HYPOTHALAMIC AND ANTERIOR PITUITARY HORMONES

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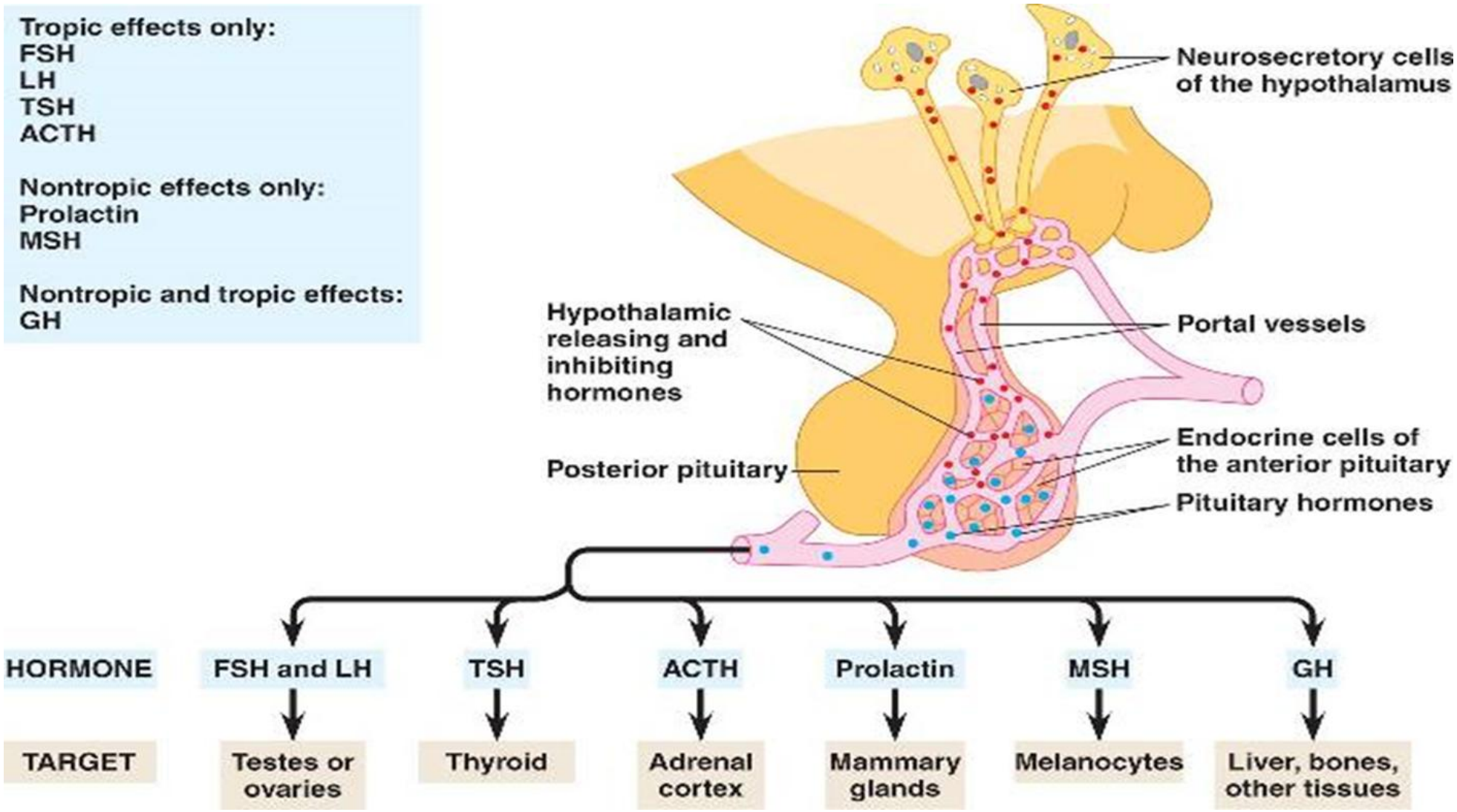
HYPOTHALAMIC-PITUITARY RELATIONSHIP

Tropic effects only:
FSH
LH
TSH
ACTH

Nontropic effects only:
Prolactin
MSH

Nontropic and tropic effects:
GH



HYPOTHALAMIC-PITUITARY RELATIONSHIP

- Pituitary gland is connected to hypothalamus by the stalk that contains neurosecretory fibers, capillaries & the hypophyseal portal system that drains the hypothalamus & perfuses the anterior pituitary by a number of releasing factors (RF) or releasing hormones.
- These hypothalamic releasing factors/hormones stimulate the anterior pituitary to produce & secrete a number of tropic hormones, that in turn stimulate target glands to secrete hormones which finally act on the cells of target organs far away from the site of their release.
- Pituitary hormone secretions are regulated by negative feedback mechanisms. These pathways are “long” as well as “short” negative feedback pathways.
- If the hormone secreted affects both the hypothalamus & pituitary, then it makes a long negative feedback loop. If they affect only pituitary, then it is a short negative feedback loop.

PITUITARY HORMONES (Overview)

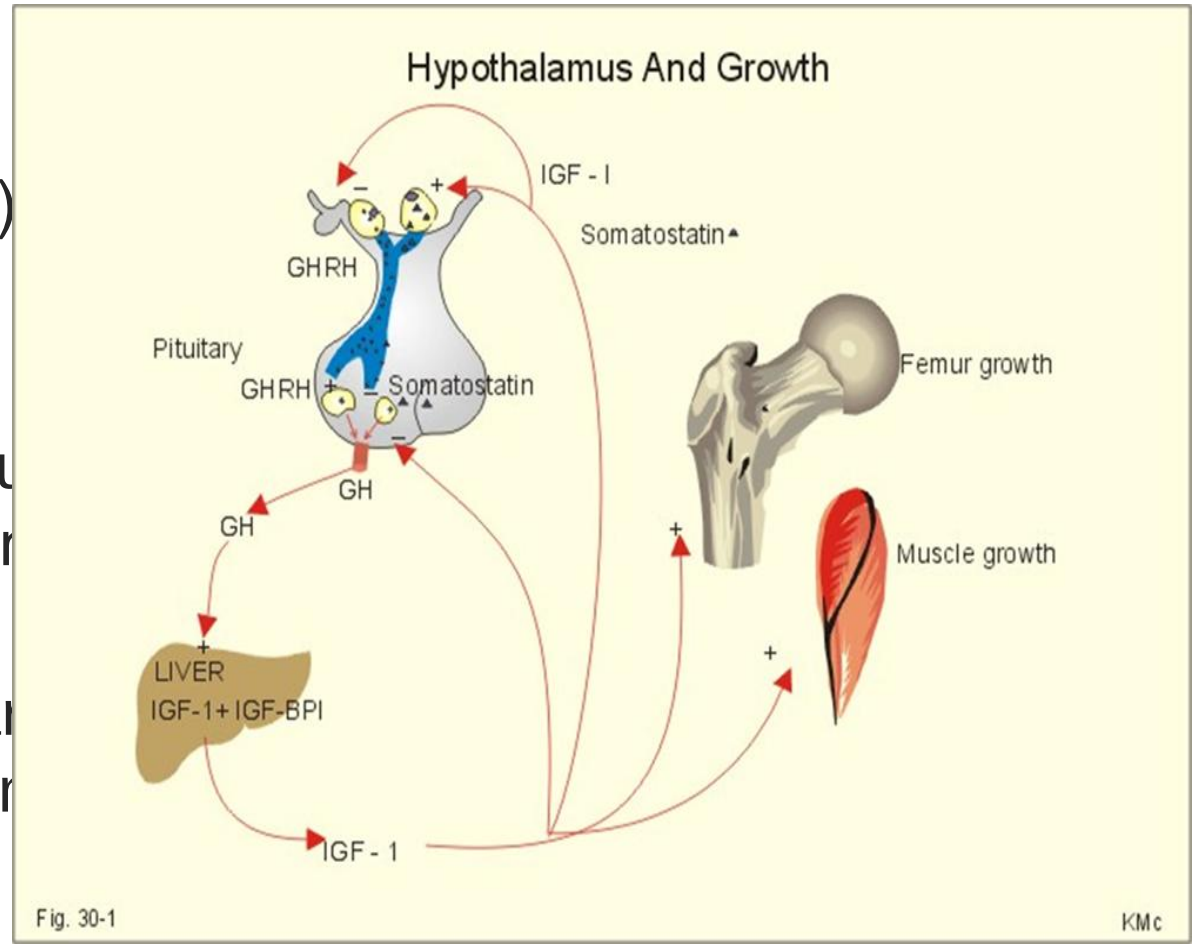
Anterior Pituitary (Adenohypophysis)	Growth hormone (GH)
	ACTH
	TSH
	FSH
	LH
	Prolactin
Intermediate Pituitary	Melanocyte Stimulatory Hormone (MSH)
	γ- lipoprotein
Posterior Pituitary (Neurohypophysis)	Vasopressin (ADH)
	Oxytocin

GROWTH HORMONE (GH)

- GH secretion is high in newborn till 4 yrs of age & starts declining after 25 yrs.
- Pharmacological Effects of GH:

-↑protein synthesis (anabolic)

- Positive N2 balance (↑AA uptake in cells)
- Anabolic effects are mediated by somatomedins (IGF-1 & IGF-2)
- Initially insulin like effects & later anti-insu effects: ↑blood glucose, ↑FFA mobilizatior ketone body formation.
- IGF-1 inhibit GH release from ant. pituitar stimulate GHRIH release from hypothalar



GH Regulating Factors

- GHRH (Growth hormone releasing hormone):- released from hypothalamus, regulate GH release.
- GHRH analogue: *Sermorelin*- used as diagnostic agent for testing pituitary GH secretion capability in childhood short stature.
- GHRIH (Growth hormone release-inhibiting hormone) – Somatostatin
  It inhibits secretion of GH, TSH, insulin & gastrin.
  Uses: upper GI bleed (oesophageal varices, haemorrhagic gastritis)
- Somatostatin analogues: *Octreotide, Sandostatin, Lanreotide*
- GH receptor antagonist: *Pegvisomant*

Somatostatin analogues

- Octreotide:

  Inhibits GH release
  Long acting & more potent than somatostatin
  Dose: 50-200 µg S.C. TDS
  Uses: GH-secreting pituitary tumours
  Carcinoid syndrome, VIP-secreting tumour
  Gastrinoma, Insulinoma
  Diarrhoea associated with diabetes & AIDS
  Oesophageal varices & bleeding peptic ulcer (↓mucosal blood flow)
  A/E: abdominal pain, nausea, steatorrhoea, gall stones

- Sandostatin:

  slow release formulation of octreotide

Excess GH Production

- Before puberty, it causes gigantism
- After puberty, it causes acromegaly (enlargement of legs, arms & lower jaw protrusion)
- Treatment of Acromegaly:
    - Dopamine agonists (L-dopa, bromocriptine)
    - Surgical intervention
    - Octreotide
    - Lanreotide – longer formulation, recently approved
    - Pegvisomant – new drug approved
        GH receptor antagonist
        also ↓serum IGF-1 levels

GH Deficiency

- It leads to dwarfism (short stature).
- Recombinant human GH (rhGH): *Somatropin* & *Somatrem* most commonly used.
- *Somatropin*: children with short stature
  for increasing height of girls with Turner syndrome
  AIDS related muscle wasting
  Burn injuries
  Abused by athletes for anti-aging effects
- Adverse effect of *Somatropin* : type 2 DM precipitation, insulin resistance, arthralgia, pain at injection site, lipodystrophy, fluid retention & headache.
- During GH treatment , hypothyroidism may be unmasked, so periodic assessment of TSH is necessary.

GH Deficiency

- Short statured children may have IGF-1 deficiency which does not respond to GH treatment.
- IGF-1 deficiency may be due to the following reasons:
  - mutant GH receptor with aberrant GH signaling
  - development of antibodies against GH
  - deficiency of IGF-1 binding protein(IGFBP-3), which decreases IGF-1 t½
- *Mecasermin*: rhIGF-1 + rhIGFBP-3
  - It maintains desired t½ of IGF-1
  - adverse effect: hypoglycaemia (given with food)
    - reversible elevation of liver enzymes
    - intracranial hypertension

THYROID STIMULATING HORMONE (TSH)

- Pulsatile secretion which follows biological rhythm, highest during sleep in night.
- Stimulates thyroid to produce T_3, T_4 & thyroglobulin.
- Promotes trapping of iodine by thyroid.
- Thyrotropin alpha/ recombinant human TSH(rhTSH): used in detection of metastatic differentiated thyroid carcinoma (↑ I^{131} uptake by cancer cells).
- TSH secretion is controlled by TRH(from hypothalamus), which in turn is inhibited by T_3 & T_4 negative feedback mechanism.
- TRH (protirelin) also stimulates lactotrophs to secrete prolactin.

PROLACTIN

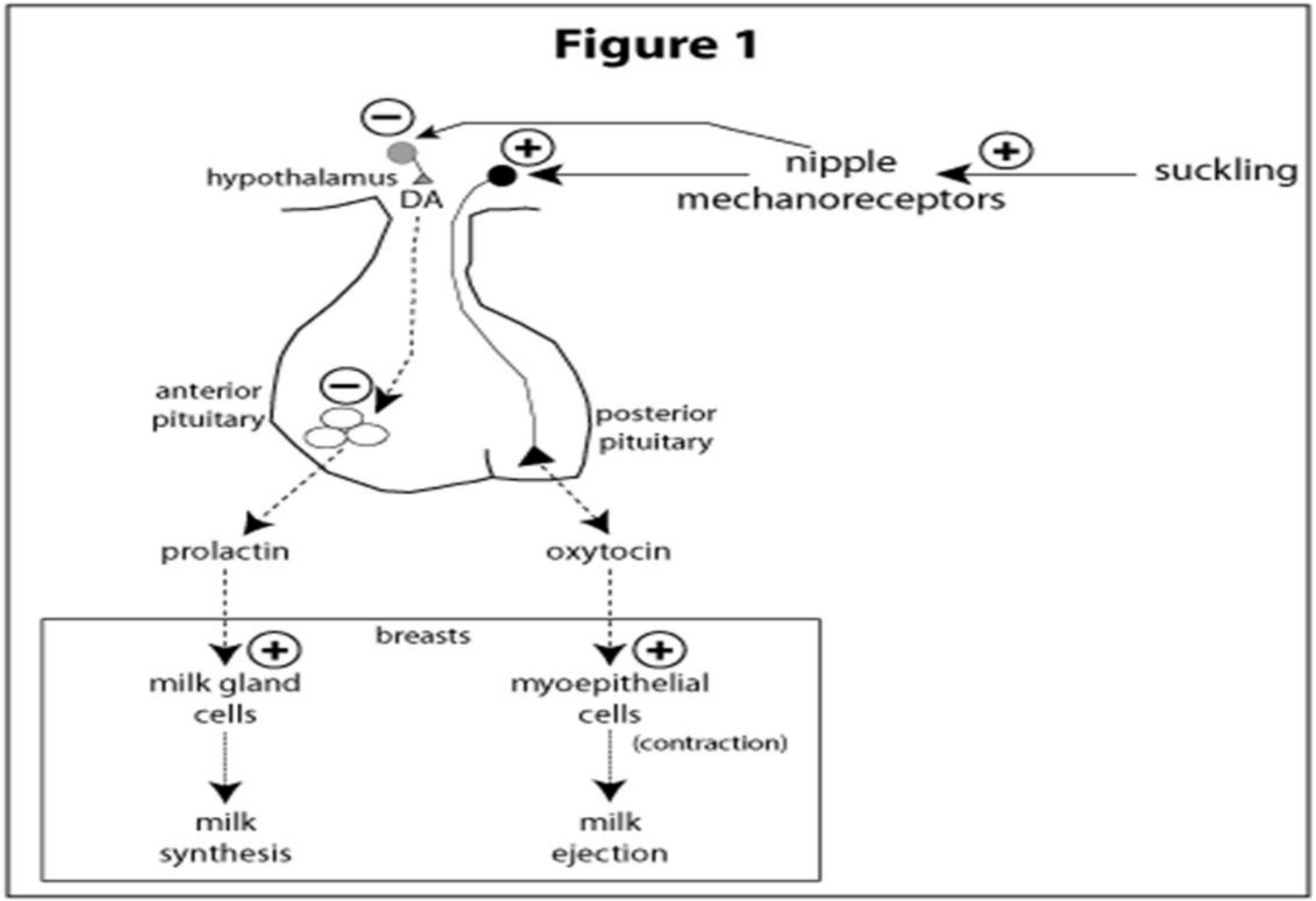
- PRL is mammotropic (growth of milk secreting epithelium) & lactogenic (milk producing) hormone.
- PRL release inhibiting hormone is dopamine (act on D_2 receptors of lactotrophs).
- Conversely, DA antagonists ↑ PRL release. E.g., Chlorpromazine, haloperidol, metoclopramide, α- methyldopa. Hence, these drugs have S/E of galactorrhoea & gynaecomastia.
- PRL release stimulating factors: suckling, sleep, orgasm, stress, hypoglycaemia, VIP, hypothyroidism & chronic renal failure.

PROLACTIN

- PRL deficiency: failure to lactate or luteal phase defect
- PRL excess (hyperprolactinaemia):
  Females: galactorrhoea, amenorrhoea, infertility
  Males: gynaecomastia, hypogonadism, loss of libido & impotence
  Treatment: DA agonist (bromocriptine, cabergoline, pergolide, quinagolide)
  -They reduce size of pituitary prolactinomas.
  Adverse effects: syncope, nausea and vomiting, constipation, hallucinations.

Prolactin & Oxytocin

Suckling stimulate mechanoreceptors in nipples which stimulates Oxytocin release and also prolactin release by inhibiting the PRL inhibiting hormone, i.e., dopamine. Prolactin & Oxytocin together controls milk synthesis & milk ejection respectively.



THANK YOU