CME: Mineralocorticoids

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But first..

News Flash: Death by Candy

Because 2020 hasn't provided enough extraordinary ways to die, the universe offers a grim reminder that eating too much licorice candy can be deadly.

FURTHER READING
Here are the intriguing toxins that spice up our favorite holiday dishes

A 54-year-old construction worker died in Massachusetts recently after eating an excessive amount of black licorice—which naturally contains a toxin called glycyrrhizin, aka glycyrrhizic acid. Doctors published a case study of his poisoning in the New England Journal of Medicine this week.

According to the study, the poor fellow was at a fast-food restaurant when he abruptly went into cardiac arrest. He "gasped suddenly, with full-body shaking and loss of consciousness," the doctors report. Paramedics arrived within minutes and revived him with four shocks and CPR. But when he was admitted to the hospital about 30 minutes later, doctors found he had multi-organ failure, "profound metabolic derangements," dangerously low levels of potassium in his blood, and cardiac arrest associated with ventricular fibrillation, which is when the lower chambers of the heart twitch erratically without pumping blood. All of these conditions are consistent with licorice poisoning.

A thorough medical investigation noted he seemed to have no previous history of heart problems, and doctors pinned his condition to the candy. Discussions with his family revealed he had been eating one to two "large" bags of black licorice every day for about three weeks before his heart stopped. By the time he arrived at the hospital, too much damage had already been done. He died about 32 hours later, with his family at his bedside.

- Liquorice can cause effects of too much mineralcorticoids.
- It is a special sweet derived from liquorice plant (herb).
- Have you heard of a man (Mr A) died because of liquorice?
- His symptoms are quite similar to mineralocorticoid excess (hyperaldosteronism).

Let's find out more about mineralocorticoids. Then we will find out the cause of his death.

Mineralocorticoids

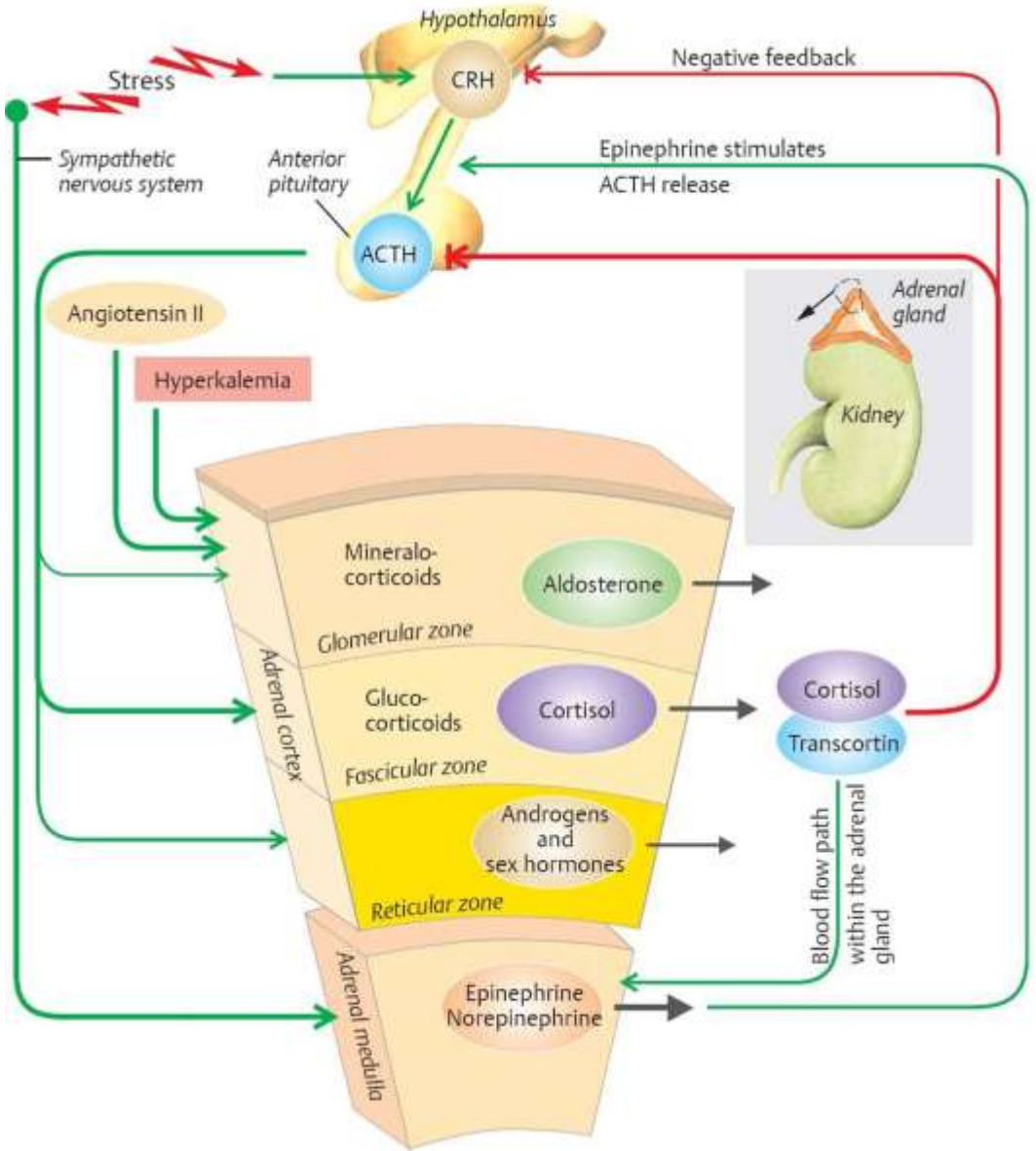
- Aldosterone is mineralocorticoid. It was named that way because it influences mineral namely Sodium and Potassium and fluid balance in blood.
- Released from zona glomerulosa of adrenal cortex gland in diurnal fashion.
- Released by stimulation of Angiotensin II from RAAS (Renin-Angiotensin-Aldosterone system), ACTH (adrenocorticotrophic hormone) and other factors such as following:

High potassium level	Low blood pressure	Low Sodium
Adrenoglomerulotrophin	Low blood pressure relayed by stretch receptors in heart	Plasma acidosis

Aldosterone

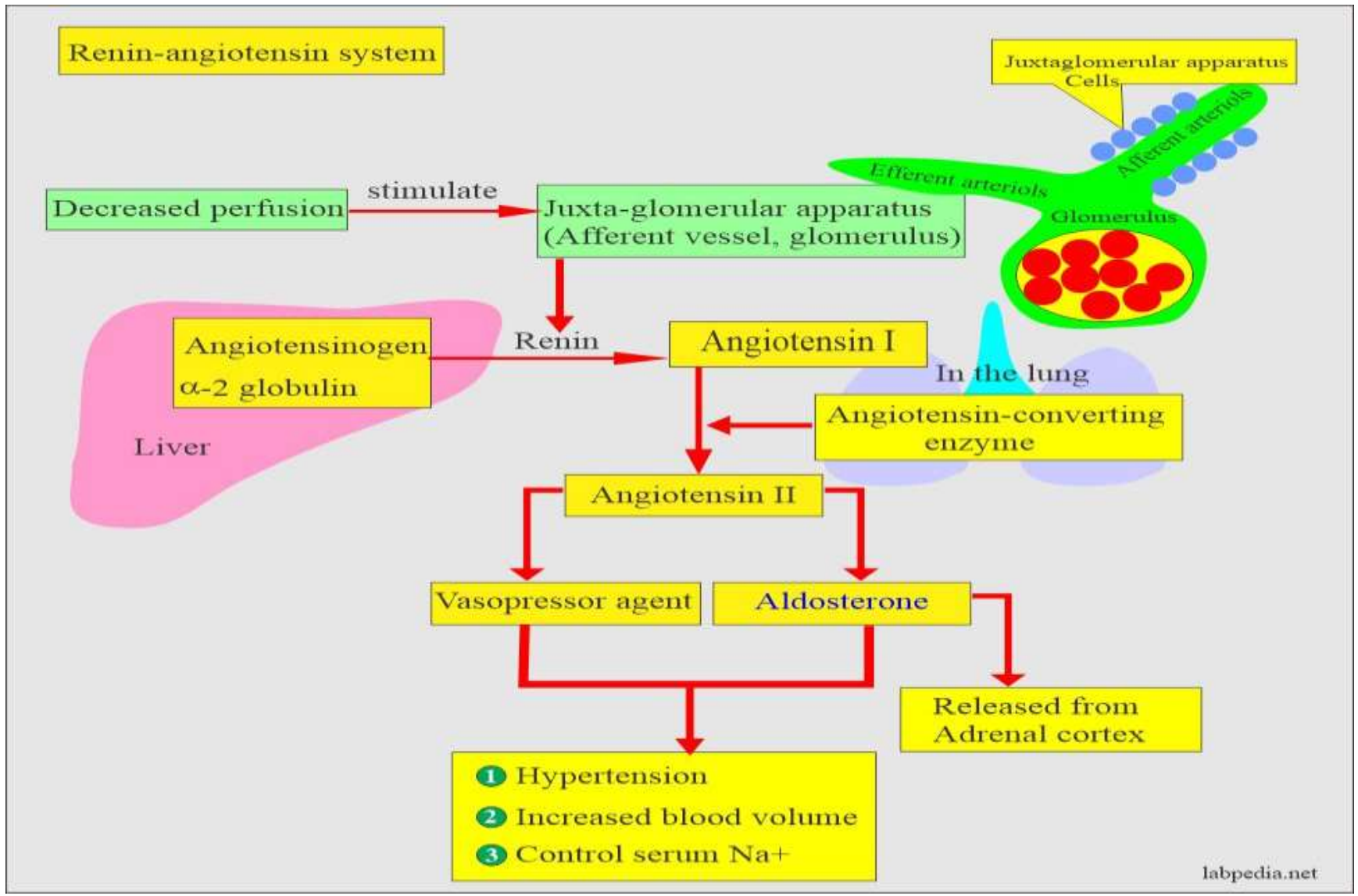
	Explanation
Role	Regulate sodium and potassium (Na+ in, H+ and K+ out), homeostatic regulation of blood pressure and maintains fluids and electrolytes balance
Action	It causes the reabsorption of sodium and excretion of potassium and hydrogen ions (from and into the tubular fluids, respectively) of the kidney, thereby indirectly influencing water retention or loss, blood pressure and blood volume
Inhibitors	ACE inhibitors (e.g captopril) indirectly inhibits action of Aldosterone by inhibiting Renin-Angiotensin-Aldosterone System (RAAS). Spironolactone -Aldosterone antagonist

Stimulation of Aldosterone release by ACTH



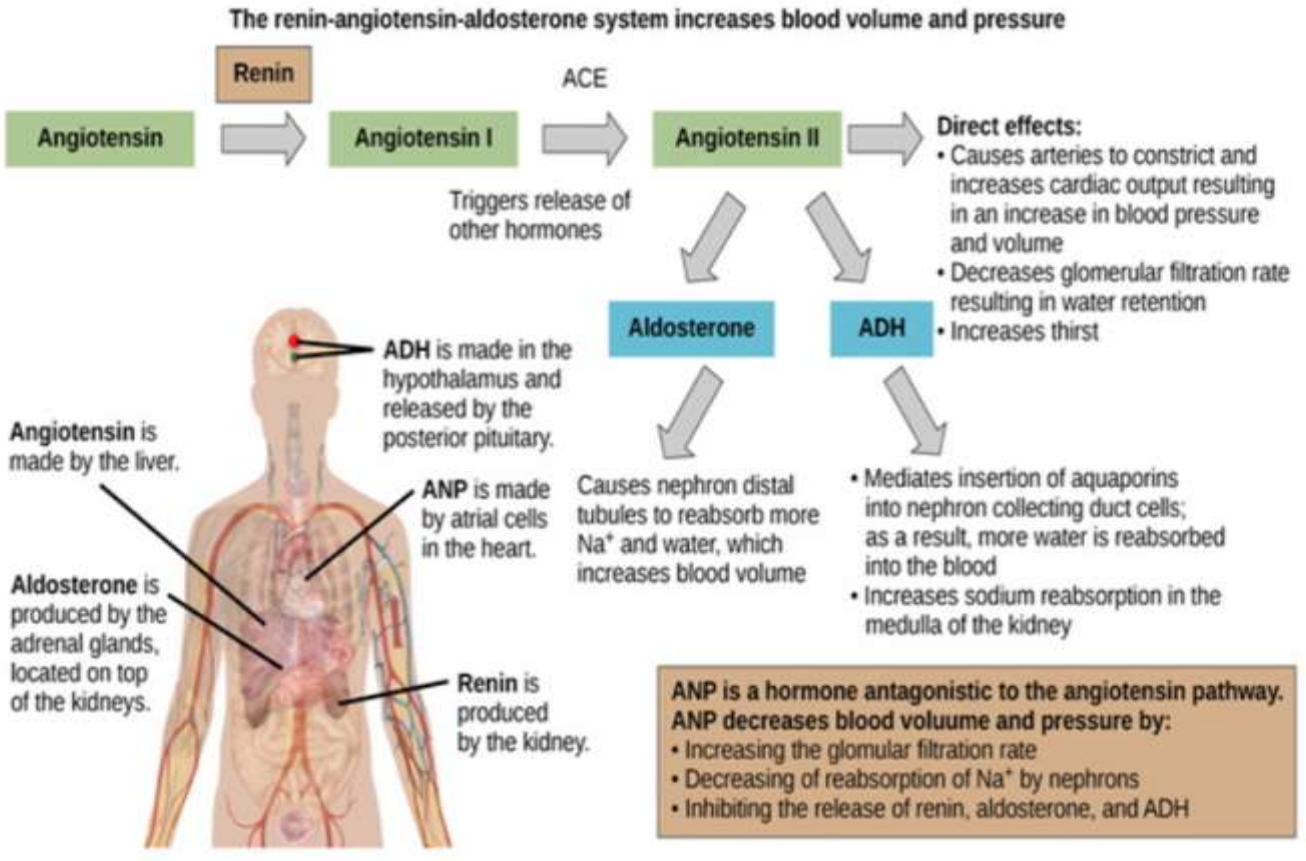
- Adrenocorticotropic hormone (ACTH) from pituitary can stimulate aldosterone secretion acutely and transiently under normal conditions, but to a lesser extent than angiotensin II (from RAAS) and potassium.
- Corticotrophic Releasing Hormone from hypothalamus stimulates ACTH release from pituitary gland. ACTH stimulates release of Cortisol, Aldosterone and androgen hormones from adrenal gland.
- ACTH is controlled by negative feedback regulation by Cortisol.

Summary of RAAS (Renin-Angiotensin-Aldosterone system)



Regulation of Aldosterone Secretion

- Angiotensin II also acts as vasoconstrictor (to maintain blood pressure), stimulates thirsts by increasing ADH and directly/indirectly decreases Na excretion in urine, feces and sweats
- Secretion of Renin is governed by negative feedback by Angiotensin II (short neg feedback loop) and renal arterial pressure (long neg feedback loop-as described below)
- Renin is also released by other stimuli such as hyperkalaemia, low blood sodium and plasma acidosis.
- Aldosterone activates Na/K transporter at kidney tubule which increases Na reabsorption in exchange of K and H+ ions (excretion)
- Increased renal arterial pressure→ detected by stretch receptors of glomerular afferent arteriolar wall →decrease Renin secretion→ decrease Aldosterone secretion
- The atrial natriuretic peptide (ANP) has opposite effect to Aldosterone. It acts as a vasodilator and lower blood pressure by preventing sodium reabsorption.
- Blood pressure can be controlled by drugs that inhibit ACE (called ACE inhibitors)



Renin-angiotensin-aldosterone system: The renin-angiotensin-aldosterone system increases blood pressure and volume. The hormone ANP has antagonistic effects.

Role of ACE inhibitors

Mechanism 1: Systemic Vasodilation.

ACE inhibitors are vasodilators. They dilate systemic blood vessels and thus help improve blood flow. This decreases the amount of work the heart has to do. ACE inhibitors inhibit the production of angiotensin II (a potent vasoconstrictor) whose production is increased as a result of heart failure. When the heart is failing and not pumping well, angiotensin II is released to constrict the vessels to maintain enough blood pressure to perfuse vital organs

Mechanism 2: Sodium and water excretion.

ACE inhibitors lower the amount of salt (sodium) and water in your body, which also helps to lower your blood pressure.

They are also used to control high blood pressure, prevent kidney damage from diabetes (renoprotective), and prevent more heart damage after a heart attack.

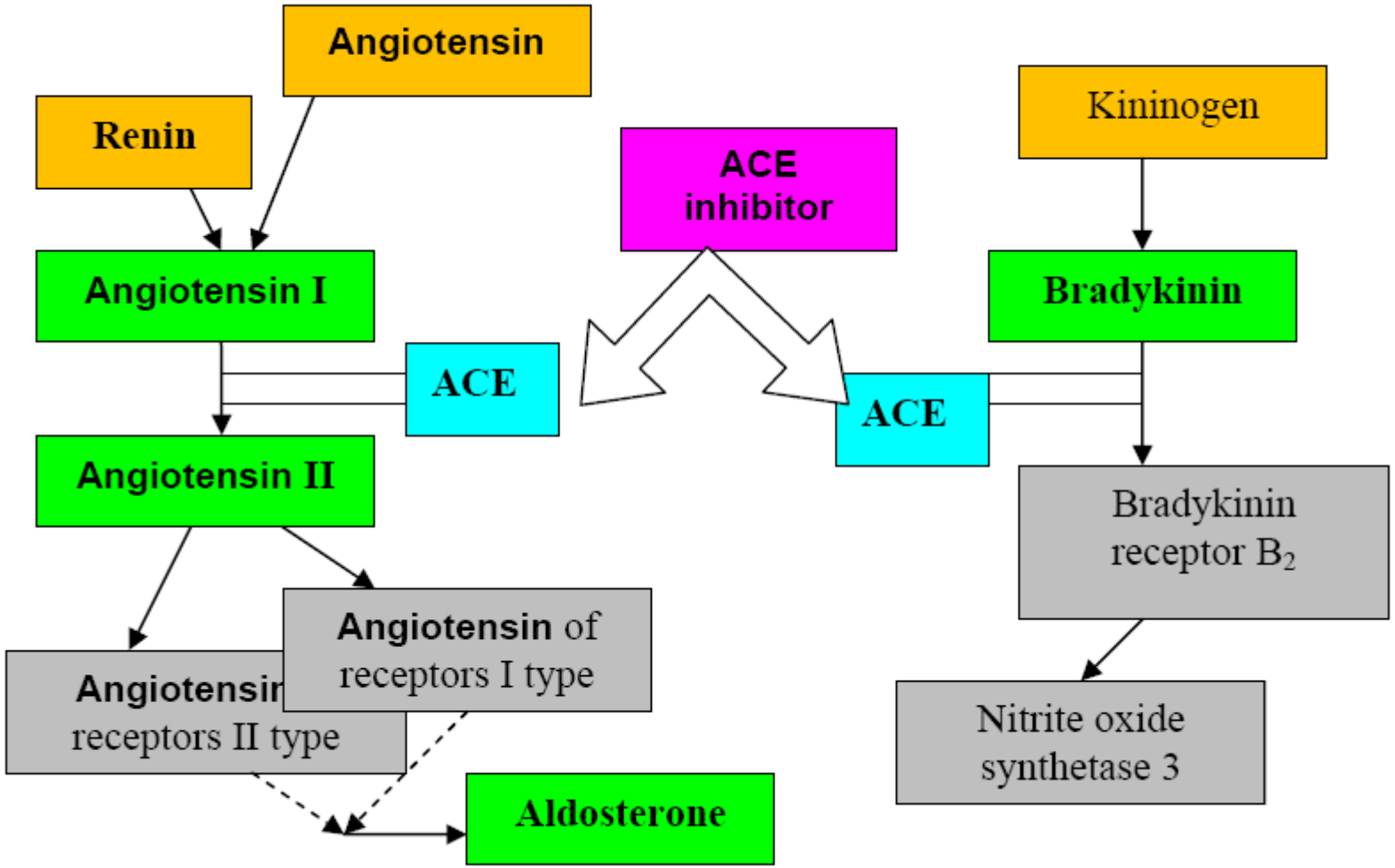
ACE inhibitors are critical in the treatment of heart failure when systolic dysfunction is present and may also be prescribed for the treatment of diastolic dysfunction.

Example of ACE inhibitor: Lisinopril and captopril

Common side effects: Dry cough, dizziness, hypotension, hyperkalemia, increased BUN and CREAT

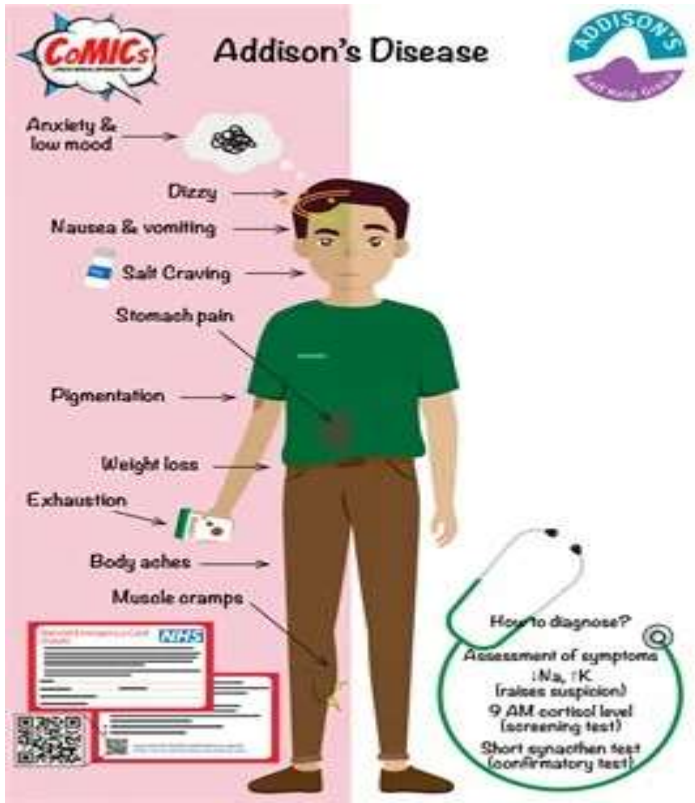
Note: ACE metabolizes bradykinin and other local molecules. Inhibiting ACE in the lung increases the concentration of kinins, causing bronchial irritation. After discontinuation of ACE inhibitor therapy, an angiotensin receptor blocker (ARB) can be initiated as an alternate therapy.

Summary of action of ACE inhibitors

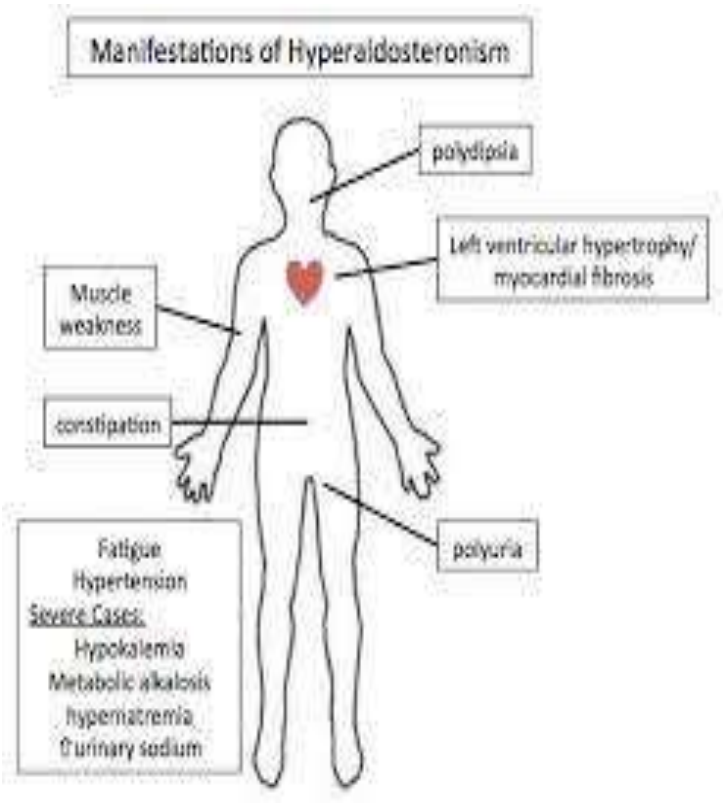


Mineralocorticoid Disorders

Hypoaldosteronism



Hyperaldosteronism



Hypoaldosteronism

Primary Adrenocortical insufficency

- Primary - referring reduced secretion of Aldosterone from within adrenal gland due to hypofunction
- Occurs in Chronic Hypoadrenalism (Addison Disease) - which may caused by autoimmune destruction of adrenal gland/ haemorrhage/ lymphoma or metastatic malignancy/ infection such as TB, HIV/CMV /Adrenalectomy
- Symptoms: Low serum Na, hyperkalaemia, dehydration, postural hypotension, weight loss, high plasma renin
- Note: ACTH hyposecretion (Secondary Adrenocortical Insufficiency) normally do not cause low aldosterone. it causes atrophy of zona fasciculate zona reticularis. Therefore aldosterone is normal.

Hypoaldosteronism Investigation

Investigation to confirm Adrenal Hypofunction/ hypoadrenalism

1. Plasma/ serum cortisol (if at 9 am, cortisol is < 50nmol/l→ adrenal failure)
2. ACTH stimulation test (Synacthen test). Synacthen is synthetic ACTH and is used to test the function of the adrenal gland. Failure to respond indicates adrenal insufficiency.
3. Plasma ACTH – to differentiate between primary and secondary adrenal failure

   In primary: ACTH is ↑↑ due to lack negative feedback by cortisol

   In secondary : plasma ACTH is↓

Hyperaldosteronism

Primary hyperaldosteronism or Primary Aldosteronism (PA)

- In primary aldosteronism, excessive aldosterone production originates from within the adrenal gland.
- ↑plasma aldosterone→↓plasma Renin
- Autonomous overproduction of Aldosterone due to adrenal adenoma (Conn's syndrome), zona glomerulosa hypertrophy (idiopathic adrenal hyperplasia)

Hyperaldosteronism

Secondary hyperaldosteronism

- In secondary aldosteronism, a stimulus outside the adrenal gland activates the Renin- Angiotensin system. Adrenal glands still respond to their normal trophic stimulus
- Usually occurs in oedematous state (intravascular volume depletion causes renin production), and hypokalemic alkalosis.
- ↑plasma Renin→ ↑plasma aldosterone
- Causes: Congestive heart failure, Liver cirrhosis with ascites, nephrotic syndrome
- Symptoms: Hypertension due to Na retention, hypokalaemia, muscle weakness, high urine potassium, polyuria and polydipsia

Hyperaldosteronism Investigation

Investigation

Investigations:

1. Screening test: Plasma Aldosterone: Renin Ratio
2. Diagnostic test: Saline infusion test

   Infuse 1.25L of 0.9% saline over period of 2 hour

   Rationale: Sodium loading will inhibit aldosterone secretion

   Conn's syndrome confirmed if plasma aldosterone remains high (> 240 pmol/L)

Warning!!

Screening test for plasma Aldosterone: Renin ratio is sensitive to postural changes.

Fall in renal arterial perfusion from upright posture especially after 120min of standing induces increased renin secretion and subsequent release of Aldosterone (regardless Sodium intake in diet).

Case studies

- 57 year old man complained of generalized muscle weakness and headache. BP 180/100, both in lying and standing positions. Lab results as follows:

1. What do you expect the Renin and Aldosterone results (high/low?) if the patient is having Conn's syndrome?
2. What type of acid-base imbalance does the patient have? What has caused this imbalance?

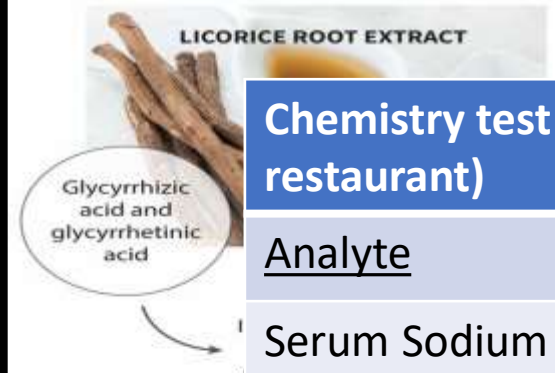
Analyte	Results (Normal Range)
Serum Sodium	148 (135-145 mmol/L)
Serum Potassium	2.0 (3.5-5.0 mmol/L)
Creatinine Serum Aldosterone Plasma Renin Activity	85 (<104 umol/L) 30 (3.6- 24 ng/dL) 0.1 (0.5 - 2.0 ng/ml per h)
Arterial Blood gas: pH pCO2 Bicarbonate	 7.50 (7.35-7.45) 48 (35-45 mmHg) 36 (22-26 mmol/L)
Urine 24 hours Sodium excretion Potassium excretion Urinary catecholamine	 Normal Elevated Normal

Answers:

1. Renin-low, Aldosterone-High. Yes, Conn's syndrome.
2. Metabolic alkalosis with partial correction because H ions were excreted together with Potassium in the kidney in order to reabsorbed Sodium in tubular cells. Partial correction is indicated in the rise in pCO2.

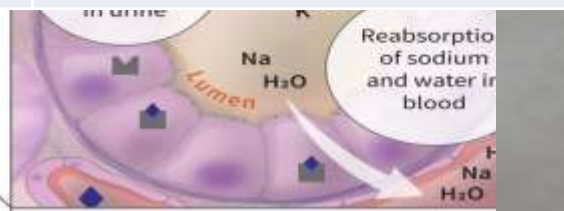
Now back to the news..

Liquorice Poisoning



Chemistry test results for Mr. A (who died in fast food restaurant)

Analyte	Results (Normal Range)
Serum Sodium	155 (135-145 mmol/L)
Serum Potassium	2.0 (3.5-5.0 mmol/L)
Serum Aldosterone Plasma Renin Activity	2.8 (3.6- 24 ng/dL) 0.4 (0.5 - 2.0 ng/ml per h)



Excess licorice root extract causes pseudoaldosteronism:

- Water retention
- Elevated blood pressure
- Hypokalemia
- Metabolic alkalosis

The man died was not caused by Aldosterone!
Moreover, the Renin and Aldosterone concentration in the man was low..
But the aldosterone receptors in the kidney were activated!! But by what?
Answer: Liquorice causes the aldosterone receptors activated by cortisol

Explanation to the liquorice toxicity

- Liquorice's active ingredient is glycyrrhizin which is hydrolysed in vivo to glycyrrhetinic acid.
- Glycerrhetinic acid inhibits 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), an enzyme located in renal tissue that converts active cortisol to inactive cortisone.
- Inhibition of 11β-HSD2 results in a significant increase in cortisol concentration at the renal mineralocorticoid receptors. The consequent increased mineralocorticoid like activity as there are structural similarities between cortisol and aldosterone, leads to unrestricted sodium reabsorption and potassium excretion. This results in hypertension, hypokalaemia and suppression of the renin–aldosterone axis.
- This pattern of an elevated blood pressure and hypokalaemia in the context of a suppressed plasma renin and aldosterone is referred to as pseudohyperaldosteronism

Future Investigation
ACE receptor and Covid 19 (2)

- People with hypertension and other traits have shown to have an imbalance in ACE/ ACE2 levels and reduced levels of ACE2 could enhance the risk of adverse outcome in patients with COVID-19.

- Both SARS-CoV-2 and SARS-CoV enter host cells via the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in various human organs

- There is a concern that pre-existing treatment with ACE inhibitors or ARB might increase the risk of developing severe or fatal acute respiratory syndrome in case of COVID-19 infection

- Restoring the balance between the RAS and ACE2/angiotensin may help reduce organ injuries but research is still ongoing.

References

- **(1): Aldosterone-to-renin ratio is related to arterial stiffness when the screening criteria of primary aldosteronism are not met- Kokko. E. *et al*, Scientific Reports volume 10, Article number: 19804 (2020)**
- **(2) Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Wentao Ni. *et al* Critical Care volume 24, Article number: 422 (2020)**
- **Aldosterone Wikipedia**
- **lumenlearning.com**
- **Role of ACTH and Other Hormones in the Regulation of Aldosterone Production in Primary Aldosteronism. Nada El Ghorayeb et al, Front Endocrinol (Lausanne). 2016; 7: 72**

THANK YOU!!

If RAAS is expressed in Lego:

I am Ronin.
I cut Aang's hair

I am Aang from Liverpool. I got my 2nd haircut from ACE hardware store at Kuala LUNG-pur.. Then gonna party at Zona Glomerulosa with the Aldosterone bro..

Hi! I am Al of Aldosterone brothers. I am taking care of salty water reservoir n fix the pump so there won't be any leaky pipes and low pressure! This is ain't party!!