reflex

• As this reflex is initiated by nervous factor & completed by hormonal acn → neuroendocrine reflex

• Another eg: is parturition reflex

• Descent of baby → dilation of cervix → rec. of cervix are stimulated → afferent impulse reach hypothalamic nuclei → ↑ in secretn of oxytocin → ~~↑ further et~~ ↑ uterine contracn. [diagram from text]

Therapeutic uses of oxytocin

- Induction of labor
- Arresting uterine bleeding
- Used in dairy farming to ↑ milk output

15/03/2023 wed

Thyroid gland

- Thyroid gland is the largest endocrine gland of the body
- It is a bilobed gland situated in front of trachea
- The two lobes of human thyroid are connected by a bridge of tissue, the thyroid ~~th~~ isthmus, and there is sometimes a pyramidal lobe arising from the isthmus in front of larynx
- The gland is well vascularized, and the thyroid has one of the highest rates of blood flow per gram of tissue of any organ in the body.
- The gland has 2 lobes

* The first is to secrete the thyroid hormones, which maintain the level of metabolism in tissues
* The second fn of thyroid gland is to secrete calcitonin, a hormone that regulates circulating levels of Ca^{2+}

Histology of Thyroid gland.

- A no: of lobules are present in thyroid gland.
- Each lobule contains 20-40 acini or follicles
- Acini form the structural & fnal unit of gland
- Each acinus is surrounded by a single layer of cuboidal follicular cells and is filled with proteinaceous material called colloid.
- Main constituent of colloid is a big protein molecule - thyroglobulin which contains thyroid hormones attached to it.

- The size of the follicle varies with the activity of the gland.
- when inactive, the amnt of colloid is abundant & the follicle will be large with flat epithelial cells.
- when the gland is active, the follicle is smaller in size, amnt of colloid is less & cells lining are cuboidal/columnar

- Hormone of thyroid gland
  - * Thyroxine - T_4
  - * Triiodothyronine - T_3
  - * Calcitonin

Biosynthesis of thyroid hormones

Imp

- Iodine is essential for the synthesis of thyroid hormone
- It is ingested in the form of iodides
- Dietary iodide is absorbed by the intestine & enters the circulation.
- The minimum daily iodine intake that will maintain normal thyroid fn is 150 µg in adults
- The principal organs that take up circulating Iodine - are the thyroid, which uses it to make thyroid hormones, and the kidneys, which excrete it in urine

Synthesis & secretion of thyroglobulin

- Thyroglobulin is a large glycoprotein synthesised on RER of thyroid epithelial cells.
- The completed glycoprotein is contained in small vesicles, which move to the apical plasma membrane and release into the lumen of the follicle
- Each molecule of thyroglobulin contains about 140 tyrosine residues which can serve as substrate for iodine for the formation of thyroid hormones
- It is also the storage site of 2 hormones — within the thyroid gland.

Steps in synthesis of thyroid hormone

① IODIDE TRAPPING

* Iodide is transported from blood to thyroid cells
* The RMP of follicular cells is -50mV.
* Iodide is actively transported against the electric gradient into the cell by iodide pump, a Na^+/I^- Na^+I^- co transporter which is situated in the basal membrane of the thyroid cell.

- From the thyroid cell iodide is transported into the colloid by a $Cl^- I^-$ exchanger known as pendrin

* Iodide trapping is stimulated by TSH & inhibited by perchlorate & thiocyanate

② OXIDATION OF IODIDE

* The iodide is then immediately oxidised to iodine by the enz- peroxidase present near the apical border of epithelial cells.

* Thyroid is the only tissue that can oxidize iodide to iodine

* TSH promotes this rxn while antithyroid drugs (thiourea, thiouracil, methimazole) inhibit

③ ORGANIFICATION OF THYROGLOBULIN

Iodination of tyrosine residues present in the thyroglobulin molecule

* This rxn occurs at the apical membrane of the cell as soon as thyroglobulin molecule is released by the secretory granules by exocytosis, and requires thyroid peroxidase

* Tyrosine (of thyroglobulin) is first iodinated @ posn 3 to form mono-iodotyrosine (MIT) & then @ posn 5 to form diiodotyrosine (DIT)

- This rxn is also stimulated by thyroid peroxidase

④ COUPLING REACTION

- Two molecules of DIT couple to form Thyroxine (T_4)
- One molecule of MIT, when coupled with one molecule of DIT, Triiodothyronine (T_3) is produced
- When condensation of DIT occurs with MIT, reverse $-T_3$ (RT_3) is formed.
- Enzyme peroxidase is required during coupling as well as for iodination
- Once thyroglobulin has been iodinated, it is stored in the lumen of the follicle as colloid for several months.

HORMONE SECRETION

- The colloid containing iodinated thyroglobulin is retrieved from the lumen of the follicle by the epithelial cells through endocytosis
- By this process, the colloid enters the cytoplasm in the form of colloid droplets, which move through the cytoplasm towards the basal membrane
- The colloid droplets fuse with the lysosome vesicles containing proteolytic enz.
- The proteases digest the thyroglobulin molecule releasing T_4, T_3, DIT, MIT & other a.a constituents into the cytoplasm of epithelial cells

- T_4 & T_3 diffuse through the basal border of epithelial cells into the bloodstream.
- MIT & DIT are rapidly deiodinated within the follicular cells by the enz. iodotyrosine deiodinase

* T_4 is the 1° hormone secreted by the thyroid gland but T_3 has much biological activity than T_4.

- Secreted T_4 & T_3 circulate in the bloodstream in 2 forms: bound & free.
- T_4 is more tightly bound to IPlasma protein than T_3.
- T_3 is specifically generated at its site of action in peripheral tissues by deiodination of T_4.
- T_3 is seen more in the free form & it has greater affinity for thyroid receptors T_3 has a shorter half life and action is rapid.
- ~~T_4 some~~ Some T_4 is converted to RT_3 & RT_3 is physiologically inert

Metabolism of thyroid hormones

- Thyroid hormones are metabolised in the liver, kidney & many other tissues
- 80% of T_4 & T_3 are deiodinated into iodotyrosines
- 20% of T_3 & T_4 undergo conjugation in liver to glucuronides & sulphates.
- These enter bile & in the intestine undergoes hydrolysis
- A portion of iodine released undergoes enterohepatic circulation & rest is excreted through feces
- Rest of the unbound & unconjugated T_3 & T_4 undergoes oxidation, decarboxylation, deamination & deiodination in liver & muscle into tetraiodothyroacetic ā and triiodothyroacetic ā

Mechanism of action

- T_3 binds to specific thyroid receptors in the nucleus → hormone receptor complex → binds to the DNA molecule → specific mRNA is formed → specific enzymes → physiological action

* Thyroxine synthesizes more Na-k ATPase and more of ATP is utilised by the cell.

* Thyroxine ↑ses the number & size of mitochondria & leads to ↑sed production of ATP.

[Pending] (also thyroid)

Actions of TSH

- TSH stimulates thyro synthesis and secreti influencing almost a involved in it.
- This includes iodide iodide binding, syn and T_4 (coupling in thyroglobulin into the endocytosis of collo
- TSH ↑ blood supp gland
- TSH ↑ the size &
- It causes growth of thyroid gland, in TSH: caus thy or goitre

Regulation of thyroid

- TSH from ant. pit 1° regulatory factor
- TSH is essential growth and secreti the thyroid gland
- TSH secre from regulated by 2

[pending] (also thyroid fn test)

16/3/23

Actions of TSH

- TSH stimulates thyroid hormone synthesis and secretion by influencing almost all the steps involved in it.
- This includes iodide trapping, iodide binding, synthesis of T_3 and T_4 (coupling rn), secretn of thyroglobulin into the colloid & endocytosis of colloid
- TSH ↑ blood supply to thyroid gland
- TSH ↑ the size & no: of
- It causes growth & hypertrophy of thyroid gland, ∴ chronic rise in TSH ; cause thyroid hypertrophy or goitre

Regulan of thyroid hormone

- TSH from ant. pituitary is the 1° regulatory factor of thyroid gland.
- TSH is essential for the normal growth and secretory activity of the thyroid gland
- TSH secretn from ant. pit. is regulated by 2 mechanisms
  - -ve feedback mechanism through conc. of circulating thyroid hormone.
  - A fal

Regulation

- Hypothalamus produces thyrotropin releasing hormone, which stimulates the release of TSH from ant. pit.
- Negative feedback mechanism through conc. of circulating thyroid hormones may affect TRH from hypothalamus
- Nervous stimuli like emotion, stress & exposure to cold, etc. may effect TRH release from hypothalamus

Intrinsic mechanism of regula

- Iodide is an imp. factor regulating the synthesis of thyroid hormones.
- When iodide intake is ↑sed, iodide conc. in the gland is ↑sed & it inhibits thyroid homone synthesis - Wolff Chaikoff effect
  - when there is deficiency of iodine content in the diet then the iodine trapping mechanism of the follicular cells becomes efficient.

Diseases of thyroid gland

- Normally functioning thyroid.
  - ↳ Euthyroid
- D/s result in hyperfunctioning or hypofunctioning of the gland
- Most imp. clinical condition is called goitre.
- Other conditions are thyroiditis & thyroid carcinoma.

Goitre

- Goitre refers to any abnormal ↑ in the size of thyroid gland
- The term goitre does not denote the functional status of thyroid gland, because it may be associated with:
  - Euthyroid, ie normal thyroid hormone level.
  - Hypothyroidism, ↓ thyroid level
  - Hyperthyroidism, ↑ thyroid level

ENDOCRINE PANCREAS

- Dr. Meera Arun

- Exocrine & endocrine part
- Exocrine : 80%
- Endocrine: cluster of cells called islets of Langerhans

Islets of Langerhans

- 1-2 million cells
- Scattered within pancreas, abundant in tail

Depending on staining properties,

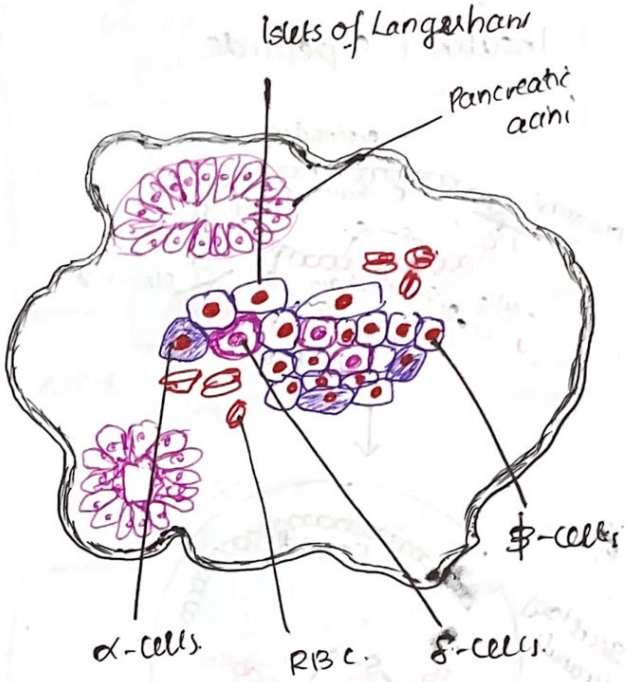
α cells secrete Glucagon

β cells secrete Insulin, amylin

δ cells secrete Somatostatin

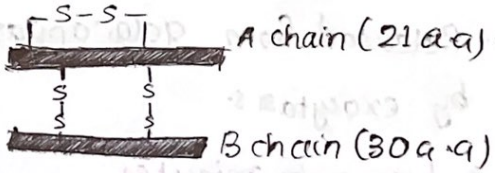
F cells secrete pancreatic polypeptide

- β cells / B cells are most abundant forms central mass (60-75%)
- α cells / A cells constitute outer rim (20%)
- δ cells / D cells interposed b/w the rim of β & α cells
- Rest of cells (PP cells) are seen scattered.



INSULIN

- Discovered by Banting & Best
- Insulin is a polypeptide hormone containing two chains of amino acids linked by disulfide bridges
- A chain : 21 a.a B chain : 30 a.a
- Only pp hypoglycemic hormone in the body



Synthesis of Insulin

Preprepro insulin

↓

pro insulin

↓

Insulin + C peptide

occurs in RER of β cells & transported to golgi apparatus & packed in membrane bound granules

Insulin & C peptide are packaged in the secretory granules and secreted in equimolar amounts with 5-10% pro insulin.

- Released from golgi apparatus by exocytosis.
- $t_{1/2}$ = 5 minutes
- Target organ: liver, muscle, adipose tissue
- Degraded by insulinase in liver, kidneys.

C-Peptide

★ Levels indicate β cell activity... measured diabetic patients to assess the amount of natural insulin secretion (much decreased in Type I diabetes)

- Activates Na K ATPase and Endothelial NO synthase

How glucose enters the cell

2 mechanisms:

- facilitated diffusion via glucose transporters
- secondary active transport with sodium via sodium dependent glucose transporters SGLT (intestine & kidney)

Amount of glucose entering the cell depends on the conc. of glucose

Glucose transporters (GLUT)

7 types identified (GLUT-1 to GLUT-7)

- GLUT-1 & GLUT-3 - in most tissues specially CNS & RBC for basal uptake of glucose

organ: liver, muscle, adipose tissue

d by insulinase in
d neys

Peptide

indicate β cell activity...
diabetic patients
the amount of natural
cretion, (much decreased
diabetes)

Na K ATPase and
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& kidney)

glucose entering the
on the conc. of glucos

transporters (GLUT)

lentified (GLUT-1 to GLUT-7)

nLUT-3 - in most tissues
is & RBC for basal uptake

- GLUT-2 - β-cells, Liver, Intestine, Kidney.
- GLUT-4 - Skeletal m., & adipose tissue
  - * Most insulin sensitive

★ For most of the CNS cells insulin is not needed for glucose entry. Glucose is the main source of energy.

Insulin independent glucose entry can occur in skeletal muscles during exercise.

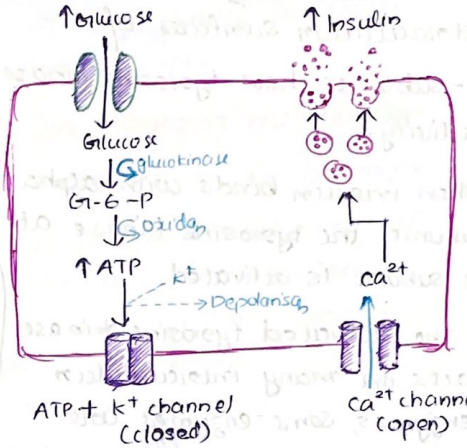
★ Mechanism of release of Insulin

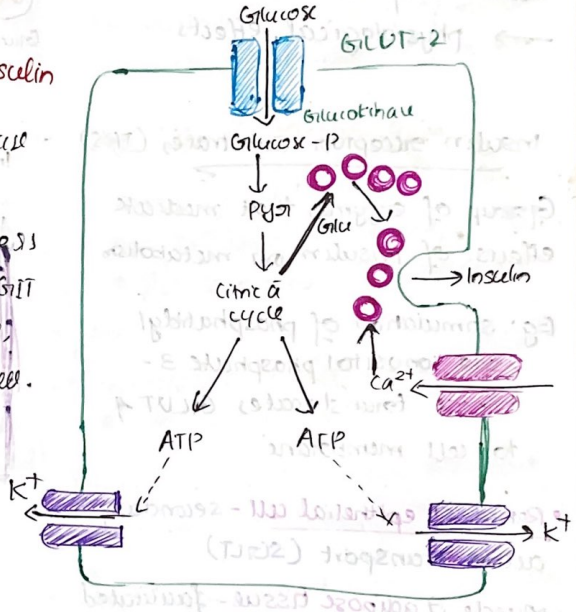
- Most potent stimulus for release of insulin - Glucose
- Following a meal - glucose enters the portal circulation from GIT ... glucose is a large molecule, so can't diffuse freely into the cell.

Insulin receptor.

- Glycoprotein tetramer
- 2 α & 2 β subunits
- α subunit extracellularly
- β subunit transverse the membrane
- The α & β subunits are linked to each other by disulphide bonds

Mechanism of insulin release from β-cells





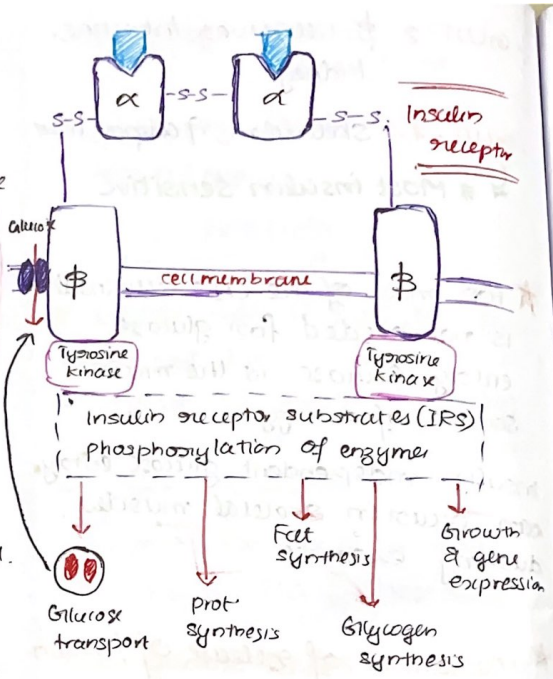
Mechanism of action of Insulin

Intracellular surfaces of β-subunits have tyrosine kinase activity.

When insulin binds with alpha subunit, the tyrosine kinase at β subunit is activated.

* The activated tyrosine kinase acts on many intracellular enzymes, some enzymes are activated & some are inactivated.

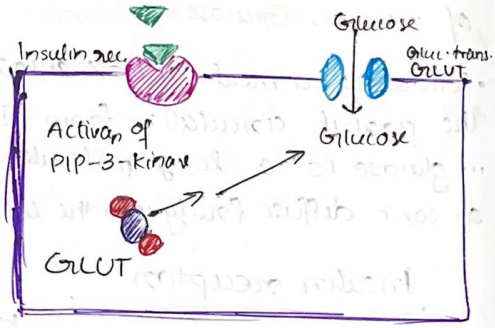
→ physiological effects



Insulin receptor substrates (IRS)

Group of enzymes that mediate effects of insulin on metabolism

Eg: stimulation of phosphatidyl inositol phosphate 3-kinase translocates GLUT 4 to cell membrane



Phosphatidyl inositol phosphate 3-kinase

- Renal & epithelial cell - secondary active transport (SGLT)
- Muscle & adipose tissue - facilitated diffusion by GLUT-4
- Exercise - more GLUT insertion, not insulin dependent
- Glucose entry into majority of brain cells is not insulin dep.
- Glucose is the main source of energy for the brain cells (& for retina & germinal epithelium of gonads also)

Actions of Insulin

"Hormone of Abundan

- Secreted when nutri abundant

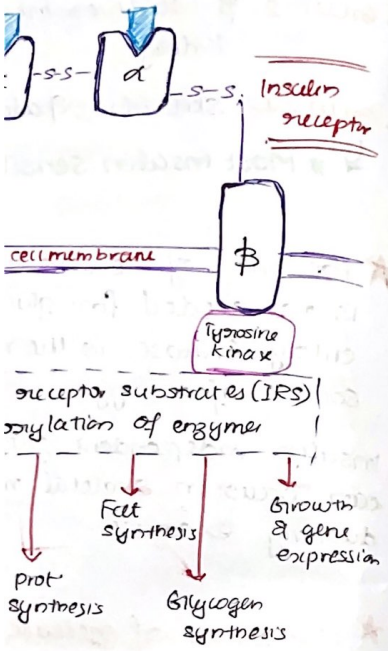
Actions : on metaboli
on growth
other action

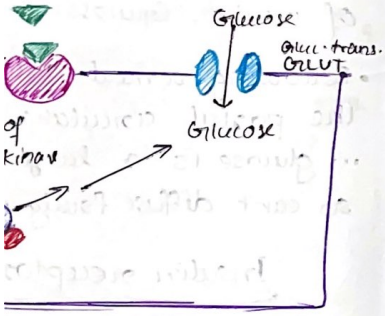
ON METABOLISM

* On carbohydrate m

Hypoglycemic hormone

- ↓ blood glucose
- ↑ glucose entry into sensitive cells by ins GLUT transporters
- ↑ peripheral utilizati glucose (Glycolysis in muscle are promot
- promotes storage as glycogen (Glycoge ↑sed to 5-6%. Glycogen synthase
- converts excess g fatty acids & sto tissue (+ Lipoprote - hormone sensi
- Inhibits glycogenoly (Inactivate glycog





idyl inositol phosphate
3- kinase

is the main source of
& the brain cells
na & germinal epithelium
s also)

Actions of Insulin

"Hormone of Abundance"

- Secreted when nutrients are abundant

Actions : on metabolism
on growth
other actions

ON METABOLISM

* On carbohydrate metabolism

Hypoglycemic hormone:

- ↓ blood glucose
- ↑ glucose entry into insulin sensitive cells by inserting GLUT transporters
- ↑ peripheral utilization of glucose (Glycolysis in liver & muscle are promoted)
- promotes storage of glucose as glycogen (Glycogen storage ↑sed to 5-6% liver mass. Glycogen synthase is stimulated)
- converts excess glucose to fatty acids & store it in adipose tissue (+ Lipoprotein lipase & − hormone sensitive lipase)
- Inhibits glycogenolysis (Inactivate glycogen phosphorylase)
- Inhibits gluconeogenesis. (Inactivate ~~glycogen~~ formation of new glucose molecules from amino acids)

On Protein metabolism

- Protein anabolic hormone

1. It promotes the entry of amino acids into the cell.
2. Inhibits gluconeogenesis so that more AA are available for protein synthesis
3. Acts directly on ribosomes & stimulates translation of mRNA
4. Inhibits catabolism of proteins

On Lipid Metabolism

Fat sparing action of insulin (glucose utilized for energy) leads to ↑ fat synthesis in adipose tissue

- ↑ synthesis of f.ā from acetyl CoA in the liver.
- Promotes triglyceride transport & deposit in adipose tissue.
- Fatty ā are packed into triglycerides in the liver & transported in the form of VLDL & deposited in adipose tissues ... activate lipoprotein lipase

- Inhibits lipolysis by inhibiting the action of hormone sensitive lipase
- Increase the transport of glucose into adipose tissue (glucose used for formation of α-glycerol phosphate which supplies Glycerol for the formation of triglycerides)

- **Anti-ketogenic action:**

In the presence of insulin only minute amounts of ketone bodies like acetoacetate are formed and they are completely utilized in the peripheries

On cholesterol metabolism

Insulin is required for the utilization of VLDL & LDL. In diabetics, plasma cholesterol ↑ser.

ON GROWTH

- ↑ protein synthesis promotes growth
- Insulin acts synergistically with GH (Growth hormone) to stimulate growth.
- ↑ availability of glucose in cells → favour growth

OTHER ACTIONS

1. Stimulates entry of K^+ into cells.
2. Decrease plasma potassium levels.
3. Stimulate Na-K ATPase
4. ↑ entry of phosphate & magnesium into cell
5. Insulin inhibits Glucagon ~~sec~~ secretion.

RAPID ACTION OF INSULIN (in seconds):

Increase transport of glucose, a.a and potassium into insulin sensitive cells

INTERMEDIATE ACTIONS (minutes)

- Stimulate glycolysis & glycogen synthesis
- Inhibit gluconeogenesis
- Stimulate protein synthesis and inhibit catabolism

LATE / DELAYED ACTIONS (hours)

- Increase mRNA for fat synthesis

NSILA (Non suppressible insulin like activity)

- Plasma contains a few substances in addition to insulin, with insulin like activity
- Their actions persist even pancreatectomy
- IGF 1 & IGF 2

★ Normal plasma glucose

* Fasting Blood Glucose (FBS :- 80 - 100 mg/dL
* postprandial blood Gluco :- ≤ 140 mg/dL

Glycated Hb (HbA1c): les

★ Regulation of insulin

1. Blood glucose levels
2. Blood amino acid le
3. Hormonal regulation
4. Neural regulation

1. Blood glucose level

➤ ↑ in blood glucose → ↑ insulin se

➤ Fasting → minimal secretion

➤ After meals... acute in blood glucose levels ↑ insulin release.

Insulin released in 2 p

BIPHASIC RESPONSE.

ER ACTIONS

ites entry of K^+ into

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ON OF INSULIN (in seconds):

ransport of glucose, otassium into insulin s

ATE ACTIONS (minutes)

ycolysis & glycogen

neogenesis

otein synthesis and olism

ED ACTIONS (hours)

VA for fat synthesis

ppressible insulin

ins a few substances insulin, with ivity

- Their actions persist even after pancreatectomy
- IGIF 1 & IGIF 2

★ Normal plasma glucose levels

* Fasting Blood Glucose (FBS) :- 80 - 100 mg/dL
* postprandial blood Glucose (PPBS) :- ≤ 140 mg/dL

Glycated Hb (HbA1c) : less than 6%.

★ Regulation of insulin secretion

1. Blood glucose levels
2. Blood amino acid levels
3. Hormonal regulation
4. Neural regulation

1. Blood glucose level

➤ ↑ in blood glucose ⟶ ↑ insulin secretion

➤ Fasting ⟶ minimal insulin secretion

➤ After meals... acute increase in blood glucose levels ⟶ ↑ insulin release.

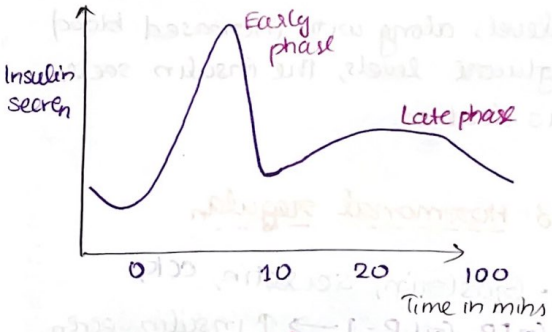
Insulin released in 2 phases - BIPHASIC RESPONSE.

- sharp increase in 3-5 mts (100 micro units/ml) stored insulin
↓
- Decrease in 10 mts (40-50 micro units/ml)
↓
- again rise after 15-20 mts and remain plateau for next 2-3 hrs.

In first 5 minutes - due to release of stored insulin

After 15 mts - due to stimulation of insulin synthesis & secretion. Lasts for 2-3 hrs.

(intracellular Glutamate second messenger system is responsible for the prolonged phase of Insulin release)



★ Oral intake of glucose has a greater insulin response than intravenous administration. Why?

- Oral intake causes release of a group of peptide hormones from wall of GIT - called INCRETINS.
- GLP-1 (L-cells), GIP (K cells), cholecystokinin (I cells).
- Incretins stimulate insulin secretion & glucose increases the secretion even further
- Vagal stimulation of β-cells primes the islets for an amplified response

2. Blood amino acids

- Arginine & lysine → ↑ insulin secretion
- Amino acids potentiates glucose stimulus for insulin secretion
- If there is increase in amino acids levels along with increased blood glucose levels, the insulin secretion is doubled

3. Hormonal regulation

- Gastrin, secretin, CCK, GIP, GLP-1 → ↑ insulin secretion (after meals)
- Glucagon - ↑ insulin secretion
- Somatostatin - ↓ insulin secretion
- cortisol, ACTH, Thyroxine, GH, Estrogen, progesterone stimulates insulin secretion etc indirectly

★ increased risk of diabetes in patients on long term steroids, hormone therapy, giants, acromegaly ...

eg: metahypophyseal diabetes

Hormones affecting blood glucose

↑ blood glucose	↓ Blood glucose
• cortisol	• Insulin
• ACTH	
• Glucagon	
• Growth hormone	
• Estrogen	
• Progesterone	

Organs controlling blood glucose: Liver, skeletal muscle

4. Neural Regulation

- Parasympathetic → stimulates β-cells → ↑ insulin secretion
- Sympathetic effect - depends on the receptors stimulated
- β-receptors - ↑ insulin secretion
- α2 receptors - ↓ insulin secretion

* Net effect of E & NE on islets is ↓ insulin secretion.

Cyclic AMP & Insulin secretion

- Stimuli that increase β cAMP levels in β-cells ↑ insulin secretion including glucagon, β-adrenergic agonists.
- K depletion decreases insulin secretion.

Glycated Hb

- Glucose attached to terminal valine of β-chain of HbA
- Amount is proportional to blood glucose concentration
- Normal <6%
- Level of HbA,c indicate the glycemic state of an individual for past 2-3 months (∵ life cycle of RBC is 120 days) → 3-4 months.

Lecture note - Meera Madam.

(Beane & Levy textbook) Table 42.2 some actn of...

	Epinephrine (β)	Norepinephrine (α)
CVS	↑ Systolic BP VD, ↓ Diastolic BP ↑ HR, ↑ CO	↑ SBP, VC, ↑ DBP ↑ Mean arterial pr- ↓ HR & ↓ CO
Other systems	Smooth m. relaxation in, GIT, Bladder, Bronchus.	Constrictn of sphincters of GIT & Bladder.
Metabolic	↑ Glycogenolysis & Gluconeogenesis ↑ I^n secretn. [↑ lipolysis ↑ calorigenesis.] exclusively by EN	- same - ↓ I^n.

SW

General adaptation syndrome.

- Response to stress described by SELYE
- glucocorticoids & catecholamines
- 3 stages after...

1. Stage of alarm
2. " resistance
3. " exhaustion

Stage of alarm

- 6-24 hrs after exposure
- fatigue, scanty urine, low glucose, shrinkage of adrenal gland

(2) Stage of resistance

adaptation, recovery of animal urine output ↑, hyperplasia of adrenal cortex, ↑ scd GC

Dopamine

- Produce renal & mesenteric vasodilatation but ↓G in other part
- ↑ sys. BP, not much change in DBP.
- +ve ionotropic effect
- Prolactin inhibitory factor
- Dopamine acts as NT in Basal ganglia
- Principal NT in aortic & carotid body.

Therapeutic use ✗

Pheochromocytoma:

Adrenal medullary tumor

- Rare benign tumor of adrenal medulla.
- Excess catecholamine secretion.

(if NE ↑: hypertension
if E ↑: hyperglycosuria)

Adrenal function tests ✗ SY

- Hormone assays.
- Provocative
  - Stimulation test
  - Suppression test
- Other specific
  - Imaging

Tests for Zona Fasciculata

1. Serum cortisol measurement (diurnal variation to be considered)
2. Urinary free cortisol
3. Serum ACTH level.
4. Dexamethasone suppression test.
5. ACTH stimulation test (✗ in Sec def.)
6. CRH stimulation test in TC-def.

Test for Zona Glomerulosa

1. Plasma aldosterone level
2. Plasma Renin level
3. PRA (↑ Renin activity)
4. Furosamide stimulation test
5. Saline suppression test
6. Fludrocortisone suppression test

Adrenal medullary ✗ test

- Clonidine suppression test

.....