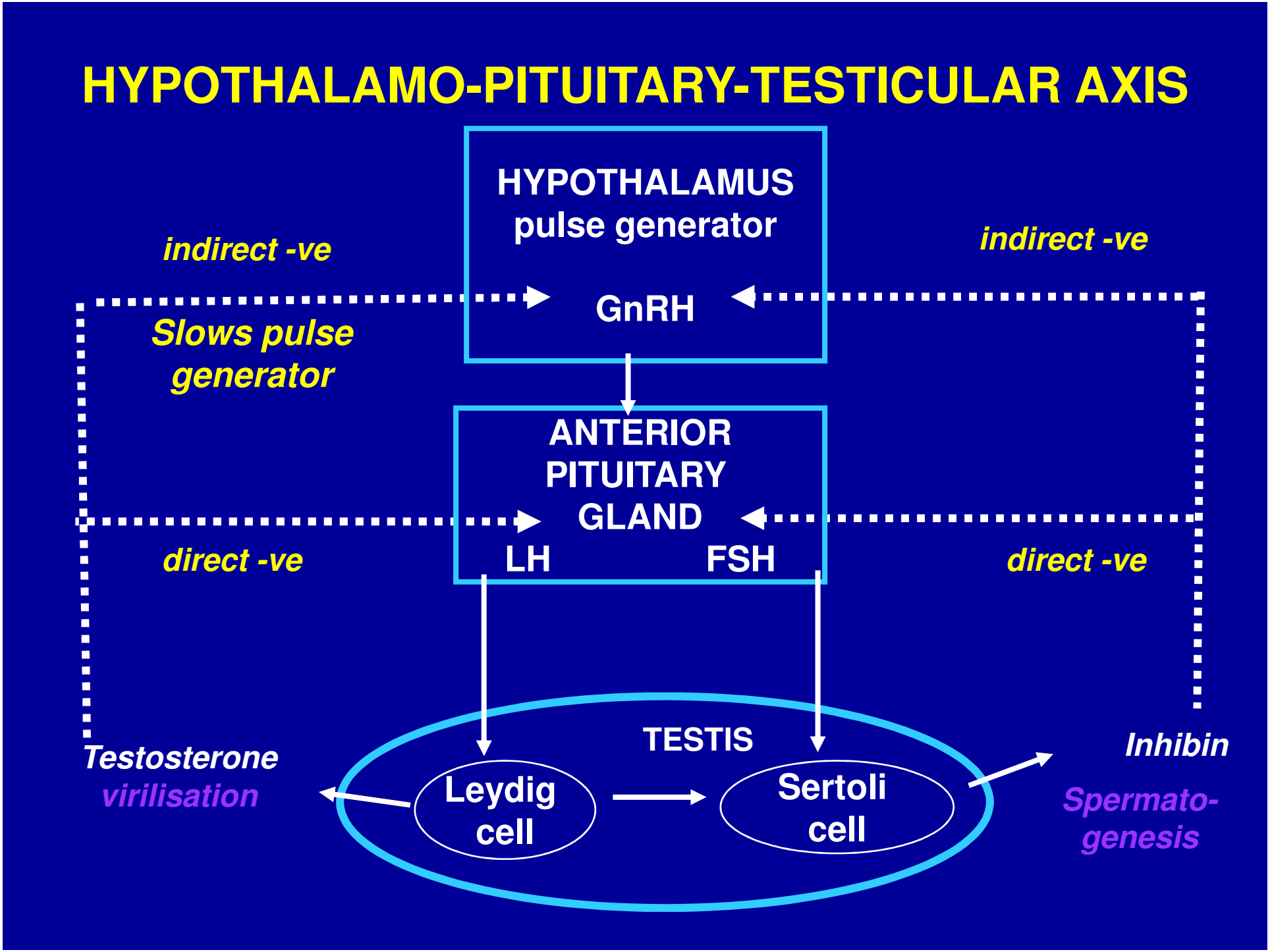
Relationship between gut / adipose hormones and reproduction

Dr Waljit S Dhillo

The Hammersmith Hospitals NHS
NHS Trust

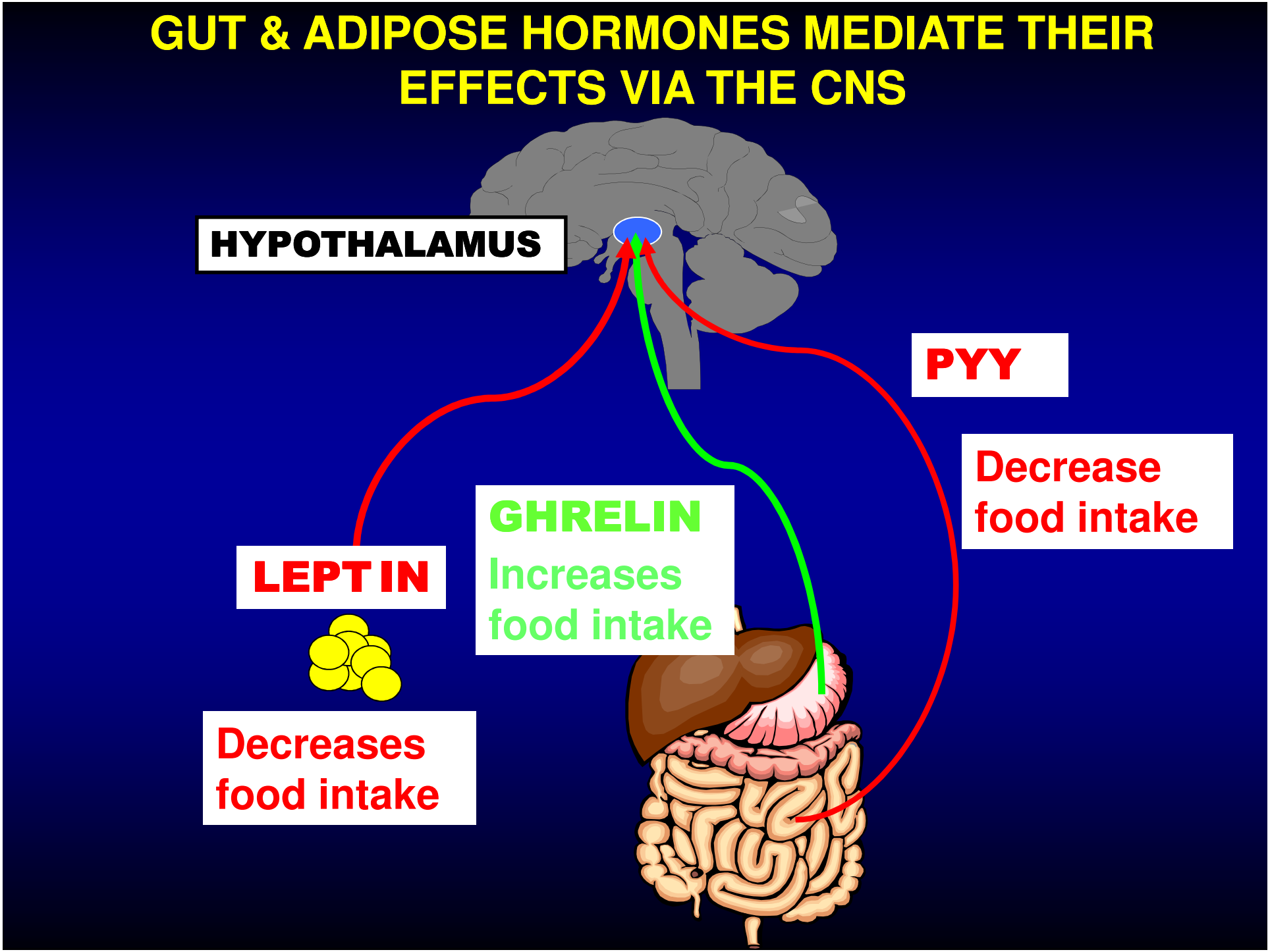
Imperial College
London


HYPOTHALAMO-PITUITARY-TESTICULAR AXIS
HYPOTHALAMUS
pulse generator
GnRH
indirect -ve
indirect -ve
Slows pulse
generator
ANTERIOR
PITUITARY
GLAND
LH
FSH
direct -ve
direct -ve
TESTIS
Leydig
cell
Sertoli
cell
Testosterone
virilisation
Inhibin
Spermato-
genesis

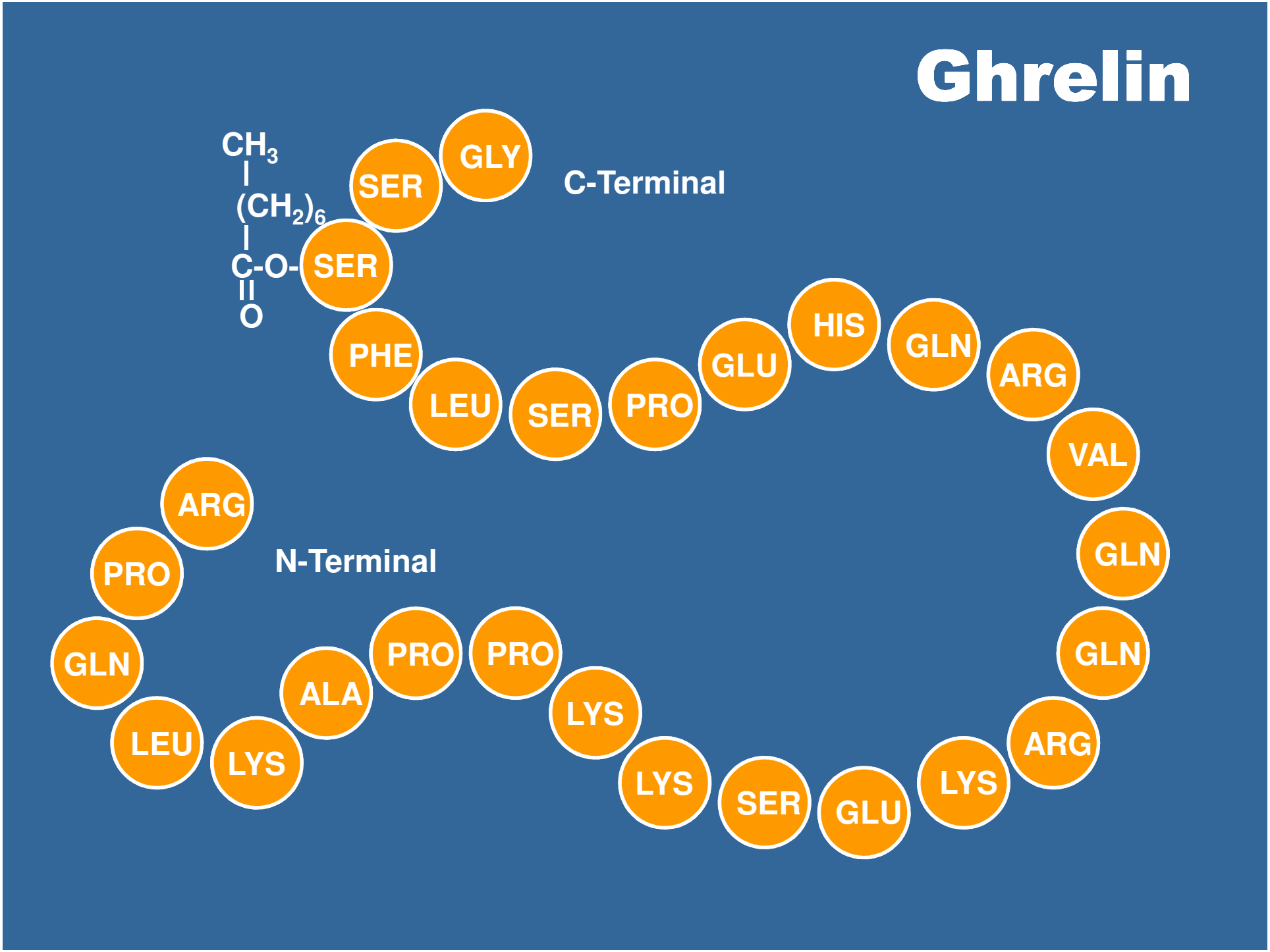
Reproductive function is regulated by nutritional status

- Body weight at menarche is tightly regulated
- Under nutrition leads to infertility in males and females
- Obesity also leads to sub fertility in males and females
- Common regulatory pathways which control energy homeostasis and reproductive function – poorly understood

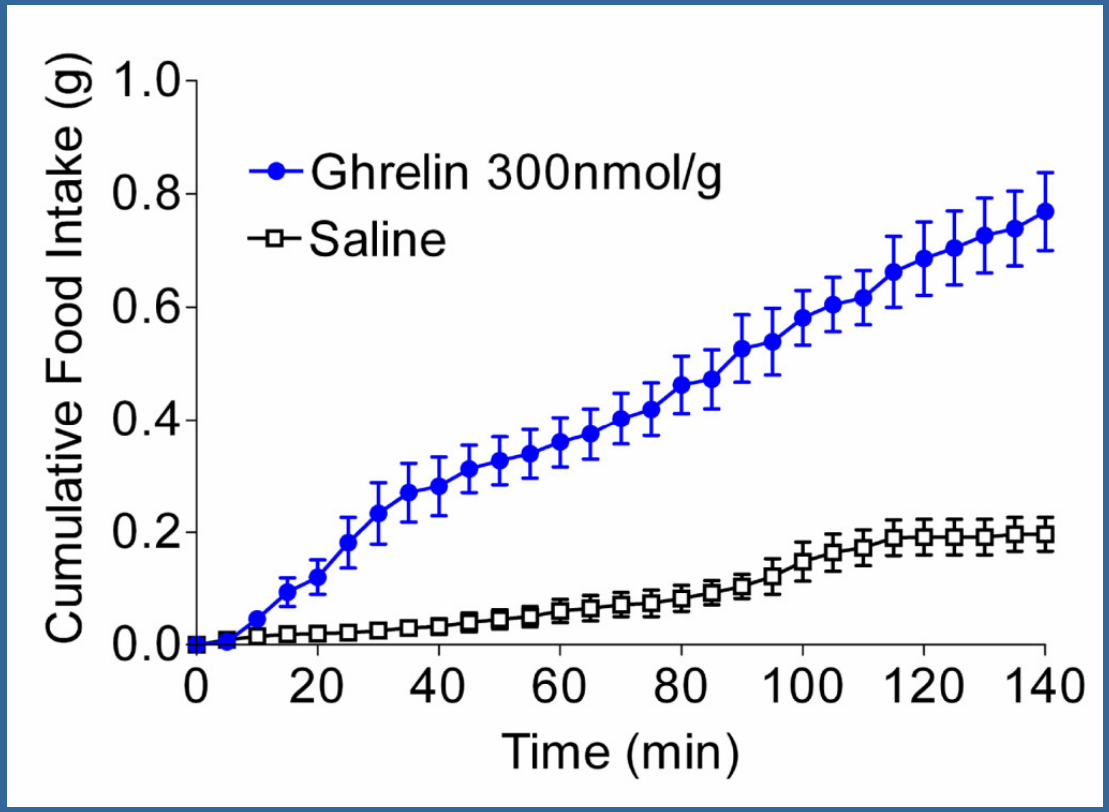
GUT & ADIPOSE HORMONES MEDIATE THEIR EFFECTS VIA THE CNS



Ghrelin

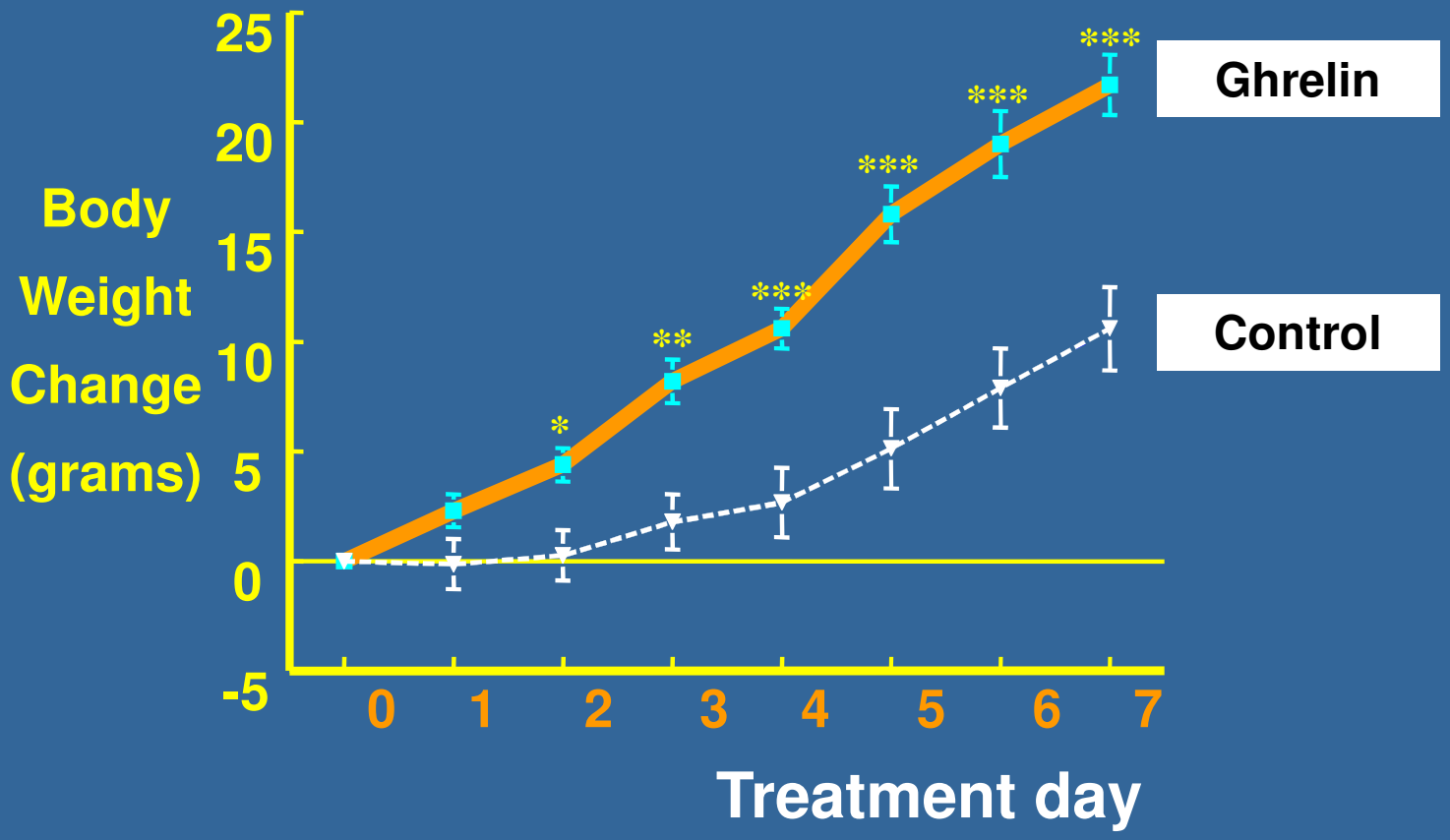

Ghrelin
CH3
(CH2)6
C-O-
O
SER
GLY
SER
C-Terminal
PHE
LEU
SER
PRO
GLU
HIS
GLN
ARG
VAL
GLN
GLN
ARG
LYS
SER
GLU
LYS
LYS
PRO
PRO
ALA
LEU
GLN
PRO
ARG
N-Terminal

Ghrelin increases food intake

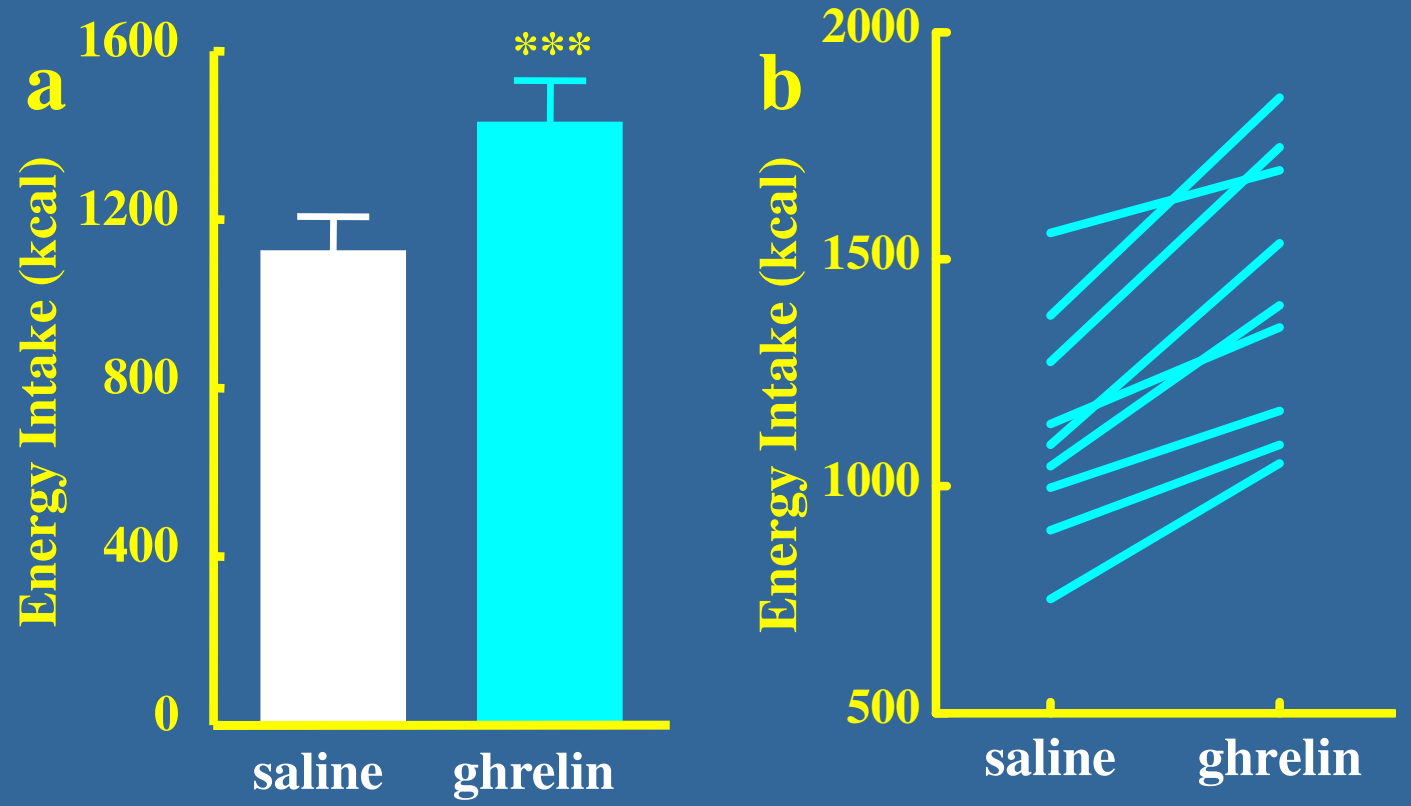


1min food intake data

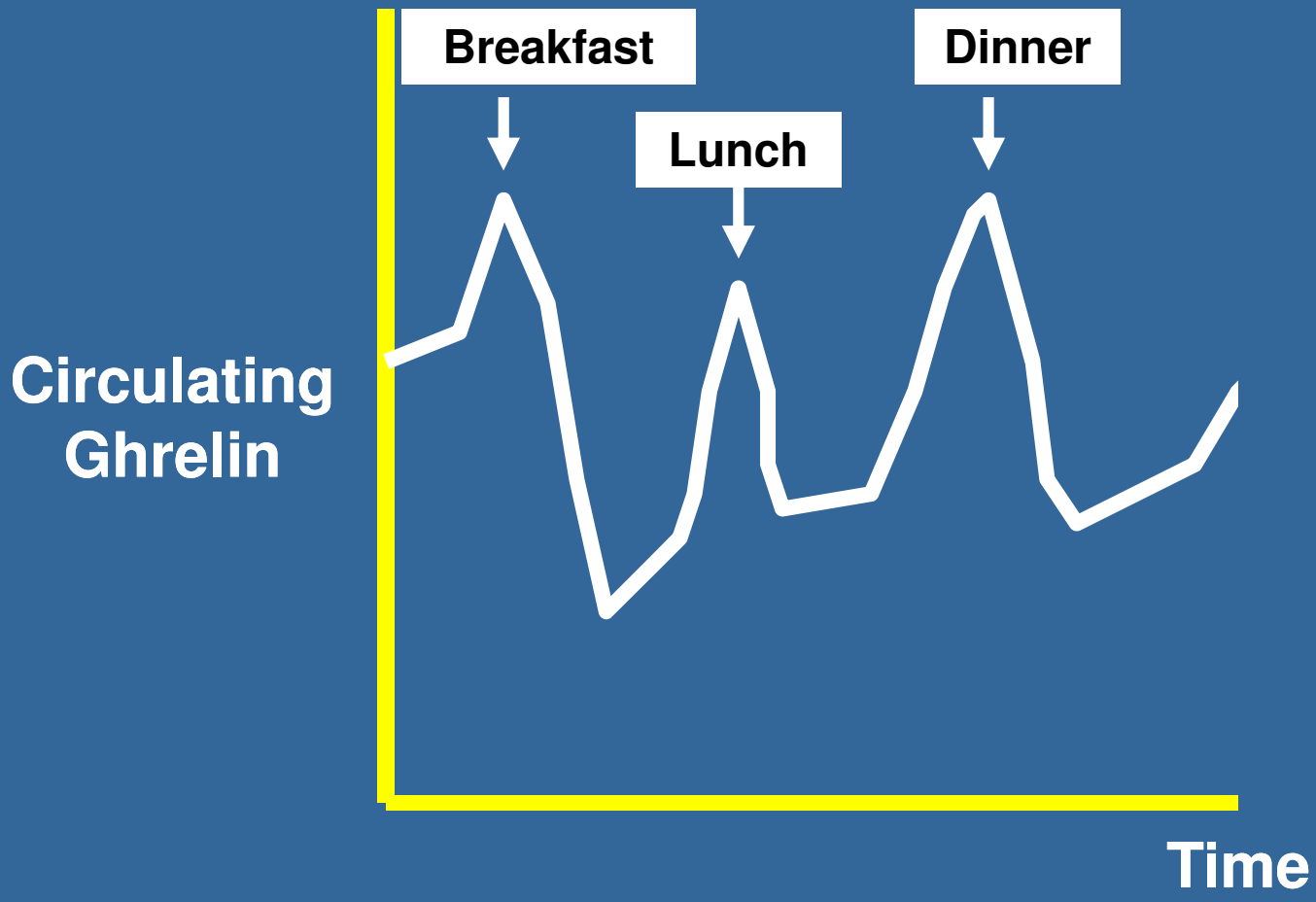
Ghrelin makes you fat

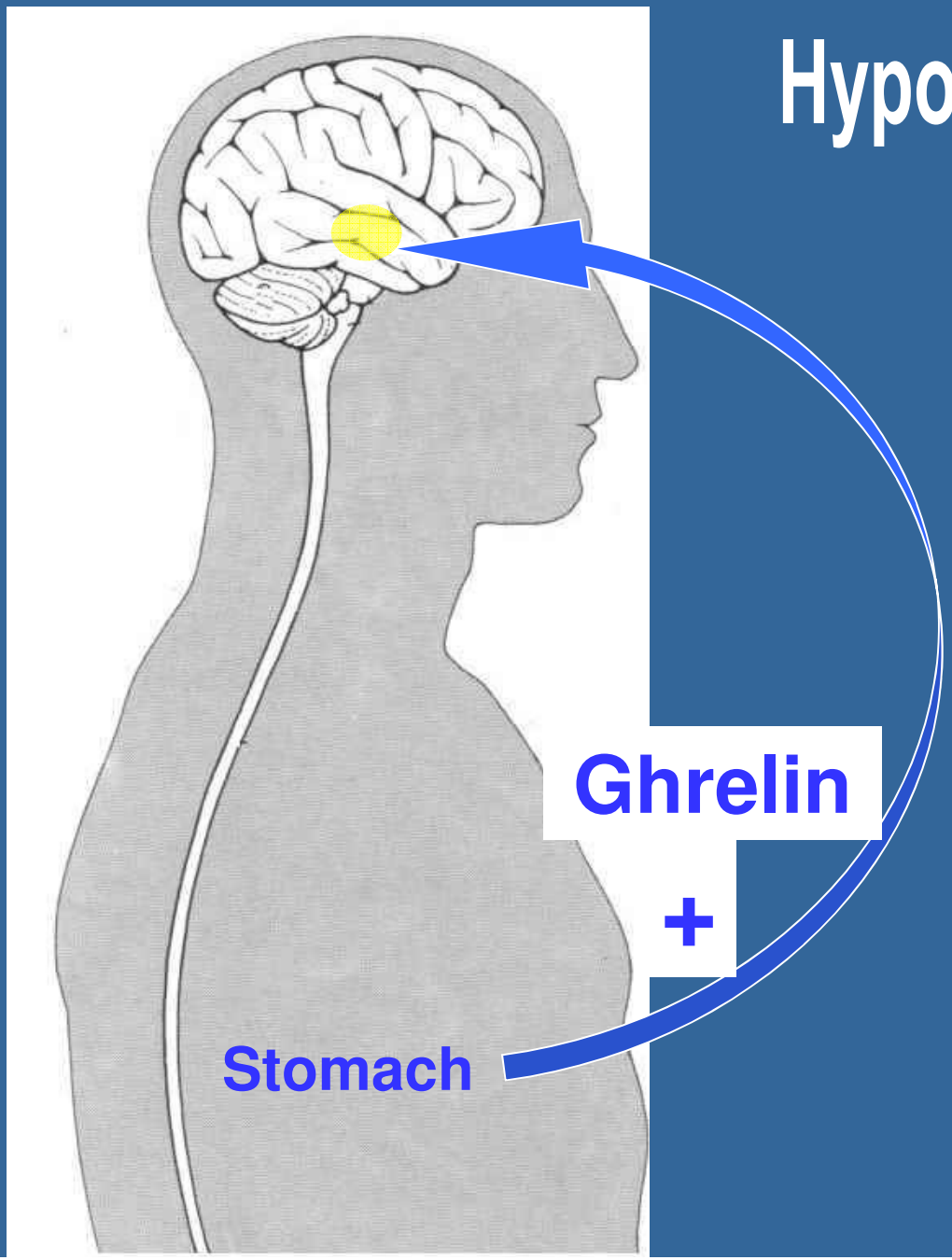


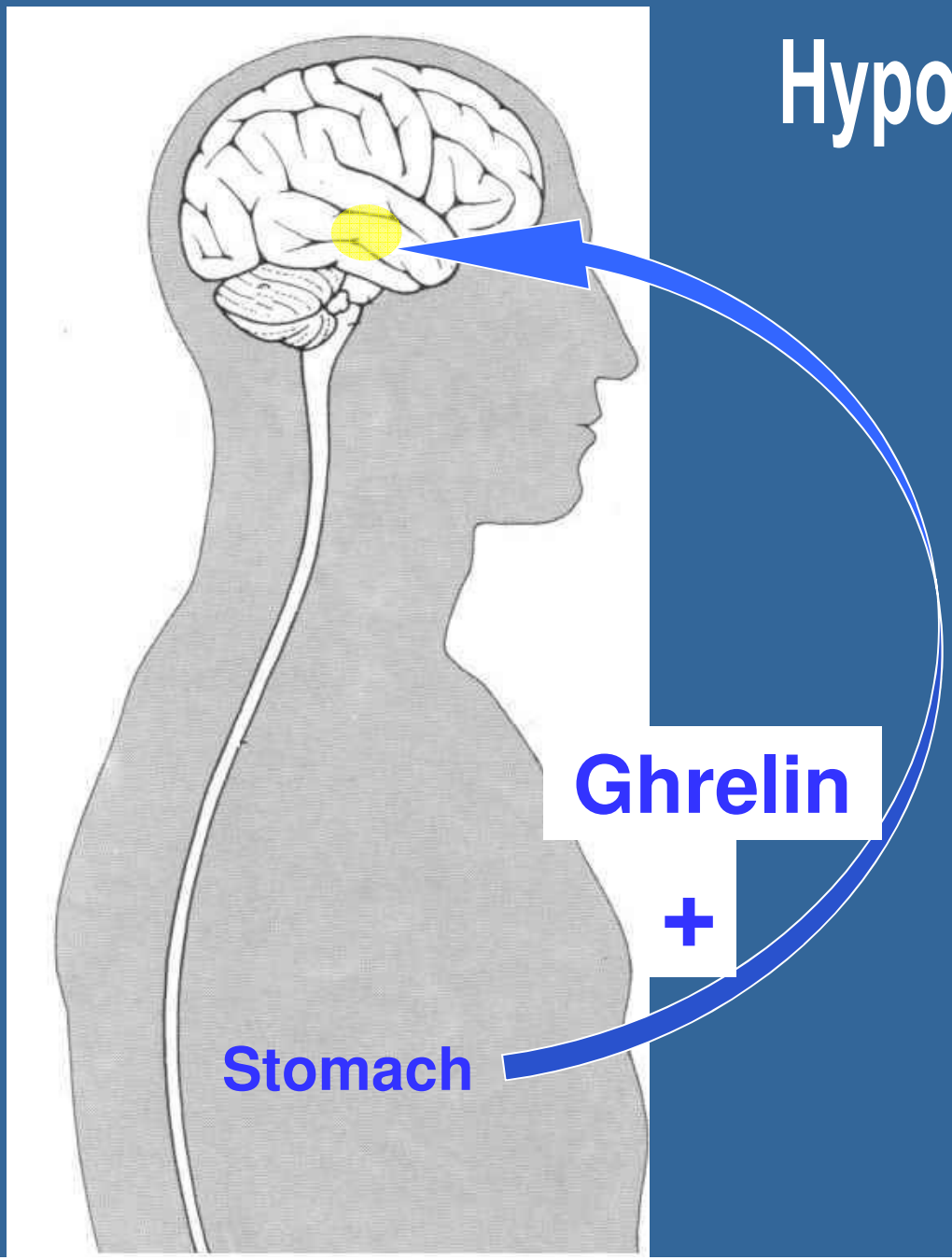
Ghrelin is the only identified hunger hormone in man

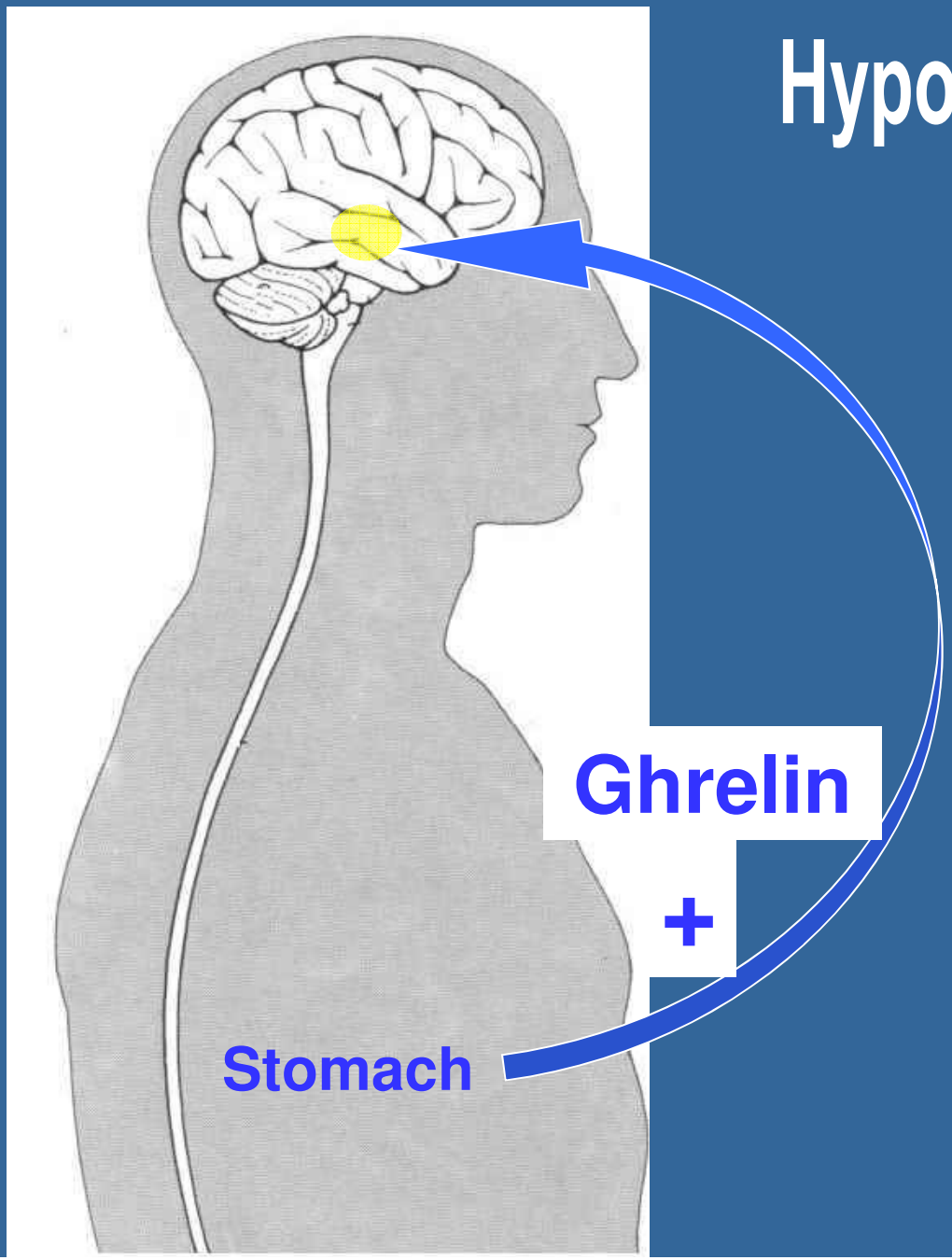


Ghrelin as a meal initiator




Hypothalamus
Ghrelin hunger signal
Ghrelin
+
Stomach


Hypothalamus
Ghrelin hunger signal
Ghrelin increases when food deprived
Ghrelin
+
Stomach

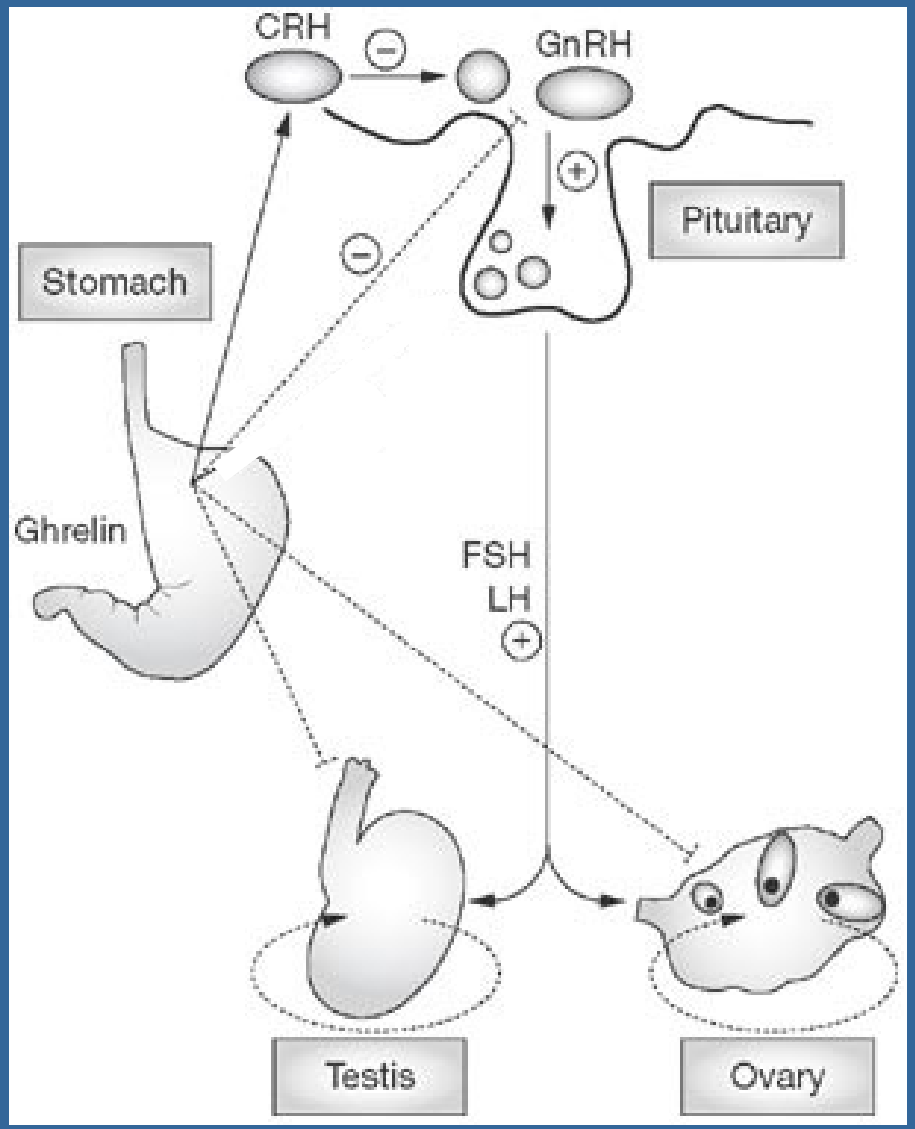


Ghrelin hunger signal

Ghrelin increases when food deprived

Ghrelin inhibits reproductive function

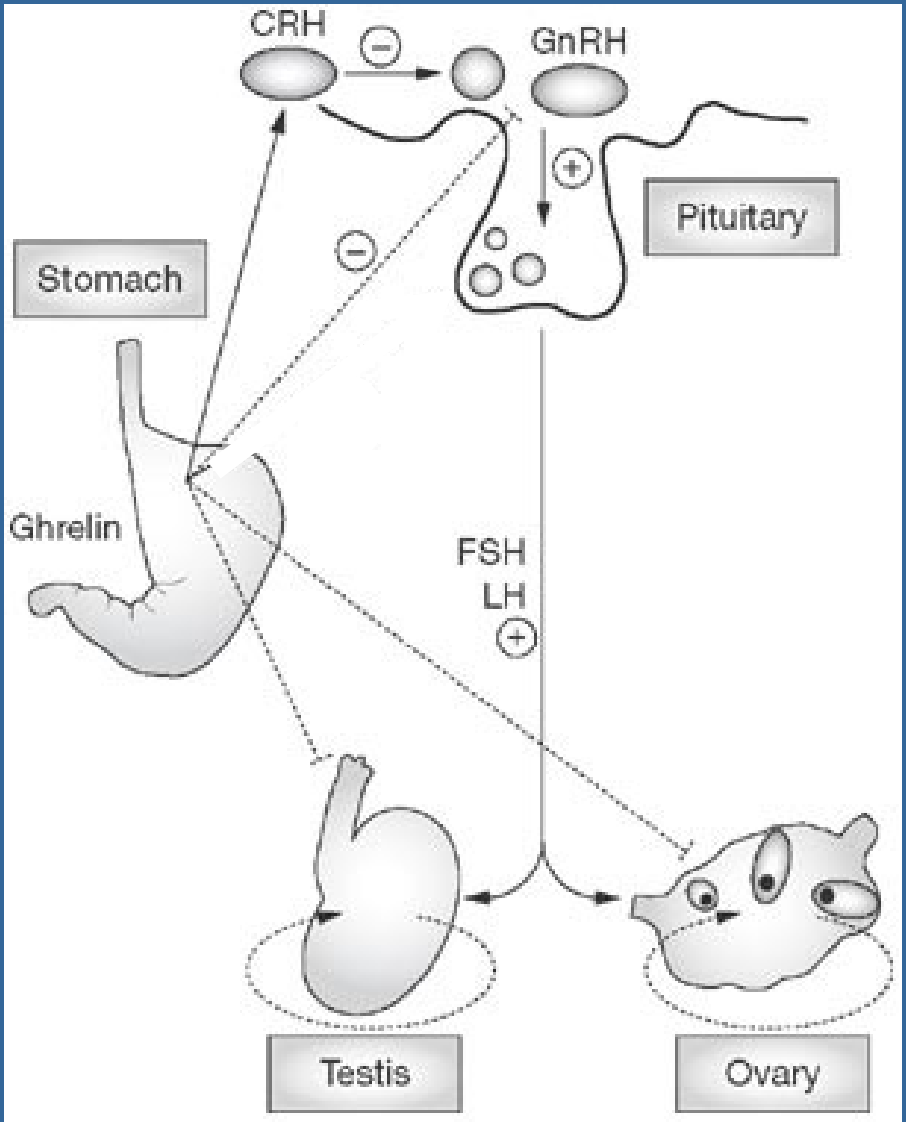
Effects of ghrelin on the HPG axis



HYPOTHALAMUS: ghrelin inhibits GnRH secretion
- directly
- indirectly via stimulation of CRH

Nat Clin Pract Endocrinol Metab. 2008 Dec;4(12):666-74.

Effects of ghrelin on the HPG axis

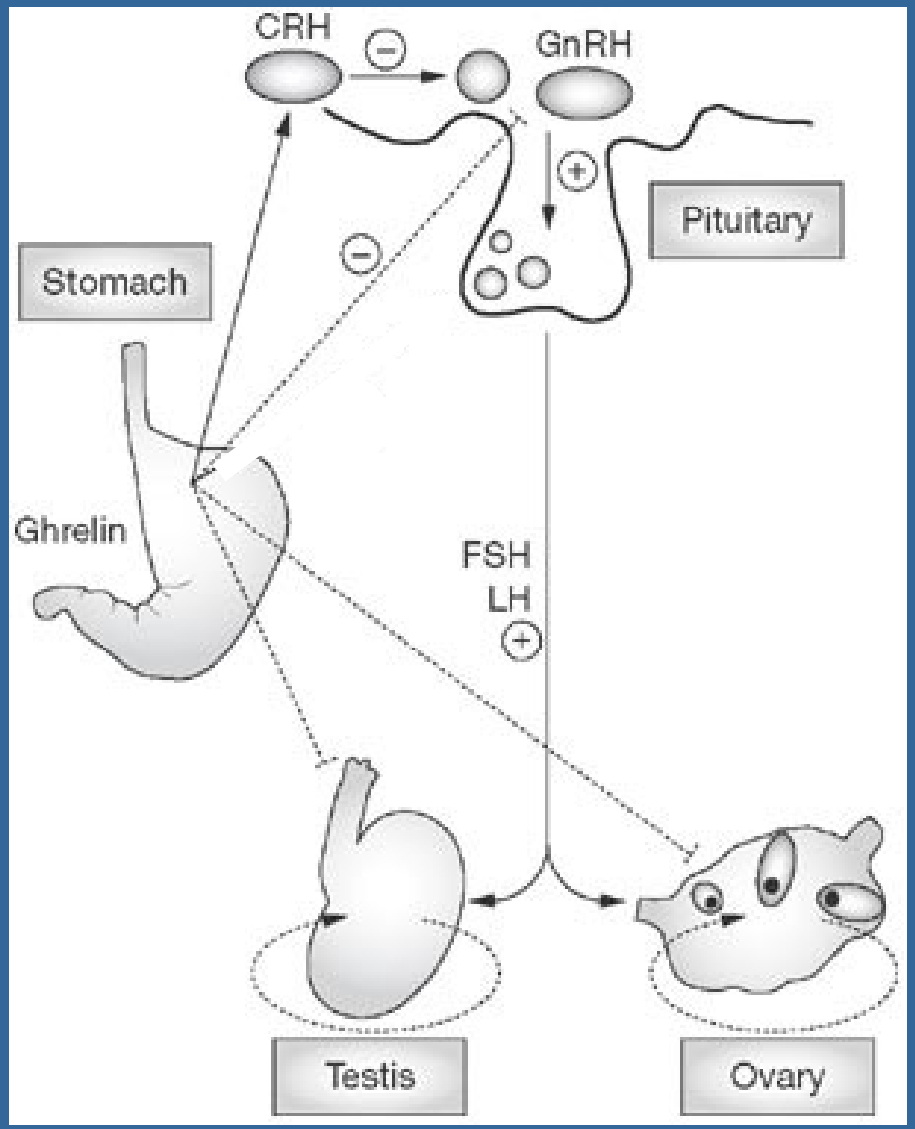


HYPOTHALAMUS: ghrelin inhibits GnRH secretion
- directly
- indirectly via stimulation of CRH

PITUITARY: Ghrelin inhibits GnRH-induced LH secretion

Nat Clin Pract Endocrinol Metab. 2008 Dec;4(12):666-74.

Effects of ghrelin on the HPG axis



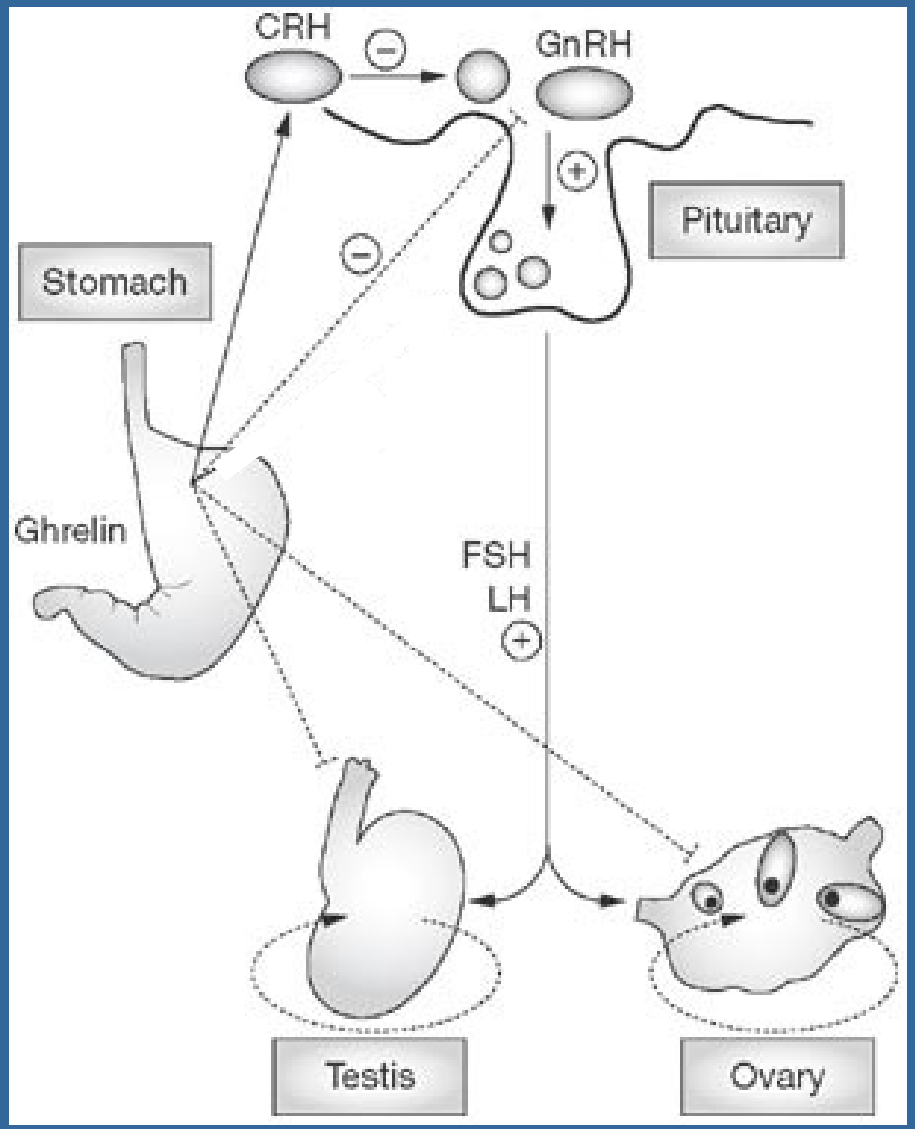
HYPOTHALAMUS: ghrelin inhibits GnRH secretion
- directly
- indirectly via stimulation of CRH

PITUITARY: Ghrelin inhibits GnRH-induced LH secretion

TESTES: affects steroidogenesis, Sertoli cell gene expression, & Leydig cell proliferation

Nat Clin Pract Endocrinol Metab. 2008 Dec;4(12):666-74.

Effects of ghrelin on the HPG axis



HYPOTHALAMUS: ghrelin inhibits GnRH secretion
- directly
- indirectly via stimulation of CRH

PITUITARY: Ghrelin inhibits GnRH-induced LH secretion

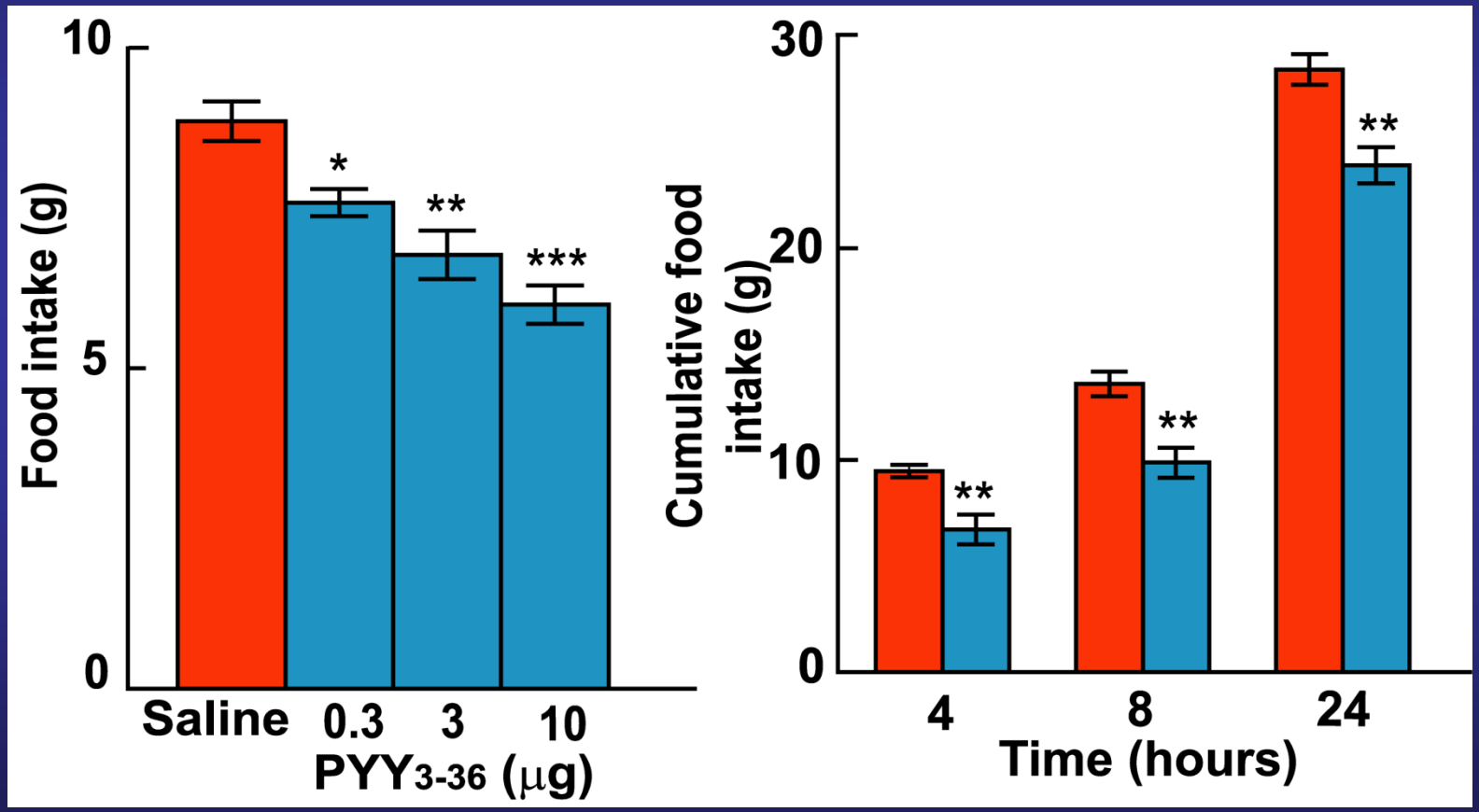
OVARY: affects steroidogenesis, luteal function and cell proliferation

Nat Clin Pract Endocrinol Metab. 2008 Dec;4(12):666-74.

Peptide YY (PYY)

- PYY is a 36 aa peptide with a tyrosine at both ends.
- PYY3-36 main stored & circulating form
- PYY3-36 selective Y2R agonist

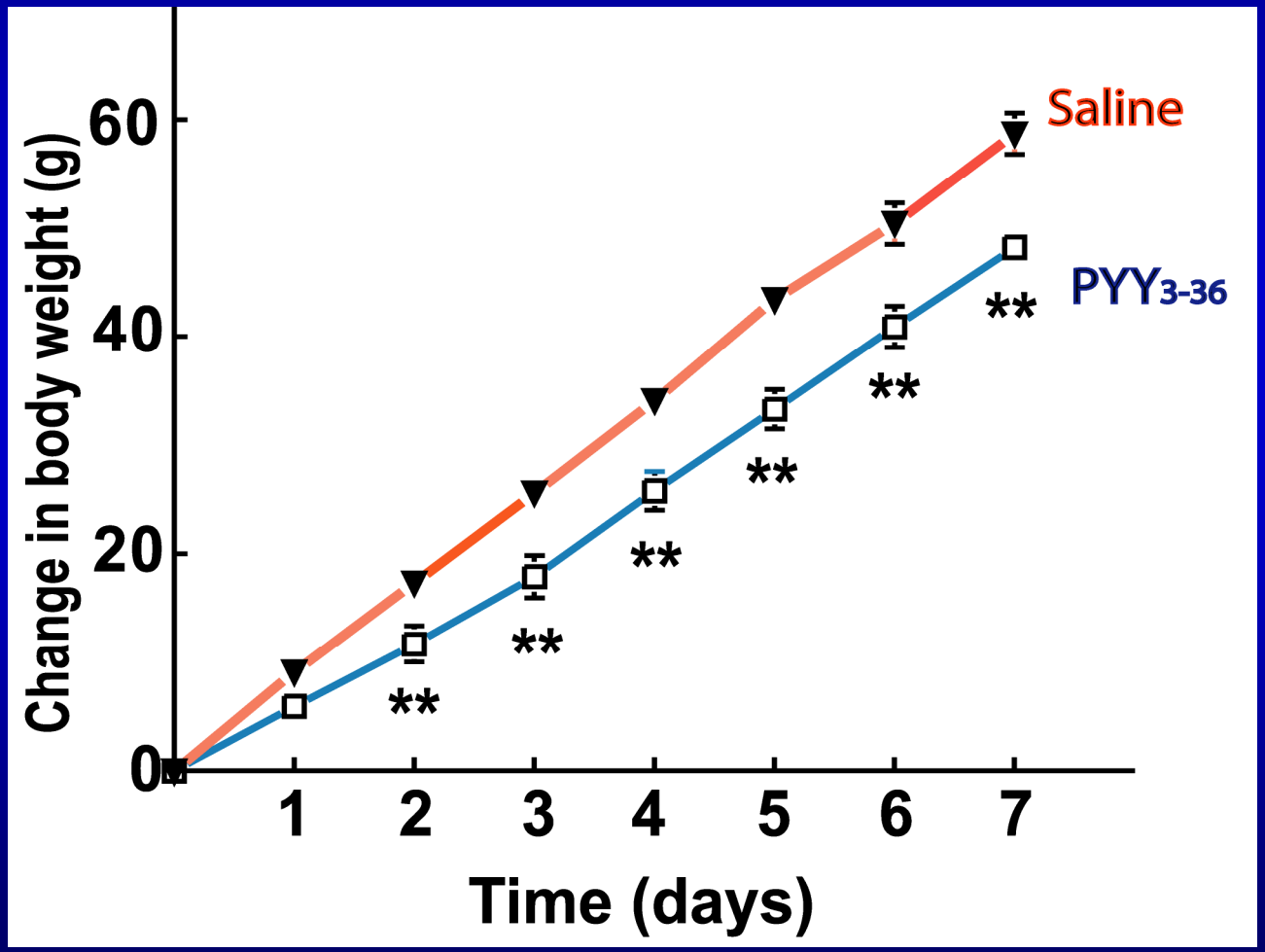
Peripheral PYY_{3-36} inhibits food intake in rats



Values = mean ± sem, n = 10-12 per group

*p < 0.05, ** p< 0.01, *** p <0.005

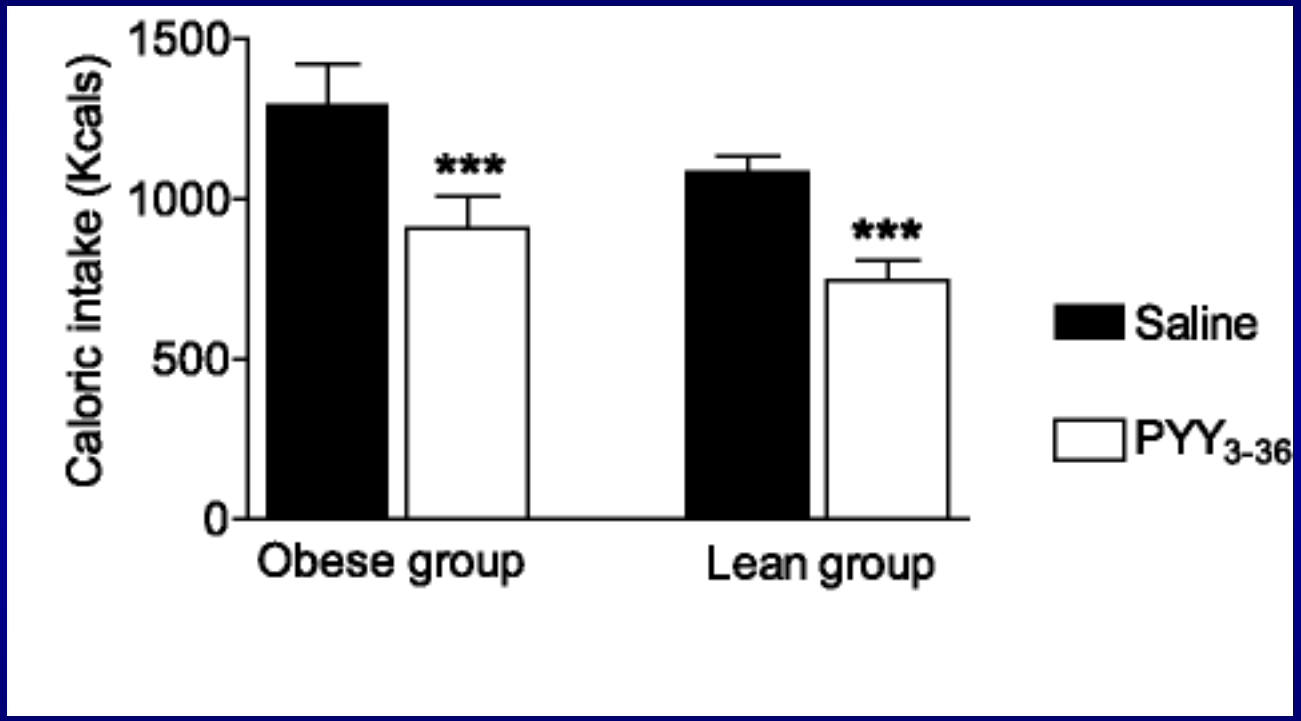
Chronic administration of PYY_{3-36} decreases body weight in rats



n = 12 per group

** $p < 0.01$

PYY_{3-36} reduces food intake in humans



Obese 29.9 ± 4.4% P<0.000001

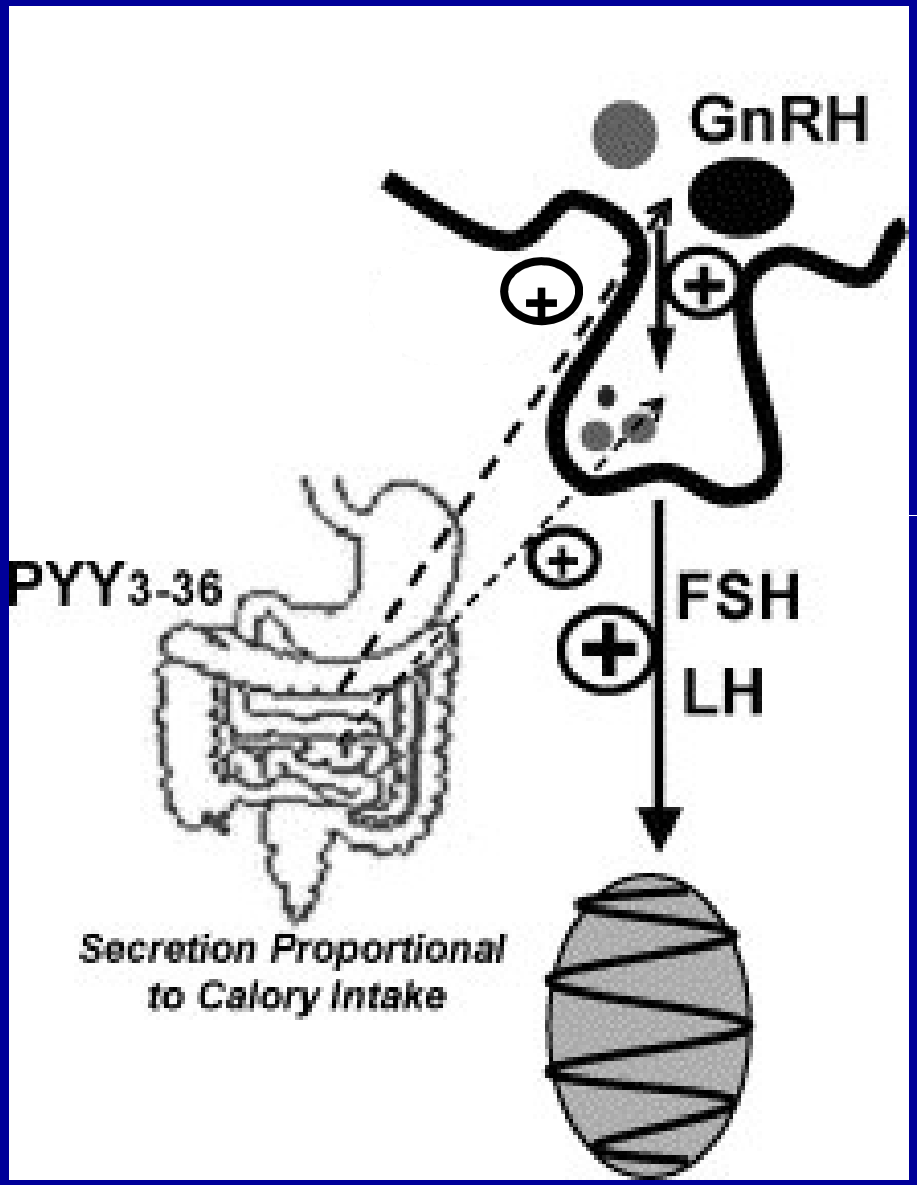
Lean 31.1 ± 4.5% P<0.0005

No effect on food preference

PYY released from gut into circulation after a meal ie high PYY levels in fed state

PYY stimulates reproductive function

Effects of PYY on the HPG axis

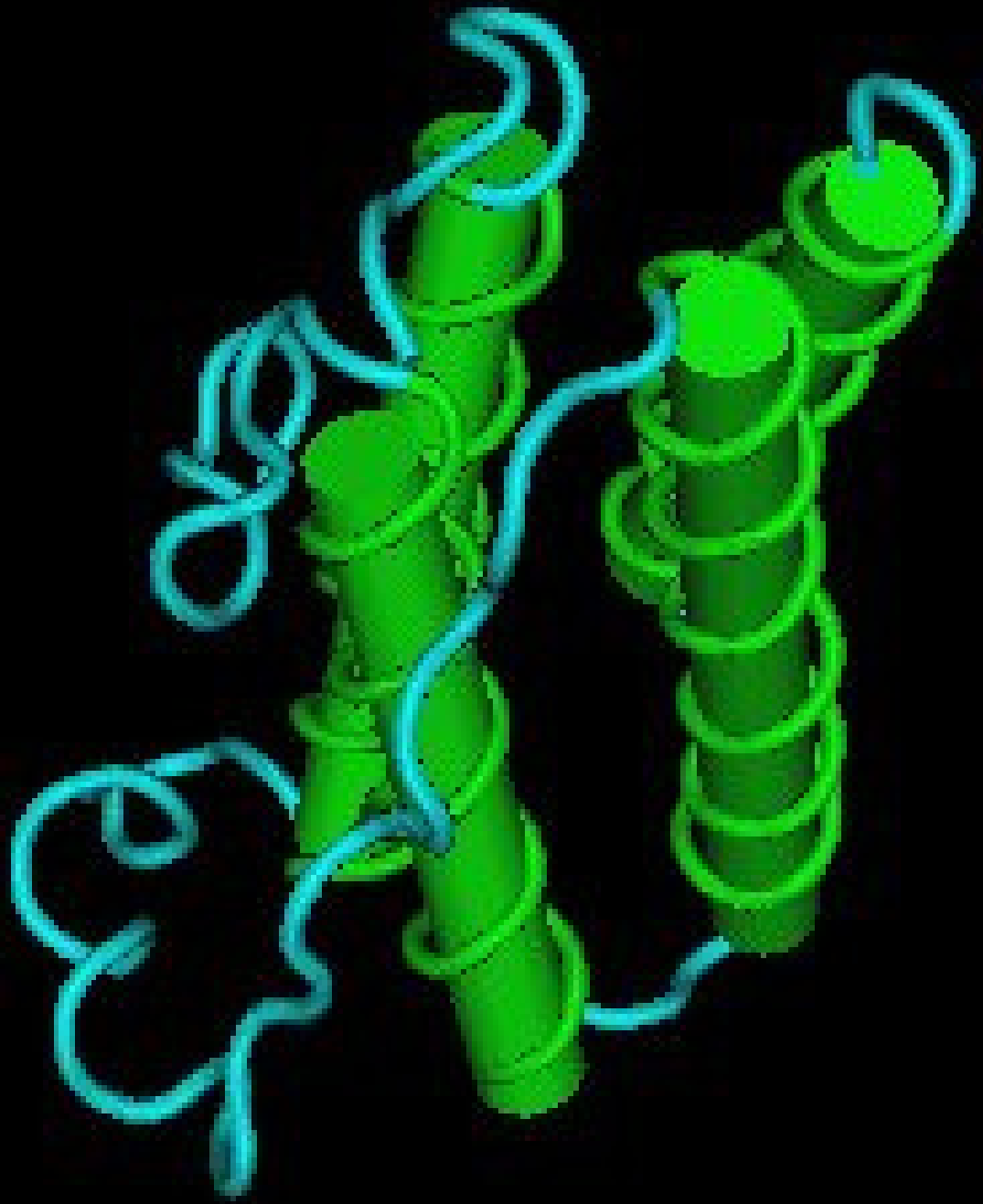


HYPOTHALAMUS: PYY stimulates GnRH secretion

PITUITARY: PYY stimulates LH and FSH secretion

Leptin

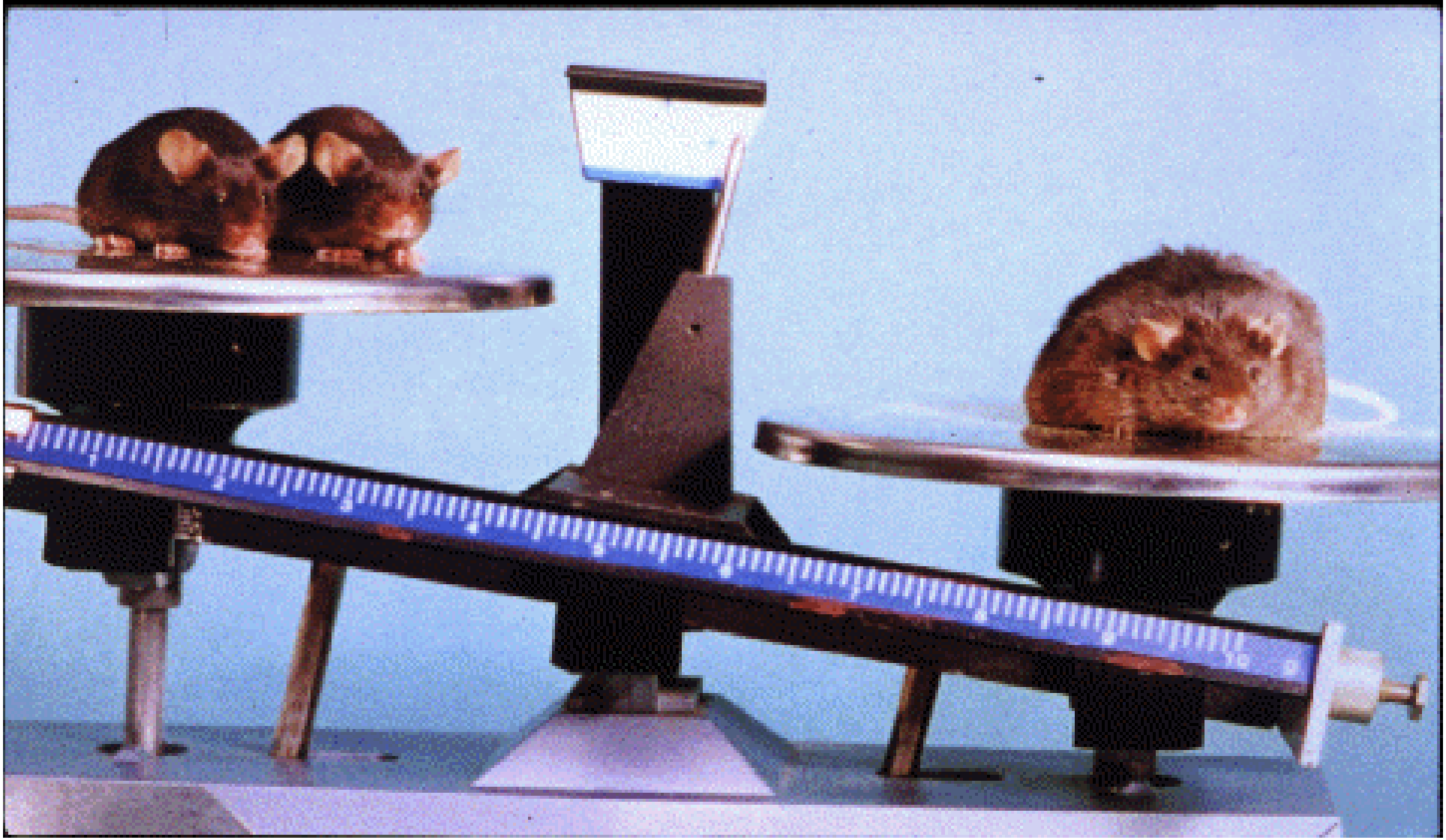
From ‘leptos’ meaning ‘thin’



Leptin

- Discovered in 1994
- Codes for 167 amino acid hormone
- Missing in the *ob/ob* mouse.

The *ob/ob* Mouse



Leptin is a long term signal of body weight

- Made by adipocytes in white adipose tissue
- Circulates in plasma in proportion to amount of adipose tissue

Leptin

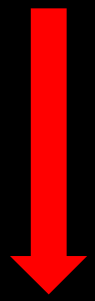
- Acts upon the hypothalamus to inhibit appetite

- Low when low body fat
- High when high body fat

Leptin signalling is required for fertility

Inactivating mutation in leptin gene (ob/ob)

Inactivating mutation in leptin receptor (db/db)



HYPOGONADOTROPHIC HYPOGONADISM

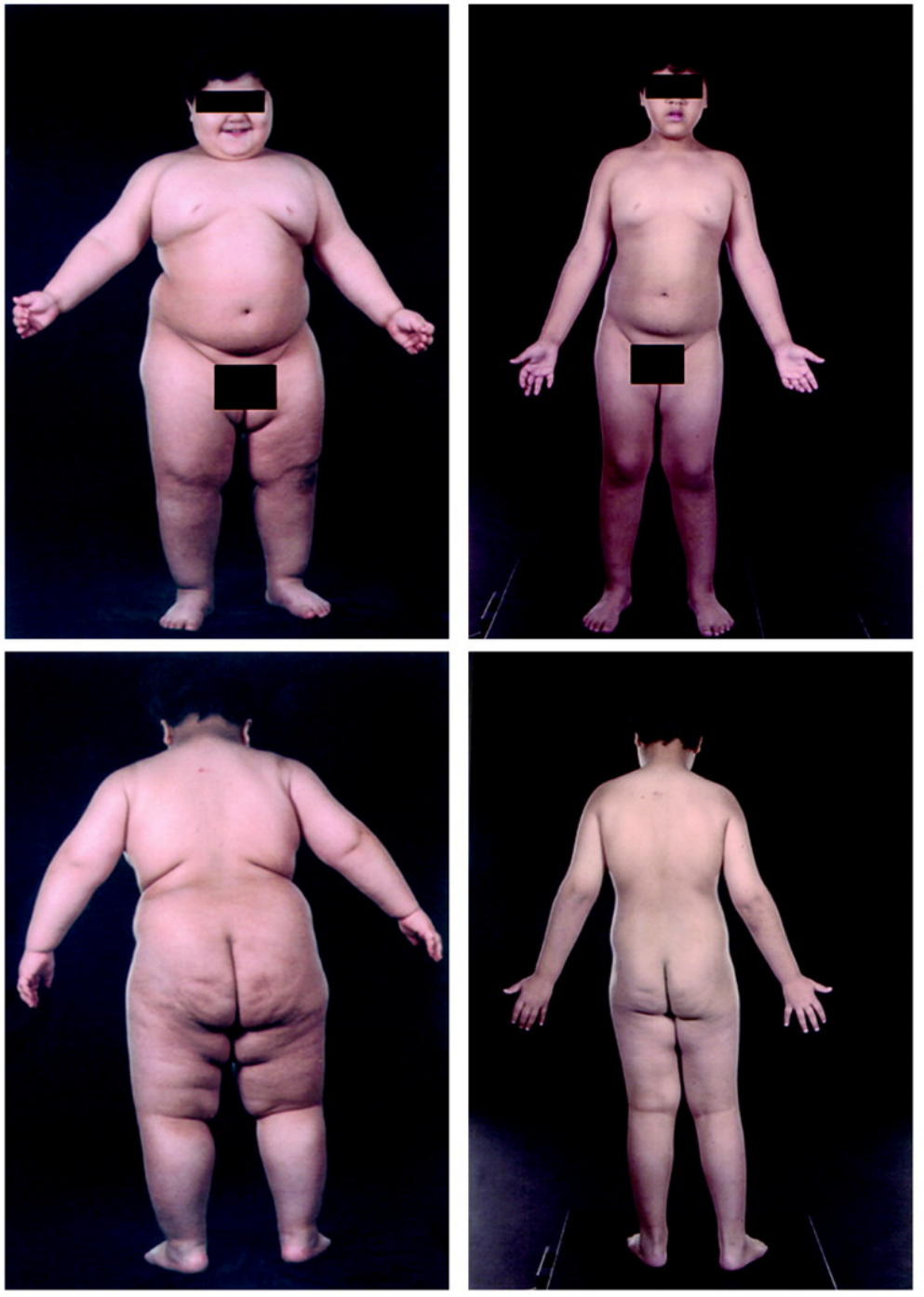
- low GnRH
- low LH / FSH
- low testosterone / oestradiol

Leptin

- Leptin replacement in the *ob/ob* mouse decreases weight and stimulates reproductive function

Congenital leptin deficiency in humans

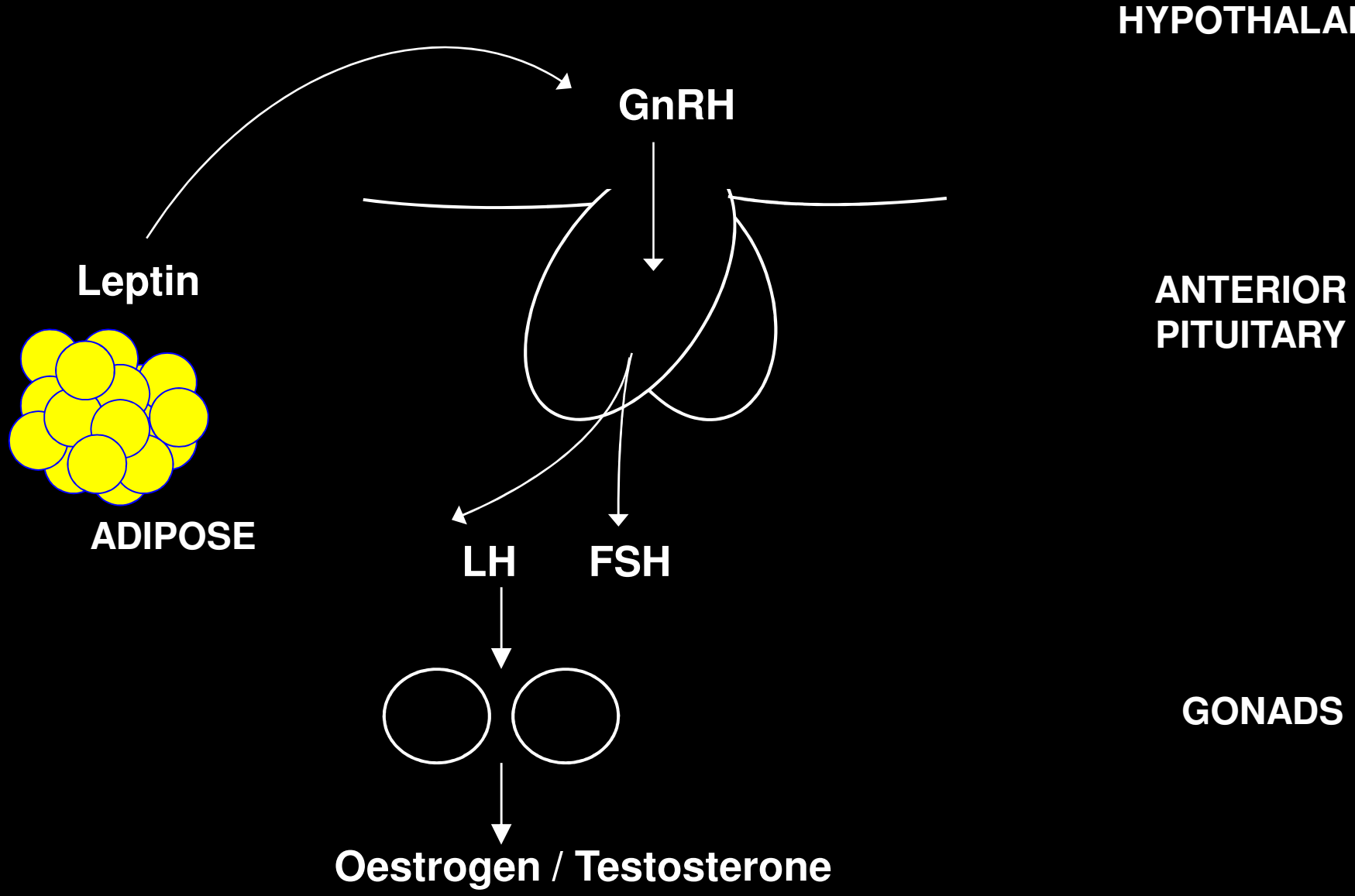
- Small number of cases identified
- Mutation in *ob* gene- homologous to *ob/ob* mouse
- Severely hyperphagic and obese
- Hypogonadotrophic hypogonadism



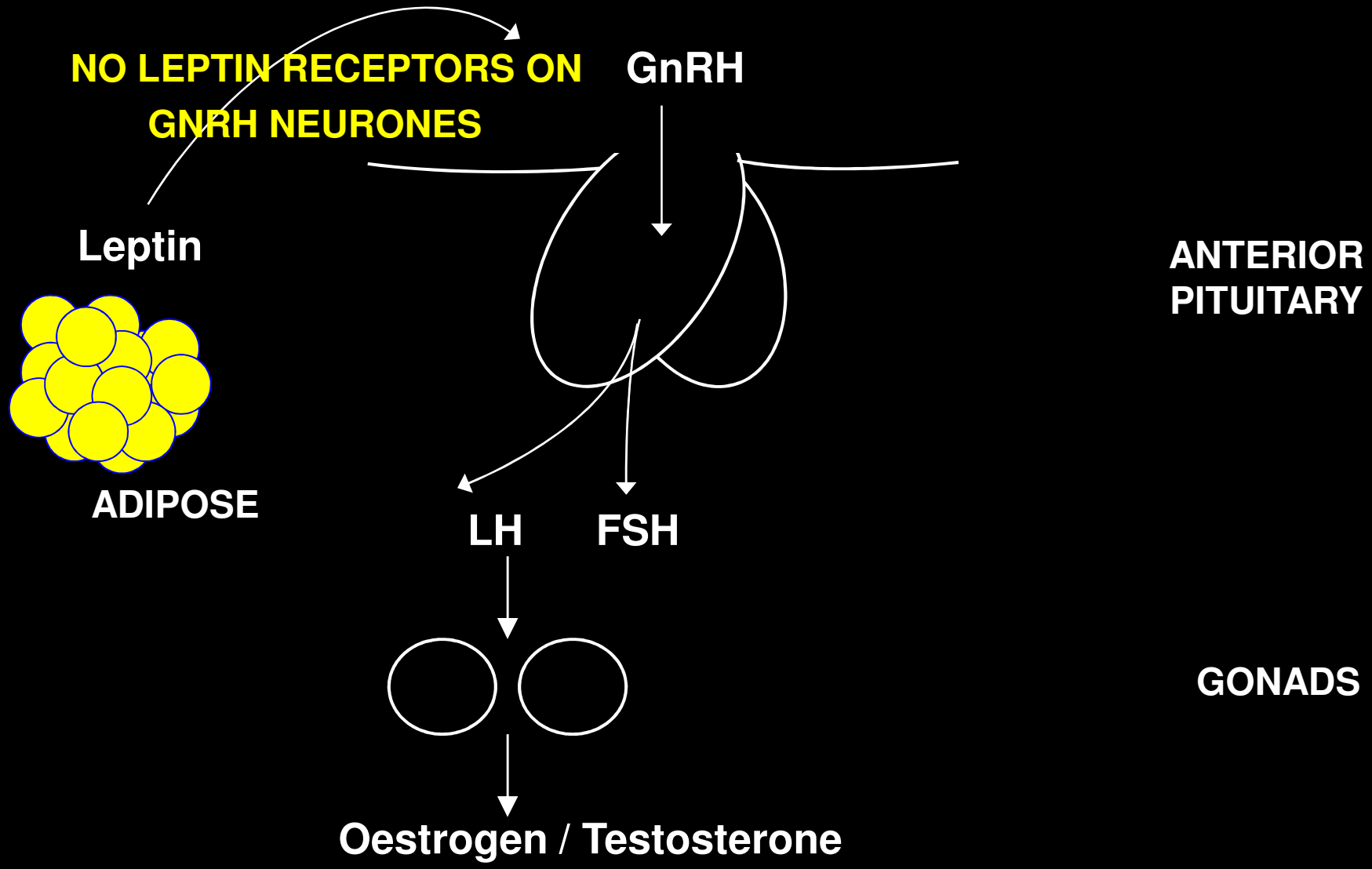
Leptin Replacement

- In these children leptin has been effective in
  - reducing body weight
  - stimulating reproductive hormone release

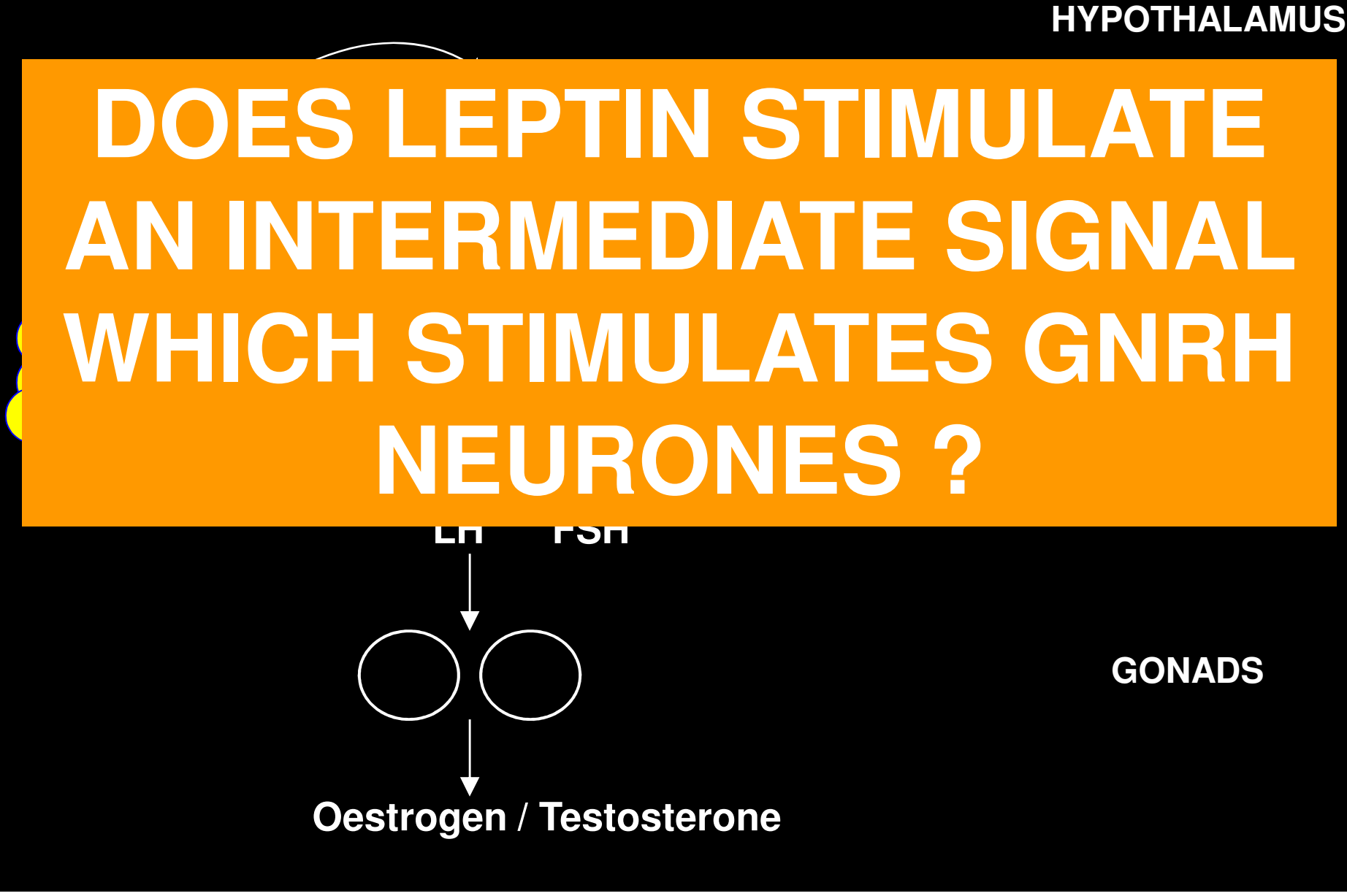
Leptin stimulates reproductive hormone release via GnRH



How does leptin stimulate GnRH release ?



How does leptin stimulate reproductive hormone release ?



Kisspeptin

- The kisspeptins are peptide products of the KiSS-1 gene.
- Highly expressed in the hypothalamus and the placenta
- Bind to G-protein coupled receptor 54

The NEW ENGLAND JOURNAL of MEDICINE

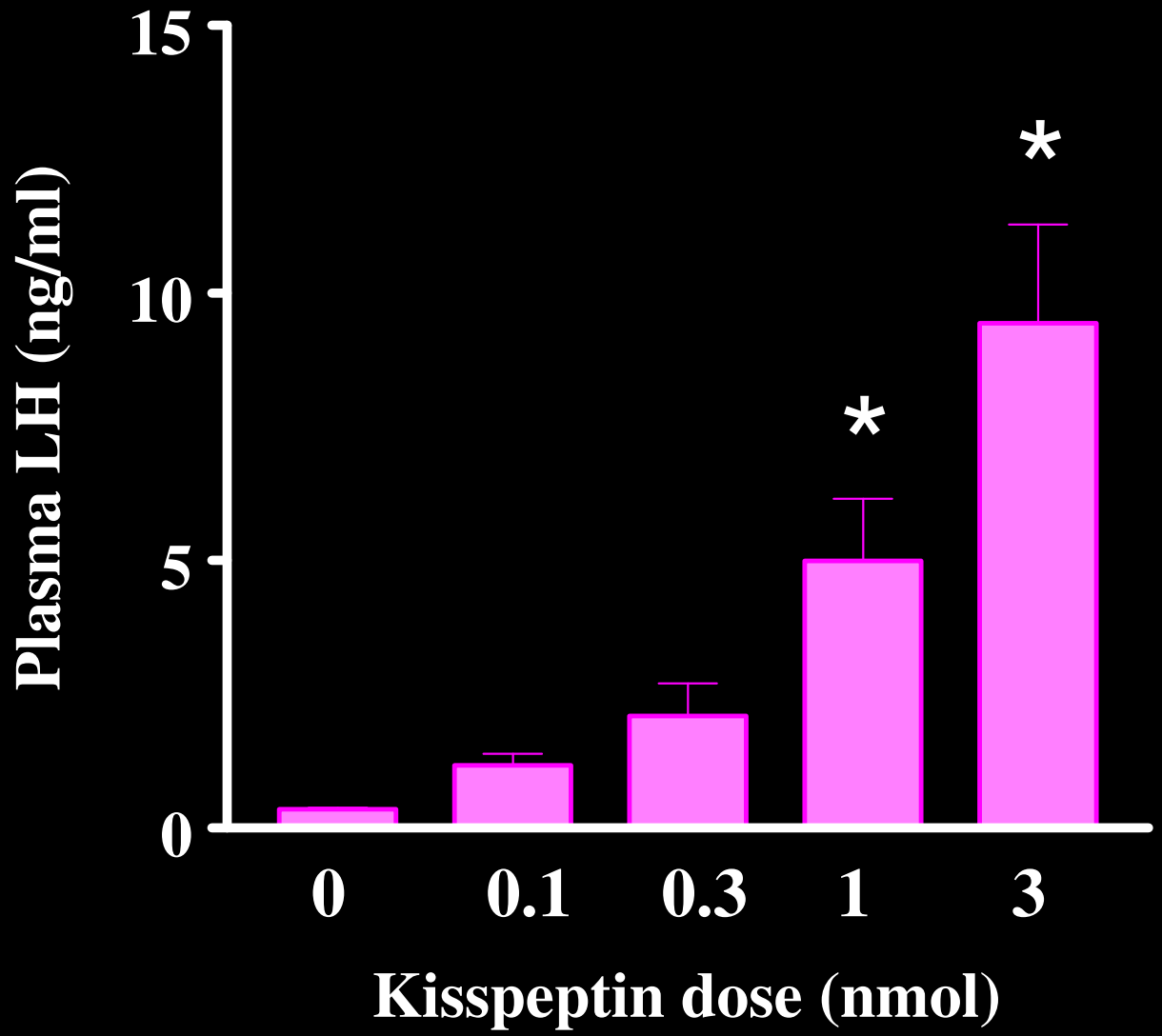
ORIGINAL ARTICLE

The GPR54 Gene as a Regulator of Puberty

Stephanie B. Seminara, M.D., Sophie Messager, Ph.D.,
Emmanouella E. Chatzidaki, B.Sc., Rosemary R. Thresher, Ph.D.,
James S. Acierno, Jr., B.S., Jenna K. Shagoury, B.S., Yousef Bo-Abbas, M.D.,
Wendy Kuohung, M.D., Kristine M. Schwinof, M.A., Alan G. Hendrick, Ph.D.,
Dirk Zahn, Ph.D., John Dixon, B.A., Ursula B. Kaiser, M.D.,
Susan A. Slaugenhaupt, Ph.D., James F. Gusella, Ph.D., Stephen O'Rahilly, M.D.,
Mark B.L. Carlton, Ph.D., William F. Crowley, Jr., M.D.,
Samuel A.J.R. Aparicio, B.M., B.Ch., Ph.D., and William H. Colledge, Ph.D.

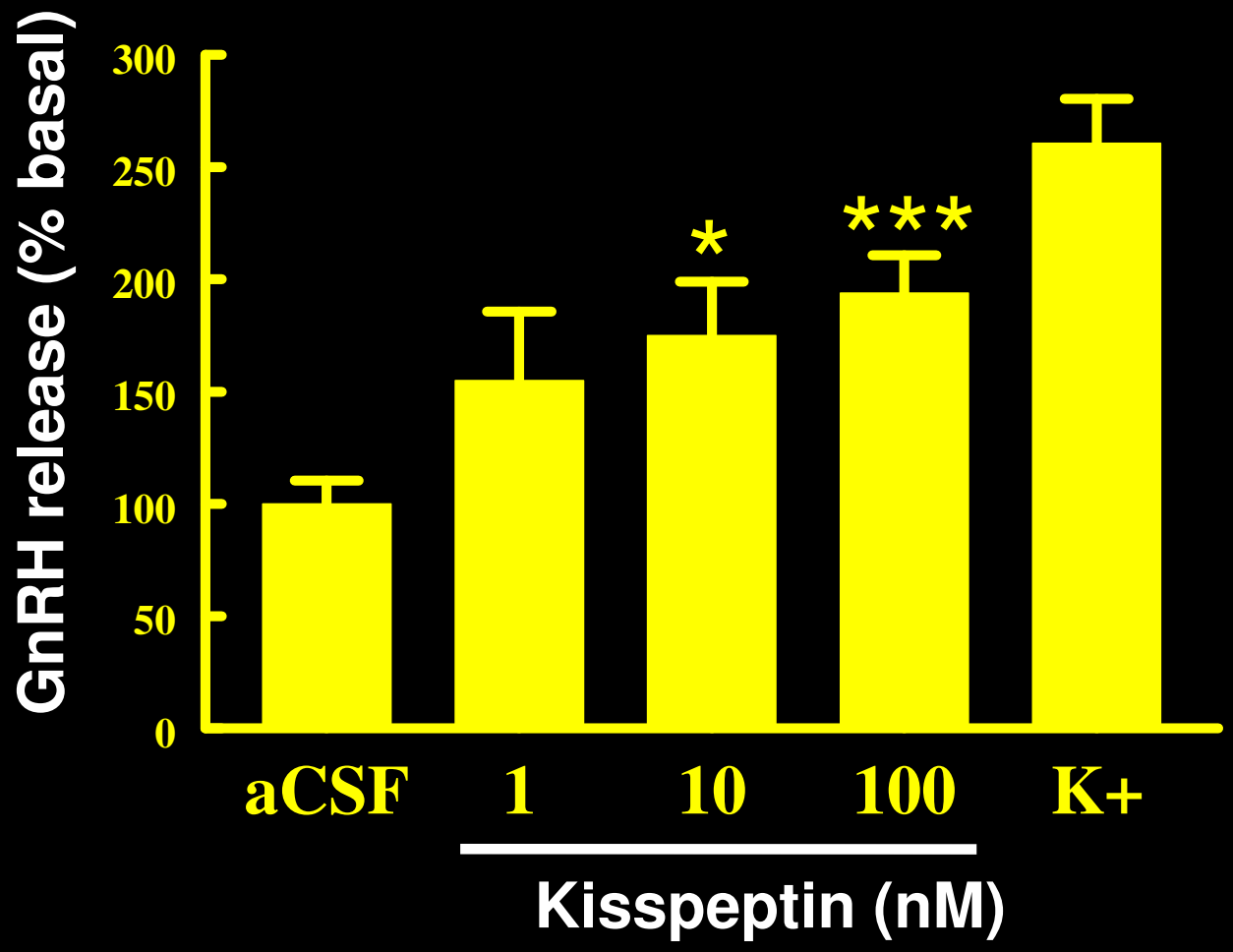
Does kisspeptin stimulate reproductive hormone release ?

ICV kisspeptin stimulates LH release in rats



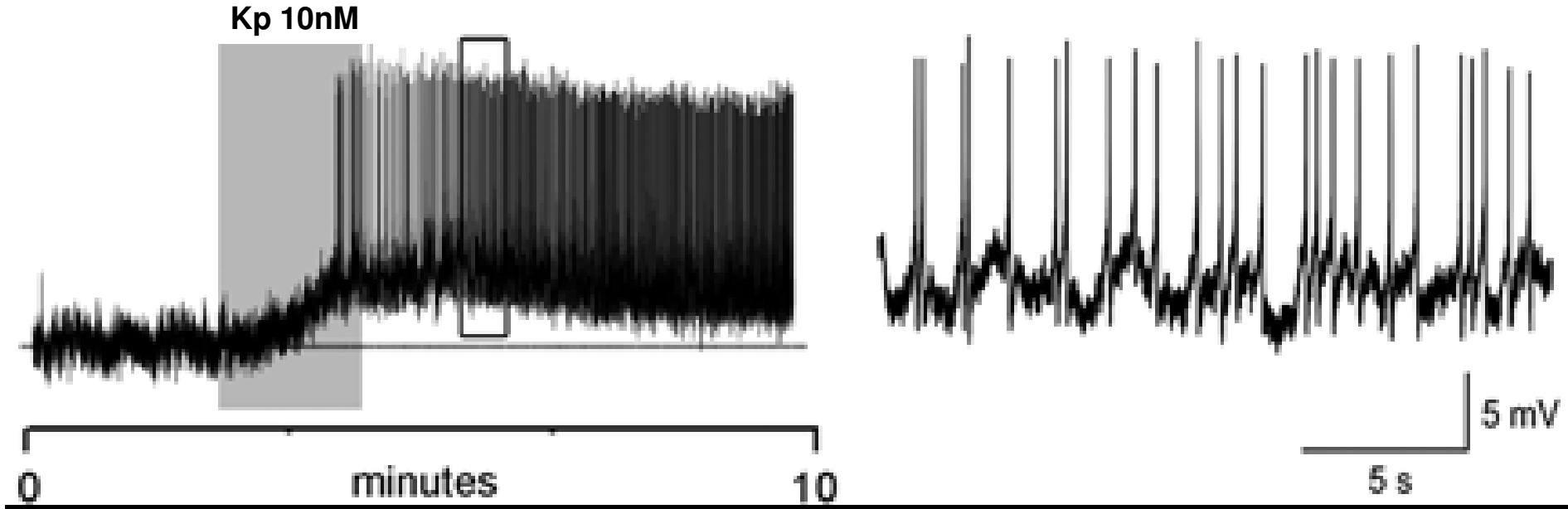
Thompson et al J Neuroendocrinol 2004

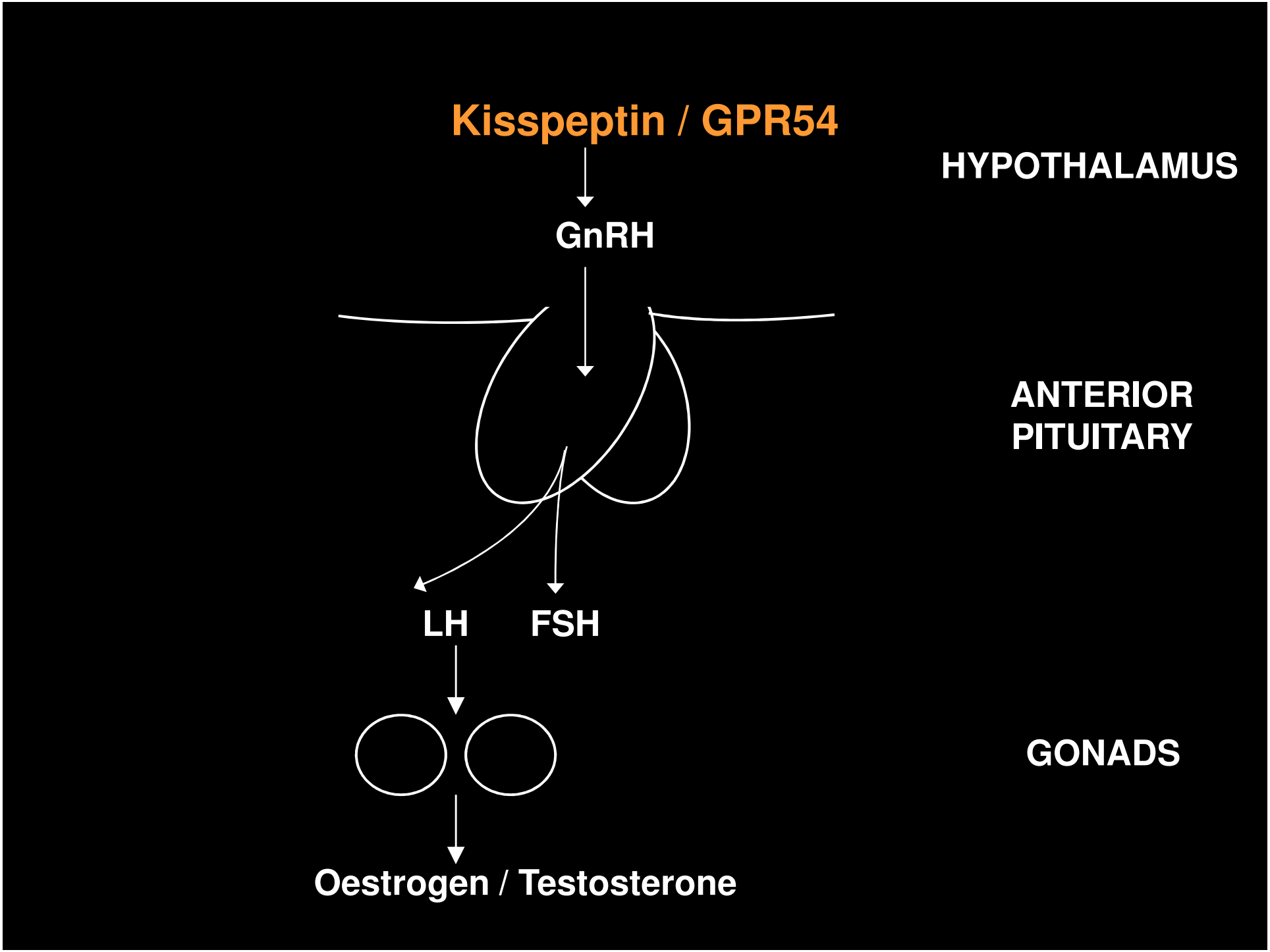
Kisspeptin releases GnRH from hypothalamic explants



Thompson et al J Neuroendocrinol 2004

Kisspeptin directly depolarises GnRH neurons



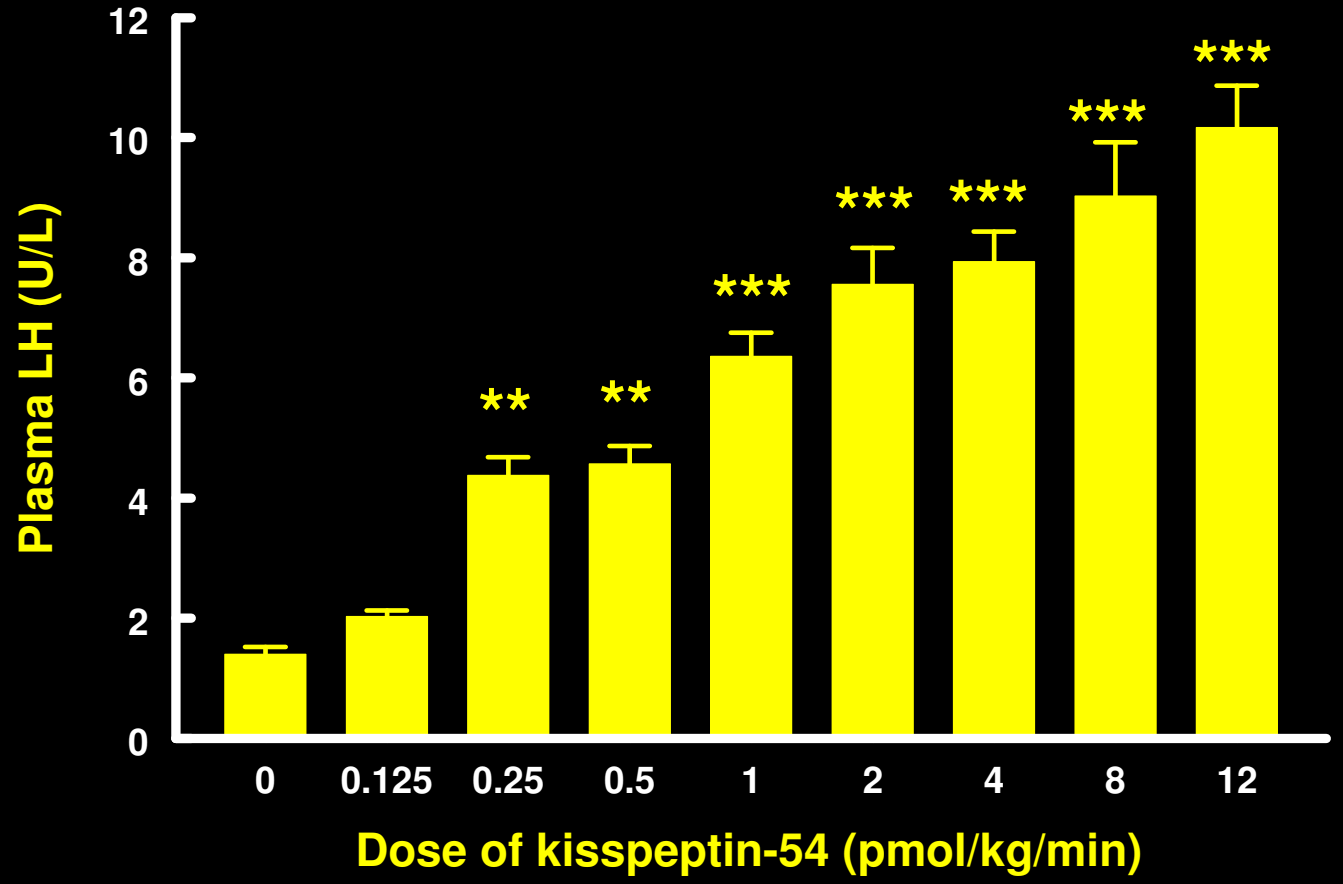

Kisspeptin / GPR54
HYPOTHALAMUS
GnRH
ANTERIOR PITUITARY
LH
FSH
GONADS
Oestrogen / Testosterone

Does kisspeptin stimulate

reproductive hormone

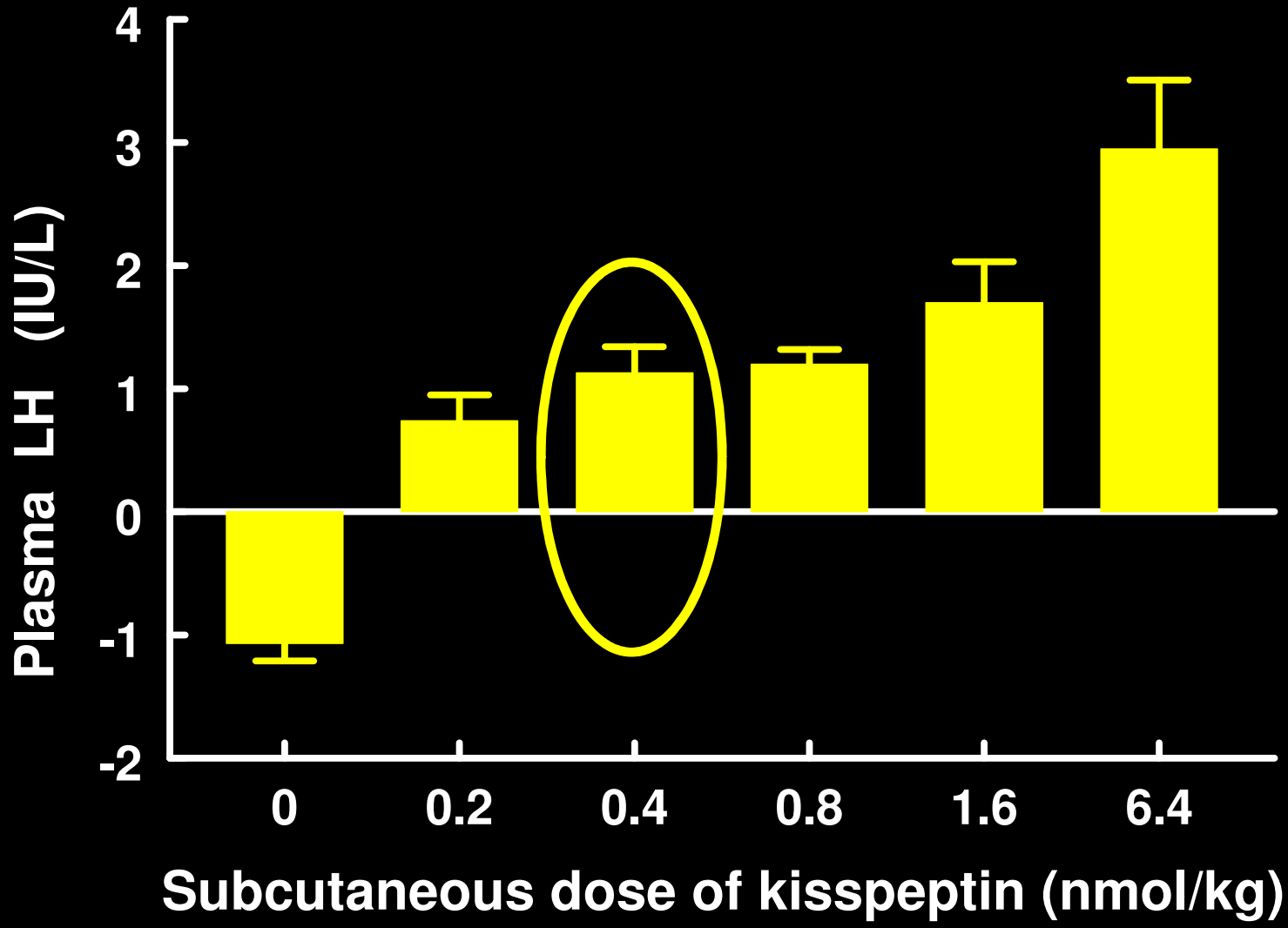
release in humans ?

Kisspeptin increases luteinising hormone release

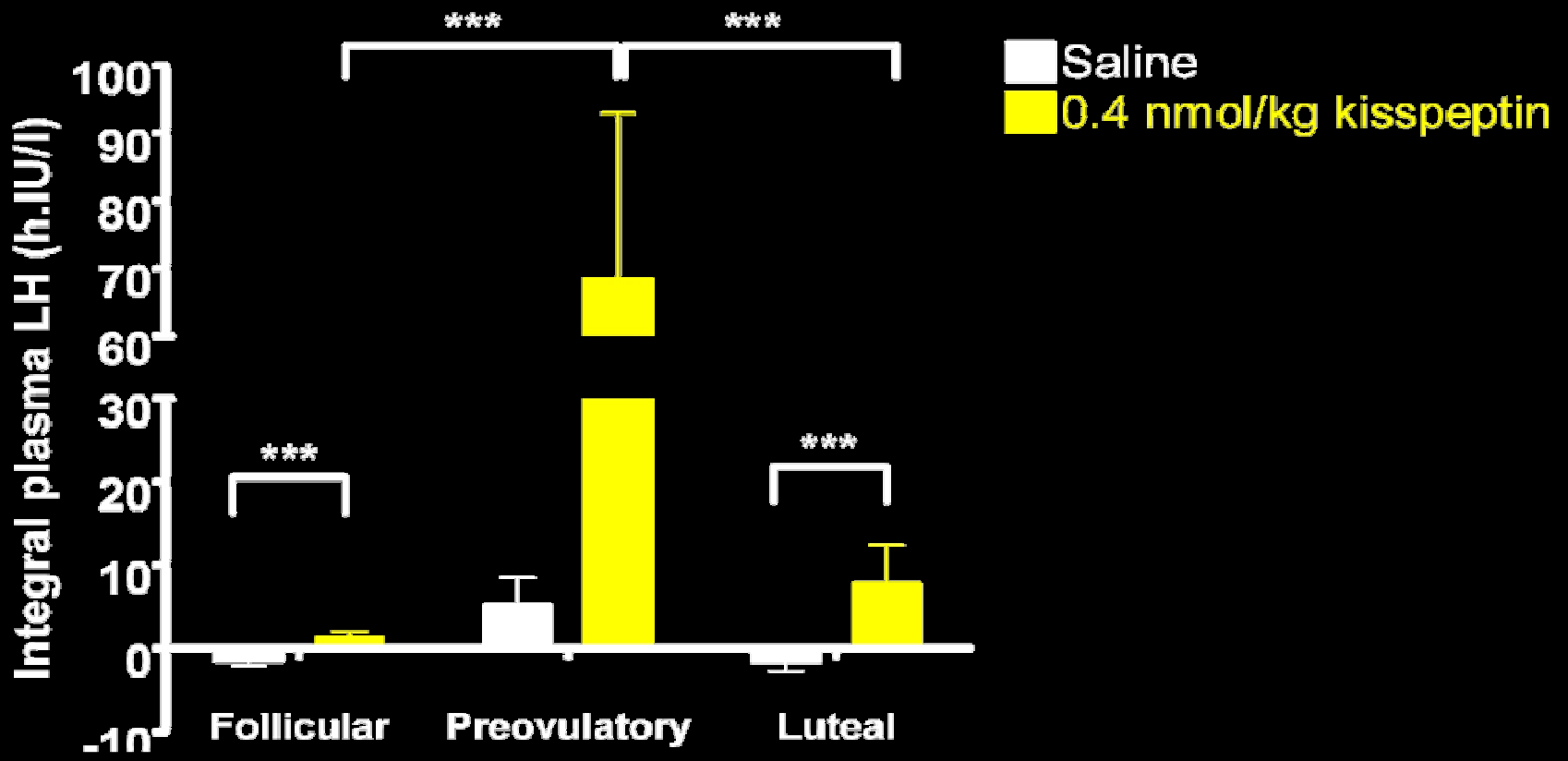


Dhillo *et al.* J Clin Endocrinol Metab 2005

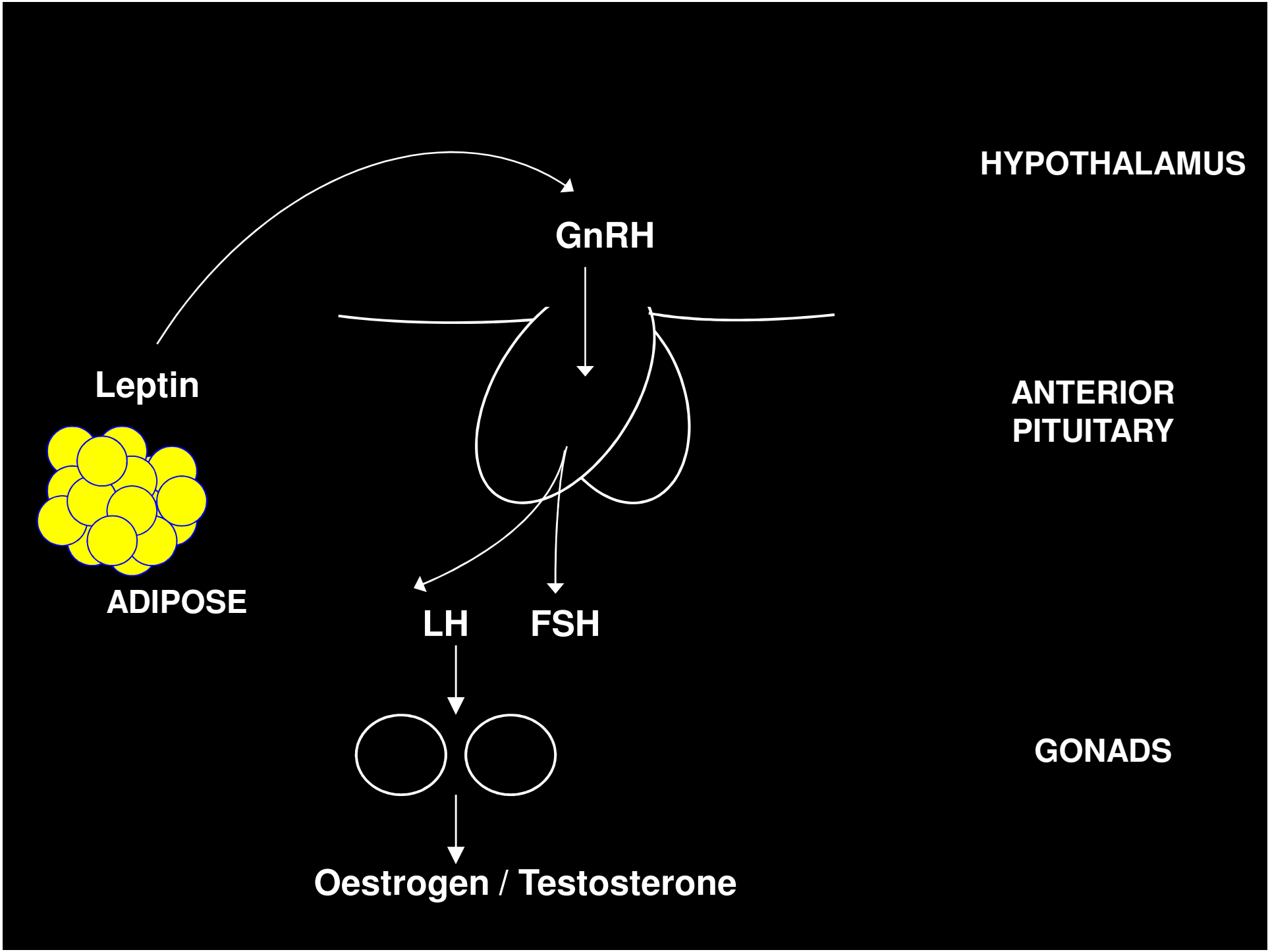
sc kisspeptin increases plasma LH in normal women

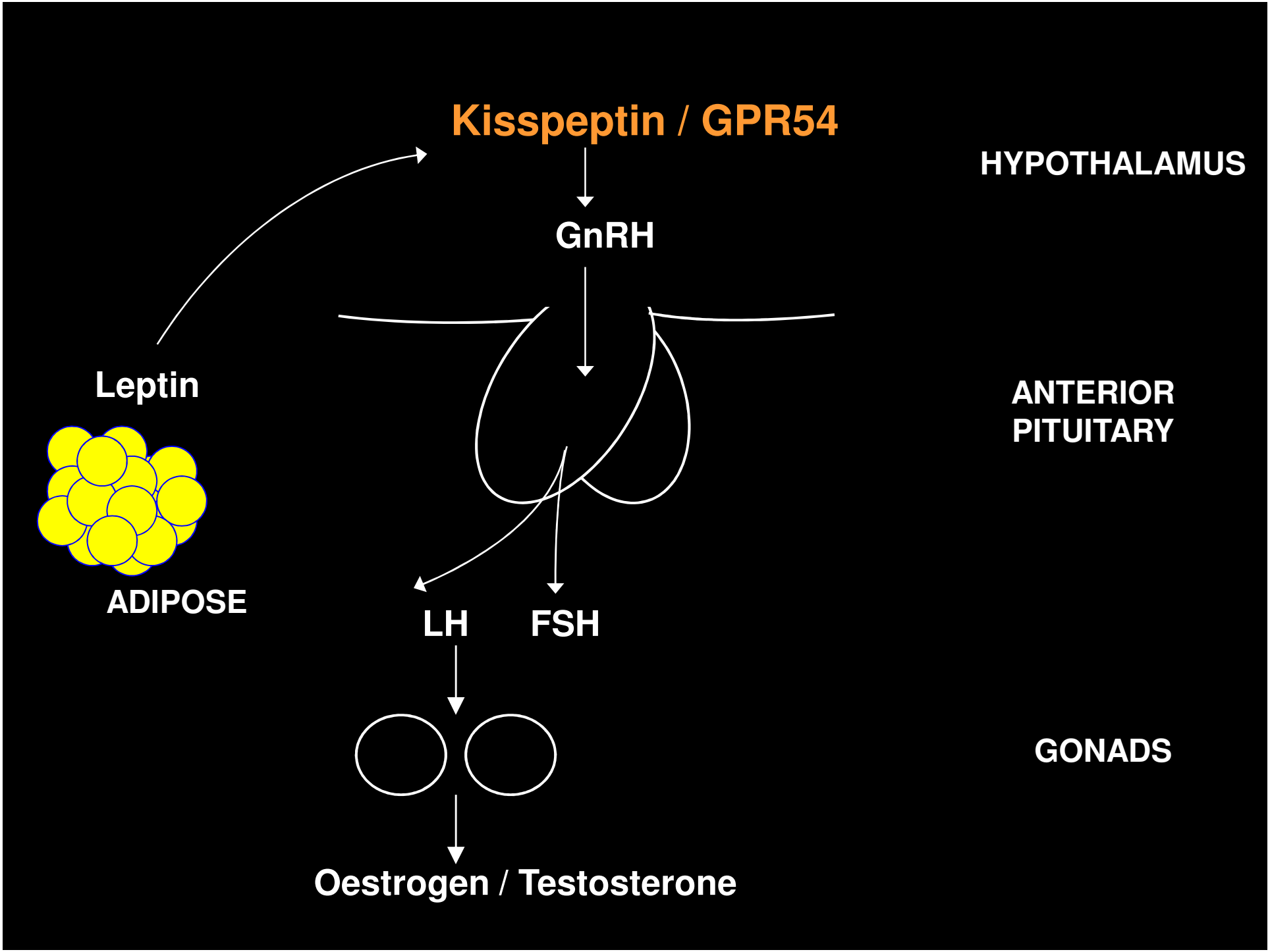


Kisspeptin increases LH release in women



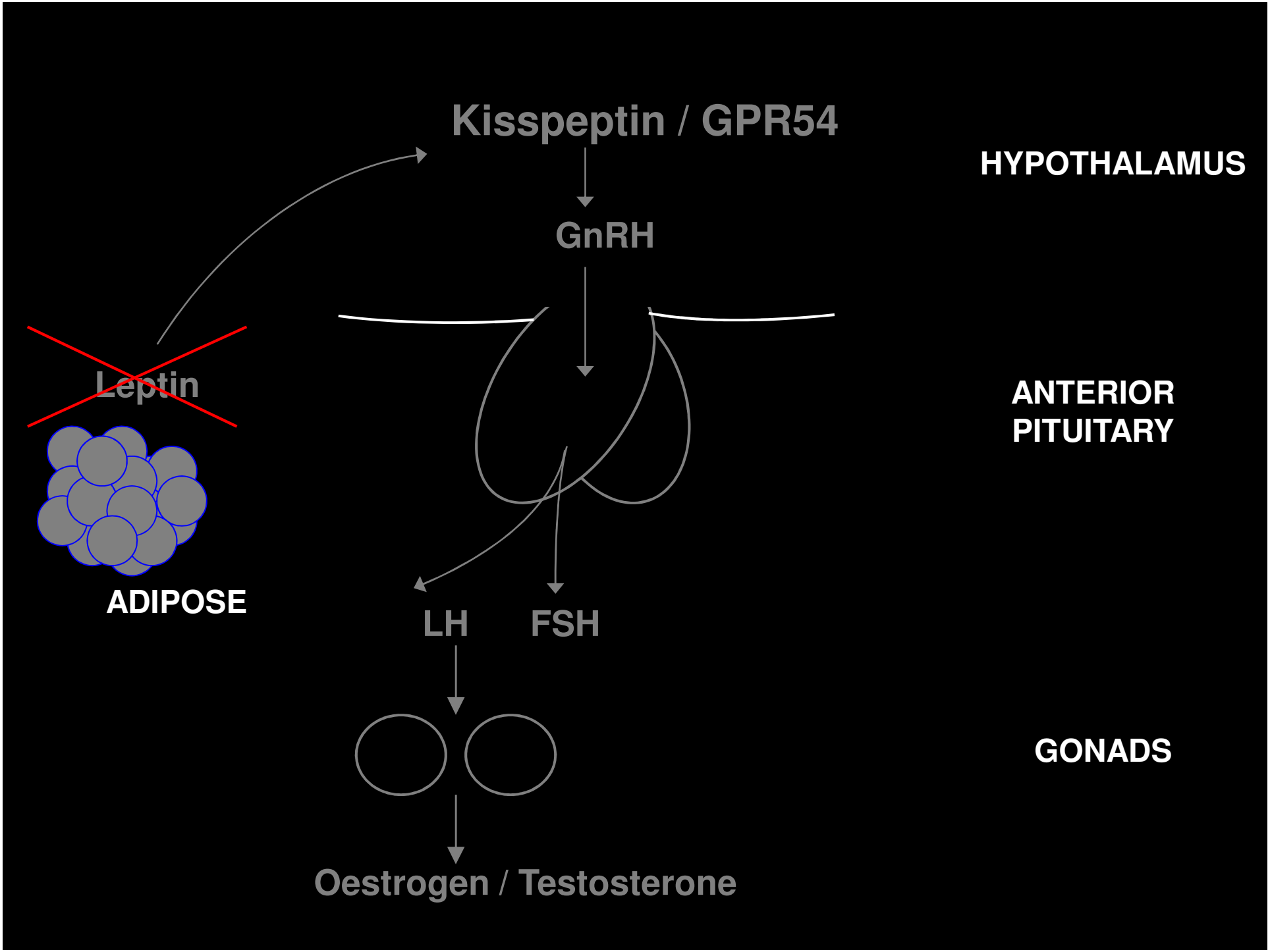
Dhillo *et al.* J Clin Endocrinol Metab 2007

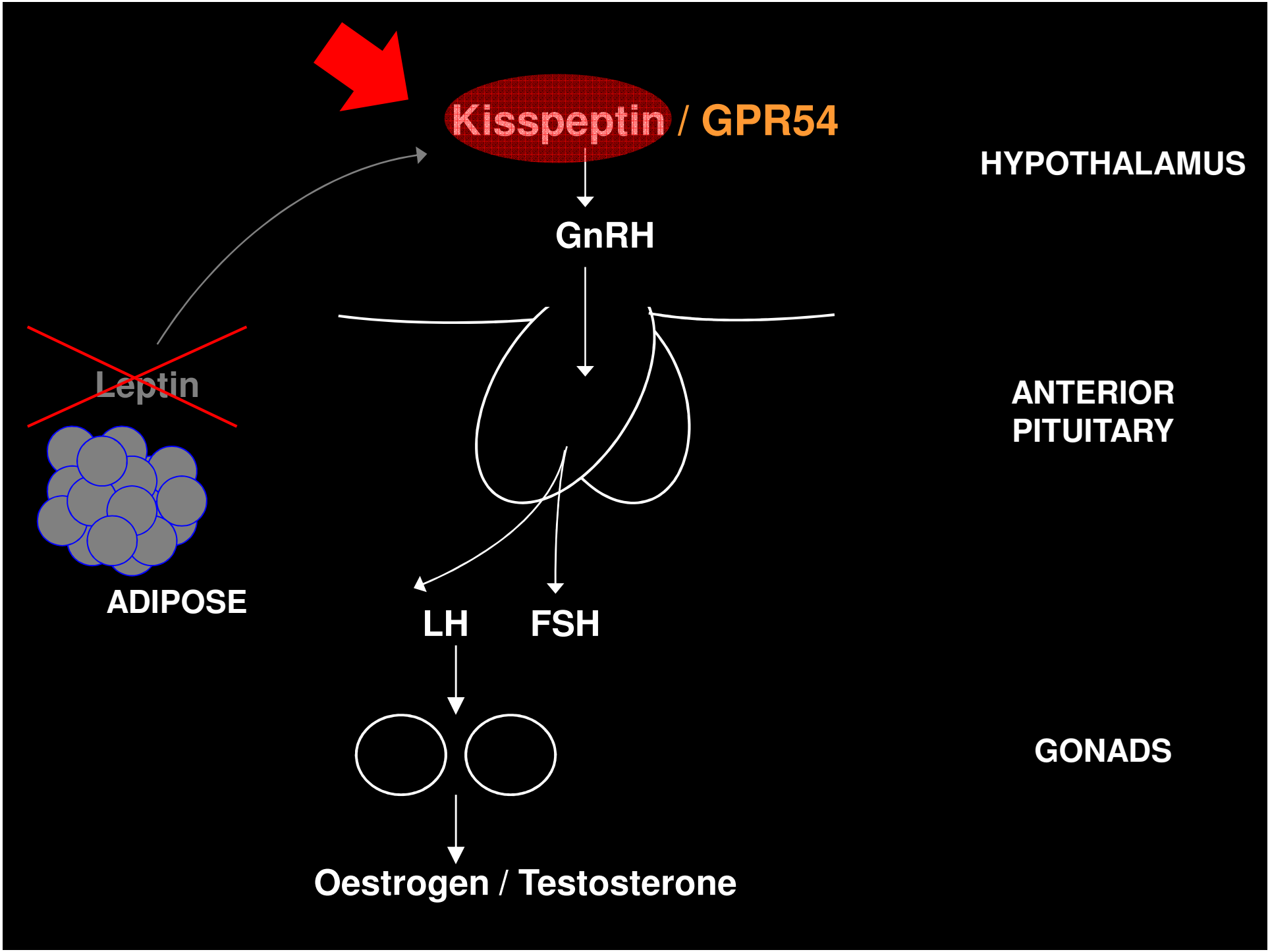

HYPOTHALAMUS
GnRH
Leptin
ANTERIOR
PITUITARY
ADIPOSE
LH
FSH
GONADS
Oestrogen / Testosterone


Kisspeptin / GPR54
HYPOTHALAMUS
GnRH
Leptin
ANTERIOR
PITUITARY
ADIPOSE
LH
FSH
GONADS
Oestrogen / Testosterone

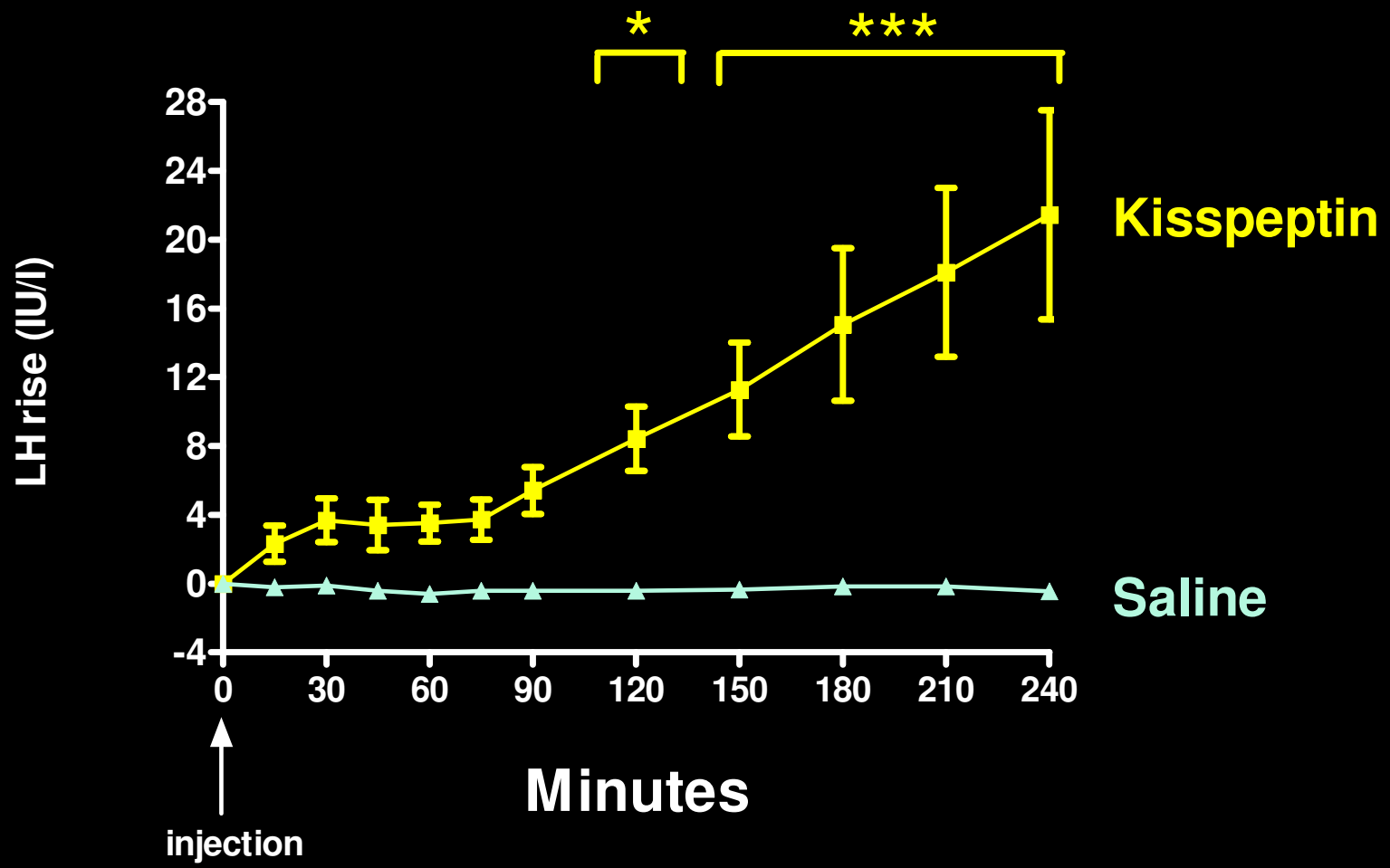
Hypothalamic amenorrhoea (HA)

- 30% of amenorrhoea in women of reproductive age
- Inadequate GnRH secretion. Mostly due to
  - weight loss
  - exercise
- Low leptin levels (70% reduction)


Kisspeptin / GPR54
HYPOTHALAMUS
GnRH
Leptin
ANTERIOR
PITUITARY
ADIPOSE
LH
FSH
GONADS
Oestrogen / Testosterone

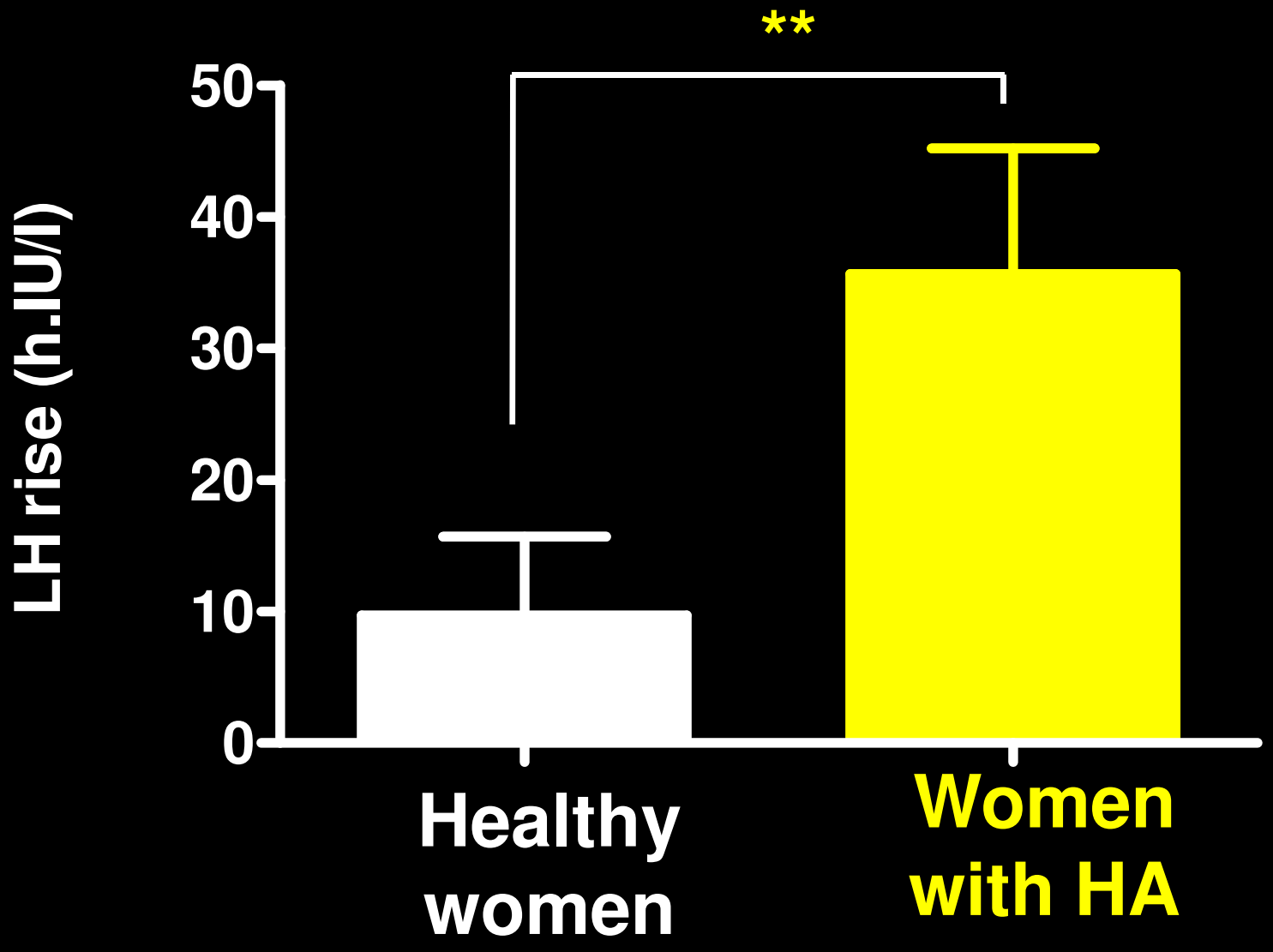

Kisspeptin / GPR54
HYPOTHALAMUS
GnRH
Leptin
ANTERIOR PITUITARY
ADIPOSE
LH
FSH
GONADS
Oestrogen / Testosterone

Kisspeptin increases luteinising hormone release in women with HA



Jayasena *et al.* J Clin Endocrinol Metab 2009 in press

Women with HA are more responsive to kisspeptin than healthy women



Summary

- Reproductive function is regulated by nutritional status
- Orexigenic factors e.g. ghrelin released in food deprivation and inhibit reproductive function
- Anorexigenic factors e.g. PYY and leptin are released when food available and stimulate reproductive function
- Leptin may stimulate reproductive function via release of kisspeptin