M.Sc. 4th Semester
Subject: Human Physiology
Paper: PHY-401
Unit:33
Module: 01
Topics: General concepts of endocrinology and hormonal actions, Neuroendocrinology
Name of the Teacher: Dr. Ankita Das

Laboratory evaluation of the endocrine system

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Endocrine disorders

(a) **Central level (Hypothalamic / pituitary disease)**

(b) **Peripheral level (Dysfunction of peripheral gland)**

(c) **Receptor / postreceptor level (Target cell insufficiency - low sensitivity to hormone action)**

Examination Methods

Laboratory tests

Plasma hormone levels (ELISA, RIA)
Hormone diurnal rhythm
hormones / metabolites
Stimulatory / inhibitory test
Standard biochemistry (Na, K, glucose...)

Graphic procedures (imaging)

Ultrasonography
CT / MRI
Scintigraphy

Other

Endoscopy
Perimeter

Na^+, K^+	... aldosterone, cortisol, ADH
Ca^{2+}	... PTH, vitamin D, (calcitonin)
Glycaemia	... insulin, glucagon, cortisoids, catecholamines, STH ...
Cholesterol	... hypothyroidism, Cushing´s syndrome
Osmolarity / diuresis	... water / osmotic polyuria (diabetes insipidus, diabetes mellitus...)

Water and Na^+/K^+ balance

- Aldosterone
- Cortisol
- Vasopressin (ADH)
- Natriuretic peptides (ANP, BNP, CNP)
- Insulin

Hormones

Examination approach

Basal hormonal concentrations

1. Basal plasma levels (one-time examination)
2. Diurnal dynamics of hormone concentrations (e.g. cortisol)
3. Other hormonal cycles (e.g. menstrual phase dynamics)
4. Urinary output
5. Hormonal metabolites - plasma, urine (e.g. C-peptide)
6. Indirect evaluation - measurement of a metabolic response
   (ADH ... diuresis, insulin ... glycaemia etc.)

Functional tests

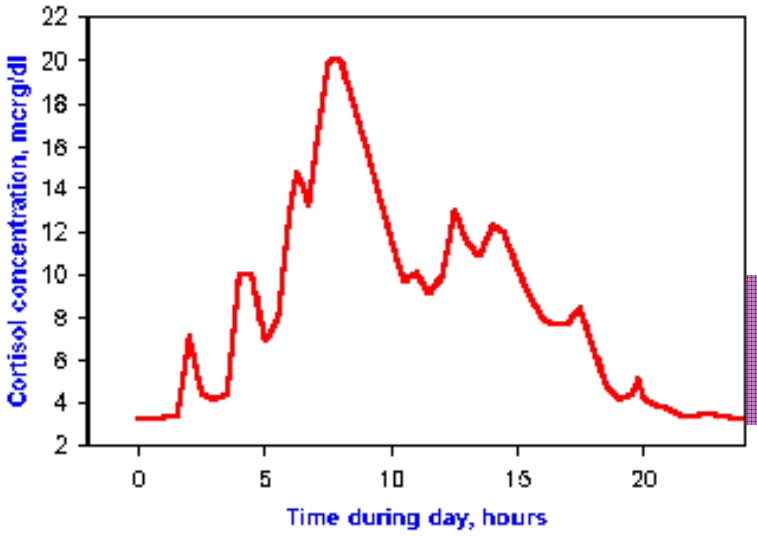
1. Inhibitory tests
2. Stimulatory tests

Hormones

Plasma levels and diurnal variability

One-time blood sample collection is a sufficient procedure for a majority of hormones.

Hormones with diurnal variability - e.g. cortisol, and growth hormone – several measurement during 24 h period needed (e.g. every 4 h or every 6 h)



P-cortisol: Physiological diurnal variability with typical overnight decrease more than 50%

Functional tests

Basal hormonal concentration very often doesn´t allow to establish a diagnosis of hypo- or hyperfunction.

Suspect hypofunction → Stimulatory tests
= quantification of functional reserve of endocrine gland

Suspect hyperfunction → Inhibitory tests
= quantification of responsibility of endocrine gland to inhibitory factors

Principles:

- **negative feedback inhibition / stimulation**
- **direct stimulation / inhibition**

Imaging methods

Indications:

1. **Localization of endocrine active tumors, hyperplasia, ectopic hormonal production**
2. **Evaluation of systemic complications**

Native X-ray exams

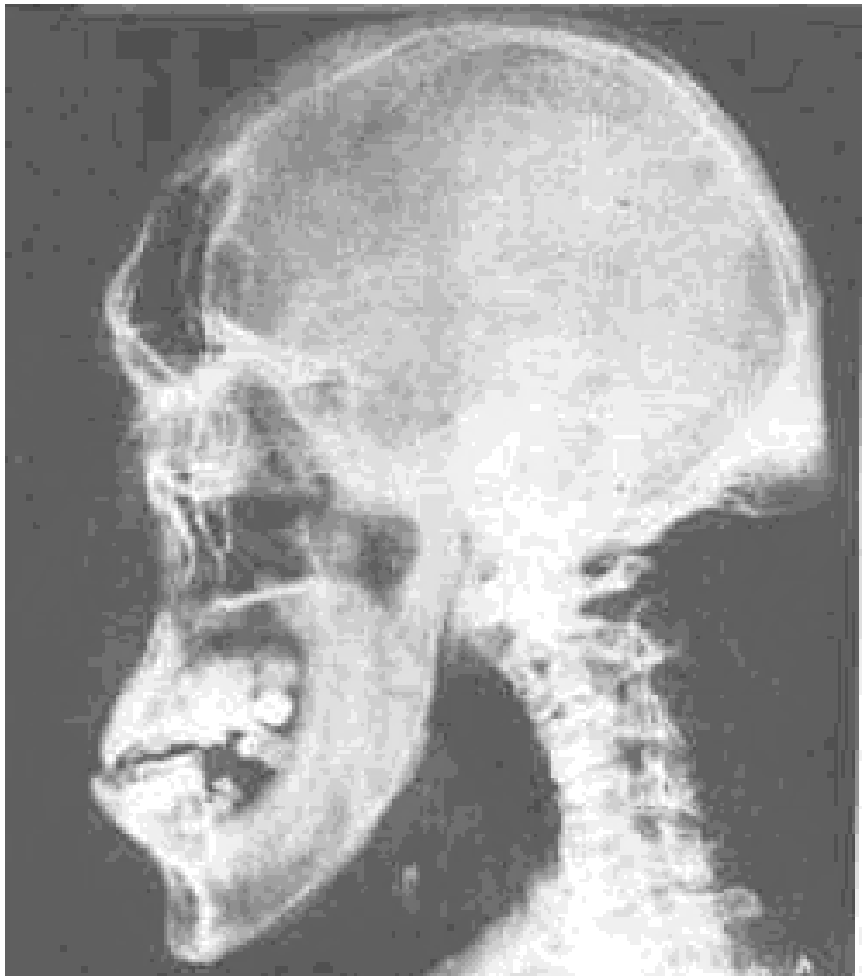
Ultrasonography

CT / MRI

Scintigraphy

Angiography

X-ray examination

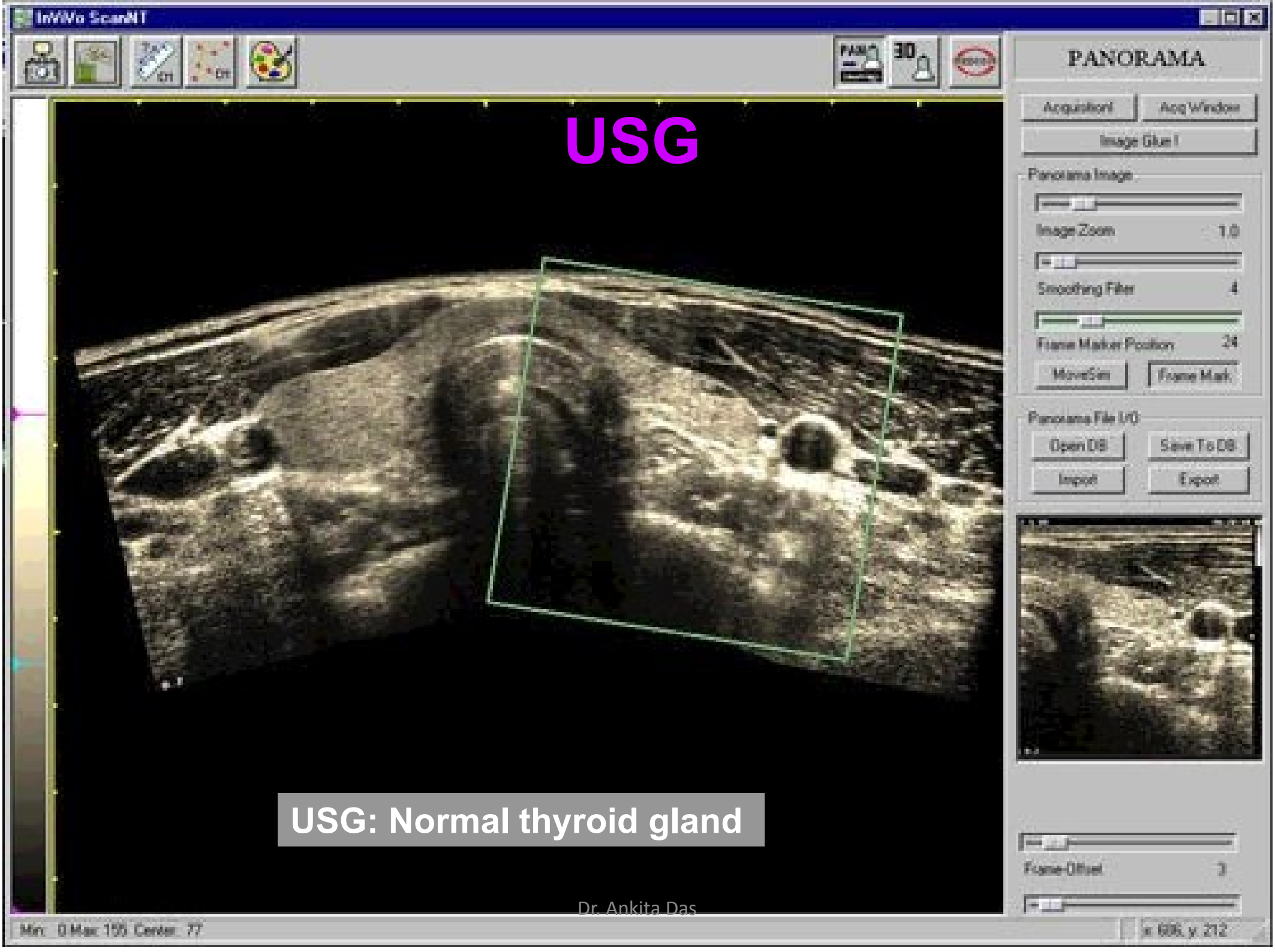


Acromegaly

X-ray examination

Acromegaly

Arachnodactylia


InVivo ScanNT
PANORAMA
Acquisition
Acq Window
Image Glue
Panorama Image
Image Zoom
1.0
Smoothing Filter
4
Frame Marker Position
24
MoveSet
Frame Mark
Panorama File I/O
Open DB
Save To DB
Import
Export
Frame Offset
3
USG
USG: Normal thyroid gland
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Min: 0 Max: 155 Center: 77
x: 606, y: 212

CT / MRI

Computed Tomography (CT)
Magnetic Resonance Imaging (MRI)

The better degree of contrast in the imaging than in USG.

The comparison of CT and MRI

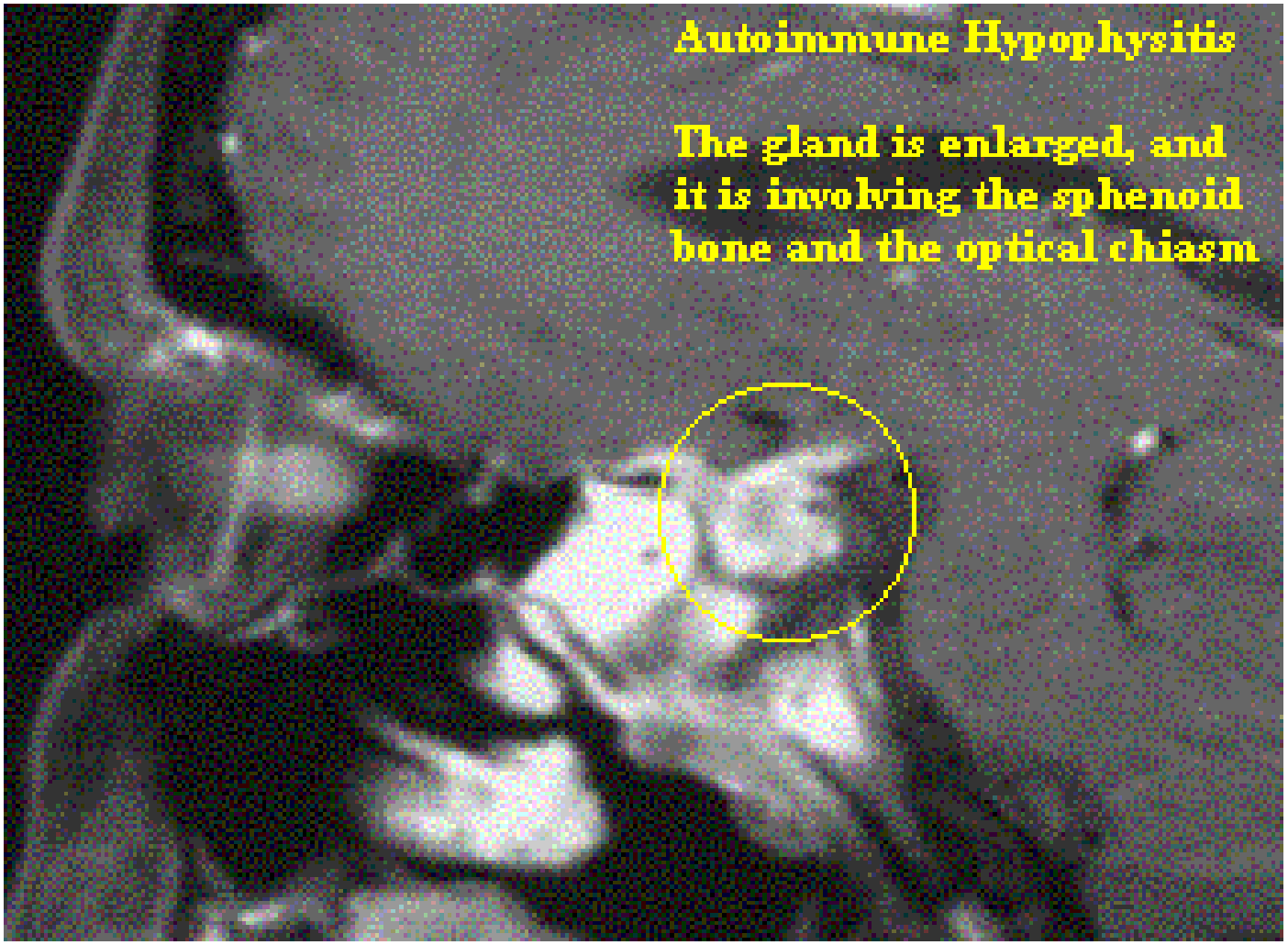
CT advantages

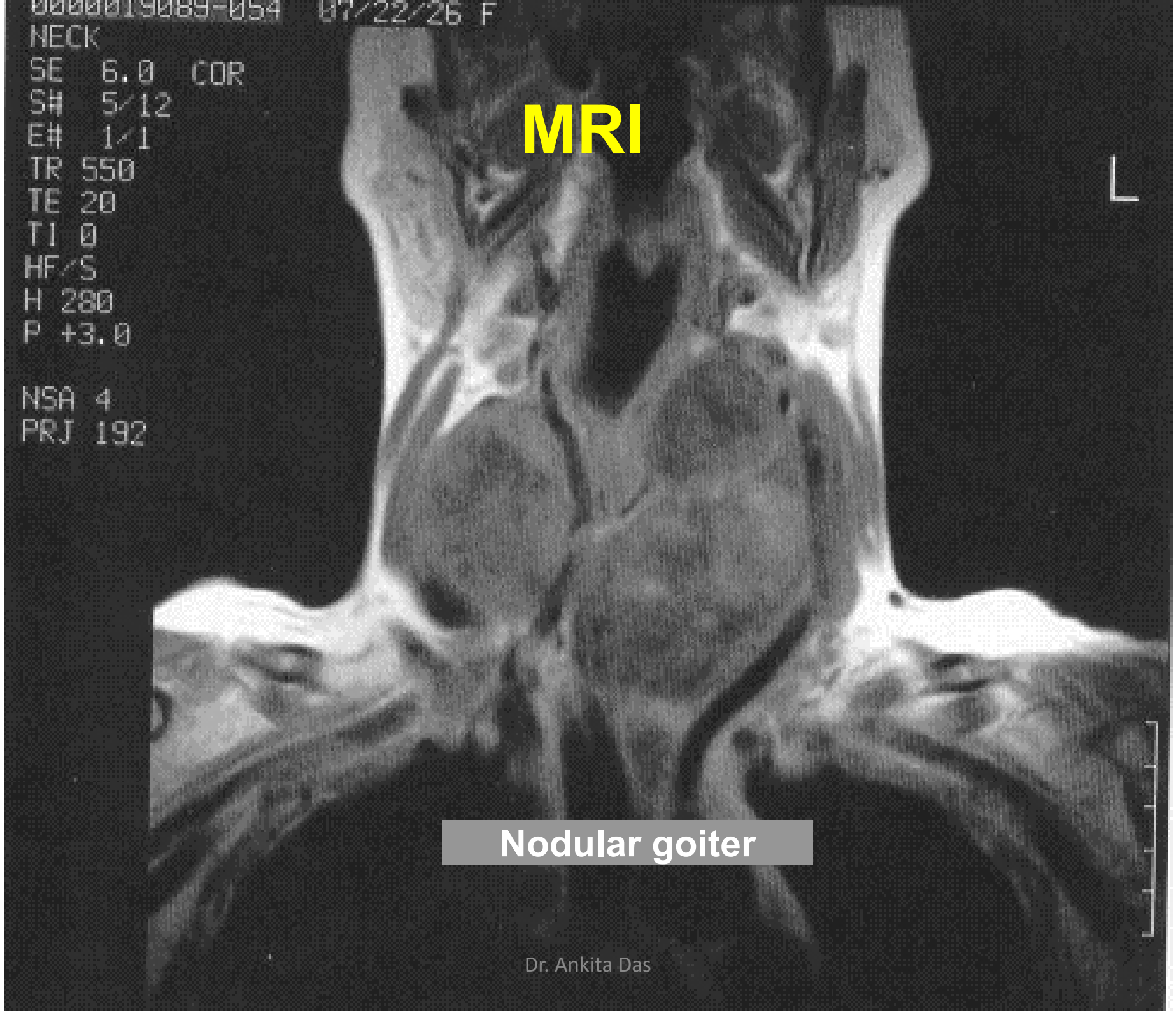
- Lower cost
- Better availability
- Beter resolution of bone structures (e.g. osteolysis)

MRI advantages

- High resolution of vascular abnorm. (e.g. differentiation of pituit. tumors and hemangiomas)
- No radiation load

CT


Autoimmune Hypophysitis
The gland is enlarged, and it is involving the sphenoid bone and the optical chiasm


0000019089-054 07/22/26 F
NECK
SE 6.0 COR
S# 5/12
E# 1/1
TR 550
TE 20
TI 0
HF/S
H 280
P +3.0
NSA 4
PRJ 192
MRI
L
Nodular goiter
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NEUROENDOCRINOLOGY

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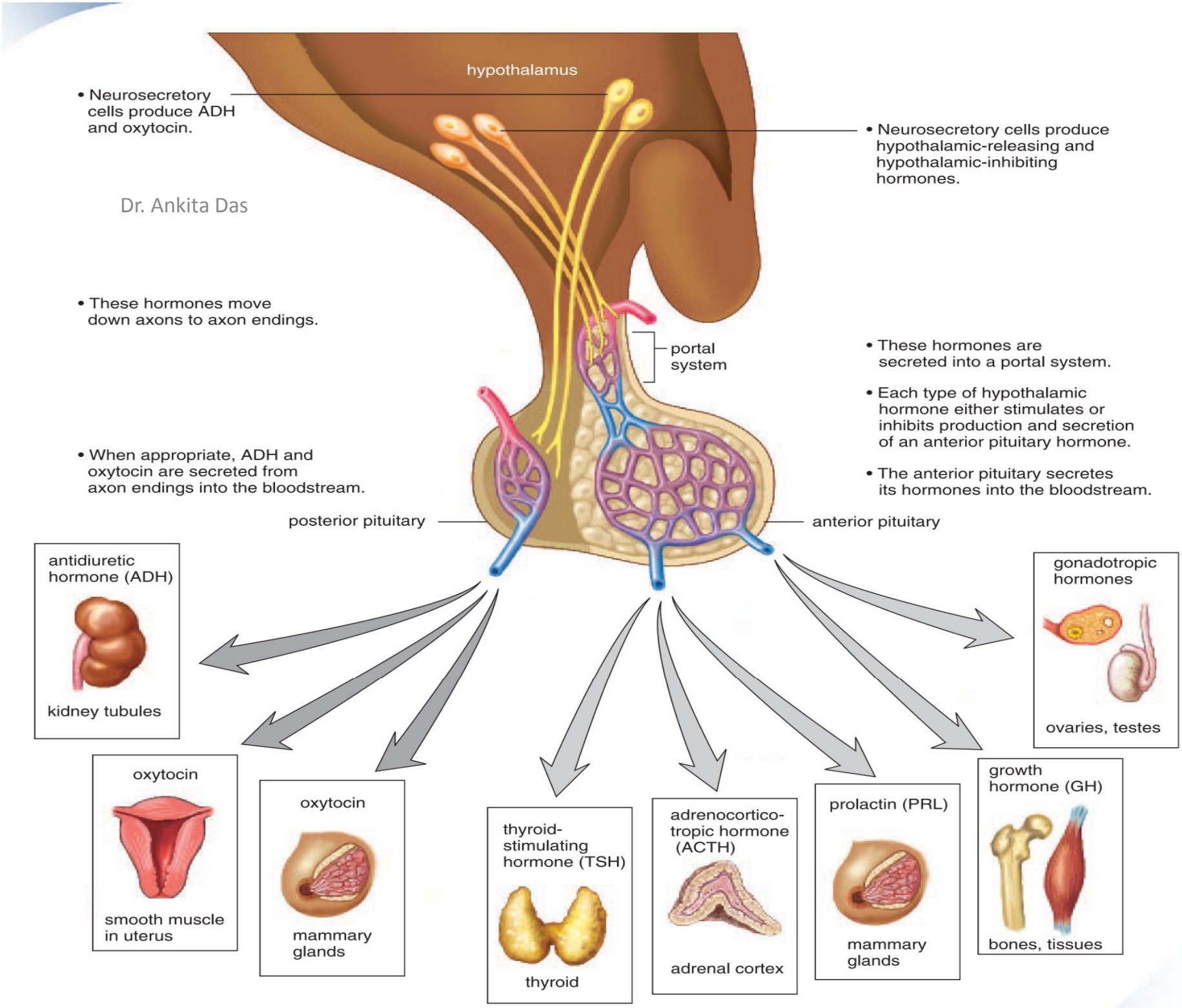
Hypothalamus and Pituitary Gland

- The hypothalamus and pituitary gland form a unit that exerts control over the function of several endocrine glands (thyroid, adrenals, and gonads), as well as a wide range of physiologic activities
- This unit constitutes an example of neuroendocrinology—brain-endocrine interactions


hypothalamus
• Neurosecretory cells produce ADH and oxytocin.
• Neurosecretory cells produce hypothalamic-releasing and hypothalamic-inhibiting hormones.
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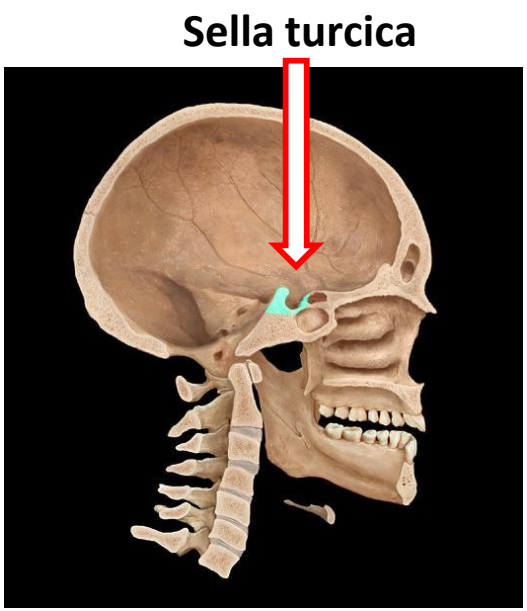
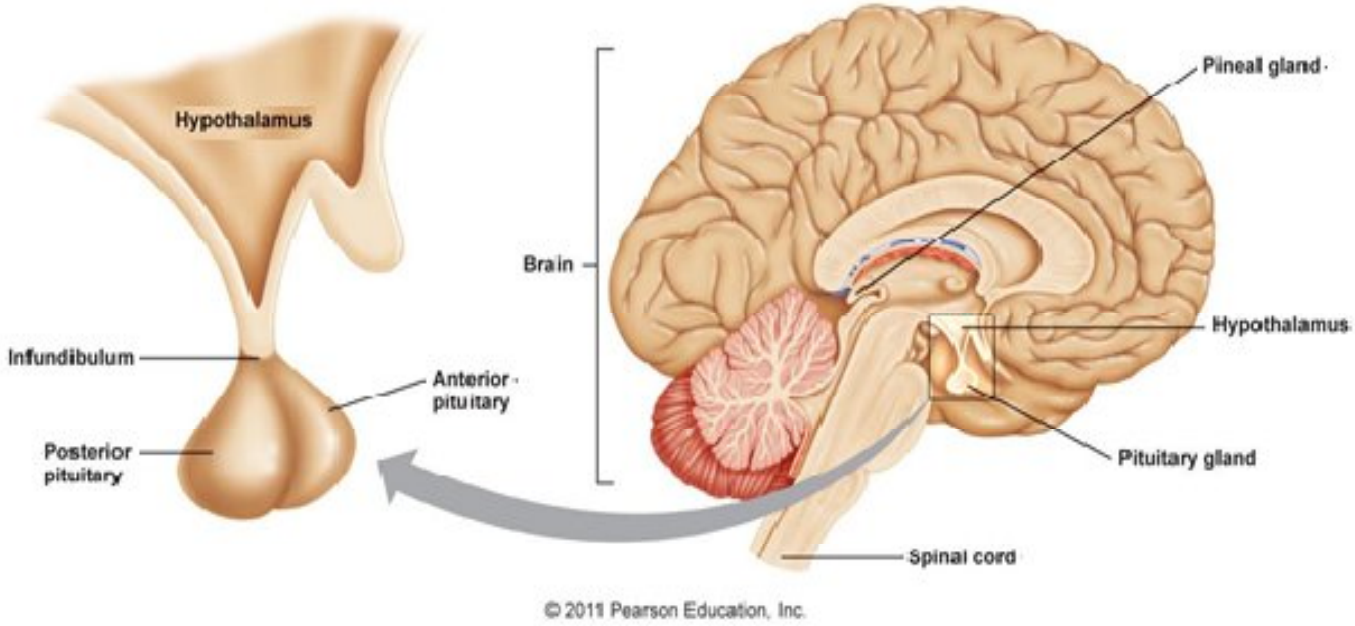
• These hormones move down axons to axon endings.
portal system
• These hormones are secreted into a portal system.
• Each type of hypothalamic hormone either stimulates or inhibits production and secretion of an anterior pituitary hormone.
• The anterior pituitary secretes its hormones into the bloodstream.
• When appropriate, ADH and oxytocin are secreted from axon endings into the bloodstream.
posterior pituitary
anterior pituitary
antidiuretic hormone (ADH)
kidney tubules
oxytocin
smooth muscle in uterus
oxytocin
mammary glands
thyroid-stimulating hormone (TSH)
thyroid
adrenocortico-tropic hormone (ACTH)
adrenal cortex
prolactin (PRL)
mammary glands
growth hormone (GH)
bones, tissues
gonadotropic hormones
ovaries, testes

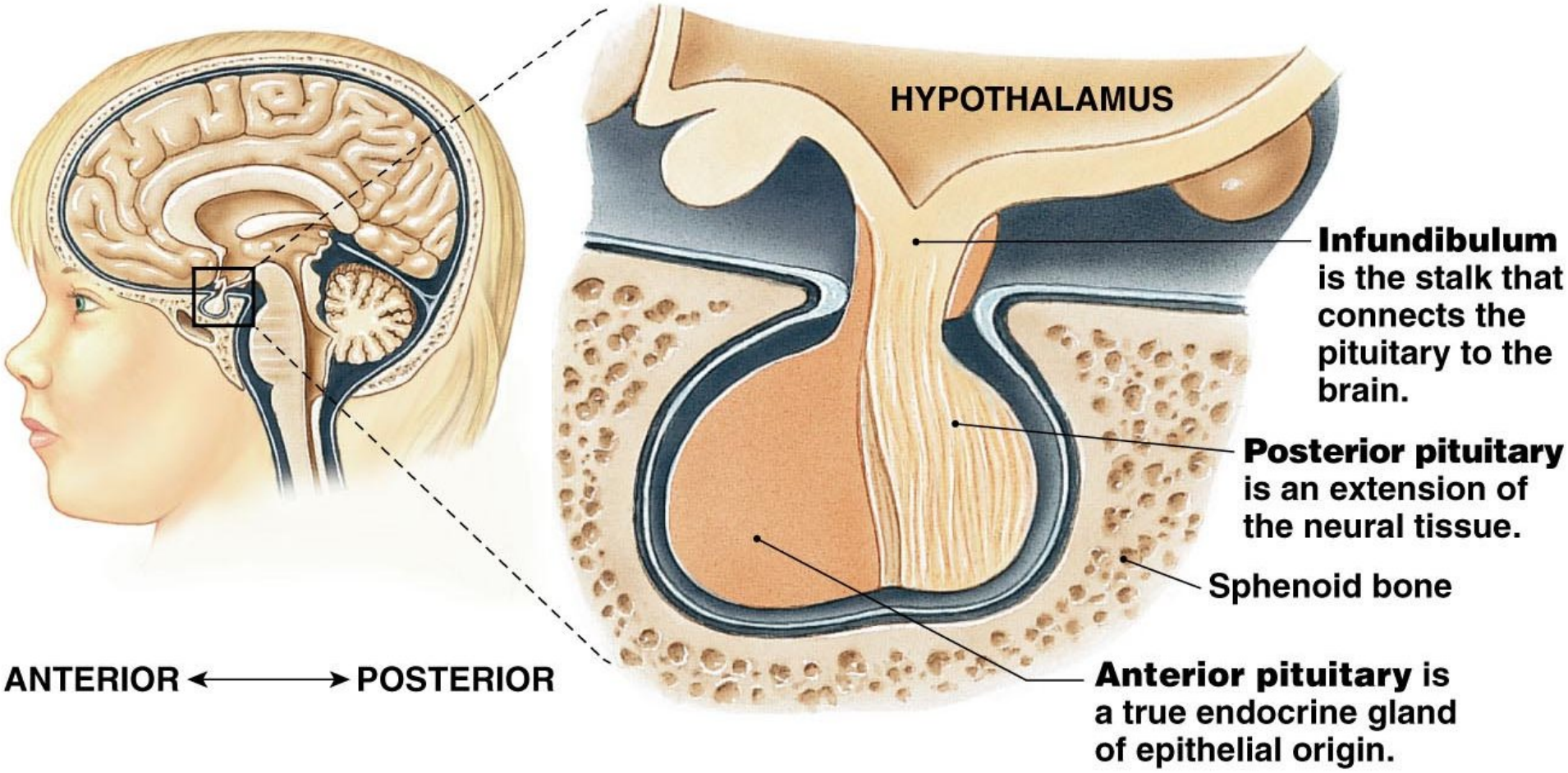
Morphology

- The pituitary gland (hypophysis) is located in a small depression in the sphenoid bone, the *sella turcica*, just beneath the hypothalamus
- It is connected to the hypothalamus by a thin stalk called the *infundibulum*

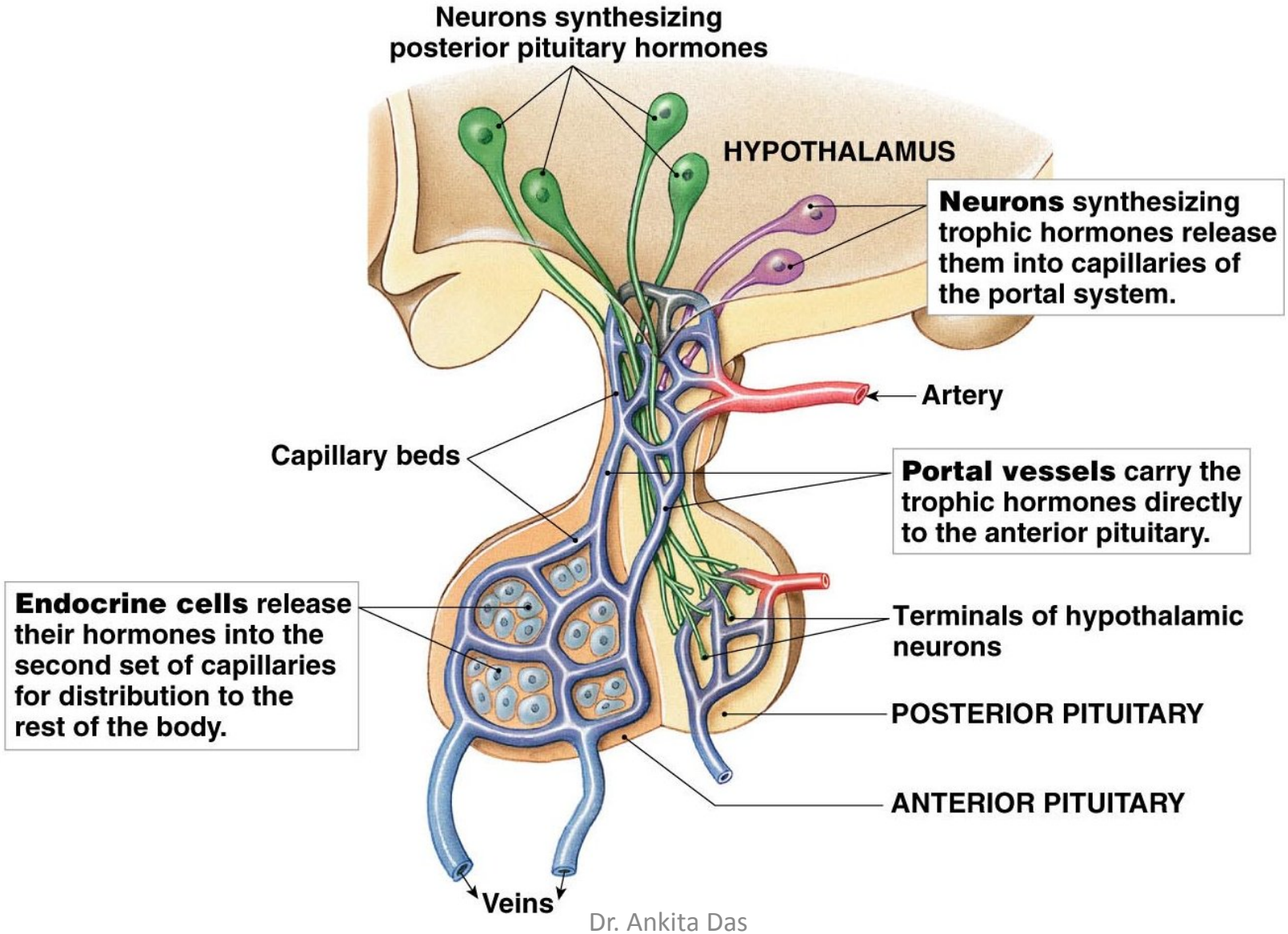




The Pituitary Gland Anatomy

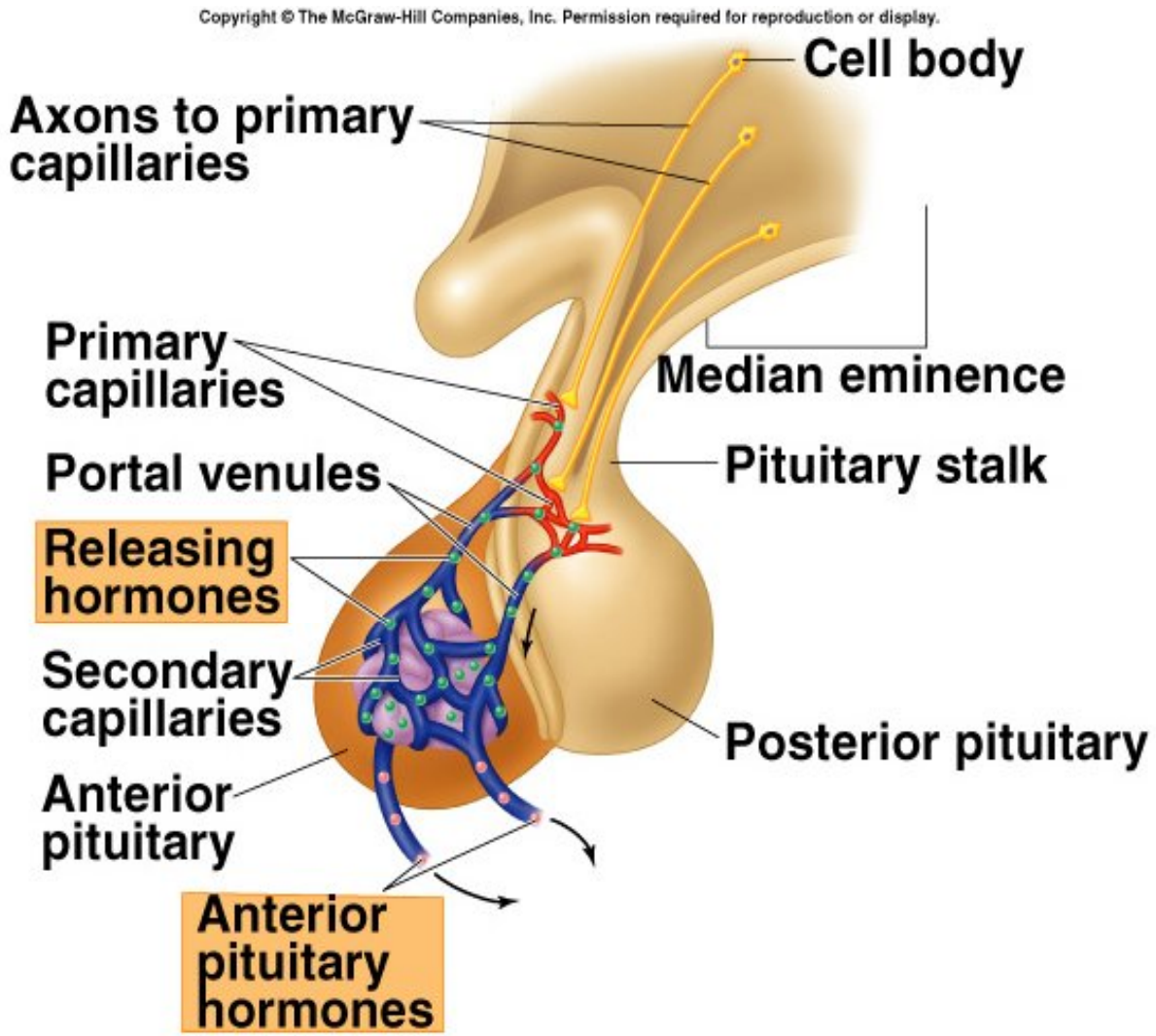


The Hypothalamic-Hypophyseal Portal System

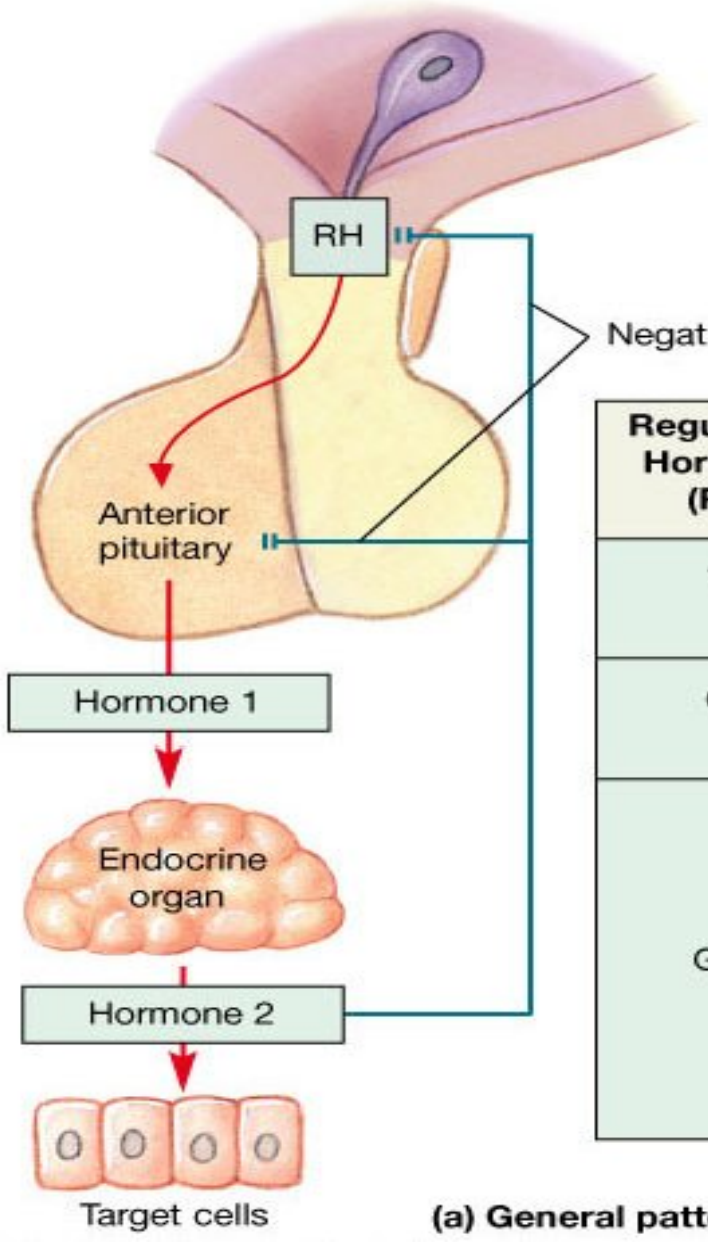


Hypothalamic Control of the Anterior Pituitary

- Hormonal control mechanism
- Hypothalamic neurons synthesize releasing and inhibiting peptide hormones.
- These are transported to axon endings in the median eminence where they are secreted into the hypothalamo-hypophyseal portal system to reach receptors that regulate the secretions of anterior pituitary hormones



Feedback control of Endocrine Secretion



(a) General pattern

Regulatory Hormone (RH)	Hormone 1 (from Pituitary)	Endocrine Target Cells	Hormone 2 (from Target organ)
TRH	TSH	Thyroid gland	Thyroid hormones
CRH	ACTH	Adrenal cortex	Gluco-corticoids
GnRH	FSH	Testes	Inhibin
		Ovaries	Inhibin, Estrogens
	LH	Ovaries	Progestins, Estrogens
		Testes	Androgens

Hypophysiotropic hormones

Hormone	Physiological actions of the pituitary
Corticotropin releasing hormone (CRH)	Stimulates secretion of ACTH, and β-lipotropin
Gonadotropin releasing hormone (GnRH), originally called luteinizing hormone-releasing hormone (LHRH)	Stimulates secretion of FSH and LH
Growth hormone-releasing hormone (GHRH)	Stimulates GH secretion
Growth hormone releasing peptide (ghrelin)	Increases response to GHRH and may directly stimulate GH secretion
Somatotropin release-inhibiting factor (SRIF); somatostatin (SST)	Inhibits secretion of GH
Prolactin-stimulating factor (?)	Stimulates prolactin secretion(?)
Prolactin inhibiting factor (PIF)	Inhibits prolactin secretion
Thyrotropin-releasing hormone (TRH)	Stimulates secretion of TSH and prolactin
Arginine vasopressin (AVP)	Acts in concert with CRH to stimulate secretion of ACTH

Pituitary & Hypothalamic Disorders

- Hypothalamic-pituitary lesions present with a variety of signs, including pituitary hormone:
  - hypersecretion and hyposecretion,
  - sellar enlargement,
  - and visual loss

Pituitary & Hypothalamic Disorders

- In adults, the most common cause of hypothalamic-pituitary dysfunction is a pituitary adenoma, of which the great majority are hypersecreting
- Thus, the earliest symptoms of such tumors are due to endocrinologic abnormalities and include:
  - Early manifestation
    - Hypogonadism, the most frequent
      - diminished functional activity of the gonads
  - Late manifestation in patients with larger tumors or suprasellar extension
    - sellar enlargement
    - headache
    - and visual loss,

Gonadotrophins Disorders

- **Hyposecretion**
  - leads to amenorrhoea,
  - sterility
  - and loss of sexual potency.
  - In the young, the sex organs and secondary sexual characteristics fail to develop (delayed puberty)
- **Hypersecretion**
  - extremely rare,
  - in children it could lead to sexual precocity (excessive premature development)

Thyrotrophin Disorders

- **Hyposecretion**
  - produces a clinical picture similar to primary thyroid deficiency
- **Hypersecretion**
  - gives the symptoms of hyperthyroidism similar to *Graves' disease*

Corticotrophin Disorders

- **Hyposecretion**
  - rare
  - causes failure of cortisol secretion,
  - a general lack of health and well being,
  - a reduced response to stress and skin depigmentation
- **Hypersecretion**
  - due to a pituitary microadenoma,
  - will result in *Cushing's syndrome*

Prolactin Disorders

- **Hyposecretion**
  - leads to failure of lactation in women
- **Hypersecretion**
  - may result from a pituitary tumour
  - principal symptoms are infertility and menstrual complaints
  - in men, decreased libido,
  - inadequate sperm production and impotence, whereas in women, there may be a complete lack of menstruation
  - inappropriate (non-pregnant) milk production

GHRH Disorders

- **Hyposecretion**
  - caused by hypothalamic or pituitary dysfunction
  - In childhood this leads to impairment of growth *(dwarfism)*
- **Hypersecretion**
  - This usually results from a benign pituitary tumour
  - In young patients, this leads to *gigantism*
  - In adults, leads to acromegaly

Vasopressin Disorders

- **Hyposecretion**
  - caused by damage or dysfunction of the hypothalamus,
  - can lead to *diabetes insipidus,*
    - excessively large amounts of dilute urine (10–15 liters/day) are produced by the kidneys
- **Hypersecretion**
  - rare condition of inappropriate AVP production is known as *syndrome of inappropriate ADH* (*SIADH)*

Hypopituitarism

- Hypopituitarism is manifested by diminished or absent secretion of one or more pituitary hormones
- Hypopituitarism is either:
  - a primary event
    - caused by destruction of the anterior pituitary gland
  - or a secondary phenomenon
    - resulting from deficiency of hypothalamic stimulatory factors normally acting on the pituitary

Leptin (OB)

16 KDa protein encoded by ob (obese) gene.

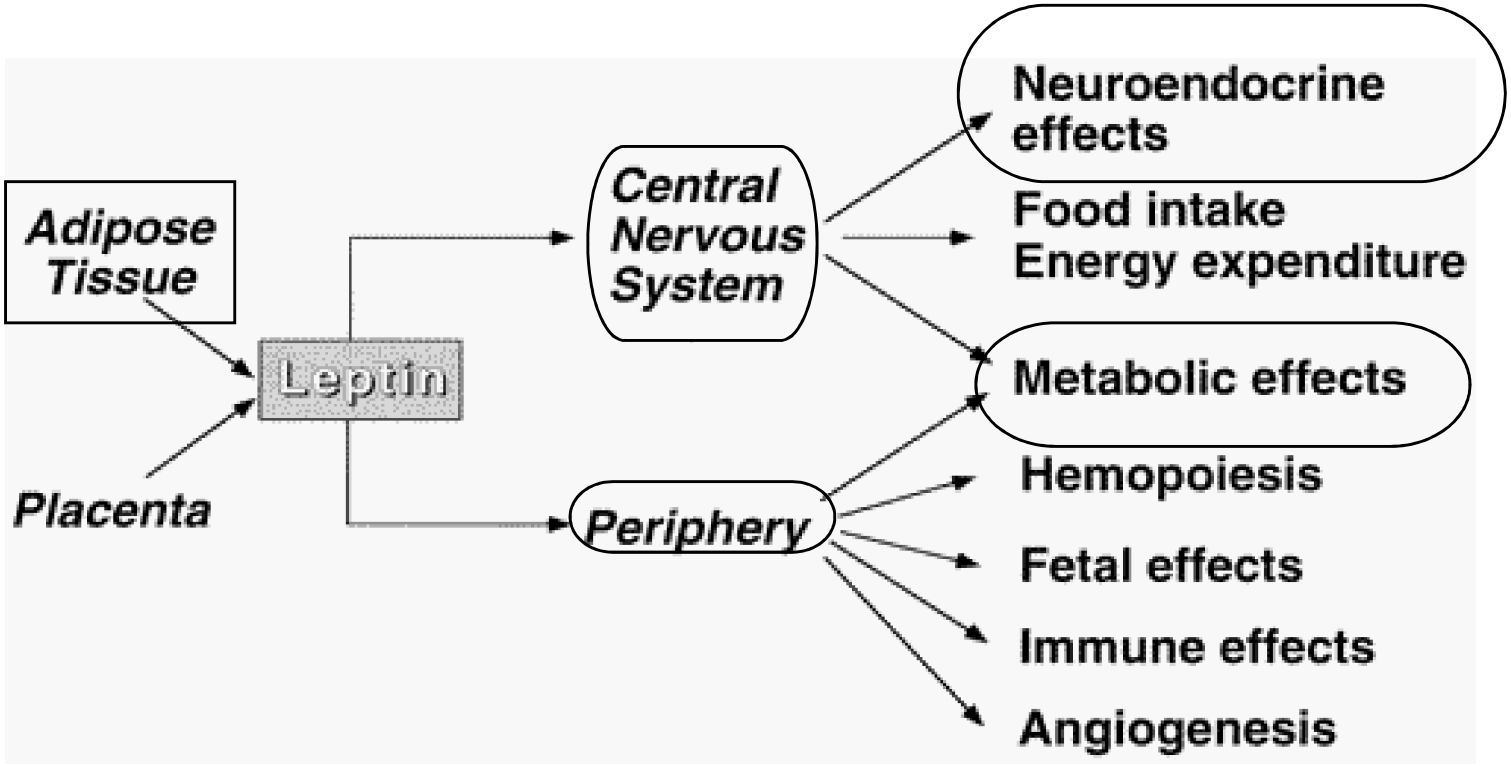
- Expressed & secreted by – adipocytes, placenta, gastric epithelium.
- Directly proportional to the total amount of fat in the body.

mice are homozygous for single gene mutation.

- ob/ob –protein hormone leptin
- db/db –receptor for leptin .

High degree of homology

How Does Leptin Interact?



Leptin Receptor (Ob-R)

- Homology to cytokine receptors
- Different forms are splice variants
- Activates JAK/STAT upon ligand binding
- Defects cause obesity & diabetes
- Highly expressed in brain (hypothalamus)

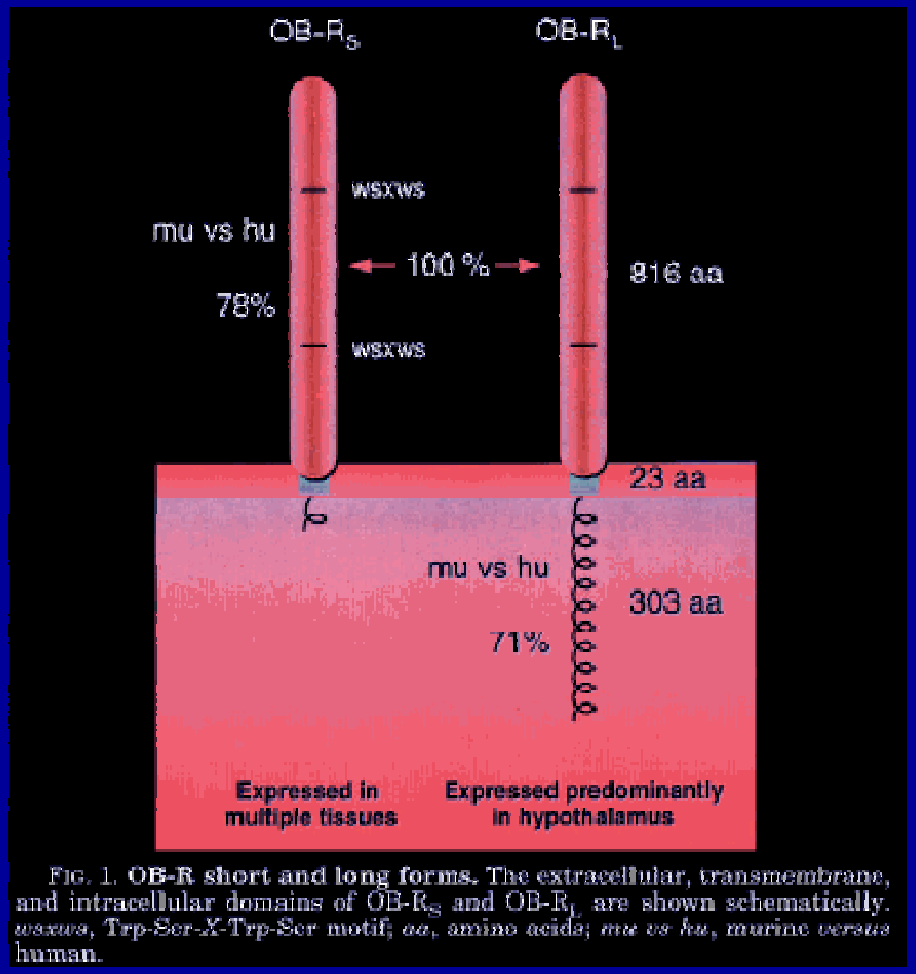
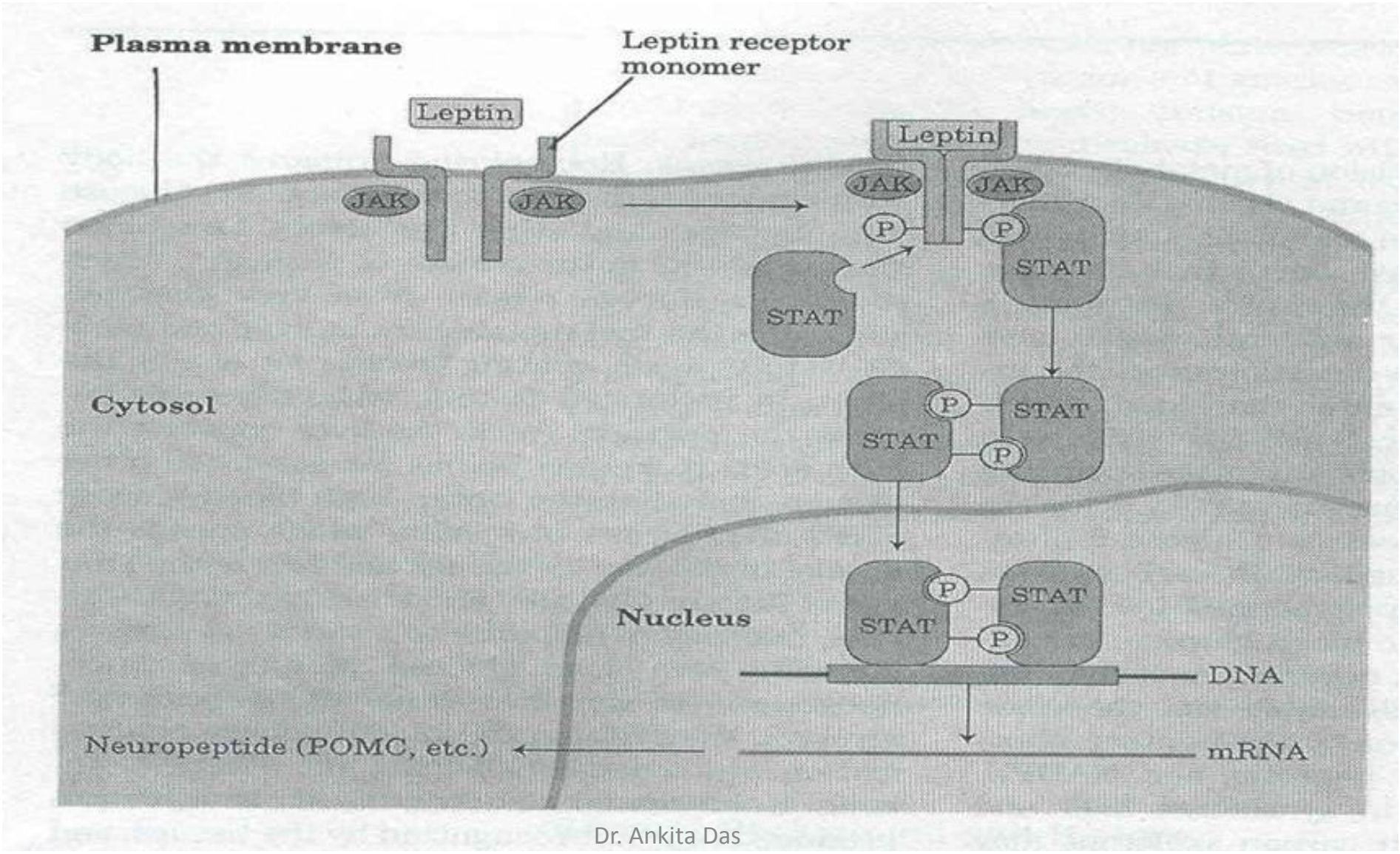


FIG. 1. **OB-R short and long forms.** The extracellular, transmembrane, and intracellular domains of OB-R$_S$ and OB-R$_L$ are shown schematically. *wsxws*, Trp-Ser-*X*-Trp-Ser motif; *aa*, amino acids; *mu vs hu*, murine *versus* human.

Signalling Pathway of Leptin Action



Physiological effects of Leptin

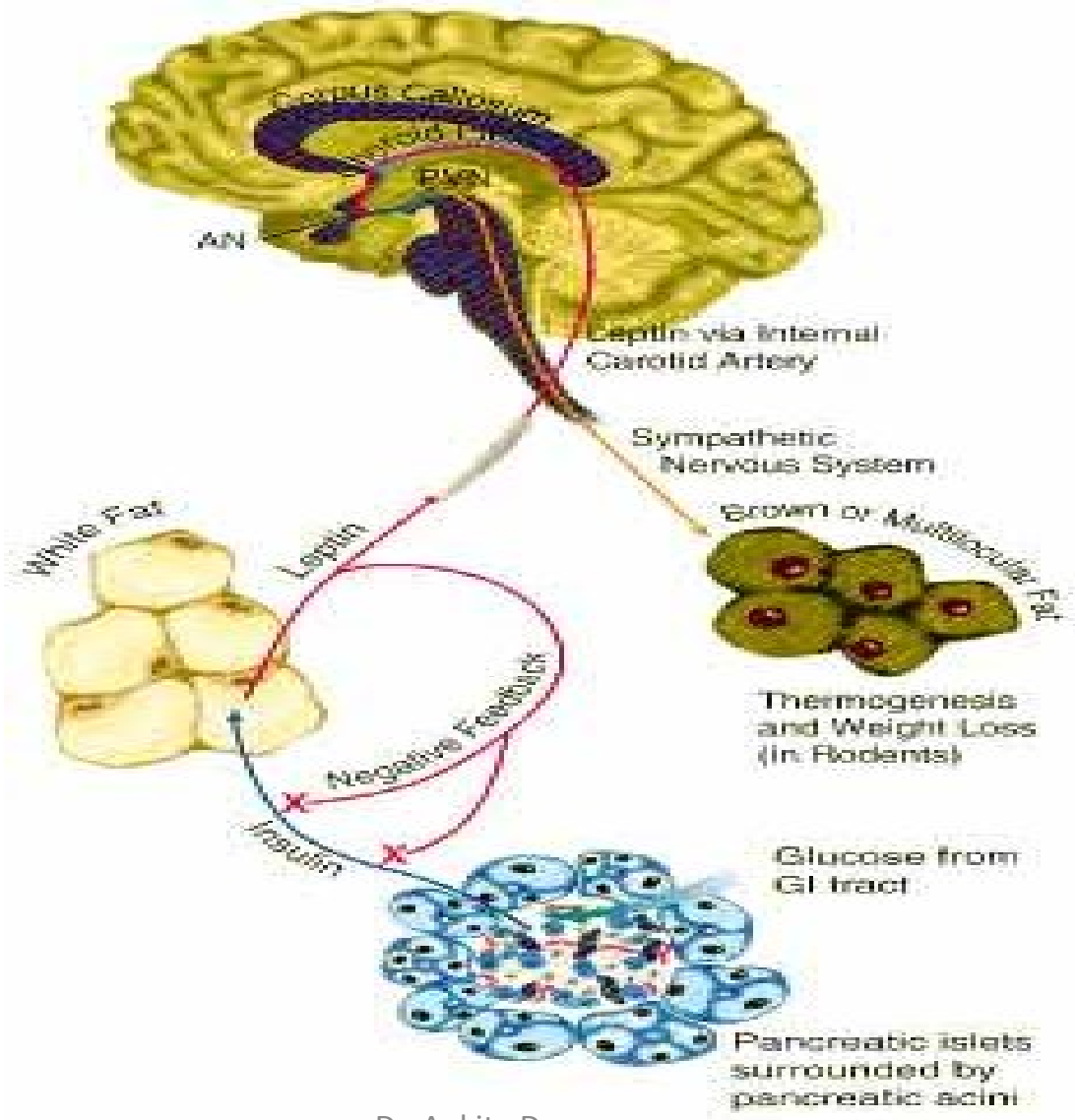
- Regulation of food intake ,energy expenditure and body weight .
- Thermogenesis .
- Reproductive function .
- Supressed bone formation .
- Directly act on the cells of liver and muscles .
- Related to inflammatory response .
- Contribute to early hematopoiesis.

Role of leptin in regulation of food intake and body weight

- Decrease hunger and food consumption - inhibition of neuropeptide Y (Appetite stimulating hypothalamic peptide)synthesis .

- Food intake linked to its ability to regulate the neuroendocrine system .

How leptin works ?

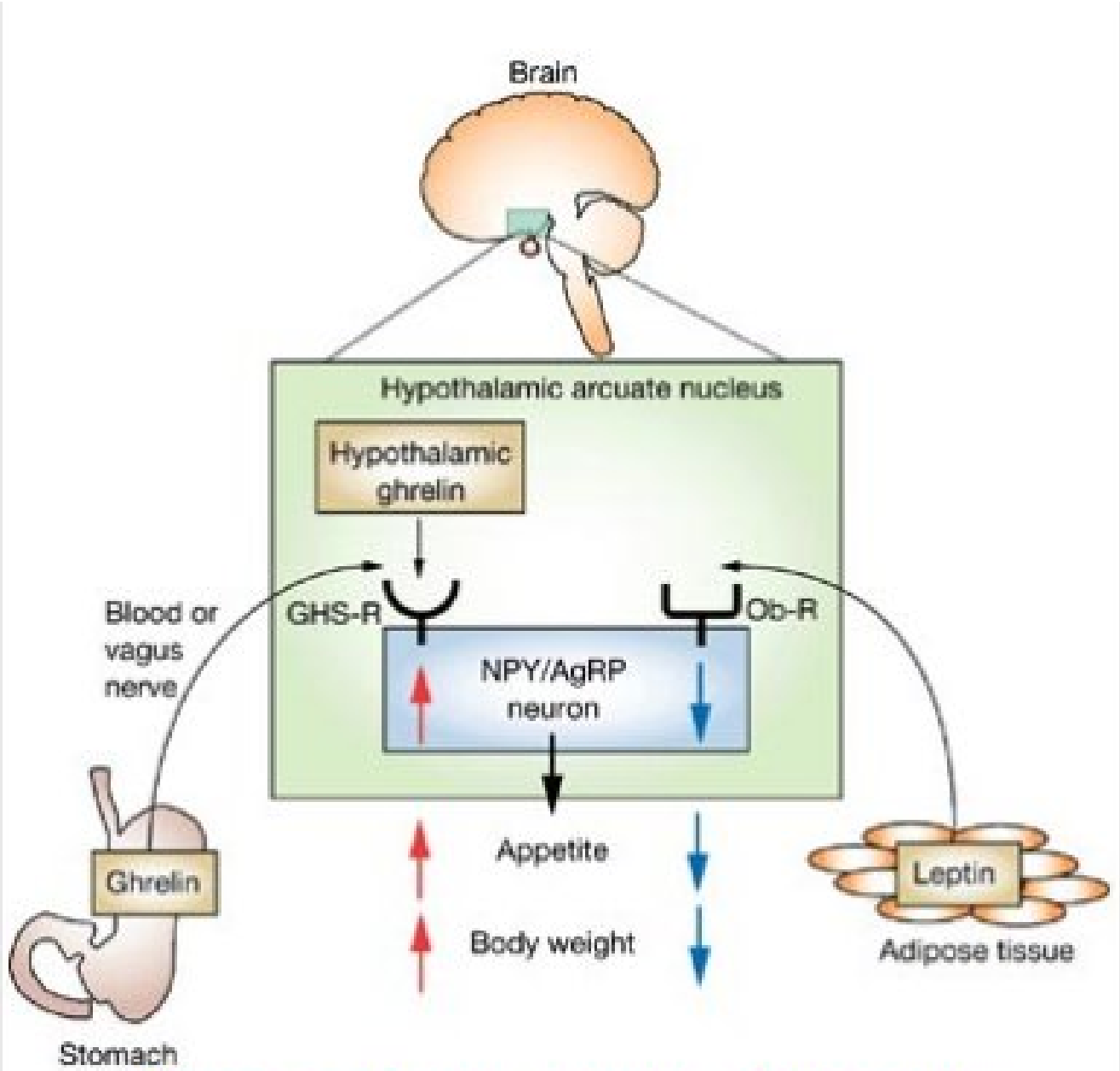


Leptin and ghrelin seem to be the big players in regulating appetite, which consequently influences body weight/fat. When we get hungrier, we tend to eat more. When we eat more, obviously, we maintain our body weight or gain that weight back.

Both leptin and ghrelin are peripheral signals with central effects. In other words, they're secreted in other parts of the body (peripheral) but affect our brain (central).

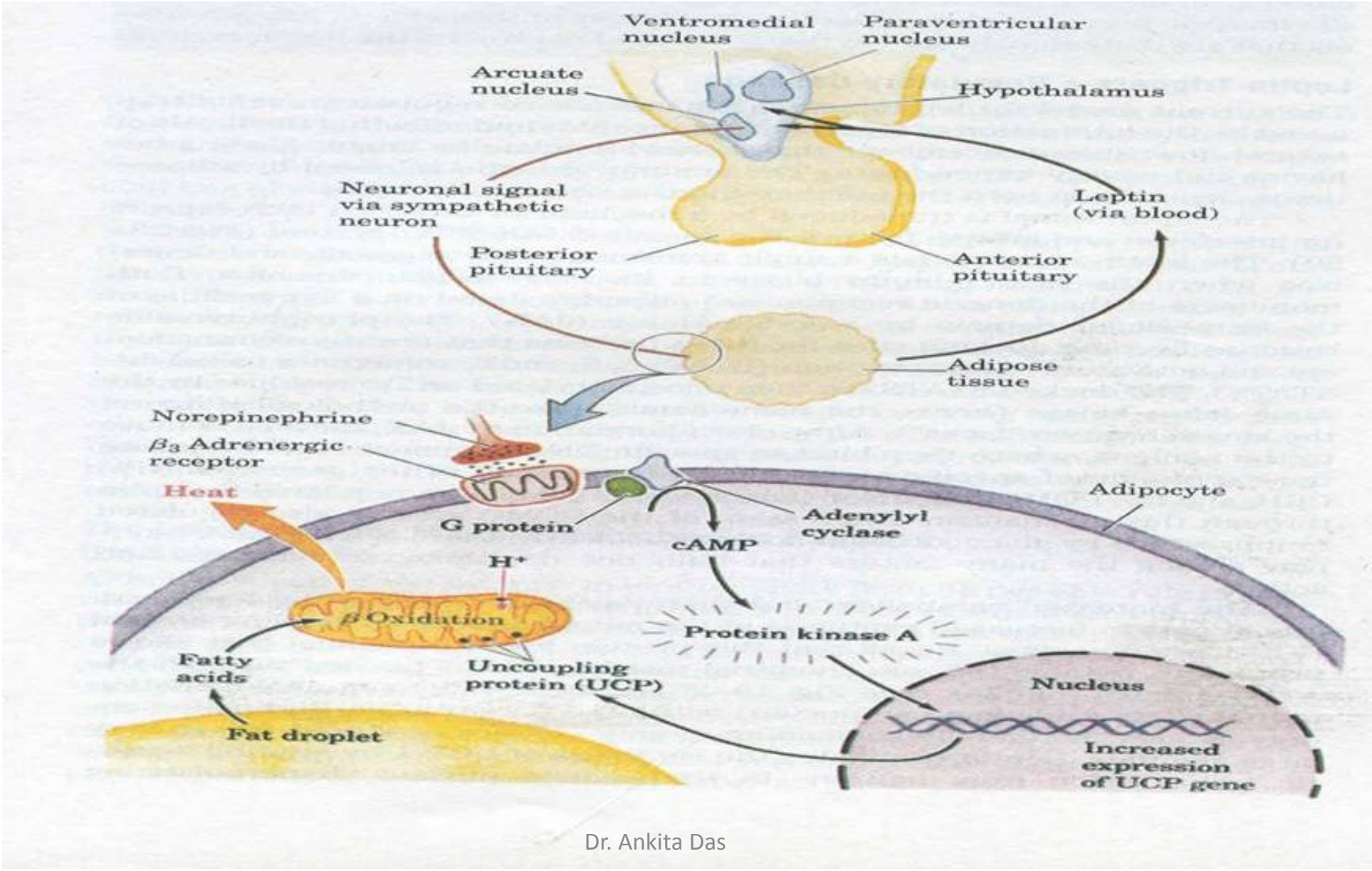
Leptin is secreted primarily in fat cells, as well as the stomach, heart, placenta, and skeletal muscle. Leptin *decreases* hunger.

Ghrelin is secreted primarily in the lining of the stomach. Ghrelin *increases* hunger.



Ghrelin and leptin act on the brain via the hypothalamus (from Kojima & Kangawa, 2006).

Role of leptin in thermogenesis



Role of leptin in reproduction

- Fertility influenced by stored body fat
- Leptin signals the onset of puberty .
- Regulates hypothalamic- pituitary – ovarian function .

Role of leptin in lipid metabolism

- Inhibits intracellular lipid concentration

- Activate 5 –AMP-activated protein kinase (AMPK)
- Inhibits acetyl coenzyme-A carboxylase (ACC)

- Increase in fatty acid oxidation and reducing the fat tissue in muscles and liver

.

- Increase insulin sensitivity .

Inflammatory response

- Long form of leptin receptor is expressed by T-lymphocytes, bone marrow, spleen.
- Leptin released in response to inflammatory cytokines attenuating its response and hence. modulating inflammatory response.
- Stimulates the expression of POMC -processed to α-MSH.
- Against the auto aggressive effects of the immune system.

Feedback loop

- Food intake trigger the output of glucocorticoids and insulin
- Favour fat accumulation & increase leptin
- Leptin travels to hypothalamus
- Regulate body mass & control body energy intake , energy expenditure
- NPY also regulate body fat mass

Books to refer:

1. Medical Physiology, Guyton and Hall
2. Medical Physiology, Ganong
3. General Physiology, A.K. Jain

Practice Questions:

1. Classify endocrine disorders with example.
2. Name two laboratory tests to evaluate endocrine complications.
3. Name the imaging methods to examine or evaluate the endocrine complications.
4. Briefly describe the hypothalamic-hypophyseal portal system.
5. Name four releasing hormones along with their endocrine target cells.
6. Write the physiological actions of a)GHRH, b)TRH, c) CRH
7. Briefly describe the thyrotropin disorders .
8. Mention the physiological effects of leptin.
9. How does leptin and ghrelin works to regulate the intake of food?
10. Describe the feedback loop of leptin action.