Polycystic Ovary Syndrome

François Pralong

Division of Endocrinology

UNIVERSITE DE LAUSANNE

CHUV

Definition

Association of clinical and/or biochemical evidence of androgen excess with chronic anovulation

Heterogeneous condition with a spectrum of clinical/biochemical features

Estimated prevalence : 25% of all women, full blown syndrome in ~5% of women of reproductive age

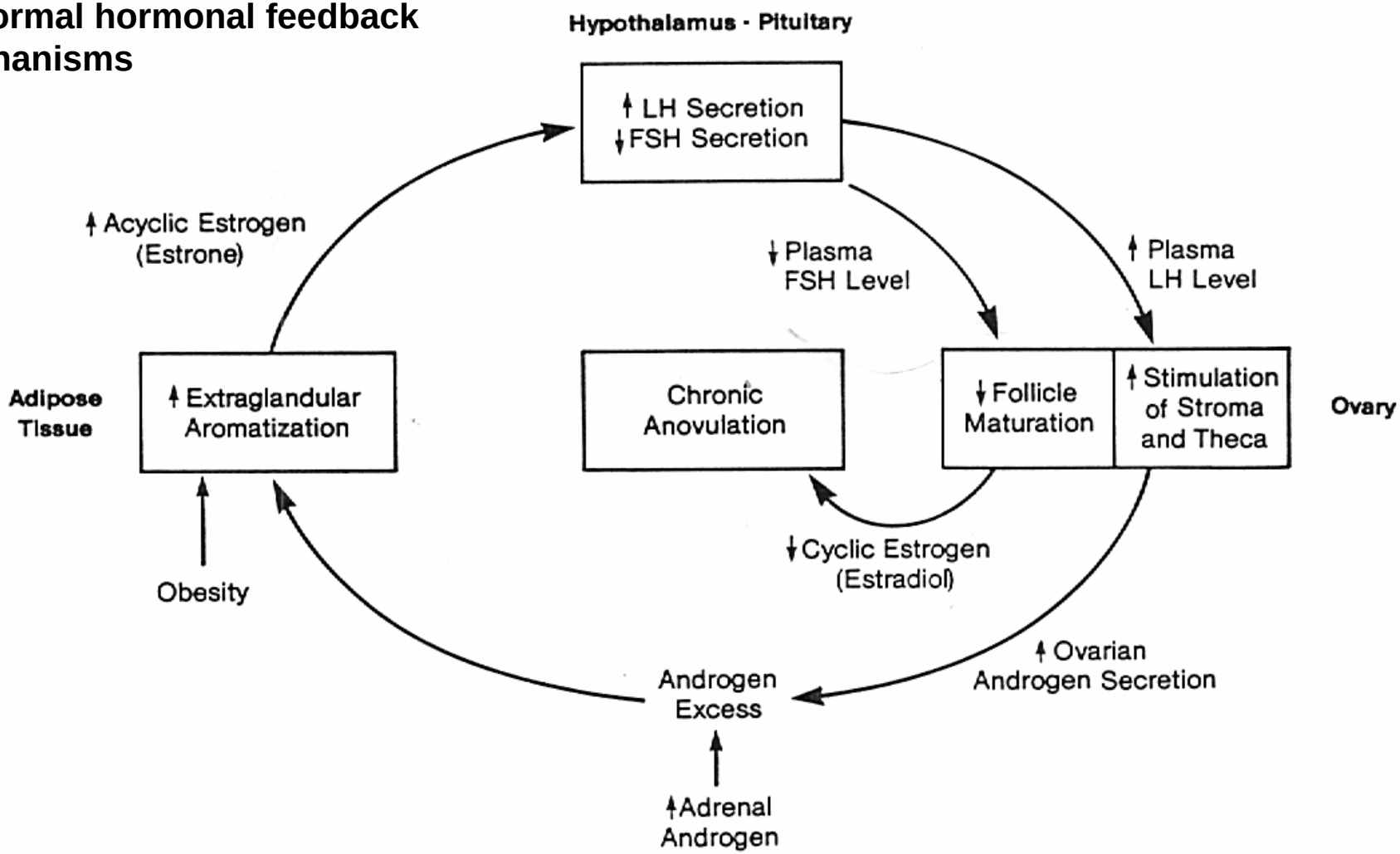
Clinical presentation

- **Hirsutism (95%), acne, alopecia**
- **Enlarged ovaries (95%)**
- **Sterility (75%)**
- **Amenorrhea (55%)**
- **Obesity (40%)**
- **Dysmenorrhea (28%)**
- **Chronic anovulation (20%)**

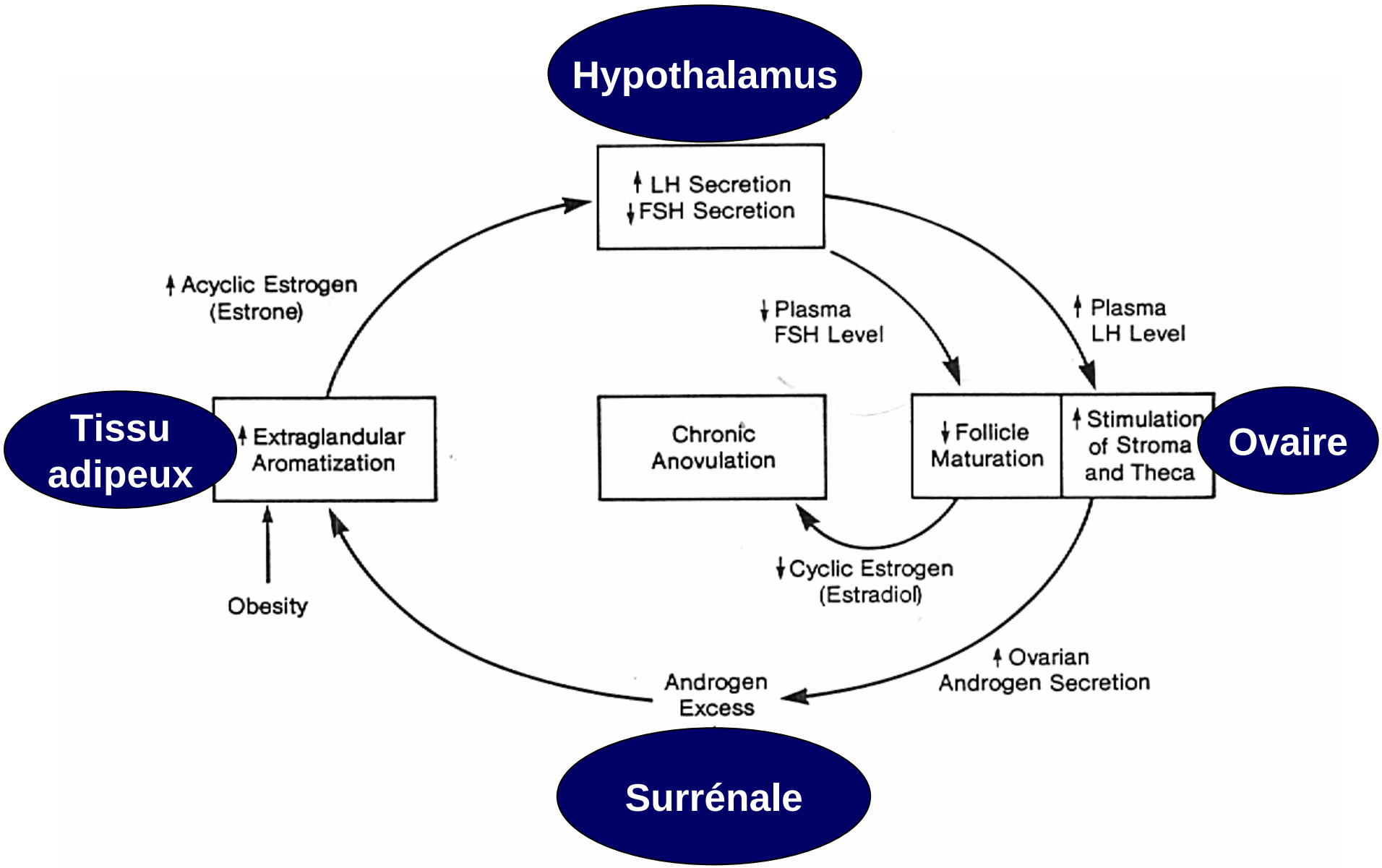
PCOS: THE TEXTBOOK VIEW I

Pathogenic hypothesis

Abnormal hormonal feedback mechanisms



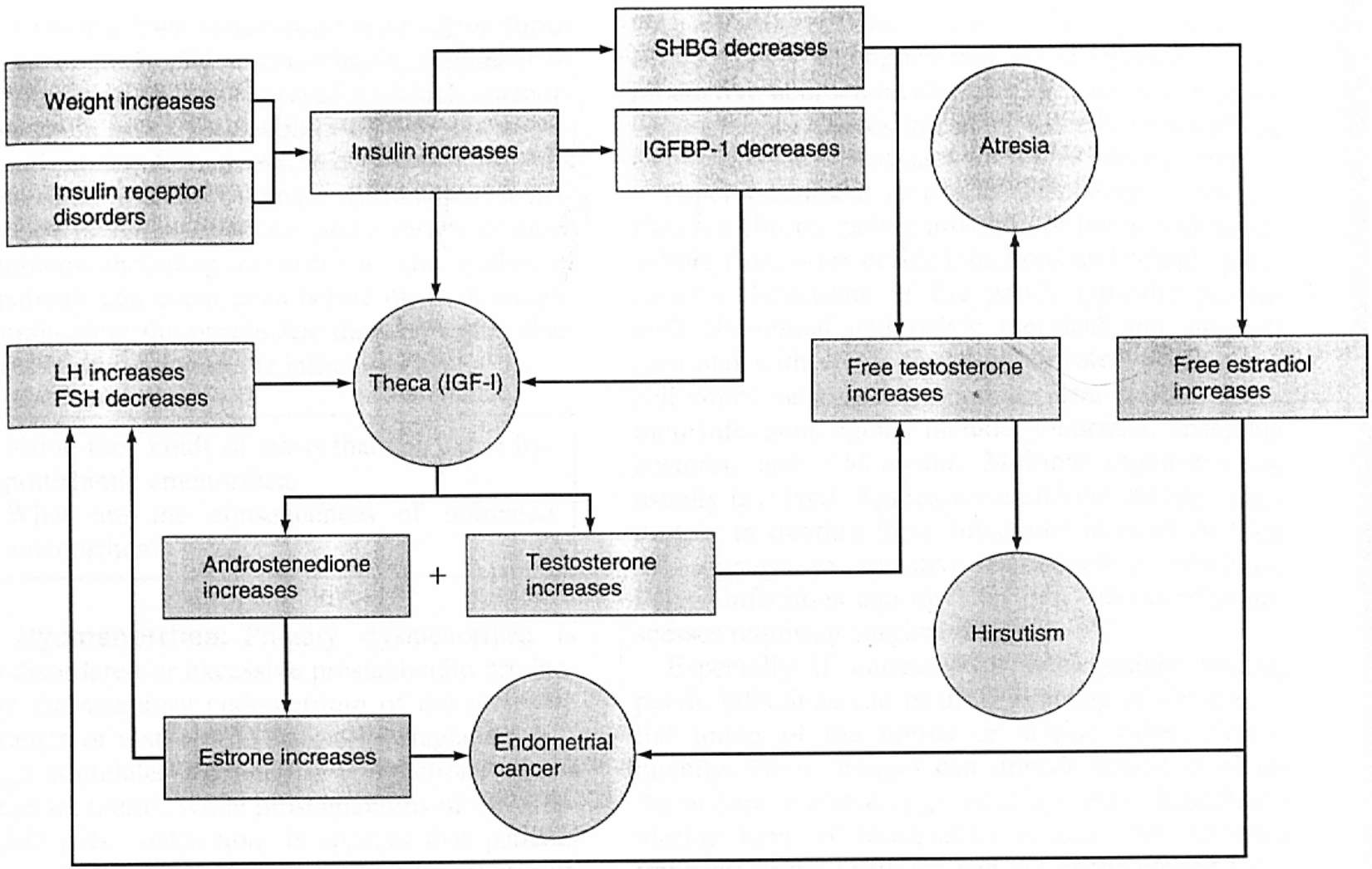
PCOS: THE TEXTBOOK VIEW I



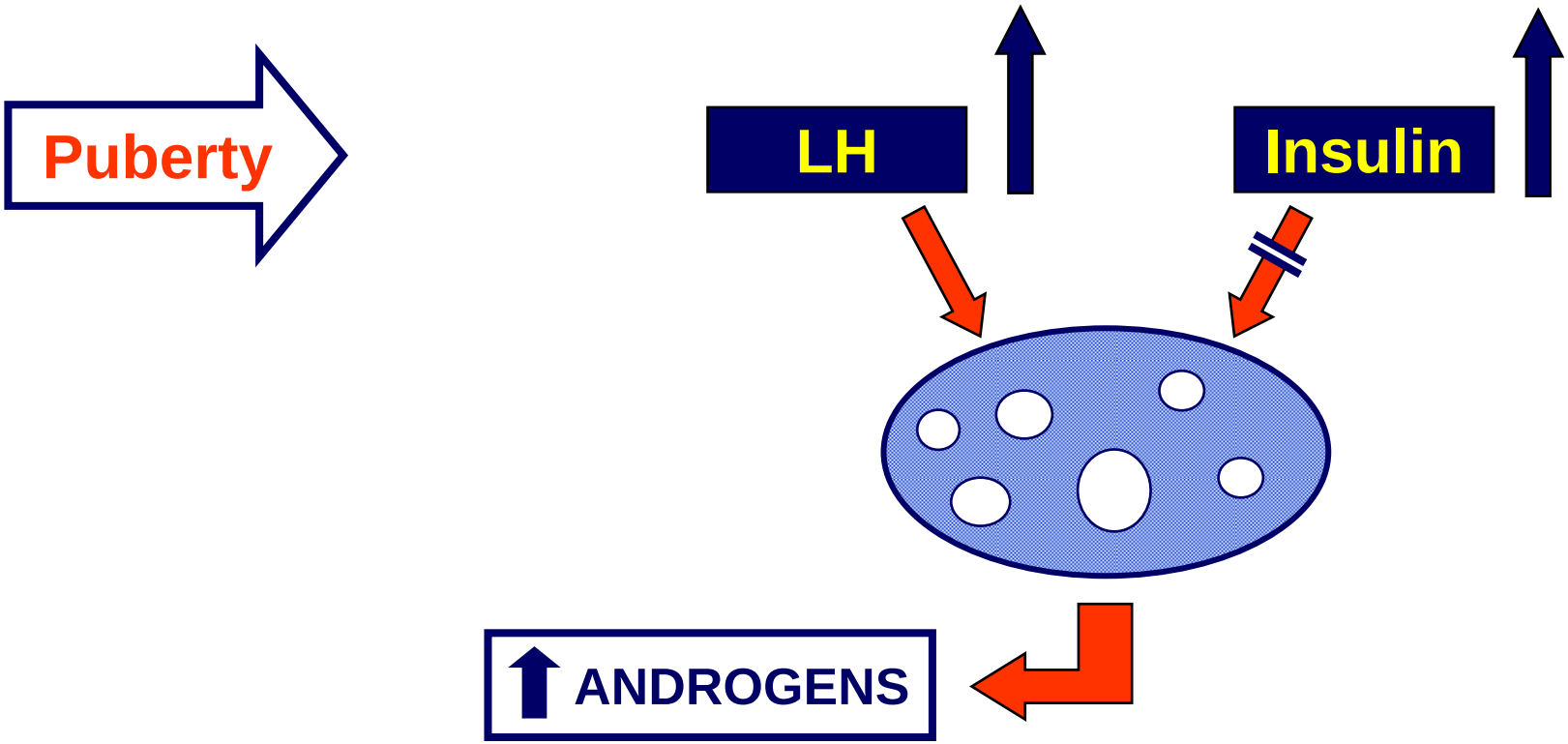
PCOS: THE TEXTBOOK VIEW II

Pathogenic hypothesis

Obesity and insulin resistance



PCOS: A DEVELOPMENTAL VIEW



- Hirsutism
- Acne
- Alopecia

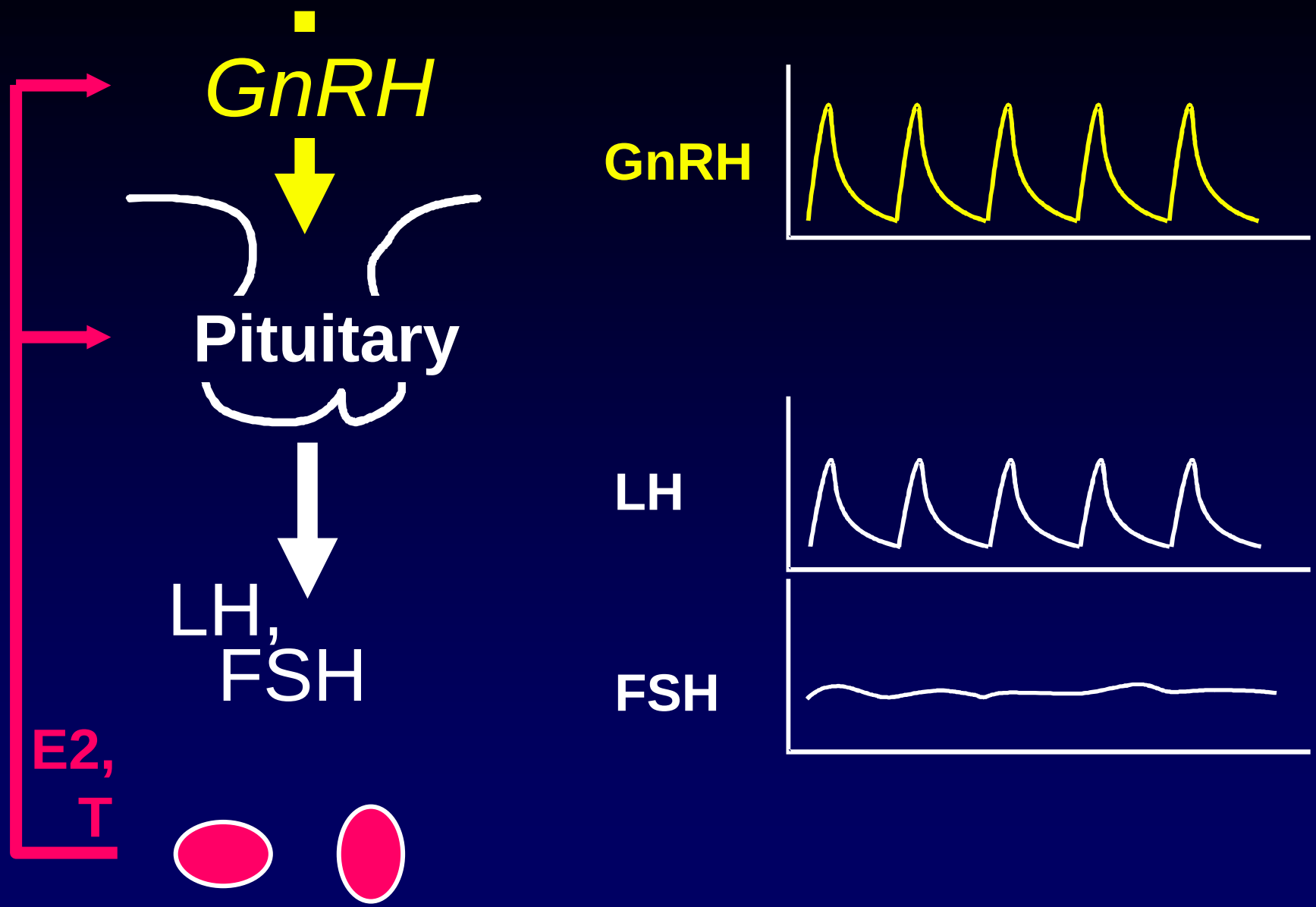
Adapted from S Franks, 2002

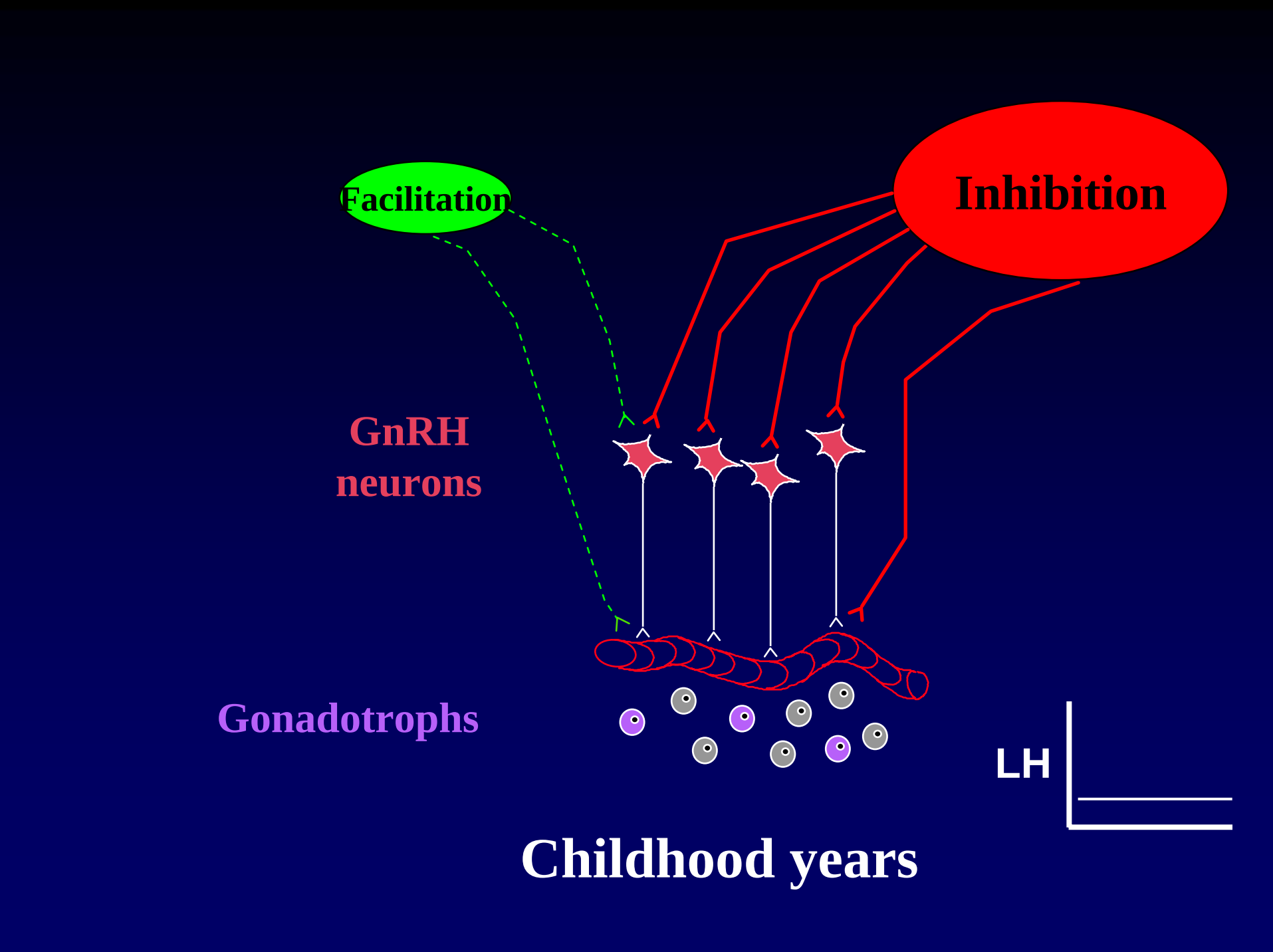
Gonadotropin Secretion in PCOS

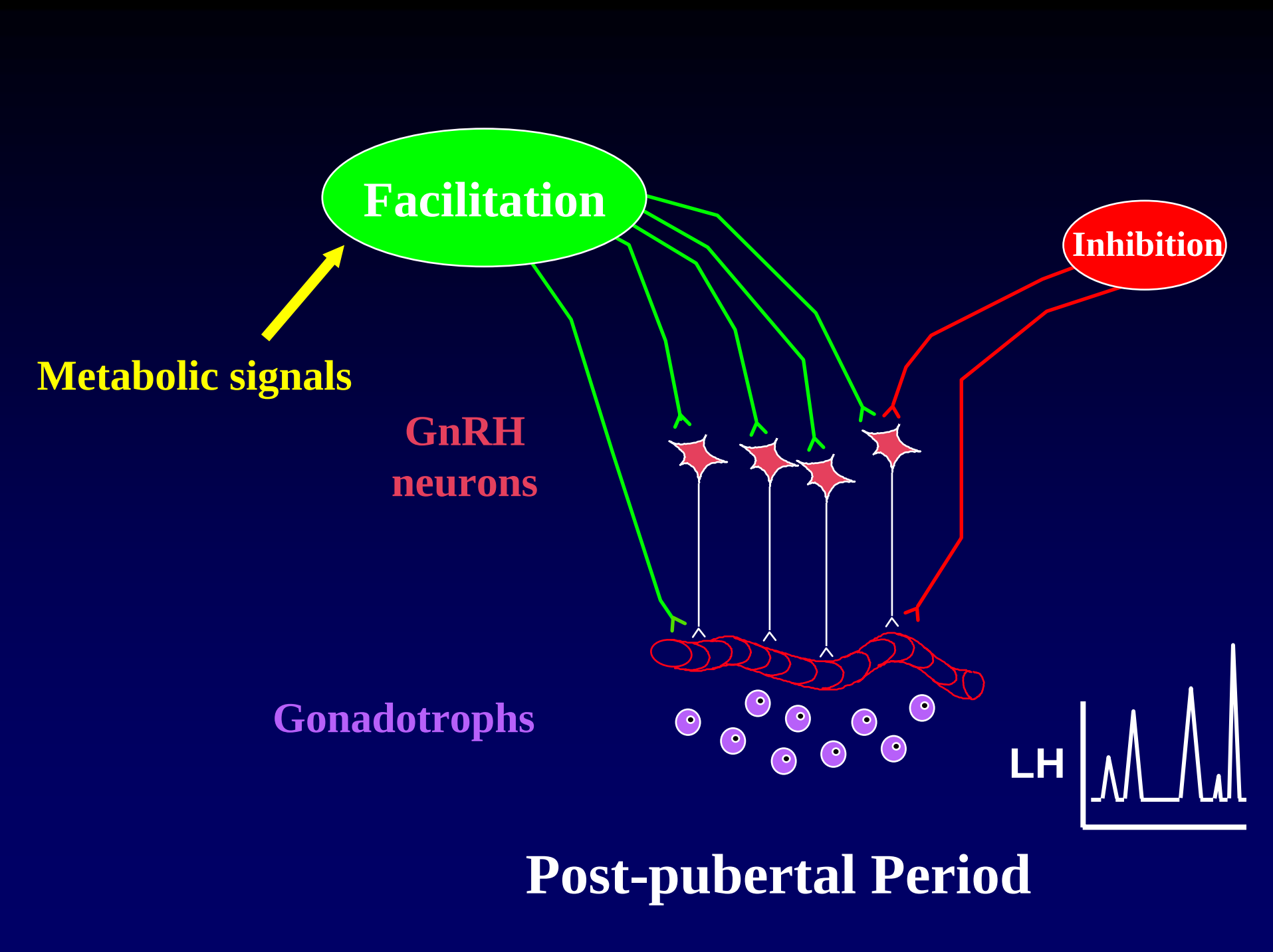
***Increased LH secretion*:**

- **Ratio of LH/FSH: 2-3/1**
- **Prevalence: 30 to 90% !**

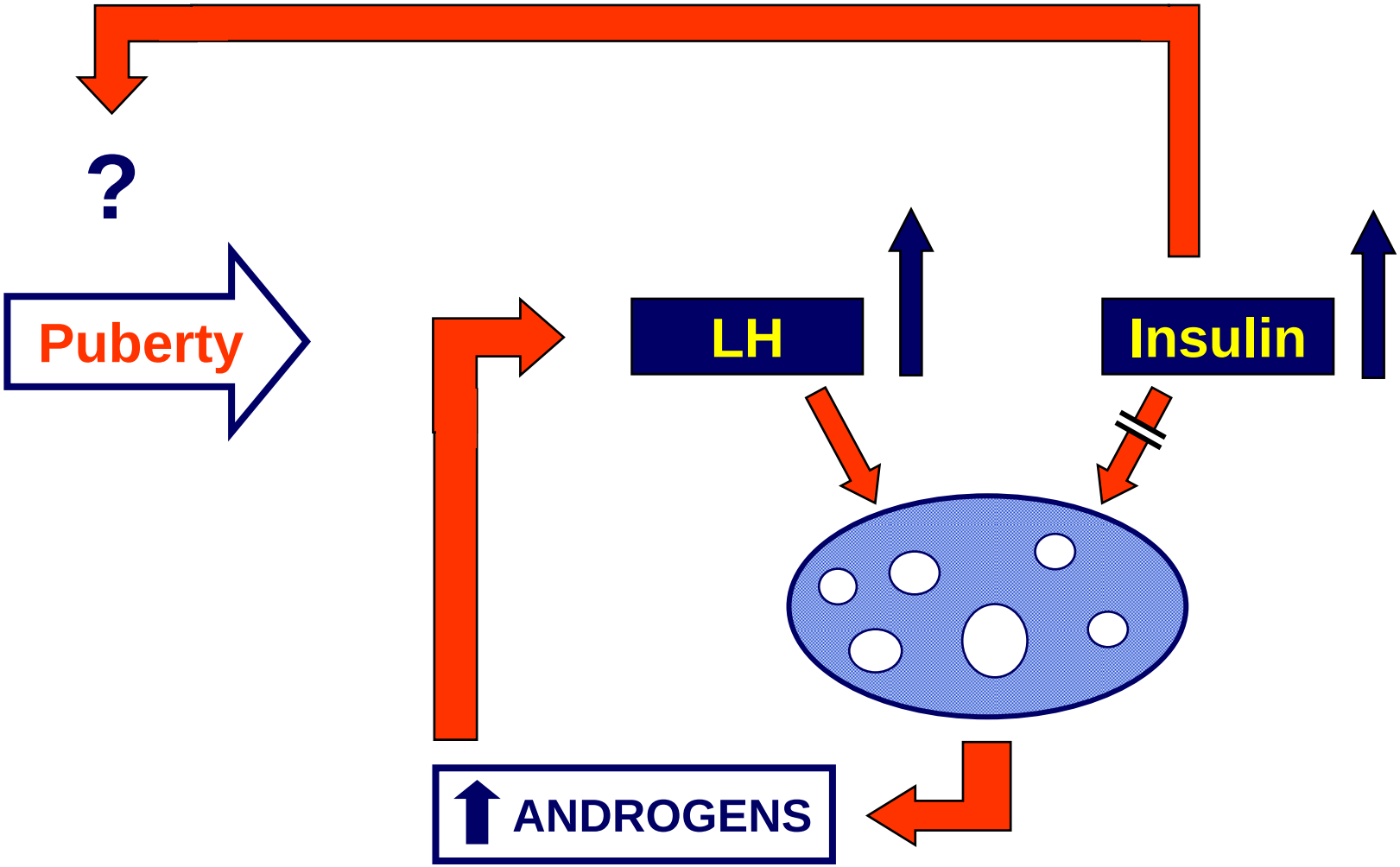
Importance of assessing LH secretion in relation to recent menses


GnRH
Pituitary
LH,
FSH
E2,
T
GnRH
LH
FSH


Facilitation
Inhibition
GnRH neurons
Gonadotrophs
LH
Childhood years



Post-pubertal Period



- Hirsutism
- Acne
- Alopecia

Adapted from S Franks, 2002

Possible Mechanisms of Abnormal LH Secretion in PCOS

***Altered sex steroid feedback*:**

- **Increased spontaneous LH pulse amplitude**
- **Increased LH response to GnRH**
- **Normal FSH response to GnRH**

Inherent neuroendocrine abnormality

A CHRONOBIOLOGIC ABNORMALITY IN LUTEINIZING HORMONE SECRETION IN TEENAGE GIRLS WITH THE POLYCYSTIC-OVARY SYNDROME

BARNETT ZUMOFF, M.D., RUTH FREEMAN, M.D., SUSAN COUPEY, M.D., PAUL SAENGER, M.D., MORRI MARKOWITZ, M.D., AND JACOB KREAM, PH.D.

Study of 5 teenage, post-pubertal girls with PCOS, compared to age-matched controls

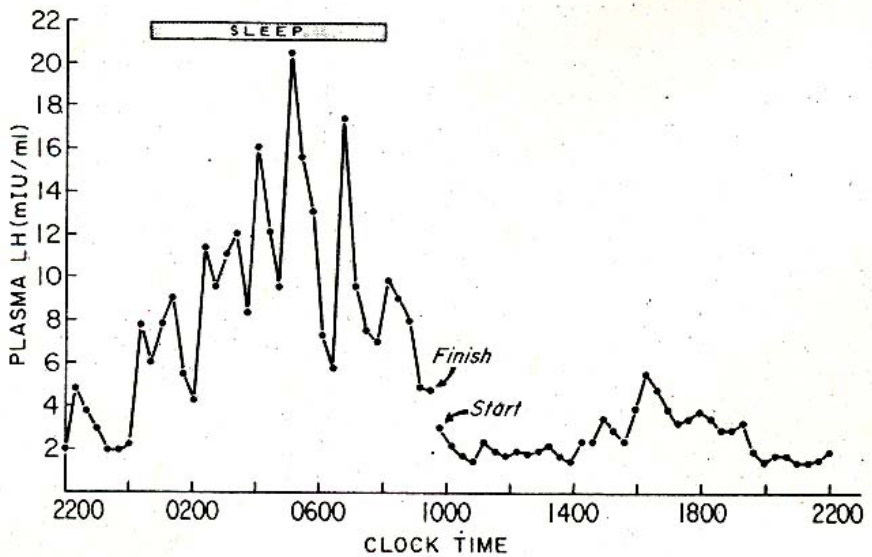
Diagnostic criteria:

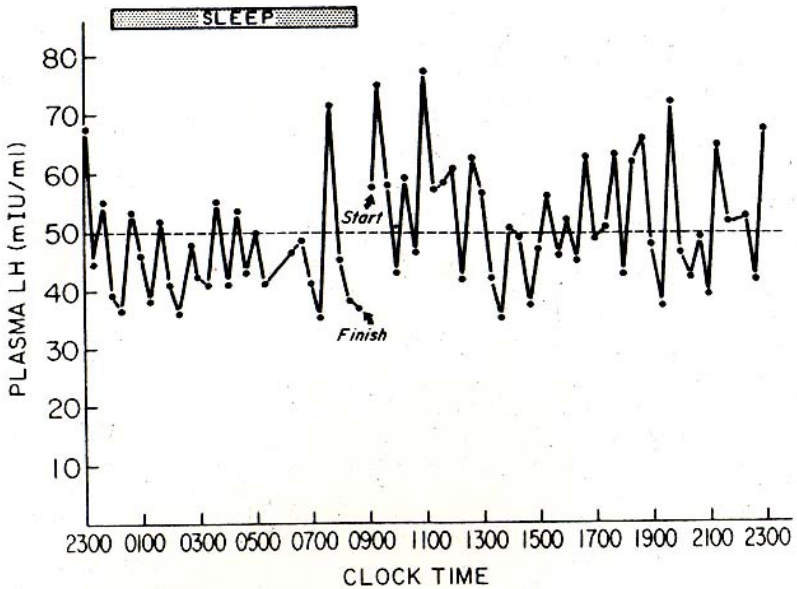
- **Chronic anovulatory syndrome**
- **Exclusion of other virilizing syndromes (Cushing, CAH…)**
- **Normal TFTs and PRL**

NEJM 309, 1983

A CHRONOBIOLOGIC ABNORMALITY IN LUTEINIZING HORMONE SECRETION IN TEENAGE GIRLS WITH THE POLYCYSTIC-OVARY SYNDROME

BARNETT ZUMOFF, M.D., RUTH FREEMAN, M.D., SUSAN COUPEY, M.D., PAUL SAENGER, M.D., MORRI MARKOWITZ, M.D., AND JACOB KREAM, PH.D.





Abnormality present in 4 of 5 patients

NEJM 309, 1983

Hyperfunction of the Hypothalamic-Pituitary Axis in Women with Polycystic Ovarian Disease: Indirect Evidence for Partial Gonadotroph Desensitization*

JOANNE WALDSTREICHER, NANETTE F. SANTORO, JANET E. HALL†,
MARCO FILICORI‡, AND WILLIAM F. CROWLEY, JR.

Study of 12 women with PCOS, compared to 21 normal controls

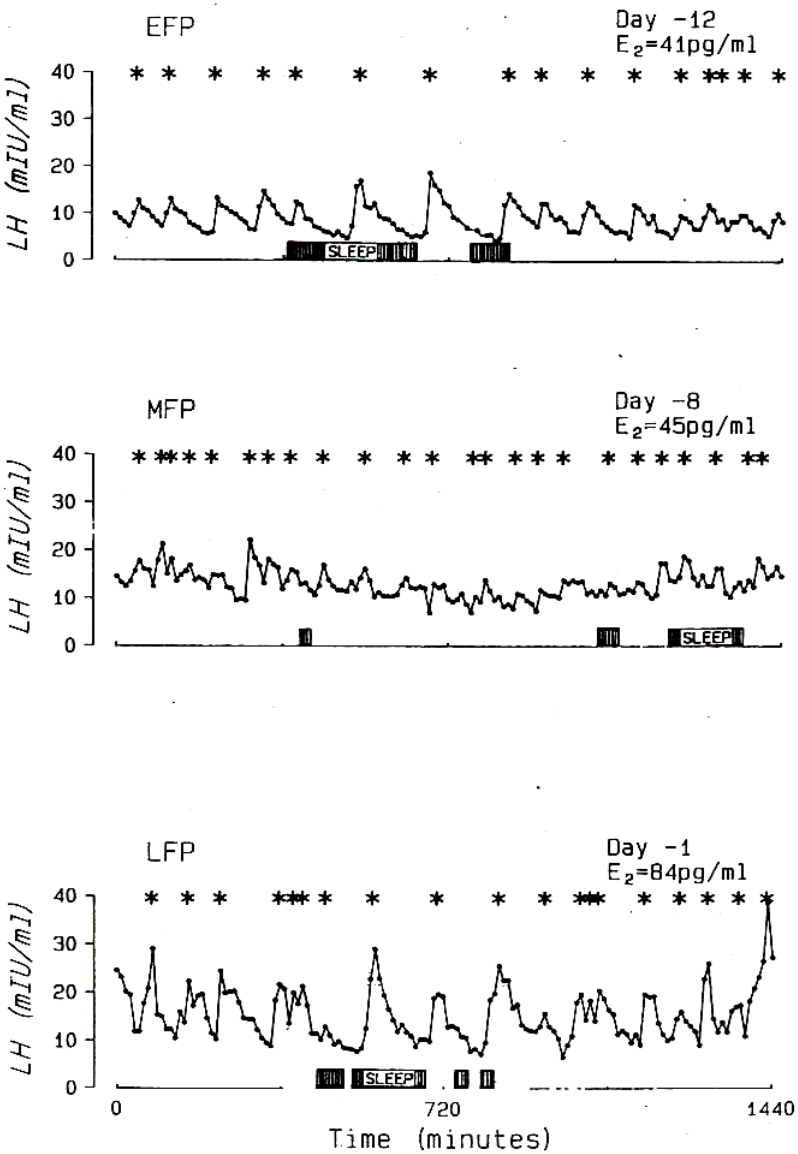
Diagnostic criteria:

- **Perimenarchal onset of oligo/amenorrhea**
- **Hirsutism and/or acne**
- **Raised LH/FSH ratio**
- **Raised T/androstenedione levels**

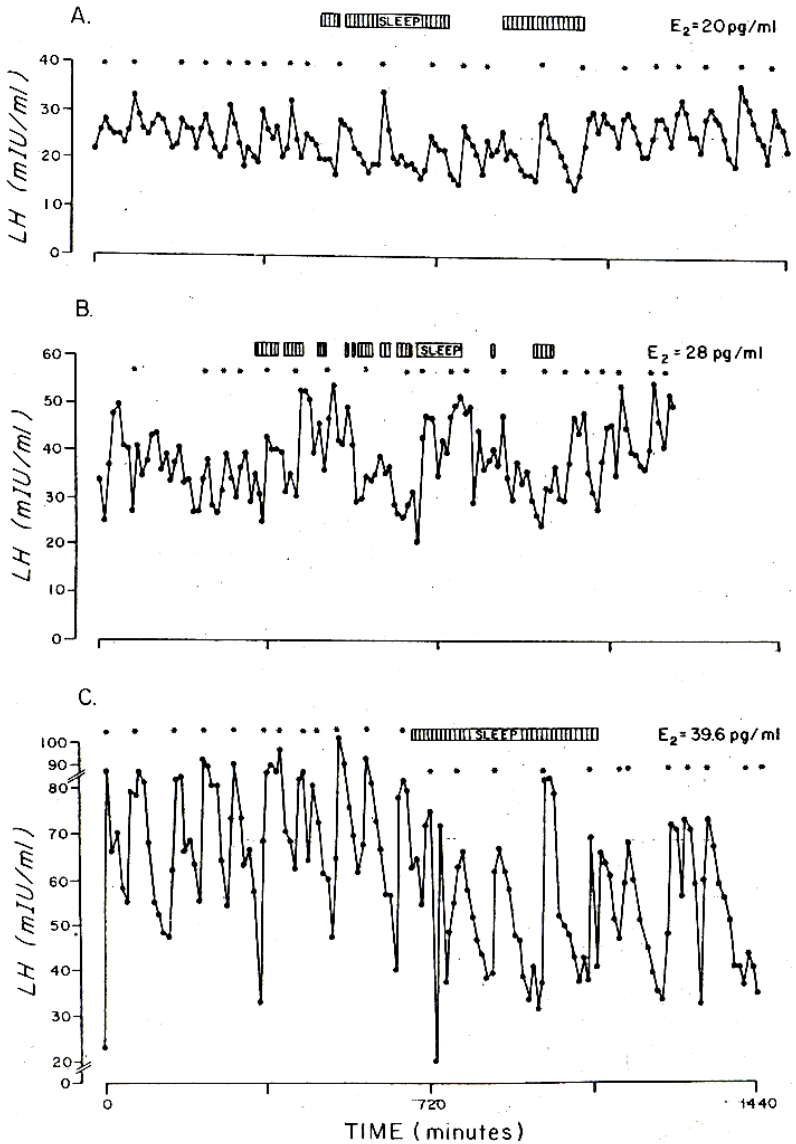
- **E2 lower than controls in MFP and LFP**
- **Estrone higher than controls in EFP and MFP, lower in LFP**

J Clin Endocrinol Metab 66, 1988

Normal

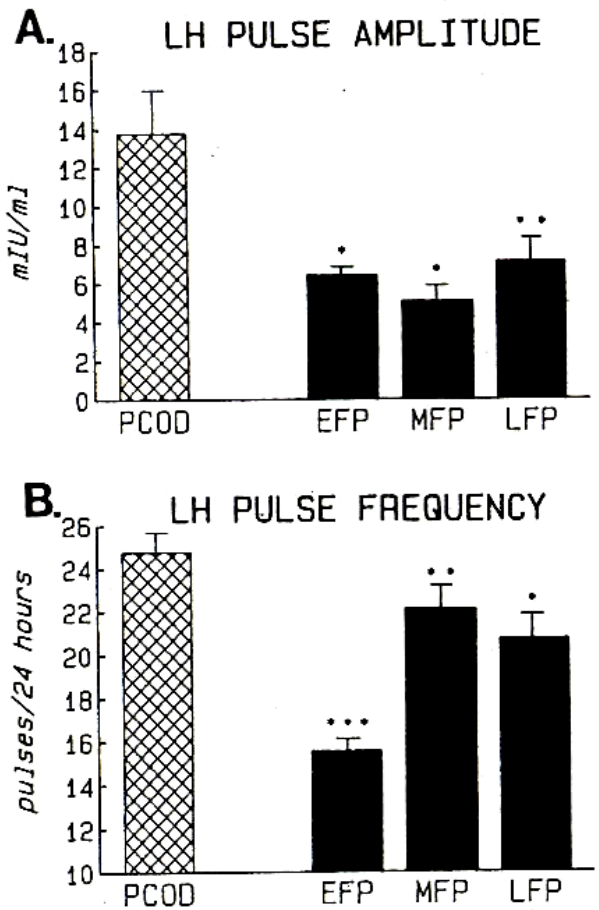


PCOS



J Clin Endocrinol Metab 66, 1988

Hyperfunction of the Hypothalamic-Pituitary Axis in Women with Polycystic Ovarian Disease: Indirect Evidence for Partial Gonadotroph Desensitization*



J Clin Endocrinol Metab 66, 1988

Accelerated 24-Hour Luteinizing Hormone Pulsatile Activity in Adolescent Girls with Ovarian Hyperandrogenism: Relevance to the Developmental Phase of Polycystic Ovarian Syndrome*

D. APTER†, T. BÜTZOW, G. A. LAUGHLIN, AND S. S. C. YEN‡

Department of Reproductive Medicine, University of California-San Diego School of Medicine, La Jolla, California 92093–0802

Study of 13 women (aged 11-18) with hyperandrogenism, compared to 28 aged-matched normal controls

Patients from Adolescent Medicine/Repro Endo clinics, UCSD

Diagnostic criteria:

- **Chief complaint: hirsutism**
- **No hormonal medication for 3 months**

J Clin Endocrinol Metab 79, 1994

Accelerated 24-Hour Luteinizing Hormone Pulsatile Activity in Adolescent Girls with Ovarian Hyperandrogenism: Relevance to the Developmental Phase of Polycystic Ovarian Syndrome*

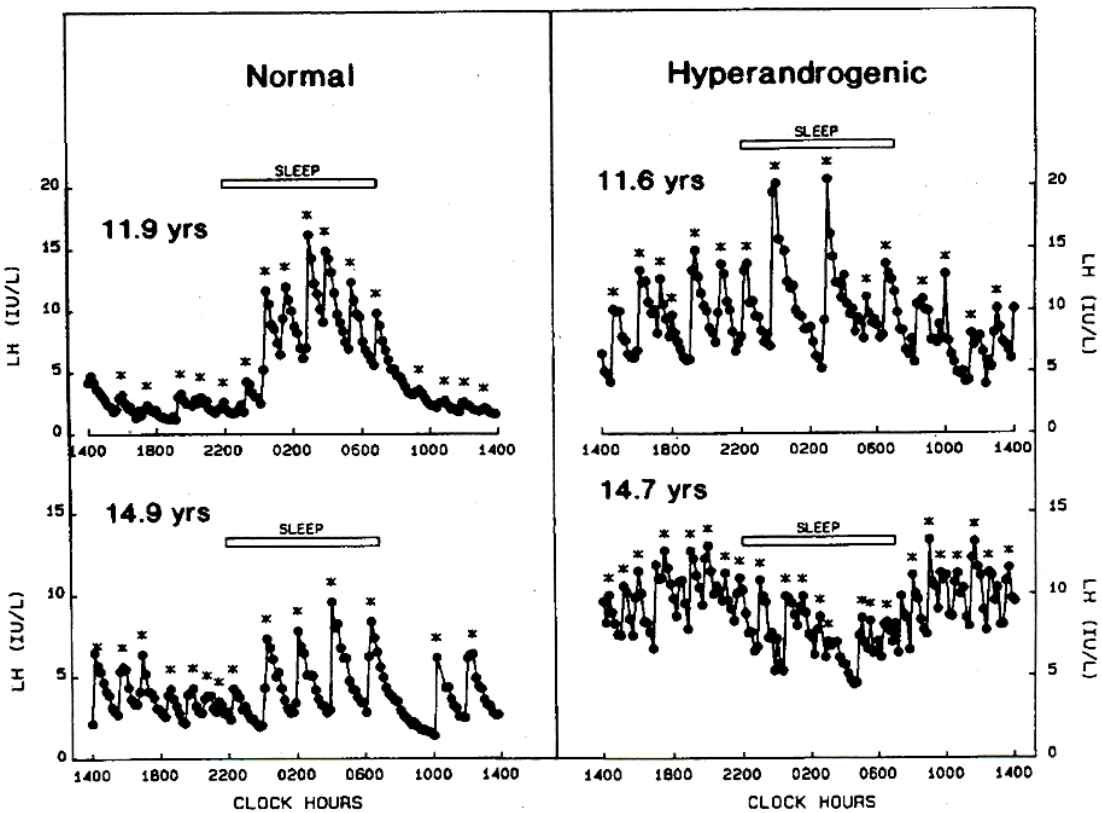
TABLE 1. Clinical characteristics of the hyperandrogenic subjects

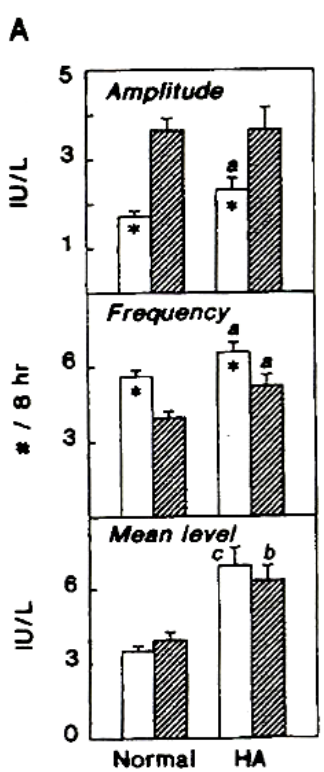
Subject no.	Age (yr)	Age at menarche (yr)	BMI	Menstrual pattern	Hirsutism score[a]	Acne	Acanthosis nigricans
1	11.6		21.8	Premenarche	10	–	No
2	11.9	11.9	34.6	Oligomenarche	7	+	Yes
3	12.8	11.5	39.5	Oligomenarche	15	+	No
4	13.5	11.6	21	Oligomenarche	10	–	No
5	14.7	12.0	33	Oligomenarche	16	++	Yes
6	14.7	12.7	33.2	Regular	10	+	No
7	15.4	12.8	34.2	Oligomenarche	12	+	No
8	16.2		43.5	Amenorrhea	20	++	Yes
9	16.4	12.2	23.1	Oligomenarche	16	+	No
10	17.1	12.5	20.4	Regular	8	–	No
11	17.1	12.1	21.9	Oligomenarche	8	–	No
12	17.7	12.6	21.7	Oligomenarche	17	–	No
13	18.1	12.5	26.4	Amenorrhea	21	++	No
HA[b]	15.1 ± 0.6	12.3 ± 0.2	28.0 ± 1.6[c]		13.1 ± 1.3		
Normal[b]	14.8 ± 0.3	12.4 ± 0.3	22.1 ± 1.2		<7.0		

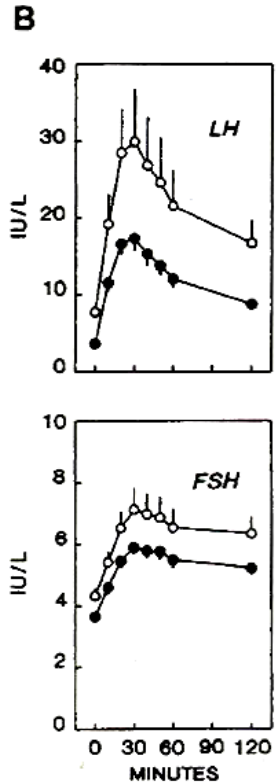
[a] According to Ferriman and Gallwey (12).
[b] Mean ± SE for group.
[c] $P = 0.005$ *vs.* normal.

J Clin Endocrinol Metab 79, 1994

Accelerated 24-Hour Luteinizing Hormone Pulsatile Activity in Adolescent Girls with Ovarian Hyperandrogenism: Relevance to the Developmental Phase of Polycystic Ovarian Syndrome*







J Clin Endocrinol Metab 79, 1994

Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

ANN E. TAYLOR*, BRIAN MCCOURT, KATHRYN A. MARTIN, ELLEN J. ANDERSON, JUDITH M. ADAMS, DAVID SCHOENFELD, AND JANET E. HALL

Reproductive Endocrine Unit and National Center for Infertility Research, Massachusetts General Hospital, Boston, Massachusetts 02114

Study of 61 women with PCOS, compared to 24 normal controls (EFP)

Diagnostic criteria:

- **Chronic oligoamenorrhea (<9 cycles/yr) or amenorrhea**
- **Hyperandrogenism (clinical or biochemical)**
- **Exclusion of late-onset CAH**
- **Normal TFT and PRL**
- **Off all medication for at least 2 months**

J Clin Endocrinol Metab 82, 1997

Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

	Anovulatory PCOS patients (n = 52)		Post-ovulatory PCOS patients (n = 9)		Normal women (n = 24)		*P* for ANOVA
	Median	Range	Median	Range	Median	Range	
Age (yr)	29	16–42	28	19–37	26	18–42	0.335
Cycle day	40[a]	4–862	2[b]	−5–6	3	1–7	**<0.001**
BMI (kg/m^2)	33.8[c]	17.0–60.2	26.2	21.5–40.1	25.4	19.6–50.9	0.022
Hirsutism score	11[a]	0–29	13.5[a]	8–18	5	0–9	**<0.001**
Ovarian volume (cm^3)	14.4[a]	5.7–44.8	14.6[c]	9.7–21.5	9.8	2.7–16.7	**<0.001**
LH pool (IU/L)	15.4[a]	5.3–112.9	8.0[b]	2.1–10.8	5.8	2.0–12.4	**<0.001**
FSH pool (IU/L)	9.5	4.0–29.1	9.4	2.0–16.4	10.8	6.7–16.4	.110
LH/FSH ratio	1.58[a]	0.70–15.68	1.05[a,b]	0.40–1.82	0.51	0.21–1.05	**<0.001**
LH pulse amplitude (IU/L)	7.1[c]	2.6–50.7	8[a]	5.3–66.5	4.5	2.0–14.9	**0.004**
LH pulse frequency (#/24 h)	18[a]	4–28	8[b]	2–13	15	6–21	**<0.001**
Testosterone (ng/mL)	1.3[a]	0.4–4.2	0.8[a,b]	0.7–1.0	0.6	0.4–1.4	**<0.001**
Androstenedione (ng/mL)	3.7[a]	1.5–12.6	2.4	1.0–5.0	2.6	0.9–5.0	**0.004**
17-OH progesterone (ng/mL)	1	0.3–3.6	0.8	0.5–2.7	0.7	0.3–2.3	0.052
DHEA-S (μg/dL)	148	20–455	150	50–592	158	20–395	0.866
Estradiol (pg/mL)	83	16–235	80	34–178	84	40–142	0.845
Estrone (pg/mL)	82	14–606	65	28–298	64	23–119	0.075

[a] $P < 0.004$ *vs.* normal.
[b] $P < 0.004$ *vs.* anovulatory PCOS.
[c] $P < 0.05$ *vs.* normal.

J Clin Endocrinol Metab 82, 1997

Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

	Anovulatory PCOS patients (n = 52)		Post-ovulatory PCOS patients (n = 9)		Normal women (n = 24)		*P* for ANOVA
	Median	Range	Median	Range	Median	Range	
Age (yr)	29	16–42	28	19–37	26	18–42	0.335
Cycle day	40[a]	4–862	2[b]	−5–6	3	1–7	**<0.001**
BMI (kg/m^2)	33.8[c]	17.0–60.2	26.2	21.5–40.1	25.4	19.6–50.9	0.022
Hirsutism score	11[a]	0–29	13.5[a]	8–18	5	0–9	**<0.001**
Ovarian volume (cm^3)	14.4[a]	5.7–44.8	14.6[c]	9.7–21.5	9.8	2.7–16.7	**<0.001**
LH pool (IU/L)	15.4[a]	5.3–112.9	8.0[b]	2.1–10.8	5.8	2.0–12.4	**<0.001**
FSH pool (IU/L)	8.5	4.0–29.1	9.1	2.0–16.4	10.5	6.7–16.4	.110
LH/FSH ratio	1.58[a]	0.70–15.68	1.05[a,b]	0.40–1.82	0.51	0.21–1.05	**<0.001**
LH pulse amplitude (IU/L)	7.1[a]	2.6–50.7	8[a]	5.3–66.5	4.5	2.0–14.9	**0.004**
LH pulse frequency (#/24 h)	18[a]	4–28	8[b]	2–13	15	6–21	**<0.001**
Testosterone (ng/mL)	1.3[a]	0.4–4.2	0.8[a,b]	0.7–1.0	0.6	0.4–1.4	**<0.001**
Androstenedione (ng/mL)	3.7[a]	1.5–12.6	2.4	1.0–5.0	2.6	0.9–5.0	**0.004**
17-OH progesterone (ng/mL)	1	0.3–3.6	0.8	0.5–2.7	0.7	0.3–2.3	0.052
DHEA-S (μg/dL)	148	20–455	150	50–592	158	20–395	0.866
Estradiol (pg/mL)	83	16–235	80	34–178	84	40–142	0.845
Estrone (pg/mL)	82	14–606	65	28–298	64	23–119	0.075

[a] $P < 0.004$ *vs.* normal.
[b] $P < 0.004$ *vs.* anovulatory PCOS.
[c] $P < 0.05$ *vs.* normal.

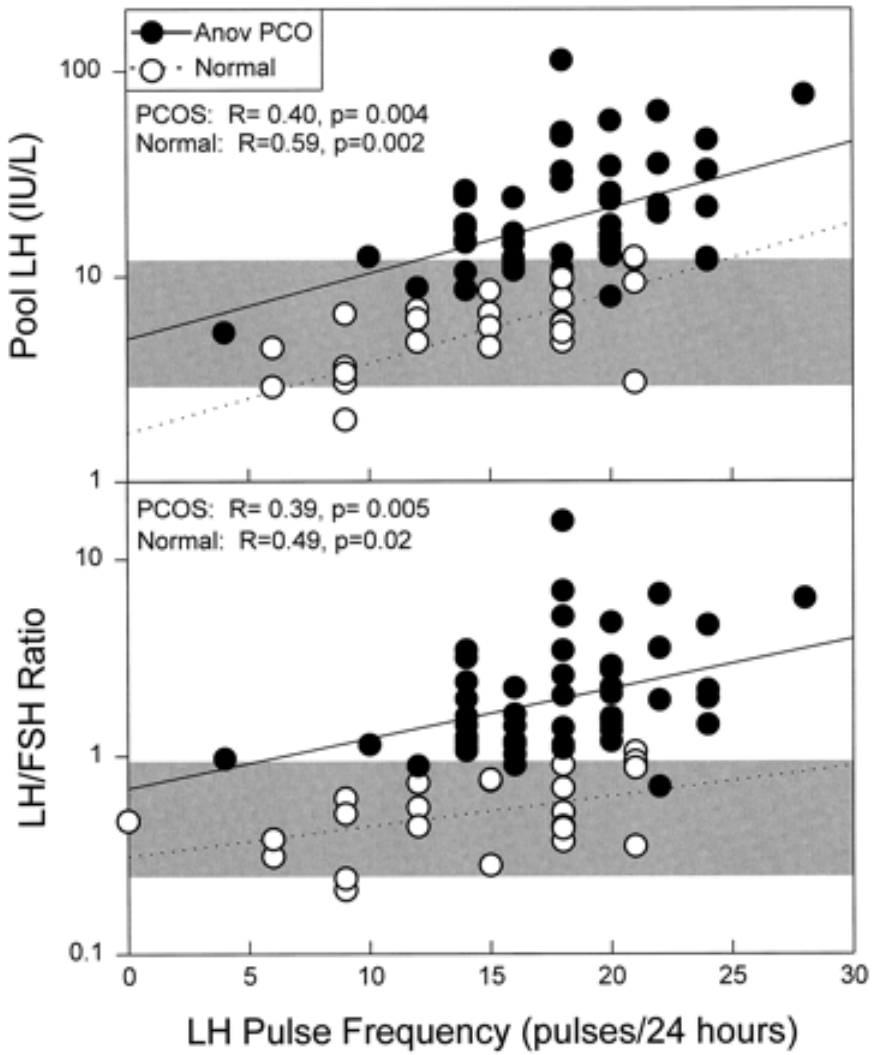
J Clin Endocrinol Metab 82, 1997

Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

	Anovulatory PCOS patients (n = 52)		Post-ovulatory PCOS patients (n = 9)		Normal women (n = 24)		*P* for ANOVA
	Median	Range	Median	Range	Median	Range	
Age (yr)	29	16–42	28	19–37	26	18–42	0.335
Cycle day	4[a]	4–862	2[b]	−5–6	3	1–7	**<0.001**
BMI (kg/m^2)	33.8[c]	17.0–60.2	26.2	21.5–40.1	25.4	19.6–50.9	0.022
Hirsutism score	11[a]	0–29	13.5[a]	8–18	5	0–9	**<0.001**
Ovarian volume (cm^3)	14.4[a]	5.7–44.8	14.6[a]	9.7–21.5	9.8	2.7–16.7	**<0.001**
LH pool (IU/L)	15.4[a]	5.3–112.9	8.0[b]	2.1–10.8	5.8	2.0–12.4	**<0.001**
FSH pool (IU/L)	8.5	4.0–29.1	9.1	2.0–16.4	10.5	6.7–16.4	.110
LH/FSH ratio	1.58[a]	0.70–15.68	1.05[a,b]	0.40–1.82	0.51	0.21–1.05	**<0.001**
LH pulse amplitude (IU/L)	7.1[a]	2.6–50.7	8[a]	5.3–66.5	4.5	2.0–14.9	**0.004**
LH pulse frequency (#/24 h)	18[a]	4–28	8[b]	2–13	15	6–21	**<0.001**
Testosterone (ng/mL)	1.3[a]	0.4–4.2	0.8[a,b]	0.7–1.0	0.6	0.4–1.4	**<0.001**
Androstenedione (ng/mL)	3.7[a]	1.5–12.6	2.4	1.0–5.0	2.6	0.9–5.0	**0.004**
17-OH progesterone (ng/mL)	1	0.3–3.6	0.8	0.5–2.7	0.7	0.3–2.3	0.052
DHEA-S (μg/dL)	148	20–455	150	50–592	158	20–395	0.866
Estradiol (pg/mL)	83	16–235	80	34–178	84	40–142	0.845
Estrone (pg/mL)	82	14–606	65	28–298	64	23–119	0.075

[a] $P < 0.004$ *vs.* normal.
[b] $P < 0.004$ *vs.* anovulatory PCOS.
[c] $P < 0.05$ *vs.* normal.

J Clin Endocrinol Metab 82, 1997



J Clin Endocrinol Metab 82, 1997

Determinants of Abnormal Gonadotropin Secretion in Clinically Defined Women with Polycystic Ovary Syndrome*

High prevalence of gonadotropin secretion abnormalities in PCOS patients

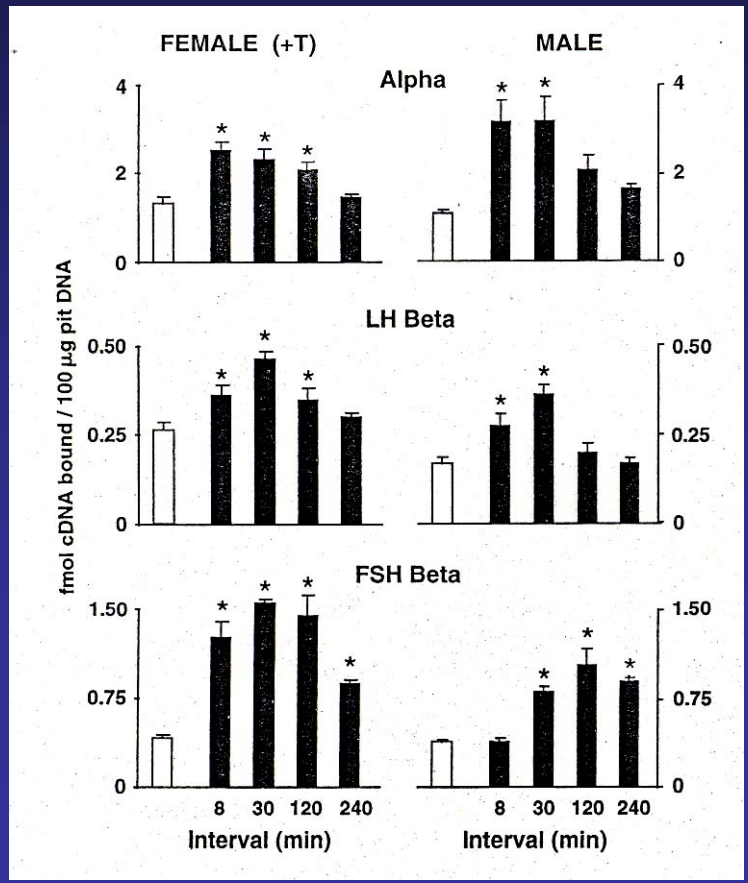
Important associations between the elevated LH secretion and recent ovulation or LH pulse frequency, *but NOT sex steroids*

Strong association between LH pulse frequency and pool LH levels or LH/FSH ratio may suggest an etiologic relationship

J Clin Endocrinol Metab 82, 1997

CONCLUSIONS

Rapid GnRH pulse frequency probably has a role in the abnormal LH secretion pattern in PCOS



Marshall and Eagleson, 1999

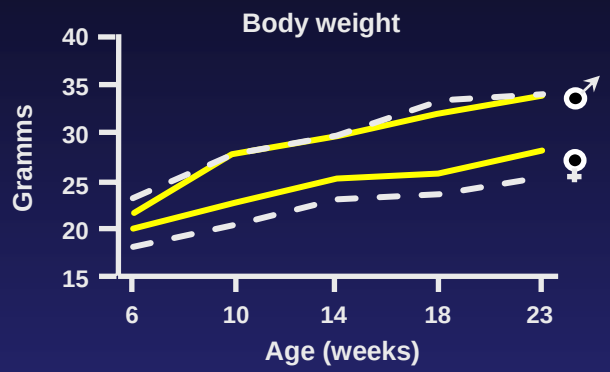
CONCLUSIONS

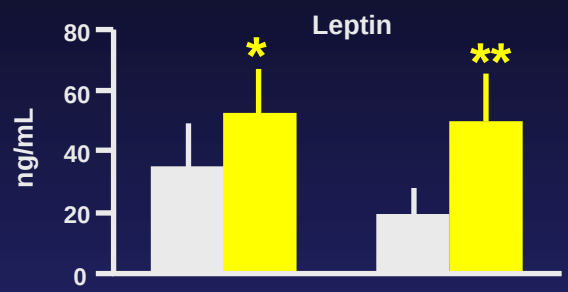
Rapid GnRH pulse frequency probably has a role in the abnormal LH secretion pattern in PCOS

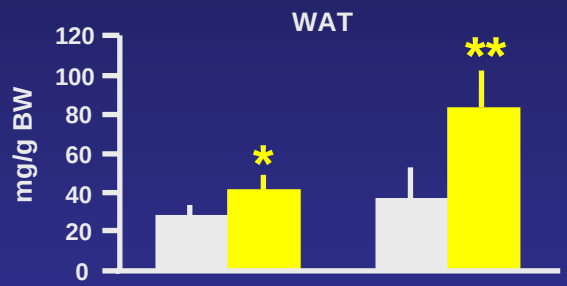
The defect in hypothalamic GnRH secretion seems to be intrinsic to PCOS patients

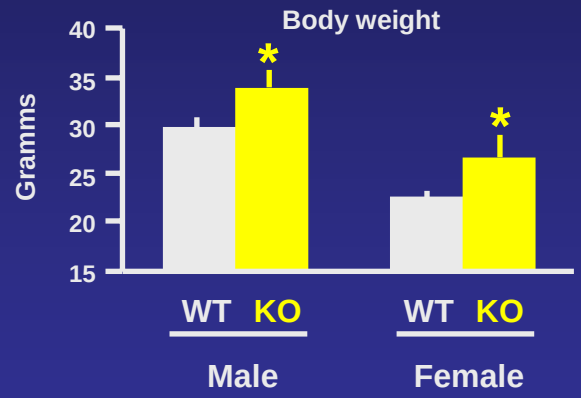
Could there be a role of elevated insulin levels/insulin resistance in this abnormal GnRH secretion pattern?

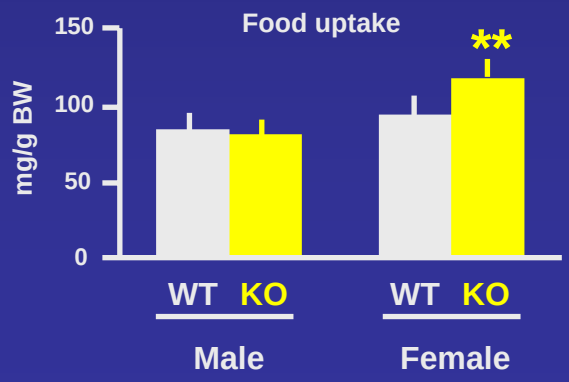
Role of Brain Insulin Receptor in Control of Body Weight and Reproduction





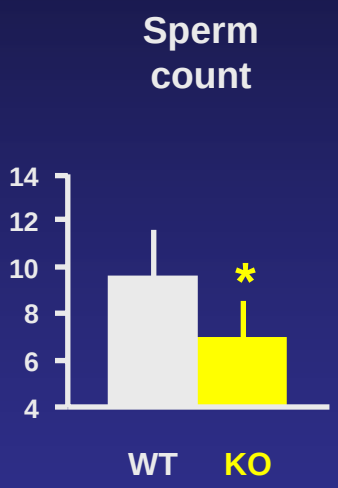


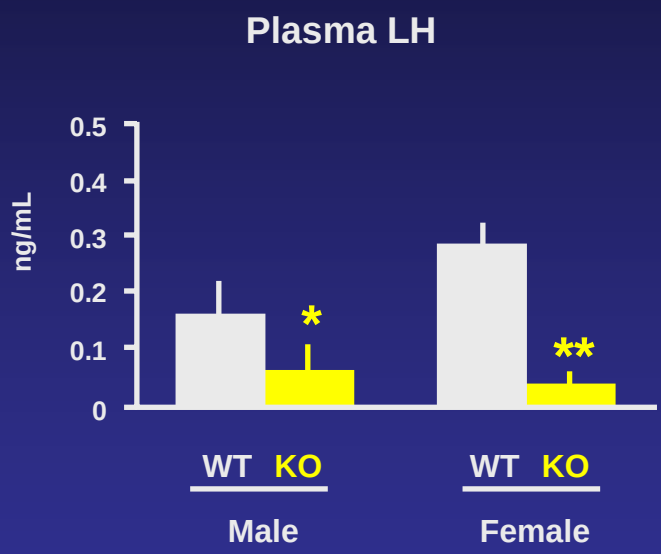


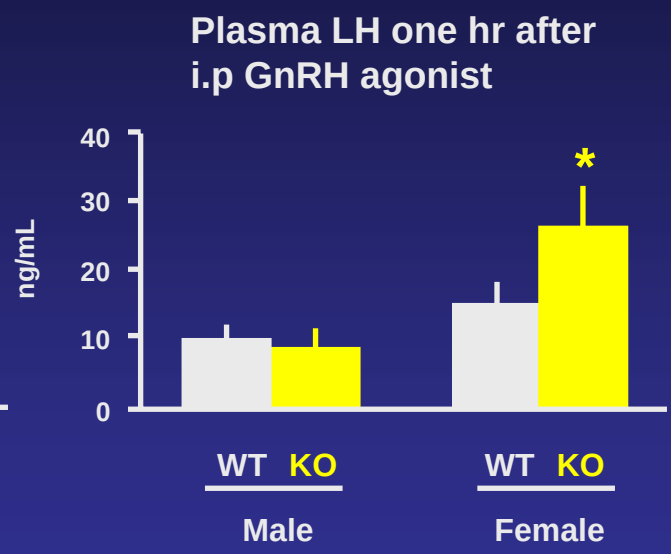


Brüning *et al.*, Science 289, 2000

Role of Brain Insulin Receptor in Control of Body Weight and Reproduction





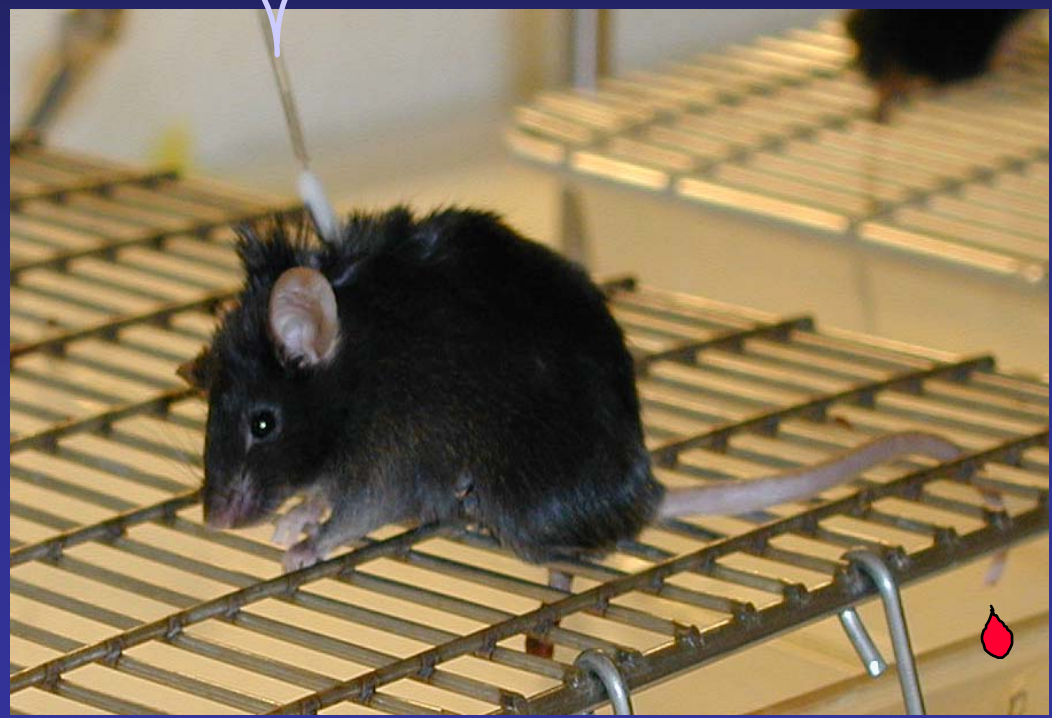


Brüning *et al*., Science 289, 2000

Euglycemic hyperinsulinemic clamp studies in mice

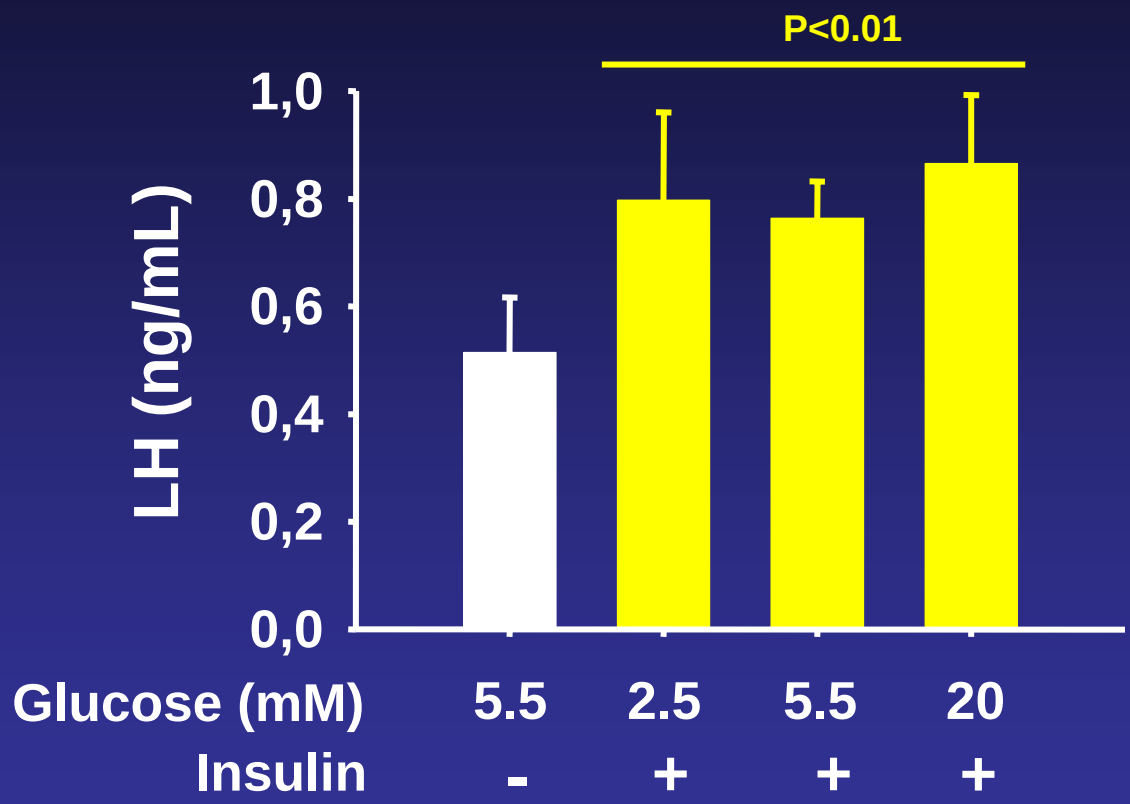
Insulin infusion

Glucose 15 % infusion



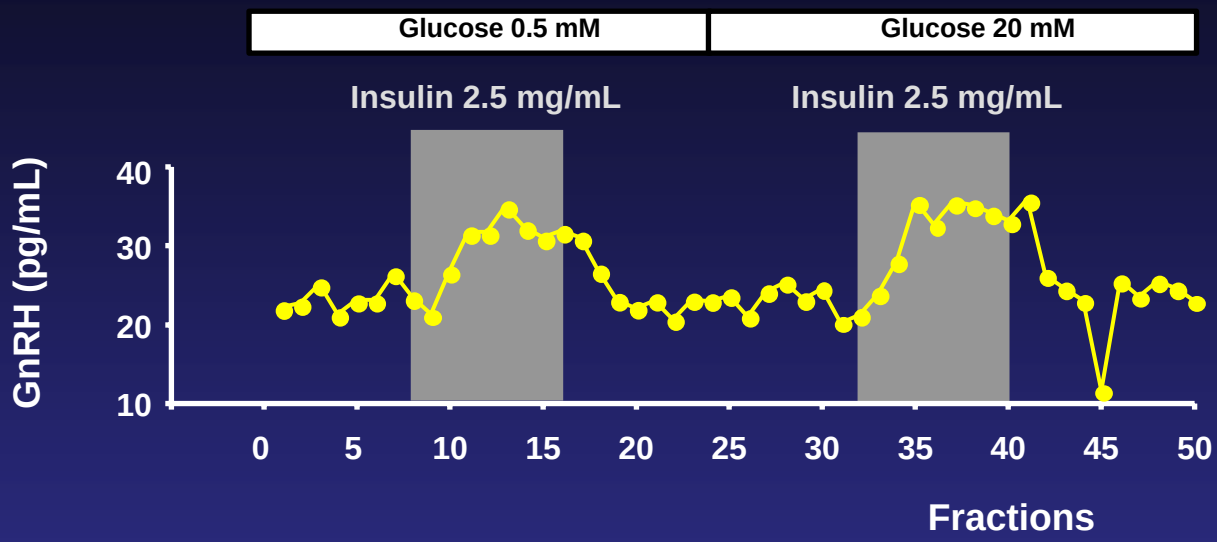
Glycemia

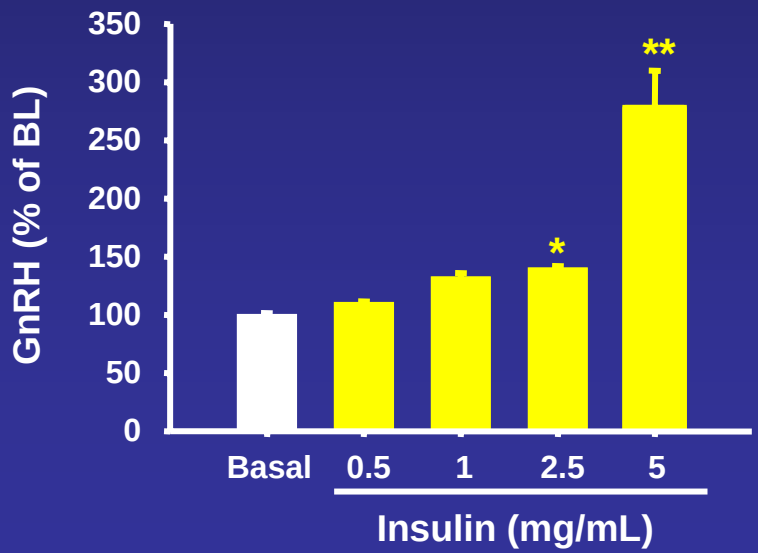
Insulin Stimulates GnRH Secretion In Vivo

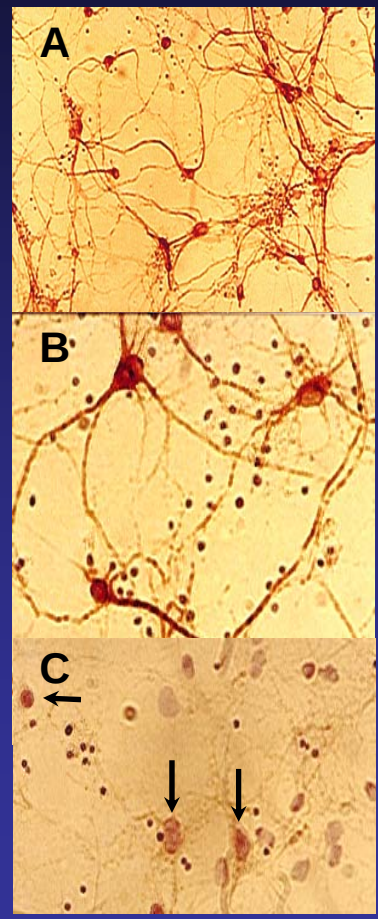


Burcelin *et al*, Endocrinology 2003

Insulin Stimulates GnRH Secretion In Vitro

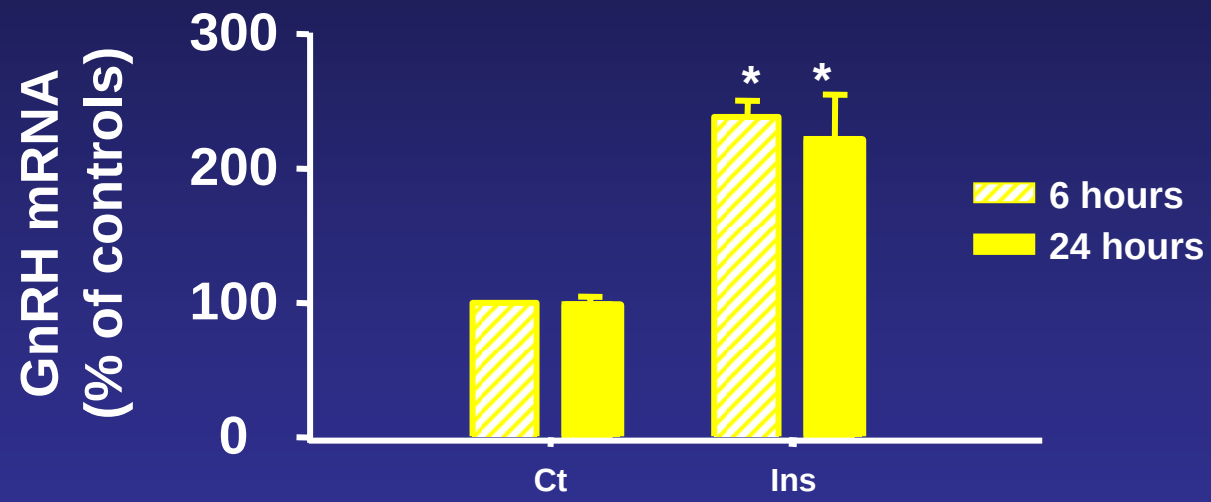






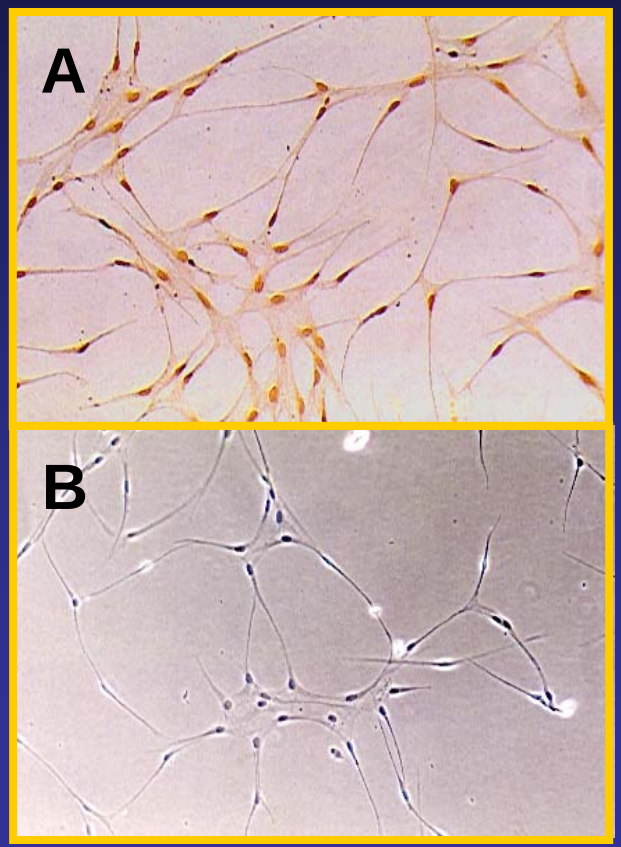
Burcelin *et al*, Endocrinology 2003

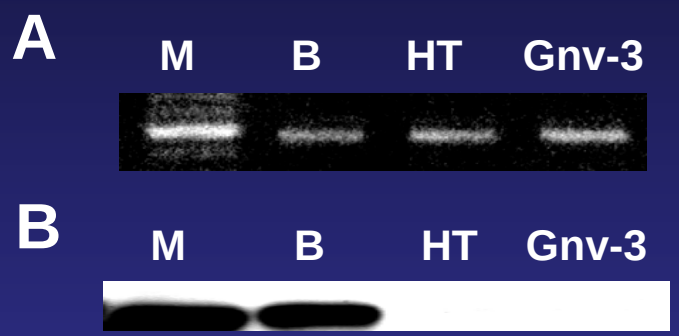
Insulin stimulates the expression of the GnRH gene



Burcelin *et al*, Endocrinology 2003

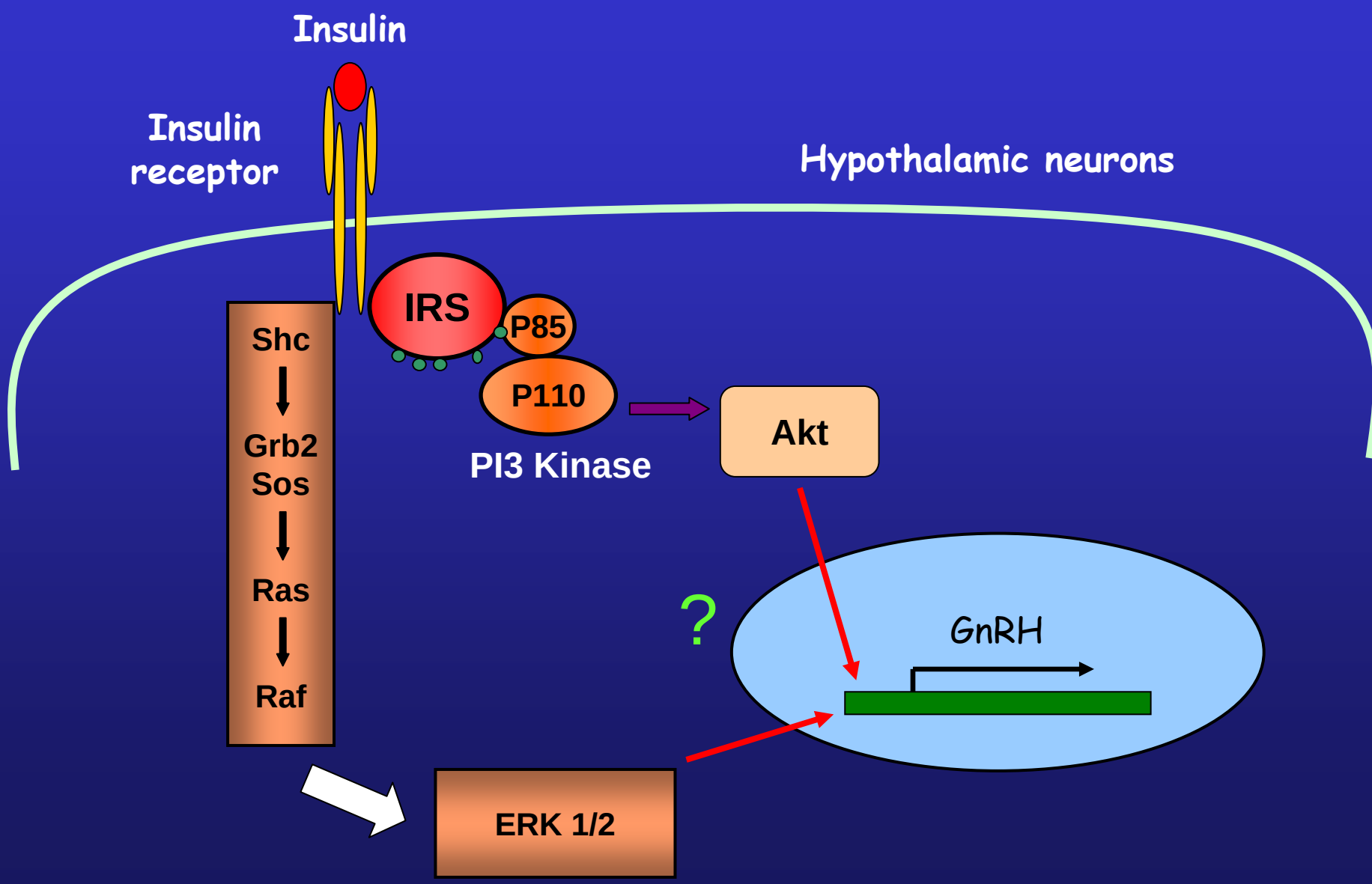
Hypothalamic GnRH neurons express a functional insulin receptor



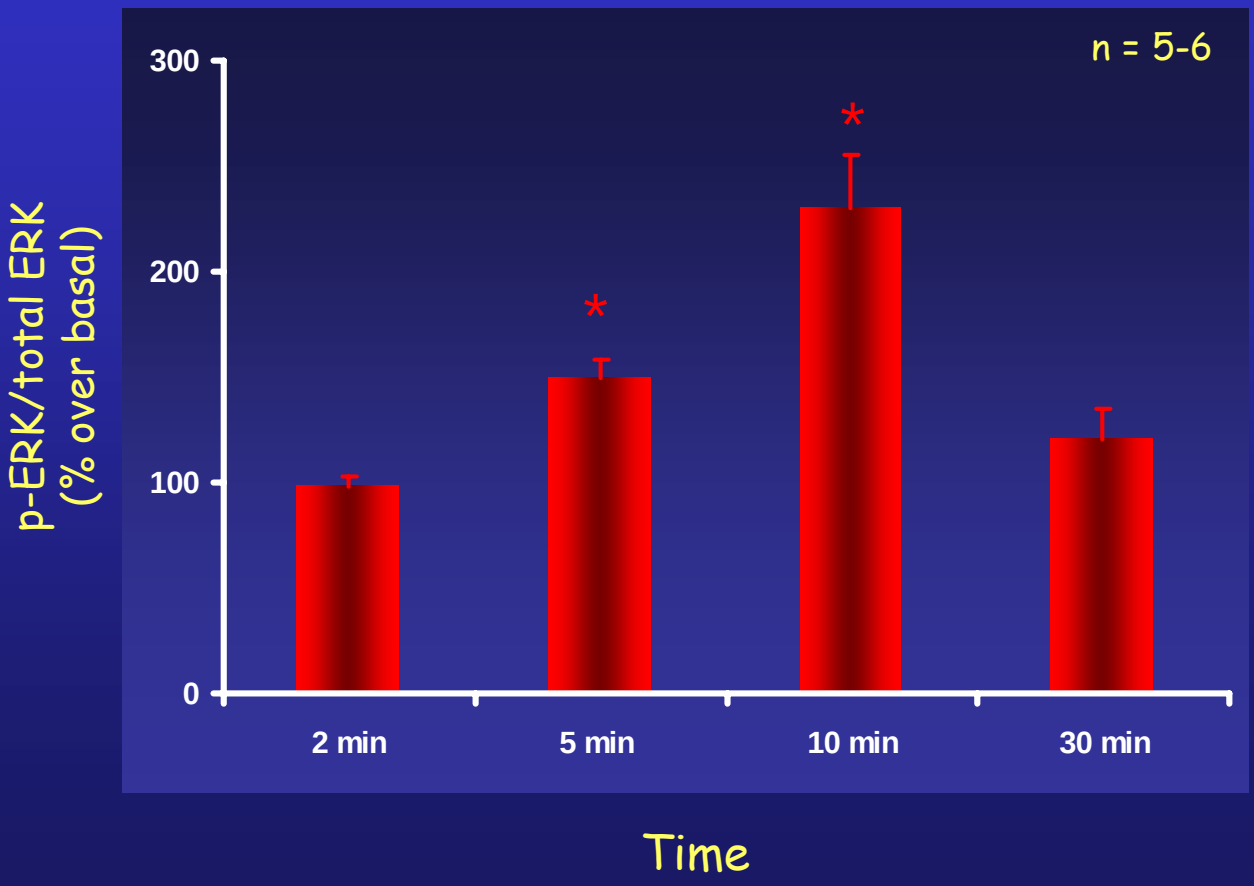


Vollenweider *et al*, Bern 2003

Insulin signaling and GnRH transcription

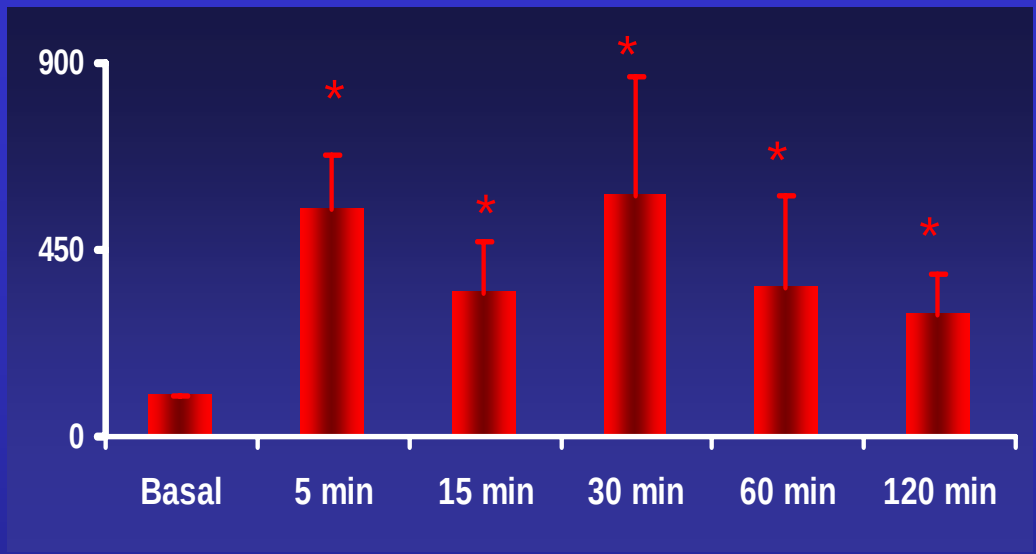


ERK1/2 activation (Phospho ERK) in primary hypothalamic cells

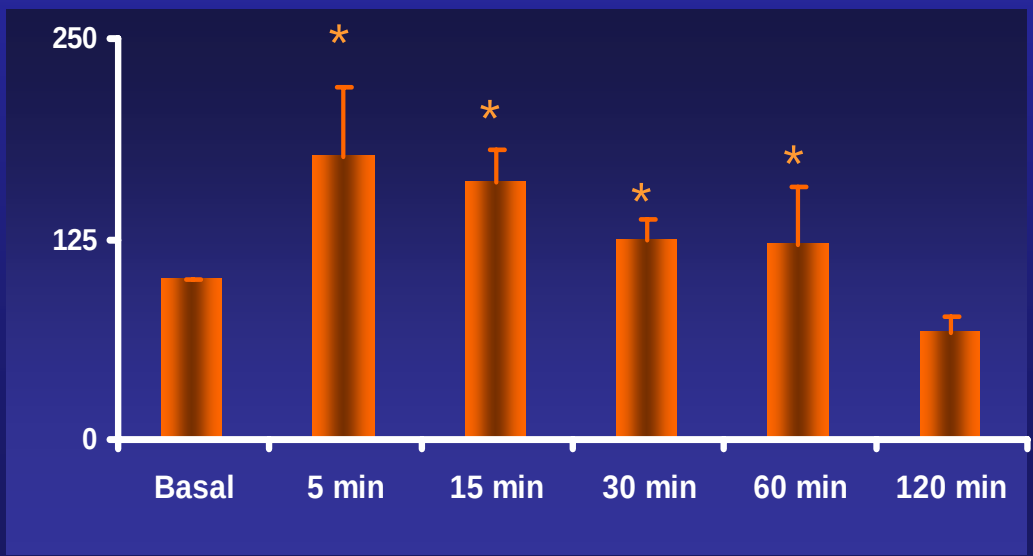


PI-3 kinase activation

IP IRS-1
PI3-kinase

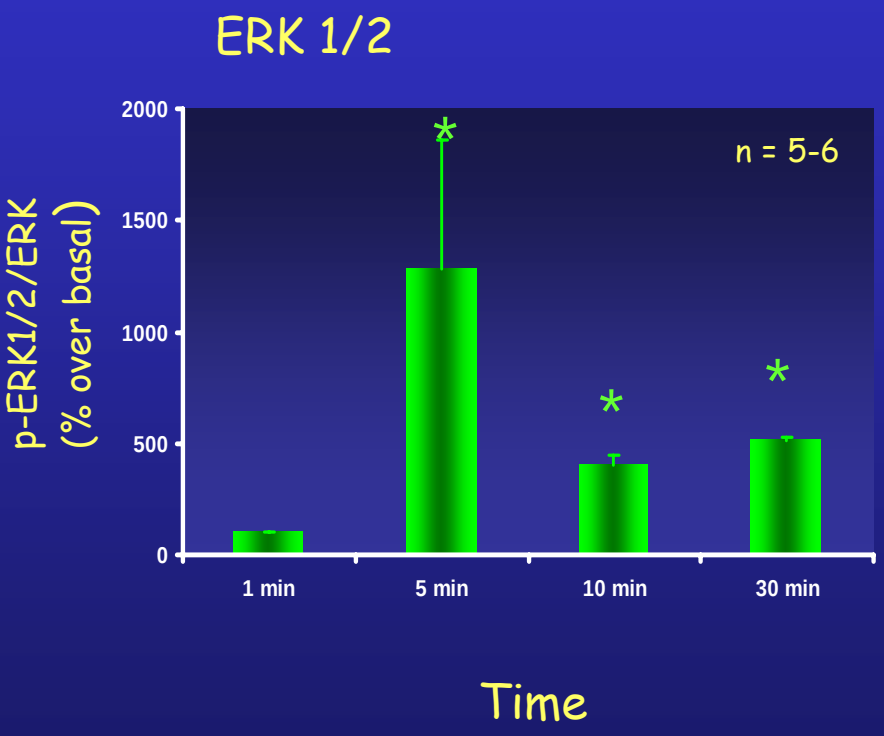


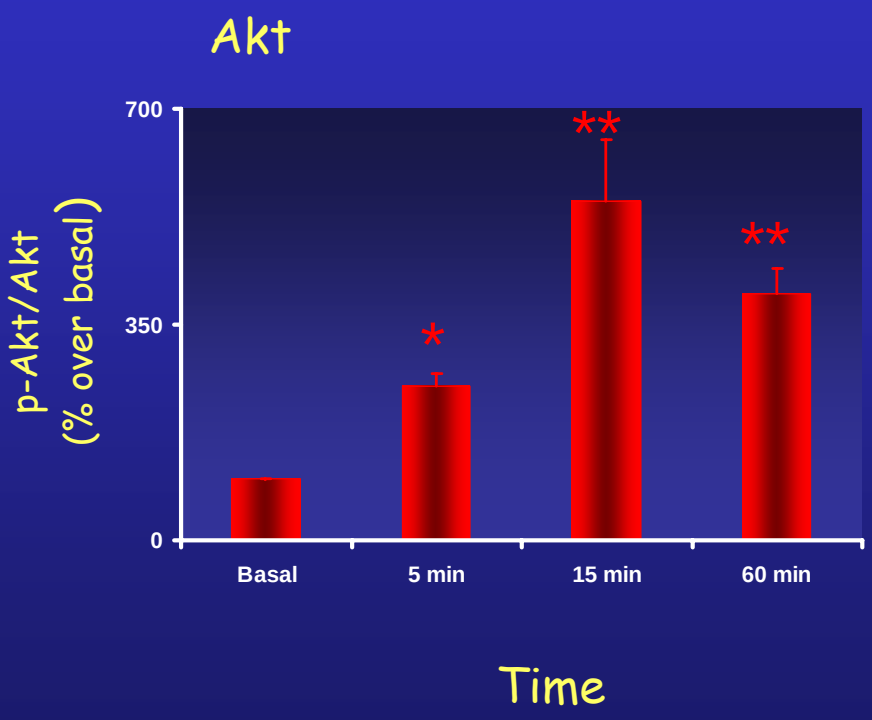
IP IRS-2
PI3-kinase



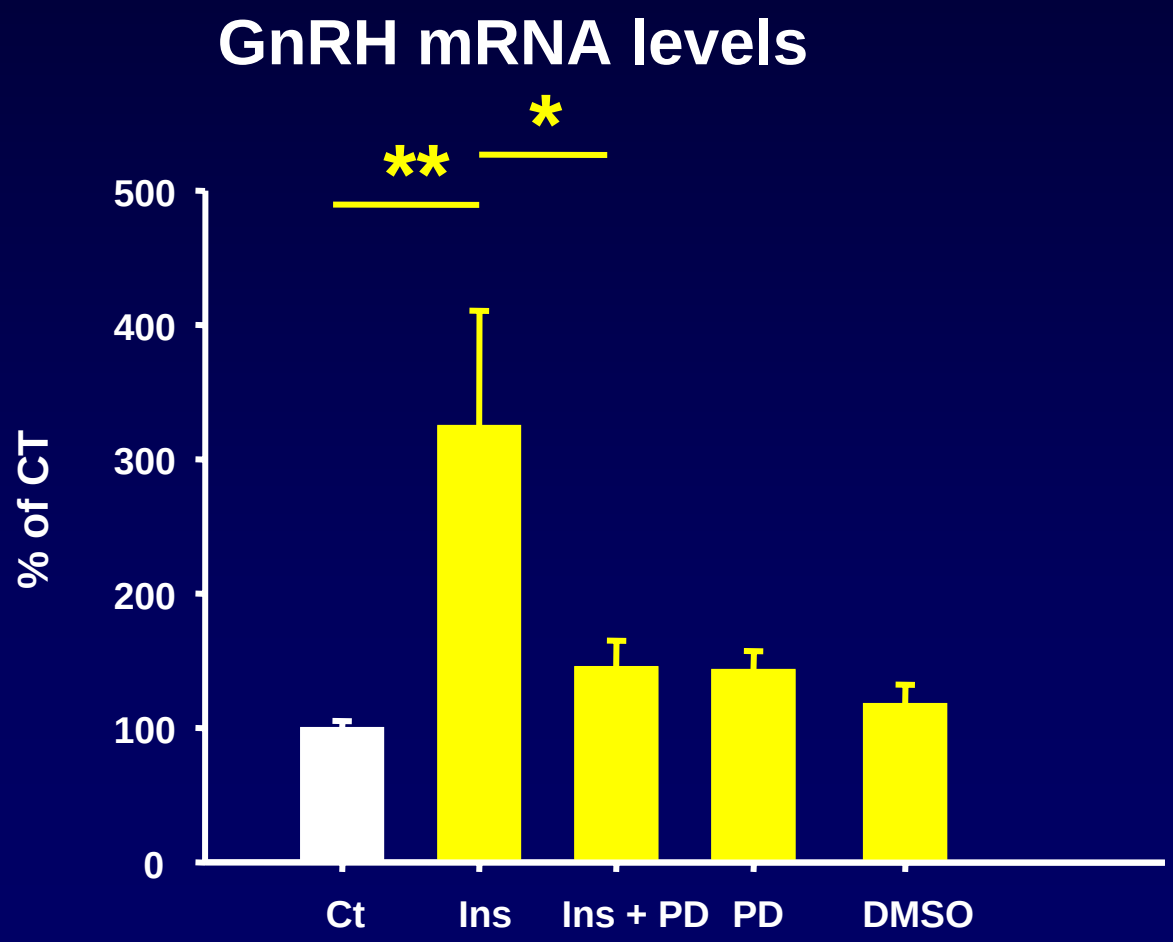
Time (min)

ERK1/2 (Phospho ERK) and Akt (Phospho-Akt) activation in GnV-3 cells

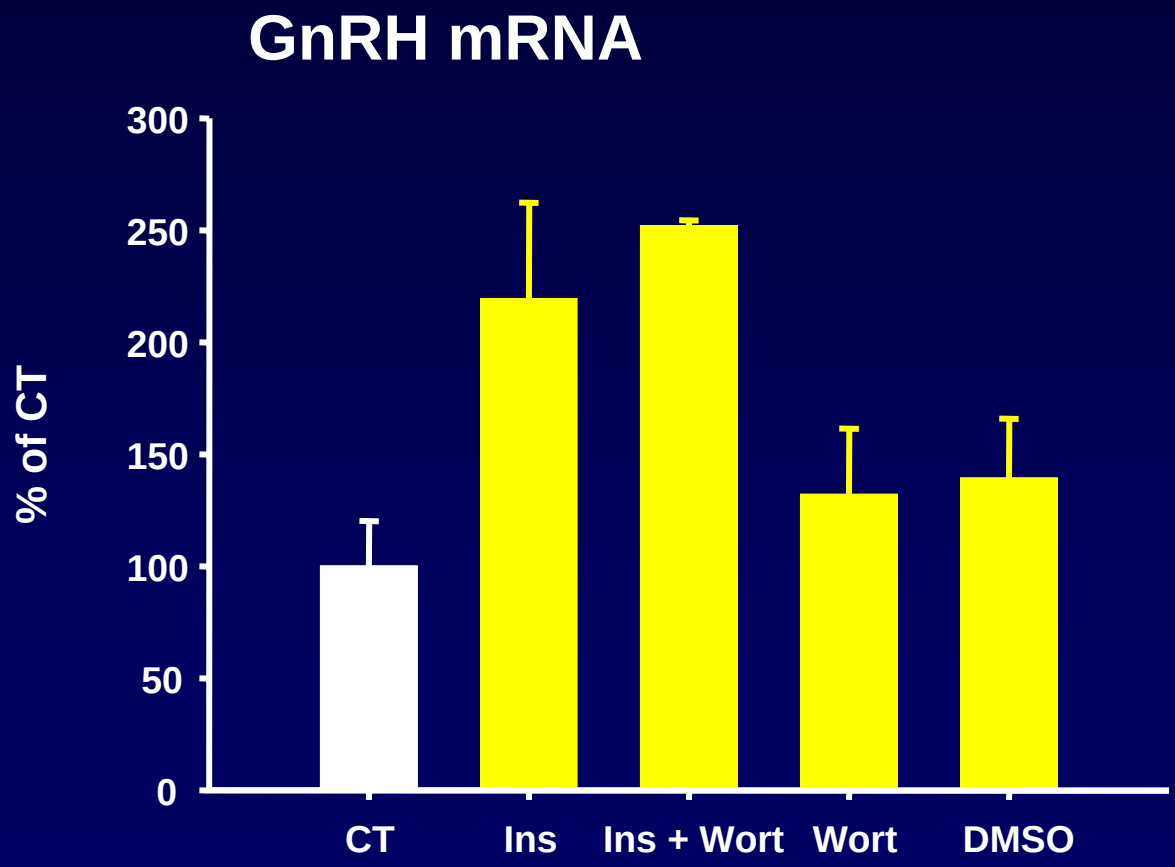




The insulin effect on GnRH gene expression is dependent upon Erk1/2 activation in primary hypothalamic neurons



The insulin effect on GnRH gene expression is independent of PI3-kinase activation in primary hypothalamic neurons



Treatment options

- **Oral contraception: retablish menstrual cycles, decrease hyperandrogenism**
- **Association with an anti-androgen**
- **Insulin sensitizers: metformin, thiazolidinediones**

Usually good clinical response to clomiphene citrate when seeking fertility

Division of Endocrinology Lausanne

Micheline Glauser
Marie-Jeanne Voirol
Marco Giacomini
Einar Castillo
Roberto Salvi
Rolf Gaillard

Department of Medicine and Botnar Center of Clinical Investigation

Peter Vollenweider
Pascal Nicod

Institute of Pharmacology and Toxicology, Lausanne

Bernard Thorens

University of Toulouse

Rémy Burcelin