Chapter 8
Adrenals and Pancreas

The adrenal gland is hormonally, two endocrine glands, the cortex and the medulla. Other than the male and female reproductive hormones, the adrenal cortex synthesizes and secrete steroid hormones that all have the cholesterol framework (good cholesterol!). The three classes of corticosteroids are androgen, the glucocorticoid and the mineralocorticoid. The latter is represented by aldosterone the key hormone that has a dual homeostatic role in potassium and sodium balance. Unlike the adrenal glucocorticoid and androgen, aldosterone is not under strict control by a hypothalamo-pituitary axis.

Cortisol, the dominant glucocorticoid is essential for life. In hypoglycemic stress, cortisol is secreted to produce metabolic effects on skeletal muscles and the liver to sustain blood glucose levels. The catecholamines from the adrenal medulla also have hyperglycemic actions and these amine hormones, made from the amino acid, tyrosine are secreted when the autonomic sympathetic nerve to the adrenal medullary cells are stimulated. Circulating adrenaline and neurotransmitted sympathetic noradrenaline are supplementary in their actions on cardiac, vascular and renal functions in arterial blood pressure regulation.

Indeed, the pancreatic insulin holds a unique homeostatic position as the only hypoglycemic hormone in blood glucose control. All other hormones involved in glucose homeostasis are counter-regulatory to insulin action, including glucagon, growth hormone. The final absorbable products from digestion of fats, proteins and carbohydrates by the enzymes from the exocrine pancreas all stimulate insulin release. Insulin is an anabolic hormone that promotes energy storage as adipose fats, protein synthesis and liver/muscle glycogenesis (insulin sounds like 'insurance'!).

Insulin from the pancreatic beta cells also acts in concert with adrenal aldosterone in potassium homeostasis. There is ongoing studies to elucidate a role of insulin in the kidneys that synergizes with aldosterone in renal handling for sodium homeostasis.

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1 How Are the Adrenal Hormones Involve in Arterial Blood Pressure Control?

Answer The adrenal medulla secretes sympathomimetic catecholamines that act on the heart and blood vessels. The glucocorticoid cortisol sensitizes the blood vessels for optimal vascular responsiveness. The mineralocorticoid aldosterone maintains sodium balance/blood volume to maintain an adequate cardiac output.

Concept Most of the catecholamines secreted from the adrenal medulla is adrenaline. Circulating adrenaline complements the action of cardiac sympathetic nerve by binding to the same beta adrenergic receptors on the myocardium and the pacemaker sino atrial cells.

The adrenal cortex secretes three categories of steroid hormones, the mineralocorticoids, glucocorticoids and the androgens. In blood pressure regulation, the determinants are the total peripheral resistance (TPR) and the ventricular cardiac output (CO). The major glucocorticoid, cortisol is needed at physiological concentration for its permissive action on arteriolar response to vaso-active agents. The requirement for this vaso-priming effect is seen in either excess or deficiency of cortisol. In Cushing's syndrome, a hyperresponsive blood vessel contributes to the hypertension. Conversely, in primary adrenal insufficiency (Addison's disease, where there is Minus of all the adrenocortical hormones!), hypotension is not only due to the volume contraction of aldosterone lack but also due to the hyporesponsive arterioles.

The major mineralocorticoid, aldosterone acts to ensure a normal sodium balance. Sodium balance is the main determinant of ECF/blood volume. The cardiac output determinant in the blood pressure relationship (BP = CO x TPR) is homeostatically under aldosterone's hormonal supervision.

Secretion of the adrenal aldosterone, cortisol and catecholamines are in turn modulated by their respective A factor. For aldosterone, it is Angiotensin II, a peptide product during activation of the renin-angiotensin system. For cortisol, the A factor is Adrenocorticotrophic hormone (ACTH), secreted from the anterior pituitary. The Autonomic cholinergic sympathetic nerve fibers innervate the adrenomedullary endocrine cells.

The adrenal glands is also called supra-renal glands. The close proximity reminds the students of the integrated function between the kidneys and the adrenals in regulation of arterial blood pressure. The kidneys are essential in long-term blood pressure mechanisms via its key role in maintain the sodium balance. The renal arterioles are also vascular targets in selective constriction by sympathetic nerve during compensatory increase in TPR. The cortisol hormonally 'permits' the vasoconstriction.

Does the 'permissive action 'of cortisol extends also to the vasodilatory effects of renal paracrines like prostaglandins or of the local natriuretic urodilatin that also reduces the renal arteriolar resistance?

The major adrenal androgen in both male and female is DHEA (dihydroepiandrosterone). DHEA is a much weaker androgen compared to testosterone. The latter

testicular male hormone does stimulate erythropoiesis which accounts for the higher hematocrit in males.

2 What Is the Potential Secondary Problem of Having One Key Hormone, Aldosterone Controlling Two Major Electrolyte Balance?

Answer If there is a primary excess of aldosterone secretion in a patient, there will be concurrent positive sodium and negative potassium balance. However, in normal individuals, a negative sodium balance is resolved without a secondary hypokalemia.

Concept The adrenal corticosteroid hormone, aldosterone is the key player in the regulation of the two cations in the ECF, sodium and potassium. Sodium balance, linked to ECF volume and potassium concentration in the ECF are both maintained by aldosterone.

For potassium homeostasis, membrane sensors are located on the endocrine cells in the zona glomerulosa of the adrenal cortex. Hyperkalemia is directly sensed and this leads to secretion of aldosterone. Aldosterone then increases the active tubular secretion of potassium at the collecting ducts of the nephron.

For sodium balance, the trigger that stimulates aldosterone release is the circulating peptide, angiotensin II that is generated when the renin-angiotensin pathway is activated.

Aldosterone acts on the same principal cells of the collecting ducts to increase active sodium reabsorption and potassium secretion. At the baso-lateral membrane the common Na/K ATPase activity is heightened. At the luminal membrane of the principal cell, the permeability to sodium and potassium is increased by an increase in sodium and potassium channels respectively.

This dual hormonal action of aldosterone poses the obvious question: Will a primary sodium or potassium imbalance leads to compensatory aldosterone action that resolves the electrolyte disturbance but ends up with a secondary cation problem? This is called the ‘aldosterone paradox’.

Physio-logically, this does not occur. A negative sodium balance is accompanied by hypovolemia, with a reduction in renal blood flow (RBF). The decreased RBF lowers the glomerular filtration rate and tubular fluid flow is consequently less. Since the luminal step of tubular epithelial secretion of potassium is by passive diffusion, a decreased tubular fluid flow will retard potassium secretion.

This is the reason why when hypovolemia activates the renin-aldosterone mechanisms, the increased tubular reabsorption of sodium is not followed by a parallel increase in potassium secretion and a resultant secondary hypokalemia.

Similarly, a primary hyperkalemia stimulates aldosterone secretion. The normalization of potassium balance is also not associated with a secondary sodium retention. Here there appears to be a direct action of hyperkalemia to inhibit proxi-

mal tubular transport of sodium (mechanism still to be elucidated) from the tubular fluid.

Pathophysiologically, a hypersecretion of aldosterone will give double Cationic trouble (Meow, Meow!). In Conn's syndrome, there is ECF volume expansion from sodium retention as well as hypokalemia from hyperkaliuria.

Conversely, in Addison's disease, a deficiency of aldosterone causes hyperkalemia and a hypotonic contraction of the ECF in the patient. The patient is hypotensive due to a reduction in blood volume.

3 What Is the Phenomenon Described as 'Aldosterone Escape'?

Answer In primary hypersecretion of aldosterone, the ECF is not expanded without limit. Anti-aldosterone actions are activated so the body 'escapes' from uncontrolled sodium and water retention.

Concept The hormone aldosterone reduces urinary sodium excretion by stimulating active tubular sodium reabsorption.

If an adrenal cortex tumour secretes excessive aldosterone, a large positive sodium balance will result. This will be followed by an overexpansion of the ECF. There is a great isotonic expansion of the ECF.

Potentially, since the secretion of aldosterone is no longer feedback controlled, retention of sodium can progress. However, the body is triggered to increase natriuresis to oppose the aldosterone effects.

One anti-aldosterone contributor is the cardiac hormone atrial natriuretic peptide (ANP). As the name suggests, ANP increases filtered sodium load by increasing the glomerular filtration rate via renal arteriolar vasodilatation. The sodium reabsorption is also reduced either by any direct tubular epithelial actions or by blocking aldosterone actions at the nephron.

The kidneys also release a local natirureitc factor, called urodilatin to promote natriuresis. As a result of this anti-aldosterone activity, the ECF expansion is restricted and the development of edema is seldom encountered.

Within the kidneys, changes in renal hemodynamics during the hypervolemia also contribute to losing more of the excess sodium into urine. The renal sympathetic nerve that acts to conserve sodium is also inhibited via the baro- and volume reflex loops.

'Aldosterone escape' is not prominent when the stimulus of aldosterone release is due to a secondary cause. For example, in left cardiac failure, the reduction in effective circulating volume will be detected by intra-renal baroreceptors at the afferent arteriole. The enzymatic hormone, renin will be secreted. Sodium and water will be retained. There is expansion of the ECF and also peripheral edema.

Why does aldosterone action remain less opposed in this secondary cause of hyperaldosteronisms? Both circulating natriuretic and urodilatin should still be operative.

Perhaps the reduction in renal sympathetic action is not as much in heart failure as it is in primary aldosteronism that produces a ECF volume expansion.

This is because since the cardiac output is weak, the baro- and volume receptors will be sensing a lower blood pressure rise even though the blood volume is expanded.

4 How Do ADH and Aldosterone Integrated Actions Account for ECF Body Fluid Changes?

Answer Changes in sodium concentration will produce a corresponding stimulation or inhibition of ADH secretion. The new equilibrium ECF volume change will eventually be normalized by aldosterone action that restores and maintains the sodium balance.

Concept Osmolarity control is functionally related to sodium concentration in the ECF since the main determinant of ECF osmolarity is sodium and its compAnions. ECF volume homeostasis is under aldosterone hormonal control and ECF volume is tied to the total body sodium or sodium balance.

When dietary sodium input increases, before compensation by urinary excretion, the total sodium balance will be positive. This will produce an isotonic expansion of the ECF. The student should note that this isotonic expansion is mediated by the sensitive mechanism that maintains normal ECF osmolarity.

If we take this dynamic mechanism step by step, net dietary sodium input initially will raise the ECF sodium concentration. The osmoreceptors in the hypothalamus detects the increased sodium concentration/osmoalrity. The posterior pituitary responds with secretion of ADH to act on the kidneys to reabsorb water in order to normalize the ECf osmolarity.

Thus, the hyperosmotic plasma has led to the final isotonic expansion of the ECF by ADH.

Since the ECF and blood volume is above normal, eventually, euvolemia has to be achieved. The next regulatory step is the co-ordinated response of the body to the hypervolemia that resulted from the positive sodium balance.

Both neural and hormonal mechanisms to promote increased sodium excretion in the urine are activated. These include an inhibition of renal sympathetic activity (reflex from volume sensors), release of natriuretic peptides and inhibition of renin secretion.

The hypervolemia does inhibit ADH secretion but on its solo action, euvolemia will not be possible as any initial increase in urine volume with ADH suppression will increase the ECF osmolarity that will then trigger ADH release again.

The effective hormonal action that is needed is a reduction in plasma aldosterone level. The inhibition of renin serves this purpose. Tubular reasorption of sodium is decreased and hypernatriuria occurs in the hormonal answer to the positive sodium balance.

Dynamically, there is no peak natriuresis with aldosterone inhibition as is the case in a water diuresis with ADH inhibition. As the excess sodium is gradually lost, an initial decreased sodium concentration reduce the ADH secretion. More urine water is then excreted.

Thus the student must not imagine wrongly that since more sodium is not reabsorbed, water is secreted by the tubule, osmotically drawn by the sodium in the tubular fluid. There is no secretion of water to produce urine volume (this is a nineteenth century hypothesis, Wow Wee!). More urine volume is always due to less water reabsorption by the nephrons in the absence of ADH.

Thus we can see the hormonal duet between Aldosterone and ADH as they sing and play harmoniously about Osmolarity and Volume regulation. Aldosterone and ADH are a Homeostatic couple that look after their two 'so dium' Kids! (kidneys involved); the girl Concentration and the boy Balance.

5 How Does the Different Normal Concentrations of ECF Sodium and Potassium Fit in with the Sensitivity of the Mechanisms that Regulate the Two Cations?

Answer ECF sodium is high, at around 145 mmol/L while ECF potassium is maintained at a low normal concentration of around 4 mmol/L. The physio-logical mechanism that controls potassium homeostasis is therefore more sensitive directly to changes in plasma potassium than the mechanisms that govern sodium balance in the body.

Concept Since fluctuations in ECF potassium concentrations above or below its low controlled value (~4 mmol/L) can cause alterations in functions of excitable cells, the sensors must monitor well the potassium changes. The potassium sensors are located at the membranes of the endocrine cells in the adrenal cortex that secrete aldosterone. The membrane detection of potassium levels is direct.

Hyperkalemia will stimulate aldosterone secretion. In turn, the adrenocortical steroid hormone, aldosterone, will increase urinary excretion of potassium by promoting its secretion by the renal tubules.

Excess aldosterone action also increases proton secretion by the nephron. This produces an alkalosis. There is an interaction between blood pH and the plasma potassium level. This is mediated via a membrane 'exchange' phenomenon that is part of intra-cellular buffering in pH regulation. In alkalosis, there is a tendency for more renal tubular secretion of potassium resulting in hyperkaliuria and thus hypokalemia. Thus aldosterone has a direct and an indirect effect on ECF potassium.

For sodium at a much higher concentration of ~145 mmol/L, a 5 mmol/L change is insignificant. Thus sodium homeostasis is less 'urgent' and this is reflected in the more prolonged activation of the renin-angiotensin system that regulates total body sodium or the sodium balance.

That said, the student should be reminded that for the control of osmolarity which is determined by sodium concentration, small changes in ECF concentration are detected rapidly by hypothalamic osmoreceptors with a corresponding change in ADH (vasopressin) secretion from the posterior pituitary.

The big picture appears to be that if small changes in a solute affect cell function, the feedback control for that solute will also be sensitive to generate the necessary physiologic compensation. The concept of a need for direct, immediate sensing for solutes that are maintained at low concentrations also applies to plasma ECF calcium, which has an even lower concentration to potassium (~2.5 mmol/L). Calcium sensors are located on the plasma membranes of the endocrine cells that secrete parathyroid hormone. Small changes in calcium affect the membrane responsiveness of excitable cells.

For glucose with a normal low range at 4–6 mmol/L, the pancreatic beta cells directly sense the post-prandial hyperglycemia and respond rapidly to secrete insulin.

6 How Do Adrenaline and Noradrenaline Infusions Separately Affect the Cardiovascular Function Differently?

Answer Experimental infusion of adrenaline increases the cardiac output but for noradrenaline, a marked increase in blood pressure due to vasoconstriction produces a reflex bradycardia that accounts for a decrease in cardiac output.

Concept Both the adrenal medullary catecholamines, adrenaline and noradrenaline bind to both alpha and beta adrenergic receptors in various degrees. In vivo, plasma noradrenaline seldom exceeds its threshold for its observed cardiovascular (CVS) and metabolic effects. Most of noradrenaline effects are from its release as neurotransmitter from post-ganglionic sympathetic neurons.

In both experimental normal animals and in humans, slow infusion of noradrenaline and adrenaline leads to quite different CVS actions and the graphs shown in some Physiology textbooks often perplexed the students. In particular, the student knows that cardiac sympathetic action will always increase cardiac output via noradrenergic neurotransmission to both the sino atrial node and the ventricle muscles. The infusion effects of noradrenaline however show instead a reduced cardiac output.

Both adrenaline and noradrenaline bind to cardiac beta1 receptors to effect their chronotropic and inotropic actions on heart rate and myocardial contractility respectively. Noradenaline also has a strong alpha receptor action to increase the total

peripheral resistance (TPR). The induced hypertension with noradrenaline (both systolic and diastolic pressure increase) triggers the baroreflex to produce a bradycardia.

The direct cardio-acceleratory effect of nordrenaline that is observed with cardiac sympathetic action is then overrided.

With adrenaline infusion, the total peripheral resistance is not markedly changed or slightly lower. This is due to the vasodilatory action of adrenaline on beta2 receptors on blood vessels in the skeletal muscles and in the liver (logical physio-logic action to increase blood flow to skeletal muscles and to promote hepatic glucose delivery during physical activity). Although adrenaline will also have alpha vasoconstrictor actions in other tissues, the net effect on TPR belongs to the beta2 binding.

Therefore with adrenaline, the pulse pressure is widen as the systolic pressure is increase but the diastolic pressure (affected by TPR) is decreased. There is no marked increase in arterial blood pressure to activate a baroreflex sufficient to produce a compensatory bradycardia. The direct actions of adrenaline on the beta1 cardiac receptors are unopposed and both heart rate and stroke volume are higher. Adrenaline causes the heart to pump out a greater cardiac output.

7 How Does Uncontrolled Diabetes Mellitus Affect the Potassium Plasma Level?

Answer The osmotic diuresis will lead to hyperkaliuria. In addition, the dehydration will further promote secretory loss of potassium by aldosterone that is increased by hypovolemia.

Concept Hyperglycemia in diabetes mellitus can overshoot the renal plasma threshold for glucose. The excess unreabsorbed glucose will interfere with the isoosmotic reabsorption of water at the proximal tubule. Since filtered potassium is passively reabsorbed at the proximal tubule down its concentration gradient generated by prior water reabsorption, less filtered potassium will be recycled back to the circulation from the tubular fluid.

The osmotic diuresis will also affect the tubular event downstream at the ascending loop of Henle and at the collecting ducts. More water retained in the nephron will dilute the tubular fluid sodium and the activity of the triple sodium coupled symporter, Na/K /Cl at the ascending limb of Henle will also be reduced.

At the principal cells of the collecting ducts, the secretion of potassium will be enhanced by the greater tubular fluid flow, since the luminal second step in the transepithelial secretion of potassium is passive.

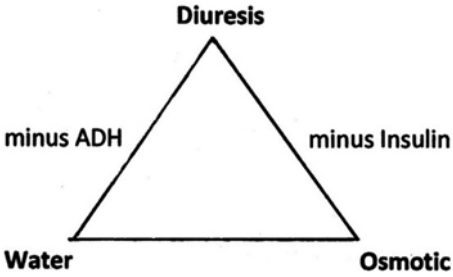
The hypovolemia resulting from increased excretion of urine volume will activate sodium conservation mechanisms which include the renin -angiotensin-aldosterone pathway. The aldosterone hormone action that recovers sodium will

also stimulate tubular potassium secretion. Overall, kaliuria is increased by the osmotic diuresis in the diabetic patient, with resulting hypokalemia.

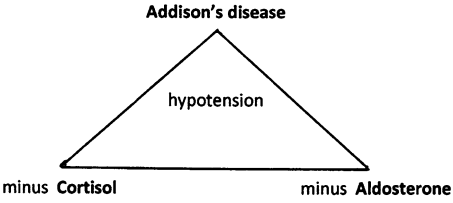
There are other factors that might potentially have hyperkalemic effects. The lack of insulin action will decrease the cellular uptake of potassium in all cells. There is some osmotic effect by the hyperosmotic plasma in diabetes to draw out some intracellular potassium. The dehydration itself from the polyuria will concentrate the plasma potassium.

Changes in pH can produce potassium shifts across cell membranes. This is part of intracellular buffering where protons are exchange for potassium cations. In diabetes mellitus with metabolic ketoacidosis, the keto anion can accompany the proton into the cell. Electroneutrality is maintained and there is no need for a potassium efflux.

In normal persons, the catecholamine adrenaline increases cellular uptake of potassium by a beta adrenergic effect. This is viewed as a useful action during physical activity to counter the exercise-induced hyperkalemia that is from the increased potassium efflux during action potential events. Exercise itself has an insulin-independent effect on cellular uptake of glucose and this provides the basis for recommending regular exercise for diabetic glucose control.

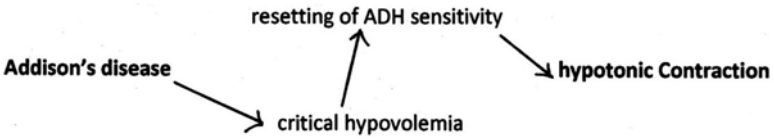


Increased urine volume excretion in two common endocrine disorders. In diabetes insipidus, lack of ADH action ('anti-dilute urine') causes inability to concentrate urine as the collecting ducts remain impermeable to water. In diabetes mellitus, increased filtered glucose load into the nephron interferes with water absorption by an osmotic effect, especially at the proximal tubules.



Primary adrenal insufficiency (Addison's disease) is a lack of all the three classes of adreno cortical steroid hormones. Little mineralocorticoid activity of aldosterone

results in hypernatriuria and a negative sodium balance. There is hypovolemia. Added to this, the absence of an optimal cortisol action for normal vaso-responsiveness explains the decreased arterial blood pressure.



Hypotonic Contraction of the ECF is not an ECF disturbance seen in normal persons with intact ADH and Aldosterone mechanisms of response. One scenario when both the osmolarity and the volume of the ECF are reduced is in Addison's disease. This is due to the shift in priority when the severe hypovolemia threatens adequate cerebral perfusion. The volume sensitivity of the ADH response is thus reset and increased at the expense of a hypo-osmotic ECF.

Aldosterone and ADH are
a **Homeostatic couple**
that look after their
two 'so dium' Kids! (kidneys);
the girl Concentration and
the boy Balance.

Sodium physiology and the two 'A' hormones; Aldosterone and ADH.

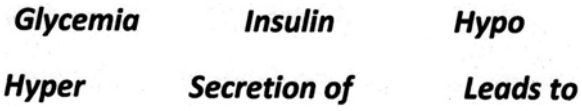
When I am down,
Cortisol Increasing
When Finals Come,
High Adrenaline

My pancreatic
Insulin/Glucagon
Ratio Reduced
Sustain blood Energy

C-R-H Up
And I can stand the tension
A-C-T H
From my Pituitary

And I'll be Strong
Prof Cheng always behind me
Finals, I come
To Ace my Physiology!

Endocrine Song to the tune of 'You Raise Me Up"!



Make three possible physiologic cause and effect statements from these words (can omit one word per sentence). They are '*Hypo Secretion of Insulin Leads to HyperGlycemia' or 'Hyper Secretion of Insulin Leads to HypoGlycemia' and 'HyperGlycemia Leads to Secretion of Insulin' ('hypo' omitted).*