



**DALHOUSIE  
UNIVERSITY**

*Inspiring Minds*



# The Effect of Opioids on Hypothalamic Pituitary Function

***S A Imran MBBS, FRCP (Edin), FRCPC  
Dalhousie University, Halifax, NS***



# OT and HP Dysfunction – The Historical Perspective

In Xanadu did Kubla Khan  
A stately pleasure-dome decree:  
Where Alph, the sacred river, ran  
Through Caverns measureless to man  
Down to a sunless sea

S. T. Coleridge (1772-1834)



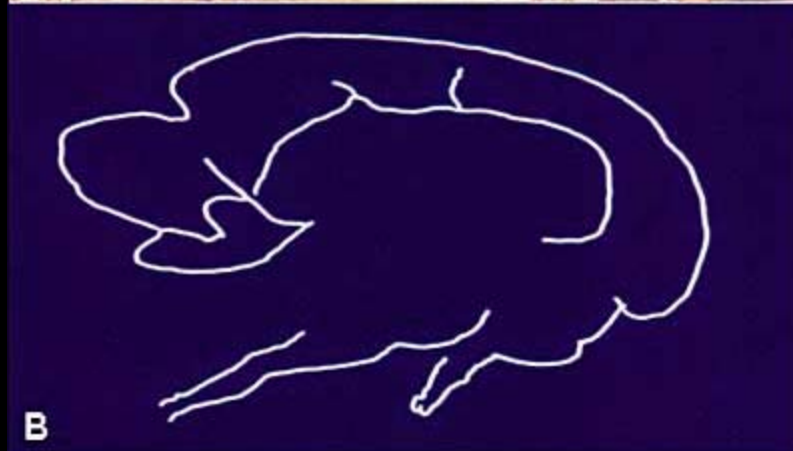
# Objectives

- Pathophysiological basis for the effect of opioid therapy (OT) on hypothalamic pituitary (HP) function
- Clinical manifestations of HP dysfunction
- Review of the current literature
- Unanswered questions
- Future direction

# Michelangelo's Creation of Adam

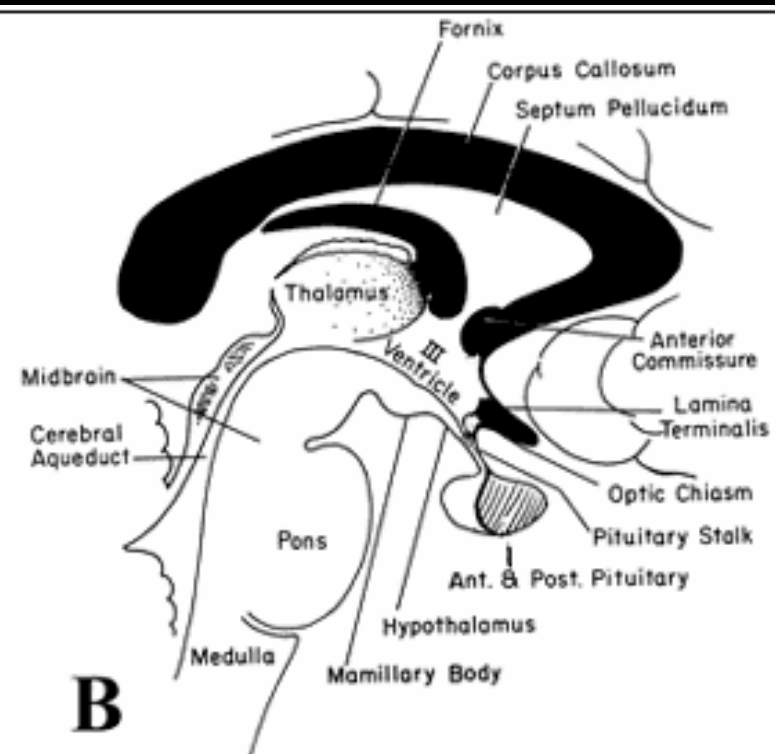
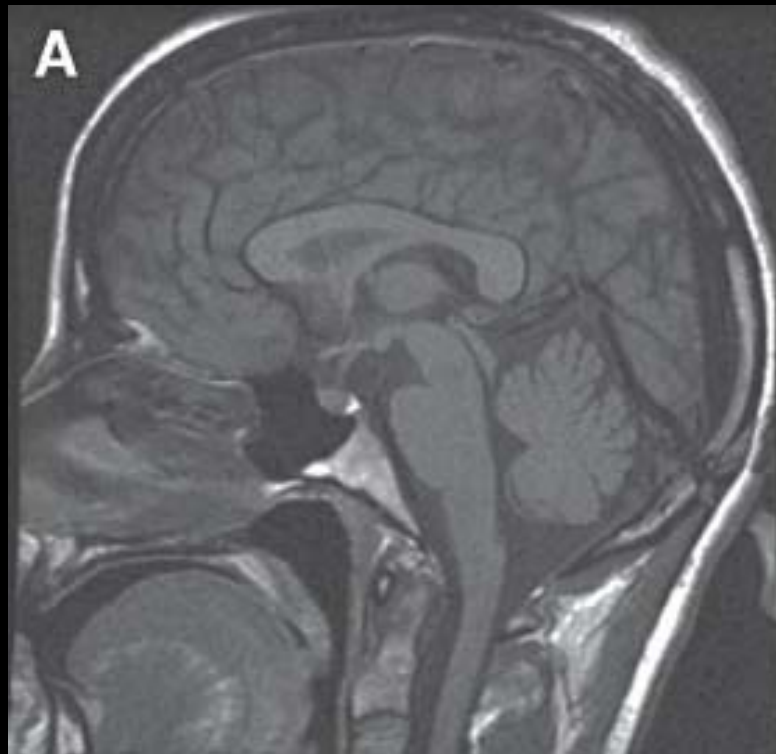


A

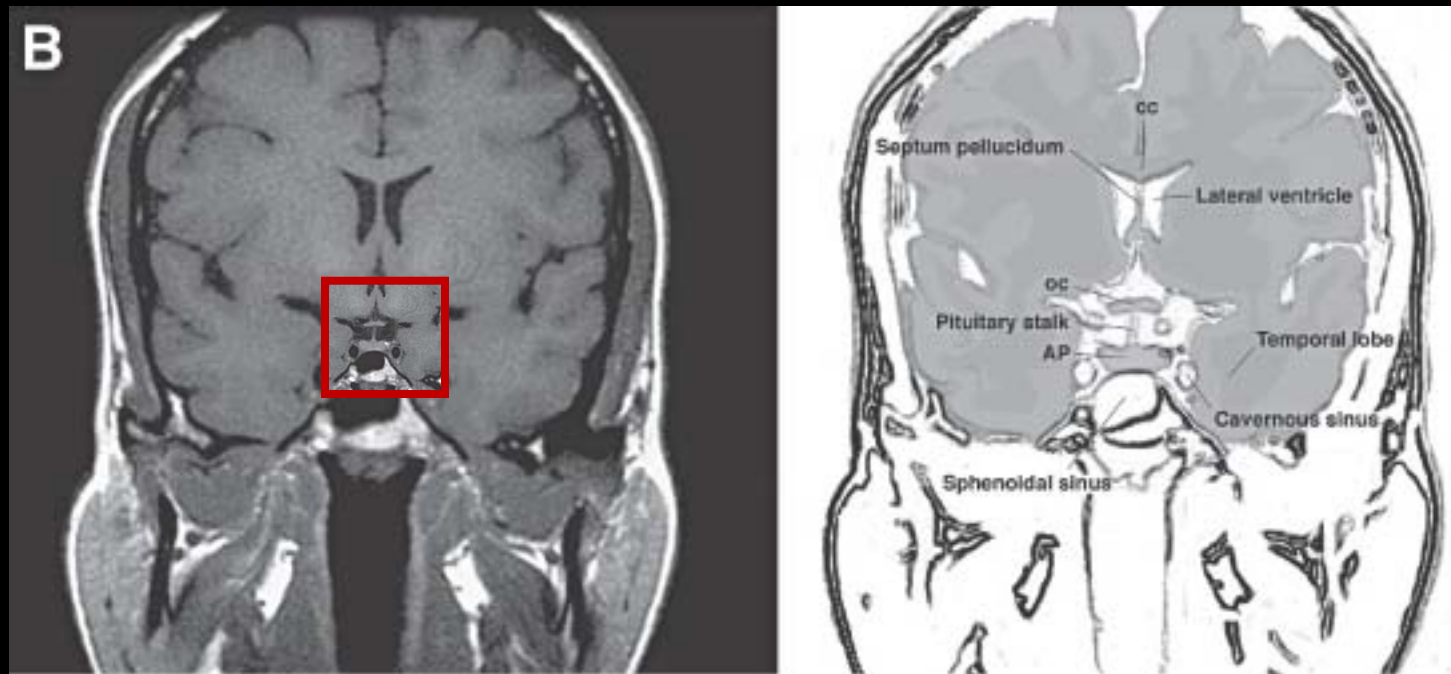


B

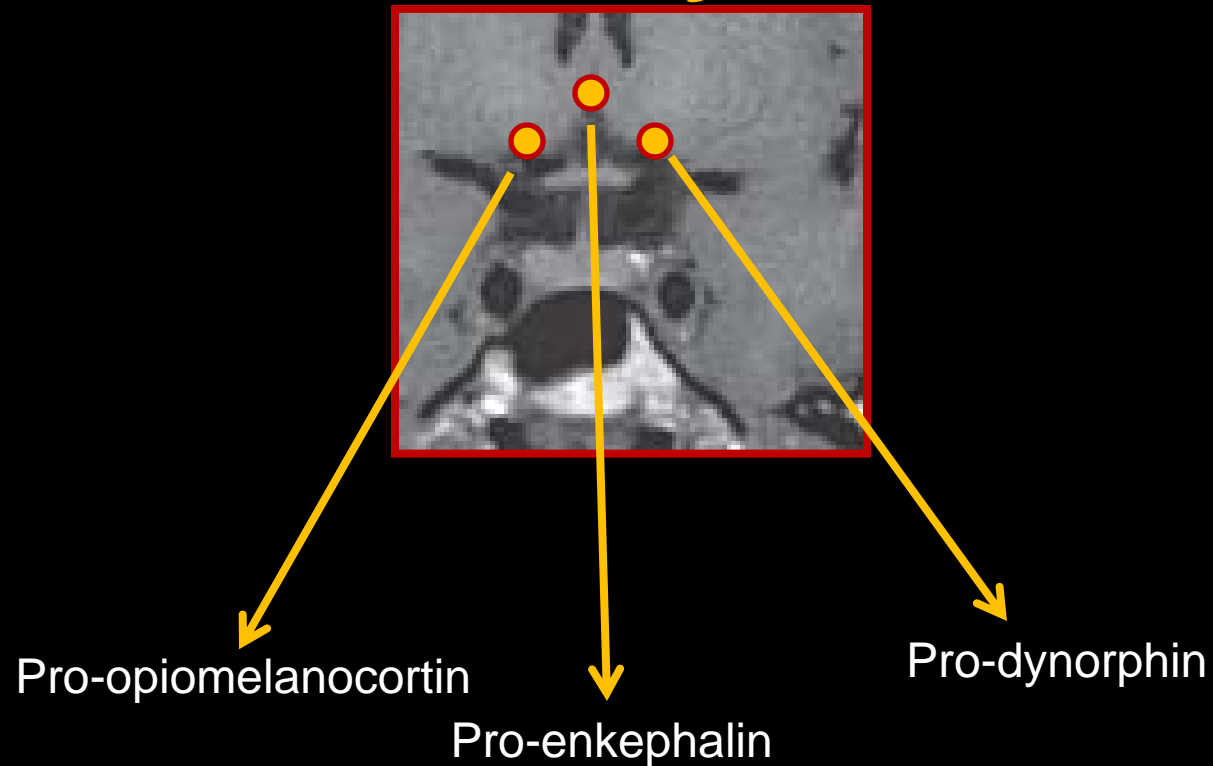
# Endogenous Opioid system and pituitary function



# Endogenous Opioid system and pituitary function



# Opioid System in Hypothalamic Pituitary Axis



# Opioid System in Hypothalamic Pituitary Axis



## Pro-opiomelanocortin

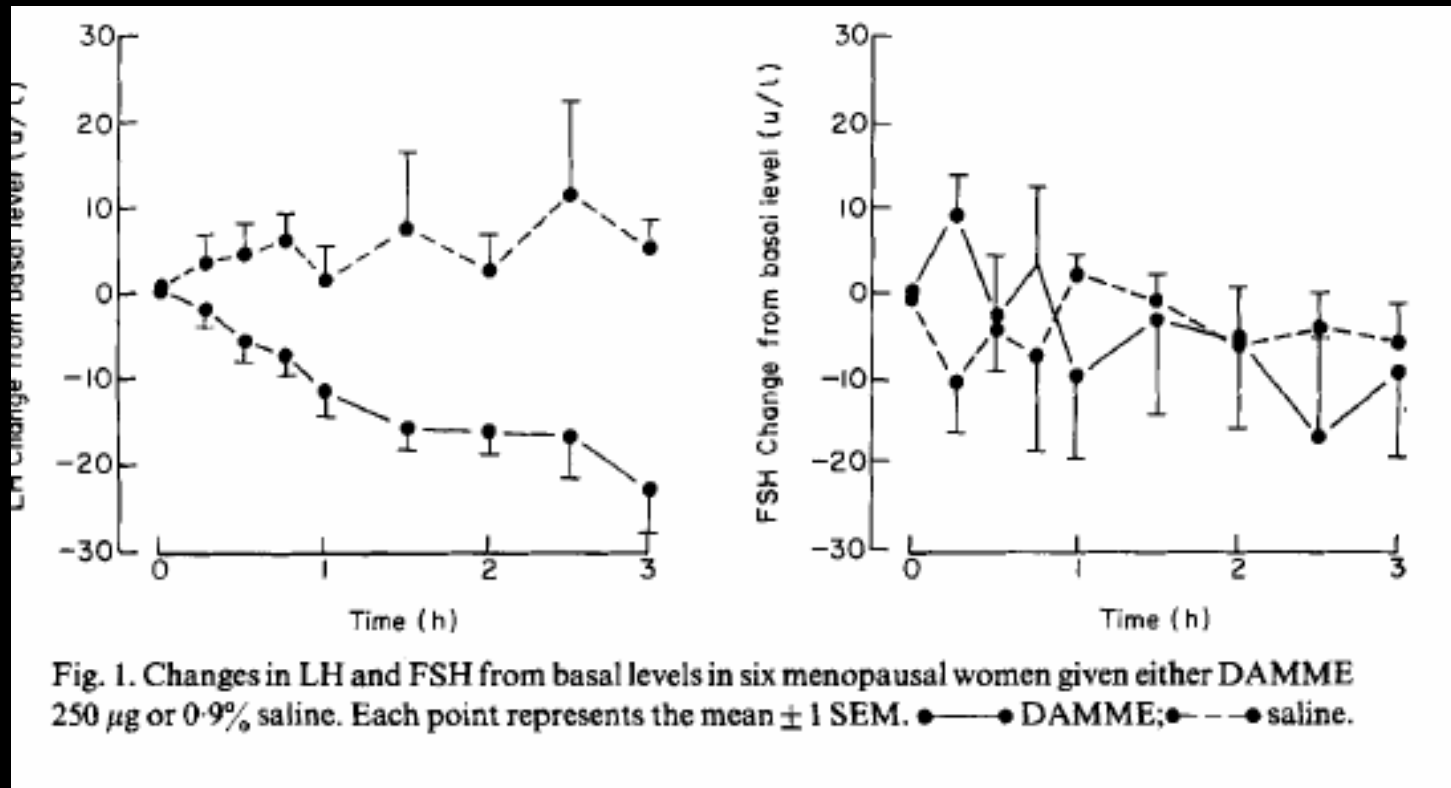
Precursor of  
-ACTH  
-MSH

## Pro-enkephalin

## Pro-dynorphin

Regulation of pituitary function and pituitary feedback

# Met-enkephalin suppresses LH secretion



# Met-enkephalin suppresses LH pulsatility

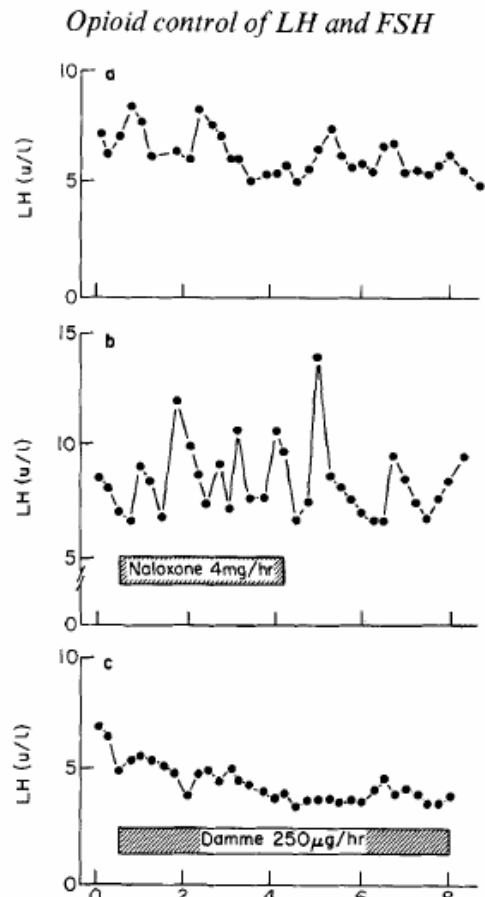


Fig. 4. Fluctuations in LH in a normal male subject infused with 0.9% saline for 8 h (a). On a separate occasion he was also infused with naloxone 4 mg/h for 4 h followed by 0.9% saline for 4 h (b), and with DAMME 250 µg/h for 8 h (c).

Normal pulsatile pattern

Loss of pulsatility

# KISS-1 is a modulator of LH pulsatility

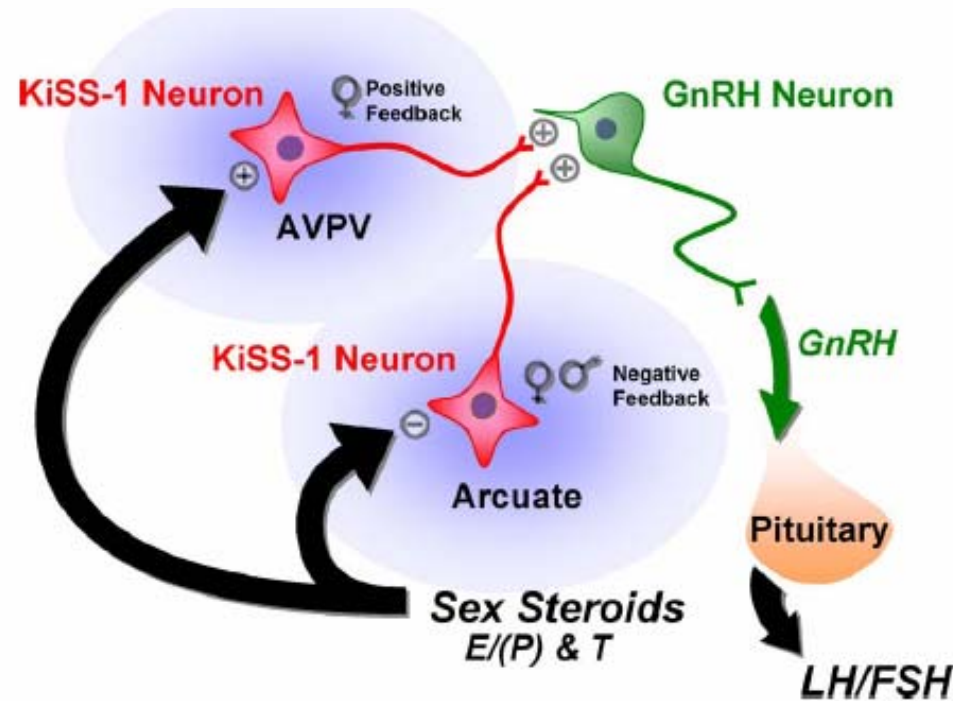
Kisspeptin-GPR54 signaling in the neuroendocrine reproductive axis

M.L. Gottsch<sup>a</sup>, D.K. Clifton<sup>b</sup>, R.A. Steiner<sup>a,b,c,\*</sup>

<sup>a</sup> Department of Physiology & Biophysics, University of Washington, Seattle, WA 98195-7290, USA

<sup>b</sup> Department of Obstetrics & Gynecology, University of Washington, Seattle, WA 98195-7290, USA

<sup>c</sup> Department of Biology, University of Washington, Seattle, WA 98195-7290, USA



Gottsch et al et al, 2006



Molecular and Cellular Endocrinology 281 (2008) 64–72



[www.elsevier.com/locate/mce](http://www.elsevier.com/locate/mce)

## *KiSS-1* mRNA in adipose tissue is regulated by sex hormones and food intake

R.E. Brown<sup>a,b</sup>, S.A. Imran<sup>a,c</sup>, E. Ur<sup>a,c</sup>, M. Wilkinson<sup>a,b,c,\*</sup>

<sup>a</sup> *Department of Obstetrics and Gynaecology, IWK Health Centre, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada B3K 6R8*

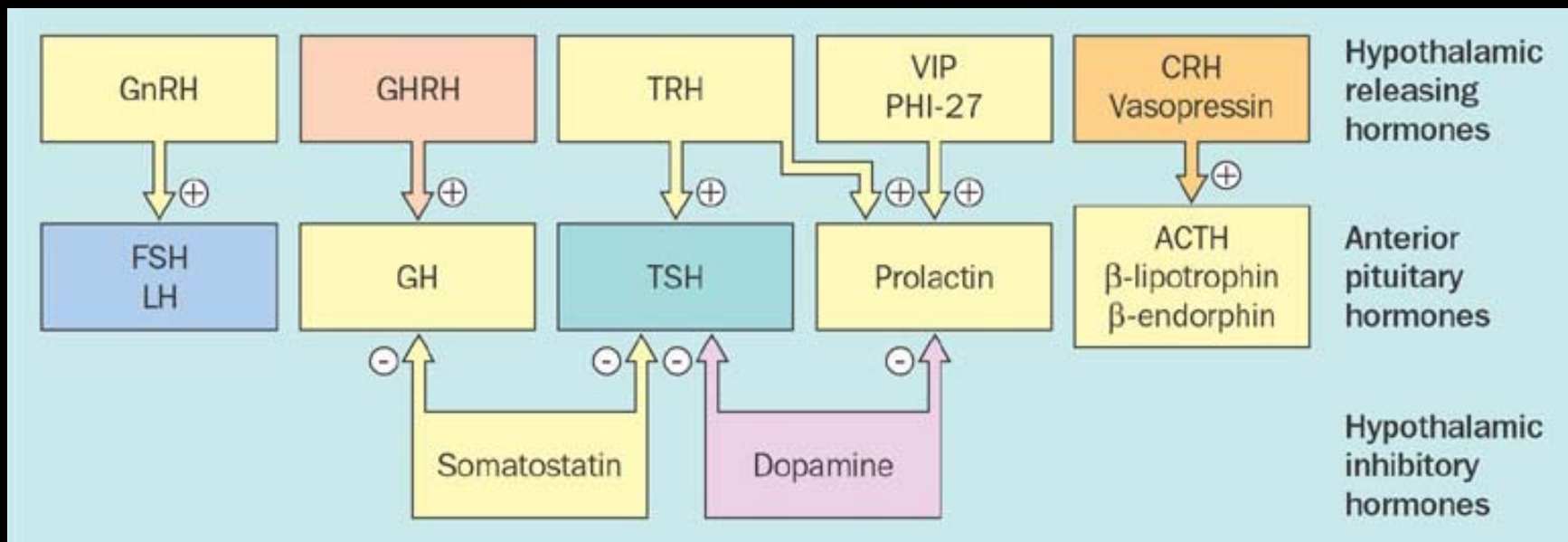
<sup>b</sup> *Department of Physiology and Biophysics, Dalhousie University, Halifax, Nova Scotia, Canada B3H 1X5*

<sup>c</sup> *Division of Endocrinology and Metabolism, VG Hospital, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada B3H 2Y9*

Received 14 September 2007; received in revised form 19 October 2007; accepted 26 October 2007

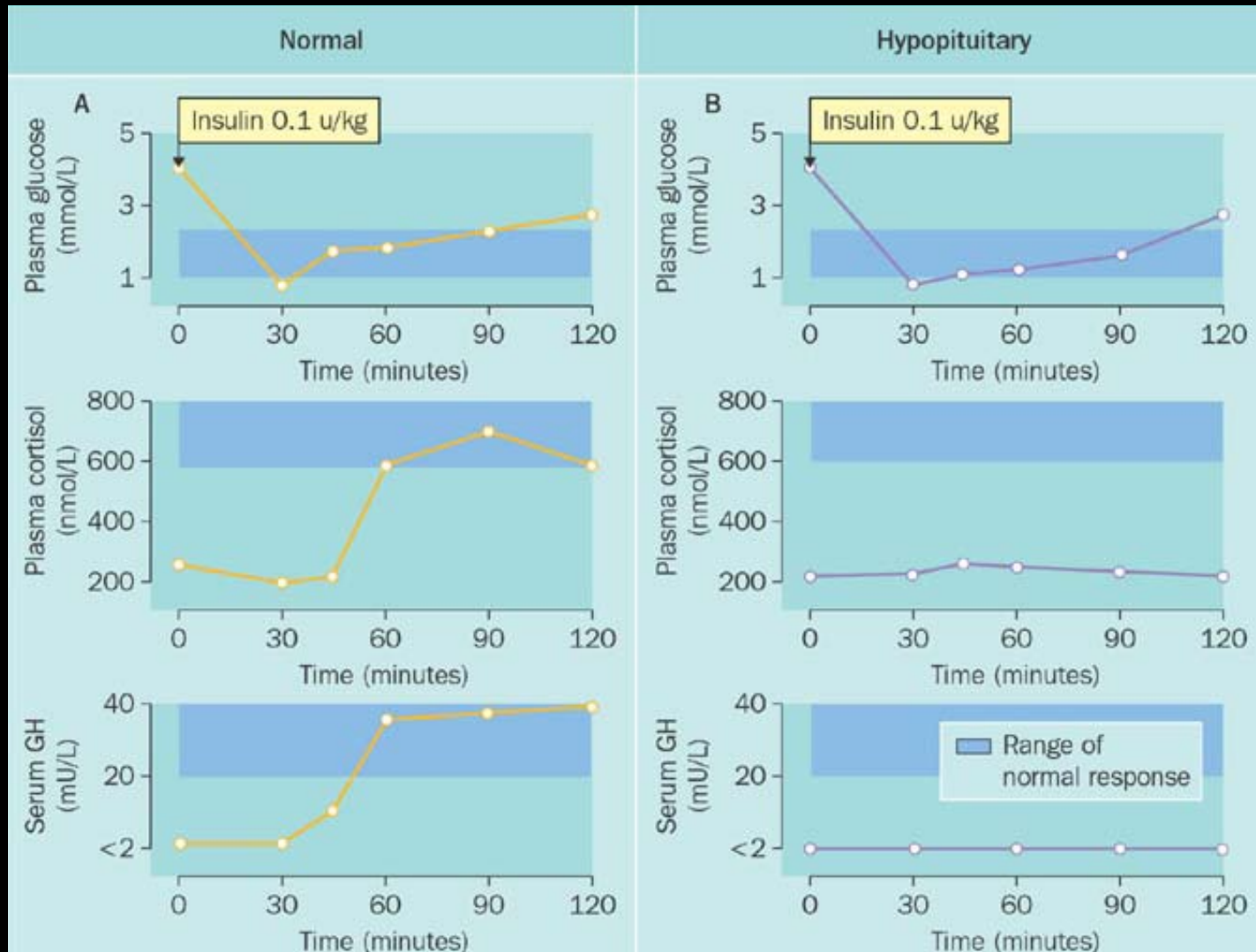
**Brown R, Imran SA et al, 2008**

# Pituitary Hormones



**DIAGNOSIS OF SUBTLE PITUITARY  
HORMONE DEFECTS GENERALLY  
REQUIRES SPECIAL TESTS AS IT MAY  
NOT BE CLINICALLY OBVIOUS!**

# Diagnosing hypocortisolism and GHD



# Consequences of pituitary dysfunction

## **HYPOCORTISOLISM**

- Hypotension
- Hypoglycemia
- Fatigue
- GI Upset
- Shock
- Death



Comprehensive Clinical Endocrinology 3e: edited by Besser & Thorner  
Elsevier Science Ltd

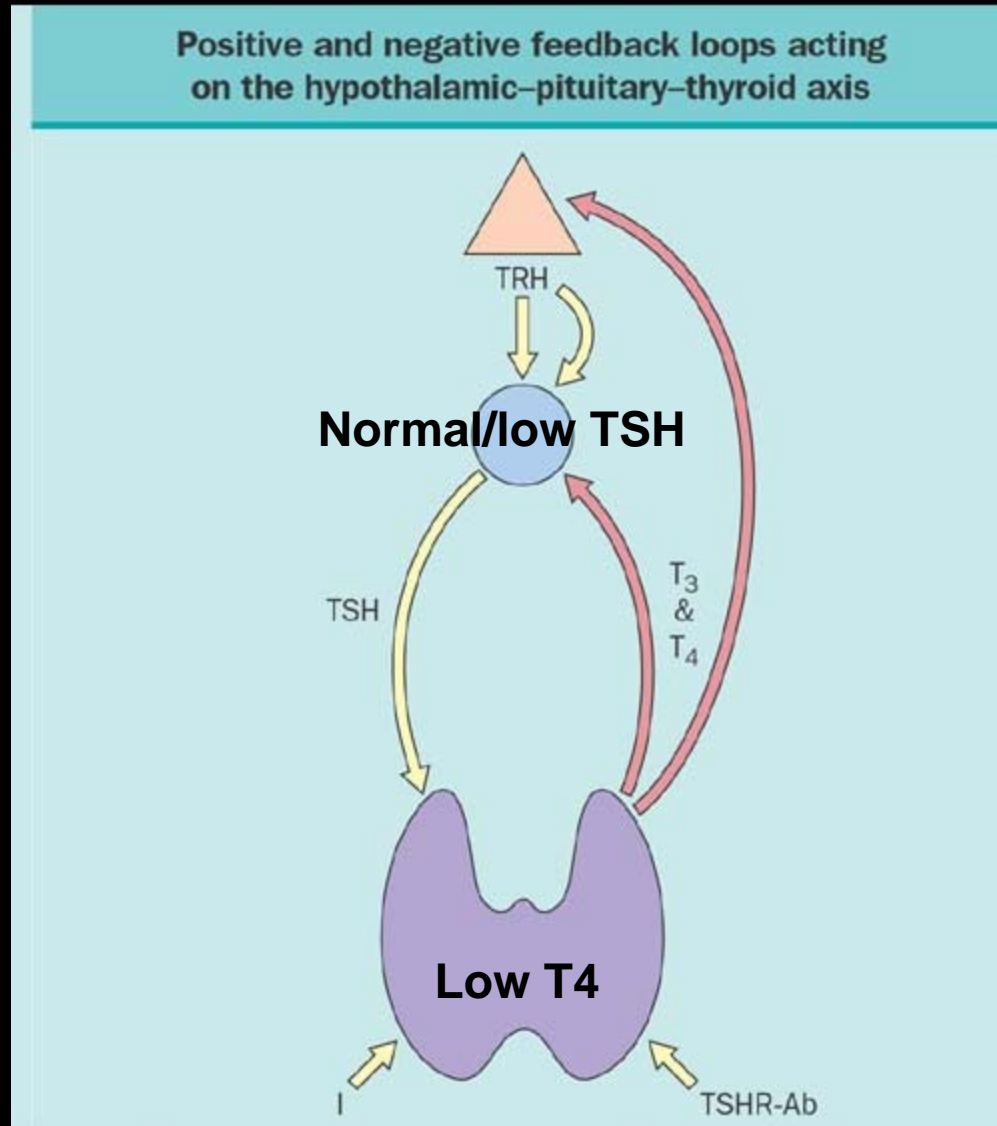
# Consequences of pituitary dysfunction

## **GROWTH HORMONE DEFICIENCY**

- Poor quality of life
- Fatigue
- Poor exercise tolerance
- Obesity
- Insulin resistance
- Poor cardiac function



# Diagnosing Hypothyroidism



# Consequences of pituitary dysfunction

## **HYPOTHYROIDISM**

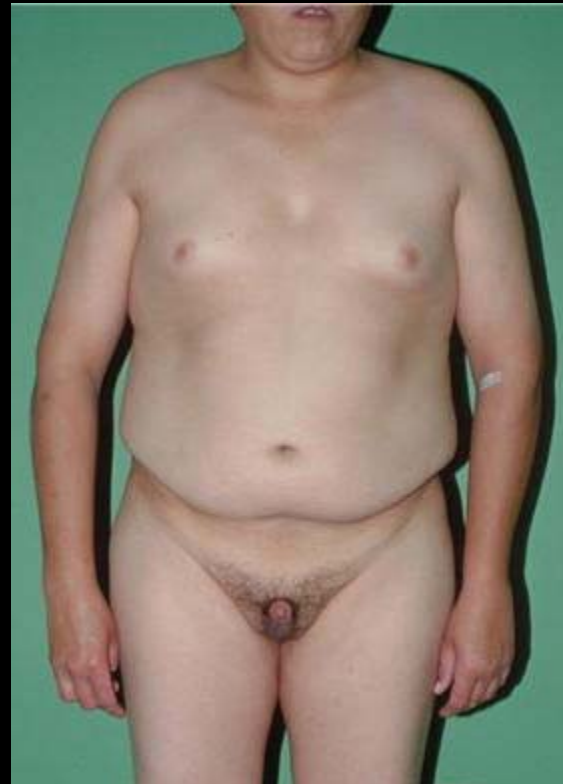
- Weight gain
- Cold intolerance
- Fatigue
- Dyslipidemia
- Coma



# Consequences of pituitary dysfunction

## **HYPOGONADISM**

- Loss of libido
- Infertility
- Irregular menstruation
- Impotence
- Osteoporosis
- Depression



# Consequences of pituitary dysfunction

## **HYPERPROLACTINEMIA**

- Loss of libido
- Infertility
- Irregular menstruation
- Impotence
- Galactorrhea
- Gynecomastia
- Osteoporosis



# The Early Clinical Data on HPA Axis

Study	Study Population	Agent	Outcome
Dackis et al, 1982	Drug Addicts	Methadone	Methadone induces hypocortisolism
Facchinetti et al, 1985	Heroin Addicts	Heroin	Heroin induces hypocortisolism
Willenbring ML et al, 1989	Drug Addicts	Methadone	Methadone induces hypogonadism
Banki CM et al, 1987	Schizophrenics & Drug Addicts	Morphine	Morphine induces hypocortisolism

# The Early Clinical Data on HPG Axis

Study	Study Population	Agent	Outcome
Mendelson JH et al, 1975	Drug Addicts	Heroin & Methadone	Opioids induce hypogonadism
Rasheed A et al, 1995	Drug Addicts	Methadone	Methadone induces hypogonadism and hyperprolactinemia

# Effect of opioids in chronic pain

0021-972X/00/03.00/0  
The Journal of Clinical Endocrinology & Metabolism  
Copyright © 2000 by The Endocrine Society

Vol. 85, No. 6  
Printed in U.S.A.

## Endocrine Consequences of Long-Term Intrathecal Administration of Opioids

ROGER ABS, JOHAN VERHELST, JAN MAEYAERT, JEAN-PIERRE VAN BUYTEN,  
FRANK OPSOMER, HUGO ADRIAENSEN, JAN VERLOOY,  
TONY VAN HAVENBERGH, MIKE SMET, AND KRISTIEN VAN ACKER

*Department of Endocrinology, University Hospital Antwerp (R.A., K.V.A.); Middelheim Hospital Antwerp (J.V., M.S.); Department of Anesthesiology, Heilig Hart Hospital Eeklo (J.M.); Maria Middelaers Hospital St. Niklaas (J.-P.V.B.); Middelheim Hospital Antwerp (F.O.); University Hospital Antwerp (H.A.); and Department of Neurosurgery, University Hospital Antwerp (J.V., T.V.H.), B-2650 Edegem, Belgium*

Abs R et al, 2000

# Effect of opioids in chronic pain

0021-972X/00/03.00/0  
The Journal of Clinical Endocrinology & Metabolism  
Copyright © 2000 by The Endocrine Society

Vol. 85, No. 6  
Printed in U.S.A.

## Endocrine Consequences of Long-Term Intrathecal

Retrospective data on 73 patients undergoing intrathecal  
Opioid treatment for chronic pain.

TONY VAN HAVENBERGH, MIKE SMET, AND KRISTIEN VAN ACKER

*Department of Endocrinology, University Hospital Antwerp (R.A., K.V.A.); Middelheim Hospital Antwerp (J.V., M.S.); Department of Anesthesiology, Heilig Hart Hospital Eeklo (J.M.); Maria Middelaers Hospital St. Niklaas (J.-P.V.B.); Middelheim Hospital Antwerp (F.O.); University Hospital Antwerp (H.A.); and Department of Neurosurgery, University Hospital Antwerp (J.V., T.V.H.), B-2650 Edegem, Belgium*

Abs R et al, 2000

# Opioids induce hypogonadism

TABLE 2. Pituitary-gonadal axis in patients receiving opioids long term intrathecally

	Normal Values	Opioid group	Control group	P
<b>Males</b>		<b>n = 29</b>	<b>n = 11</b>	
Testosterone (nmol/L)	9–26	6.9 ± 5.2 (1.4–25.0)	15.4 ± 4.4 (8.3–20.0)	<0.001
Free androgen index	20–80	23.1 ± 20.7 (5–108)	53.3 ± 19.8 (19–83)	<0.001
SHBG (nmol/L)	10–70	36.1 ± 20.9 (12–85)	31.2 ± 8.6 (24–49)	NS
LH (U/L)	2–9	1.7 ± 1.4 (0.1–7.2)	4.3 ± 2.1 (1.3–7.0)	<0.001
FSH (U/L)	2–7	4.7 ± 2.6 (0.3–10.6)	5.7 ± 4.4 (2.4–18.0)	NS
<b>Females</b>		<b>n = 44</b>	<b>n = 9</b>	
<b>Premenopausal females</b>		<b>n = 21</b>	<b>n = 3</b>	
LH (U/L)	2–8	2.7 ± 2.6 (0.1–9.0)	12.4 ± 14.2 (3.8–28.8)	NS
FSH (U/L)	2–8	6.4 ± 5.6 (0.1–26.0)	9.4 ± 9.2 (3.0–20.1)	NS
Estradiol (pmol/L)	110–800	127.0 ± 124.0 (18–437)	383.3 ± 404.6 (84–844)	NS
Progesterone (nmol/L)	3–60	1.6 ± 2.6 (0.3–11.8)	8.6 ± 13.7 (0.3–24.4)	NS
<b>Postmenopausal females</b>		<b>n = 18</b>	<b>n = 6</b>	
LH (U/L)	>13	3.3 ± 3.3 (0.1–9.4)	27.7 ± 14.1 (13.5–46.2)	<0.001
FSH (U/L)	>38	14.6 ± 17.6 (0.5–66.9)	39.8 ± 22.7 (15.9–66.7)	0.012
Estradiol (pmol/L)	<110	100.2 ± 122.6 (18–125)	55.8 ± 33.6 (29–113)	NS
Progesterone (nmol/L)	<3	1.0 ± 0.6 (0.3–1.2)	1.0 ± 0.6 (0.3–1.9)	NS

Values are the mean ± SD; the range is in parentheses.

# Opioids induce hypocortisolism

TABLE 3. Pituitary-adrenal axis in patients receiving opioids long term intrathecally

	Normal values	Opioid group		Control group		<i>P</i>
		Mean ± SD	n	Mean ± SD	n	
24-h urinary free cortisol (μg/day)	20–90	36.0 ± 21.0 (7.0–112.0)	71	50.7 ± 18.4 (20.0–80.0)	20	0.003
24-h urinary aldosterone (μg/day)	3–20	8.3 ± 7.7 (0.2–20.6)	72	7.3 ± 5.3 (0.6–17.6)	19	NS
Basal ACTH (ng/L)	10–52	20.1 ± 14.3 (4–83)	72	16.9 ± 8.9 (4–37)	20	NS
Peak ACTH after ITT		193.8 ± 157.3 (18–854)	62	202.1 ± 105.0 (18–401)	18	NS
ACTH AUC after ITT		365.9 ± 316.4 (61–2008.5)	62	357.6 ± 186.7 (54.5–738.5)	18	NS
Basal cortisol (μg/L)	50–250	135.3 ± 53.8 (20–286)	71	160.1 ± 43.9 (81–250)	20	NS
Peak cortisol after ITT		245.4 ± 62.1 (102–417)	61	300.8 ± 73.6 (200–451)	18	0.002
Cortisol AUC after ITT		1146.8 ± 323.3 (425.5–2042.5)	61	1357.4 ± 309.9 (800–1953.5)	18	0.02
CBG (μg/L)	32–50	45.2 ± 14.0 (27–111)	72	47.9 ± 11.4 (28–76)	19	NS
DHAS (μg/L)	<3000	764.2 ± 615.1 (31–2980)	72	562.9 ± 357.7 (103–1470)	19	NS
PRA (ng/Lrs)	0.3–1.1	2.1 ± 2.8 (0.0–5.9)	70	1.6 ± 1.5 (0.3–5.8)	19	NS

Abs R et al, 2000

# Opioids induce GH deficiency

TABLE 4. GH-IGF-I axis in patients receiving opioids long term intrathecally

	Opioid group		Control group		<i>P</i>
	Mean ± SD (range)	n	Mean ± SD (range)	n	
IGF-I ( $\mu\text{g/L}$ )	138.5 ± 64.1 (33–321)	72	162.0 ± 55.3 (70–270)	20	0.045
IGF-I SD score	-0.53 ± 1.45 (-5.28–2.89)	72	0.57 ± 1.00 (-1.49–2.66)	20	0.002
GH peak ( $\mu\text{g/L}$ ) after ITT	14.5 ± 12.7 (0.1–58.3)	62	20.9 ± 11.5 (3.3–46.7)	18	0.010
GH AUC ( $\mu\text{g/L}$ ) after ITT	47.0 ± 49.1 (0.8–266.0)	62	63.3 ± 42.0 (10.7–169.4)	18	0.048
GH peak ( $\mu\text{g/L}$ ) after arginine	6.4 ± 5.1 (0.5–14.7)	10			
GH AUC ( $\mu\text{g/L}$ ) after arginine	16.9 ± 12.5 (1.4–39.9)	10			
GH peak ( $\mu\text{g/L}$ ) after clonidine	2.6 ± 3.1 (0.1–13.7)	28			
GH AUC ( $\mu\text{g/L}$ ) after clonidine	7.7 ± 11.6 (0.8–59.4)	28			

Abs R et al, 2000

# Opioids induce hypothyroidism and elevated prolactin

TABLE 5. Pituitary-thyroid axis, PRL, and selected biochemical measures in patients receiving opioids long term intraspinally

	Normal values	Opioid group		Control group		<i>P</i>
		Mean ± SD (range)	n	Mean ± SD (range)	n	
fT <sub>4</sub> (pmol/L)	11.0–24.0	15.4 ± 2.6 (9.7–21.4)	72	15.9 ± 3.1 (11.3–24.5)	20	NS
fT <sub>3</sub> (pmol/L)	3.4–7.2	5.2 ± 0.7 (3.8–7.4)	70	4.6 ± 0.7 (3.8–6.8)	20	0.001
TSH (mU/L)	0.4–3.2	1.5 ± 0.9 (0.1–4.6)	72	1.2 ± 0.5 (0.4–2.6)	20	NS
TSH peak after TRH (mU/L)		8.5 ± 5.1 (0.4–36.0)	70	8.0 ± 4.2 (2.4–17.7)	20	NS
PRL (μg/L)	<20	6.8 ± 7.0 (1.0–52.6)	73	4.9 ± 2.6 (1.0–12.1)	20	NS

Abs R et al, 2000

# Unanswered Questions

- Do all patients on OT develop HP dysfunction or is it just a subset?
- What is the time course of development of HP dysfunction after starting OT?
- Is it reversible after stopping OT?
- Is there a risk of developing life-threatening HP complications?

# PITPAIN Study

- Multicentre
- Prospective
- Cohort design
- CNCP patients



# PITPAIN Study Investigators

- **Halifax, NS:** SA Imran and M Lynch
- **London, ON:** S van Uum, P Morley-Foster
- **Calgary, AB:** AJ Clark, B Corenblum

# PITPAIN Study

- **PRIMARY OBJECTIVE**

- To determine the effect of OT on the incidence and severity of HP dysfunction

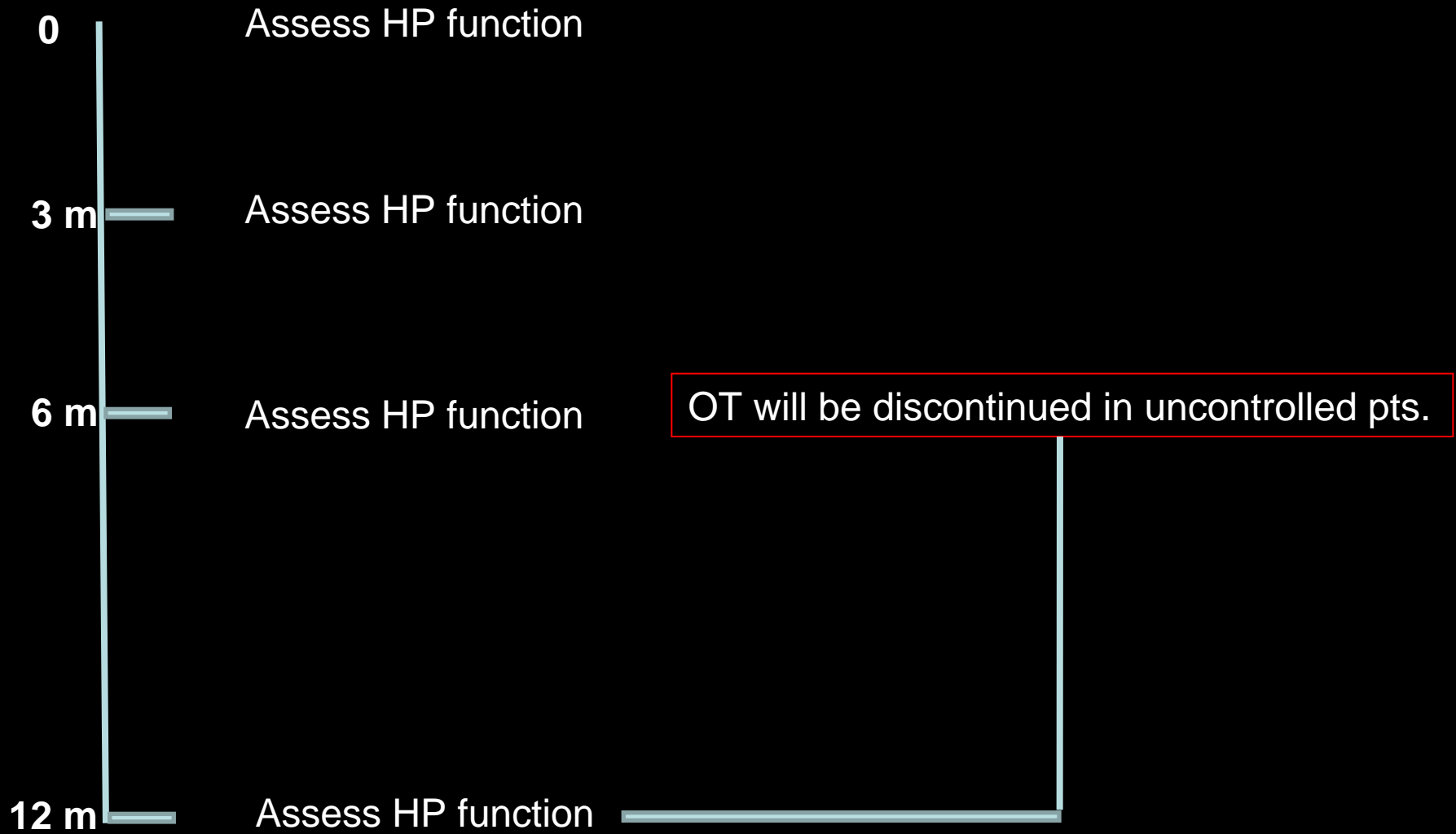
- **SECONDARY OBJECTIVES**

- To identify baseline prevalence of HP abnormalities in CNCP
- To assess the time course of HP abnormalities
- To identify the reversibility of HP abnormalities after stopping OT
- Dose-abnormalities relationship

# PITPAIN patient selection

- 330 patients between 19 and 65 yr
- CNCP > 3 months
- Moderate to severe pain (>4 on NRS-PI)
- Either not on OT or < 60 mg/24 h of Morphine equivalent
- Recruitment over 2 yrs

# PITPAIN study timeline



# Objectives

- Pathophysiological basis for the effect of opioid therapy (OT) on hypothalamic pituitary (HP) function
- Clinical manifestations of HP dysfunction
- Review of the current literature
- Unanswered questions
- Future direction

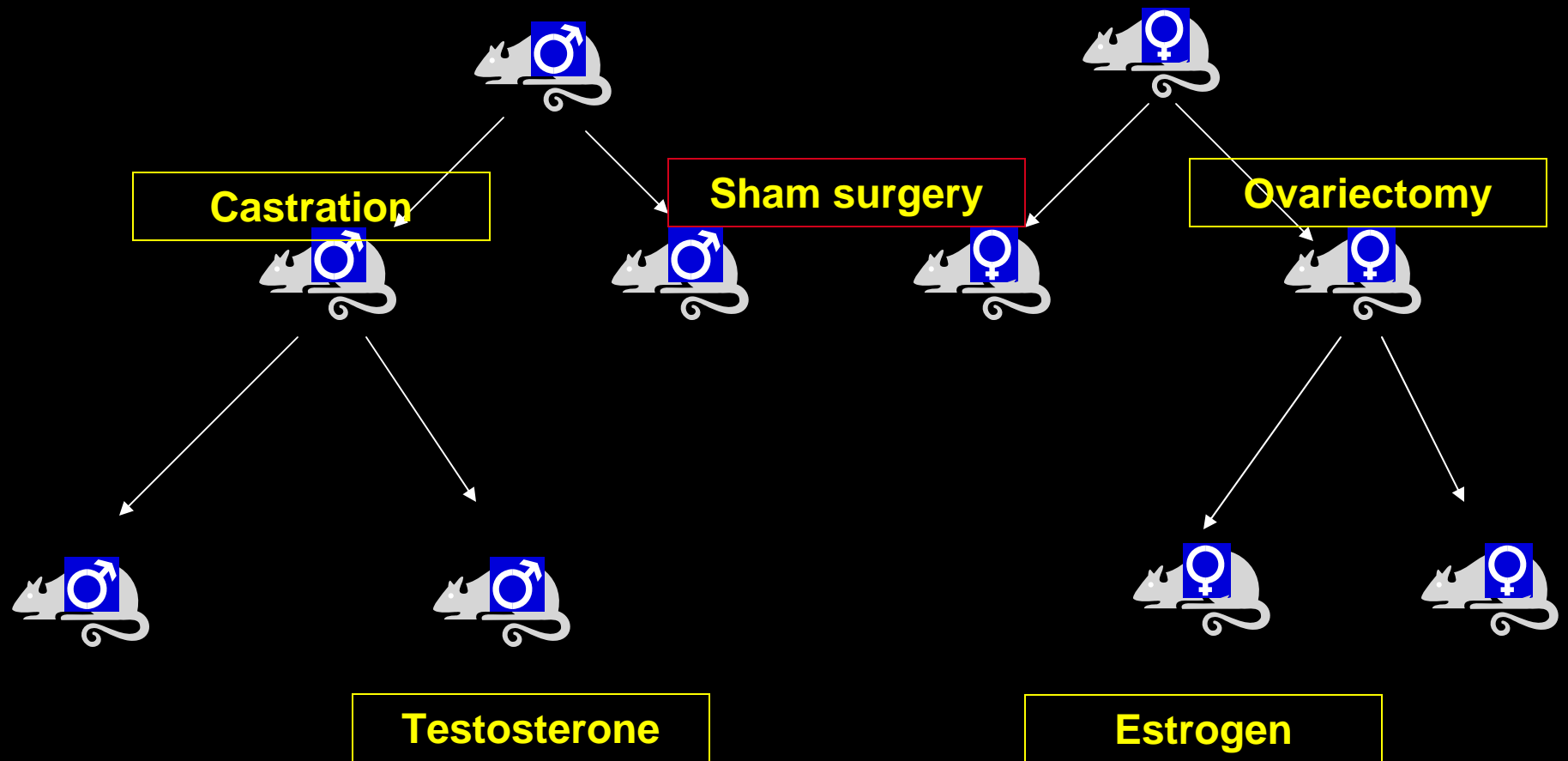
# **‘The Waterfall’ *Imran 2008***



## **Hypothesis**

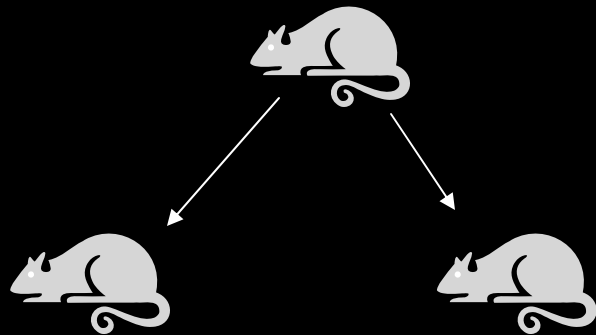
- **Kiss -1 is the link between puberty and adipose tissue regulation**
- **Hypothalamic and adipose Kiss-1 is modulated through metabolic and reproductive hormone signals**

# Experiment 1: Effect of sex hormones



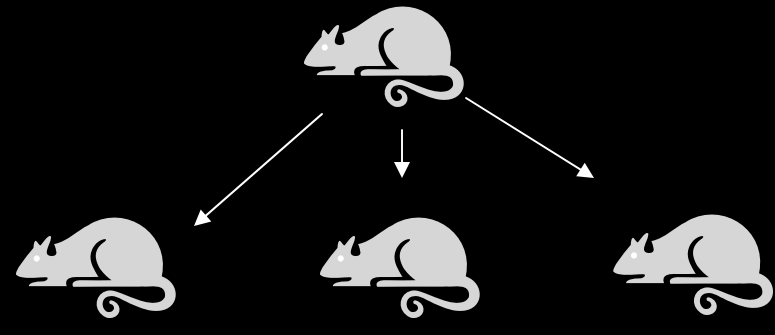
## Experiment 2: Effect of nutrition status

Both wild type and Zucker fatty rats



Chow fed

High fat diet

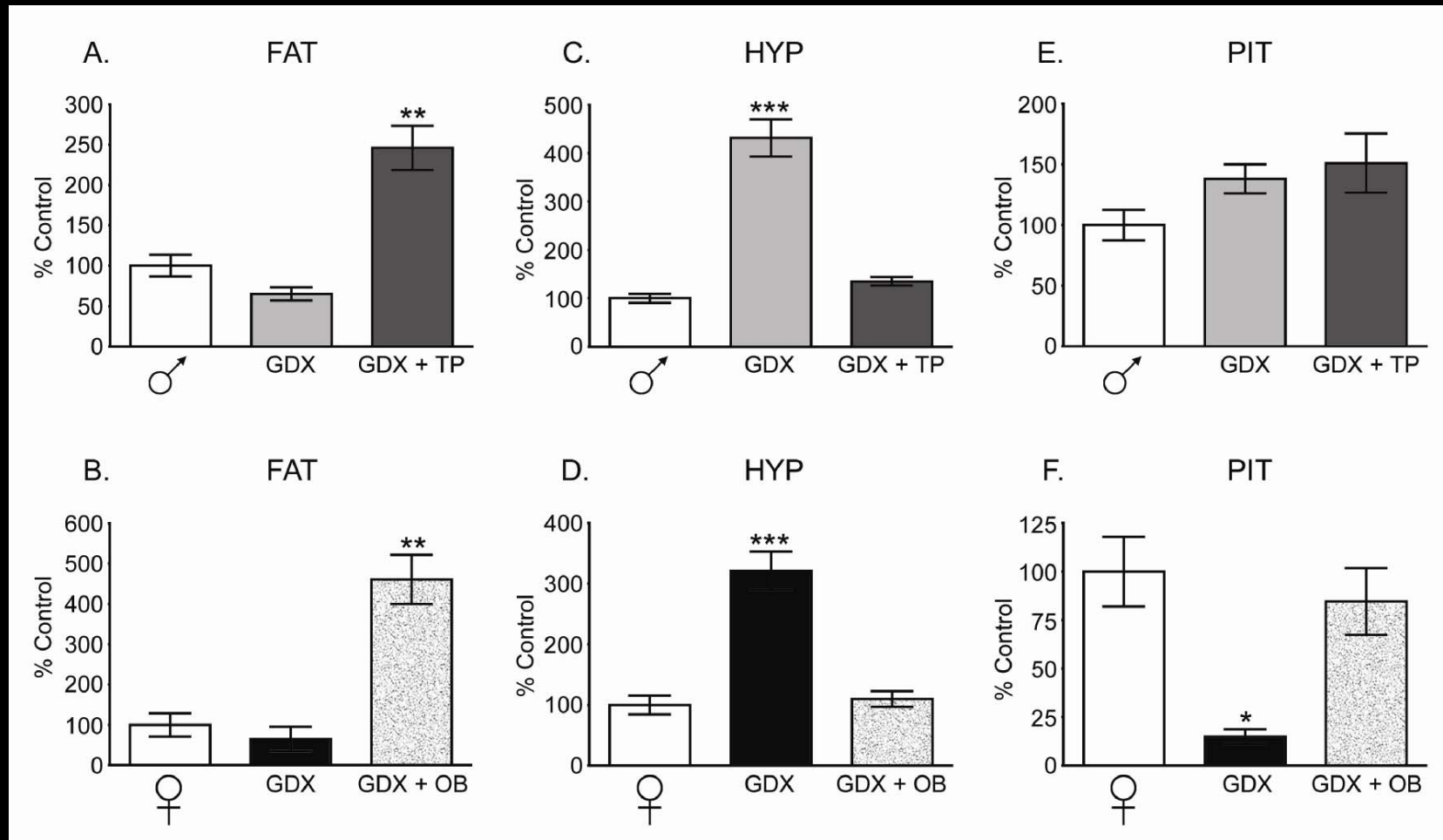


Fed

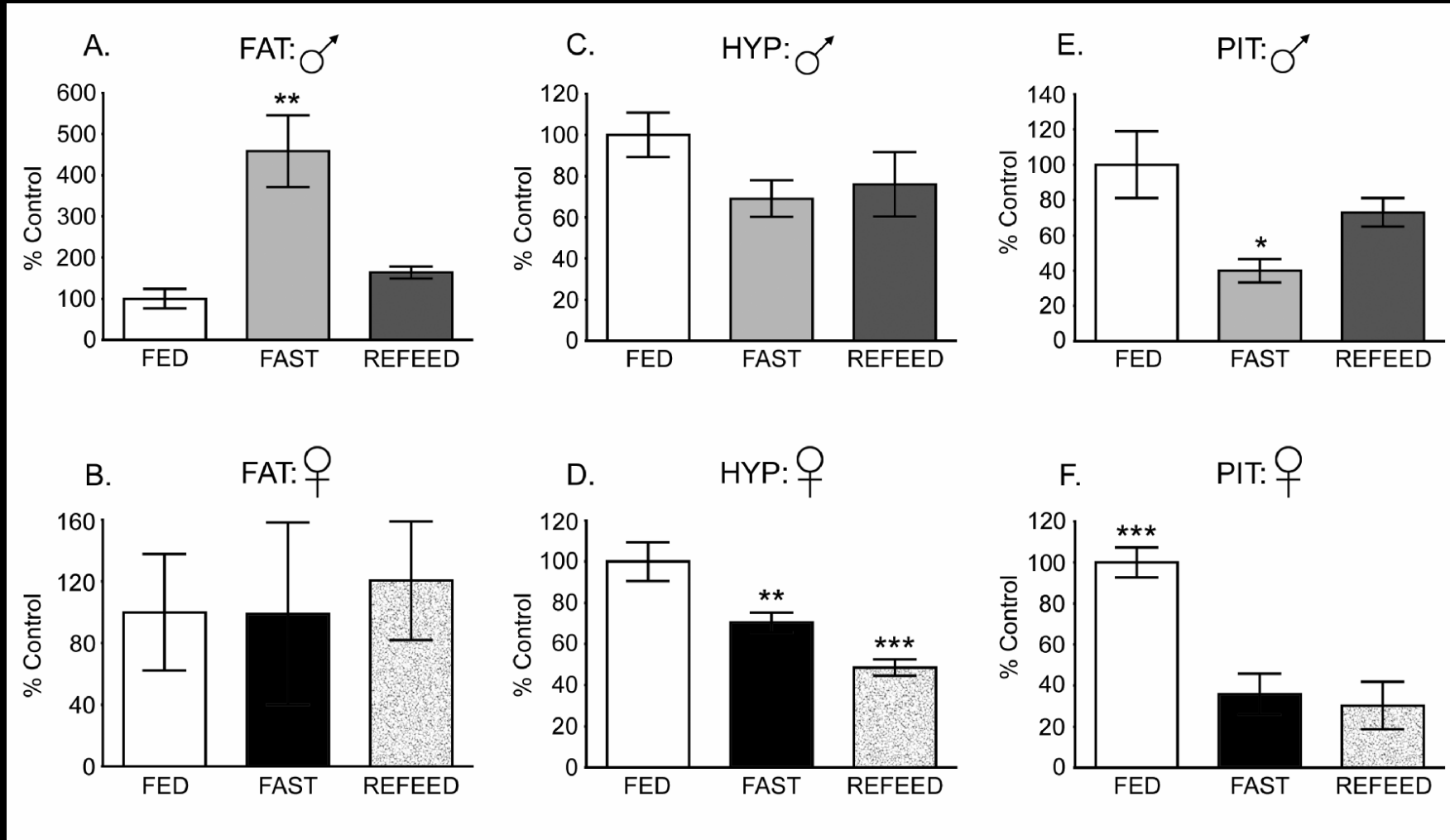
Fast 24 h

Fast 18h refed

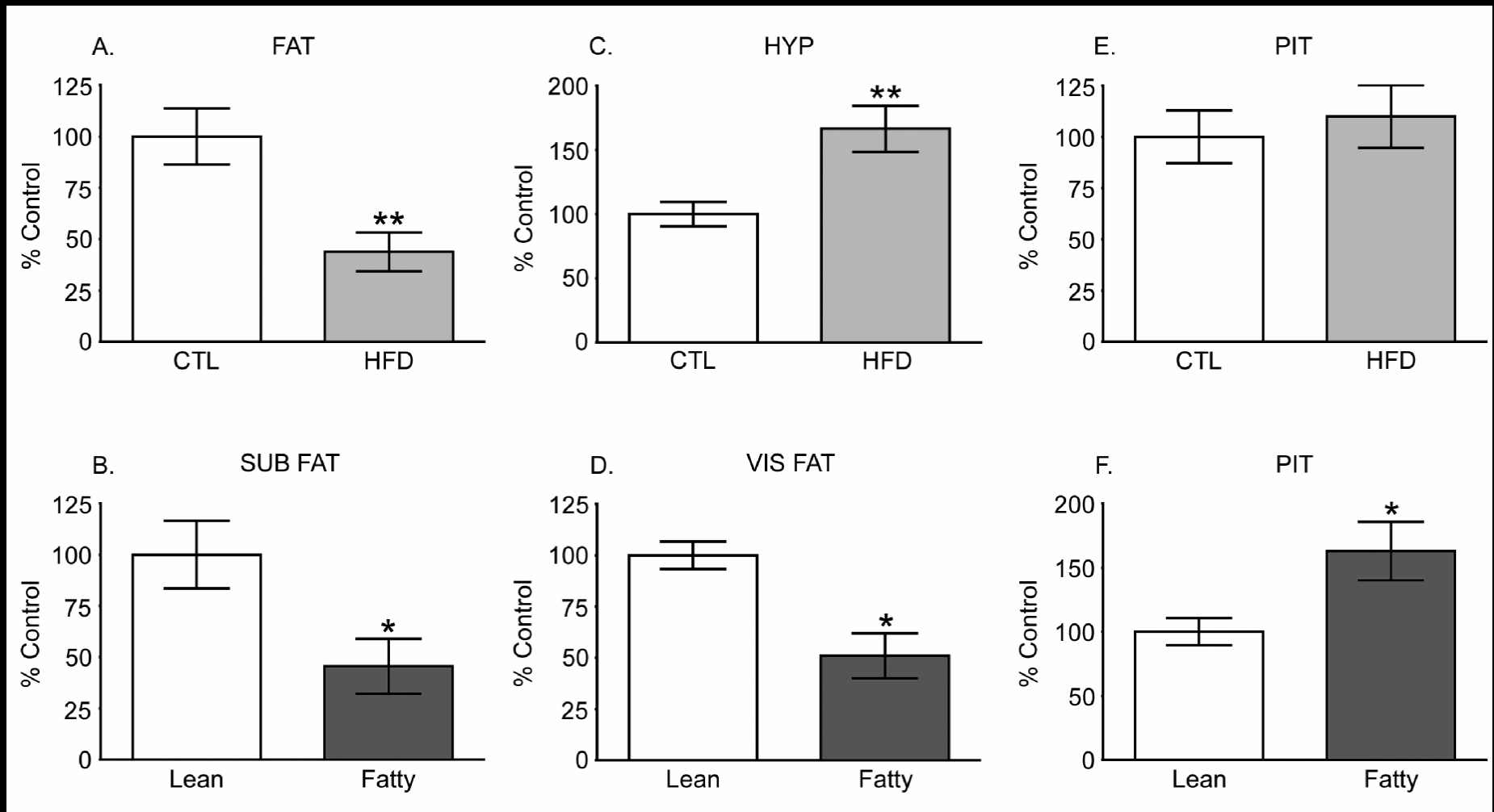
# Effect of sex steroids



# Effect of fasting and refeeding



# Effect of high fat diet in lean and fatty Zucker rats



## **Summary of Results**

- **Kiss-1 mRNA is expressed in both rat pituitary and adipose tissue**
- **Kiss-1 gene expression is sensitive to sex steroids, nutrition status, and HF diet**
- **These changes are tissue specific**
- **The disparity in adipose tissue responses in lean and fatty Zucker rats indicates that leptin signaling may have a role to play**

## Summary of Results

- **Kiss-1 may be the responsible for metabolic induced sexual maturation problems such as anorexia , depression, obesity etc.**
- **WE ARE CURRENTLY PLANNING EXPERIMENTS ON LEAN AND OBESE FEMALES AND THOSE WITH PCOS.**