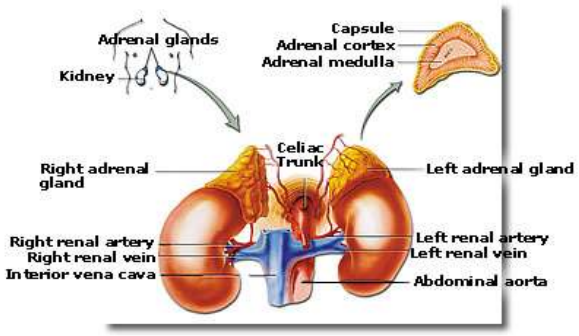
Neuroendocrinology: The Adrenal medulla, Cathecholamines and Pheochromocytoma.

Presenter : Ajime Tom Tanjeko (HS09A169)

Location and anatomy of the adrenals:



Origin and anatomy of the adrenal medulla:

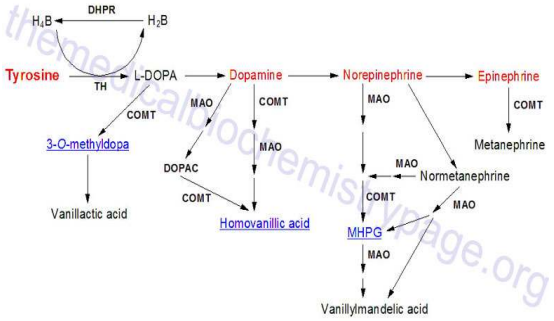
- The adrenal medulla consists of irregularly shaped cells called chromaffin cells grouped around blood vessels, ganglion cells & sustentacular cells.
- Medullary cells are derived from the embryonic neural crest (neuroectoderm) and, as such, are simply modified neurons.

- Differenciation of precursor cells is stimulated by Cortisol and nerve growth factor.
- Some cells migrate to form paraganglia.
- The largest paraganglion is called the organ of Zucherkandl.
- These cells are part of the effector limb of the sympathetic N. S. innervated by thoracolumber axons.

Functions of the adrenal medulla:

- Together with the post – ganglionic sympathetic axons, they produce and store catecholamines (epinephrine and norepinephrine and dopamine)
- Catecholamines are stored in chromaffin vessicles.
- These catecholamines function as neurotransmitters and hormones.
- They are released into the blood stream through the adrenal vein.

Catecholamine Biosynthesis and metabolism:



- Enzymes involed:
- Synthesis: thyrosine hydroxylase(TH), DOPA decarboxylase, dopamine β- hydroxylase, phenylethanolamine-*N*-metyltransferase respectively.
- Metabolism : monoamine oxidase(MAO) and catechol- O- methyltransferase (COMT)
- Catecholamines in blood are also excreted by the kidney directly or by sulphoconjugation.

Cathecholamine action:

- The physiologic effects of epinephrine and norepinephrine are initiated by their binding to **adrenergic receptors** on the surface of target cells (α and β receptors)
- The main receptor subtypes affected are: α1(vascular,vasoconstrictive), α2(neuronal and vascular), β1(cardiac, inotropic & chrnotropic), β2(vascular,vasodilatory)
- Common stimuli for secretion of adrenomedullary hormones include exercise, hypoglycemia, hemorrhage and emotional stress.

Receptor	Effectively Binds	Effect of Ligand Binding
Alpha$_1$	Epinephrine, Norepinphrine	Increased free calcium
Alpha$_2$	Epinephrine, Norepinphrine	Decreased cyclic AMP
Beta$_1$	Epinephrine, Norepinphrine	Increased cyclic AMP
Beta$_2$	Epinephrine	Increased cyclic AMP

Physiologic Effects of Medullary Hormones

- *Increased rate and force of contraction of the heart muscle.*
- *Constriction of blood vessels.*
- *Dilation of bronchioles*
- *Stimulation of lipolysis in fat cells and glycogenolysis.*
- *Increased metabolic rate.*

- *Dilation of the pupils:* particularly important in situations where you are surrounded by velociraptors under conditions of low ambient light.
- *Inhibition of certain "non-essential" processes:* an example is inhibition of gastrointestinal secretion and motor activity.

Pathophysiology

- Pathology within the adrenal medulla and the autonomic nervous system is primarily because of neoplasms.
- The most common is Pheochromocytoma occuring in the chromaffin cells
- Neoplasms may also be of neuronal lineage, such as neuroblastomas and ganglioneuromas (Lau *et al.* 2006).

Pheochromocytoma

- Phaeochromocytoma is a chromaffin cell neoplasm that typically causes symptoms and signs from episodic catecholamine release, including paroxysmal hypertension.
- The diagnosis of phaeochromocytoma is typically made in the fourth or fifth decade of life without gender differences and incidence increase with age.

- About 90% of phaeochromocytomas exist as solitary, unilateral and encapsulated adrenal medullary tumours.
- The 'rule of 10s' is useful to recall approximate frequencies of phaeochromocytoma that vary from the usual: 10% bilateral, 10% extra-adrenal, 10% malignant, 10% pediatric and 10% without blood pressure elevation (O'Connor, 2003).

Etiology of pheochromocytomas

- Familial phaeochromocytoma
- Von Hippel–Lindau syndrome, an autosomal-dominant disorder resulting from germline mutations at the *VHL* tumour suppressor locus on chromosome 3p25–p26.
- Multiple endocrine neoplasia(MEN) types 2A&B
- Hereditary neurofibromatosis, also known as von Recklinghausen's disease,

Clinical symptoms and signs of phaeochromocytoma

- The classical sign of phaeochromocytoma is hypertension, often labile or refractory to treatment.
- The classical triad of symptoms includes headache, diaphoresis and palpitations or tachycardia.
- Less common symptoms include anxiety, tremulousness, pain in the chest or abdomen, weakness or weight loss, Orthostatic hypotension, cholesterol gallstones

Laboratory diagnosis of phaeochromocytoma

- Typically, phaeochromocytoma is diagnosed by biochemical evidence of overproduction of catecholamines or their metabolites in plasma or urine samples.
- Urine tests measure free catecholamines and their metabolites(metanephrines and vanillylmandelic acid) in 24 hour urine samples and are usually highly specific

- Blood test usually measure catechoamine concentrations but are less reliable since they are easily affected by stress.
- Normal resting plasma norepinephrine = 200 – 400 pg/ml and epinephrine = 20 – 60 pg/ml
- Plasma catecholamine $\geq$ 2000pg/ml is diagnostic of pheochromocytoma

- Clonidine supression test is usually done in cases where catecholamine measurements are equivocal (1000 – 2000 pg/ml)
- Catecholamine provocative tests such as the glucagon test are also used sometimes but they are quite dangerous.
- The location of the tumour(s) is crucial to plan the proper surgical route after catecholamine increase has been confimed.

- The majority of these tumours can be visualized by one of three modalities:
- computed tomography (CT),
- magnetic resonance imaging (MRI) or
- [^{123}I]-meta-iod-obenzylguanidine (MIBG) scintigraphy.
- Ultrasound may also be utilized in cases where radiation must be minimized.

- Positron emission tomography (PET) using 6-[^{18}F]-fluorodopamine,
- [^{18}F]-fluorodeoxyglucose,
- [^{18}F]-dihydroxyphenylalanine,
- [^{11}C]-hydroxyephedrine or
- [^{11}C]-adrenaline have been evaluated as improved localization techniques for undetectable phaeochromocytoma or metastases, but are not yet widely available (Ilias *et al.* 2003).

Pathophysiology and complications of phaeochromocytoma

- In addition to catecholamines, phaeochromocytomas also release a number of potentially vasoactive substances that may modify blood pressure or metabolism, such as calcitonin (O'Connor *et al.* 1983), serotonin, vasoactive intestinal polypeptide (Gozes *et al.* 1983), enkephalins (Parmer & O'Connor 1988), atrial natriuretic factor and somatostatin.

- severe hyper-or hypotension, encephalopathy and lactic acidosis are also common.
- Congestive heart failure also occurs in some cases
- These complications are usually reversed after surgical intervention

Treatment of phaeochromocytoma

- After the diagnosis of phaeochromocytoma has been made, sufficient adrenergic alpha-blockade should be implemented for 1–4 weeks prior to surgical intervention to control blood pressure.
- Alpha-blockade is usually accomplished with oral phenoxybenzamine,
- doxazosin (at 2–8 mg once daily) or prazosin (at 0.5–16 mg per day), may be used (O'Connor, 2003).

- The beta-1-selective antagonists atenolol (50–100 mg daily) or metoprolol (50–200 mg daily) or the combined alpha/beta-antagonist labetalol (100–400 mg daily) may be effective. In subjects with contraindications to beta-blockade, lidocaine or amiodarone can be used for tachyarrhythmias.
- the tyrosine hydroxylase inhibitor alpha-methylparatyrosine can be added at an oral dose of 0.25–1.0 g four times daily.

- For intra-operative blood pressure surges, intravenous nitroprusside is often used. Alternatively, acute alpha-blockade can be accomplished with intravenous phentolamine. The calcium channel antagonist nicardipine has also been used.

- Malignant phaeochromocytoma
- Although most phaeochromocytomas are typically well-encapsulated, localized benign growths, approx. 5–10% are malignant, which is more common among extra-adrenal tumours. Because histopathology is not reliable, malignancy is diagnosed by distant metastatic spread of the tumour, commonly to the bone, lung, lymph nodes or liver.
- Increased plasma DOPA is usually an indication of malignancy.

Catecholamine deficiency disease states

- Congenital absence of the adrenal cortex may cause a developmental absence of the adrenal medulla.
- Loss of both adrenal glands seldom produces a catecholamine deficiency state.
- Deficiency states are rare and also common in diabetics receiving insulin
- Congenital deficiency of dopamine beta hydroxylase has also been observed

- Incidentalomas also occur in some individuals but are hardly life threatening and dissapear without treatment.

Conclusion

- Diseases of the adrenal medulla and chromaffin cells are fortunately rare and few in number, but they are potentially life threatening.
- Diagnosis requires a high index of suspicion and careful workup to rule out other sources of elevated catecholamines prior to diagnosis.

References

- Benn DE, Gimenez-Roqueplo AP, Reilly JR, et al. Clinical presentation and penetrance of phaeochromocytoma/paraganglioma syndromes. J Clin Endocrinol Metab. 2006;91:827–836. [PubMed]
- Bravo EL, Tarazi RC, Fouad FM, et al. Clonidine suppression test: a useful aid in the diagnosis of phaeochromocytoma. N Engl J Med. 1981;305:623–626. [PubMed]
- Brouwers FM, Eisenhofer G, Lenders JWM, Pacak K. Emergencies caused by phaeochromocytoma, neuroblastoma, or ganglioma. Endocrinol Metab Clin N Am. 2006;35:699–724.