Primary Cast Episode 21 - Endocrine Physiology

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1. **Adrenal Hormones**

Name the endogenous catecholamines and their source

- Adrenal medulla – adrenaline, noradrenaline, dopamine
- Intrinsic cardiac adrenergic cells – adrenaline
- Sympathetic nervous system cells – dopamine

What are the physiological effects of adrenaline and noradrenaline?

- Metabolic – glycogenolysis, increased metabolic rate, mobilisation of free fatty acids, increased lactic acid
- Cardiovascular – vasoconstriction and dilation, increased heart rate and contractility

Which receptors are responsible for these effects?

- α1 – constriction of blood vessels, smooth muscle (especially norad)
- α2- mixed smooth muscle effects and involved in negative feedback mechanisms
- B1- cardiac inotropy and chronotropy
- B2- smooth muscle relaxation, bronchodilation and dilation of blood vessels in the liver and muscle
- B3 – lipolysis, detrusor relaxation

2. **Aldosterone**

How does aldosterone exert its effects in the kidney?

- It is a mineralocorticoid, acting on principal cells in the collecting duct
- It binds a cytoplasmic receptor and the complex travels to the nucleus where it alters transcription of mRNA
- Aldosterone promotes resorption of Na+ and Cl from the urine in exchange for K+ and H+, via rapid insertion of preformed epithelial sodium channels (eNaC) on the cell and increased synthesis of eNAC channels.
- The action takes 30 minutes to develop.

Describe the serum and urine effects of hyperaldosteronism

- Increased sodium and chloride in plasma
- Fluid retention (follows Na)
- Hypokalaemia due to aldosterone effect in the kidney
- H+ are lost in the urine, resulting in increased urine acidity and K concentration

What are the stimuli that increase aldosterone secretion?

- ACTH from pituitary
- Renin from kidney via angiotensin II
- Direct stimulatory effect of rise in plasma K+ concentration in the adrenal cortex
- Clinical causes – surgery, haemorrhage, anxiety, trauma, reduced salt intake, secondary hyperaldosteronism i.e. CCF/cirrhosis

Describe the feedback regulation of aldosterone secretion

- Fall in ECF/blood volume
- reflex increase in renal artery nerve discharge and decrease in renal artery pressure
- increase in renin secretion → increase in angiotensin II → increase in aldosterone secretion
- Na+ and water retention → expanded ECF volume
- decrease in stimulus that initiated renin secretion

3. **Glucocorticoids**

What are the physiological effects of glucocorticoids?

- Permissive action on catecholamine effects (pressors, bronchodilation)
- Metabolic effects – increase protein catabolism, increase hepatic glycogenolysis and gluconeogenesis, increase plasma glucose, increase lipolysis
- Increased free water excretion via decreased vasopressin activity
- Immunological - decreased inflammatory and allergy response
- Haematological – increased platelets , neutrophils, red blood cells
- CNS effects – EEG slowing, personality changes

How is glucocorticoid secretion regulated?

- Glucocorticoids are secreted from the adrenal cortex, which is dependent on ACTH secretion from the anterior pituitary
- ACTHsecretion is regulated by CRH released from the hypothalamus – in response to low cortisol levels or stress
- Glucocorticoids provide a negative feedback loop on the hypothalamus and the anterior pituitary to reduce ACTH secretion

What are the vascular effects of stopping long term glucocorticoid therapy?

- Vascular smooth muscle becomes unresponsive to noradrenaline and adrenaline
- Capillaries dilate and increase in their permeability
- Failure to respond to noradrenaline impairs vascular compensation for hypovolaemia and promotes vascular collapse

What is the benefit of elevated glucocorticoid levels in stress?

Effect on vascular activity to catecholamines, plus mobilisation of FFA for emergency energy source

4. **Calcium Homeostasis**

Where in the body is calcium stored?

Bone 99%

Plasma – both bound to protein and unbound, where it is an important secondary messenger and is required for coagulation, nerve function and muscle contraction

How is the plasma calcium level regulated?

- Parathyroid hormone – increases plasma calcium by mobilising calcium from the bone. Increases calcium resorption in the kidney and increases formation of 1,25 DHCC in the kidney
- 1,25 DHCC (from Vit D) increases calcium absorption from intestines and kidneys
- Calcitonin (from thyroid) – lowers circulating calcium levels by inhibiting bone resorption. It also increases calcium loss in the urine.
- Glucocorticoids – decrease plasma calcium by inhibiting osteoclast formation and activity
- Oestrogen – inhibit the stimulatory effect of cytokines on osteoclasts
- Calcium can also be raised by pathological processes like paraneoplastic syndrome or bone erosion.

How does bone resorption occur?

- Osteoclasts – monocytes that develop from stromal cells under the influence of RANK-L
- They attach to the bone via integrins
- Hydrogen dependent proton pumps acidify the area The acid dissolves the hydroxyapatite and the acid proteases break down collagen
- Products move across the osteoclast to the interstitial fluid.

5. **Glucose**

What factors determine the plasma glucose level?

- Dietary intake
- Absorption from the intestine
- Rate of entry into cells
- Gluconeogenesis in the liver
- Reabsorption in the kidney
- Fasting status

Explain how blood glucose is maintained during fasting

- Short fasting - Liver glycogen is broken down and glucose is released into the bloodstream
- Extended fasting time – Glycogen depletion leads to gluconeogenesis from glycerol and amino acids in the liver.

What happens to glucose homeostasis in the absence of insulin?

- Hyperglycaemia due to
- Decreased peripheral uptake of glucose into muscle and fat
- Reduced glucose uptake by the liver
- Increased glucose output by the liver and lack of glycogen synthesis
- GIT, renal brain and red cells can continue uptake in the absence of insulin

How does exercise affect glucose levels?

- Increased entry of glucose into skeletal muscle via an insulin independent mechanism
- This increases GLUT 4 transporters in muscle cell membranes
- Effects persist for several hours and regular exercise can lead to prolonged increases in insulin sensitivity
- Exercise in T1DM can precipitate hypo because the absorption of injected insulin is more rapid during exercise.

6. **Glucagon**

What are the physiological actions of glucagon?

- Raises BGL via
- Glycogenolysis in the liver
- Gluconeogenesis from amino acids
- Lipolysis
- Ketogenesis
- Positive inotropic effect on the heart
- Increases blood flow to kidneys
- Stimulates secretion of growth hormone, insulin and somatostatin

What factors affect glucagon secretion?

Stimulation

- Beta adrenergic stimulants
- Cortisol
- Protein meal
- Vagal stimulation
- Starvation, stress, exercise
- CCk
- Gastrin

Inhibitors

- Glucose and insulin
- Somatostatin
- FFA
- Ketones
- Alpha adrenergic stimulators
- GABA

7. **Insulin**

What happens when insulin binds to an insulin receptor?

- The insulin receptor is a tyrosine kinase receptor with intra and extracellular components
- Insulin binding to the extracellular alpha subunits triggers tyrosine kinase activity of the beta subunits in the cell
- This leads to autophosphorylattion of the beta subunits and triggers secondary messengers
- Once bound, then insulin receptors aggregate in patches and are endocytosed
- They enter lysosomes where they are broken down or recycled

What are the principle actions of insulin

- Net effect is the storage of CHO, protein and fat
- Rapid(seconds): increase the transport of glucose, amino acids and K+ into insulin sensitive cells
- Intermediate (minutes): stimulation of protein synthesis and inhibition of protein degradation; activation of glycolytic enzymes and glycogen synthase, inhibition of phosphorylase and gluconeogenic enzymes
- Delayed (hours) increased mRNA production for lipogenic and other enzymes

What are the effects of insulin deficiency?

- Decreased peripheral utilisation of glucose
- Hyperglycaemia with low intracellular glucose
- Derangement of glucostatic function of the liver
- Hyperglycaemia with no associated decrease in gluconeogenesis
- Secondary osmotic diuresis with dehydration
- Electrolyte and calorie loss
- Catabolism of protein and fat due to low intracellular glucose
- Ketosis, leading to ketoacidosis
- Breakdown of amino acids for energy
- Increased free fatty acids from breakdown of triglycerides

8. **ACTH**

What factors determine the rate of ACTH secretion?

Increased by stress - pain, emotional distress
Driven by circadian rhythms through the hypothalamus via release of CRH
Inhibited by circulating glucocorticoids and afferent signals from baroreceptors

What happens to ACTH levels after prolonged treatment with glucocorticoids is stopped abruptly?

ACTH slowly increases over weeks
The pituitary might not be able to secrete normal amounts of ACTH for a month
Presumed to be secondary to diminished ACTH synthesis

How can this be avoided?
Slowly decreasing the dose of glucocorticoids over a long period of time

9. **Pituitary Hormones**

What hormones are secreted by the anterior pituitary?
TSH, ACTH, GH, LH, FSH

What are the clinical effects of anterior pituitary insufficiency?

- Adrenal cortical atrophy → glucocorticoid and sex hormone levels fall. Mineralocorticoid secretion is maintained so salt loss and hypovolaemia does not occur, but unable to mount a stress response
- Hypothyroidism
- Growth inhibition
- Gonadal atrophy, loss of some secondary sexual characteristics
- Tendency towards hypoglycaemia due to increased insulin sensitivity

What hormones are secreted by the posterior pituitary?
Vasopressin and oxytocin

What are the physiological effects of vasopressin?
Renal retention of water

10. **Thyroid hormones**

How are thyroid hormones regulated?

- Thyrotropin releasing hormone from the hypothalamus
- Acts on the anterior pituitary to promote release of TSH
- Causes thyroid to release T4 and some T3
- T4 is converted to T3 in periphery
- Negative feedback loop on TSH by free T3 and T4
- Secretion and synthesis of TSH is also increased by cold exposure, decreased by stress and glucocorticoids/dopamine.

What are the physiological effects of thyroid hormones?

- *Cardiovascular* - chronotropic and inotropic effects on the heart via increasing the number of beta receptors, increasing the response to catecholamines. Increase circulating volume, HR and cardiac output
- *Calorigenic* - raises metabolic rate, increases O2 consumption
- *Adipose tissue*- stimulates lipolysis
- *Muscle* - catabolism
- *Bone* - promotes normal bone development
- *Nervous system* - promotes normal brain development

Describe the steps in synthesis of thyroid hormones.

- Thyroid epithelial cells secrete thyroglobulin and iodine into colloid
- Iodide transport is via a symport with sodium (NIS)
- Thyroid peroxidase makes iodotyrosines (MIT and DIT) then combines them to make T3 and T4
- Endocytosis and lysis of colloid releases the free hormone
- T4 is converted to T3 in the periphery
- All of these steps are controlled by TSH

How do thyroid hormones alter metabolism?

Binds to intracellular receptors in the cell nuclei
Alters gene expression to increase metabolism and catabolism of most cells