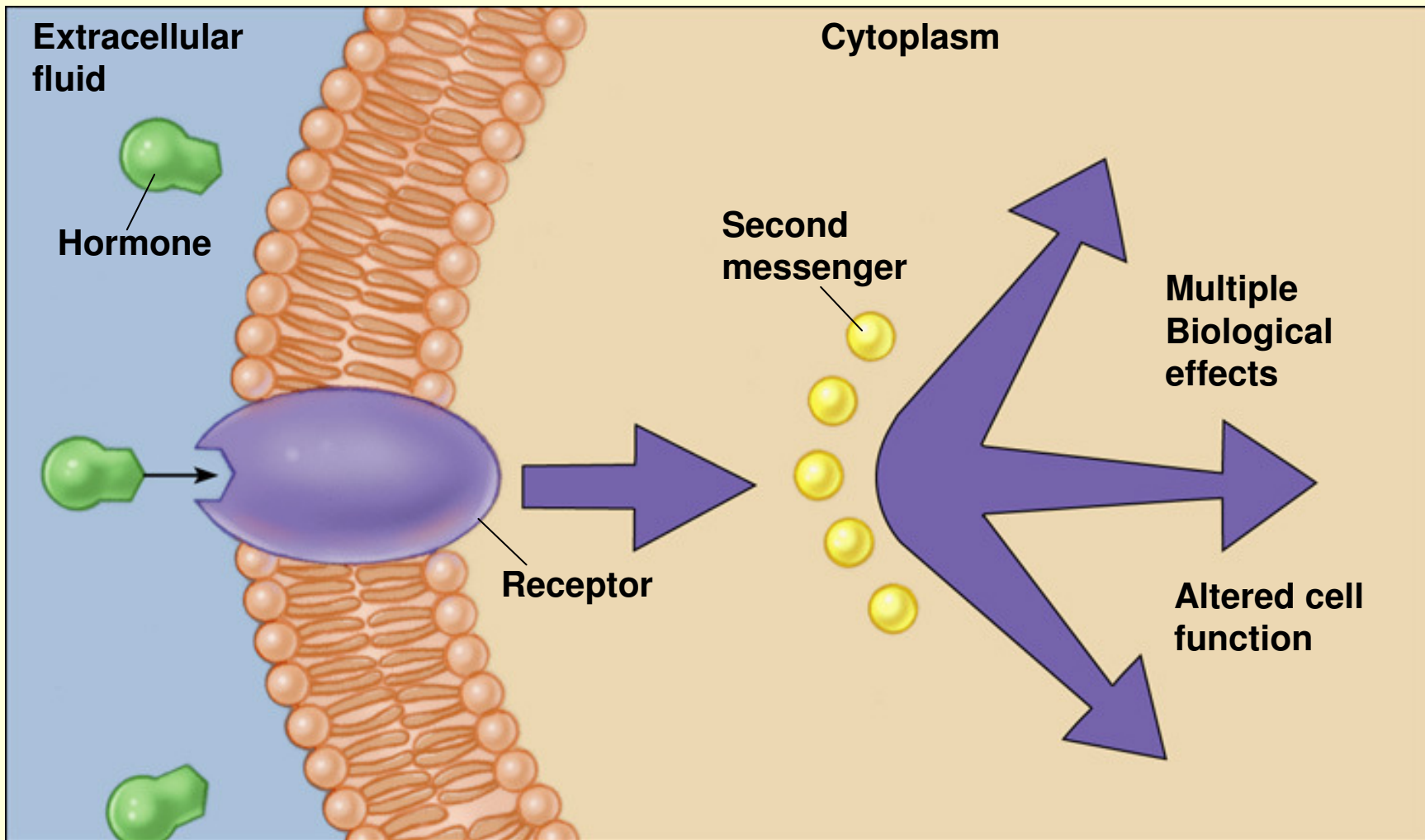
Receptors: How a target cell recognizes a hormone



Mechanism of Action of Hormones with Intracellular Receptors

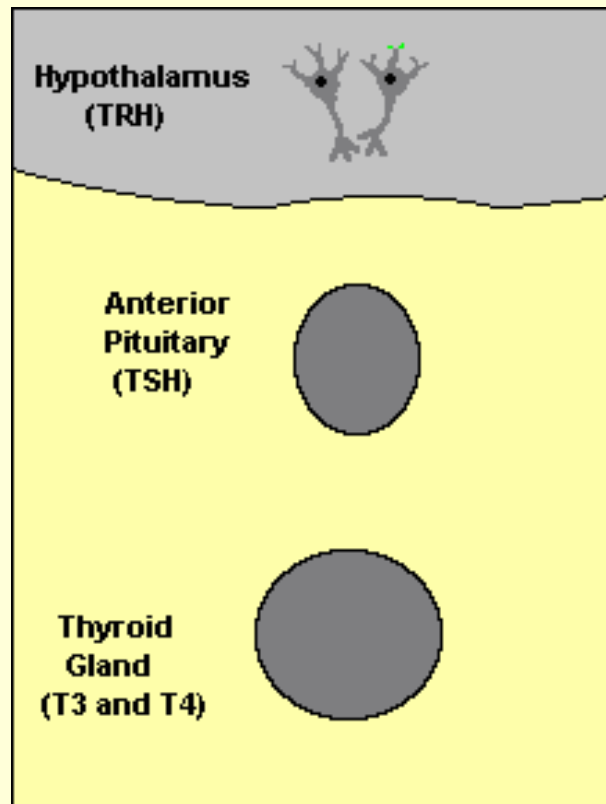


Mechanism of Action of Hormones with Membrane Receptors



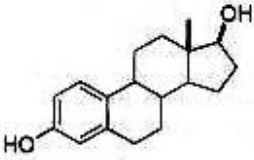
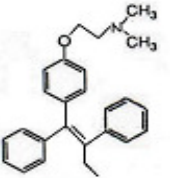
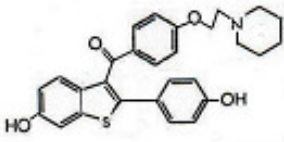
(c) 2003 Brooks/Cole - Thomson Learning

Endocrine Control Mechanisms (Negative Feedback)

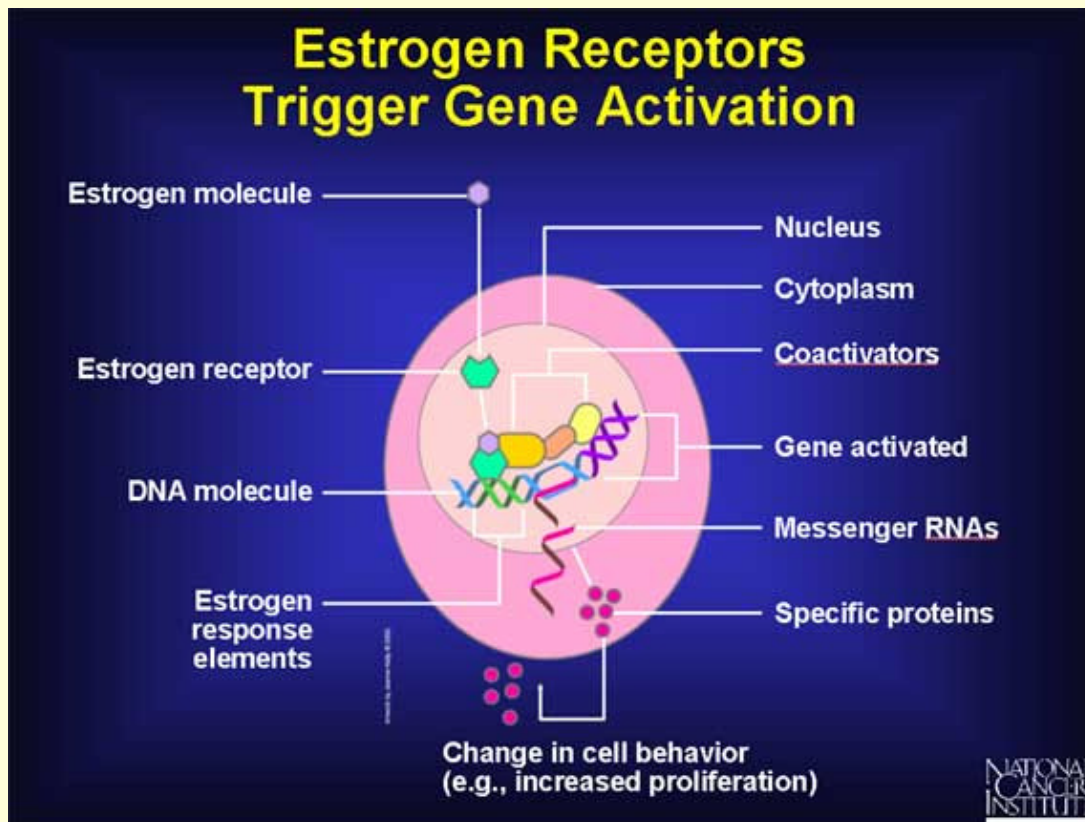


Issue 1: Receptor Binding Is Only Part of the Story

Diversity of Biological Effects of ER Ligands

ER ligand	Mammary gland	Uterus	Bone
 <p>17β-estradiol</p>	mitogenic	mitogenic	anti-osteoporotic
 <p>tamoxifen</p>	anti-mitogenic	mitogenic	anti-osteoporotic
 <p>raloxifene</p>	anti-mitogenic	anti-mitogenic	anti-osteoporotic

Factors Contributing to Diversity of Response of Estrogen Receptor Ligands



- Heterogeneity of ER isoforms (ER α and ER β)
- Ligand-specific alterations in the conformation of ER
- Heterogeneity of ER co-regulatory (co-activator and co-repressor) proteins
- Heterogeneity of ER binding sites within genome (estrogen response elements)

**Issue 2: Species Differences
May Be Critical**

Low Dose *In Utero* Effect of Bisphenol A (BPA)

- Oral exposure of pregnant mice (gd 11-17) to low dose BPA (2-20 µg/kg) was associated with the following in adult (6 mo) male offspring:
 - increases in prostatic and preputial gland weights (30-36%)
 - decreases in daily sperm production (20%) and epididymal weights (12%).

Nagel et al. (1997), Vom Saal et al. (1998)

Endocrinology of Pregnancy: Murine vs. Human

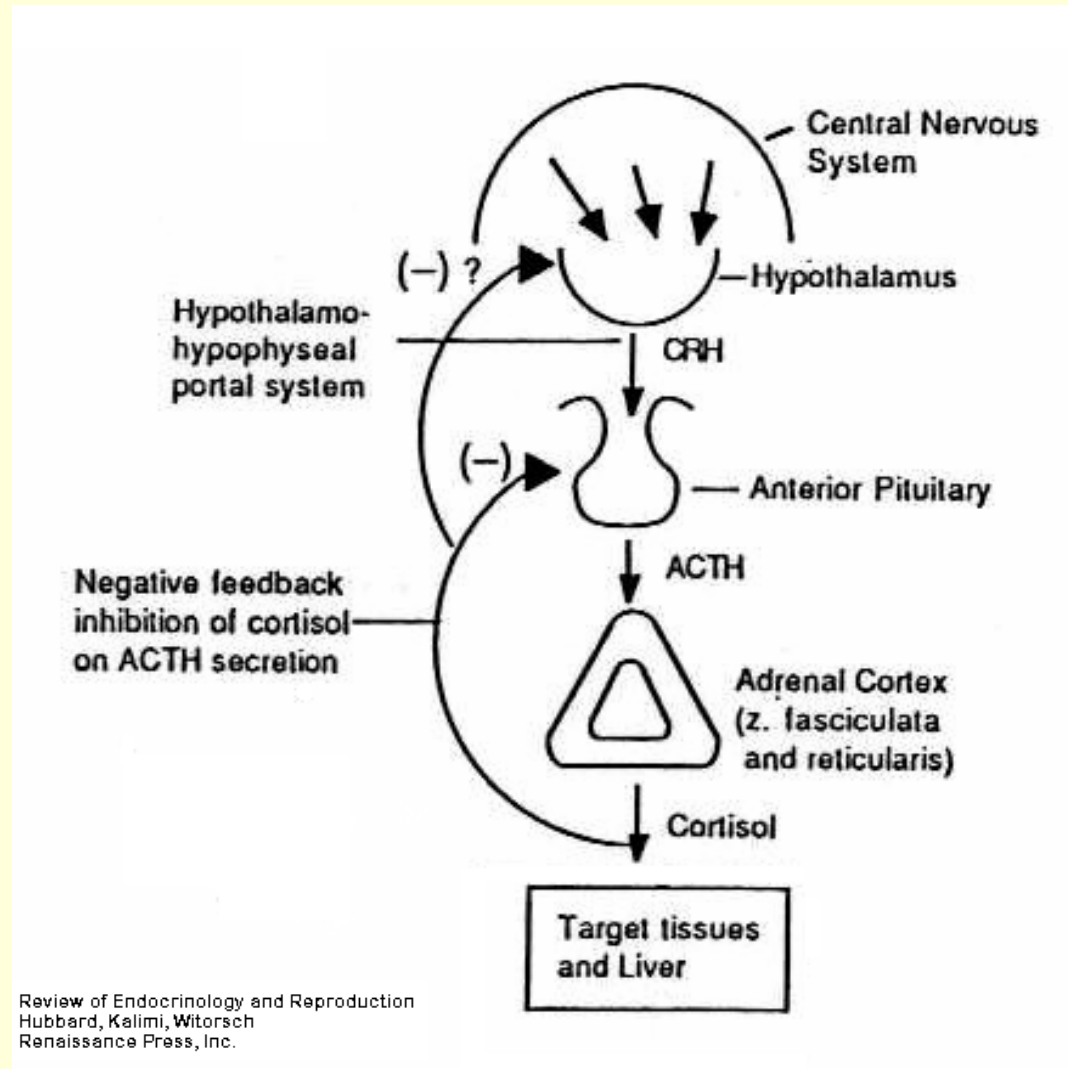
(Witorsch,RJ, Food and Chemical Toxicology 40: 905-912, 2002)

Endpoint	Murine	Human
Dominance of corpus luteum	Throughout gestation	First trimester <i>(luteal-placental shift)</i>
Estrogens produced	Estradiol, estrone	Estradiol, estrone, <i>estriol</i>
Adrenal DHEA as estrogen precursor	No	Yes
Relative bioavailable estrogen	1	<1000
Fetal loss produced by:	Increased estrogen	Decreased estrogen

In view of the foregoing:

**Weak estrogenic substances
such as BPA should have little
if any effect in human
pregnancy.**

Issue 3: Elevated (stress-induced) glucocorticoids may explain some effects of endocrine disruption.



Stress/Glucocorticoid-Induced Suppression of Testosterone Secretion in Wild Baboons

TABLE 1. Circulating concentrations of T and CORT after immobilization

Time after darting	T (ng/ml)	CORT ($\mu\text{g}/100\text{ ml}$)
9 min	13.1 ± 2.2	17.7 ± 2.1
30 min	11.1 ± 1.4	25.6 ± 3.6
60 min	9.9 ± 1.4	24.7 ± 2.5
6 h	2.9 ± 0.8	30.9 ± 2.9

TABLE 2. Effects of DEX on T concentration and T secretion rate

Time	T concentration (ng/ml)	T secretion rate (μg secreted/ml · h)
30 min before DEX	9.2 ± 1.8	
Time zero	10.8 ± 1.7	7.9 ± 2.0
3 h, post-DEX	2.7 ± 0.6	0 ± 0
6 h, post-DEX	1.1 ± 0.2	0.01 ± 0.01

(Sapolsky, 1985)

Glucocorticoids and Testosterone Secretion

- Direct inhibitory effects of glucocorticoids on testicular steroidogenesis and induction of Leydig cell apoptosis.

(Orr & Mann, 1994; Monder et al., 1994; Gao et al., 2002)

- Social status linked with resistance to stress-induced suppression of testosterone secretion (baboon and rats).

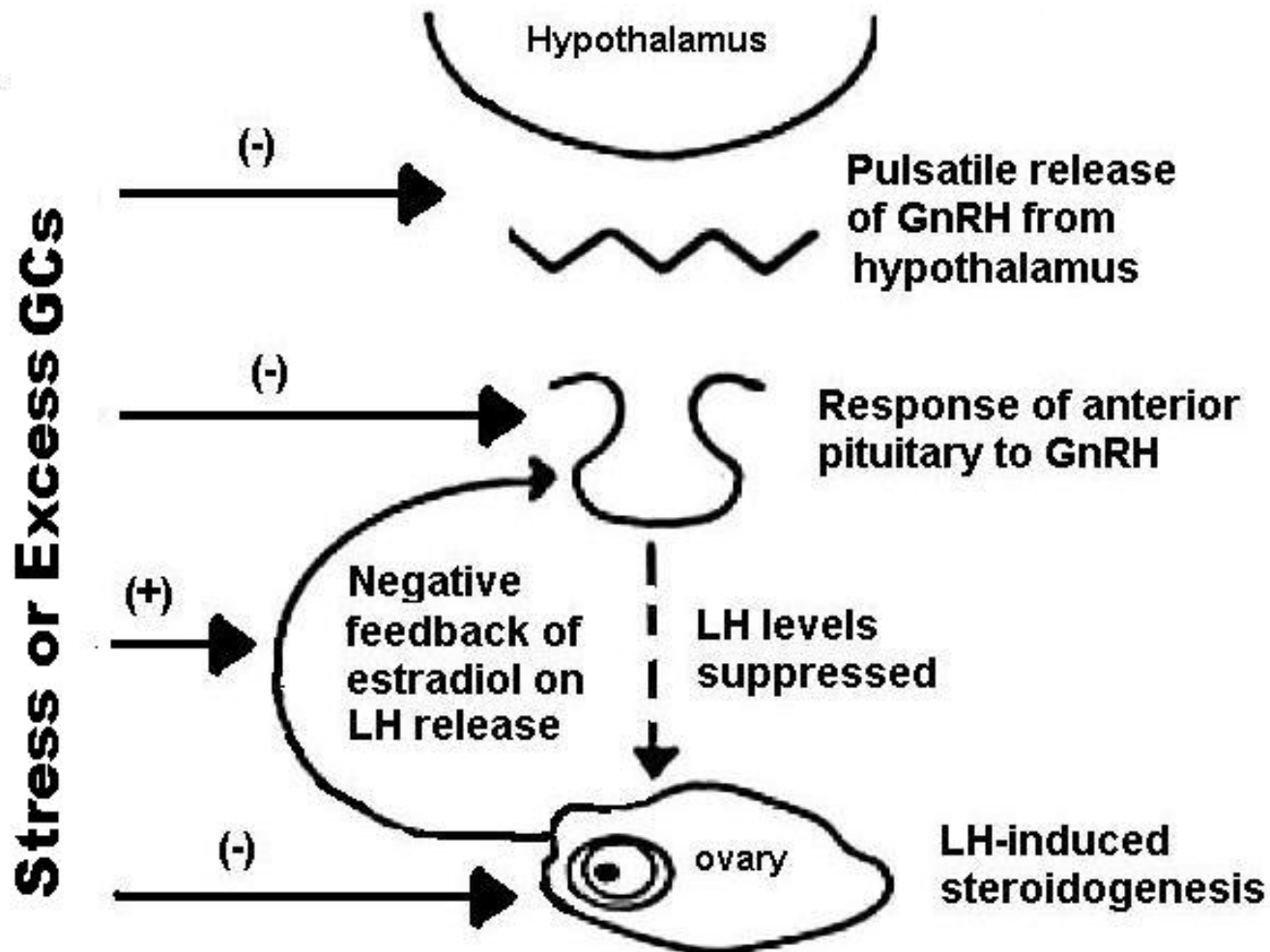
(Sapolsky, 1993; Monder et al., 1994)

Functional Hypothalamic Amenorrhea

- Also referred to as *functional hypothalamic chronic anovulation*.
- Suppression of the menstrual cycle due to severe psychological or physical stress.
- Among the symptoms observed are ovarian hypofunction, amenorrhea, infertility, and elevated cortisol.

(Ferin M, 1999)

Stress/Glucocorticoid Effects on the Hypothalamo-Pituitary-Ovarian Axis: Sites of Action



Glucocorticoids (GCs) Are Important for Gestation

- Surge in fetal cortisol secretion in late gestation is important for fetal organ maturation, particularly the CNS and lungs.
- Fetal adrenal cortisol triggers labor.

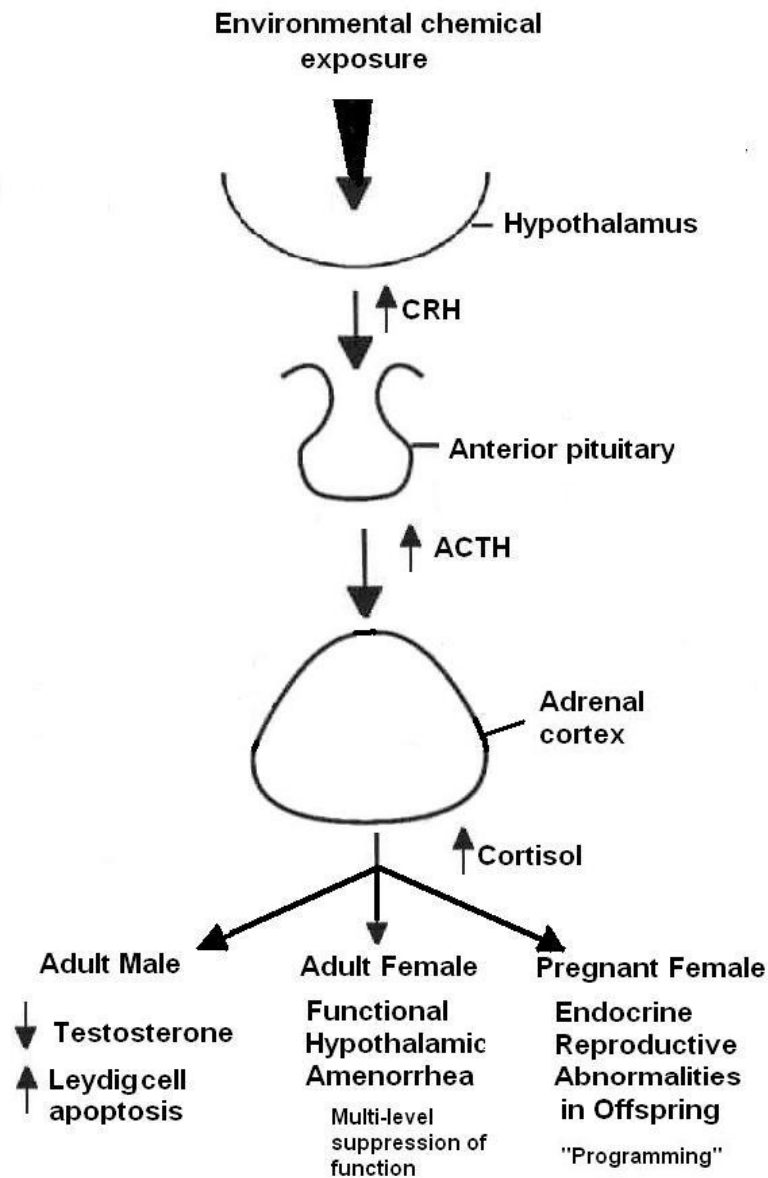
(Challis JRG, et al., 2001; McLaren WJ, et al. 2000)

Adverse Effects of Stress or GC Excess In Utero on Offspring

- Intrauterine growth retardation (IUGR)
- Postnatal endocrine/reproductive effects
 - *Insulin resistance*
 - *Feminization of sexually dimorphic areas in hypothalamus*
 - *Behavioral changes (male homosexuality)*
 - *Decreased anogenital distance of male neonates, delayed or abnormal testicular descent and decreased testicular weight*

(Challis JRG, et al., 2001; Seckl JR, 2001; Weinstock M, 2001; Page KC, et al., 2001)

Hypothesis: Stress mediation of endocrine disruptive effects



Summary and Conclusions

- A brief overview of the essentials of endocrine physiology was presented.
- Hormone-receptor interaction does *not* predict the nature of a target cell response.
- Species differences may be of importance in the response to an endocrine disruptor.
- Endocrine disruptive effects may be due to stress-induced glucocorticoid release.

Articles Cited in This Presentation

- Citations appearing on slide 15 can be found in *Witorsch, RJ, Food and Chemical Toxicology 40: 905-912, 2002.*
- Citations appearing on slides 19, 20, 21, 23, and 24 can be found in *Cooke PS, Holsberger DR, Witorsch RJ et al., Toxicology and Applied Pharmacology 194: 309-305. 2004.*