
بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیمِ

Salt Sensitivity:
Causes, Consequences, and Recent Advances

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Topics

1. Introduction
2. Pathogenesis of salt-sensitive hypertension
3. Sex-specific differences in salt-sensitive HTN
4. Animal models of salt-sensitive hypertension
5. Treatment of salt-sensitive HTN
6. Future perspectives

Global burden of CVDs: Contribution of hypertension

- ✓ The global burden of cardiovascular diseases (CVDs) is a major public health issue, compromising social and economic development worldwide and accounting for 17.9 million deaths annually (World Health Organization, 2021).

- ✓ It is well known that one of the most important risk factors for CVDs is hypertension (HTN) (Lloyd-Jones et al., 2010).

- ✓ HTN, or the silent killer, affects more than 1 billion people worldwide (WHO, 2021). A main manifestation of HTN is end-organ damage, which makes HTN a leading cause of mortality from stroke, heart failure, myocardial infarction, and kidney damage.

- ✓ In 2017, The American College of Cardiology/American Heart Association (ACC/AHA) set more stringent blood pressure (BP) goals and redefined stage 1 HTN as a sustained BP of 130/80 mm Hg or more (Whelton et al., 2018).

Salt-sensitivity definition

- ✓ It is reported that excessive salt intake is responsible for around half of the disease burden ascribed to high BP (WHO, 2012).

- ✓ ACC/ AHA: Salt-sensitivity is "a physiological trait present in rodents and other mammals, including humans, in which the BP of some members of the population exhibits changes parallel to changes in salt intake".

- ✓ Acute salt loading elicits greater surges in BP, and salt deprivation causes larger drops in BP compared to salt-resistant individuals.

Incidence and predisposing risk factors of salt-sensitive hypertension

- ✓ Salt-sensitivity affects nearly 50% of the hypertensive and 25% of the normotensive individuals, and is an important risk factor for CVD and mortality independently from BP elevation (Weinberger et al., 2001).

- ✓ WHO: Adults reduce sodium intake to less than 5 g of salt/day (2 g of sodium/day).

- ✓ Many factors contribute to salt-sensitivity: Genetic background, black race, age, sex, body mass index, and comorbidities such as HTN, diabetes, kidney disease and metabolic syndrome.

- ✓ Salt-sensitivity appears to be more common in females and obese individuals.

Salt-sensitivity: Clinical evaluation

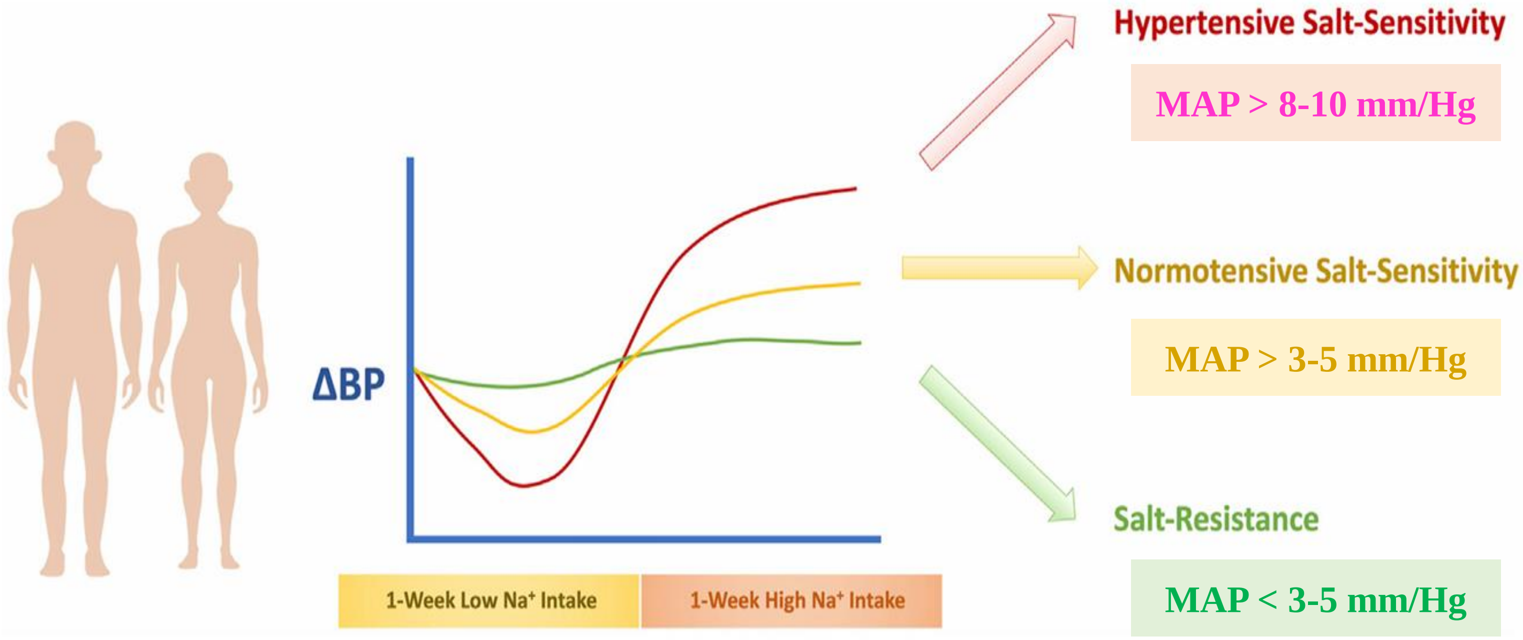
✓ Currently, there is no standardized method for diagnosing salt-sensitivity.

Salt-sensitivity

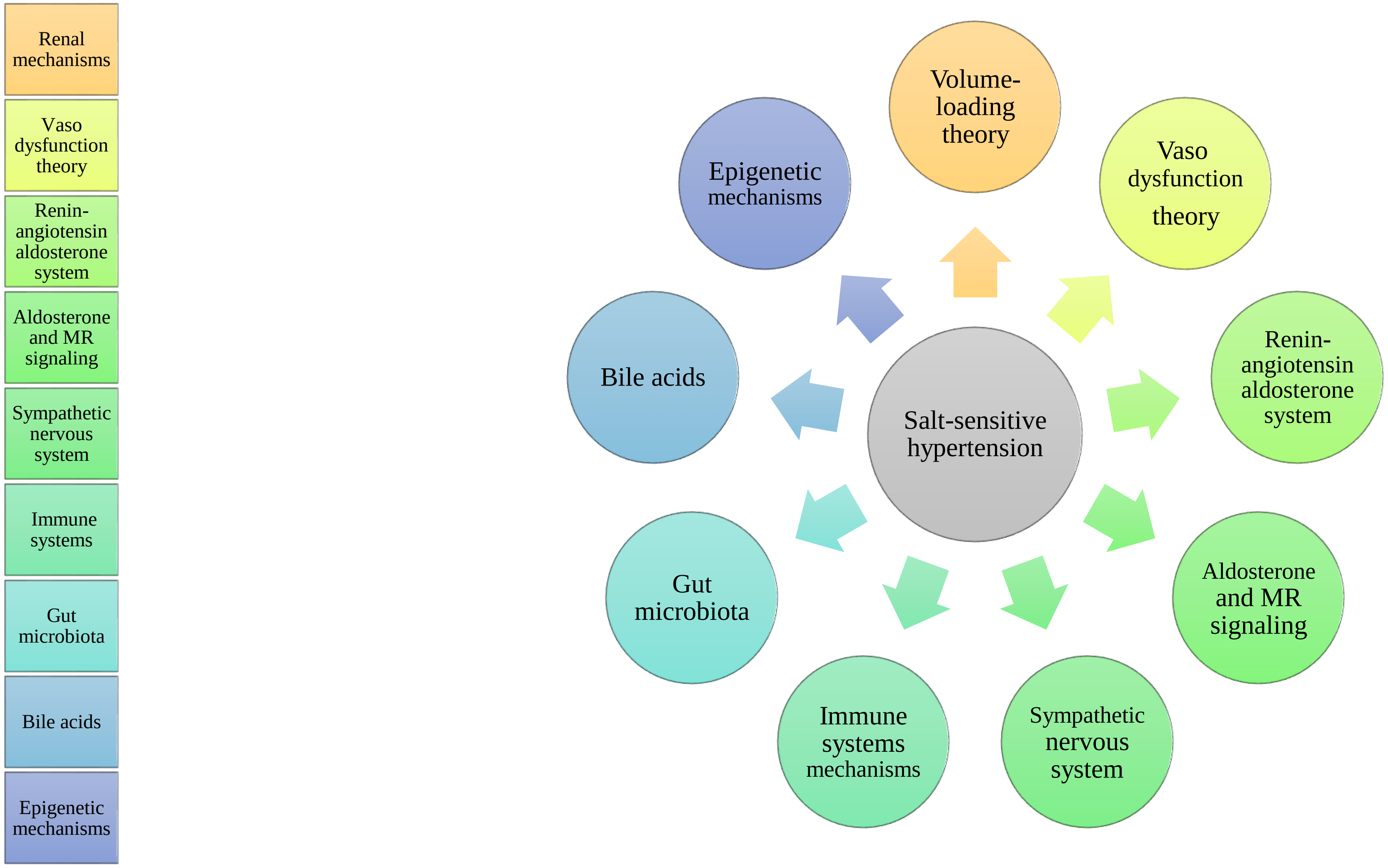
- **Outpatient**
  - 2 weeks
    - A strict low salt diet for 1 week followed by a high salt diet for the second week.
- **Inpatient**
  - 3 days
    - Rapid extracellular volume (ECV) expansion on the first day with intravenous normal saline loading, which is followed by sodium and volume depletion induced with a low sodium diet in combination with furosemide.

Determination of Salt-Sensitivity of BP

- ✓ Ambulatory BP measurement, preferred cutoff is at least a 5% change in MAP over 24 h.
- ✓ **Gold standard** approach: several 24-h urine collections.



2. Pathogenesis of salt-sensitive hypertension



Renal mechanisms

Vaso dysfunction theory

Renin-angiotensin aldosterone system

Aldosterone and MR signaling

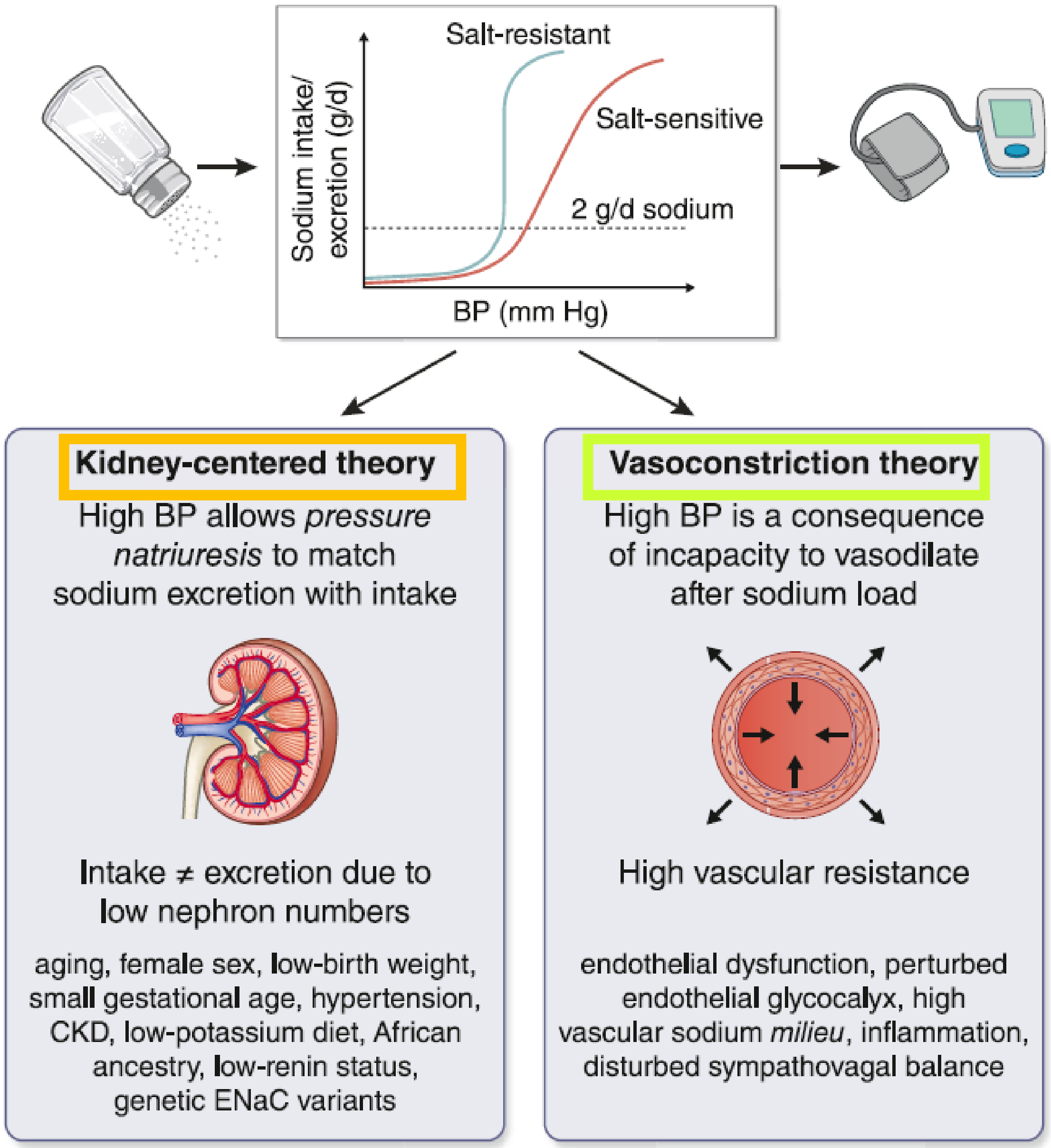
Sympathetic nervous system

Immune systems

Gut microbiota

Bile acids

Epigenetic mechanisms



Pathogenesis of salt-sensitive hypertension

Renin-angiotensin-aldosterone system dysfunction

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Immune systems
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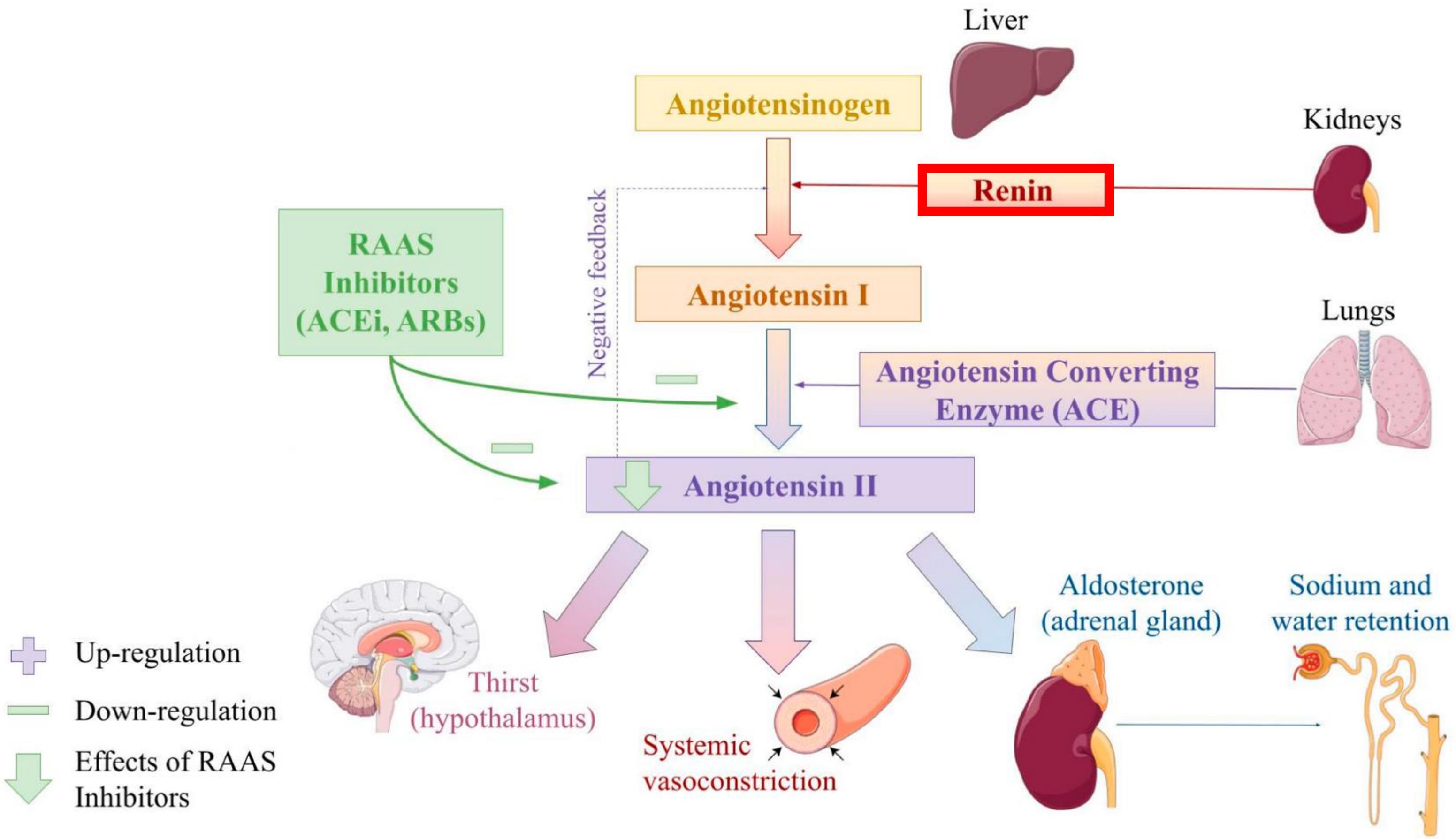
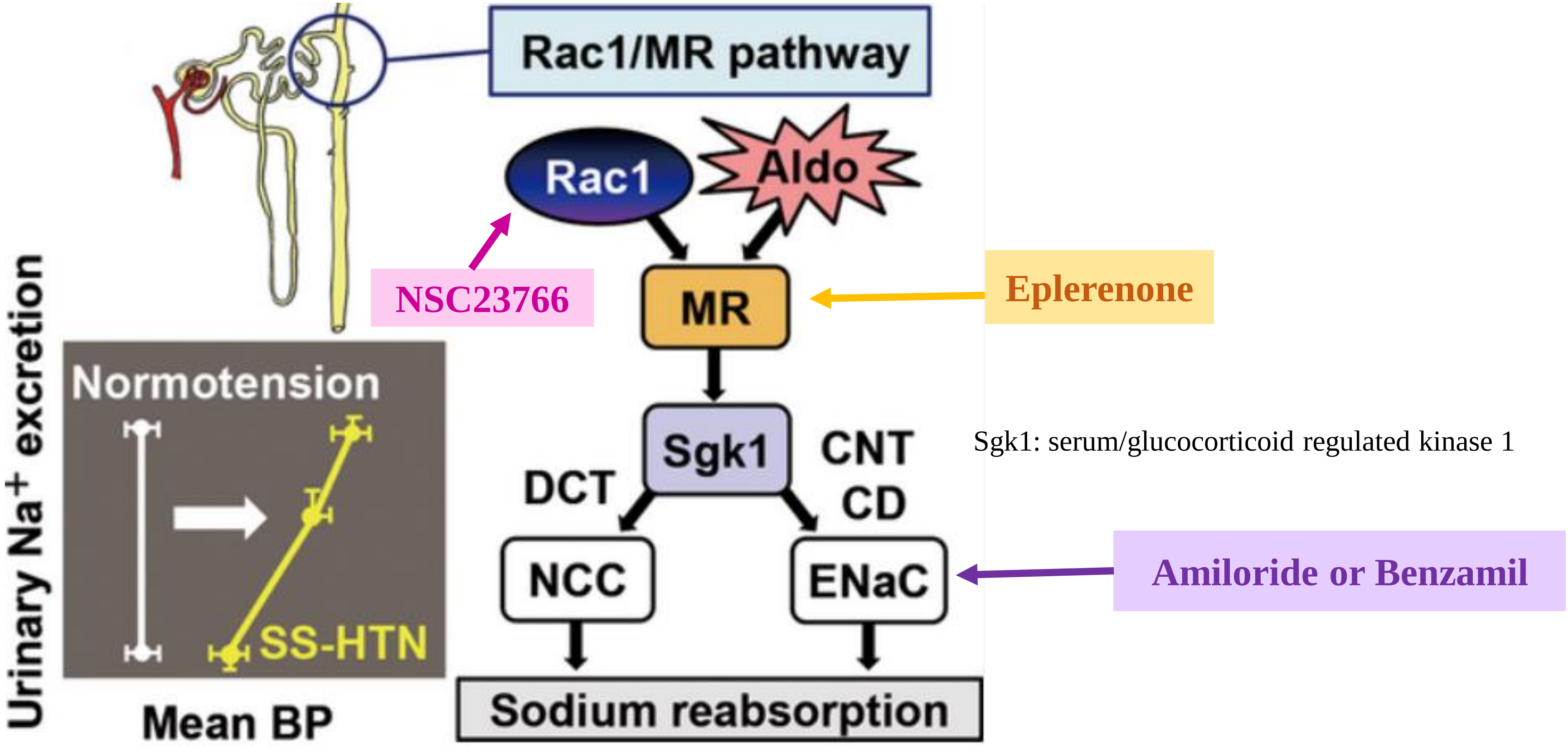


Aldosterone-dependent and aldosterone-independent mineralocorticoid receptor signaling

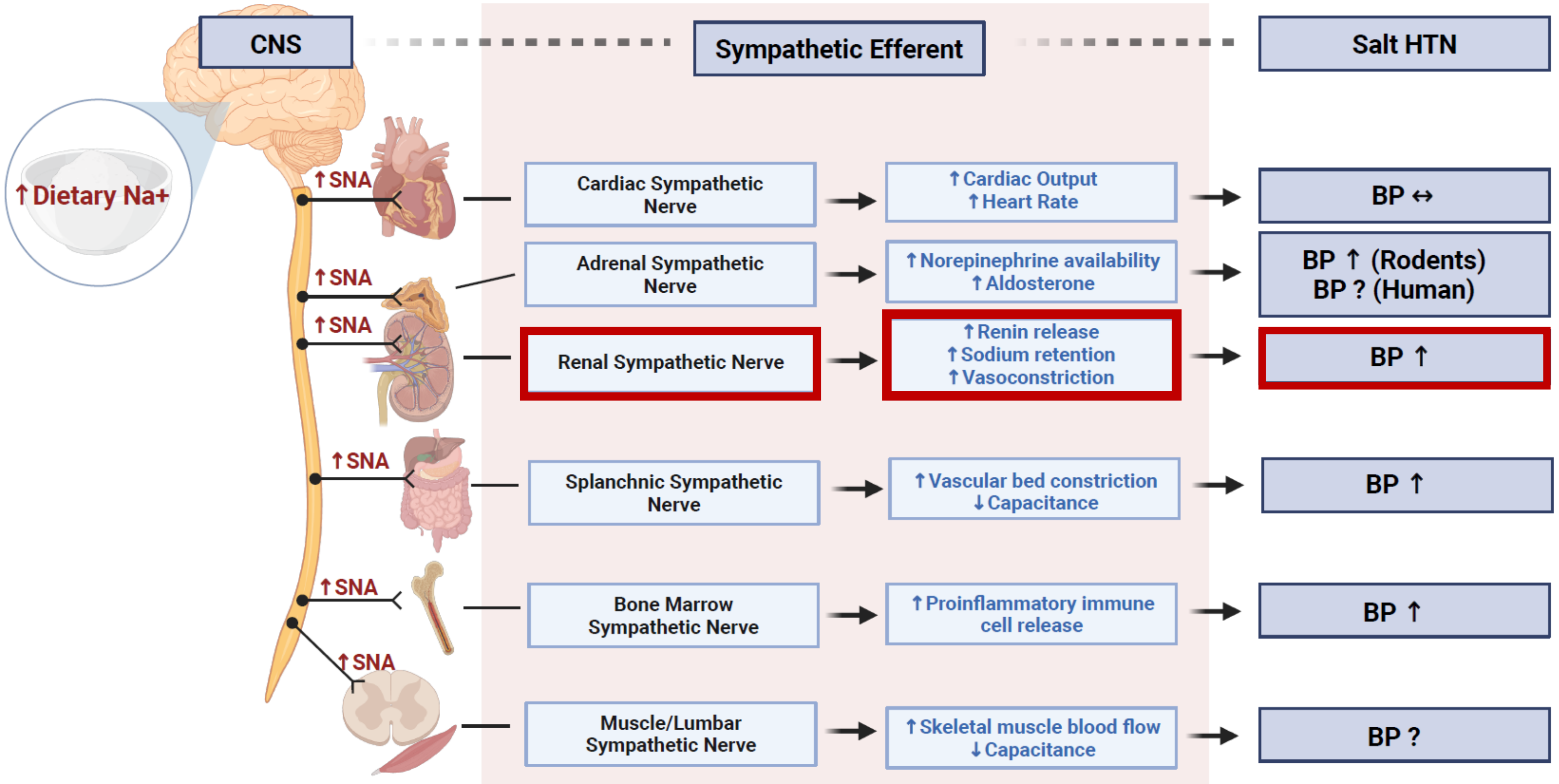


Sgk1: serum/glucocorticoid regulated kinase 1

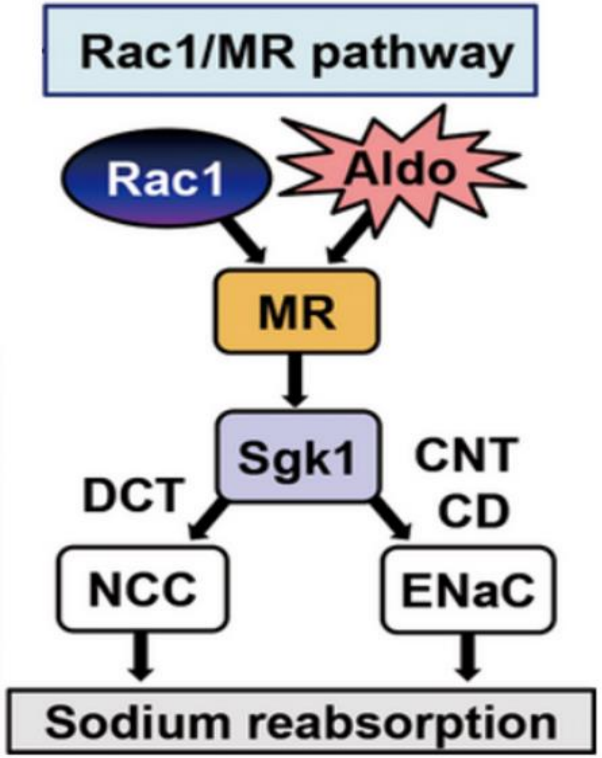
Sympathetic nervous system dysfunction

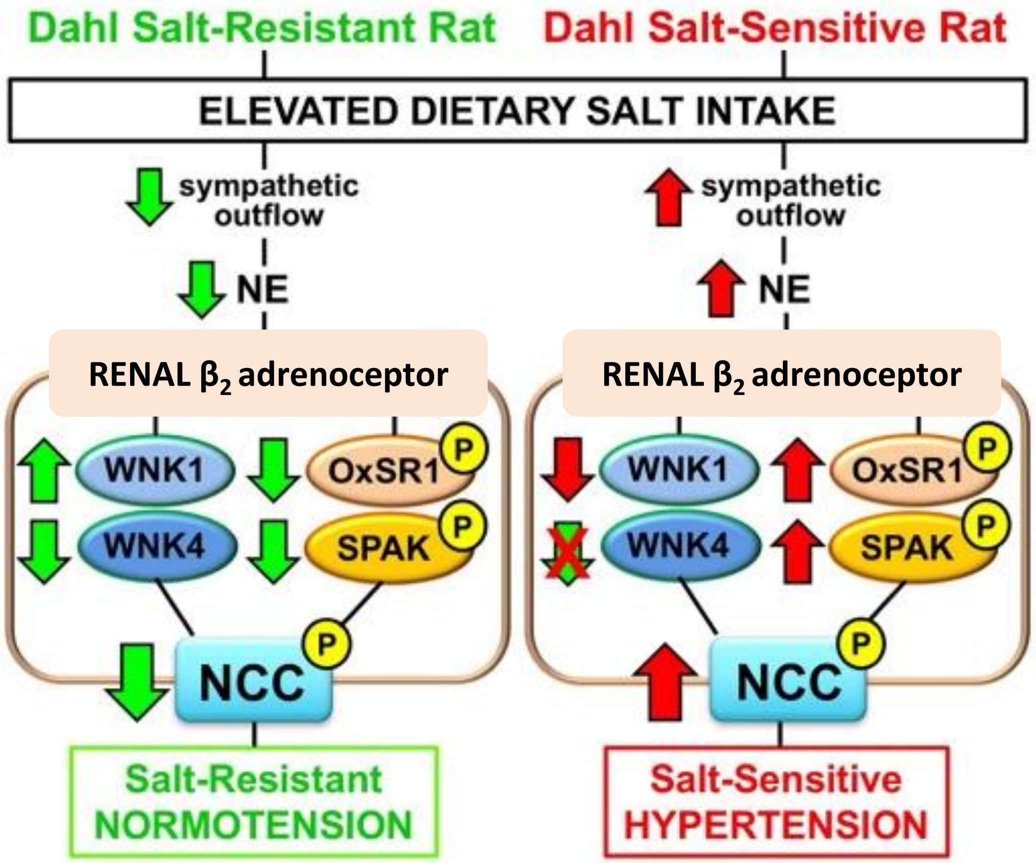
❖ Salt-sensitivity hypertension: Higher levels of circulating norepinephrine.

Compromised baroreceptor reflex control sympathetic activity.

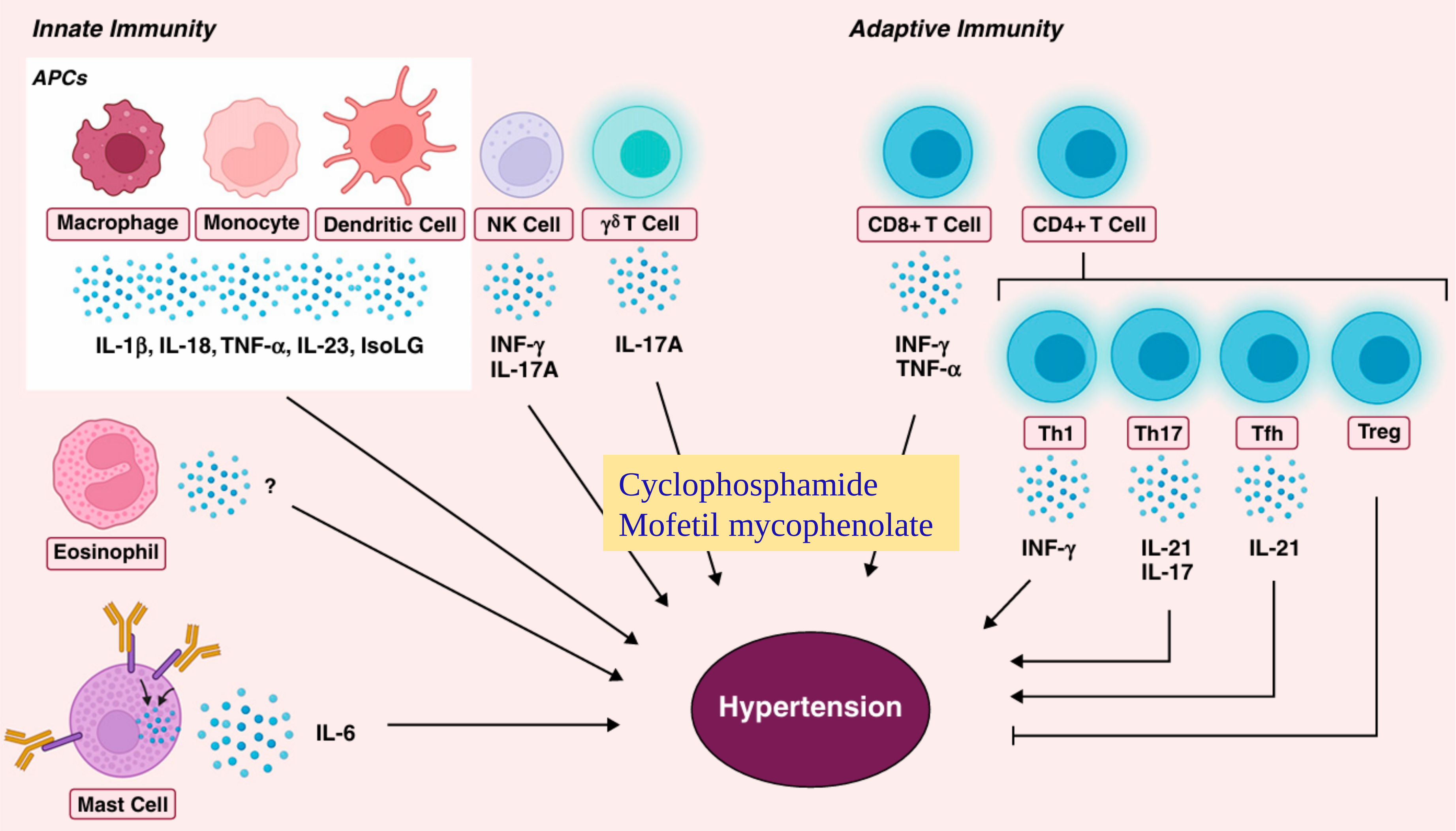


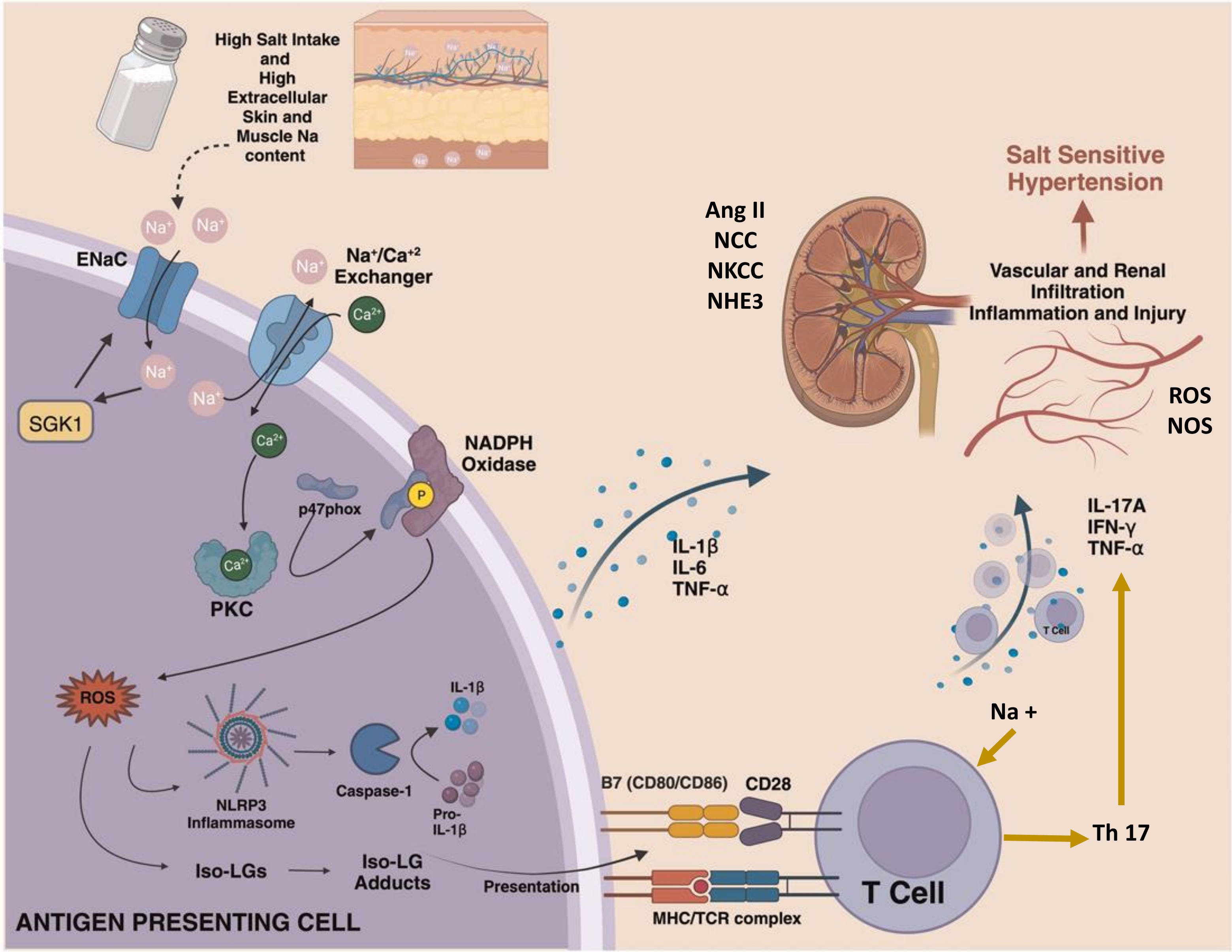
Sympathetic nervous system dysfunction





Immune systems mechanisms

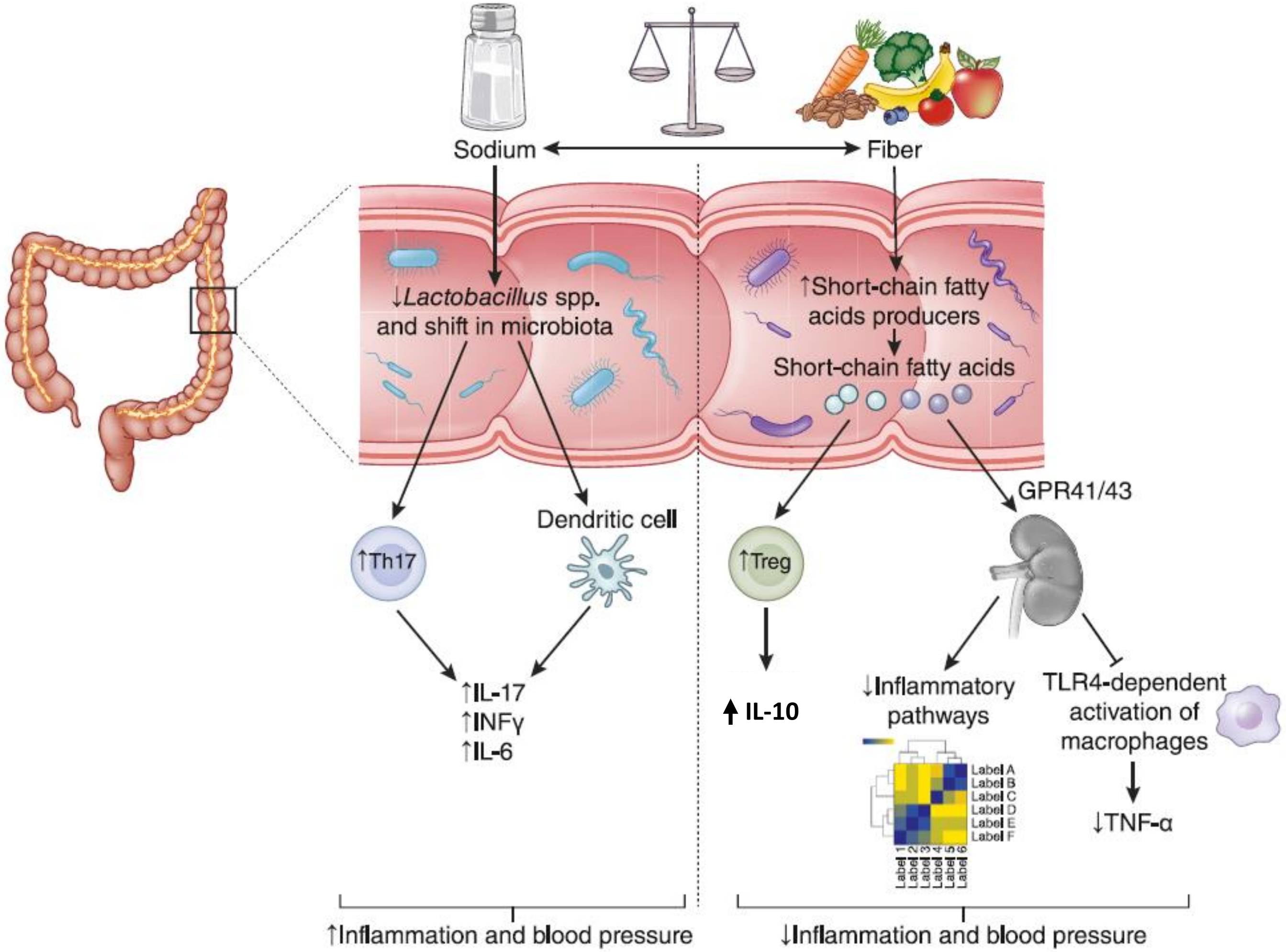




Pathogenesis of salt-sensitive hypertension

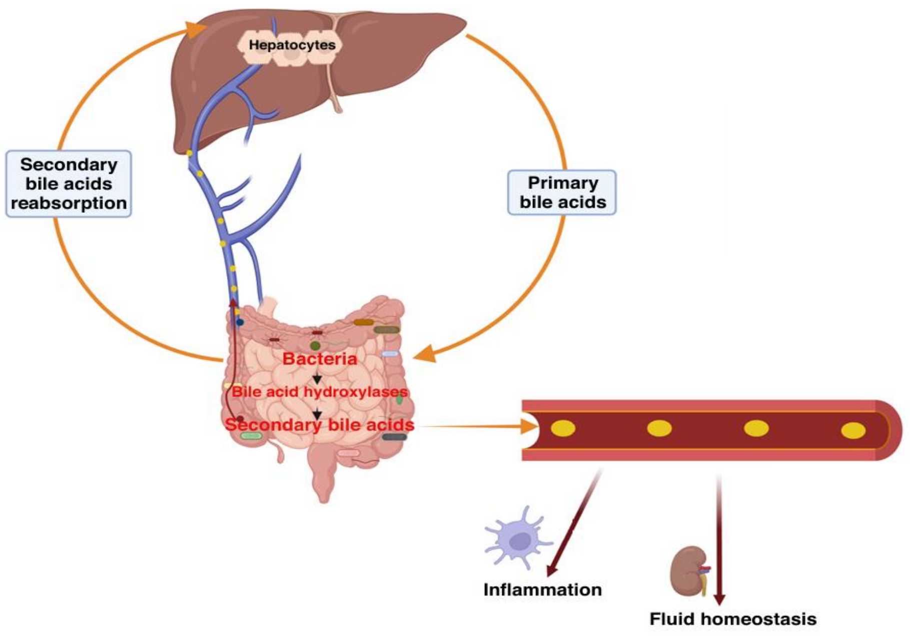
- Renal mechanisms
- Vaso dysfunction theory
- Renin-angiotensin aldosterone system
- Aldosterone and MR signaling
- Sympathetic nervous system
- Immune systems
- Gut microbiota
- Bile acids
- Epigenetic mechanisms

Gut microbiota

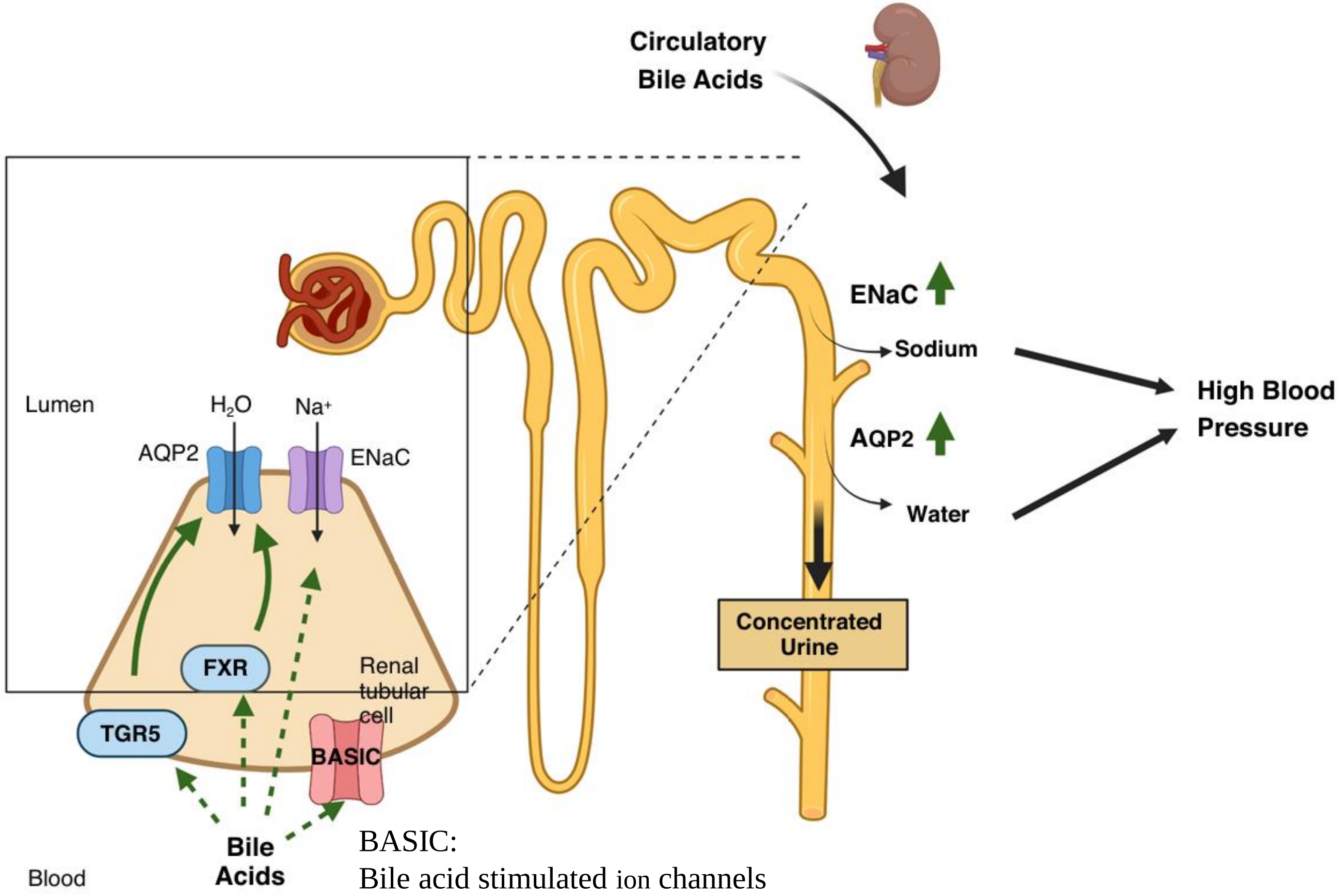


Bile acids and salt-sensitive hypertension

- ✓ Inflammation
- ✓ Gut dysbiosis
- ✓ Water and electrolyte homeostasis in the kidney



Bile acids: water and electrolyte homeostasis in the kidney



BASIC:
Bile acid stimulated ion channels

Secondary bile acids may mediate inflammation and salt-sensitive hypertension

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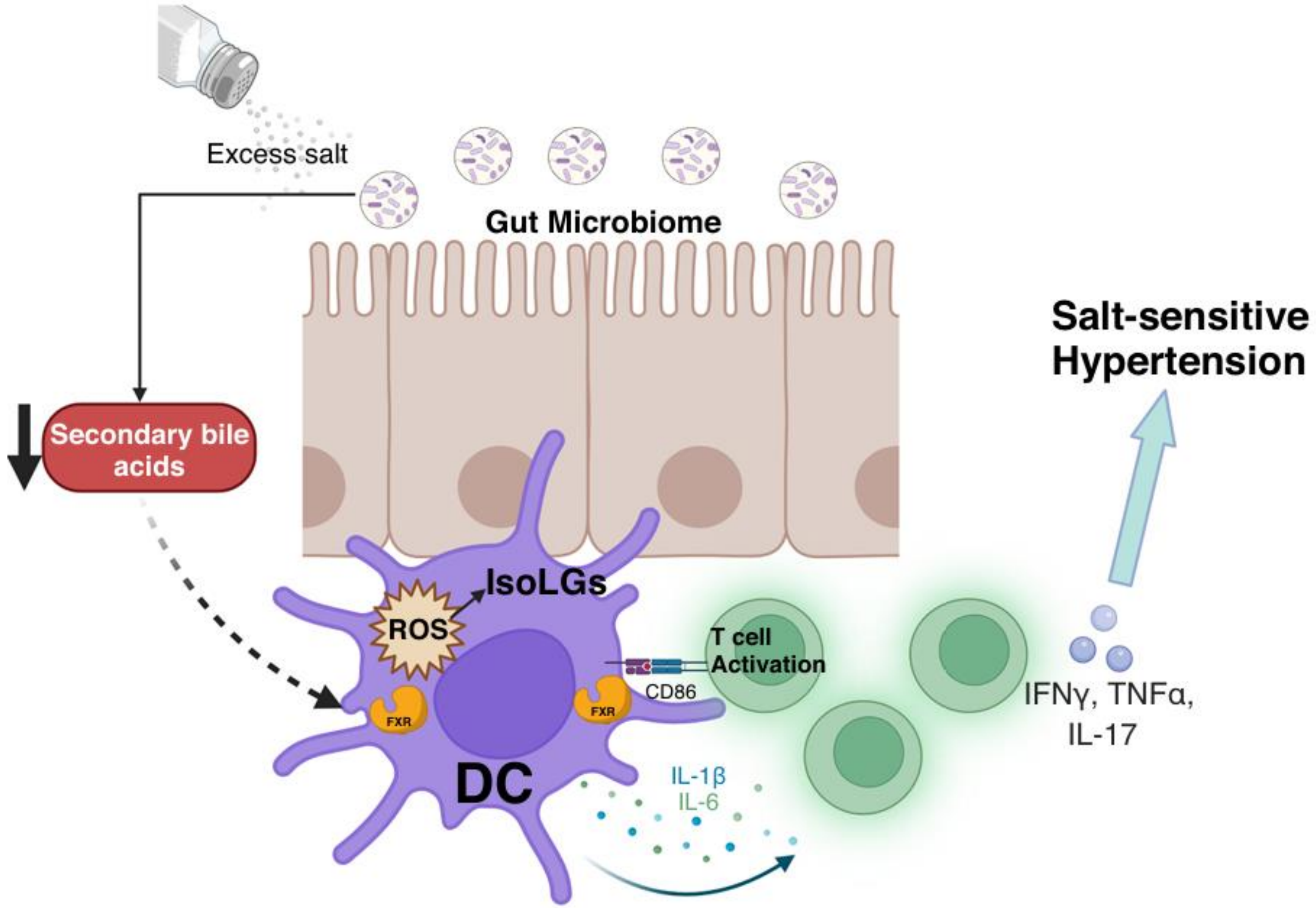

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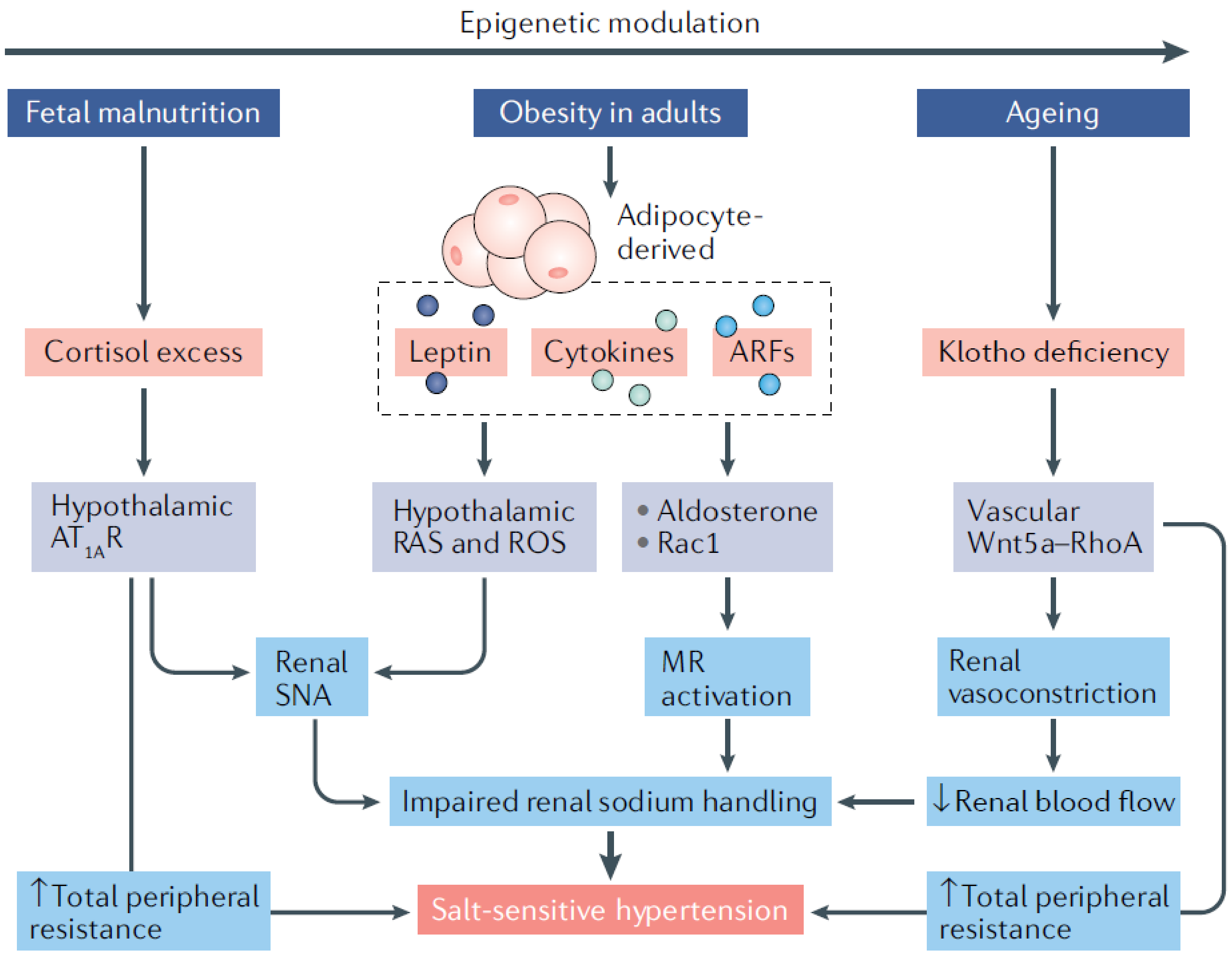


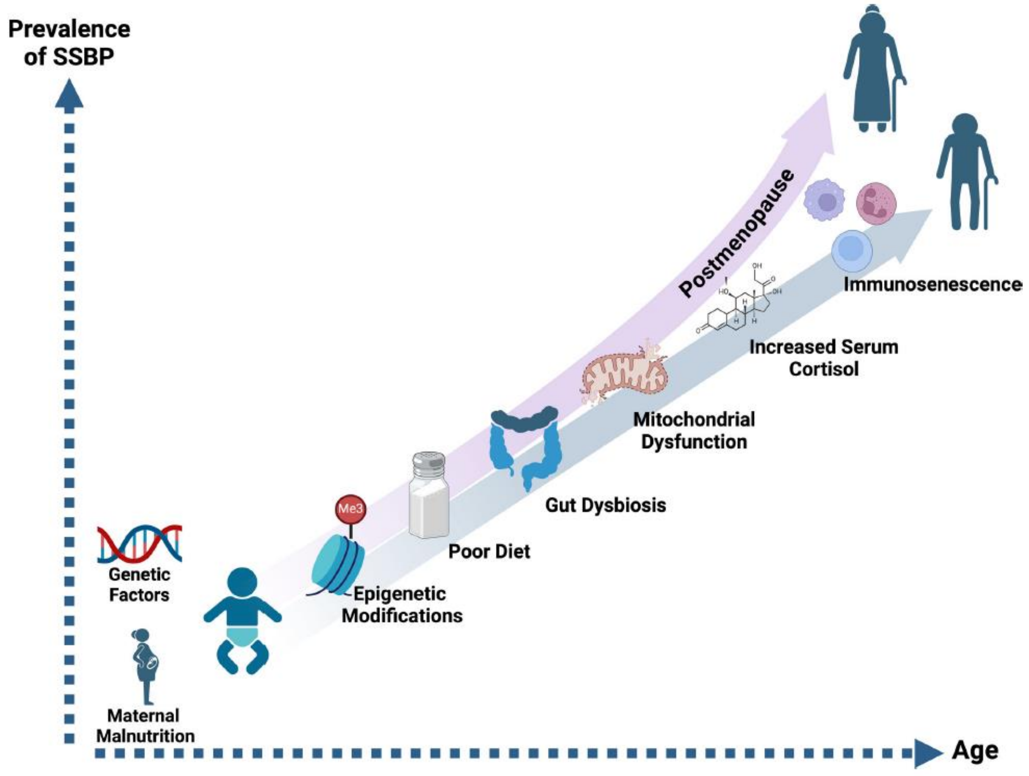
ARFs: Adipocyte- derived aldosterone- releasing factors

3. Sex-specific differences in salt-sensitive HTN

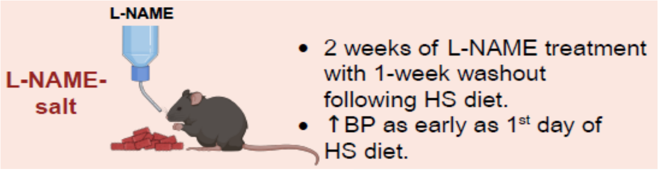
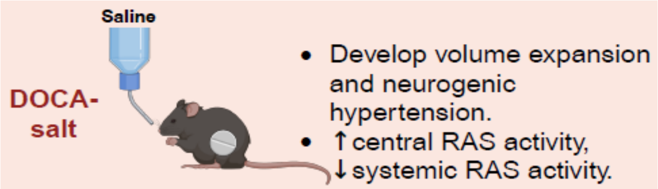
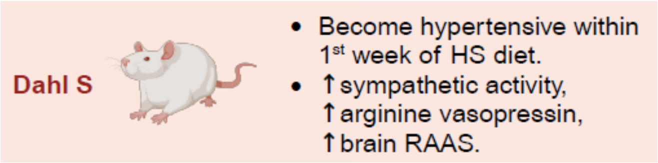
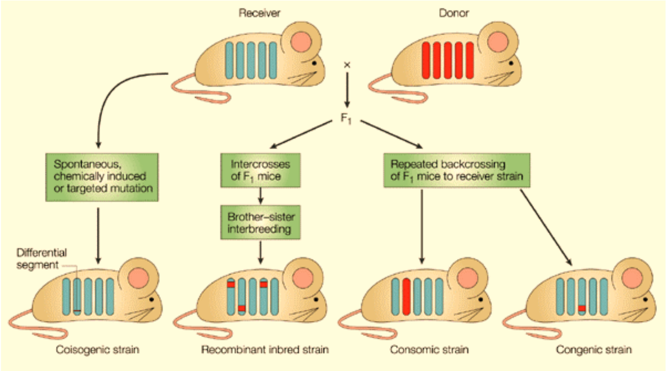
- Evidence has shown that women, primarily those under the age of 51, exhibit a reduced ability to suppress aldosterone in response to stimuli such Ang II and salt intake.

- Women typically exhibit higher aldosterone levels than men in several pathological states, such as salt-sensitive HTN, primary aldosteronism, and obesity, and appear to be more sensitive to endothelial damage.

- A high estrogen/testosterone ratio, as seen in women, is an important mediator of salt-sensitivity through differential aldosterone secretion.



4. Animal models of salt-sensitive hypertension

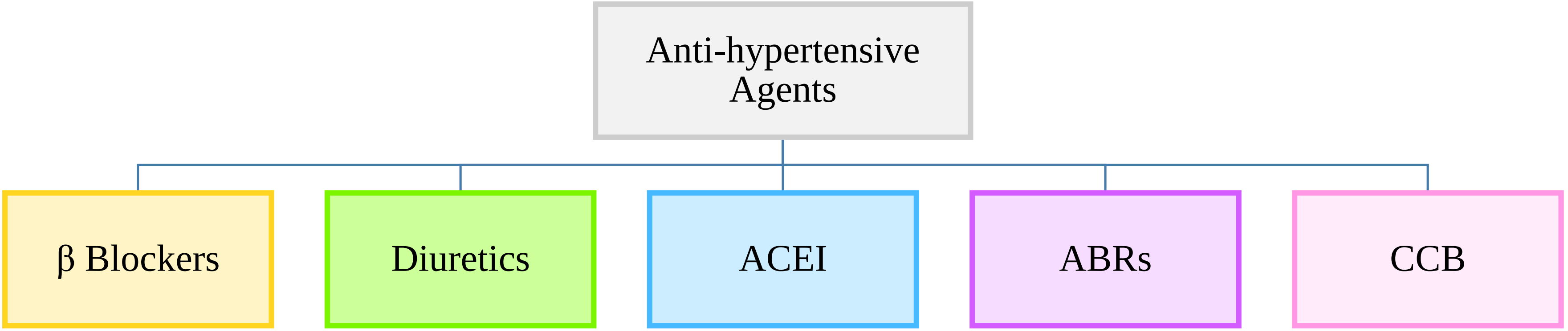
Animal models of salt-sensitive HTN	Genetically induced model of HTN	Advantages as a research tool	References
	No	Mimics salt-sensitive HTN encountered in humans	(Itani et al., 2016a)
		Induces immunological memory through repeated hypertensive stimuli and without any surgical intervention	(Itani et al., 2016a)
		Triggers endothelial dysfunction and inflammatory response	(Randolph et al., 1998; Van Beusecum et al., 2019; Wang et al., 2020)
	No	Characterized by to increase in CO and cardiac mass due to volume expansion, proteinuria, glomerulosclerosis and endothelial dysfunction	(Klanke et al., 2008; Iyer et al., 2010)
		Increases SNS and the RAAS activity	(Sawamura and Nakada, 1996)
	No	Induces HTN by increasing sodium retention and proteinuria when fed with high salt diets	(Dahl et al., 1962; Dahl et al., 1963; Khan et al., 2012)
		Promotes endothelial dysfunction, glomerulosclerosis and cardiac hypertrophy and fibrosis	(Raij et al., 1984; Hayakawa et al., 1997; Yu et al., 2003)
		Triggers T cell and macrophage infiltration in the cortex and medulla	(Hayakawa et al., 1997; Mattson et al., 2006; De Miguel et al., 2010)
	Yes	Induces HTN, hypokalemia, metabolic alkalosis and cardiac and renal hypertrophy	(Warnock, 1998)
	Yes	Enables understanding of functional significance of a chromosome/gene/allele to disease pathophysiology	(Kunert et al., 2006; Liang et al., 2008; Moreno et al., 2011a; Cowley and Dwinell, 2020)
	No	Exhibit higher levels of aldosterone synthase and aldosterone compared to males	Faulkner et al. (2018)
		Impaired endothelium-dependent vasodilation	
		Important for studying sex-specific differences in salt-sensitive HTN	

5. Treatment of salt-sensitive HTN

- ✓ The WHO recommends an upper limit of 2 g/day of salt consumption.
- ✓ Increasing dietary potassium (“Ushaped” association between K+ consumption and BP).
- ✓ Dietary K+ intake below 30 or above 80 mmol/day was associated with elevated BP.
- ✓ Enhanced K+ levels promote endothelium-dependent vasodilation through hyperpolarization Kir channels.

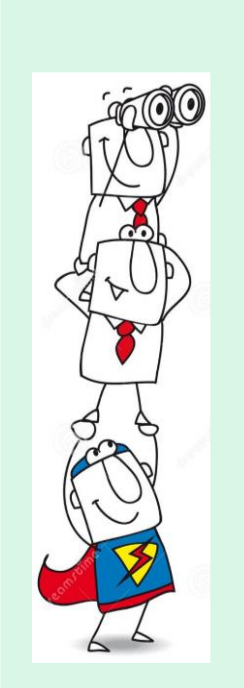
- Researchers found that a combination of a CCB with hydrochlorothiazide, a diuretic, worked best for patients with moderate salt intake.

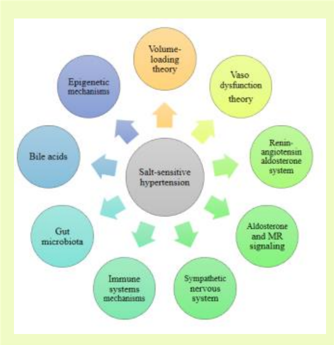
- For obese patients with moderate salt intake, a combination of a CCB with metformin was the most effective at lowering BP.



6. Future perspectives

1. **Transgenic Studies:** Knockout of genes that regulate natriuresis.
2. **Immunological Memory:** Repeated bouts of emotional stress or dietary oversights are typical of everyday life.
3. **TCR Sequencing:** Characterization of T cell population diversity. Peptide sequence patterns that may provoke or inhibit a T cell response. Vaccines targeting a self-antigen or a neoantigen (An important vaccine for HTN currently being developed is the **AGMG0201** angiotensin II vaccine).
4. **Gut Microbiome:** in immune cell activation.
5. **Advanced Tracking Techniques:** Demonstrating T cell movement in and out of the bone marrow are crucial for understanding T cell activation and migration patterns in HTN (for example S1P; SIP-SIPR1 signaling, **FTY720**, has been approved for the treatment of multiple sclerosis).
6. **Organ-Specific Progenitor/Stem cells**
7. **miRNAs:** miRNA-429





Salt-sensitive hypertension
Volume-loading theory
Vaso dysfunction theory
Renin-angiotensin aldosterone system
Aldosterone and MR signaling
Sympathetic nervous system
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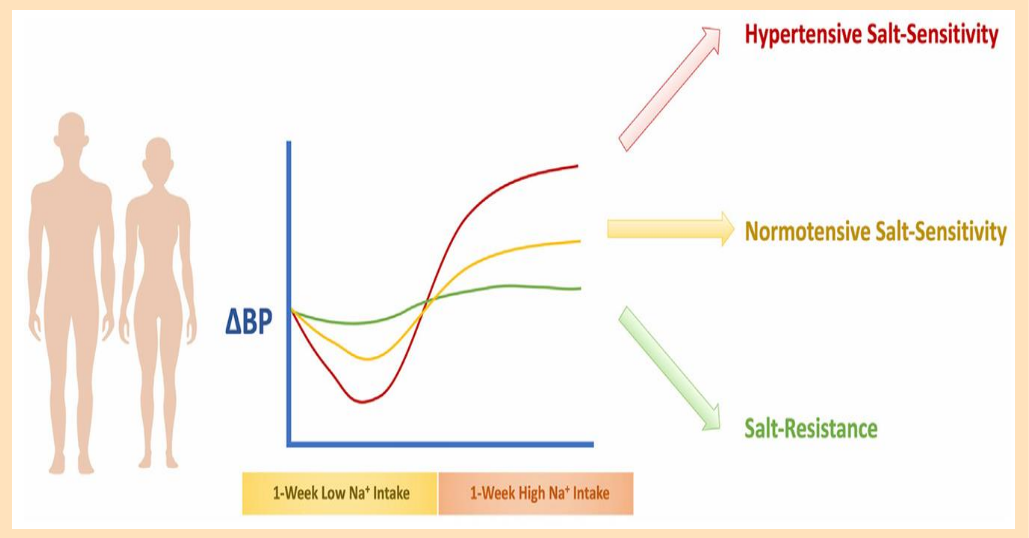
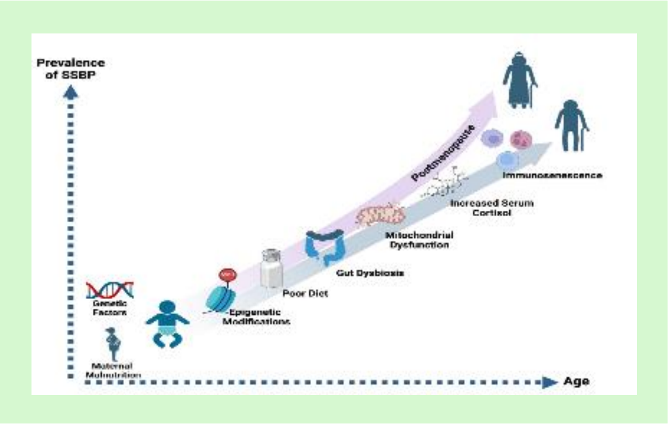
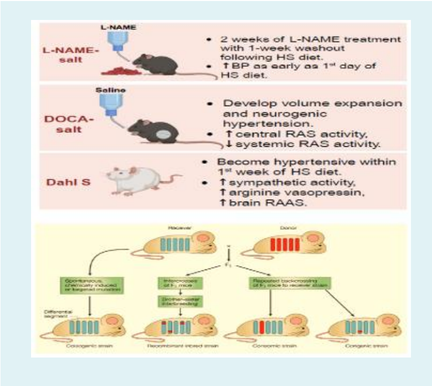


ΔBP
Hypertensive Salt-Sensitivity
Normotensive Salt-Sensitivity
Salt-Resistance
1-Week Low Na⁺ Intake
1-Week High Na⁺ Intake



Prevalence of SSBP
Age
Maternal Malnutrition
Genetic Factors
Epigenetic Modifications
Poor Diet
Gut Dysbiosis
Mitochondrial Dysfunction
Increased Serum Cortisol
Immunosenescence
Postmenopause

Avocados
485 mg Potassium
Pumpkins
340 mg Potassium
Pomegranate
236 mg Potassium
Banana
358 mg Potassium
Lentils
Mushrooms
Coconut Water
Peas
244 mg Potassium
Watermelon
112 mg Potassium
Spinach
Potatoes
Cucumbers
147 mg Potassium



L-NAME
L-NAME-salt
• 2 weeks of L-NAME treatment with 1-week washout following HS diet.
• ↑BP as early as 1st day of HS diet.
Saline
DOCA-salt
• Develop volume expansion and neurogenic hypertension.
• ↑central RAS activity, ↓systemic RAS activity.
Dahl S
• Become hypertensive within 1st week of HS diet.
• ↑sympathetic activity, ↑arginine vasopressin, ↑brain RAAS.


سپاس از توجه شما