

**GUT & ADIPOSE TISSUE
HORMONES
IN**

INFERTILITY & R. P.L

ANOREXIA

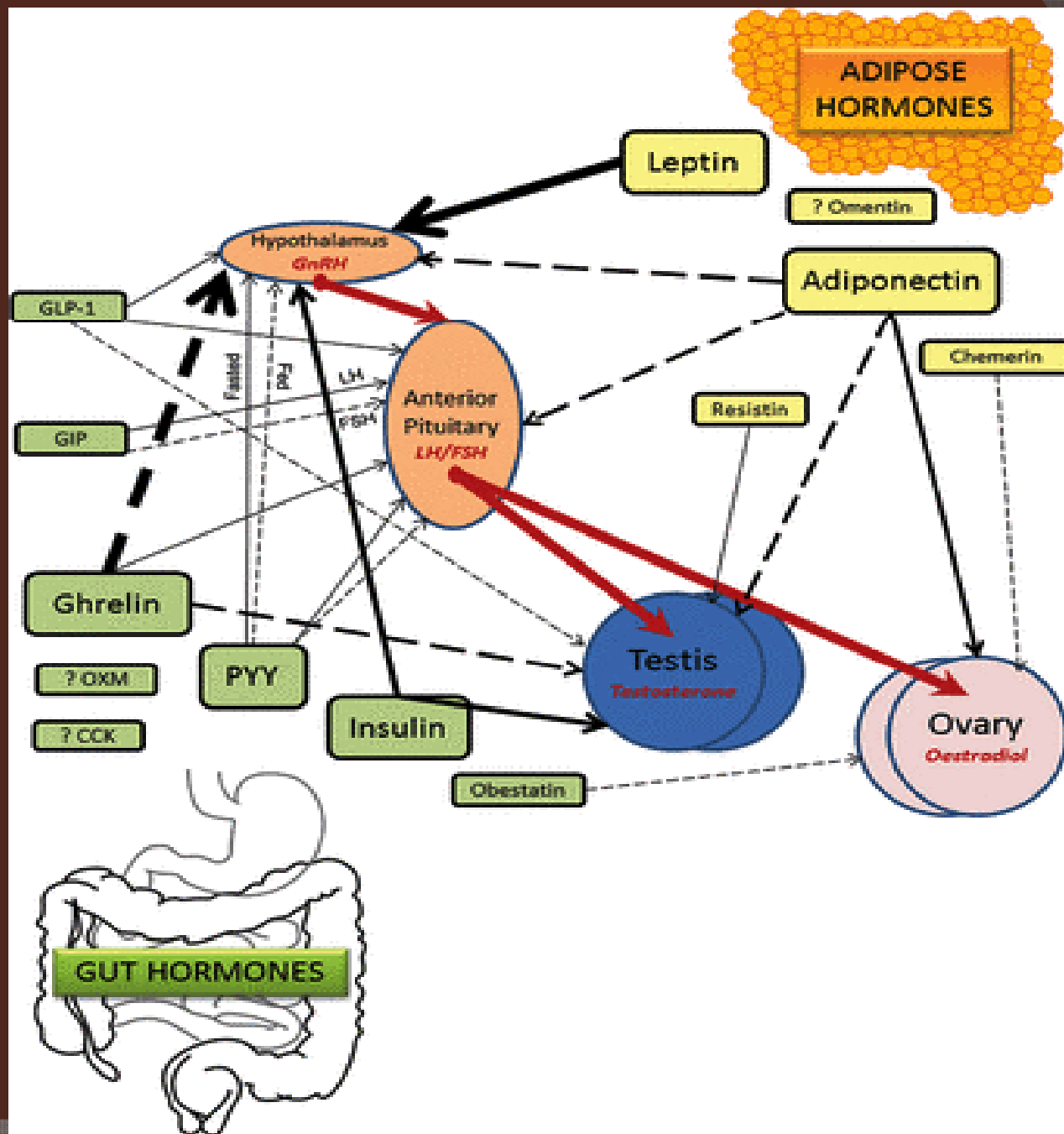
NEVROSA 1960

Gut hormones

- ① 1-Ghrelin
- ② 2-Obestatin
- ③ 3- insulin
- ④ 4-peptide Y Y
- ⑤ 5-Glucagon like peptide
- ⑥ 6-Glucose dependent insulin tropic peptide
- ⑦ 7-Oxyntomodulin
- ⑧ 8- Cholecystokinin

Adipose Hormones

- ① 1- Leptin
- ② 2- Adiponectin
- ③ 3- Resistin
- ④ 4- Omentin
- ⑤ 5- Chemrin



Ghrelin

Secreted by oxynotic cell gastric mucosa

- In male : low level than female
 - Action : increase food intake
 - Receptors : in germ cells & hypothalamus
- In female blood level unchanged by M cycle

High level Ghrelin :

- ① 1- Block LH Surge
- ② 2- Luteolysis
- ③ 3- increase prolactin
- ④ 4- Decrease testosterone
- ⑤ 5- inhibits GnRH pulse
- ⑥ 6- Down regulation kisspeptin (exercise amenorrhoea)

Cyclic expression in endometrium

Low expresstion in unexplain infertility

Insulin

Stimulatory effects on gonad more in female

In female insulin resistant P.C.O & Hyperandrogenism by

- ① 1- Receptor insensitivity
- ② 2- Increase leptin level
- ③ 3- Pro-opiomelanocortin neurons dysfunction

Peptide YY

- Secreted by ileum by food intake
- Increase gonadotropin secretion more in male
- In AN 3 fold Secreted

Glucagon peptide 1

- ⦿ Secreted by ileum terminal with food
- ⦿ Action : regulation of insulin secretion
- ⦿ Increase GnRH release in female
- ⦿ Decrease testosterone in male

Other Gut hormone s had no effects on
Reproduction

Table I

Gut hormones: metabolic and reproductive summary.

| Gut hormone | Metabolism Predominant site of secretion | Stimulus for secretion | Metabolic effects | Reproduction Hypothalamic effects | Pituitary effects | Gonadal effects | Overall effect on reproductive axis |
|-------------|--|------------------------|--|--|--|---|-------------------------------------|
| Ghrelin | Oxyntic cells of gastric mucosa | Fasting | ↑ Feeding/appetite (orexigenic) ↑ Growth hormone | ↓ GnRH | ↑ LH from animal explants ↑ Prolactin | ↓ Leydig cell proliferation, testosterone secretion, luteal function and progesterone release | ↓ |
| Obestatin | Oxyntic cells of gastric mucosa | Fasting | May have similar effects to ghrelin | — | — | ↓ Human luteal cell function | Unclear |
| Insulin | Pancreatic β-cells | Glucose intake | Multiple effects on glucose homeostasis | ↑ LH in mice via GnRH ↑ LH pulse frequency in women | — | ↑ Spermatozoal DNA synthesis and differentiation in newt Exogenous insulin can regenerate testis and restore fertility in hypogonadal rats | Permissive/↑ |
| PYY | Entero-endocrine L-cells of distal ileum and colon | Food intake | Glucose homeostasis, anorectic | ↑ GnRH release in fasted but ↓ GnRH in fed adult rat | Controversial. ↓↑ Gonadotrophins in adult male rats ↓ Gonadotrophins in prepubertal male rats (no change in females) | — | ↓ |
| GLP-1 | Ileum and colon | Carbohydrate and fat | Insulin release, delayed gastric emptying, anorectic | ↑ GnRH | ↑ LH in male rats <i>in vivo</i> ↔LH in healthy men | ↓ LH-independent testosterone pulse frequency in healthy men | Unclear |
| GIP | K-cells of small intestine | Carbohydrate and fat | Insulin release | — | ↑ LH and FSH secretion <i>in vitro</i> ↓ FSH (but not LH) <i>in vivo</i> (rat) | — | Unclear |
| OXM | Entero-endocrine L-cells of distal ileum and colon | Carbohydrate and fat | Decrease gastric acid secretion and ghrelin, anorectic | — | — | — | Unclear |
| CCK | Entero-endocrine L-cells of upper small intestine | Fat/protein | pancreatic enzyme, bile and insulin release, anorectic | — | — | — | Unclear |

Hypothalamic effects include studies where proven GnRH-dependent gonadotrophin changes were observed (otherwise listed as pituitary effect). The overall effect on the reproductive axis determined by review of currently available data. The '—' symbol signifies no data available. (CCK, cholecystokinin; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; OXM, oxyntomodulin; PYY, peptide YY3-36.)

Leptin

- The gene located in chromosome 7
- Two receptors
- 8 mutation in gene & 3 mutation in receptors
- All are in eastern countries and led to obesity

Site of synthesis Leptin Leptin

- ◉ White & brown adipose tissue
- ◉ Placenta & Ovary
- ◉ Skeletal muscles & bone marrow
- ◉ Stomach lower part fundic glands

Leptin level Increase by :

- ⦿ Food intake
- ⦿ Obstructive sleep apnea
- ⦿ Emotional stress
- ⦿ Testosterone ; dexametazon ; insulin ; estrogen
- ⦿ Paradoxically in obesity; P.C.O
- ⦿ DECREASE by ; fasting ; physical exercise
- ⦿ Sleep deprivation ; melatonin

Site of action

- Central : hypothalamic inhibit hunger
- Cognitive change : improve Alzheimer
- Induce GnRH production (early menarche)
- Genetic leptin deficiency : hypothalamic delay
- Puberty & severe obesity
- Leptin & kisspeptin with glutamate in female
- Regulate GnRH production

Peripheral

- ⦿ Leptin modulate I.G.F on granulosa cell
- ⦿ Increase estrogen decrease progesterone
- ⦿ Decrease A.M.H;
- ⦿ Increase beta2 integrin; L.I.F.; iL1 in endometrium
- ⦿ Hyperprolactinemia
- ⦿ High level in peritoneal fluid of endometriosis

Pregnancy

- ⦿ Stepwise increase between 5 to 8 weeks
- ⦿ High level with insulin resistant ;abortion
- ⦿ Low level in this time ;abortion
- ⦿ Induce hyper emesis
- ⦿ Inhibit uterine contraction
- ⦿ Fetal lung : induce surfactant
- ⦿ Increase in R.P.L

Circulatory system

- ⦿ Angiogenesis VEGF increase
- ⦿ As iL6 induce hypo-adrenal axis
- ⦿ Pro inflammatory & mitogenic factor modulate
- ⦿ T cells

Adiponectin

- ⦿ Exclusively from white adipose tissue ;placenta
- ⦿ Level related to percentage fat index
- ⦿ Decrease by obesity; metabolic syn. Fatty liver;
- ⦿ Diabetes type 2; Atherosclerosis. C.R.P .T.N.F
- ⦿ Increase by exercise ; fasting; weigh reduction;
- ⦿ E.P.A ; D.H.A ; nyasine ; sweet potato
- ⦿ T.N.F alpha inhibitor

Circulatory effect

- ⦿ Antagonist leptin action
- ⦿ Decrease T.N.F alpha
- ⦿ Protection endothelial from atherosclerosis
- ⦿ Decrease hypertension
- ⦿ Syncitualisation of trophoblast
- ⦿ Anti inflammatory action in decidua

Metabolic effects

- Increase glucose uptake
- Decrease gluconeogenesis
- Triglyceride clearance
- Beta oxidation of lipid
- Insulin sensitivity
- Weight loss

Three receptors 1;2; T cadherin

Receptor 1 Semeniferous tubule

2 gonadotrope

Leptin /adiponectin ratio correlated with B.M.I

$-.3 - -.8$

Omentin

- ⦿ Anti inflammatory action
- ⦿ Increase by metformine ; insulin
- ⦿ Decrease by diabetes 2 ; obesity P.C.O

Chemerin

- ⦿ Increase in P.C.O; diabetes 2; obesity
- ⦿ Decrease hormone production in follicle

Resistin (resist in insulin)

- Decrease insulin sensitivity; increase inflammatory cytokine
- Level not change in obesity .P.C.O.
- Increase in diabetes 2; M.S . breast ca.

The relationship between gut and adipose hormones, and reproduction

Table II
Adipose hormones: metabolic and reproductive summary.

| Adipose hormone | Metabolism | | | Reproduction | | | Overall effect on reproductive axis |
|-----------------|------------------------------------|-----------------------------------|---|--|--|--|-------------------------------------|
| | Predominant site of secretion | Stimulus for secretion | Metabolic effects | Hypothalamic effects | Pituitary effects | Gonadal effects | |
| Leptin | Adipocytes | Adipocyte reserves | Marker of energy stores, anorectic | Permissive role in kiss/glut-stimulated GnRH secretion | — | — | ↑ (permissive) |
| Adiponectin | Adipocytes in white adipose tissue | Negative correlation with obesity | ↑ Insulin sensitivity ↑ Fatty acid oxidation | ↓ GnRH secretion (via ↓ KISS1 transcription) | ↓ LH secretion in rodents | ↑ Ovarian IGF-induced progesterone and estrogen production in rat ↓ Choriogonadotrophin-stimulated testosterone secretion in rat testis | ↓ |
| Resistin | Adipocytes and macrophages | Inflammatory stimuli | ↑ Insulin resistance, role in inflammatory pathways | Resistin mRNA expressed | Resistin mRNA expressed with peak expression during puberty (mice) | ↑ hCG-stimulated testosterone secretion <i>in vitro</i> Gonadotrophins ↑ resistin expression in Leydig and Sertoli cells | ?↑ |
| Omentin | Adipocytes, placenta, ovary | Inflammatory stimuli | ↑ Insulin sensitivity, inflammatory pathways | — | — | — | Unclear (lower levels in PCOS) |
| Chemerin | Adipocytes and liver | Inflammatory stimuli | Adipocyte differentiation, glucose homeostasis, inflammatory pathways | — | — | ↓ Progesterone and estradiol | ?↓ |

Hypothalamic effects include studies where proven GnRH-dependent gonadotrophin changes were observed (otherwise listed as pituitary effect). The overall effect on the reproductive axis determined by review of currently available data. The '—' symbol signifies no data available. (PCOS, polycystic ovary.)

Cytokines made by adipose tissues

- ① 1- iL 6 / iL 8 / iL 10
- ② 2- T . N . F alpha
- ③ 3- I . N . F gama
- ④ 4- Monocyte chemotactic protein 1
- ⑤ 5- Visfatin
- ⑥ 6- P.A.I

In treatment for infertility & RPL

Gut & adipose tissue hormone assay

With BMI must be in close with others

Investigation

Thank you for your attention

