
به نام خدایی که در این نزدیکی است

RENAL MECHANISMS OF HYPERTENTION

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The kidneys are both the culprit and the victim in hypertension

RENAL MECHANISMS OF HYPERTENTION:

EXCESS SODIUM INTAKE

VASCULAR MECHANISMS

HORMONAL MECHANISMS

TCLL AND HYPRETENTION

Excess Sodium Intake:

TABLE 3-2 How Sodium Retention Can Elevate BP

Volume-dependent mechanisms
Autoregulation
Production of endogenous ouabain-like steroids[a]
Volume-independent mechanisms
Angiotensin-mediated CNS effects
Increase in sympathetic nervous system activity
Hypertrophy in cardiac myoblasts and contractility of vascular smooth muscle cells
Increase in production of NF-κB
Increase in expression of AT1r in renal tissue
Increase in TGF-β production

Volume-Dependent Mechanisms:

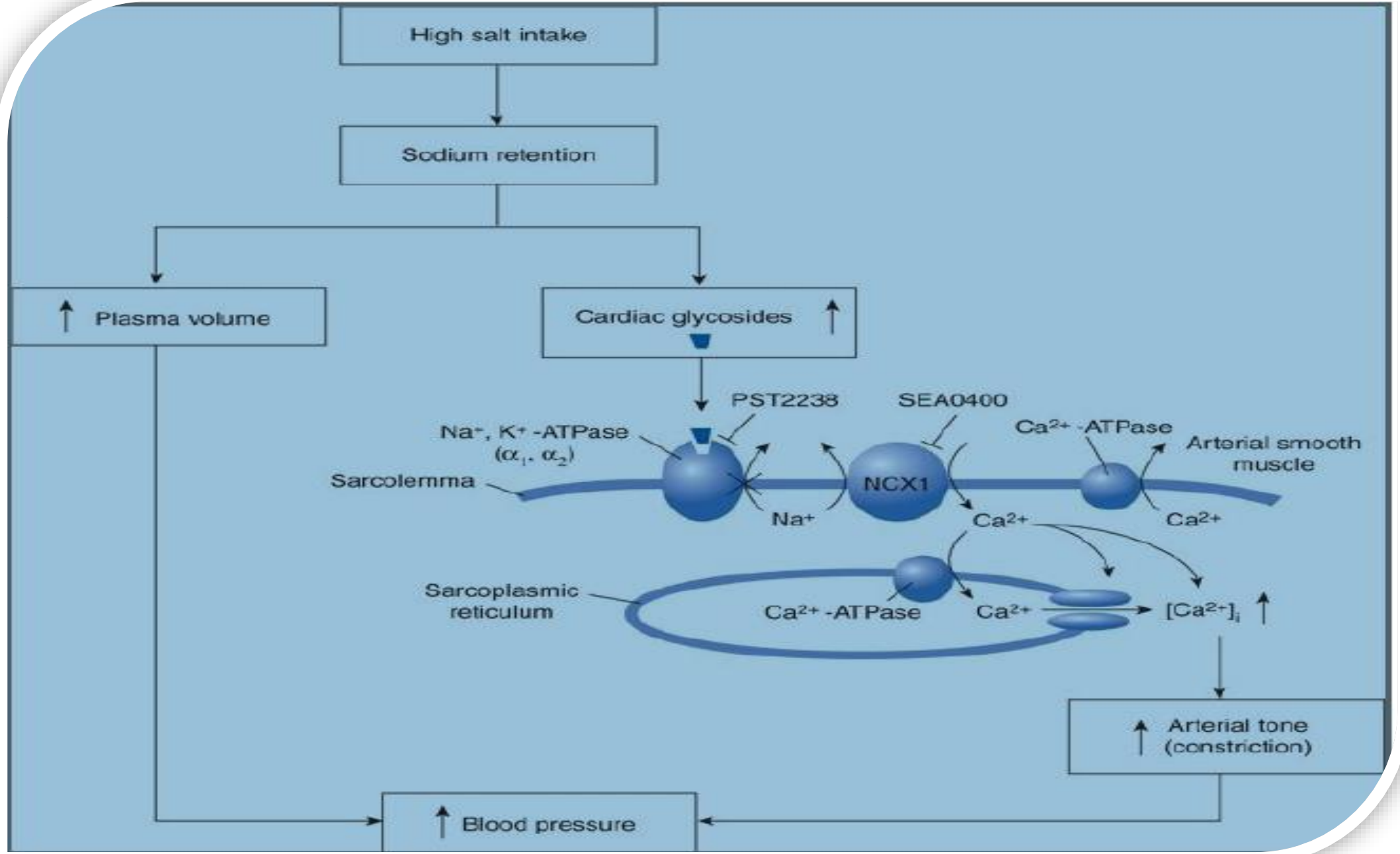
Autoregulation:

renal sodium retention is the inciting event in all hypertensive states,The expanded blood volume increases cardiac preload and thus cardiac output, which increases perfusion of peripheral tissues, As tissue perfusion exceeds metabolic demands, the resistance arteries constrict, thereby stopping overperfusion but at the expense" of increases in systemic vascular resistance and BP. The resultant increase in cardiac afterload returns cardiac output to normal.

The term autoregulation implies that the vasoconstrictor response is an intrinsic property of vascular smooth muscle and does not require hormonal or neural inputs.

OUBAIN LIKE STEROIDS:

Ouabain inhibits the Na-K-ATPase membrane pump, resulting in an increase in intracellular sodium and calcium concentrations. Increased intracellular concentrations of calcium may promote activation of contractile proteins (e.g., actin, myosin).


High salt intake
Sodium retention
Plasma volume
Cardiac glycosides
PST2238
SEA0400
Na+, K+ -ATPase
(α1, α2)
Sarcolemma
NCX1
Ca2+ -ATPase
Arterial smooth muscle
Na+
Ca2+
Ca2+
Sarcoplasmic reticulum
Ca2+ -ATPase
Ca2+
[Ca2+]i
Arterial tone (constriction)
Blood pressure

Salt Sensitivity and Salt Resistance:

Weinberger et al ,evaluated in 378 normotensive and 198 hypertensive humans by two approaches.

Blood pressure was measured after an intravenous infusion of 2 L of normal saline (0.9%) and after sodium and volume depletion induced by a low sodium diet and furosemide administration. They arbitrarily separated the population into two groups, those in whom mean arterial blood pressure decreased by at least 10 mmHg after sodium and volume depletion were considered sodium-sensitive, and those with a decrease of 5 mmHg or less (including an increase in pressure) were considered sodium resistant.

Most studies find BP to be more salt sensitive among persons who are older, overweight, hypertensive, or of African descent.

Importance of Pressure–Natriuresis:

In normotensive people, when BP rises, renal excretion of sodium and water increases, shrinking fluid volume and returning The BP to normal—the phenomenon of pressure–natriuresis.

In patients with primary hypertension resetting of the pressure–sodium excretion curve prevents the return of BP to normal so that fluid balance is maintained but at the expense of high BP ,indicates that the resetting plays a key role in causing hypertension and is not merely an adaptation to increased BP.

Importance of Renal Inflammation

Rodent studies point to renal inflammation as both a cause and a consequence of renal medullary ischemia.

Renal inflammation—is a hallmark of both the initiation and progression of experimental salt-sensitive hypertension.

Eventually, on-going renal ischemia will kill enough nephrons to decrease GFR.

VASCULAR MECHANISMS

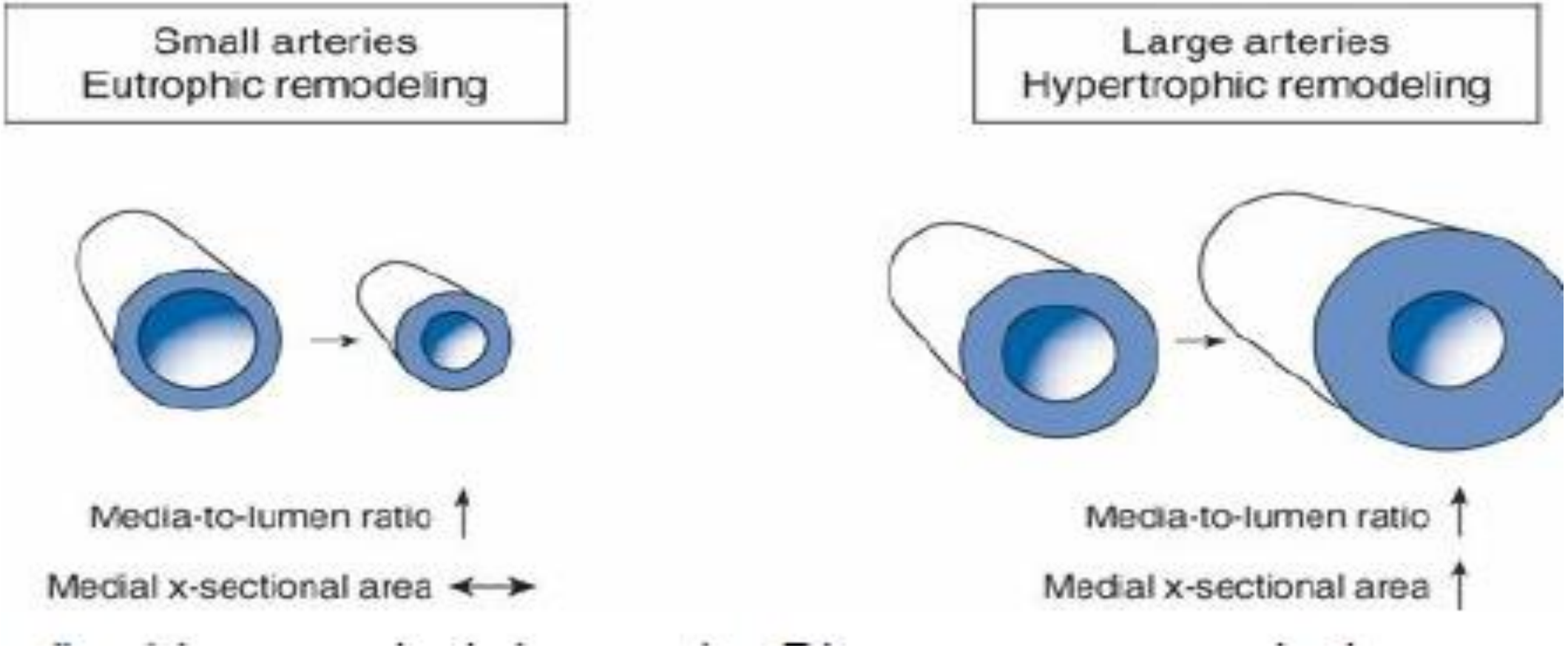
Dysfunctional endothelium, a hallmark of hypertension, is characterized by impaired release of endothelial-derived relaxing factors (NO), and enhanced release of endothelial-derived constricting, include endothelin, thromboxane, and transforming growth factor-β (TGF-β).

One of the principal mechanisms of endothelial cell dysfunction in hypertension is the production of superoxide anion and other ROS that quench NO, thereby reducing its bioavailability. The term "oxidative stress" refers to chronic elevations in ROS, which are associated with hypertension, atherosclerosis, and diabetes.

Asymmetric dimethyl arginine (ADMA) is an endogenous NOS inhibitor and, as such, is an attractive but unproven mechanismof endothelial dysfunction and hypertension.

Thus, the NO pathway is thought to be one of the most important regulatory mechanisms that protects against hypertension, and NO deficiency is thought to contribute to hypertension.

VASCULAR REMODELING:

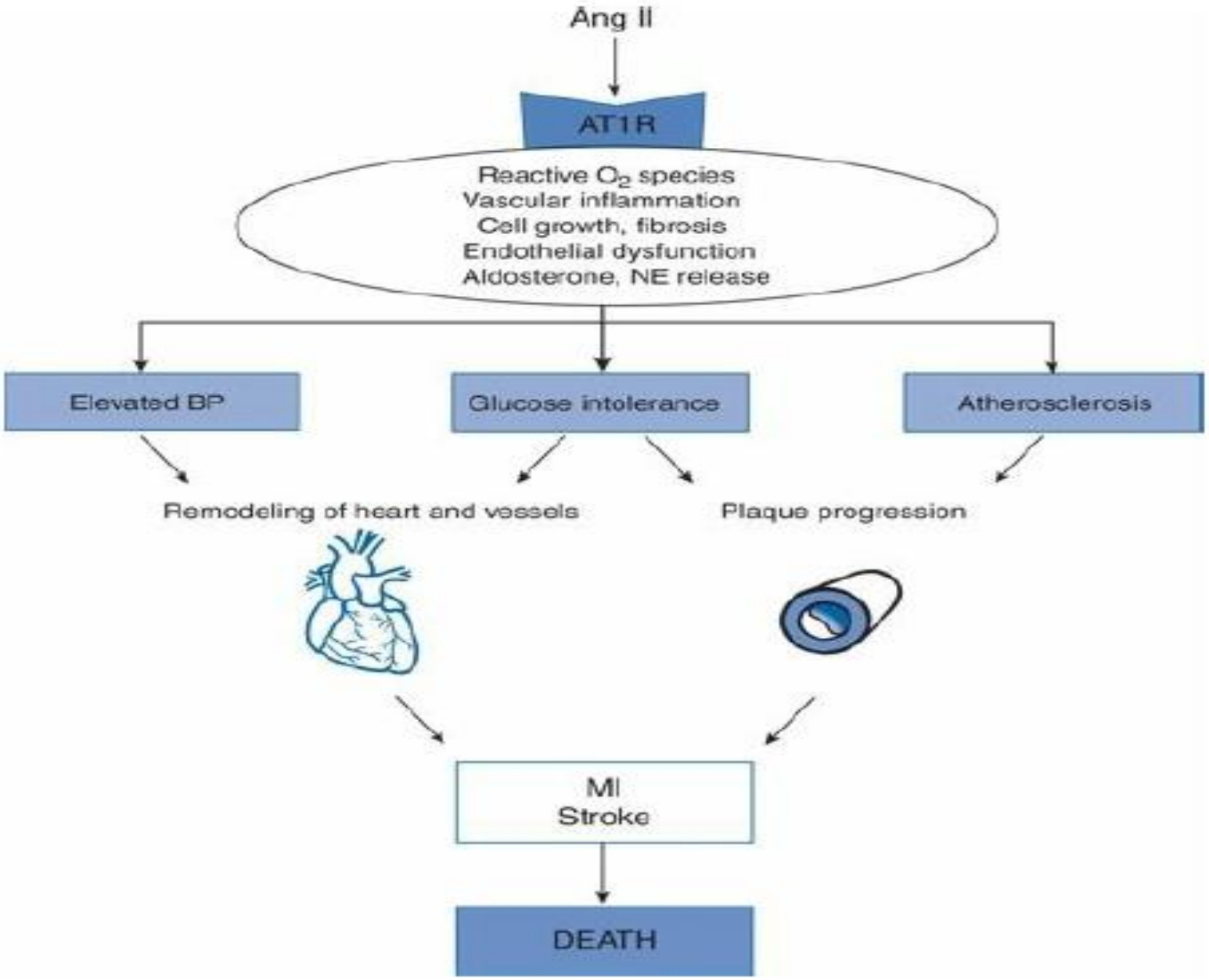


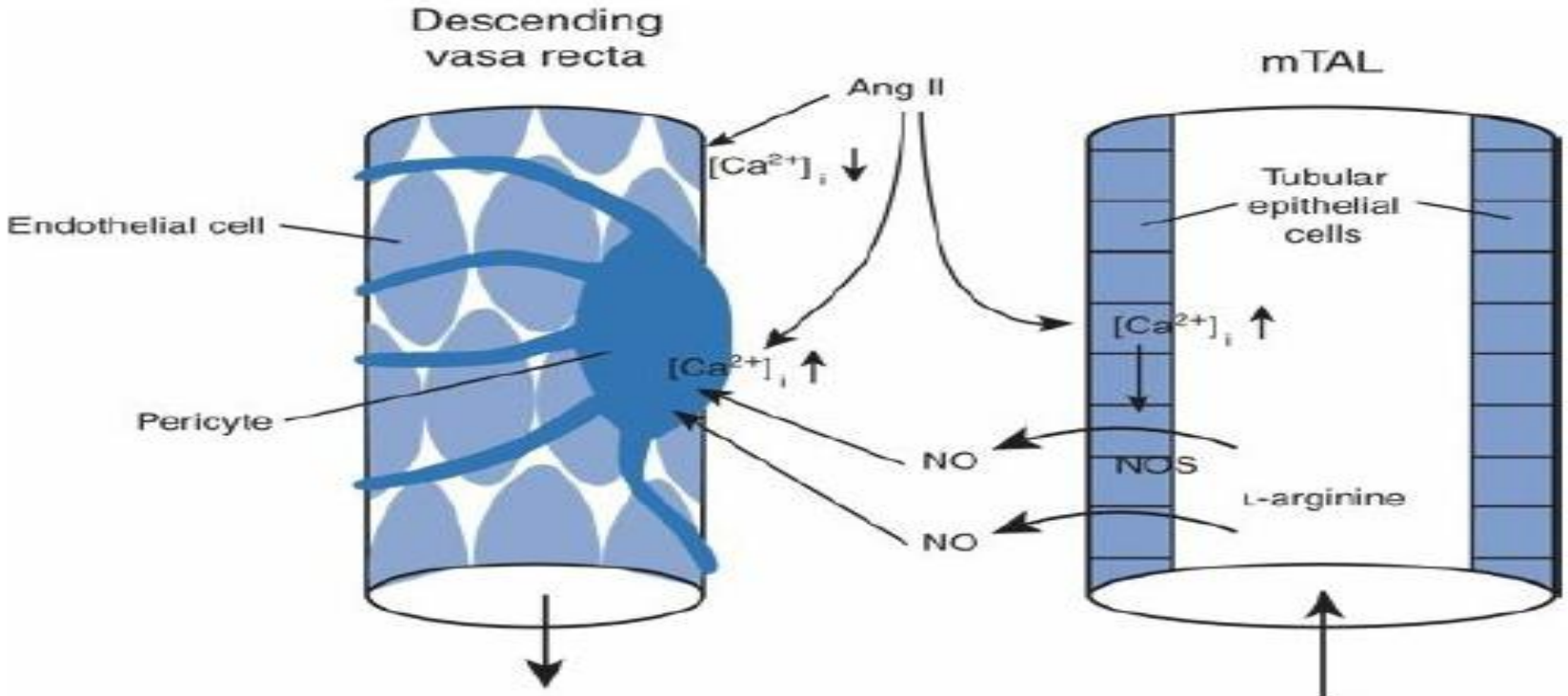
HORMONAL MECHANISMS:

INTRA RENAL RAAS:

Ag II has been shown repeatedly to cause a rightward shift in the pressure–natriuresis curve ,The effect is potent because sodium retention is greatly augmented at Ang II concentrations far below those needed to cause vasoconstriction

One reason the RAAS is so important in renal sodium handling is that Ang II is selectively concentrated in the kidney , intrarenal concentrations of Ang II are several-fold higher than circulating blood levels because the kidney actively produces and sequesters Ang II,renal Ang II levels are high even when plasma levels are normal or low.


Ang II
AT1R
Reactive O_2 species
Vascular inflammation
Cell growth, fibrosis
Endothelial dysfunction
Aldosterone, NE release
Elevated BP
Glucose intolerance
Atherosclerosis
Remodeling of heart and vessels
Plaque progression
MI
Stroke
DEATH



Ang II increases [Ca2+]i in pericytes of the descending vasa recta and reduces it in endothelium of the descending vasa recta. Ang II increases [NO]i in the pericytes of the descending vasa recta but only when these cells are in proximity to the tubules surrounding the mTAL. Ang II increases [Ca 2+]i and [NO]i in mTALs even when these tubules were observed in isolation.

This indicates that Ang II exerts a constrictor effect on the descending vasa recta by its action on pericytes, and this constrictor action is buffered by NO diffusing from mTALs to the pericytes of the descending vasa recta.

Plasma Renin Activity as a Clinical Index of RAAS Activity

Decreased PRA	Increased PRA
Expanded fluid volume	Shrunken fluid volume
Salt loads, oral or intravenous	Sodium restriction
Primary salt retention	Fluid losses
Liddle syndrome	Diuretic induced
Gordon syndrome	Gastrointestinal losses
Mineralocorticoid excess	Hemorrhage
Primary aldosteronism	Decreased effective plasma volume
Cushing syndrome	Upright posture
Congenital adrenal hyperplasia	Cirrhosis with ascites
DOC, 18-hydroxy-DOC excess	Nephrotic syndrome
11β-Hydroxysteroid dehydrogenase inhibition (licorice)	Decreased renal perfusion pressure
Sympathetic inhibition	Renovascular hypertension
Autonomic dysfunction	Accelerated–malignant hypertension
Therapy with adrenergic neuronal blockers	Chronic renal disease (renin dependent)
Therapy with β-adrenergic blockers	JG hyperplasia
Hyperkalemia	Sympathetic activation
Decreased renin substrate	Therapy with direct vasodilators
Androgen therapy	Pheochromocytoma
Decrease in renal tissue	Stress: exercise, hypoglycemia
Hyporeninemic hypoaldosteronism	Hyperthyroidism
Chronic renal disease (volume dependent)	Sympathomimetic agents (caffeine)
Anephric	Hypokalemia
Increasing age	Increased renin substrate
Unknown	Pregnancy
Low-renin primary hypertension	Estrogen therapy
Black race	Autonomous renin hypersecretion
	Renin-secreting tumors
	Acute damage to JG cells
	Acute glomerulonephritis
	Decreased feedback inhibition
	Low A II levels (ACEI therapy)
	Unknown
	High-renin primary hypertension

Renal Medullary Endothelin System

Endothelin, discovered as a potent endothelium-derived vasoconstrictor, also is plentiful in the renal medulla where it causes vasodilation and natriuresis, thus reducing BP and protecting against salt-induced hypertension, These effects are mediated by the ETB receptor, whereas the vasoconstrictor and prohypertensive actions of endothelin are mediated by the ETA receptor.

A high-salt diet drives endothelin expression in the kidney, increasing renal medullary blood flow via prostaglandins and NO and inhibiting the antinatriuretic effect of vasopressin).

endothelin receptor antagonists inhibit both ETA and ETB receptors, which likely explains their disappointingly small effect on BP, despite showing much promise for treating pulmonary hypertension.

T Cells and Hypertension:

subfornical organ (SFO), have a poorly formed blood–brain barrier and are responsive to circulating ang ii and sodium.,production of ROS, which provide input into hypothalamic centers including (PVN),Microglial cells are activated in this process and increase input into brainstem centers, including the (VLM) and the(NTS). These increase sympathetic outflow, causes a modest elevation in BP to levels compatible with prehypertension.

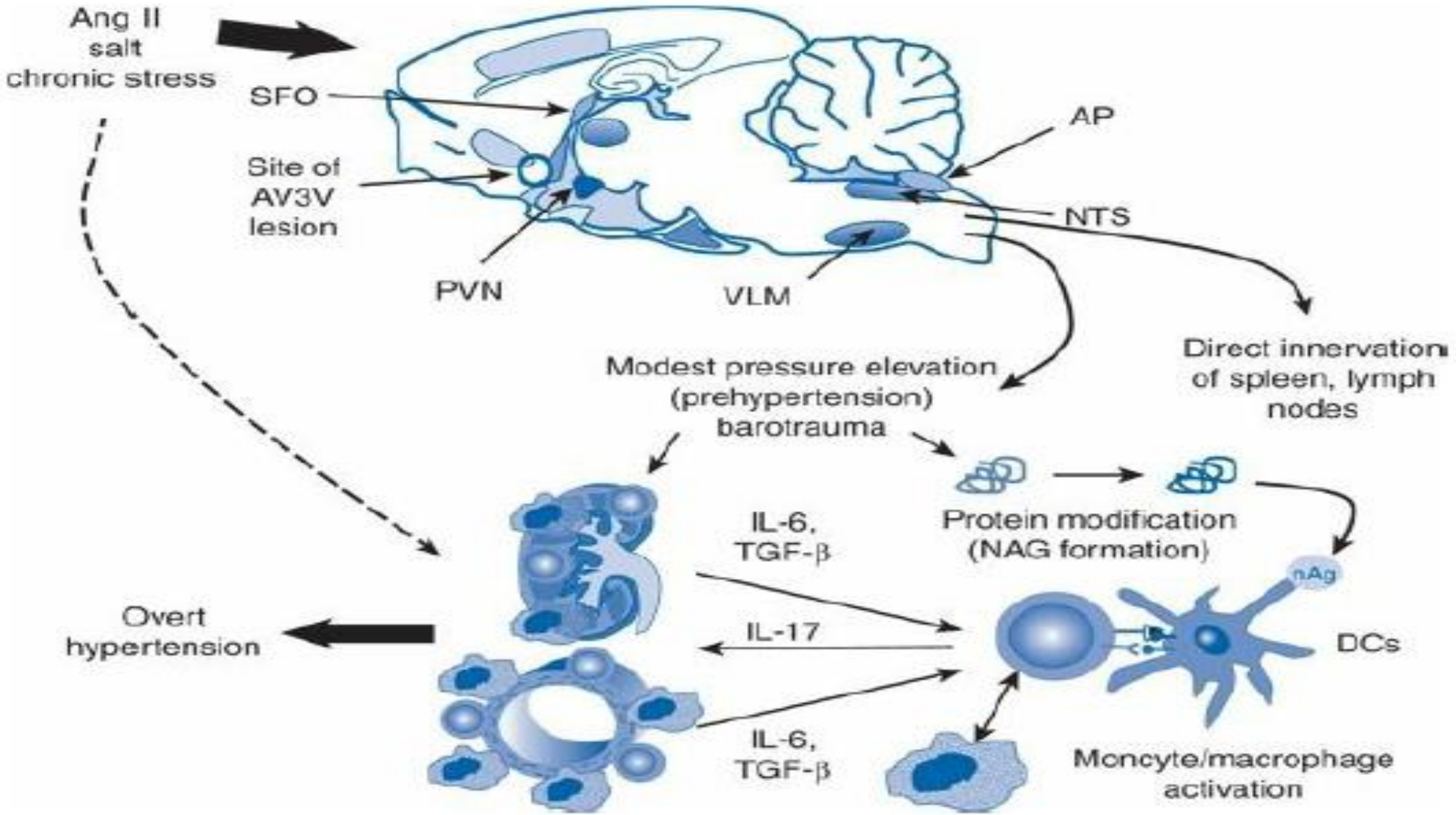
Sympathetic activation also increases renal production of IL-6 and acts on T-cell adrenergic receptors to

modify their polarization.

The elevations of pressure, direct actions, and Ang II and catecholamines activate ROS production in the kidney and vasculature, increasing chemokine production and adhesion molecule expression Neoantigens (NAG) are formed from endogenous proteins in the kidney and vasculature, which are presented by DCs to T cells.

Activated T cells interact with monocytes/macrophages, promoting macrophage transformation, and these leukocytes accumulate in the kidney.

IL-6 and TGF-β, produced in these organs, help direct T-cell IL-17 production ,promote ROS production in the vascular smooth muscle and kidney, leading to vasoconstriction, sodium retention, and ultimately severe hypertension.


Ang II
salt
chronic stress
SFO
Site of
AV3V
lesion
PVN
VLM
AP
NTS
Direct innervation
of spleen, lymph
nodes
Modest pressure elevation
(prehypertension)
barotrauma
Protein modification
(NAG formation)
nAg
DCs
IL-6,
TGF-β
IL-17
IL-6,
TGF-β
Overt
hypertension
Moncyte/macrophage
activation

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