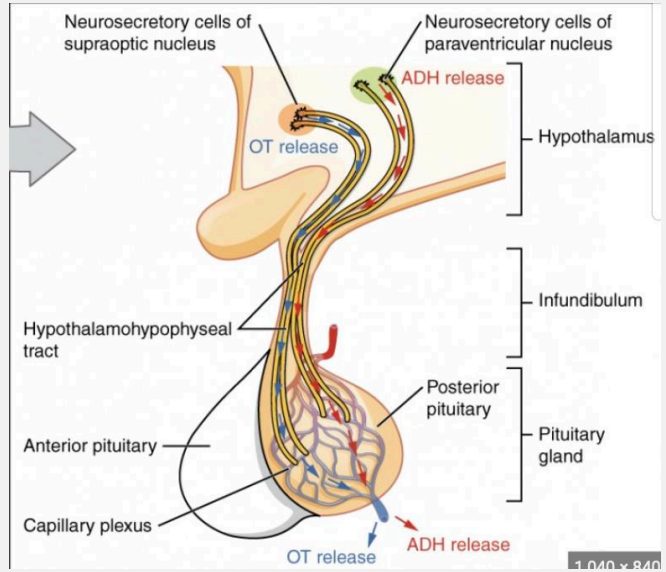
HYPOTHALAMUS, PITUITARY & DIABETES

ANATOMY

- Hypothalamus = collection of neurones, controls basically whole endocrine system
- Connected to pituitary gland by infundibulum/pituitary stalk



- Pituitary gland = gland that sits in fossa in sella turcica of sphenoid bone
- Spilt into 2 divisions; anterior and posterior
  - Anterior – makes + secretes hormones
  - Posterior – only stores + secretes hormones (hormones made in hypothalamus)

- Infundibulum contains hypothalamo-hypophyseal portal system + hypothalamo-hypophyseal tract

Blood vessels which connect hypothalamus to ant. pituitary

Nerve axons which connect nuclei in hypothalamus to post. pituitary

ANTERIOR PITUITARY

LEARN!!!

Hypothalamus	Anterior pituitary cells	Pituitary Hormone Secreted	Target gland	Endocrine hormones and function
Growth hormone releasing hormone GHRH (+) Somatostatin (-)	Somatotrophs	Growth hormone (GH)	Bone, liver Adipose, Muscle	IGF-1 Growth and metabolic function
Corticotrophin releasing hormone CRH (+)	Corticotrophs	Adrenocortico-tropic hormone (ACTH)	Adrenal gland cortex	Cortisol and androgens synthesis/ release
Thyrotophin releasing hormone TRH (+)	Thyrotrophs	Thyroid Stimulating hormone (TSH)	Thyroid gland	Thyroid hormone synthesis & release
TRH (+) Dopamine (-)	Lactotrophs	Prolactin	Breast	Direct action Milk production
Gonadotrophin releasing hormone GNRH (+)	Gonadotrophs	Follicle stimulating hormone (FSH) Luteinizing hormone (LH)	Ovaries (females) Testes (males)	Oestrogen Progesterone Testosterone Egg/sperm production

Hypothalamus releases a stimulating hormone

↓

Acts on cells in ant. Pituitary to release hormone

↓

Acts on target gland so it can carry out its function

Important inhibitors…

- The hypothalamus also secretes **dopamine**, which **inhibits the release of prolactin** from the anterior pituitary gland. This is why dopamine is also called prolactin inhibitory hormone (PIH). So having low dopamine will cause anterior pituitary gland to release prolactin.
- Hypothalamus secretes **somatostatin** which **inhibits release of growth hormone** from the anterior pituitary gland. Having low somatostatin will cause anterior pituitary to release growth hormone.

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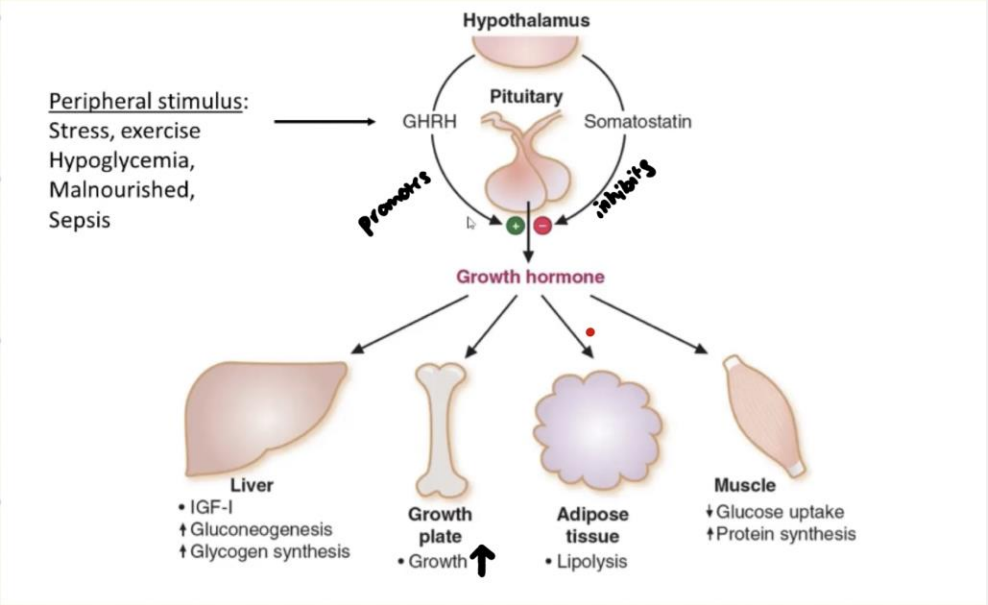
GROWTH HORMONE

Stimulus: low proteins/high amino acids, low glucose, low fatty acids, ghrelin (hunger hormone)
Hypothalamus: releases growth hormone releasing hormone
Anterior pituitary: somatotroph cells releases growth hormone
Effects:

- Increase protein synthesis
- Increase gluconeogenesis/glycogenolysis
- Increase fatty acids by lipolysis
- Liver releases IGF-1

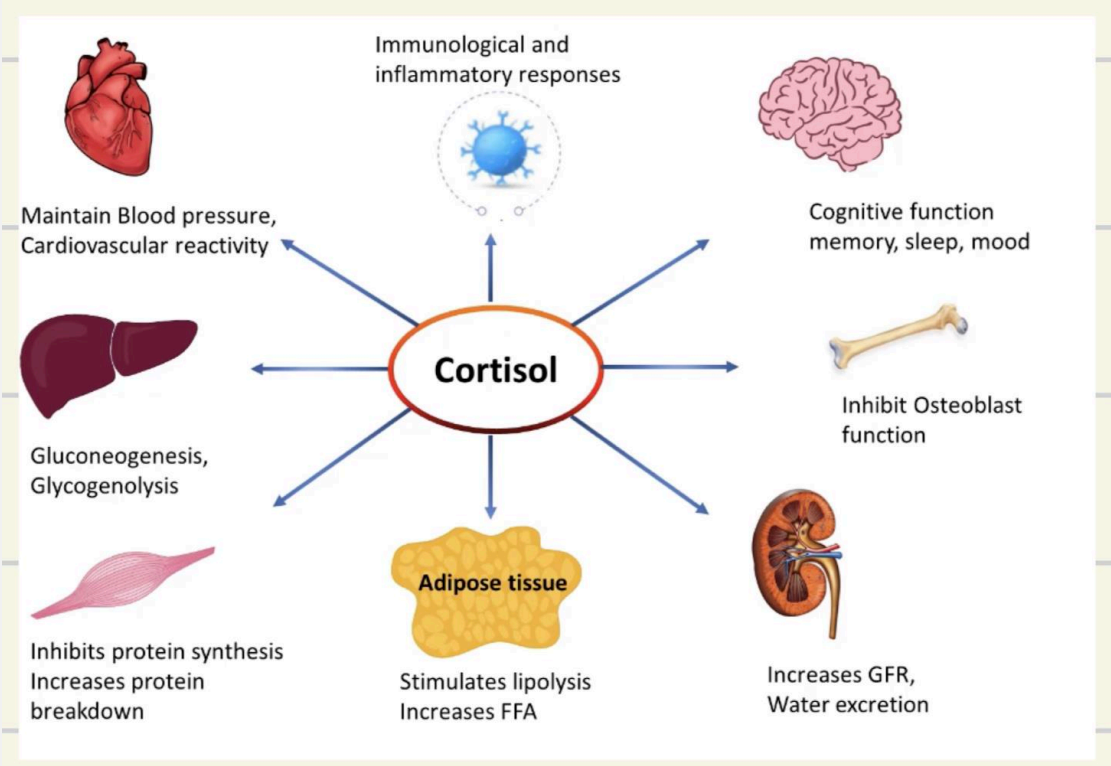


IGF-1 = protein secreted from liver due to growth hormone. It stimulates growth of bones, tissues, cells and regulates metabolism of carbs, proteins and fats

ACTH

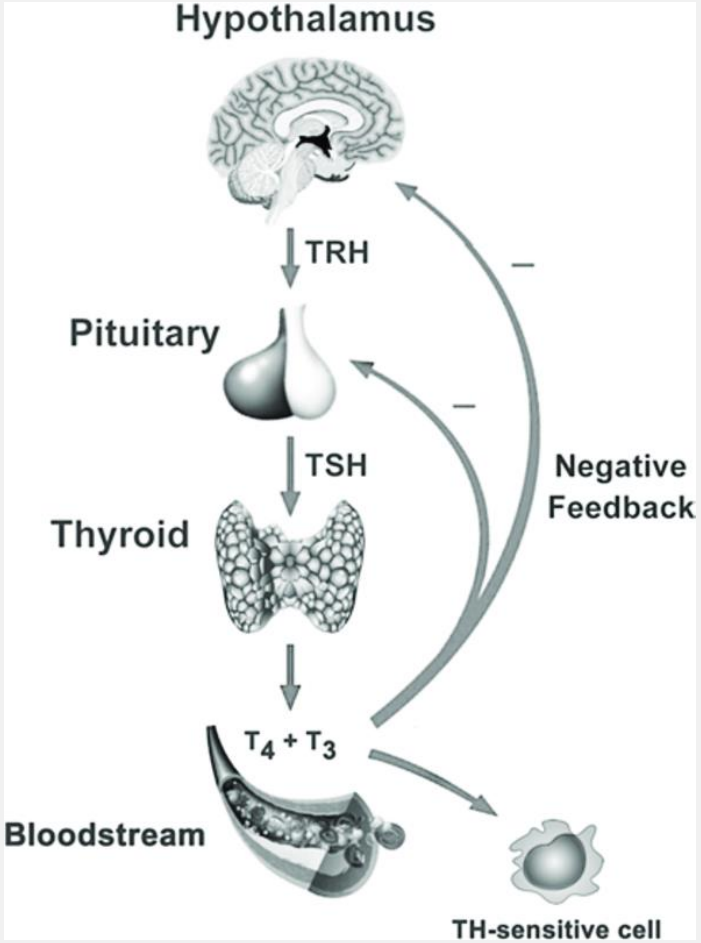
- **Stimulus**: Stress, low glucose
- **hypothalamus**: corticotropin releasing hormone
- **anterior pituitary:** corticotrophs **release** ACTH
- **effects:** release cortisol (from adrenal gland), increase gluconeogenesis, lipolysis, proteolysis, maintains BP
- **Inhibition:** cortisol (due to direct feedback)

Cortisol is a stress hormone



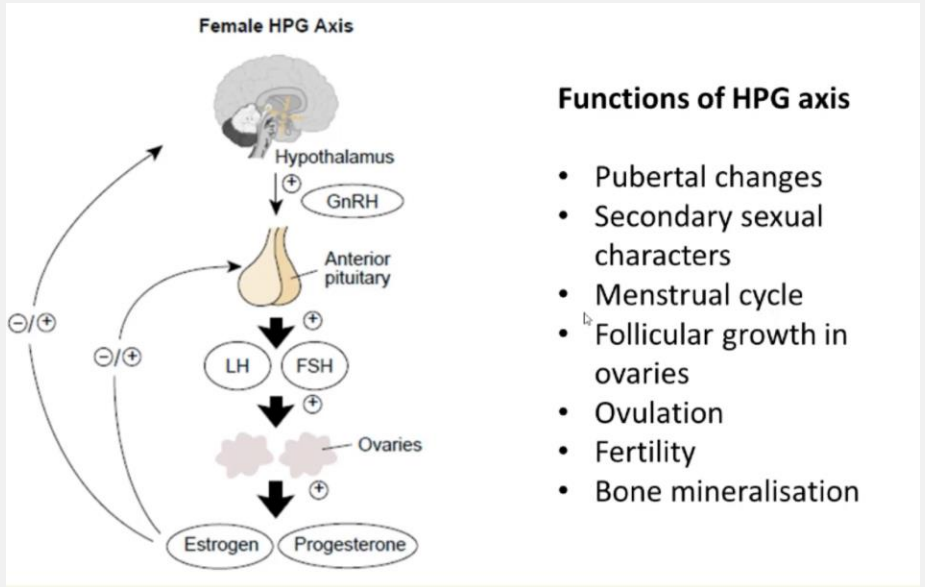
TSH

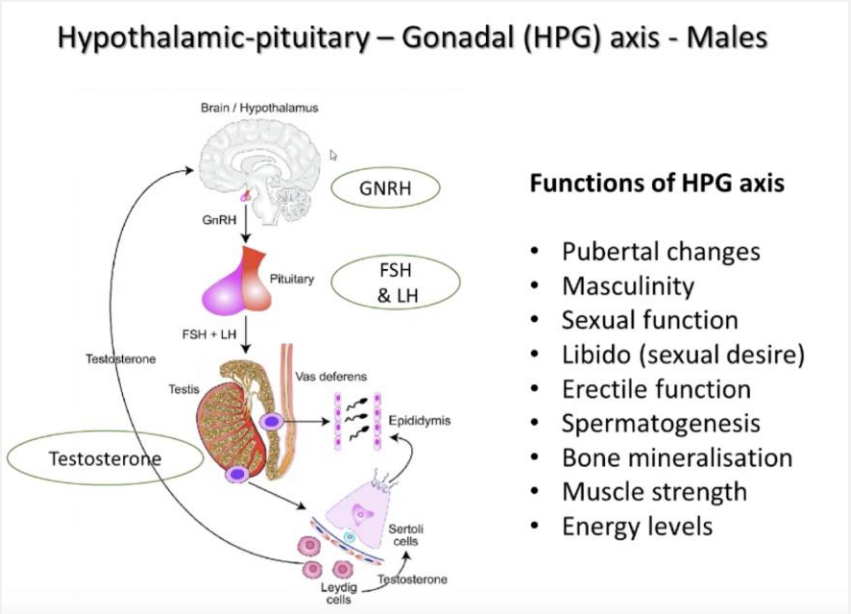
- **Stimulus**: low **T3 and T4**
- **hypothalamus**: thyroid releasing hormone
- **anterior pituitary:** thyrotropin release thyroid stimulating hormone
- **Effects:** increase basal metabolic rate eg increase heart rate, bone turnover, gut motility
- **Inhibition:** T3 & T4



LH/FSH

- **Stimulus**: oestrogens
- **hypothalamus**: gonadotropin releasing hormone
- **anterior pituitary:** gonadotrophs release LH, FSH
- **Effects** : FSH (germ cell development), LH (triggers ovulation, testosterone – in Leydig cells)
- **Inhibition:** Oestrogen & progesterone





PROLACTIN

- **Stimulus**: low dopamine, baby suckling on nipple
- **hypothalamus**: thyrotropin releasing hormone
- **anterior pituitary:** lactotrophs - prolactin
- **Effects:** produce milk after childbirth
- **Inhibition:** dopamine

POSTERIOR PITUITARY

- Releases 2 hormones which are both made in supraoptic and paraventricular nuclei in hypothalamus
- Hormones then travel from nuclei through axons in tract to posterior pituitary where they are stored and released

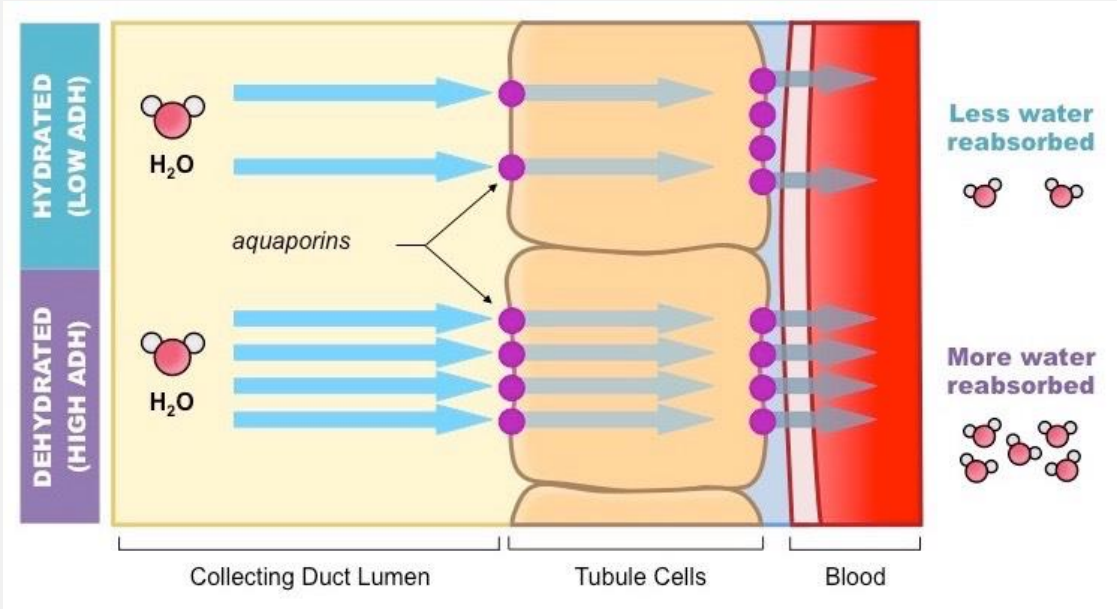
1. Vasopressin/ADH (anti-diuretic hormone)

Overall function = conserve body water so less lost in urine

Causes aquaporins (channels) to bind to collecting duct of nephron in kidneys.

This means water moves from filtrate in duct to interstitial fluid to blood in capillaries i.e. retains water

High ADH = high aquaporins = saves water from being lost eg when dehydrated



POSTERIOR PITUITARY

- Releases 2 hormones which are both made in supraoptic and paraventricular nuclei in hypothalamus
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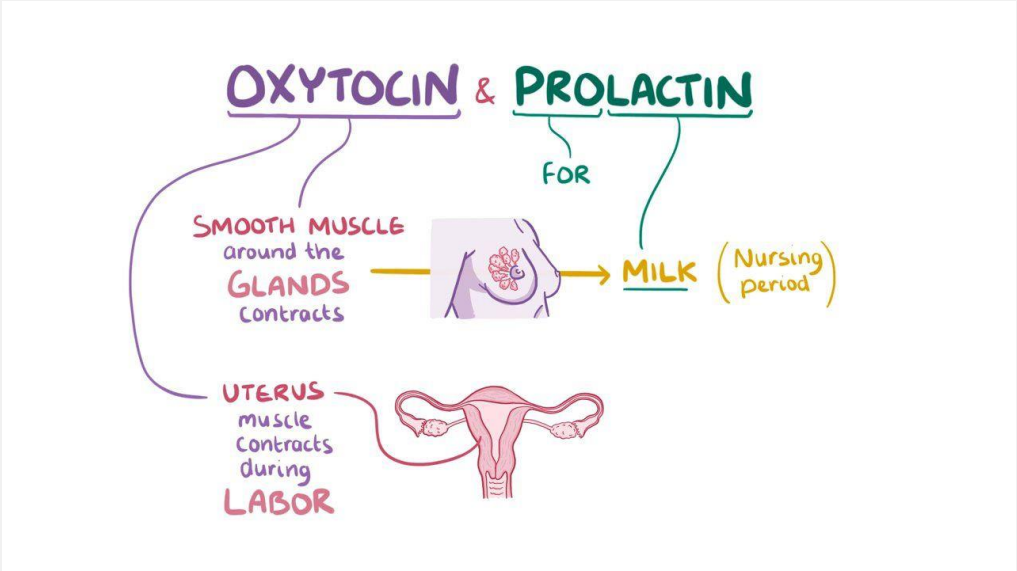
2. oxytocin

Overall function = stimulates myoepithelial contractions in uterus during childbirth + milk ejection from lactating mammary gland

Uterine contractions: +ve feedback, more oxytocin, more contractions

Milk ejection: suckling is a stimulus for oxytocin release



Oxytocin for milk EJECTION, prolactin for milk PRODUCTION

A. pituitary

Stimulus	Hormone Released by Hypothalamus	Cell Stimulated in Anterior P.	Hormone by the Anterior P.	Effect of the Anterior P. Hormone	Hormone + Receptor	Hormone Inhibitor
Hypoglycemia, Low FAs, High a.a's, Ghrelin	Growth Hormone RH (GHRH)	Somatotrophs	Growth Hormone (GH)	Directly binds to adipocytes □ **increases FAs** by breaking down triglycerides Indirectly causes hepatocytes to release IGF-1 □ **increases protein synthesis** and **glucose**	Peptide GPCR	Somatostatin (GHIH)
Stress, Low glucose	Corticotropin RH (CRH)	Corticotrophs	Adrenocorticotropic Hormone (ACTH)	Stimulates the adrenal gland to release cortisol □ **'fight or flight' hormone.** Increases glucogenesis, lipolysis, proteolysis, maintains BP	Peptide GPCR	Cortisol
Low T_3 and T_4	Thyroid RH (TRH)	Thyrotrophs	Thyroid Stimulating Hormone (TSH)	Stimulates the thyroid gland to release T_3 and T_4 □ regulates basal **metabolic rate**	Peptide GPCR	T_3 and T_4
Oestrogens	Gonadotropin RH (GnRH)	Gonadotrophs	LH, FSH	FSH □ **germ cell development**, oestrogen LH □ **ovulation**, testosterone	Peptide GPCR	Oestrogen + Progesterone
Low dopamine prior to menses, Baby suckling at nipple	*Hypothalamus reduces dopamine release*	Lactotrophs	Prolactin	Acts on mammary glands in the breast to **release milk** after childbirth	Peptide GPCR	Dopamine

Credit- Aarifa Khanom (Y4)

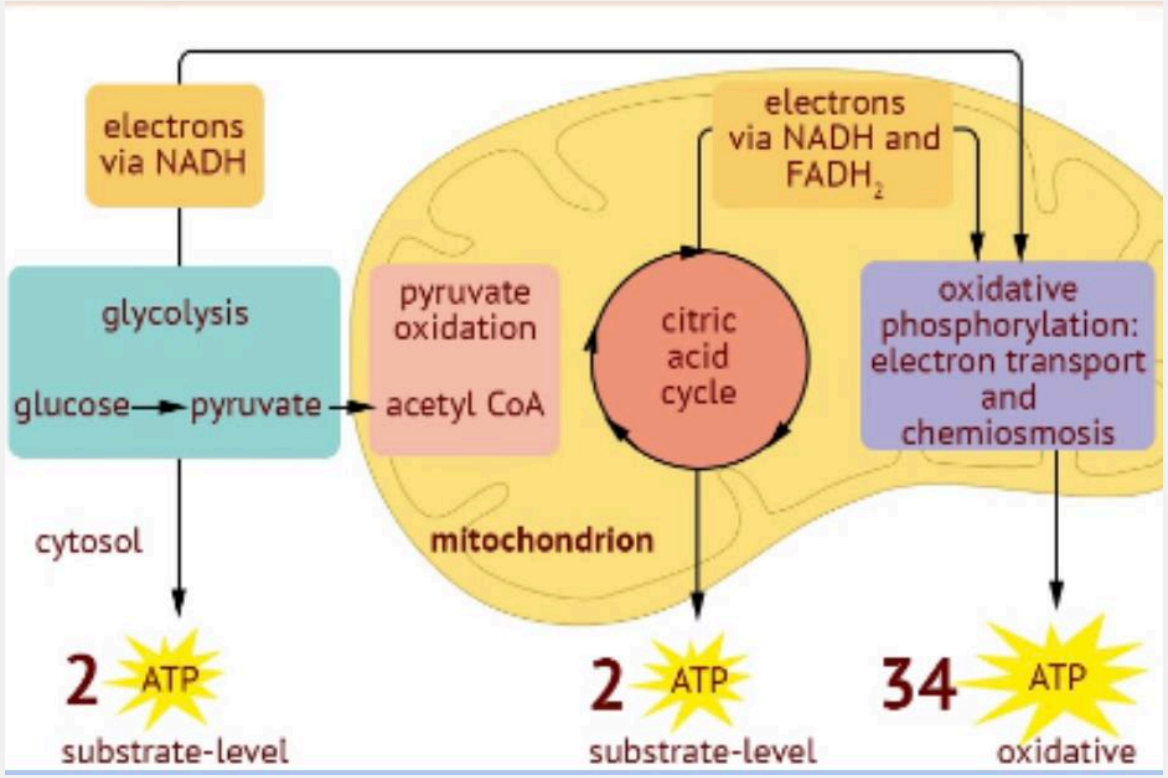
Posterior Pituitary

Stimulus	Hormone Released by Hypothalamus + Stored in the Posterior Pituitary	Effect of the Hypothalamus/Posterior Pituitary Hormone	Hormone + Receptor	Hormone Inhibitor
Uterine stretching during labour	Oxytocin	Uterine contraction (positive feedback loop) Milk ejection	Peptide Hormone GPCR	Catecholamines (adrenaline, noradrenaline)
Osmoreceptors in the hypothalamus detect high blood osmolarity (low water levels)	ADH (Vasopressin)	Causes aquaporin to bind to the collecting duct of nephrons inside the kidneys □ increases water retention	Peptide Hormone GPCR	Alcohol Low blood osmolality (high water levels)

Credit- Aarifa Khanom (Y4)

GLUCOSE

- Normal levels = 4-7mmol/L
- Essential for brain function and many other tissues
- Regulated by hormones, most important one being insulin

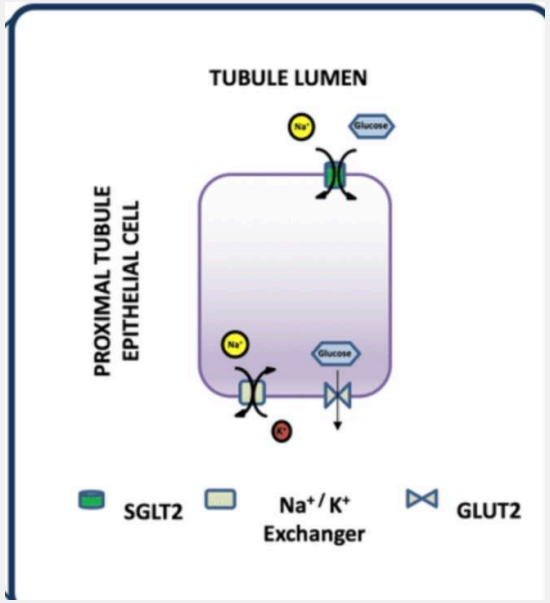


GLUCOSE TRANSPORTERS

- GLUT1 = brain, erythrocytes, placenta, fetal tissue
- GLUT2 = pancreatic beta cells, liver, kidney, intestine
- GLUT3 = brain – preferential uptake in hypoglycaemia
- GLUT4 = muscle and adipose tissue, insulin sensitive
- GLUT5 = jejunum

- SGLT 1 + 2 (sodium dependent glucose transporters) = small intestine + PCT. Need Na gradient from lumen into cell

K.M. = how much glucose is needed for transporter to work. If low KM, means need less glucose for transporter to work



NAME	Tissue location	Km	Comments
GLUT1	Most all mammalian tissues	1-2 mM	Basal glucose uptake
GLUT2	Liver and pancreatic cells. Basolateral membrane of small intestines.	15-20 mM	Removes excess glucose from blood and plays a role in insulin secretion. Insulin insensitive.
GLUT3	Like GLUT1	1 mM	Like GLUT1
GLUT4	Muscle and fat cells	5 mM	Insulin sensitive
GLUT5	Mucosal membrane of small intestine. Spermatozoa	10 mM	Fructose transport

GLUT 2 MECHANISM

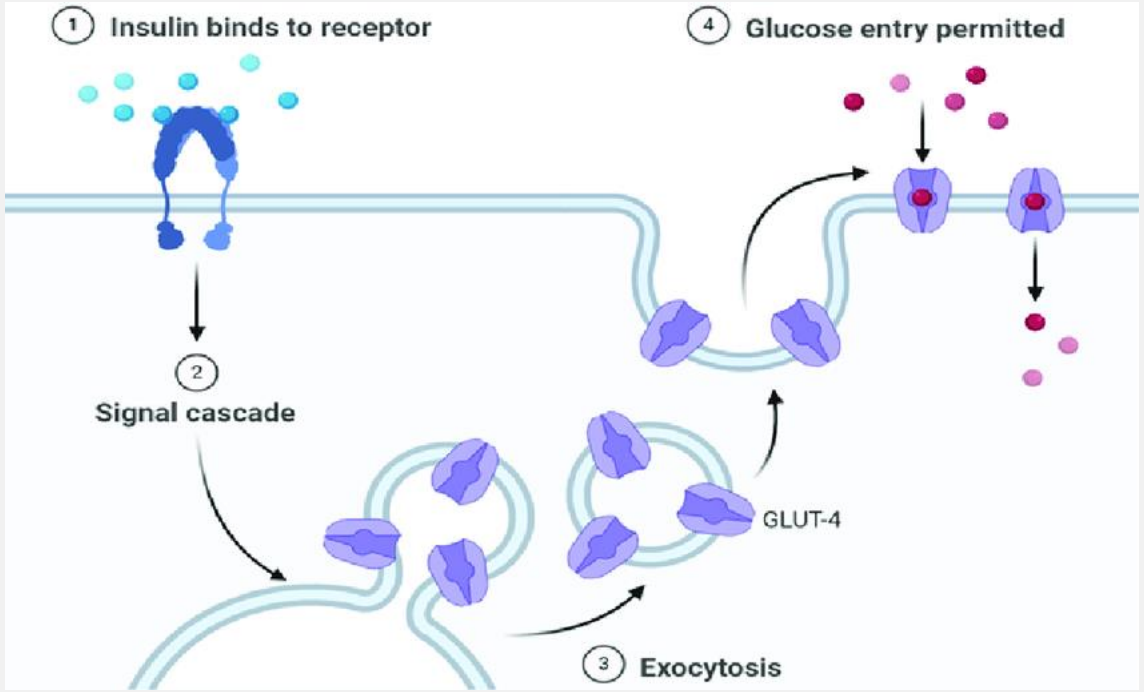
- Glucose enters liver cells via GLUT 2
- Glucose occupies glucokinase sites in cells
- Glucokinase then turns glucose into glucose 6-phosphate
- The G6P + insulin = glycogen build-up in liver so when blood glucose levels are low, glycogen can be released

Insulin speeds up how fast glucose is taken up by liver cells – it is not necessary for uptake of glucose in liver, only accelerates the process

GLUT 4 MECHANISM

- Mainly in muscle and adipose tissue
- For glucose uptake here, insulin is necessary hence why glut 4 transporters are insulin sensitive

1. Insulin binds to tyrosine kinase receptors
2. Triggers protein kinase cascade
3. Vesicles with glut4 in them fuse with CSM
4. Glucose enters cell via glut4



- **In adipose tissue glucose is converted into fatty acids**
- **In skeletal muscle and liver glucose is converted to glycogen**

PANCREAS

- Retroperitoneal except for tail which is intraperitoneal
- Exocrine function: secrete substance into duct (90% of total function) – mainly for digestion
- Endocrine function: secrete hormones into bloodstream so they can go to distant organs (10% of total function)

Endocrine cells = islets of Langerhans cells

1. Alpha – glucagon
2. Beta – insulin
3. Delta – somatostatin which inhibits secretion of glucagon and insulin
4. Pancreatic polypeptide – inhibit secretion of somatostatin

ALPHA CELLS

- Secrete glucagon
- Main target of glucagon is liver
- Main function is to increase blood glucose levels
- **Stimulus:** low blood glucose in fasting state, sympathetic NS, rise in blood amino acids
- **Function:** increase blood glucose levels, stimulate glycogenolysis & gluconeogenesis, increases lipolysis & inhibit glycogenesis i.e. break things down
- **Inhibited by:** somatostatin and insulin

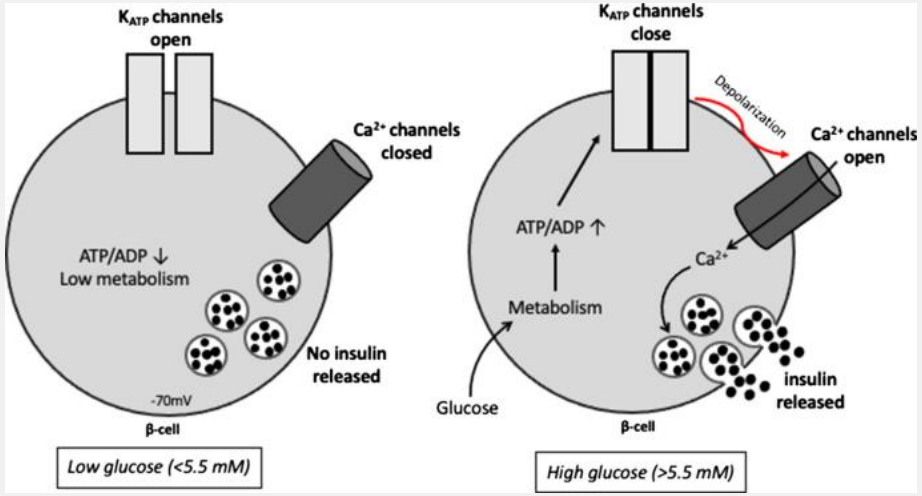
BETA CELLS

- Secrete insulin
- Main function is to decrease blood glucose levels
- **Stimulus:** high glucose In fed state, parasympathetic NS, gastric inhibitory peptide (GIP) and glucagon like peptide 1 (GLP1)
- **Function:** lower blood glucose levels, increase glycogenesis, lipogenesis, protein synthesis so there's more storage of glucose, amino acids and fatty acids in liver and muscle tissue i.e. build things up

HOW DO BETA CELLS WORK?

- At rest, K+ channels are open so K+ diffuses out and p.d. in cell is more negative than outside. Ca^{2+} channels are closed.

1. Blood glucose levels increase
2. Glucose enters beta cells via glut2
3. Glucose > G6P via glucokinase
4. G6P stimulates glycolysis to produce ATP
5. ATP sensitive K^+ channels close so K^+ builds up in cell
6. P.d. gets more positive so voltage-gated calcium channels open
7. Calcium diffuses in causes vesicles with insulin in to fuse with CSM
8. Insulin then released into bloodstream



INCRETINS

- Gut hormones secreted by enteroendocrine cells into the blood **after eating**

Main 2 = GLP-1 and GIP

1. GLP-1

- released from the L cells of the small intestine in response to food
  - stimulates the release of insulin from pancreatic beta cells
  - suppresses the release of glucagon, which reduces glucose production by the liver.
  - Slows down the emptying of the stomach, which helps to regulate the rate at which nutrients are absorbed into the bloodstream.

2. GIP

- Released from K cells of small intestine in response to food
  - Stimulate release of insulin from pancreatic beta cells when blood glucose cells are high

TYPE I DIABETES

- Autoimmune destruction of beta cells
- No insulin (or v little levels) so can't reduce blood glucose levels
- Most commonly in children
- Leads to:
  - Uncontrolled gluconeogenesis > hyperglycaemia
  - No glucose uptake in muscle and fat
  - Use of alt. fuels eg fatty acids
  - ketoacidosis, coma, death

Ketoacidosis = no insulin so glucose can't be processed so turn to other sources of energy eg fat breakdown which produces ketones. Build up of ketones which are acidic

Symptoms:

- Thirst
- Large volume of dilute urine (polyuria)
- Weight loss
- Fatigue

TYPE 2 DIABETES

- Resistance to insulin – initially excess insulin produced to compensate but overtime beta cell function declines > high glucose levels > hyperglycaemia
- Mostly in over 40s, obesity, genetics, lack of exercise are risk factors,

Symptoms

- Thirst
- Large volumes of dilute urine produced
- Weight loss
- fatigue

QUESTION 1

1. What hormone stimulates milk ejection?

a. Oxytocin

b. Prolactin

c. Dopamine

d. oestrogen

OXYTOCIN

- Prolactin – milk production
- Dopamine – inhibits prolactin

QUESTION 2

2. Which hormone doesn't stimulate insulin release?

a. GLP-1
b. GIP
c. Somatostatin
d. cortisol

SOMATOSTATIN

- GLP-1 and GIP = incretins, stimulate insulin release
- Somatostatin released by delta cells of pancreas inhibit release of insulin and glucagon
- Cortisol stimulates insulin release

QUESTION 3

3. Which of the following statements is false?

a. Aldosterone is created in the adrenal cortex

b. oxytocin is created in the posterior pituitary gland

c. Follicle stimulating hormone is created in the anterior pituitary gland

d. Glucagon is created in the pancreas

OXYTOCIN IS CREATED IN THE POSTERIOR PITUITARY GLAND

- Oxytocin only stored and released in posterior pituitary gland – made in nuclei in hypothalamus