Relationship between gut / adipose hormones and reproduction

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**HYPOTHALAMO-PITUITARY-TESTICULAR AXIS**

- **HYPOTHALAMUS**: pulse generator
  - **indirect -ve**: Slows pulse generator
  - **indirect -ve**: Testosterone virilisation

- **ANTERIOR PITUITARY GLAND**:
  - **direct -ve**: LH
  - **direct -ve**: FSH

- **TESTIS**:
  - **direct -ve**: Inhibin
  - **Spermato-genesis**

- **Leydig cell**: Testosterone
- **Sertoli cell**: 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

HYPOTHALAMUS

LEPTIN
- Decreases food intake

GHRELIN
- Increases food intake

PYY
- Decrease food intake
Ghrelin
Ghrelin increases food intake

1min food intake data
Ghrelin makes you fat

Body Weight Change (grams)

Treatment day

Ghrelin

Control
Ghrelin is the only identified hunger hormone in man.
Ghrelin as a meal initiator

Circulating Ghrelin

Breakfast → Lunch → Dinner

Time
Ghrelin hunger

Stomach

Hypothalamus

Ghrelin

+ Stomach

Ghrelin hunger signal
Ghrelin increases when food deprived

Hypothalamus

Ghrelin hunger signal

Ghrelin

Stomach
Ghrelin increases when food deprived

Ghrelin inhibits reproductive function

Ghrelin hunger signal
Effects of ghrelin on the HPG axis

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

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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

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

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

![Bar graph showing caloric intake in Obese and Lean groups with and without PYY$_{3-36}$.]

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

Secretion Proportional to Calory Intake
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
- Hypogonadadotrophic 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?

- No leptin receptors on GnRH neurones

Leptin from adipose tissue stimulates GnRH neurons in the hypothalamus.

GnRH is released, which in turn stimulates the release of LH and FSH from the anterior pituitary.

LH and FSH then act on the gonads to stimulate the production of oestrogen and testosterone.

Oestrogen / Testosterone
How does leptin stimulate reproductive hormone release?

Does leptin stimulate an intermediate signal which stimulates GNRH neurones?
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 GPR54 Gene as a Regulator of Puberty

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

GnRH release (% basal)

Kisspeptin (nM)

aCSF 1 10 100 K+

Thompson et al J Neuroendocrinol 2004
Kisspeptin directly depolarises GnRH neurons
Kisspeptin / GPR54

GnRH

LH

FSH

Oestrogen / Testosterone

HYPOTHALAMUS

ANTERIOR PITUITARY

GONADS
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

Dhill et al. J Clin Endocrinol Metab 2007

Dhill et al. J Clin Endocrinol Metab 2007
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

GnRH

GONADS

ADIPOSE

ANTERIOR PITUITARY

HYPOTHALAMUS

Leptin

LH

FSH

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