Pathogenesis of essential hypertension

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Hypertension is a significant risk factor for cardiovascular and cerebrovascular diseases (CVDs) and is the leading cause of premature death worldwide

The estimated prevalence of hypertension in the global adult population was 31.1% (1.39 billion) in 2010 and is still on the rising

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and	80–84
High-normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[a]	≥140	and	<90
Isolated diastolic hypertension[a]	<140	and	≥90

Essential HTN

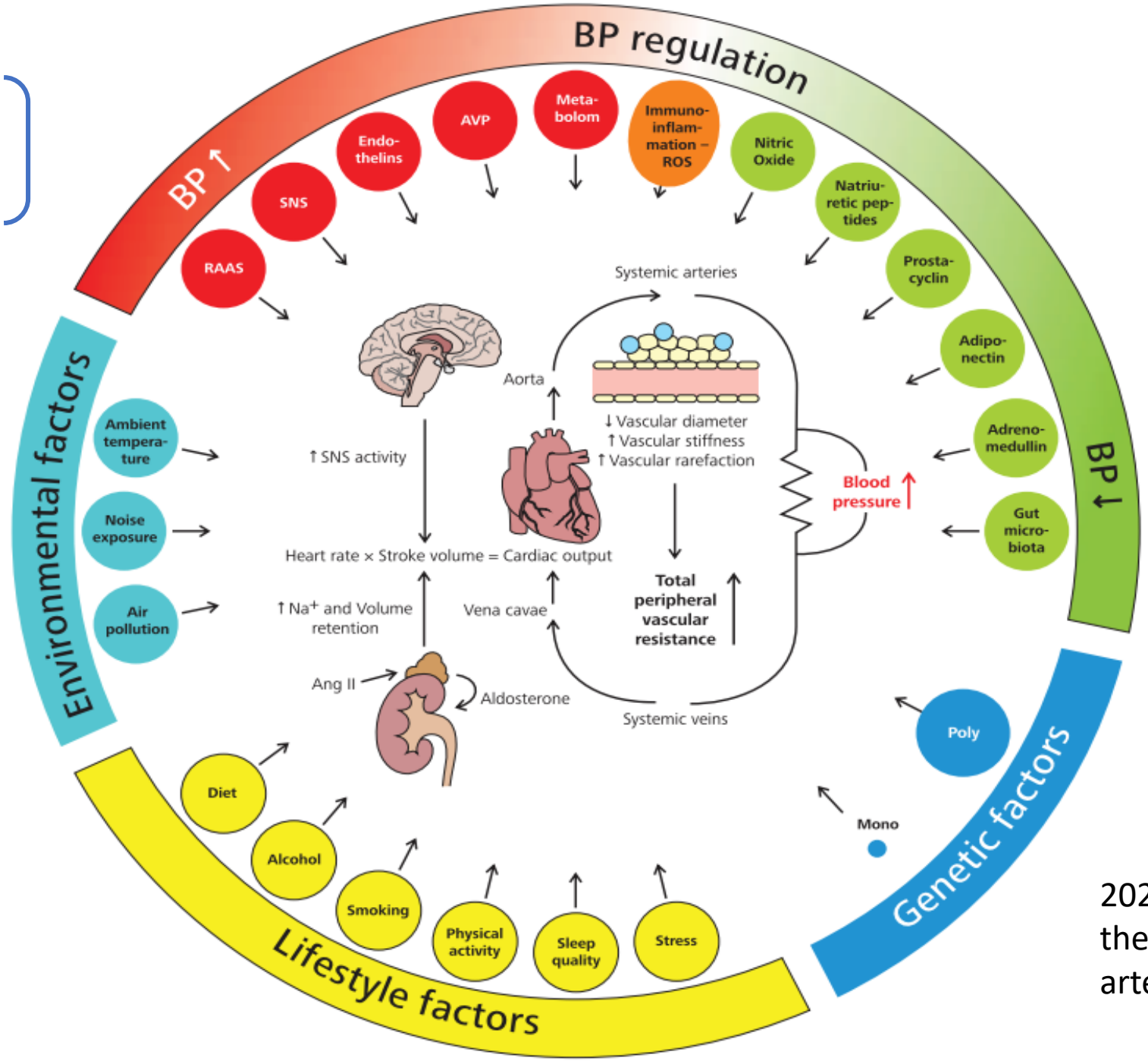
Secondary HTN

Product of cardiac output and total peripheral vascular resistance (the hallmark hemodynamic abnormality)

- Multifactorial and highly complex
- complex interaction between a genetic background, a large number of environmental factors and the aging process.
- Alterations of the RAAS, central and peripheral autonomic cardiac and vascular regulation, the endothelin system and other systems controlling vascular function, including nitric oxide and natriuretic peptides

- More than 70 years research
- More than 1000 genetic factors being identified
- New environmental factors (e.g. air pollution and noise)
- Pressogenic effects (increased sodium sensitivity) of gut microbial dysbiosis
- The immune system is likely to play a pathophysiologic role, primarily mediated by inflammation
- Essential hypertension progresses from occasional to established hypertension

Mosaic theory



2023 ESH Guidelines for the management of arterial hypertension,

Two factors that affect BP directly

vasodilation capacity

- Affected by vascular elasticity, caliber, and reactivity
- reflects the buffering capacity of vessels against pressure shocks
- Poorer the vasodilatation capacity, higher the BP

volume of intravascular fluid

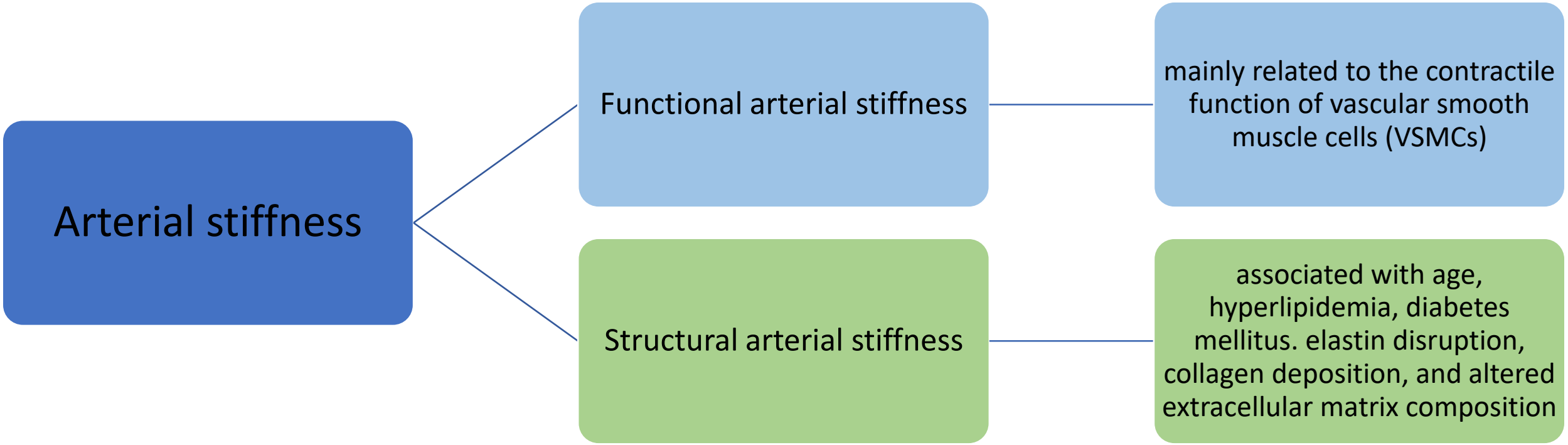
- Regulated by the body's intake and elimination of fluid
- Increase in the amount of intravascular fluid can directly result in an increase in BP

Arterial stiffness

Arterial stiffness

Essential HTN (ISH)

- Reduction in elasticity and distensibility of arteries
- pulse wave velocity (PWV): the degree of stiffness in large arteries
- An increase in PWV indicates severe arterial stiffness and impaired in arterial dilatation capacity



- Unlike functional arterial stiffness, there is no effective treatment for structural arterial stiffness yet
- The phenotypic transition of VSMCs directly affects the structural arterial stiffness.
- Six phenotypes of VSMCs : contractile phenotype is rich in a-smooth muscle actin (a-SMA) and has the strongest contractile function.
- Switch from contractile to other phenotypes (such as macrophage-like phenotype), the contractile function of the cells decreases significantly

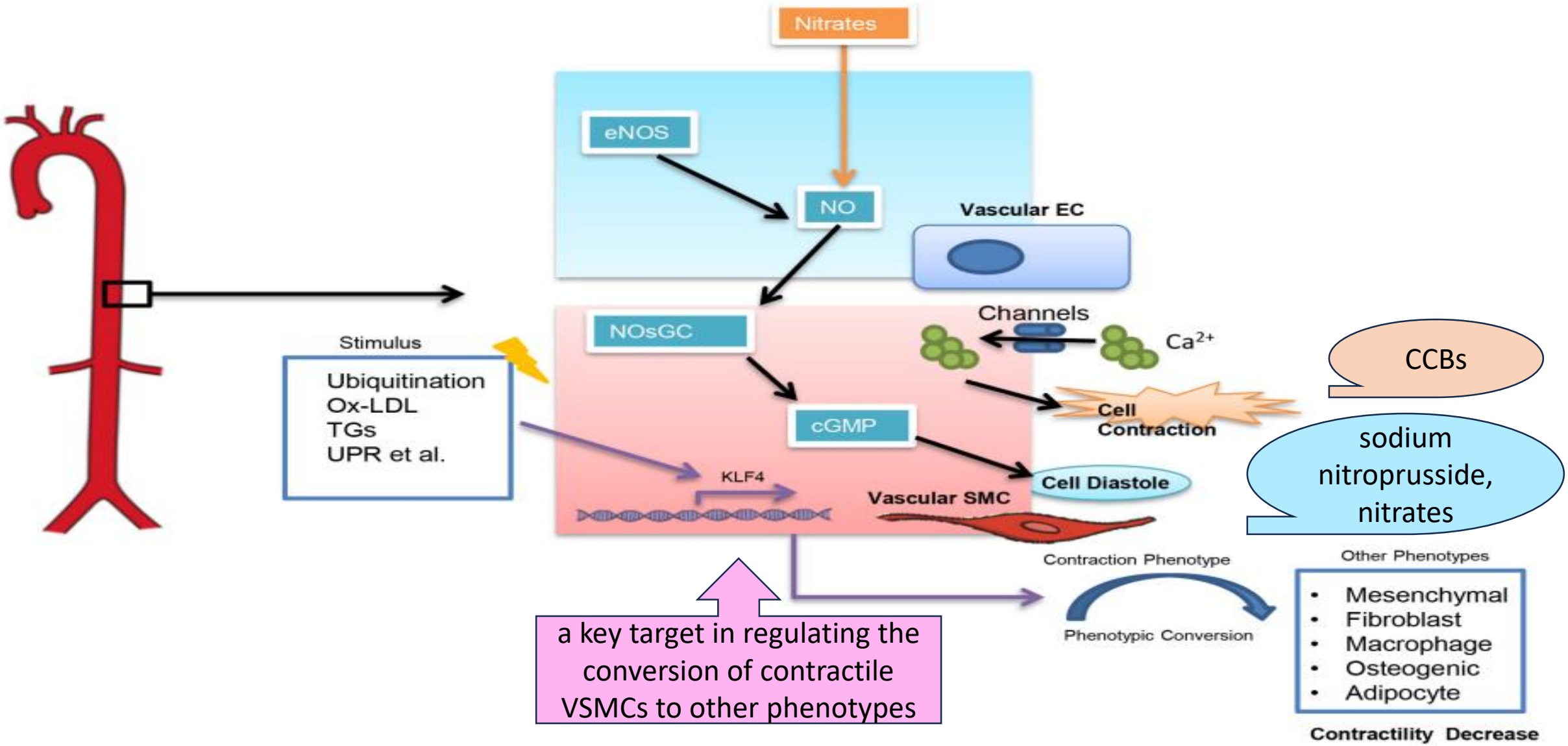
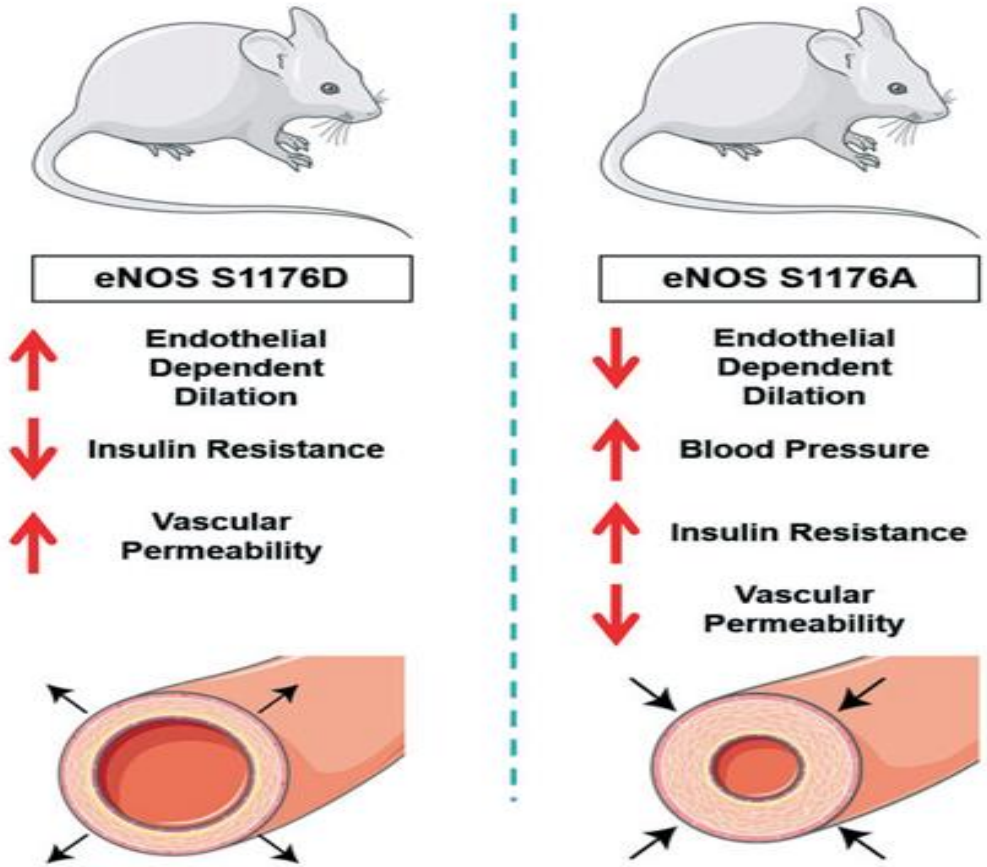


FIGURE 1
Factors influencing the contractile function of smooth muscle cells. Ox-LDL, Oxidized low-density lipoprotein; TGs, Triglycerides; UPR, unfolded protein response; KLF4, Krüppel-Like Factor 4.

nitric oxide-sensitive guanylate cyclase (NOsGC)-

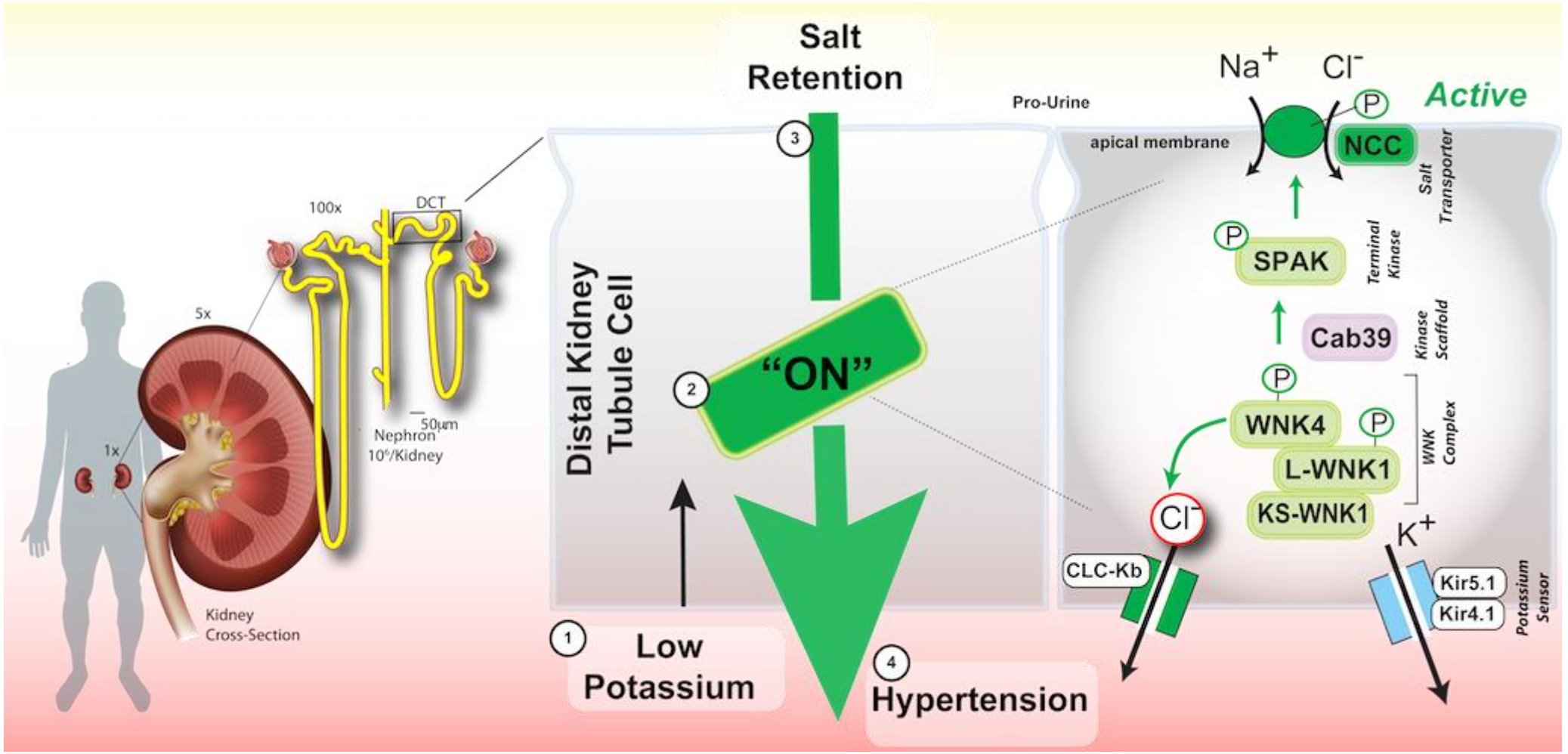

eNOS S1176D
Endothelial Dependent Dilation
Insulin Resistance
Vascular Permeability
eNOS S1176A
Endothelial Dependent Dilation
Blood Pressure
Insulin Resistance
Vascular Permeability

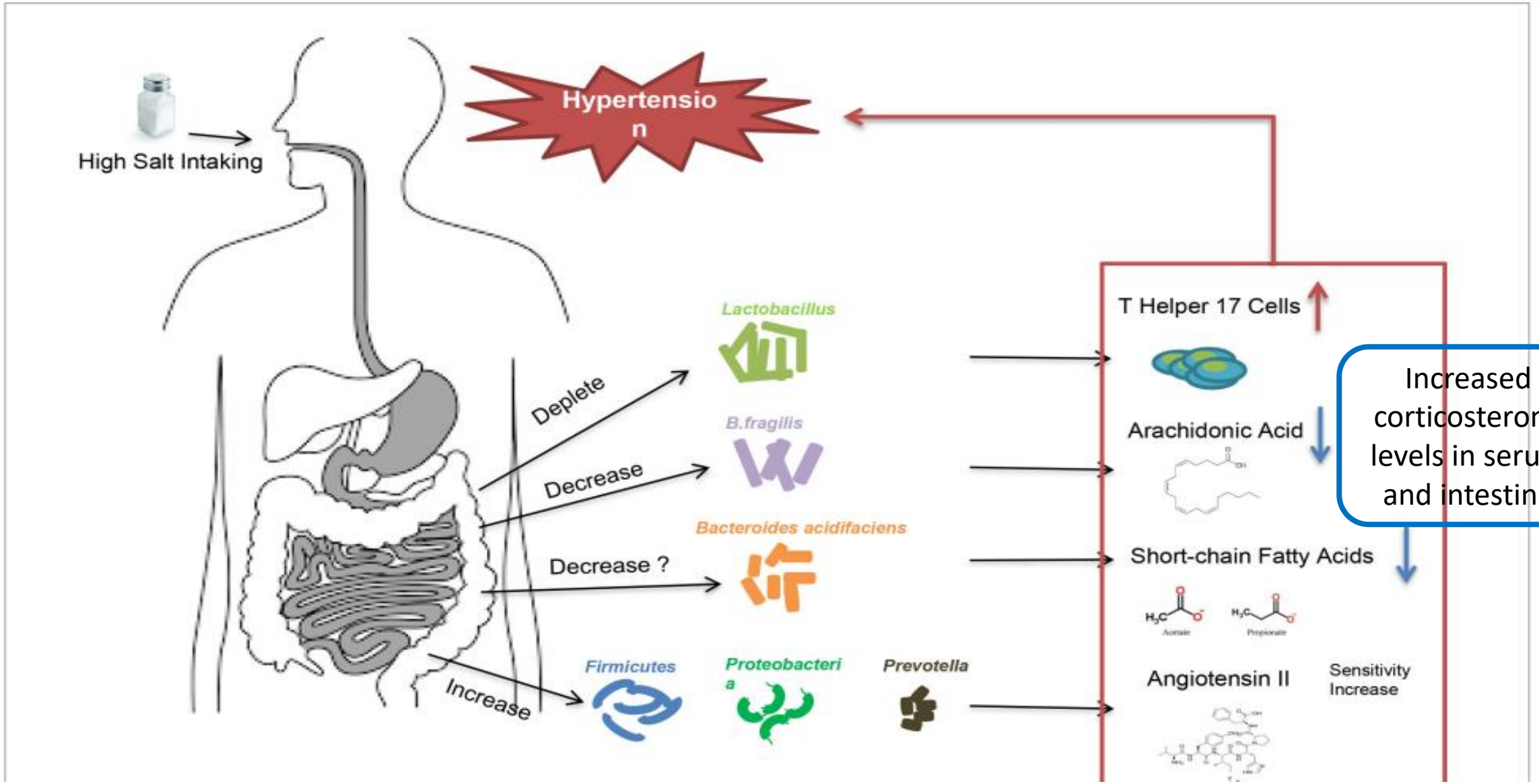
Water-sodium retention and salt-sensitive

Water-sodium retention is a key cause of abnormal increases in intravascular fluid volume (both kidney dysfunction and Essential HTN)	Salt sensitive HTN
	Salt resistant HTN

Multiple factors may contribute to the development of salt-sensitive hypertension, including age, obesity, genetic background, and maternal conditions during fetal life

Potassium Switch theory





Intestinal flora is closely associated with salt sensitive hypertension

- The role of intestinal flora in human was extremely complex
- The intestinal flora is not only involved in salt sensitivity, it also participate in other underlying mechanisms of hypertension including RAAS, vascular endothelium, and renal dysfunction
- Intestinal flora also has the potential to be an independent mechanism of essential hypertension.

Dietary sodium reduction (Excessive sodium intake: an increase in circulating fluid)

+

Dietary potassium supplementation (potassium intake has a diuretic effect)

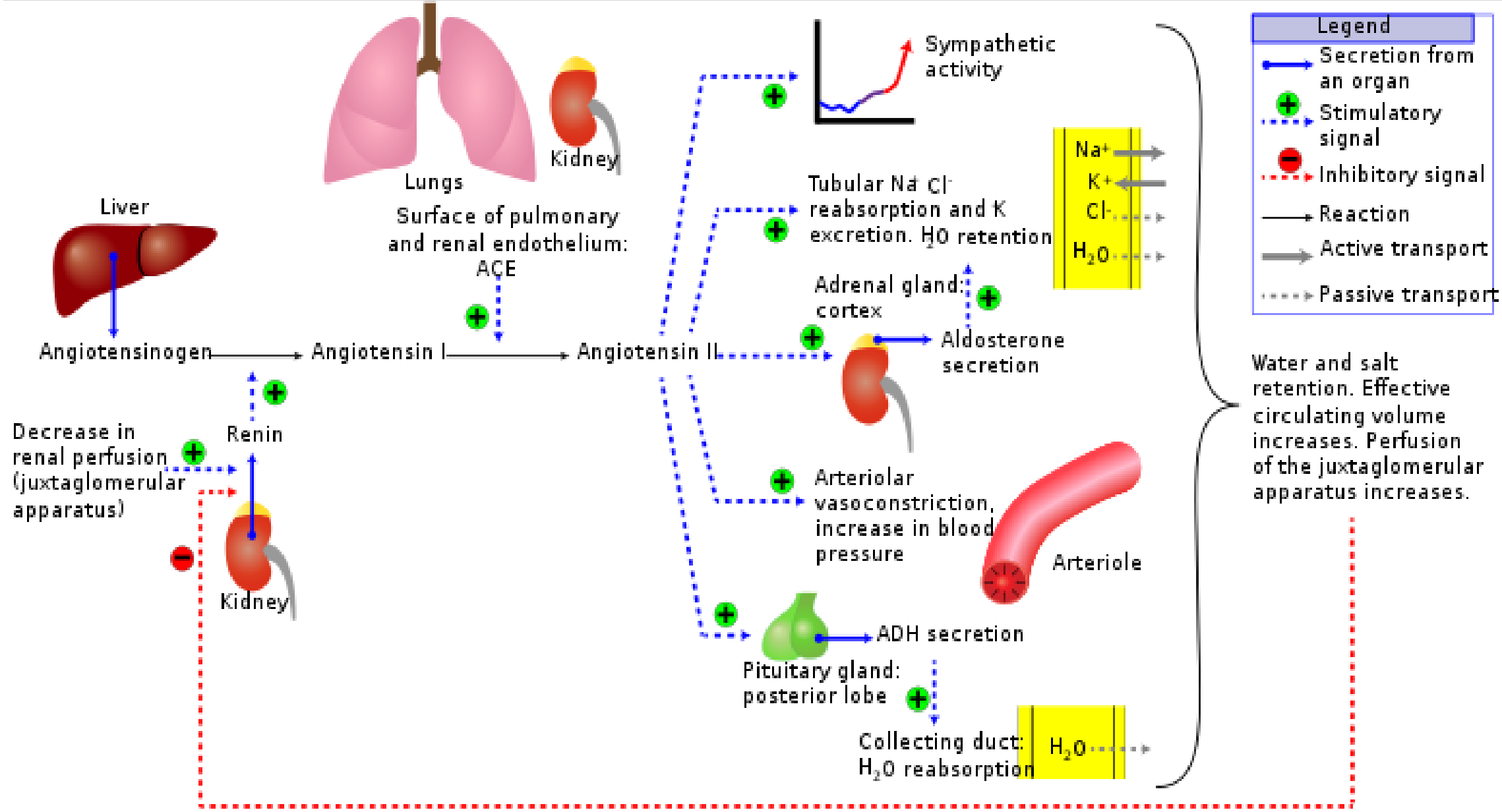
increased risk of cardiovascular disease

Salt substitution reduces sodium chloride and increases potassium chloride, thus exerting its antihypertension effects:

- sodium chloride and potassium chloride
- magnesium sulfate in addition to sodium chloride and potassium chloride

both types of salt substitution not only lower BP but also reduce cardiovascular events in patients

Renin–angiotensin–aldosterone system



- Both circulating RAAS and tissue RAAS (cardiac RAAS, vascular RAAS, intra-renal RAAS, brain RAAS and adipose tissue RAAS) have been involved in the pathogenesis of essential hypertension and related target organ damage
- RAAS including angiotensinogen, renin, angiotensin converting enzyme, angiotensins with various subtypes (Ang I, Ang II, Ang III, Ang IV, Ang 1-7), aldosterone and aldosterone receptors
- ACEi, ARBs, Angiotensin receptor-neprilysin inhibitor (ARNI), MRAs
- Hypertension vaccines (since 30 years ago):
- Renin vaccines are the first vaccines developed, causing autoimmune diseases
- other vaccines targeting Ang I, Ang II, AT1R: lowered BP without significant side effects: CYT006-AngQb, an Ang II Vaccine, clinical phase II
- non-RAAS-targeted vaccine, short peptide ADR004 (cgiteeagy), α1D-adrenoceptor (α1D-AR), lowered BP, target organ protection

Sympathetic dysregulation

- An important cause of essential hypertension
- Increased cardiac output, increased systemic vascular tone, and elevated plasma catecholamine levels
- Patients with hypertension: greater muscle sympathetic nerve activity (MSNA) and lower baroreflex response
- MSNA plays a significant role in determining total peripheral resistance and vasoconstrictive function by controlling skeletal muscle
- Sympathetic hypertension varies widely among individuals :associated with circadian patterns and mental status

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Journal of Human Hypertension

ARTICLE OPEN

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Sympathetic-transduction in untreated hypertension

Matthew D. Kobetic[1], Amy E. Burchell[2], Laura E. K. Ratcliffe[3], Sandra Neumann[1,2], Zoe H. Adams[1,2], Regina Nolan[2], Angus K. Nightingale[1,2], Julian F. R. Paton[1,2] and Emma C. Hart[1,2]✉

Transduction of muscle sympathetic nerve activity (MSNA) into vascular tone varies with age and sex. Older normotensive men have reduced sympathetic transduction so that a given level of MSNA causes less arteriole vasoconstriction. Whether sympathetic transduction is altered in hypertension (HTN) is not known. We investigated whether sympathetic transduction is impaired in untreated hypertensive men compared to normotensive controls. Eight untreated hypertensive men and 10 normotensive men (age 50 ± 15 years vs. 45 ± 12 years (mean ± SD); $p = 0.19$, body mass index (BMI) 24.7 ± 2.7 kg/m^2 vs. 26.0 ± 4.2 kg/m^2; $p = 0.21$) were recruited. MSNA was recorded from the peroneal nerve using microneurography; beat-to-beat blood pressure (BP; Finapres) and heart rate (ECG) were recorded simultaneously at rest for 10 min. Sympathetic-transduction was quantified using a previously described method. The relationship between MSNA burst area and subsequent diastolic BP was measured for each participant with the slope of the regression indicating sympathetic transduction. MSNA was higher in the hypertensive group compared to normotensives (73 ± 17 bursts/100 heartbeats vs. 49 ± 19 bursts/100 heart bursts; $p = 0.007$). Sympathetic-transduction was lower in the hypertensive versus normotensive group (0.04%/mmHg/s vs. 0.11%/mmHg/s, respectively; $R = 0.622$; $p = 0.006$). In summary, hypertensive men had lower sympathetic transduction compared to normotensive individuals suggesting that higher levels of MSNA are needed to cause the same level of vasoconstrictor tone.

Journal of Human Hypertension (2022) 36:24–31; https://doi.org/10.1038/s41371-021-00578-5

- The manifestations of BP changes in sympathetic hypertension (all be associated with autonomic dysregulation): morning hypertension, nocturnal hypertension, sleep apnea–related hypertension, orthostatic hypertension, resistant hypertension
- Sympathetic overdrive: promotes hypertension-related target organ damage, such as left ventricular hypertrophy and dysfunction, congestive heart failure, renal insufficiency
- Exercise is an important way of controlling sympathetic hypertension: high-intensity interval training can reduce BP by reducing MSNA
- Renal denervation (RDN), Abrogation of renal sensory afferent nerves: a potential treatment for resistant hypertension caused by sympathetic dysregulation.

Genetics

- More than 500 loci involved in the regulation of BP by GWAS, taking the total number of BP genetic loci to over 1,000.
- single nucleotide polymorphism (SNPs) provide a potential pathogenic mechanism for essential hypertension
- In a recent study: multiple SNP analyzed as a polygenic risk score (PRS) was predictive of early-onset hypertension in a progressive fashion, those with the highest of 2.5% of PRS had an almost 3-fold risk of developing hypertension, whereas a low PRS was protective
- Proper use of SNPs may provide potential ways to diagnose and treatment of hypertension.

Polygenic Risk Scores Predict Hypertension Onset and Cardiovascular Risk

Felix Vaura, Anni Kauko, Karri Suvila, Aki S. Havulinna, Nina Mars, Veikko Salomaa, FinnGen, Susan Cheng, Teemu Niiranen

ABSTRACT: Although genetic risk scores have been used to predict hypertension, their utility in the clinical setting remains uncertain. Our study comprised N=218 792 FinnGen participants (mean age 58 years, 56% women) and N=22 624 well-phenotyped FINRISK participants (mean age 50 years, 53% women). We used public genome-wide association data to compute polygenic risk scores (PRSs) for systolic and diastolic blood pressure (BP). Using time-to-event analysis, we then assessed (1) the association of BP PRSs with hypertension and cardiovascular disease (CVD) in FinnGen and (2) the improvement in model discrimination when combining BP PRSs with the validated 4- and 10-year clinical risk scores for hypertension and CVD in FINRISK. In FinnGen, compared with having a 20 to 80 percentile range PRS, a PRS in the highest 2.5% conferred 2.3-fold (95% CI, 2.2–2.4) risk of hypertension and 10.6 years (95% CI, 9.9–11.4) earlier hypertension onset. In subgroup analyses, this risk was only 1.6-fold (95% CI, 1.5–1.7) for late-onset hypertension (age ≥55 years) but 2.8-fold (95% CI, 2.6–2.9) for early-onset hypertension (age <55 years). Elevated systolic BP PRS also conferred 1.3-fold (95% CI, 1.2–1.4) risk of CVD and 2.3 years (95% CI, 1.6–3.1) earlier onset. In FINRISK, systolic and diastolic BP PRSs improved clinical risk prediction of hypertension (but not CVD), increasing the C statistics by 0.7% (95% CI, 0.3–1.1). We demonstrate that genetic information improves hypertension risk prediction. BP PRSs together with traditional risk factors could improve prediction of hypertension and particularly early-onset hypertension, which confers substantial CVD risk.
(*Hypertension*. 2021;77:1119-1127. DOI: 10.1161/HYPERTENSIONAHA.120.16471.) • **Data Supplement**

Epigenetics

- Genetics alone is not sufficient to explain the variability in BP
- Potential contribution of epigenetic mechanisms in essential hypertension.
- Genome-wide DNA methylation has been associated with susceptibility to hypertension in human.
- RNA methylation may also contribute to essential hypertension
- Other epigenetic modifications, including post-translational histone modifications, non-coding RNA

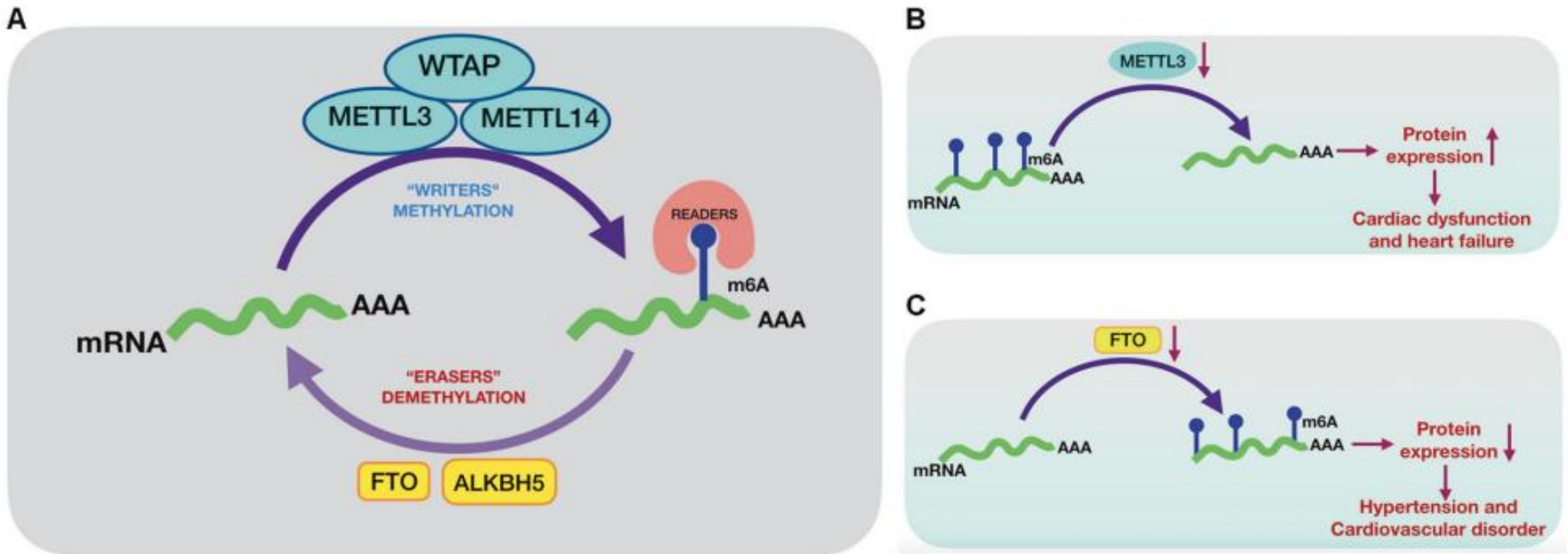


Fig. 1 **a** N6-methyladenosine (m6A) the most prevalent modification in mRNAs, which regulated by writers, erasers, and readers and plays a broad role in RNA processing. **b** The decreased m6A mRNA methylation in cardiomyocytes caused by the decreased METTL3 expression associated with cardiac dysfunction and heart failure. **c** The increased m6A mRNA methylation in cardiomyocytes caused by decreased FTO expression and FTO gene mutations associated with hypertension and cardiovascular diseases

N6-adenosine methylation (m6A): a promising new molecular target in hypertension and cardiovascular diseases. Hypertension Research https://doi.org/10.1038/s41440-019-0338-z

Interactions between the pathogenesis of hypertension

- Mosaic Theory: explain the pathogenesis of hypertension, in which hypertension is considered as a response to different combinations of traits and stressors.
- In addition to vascular function, salt intake, sympathetic activation, genetics, microbiome, and renal mechanisms, the new Mosaic Theory also highlights inflammation and oxidative stress

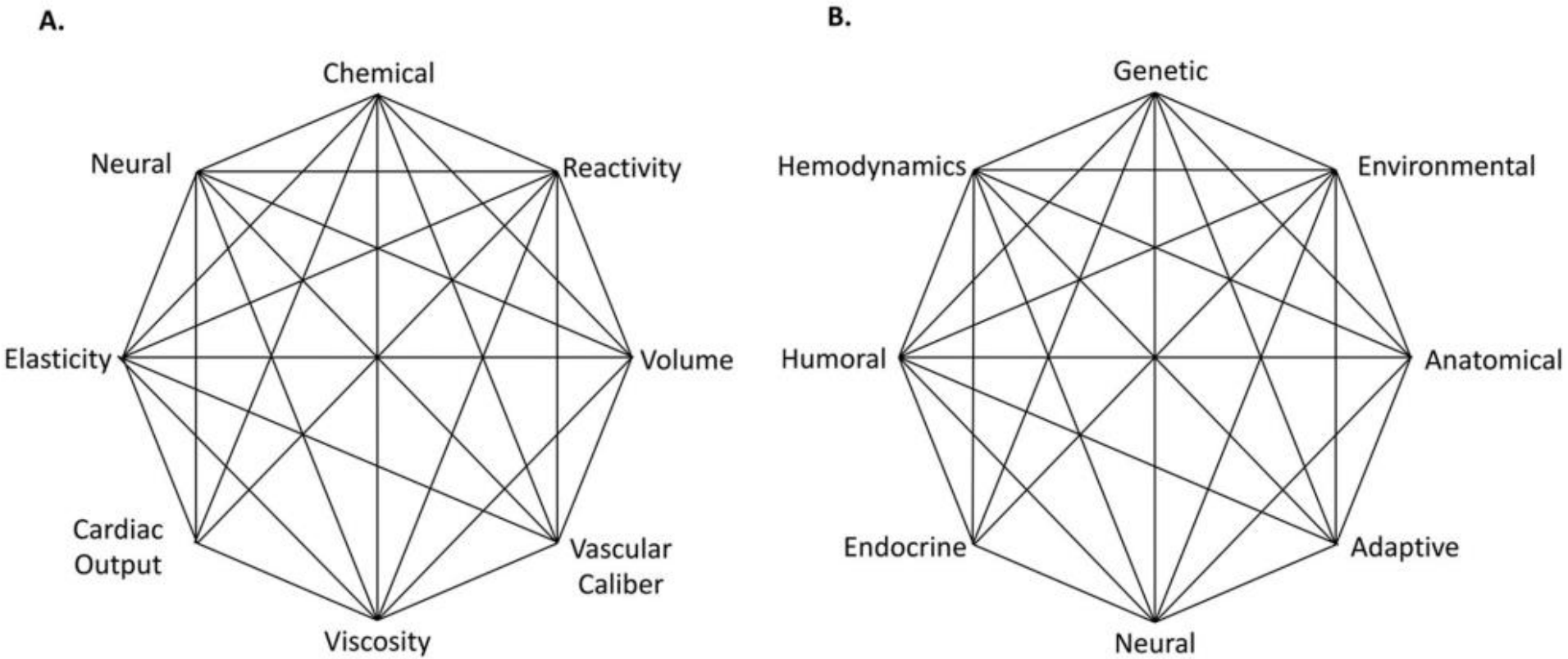


Figure 1:
The original (A) and revised (B) Mosaic Theories proposed by Page.

Circ Res. 2021 April 02; 128(7): 847–863. doi:10.1161/CIRCRESAHA.121.318082.

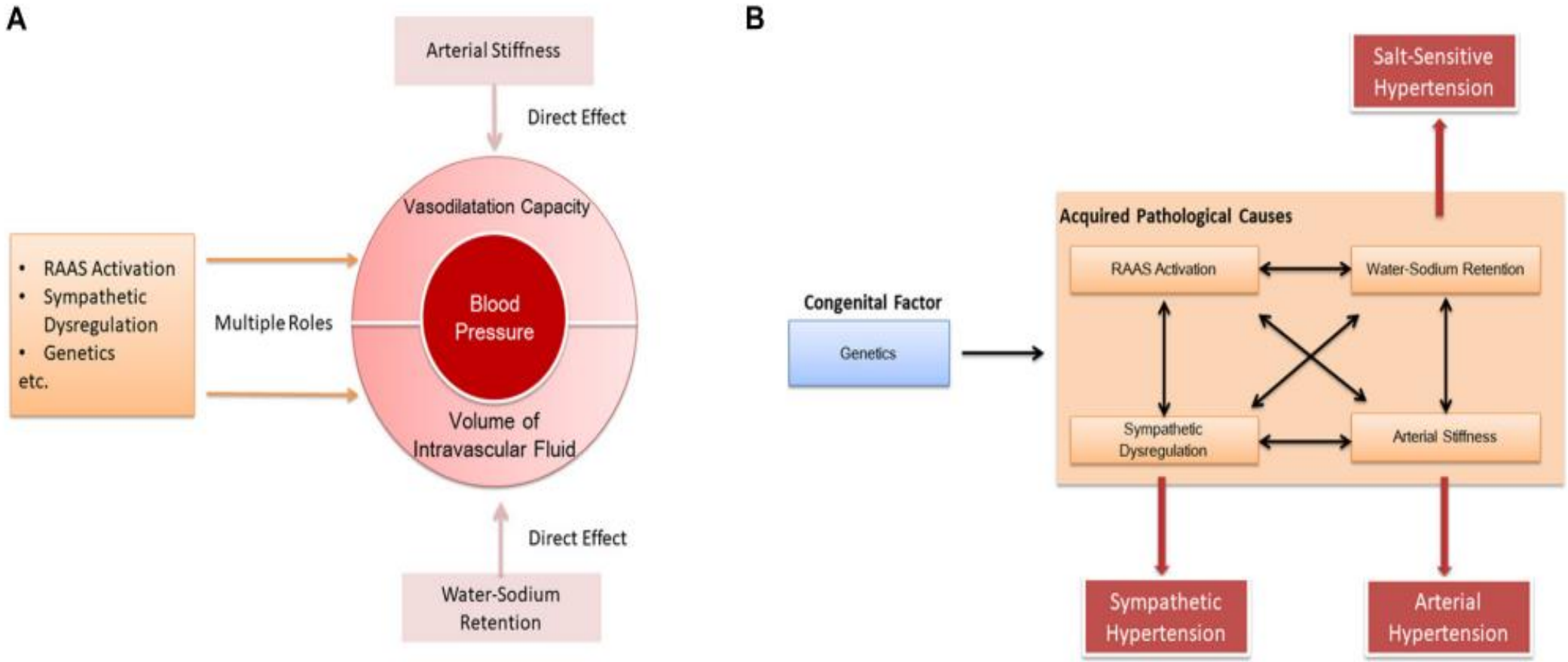
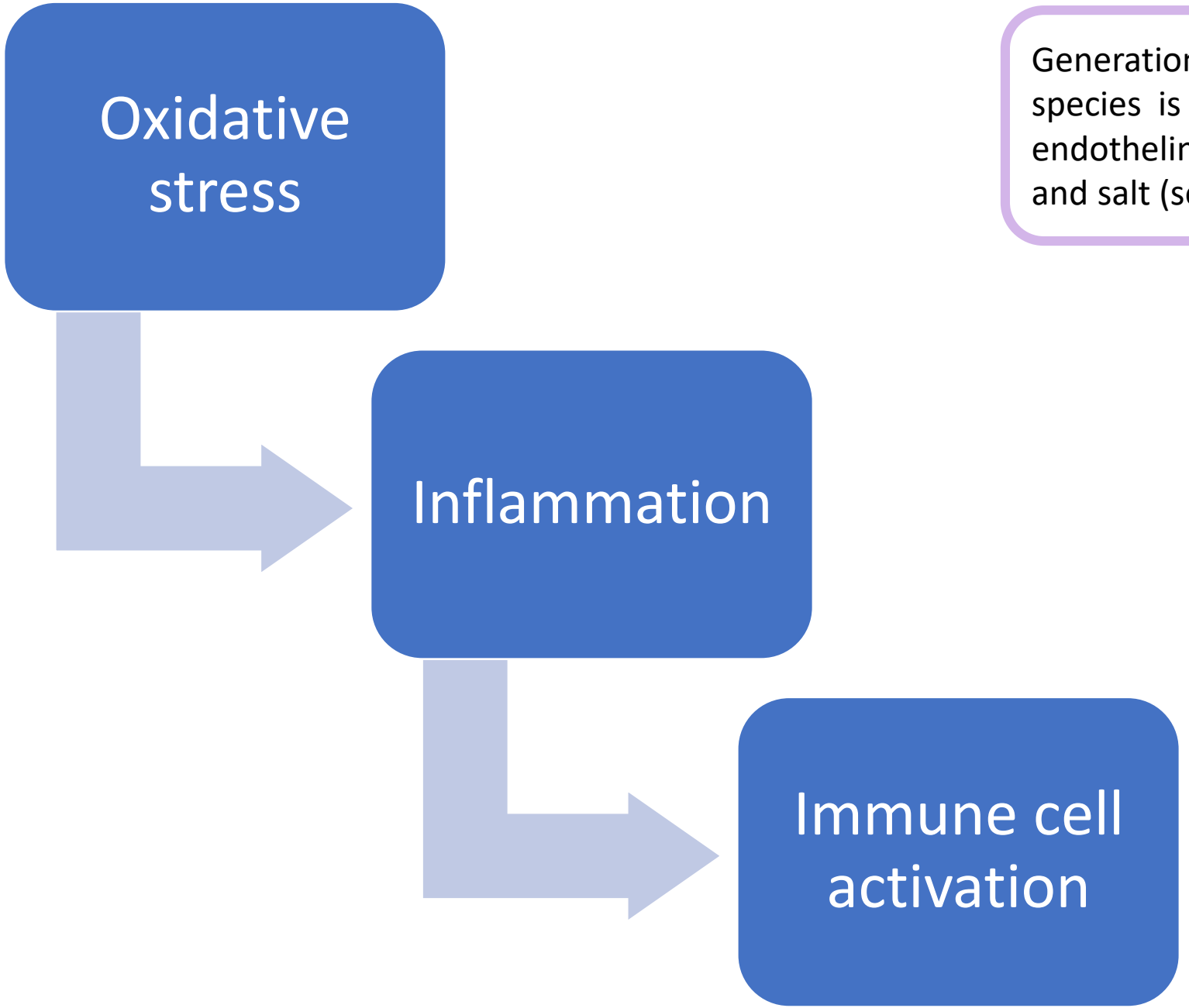


FIGURE 3
Interaction between the pathogenesis of hypertension. **(A)** Causes of elevated blood pressure by different pathogenesis. **(B)** Interaction between pathogenic mechanisms.



Generation of reactive oxygen species is influenced by Ang II, endothelin-1 (ET-1), aldosterone and salt (sodium)

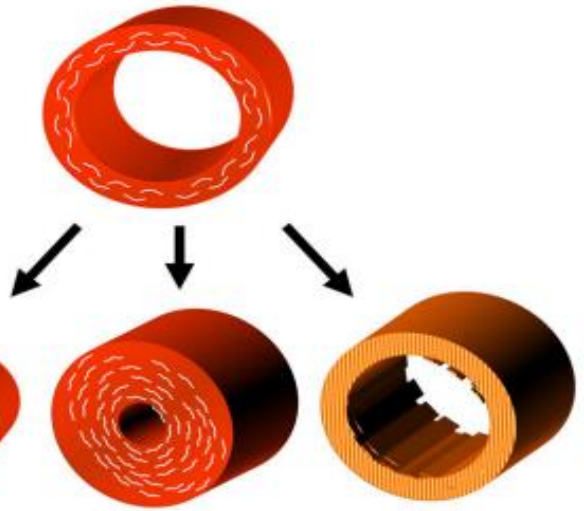
- Characterized by excessive production of reactive oxygen species and an altered oxidation–reduction (redox) state

- Immunoinflammation is promoted by genetic susceptibility, neurohumoral activation, salt influences, and gut microbiome
- Inflammation and the dysregulated immune system are closely linked to each other and that immunoinflammation is involved in hypertension
- Oxidative stress and increased generation of reactive oxygen species represent the common molecular basis linking immunoinflammation to hypertension,

A.

Increased sodium retention/
Altered pressure natriuresis
Increased renin release
ROS induced ADMA production
Enhanced renal afferent nerve traffic
Immune activation

B.



Altered
Vasomotor Tone

Remodeling/VSM
Hypertrophy

Vascular Stiffening/
Fibrosis

Enhanced vasoconstrictor activity
due to altered GPCR activation
Reduced NO bioavailability
Loss of myoendothelial junctions
Increased stretch/endothelial
activation leading to immune
activation and pro-thrombosis

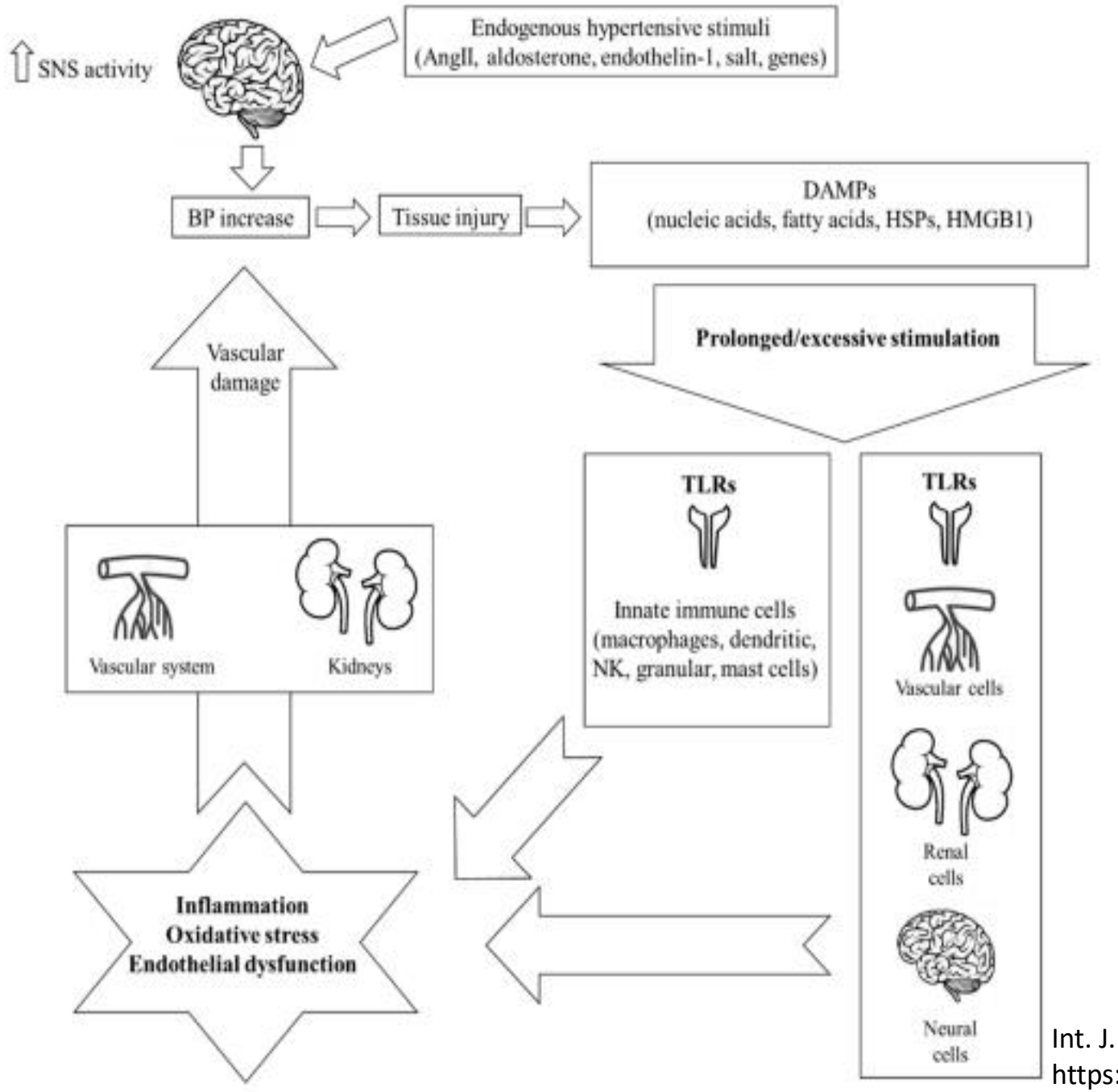
C.

Enhanced sympathetic outflow
Vasoconstriction
Increased sodium retention
Increased Renin release from JG cells
Immune activation
Altered vagal activity and defective immune reflex

Figure 2:
Perturbations of the kidney (A), vasculature (B) and central nervous system (C) contributing to hypertension.

Circ Res. 2021 April 02; 128(7): 847–863.doi:10.1161/CIRCRESAHA.121.318082.

Toll like receptor and innate immunity



Int. J. Mol. Sci. 2021, 22, 3451. https://doi.org/10.3390/ijms22073451

British Journal of Pharmacology

Themed Section: Immune Targets in Hypertension

British Journal of Pharmacology (2019) **176** 1829–1838 1829

REVIEW ARTICLE

The role of autoimmune reactivity induced by heat shock protein 70 in the pathogenesis of essential hypertension

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Received 29 January 2018; **Revised** 26 March 2018; **Accepted** 28 March 2018

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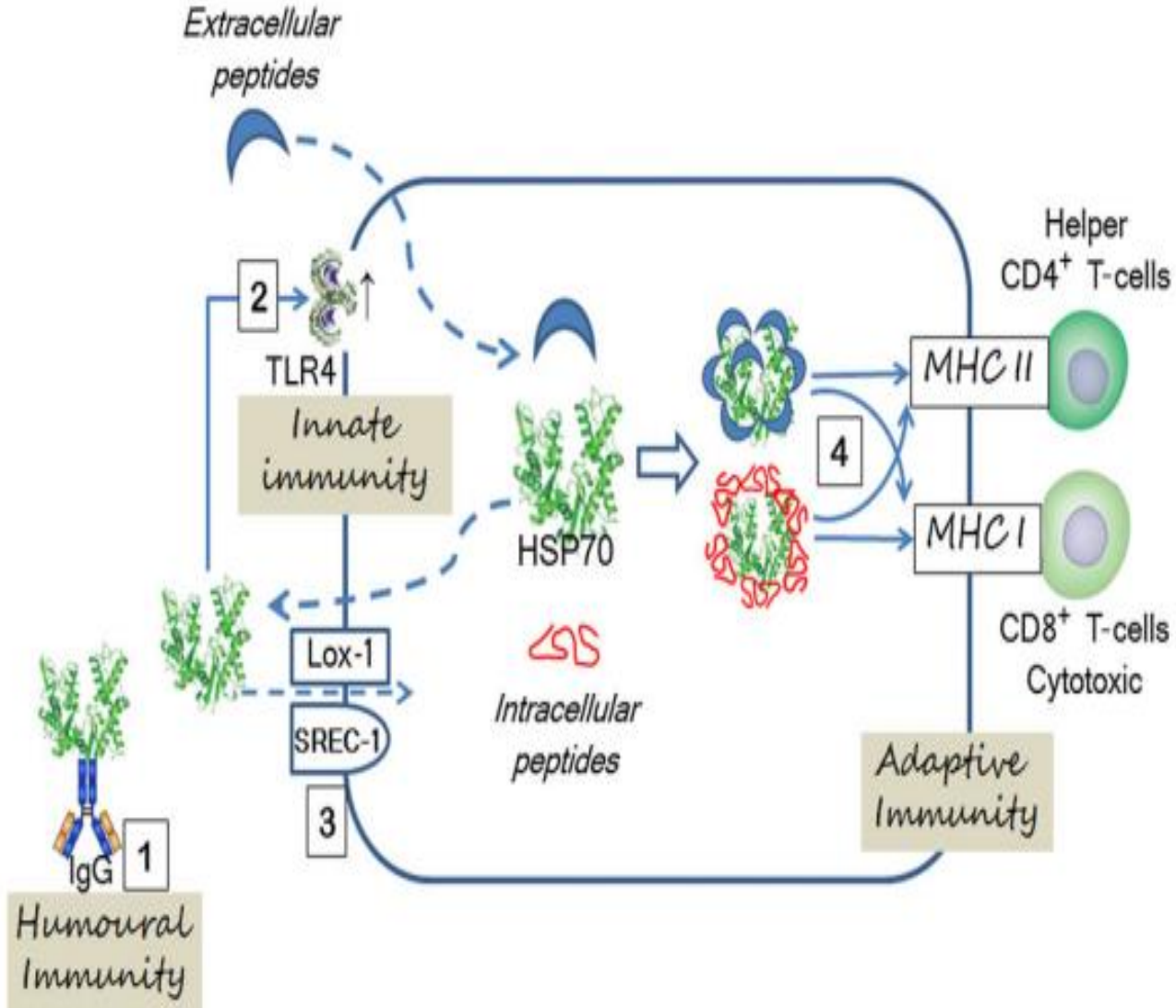
Autoimmunity is increasingly recognized as having a central role in essential hypertension. Heat shock proteins (HSPs) are immunodominant molecules with high interspecies homology and autoimmune reactivity directed against HSP70 may play a role in the pathogenesis of hypertension. Autoimmunity to HSP70 may result from molecular mimicry between human HSP and bacterial HSP or, alternatively, as a response to HSP70–peptide complexes generated during cellular stress and delivered to the major histocompatibility complex by antigen-presenting cells. HSP70 is increased in the circulation and kidney of hypertensive patients, and genetic polymorphisms of HSP70 are associated with essential hypertension. Depending on the route and conditions of administration, HSP70 may induce or suppress immune-related inflammation. Renal inflammation induced by immunity to HSP70 causes hypertension in laboratory animals, and administration of specific peptide sequences of HSP70 results in a protective anti-inflammatory response that prevents and corrects salt-induced hypertension. Potential therapeutic uses of HSP70 in essential hypertension deserve to be investigated.


Extracellular peptides
2
TLR4
Innate immunity
HSP70
Helper CD4+ T-cells
MHC II
4
MHC I
CD8+ T-cells Cytotoxic
Lox-1
SREC-1
3
Intracellular peptides
Adaptive Immunity
IgG
1
Humoural Immunity

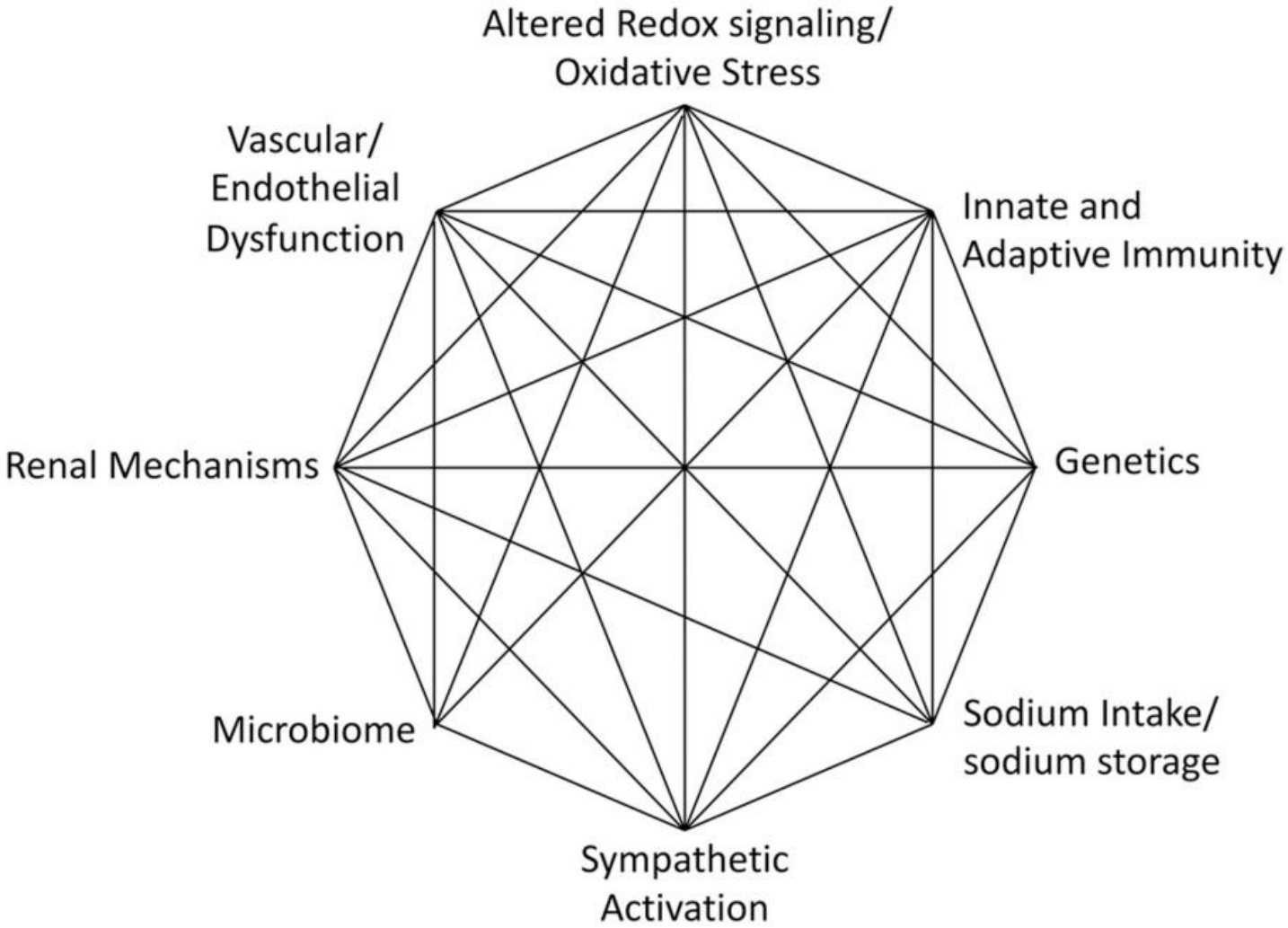


Figure 3:
A revised Mosaic Theory incorporating new understanding of cellular, environmental and genetic mechanisms.

Circ Res. 2021 April 02; 128(7): 847–863. doi:10.1161/CIRCRESAHA.121.318082.

Circulating biomarkers

- Biomarkers for patient classification, risk stratification and monitoring of response to therapy is an important integral component of diseases diagnosis and treatment
- Several novel measurable circulating biomarkers have been identified
- Pentraxin 3 (PTX3) induced endothelial dysfunction and increased blood pressure
- Compared with normotensive subjects, hypertensive patients have higher plasma levels of PTX3 and its mediators P-selectin and matrix metalloproteinase-1 (MMP1, regulated by PTX3)
- Combination of PTX3, P-selectin and MMP-1 may be a novel biomarker for predicting the onset of vascular dysfunction in hypertensive patients

Sortilin, a member of the vacuolar protein sorting 10 (VPS10P) family of receptors: positively correlated with vascular and metabolic disorders

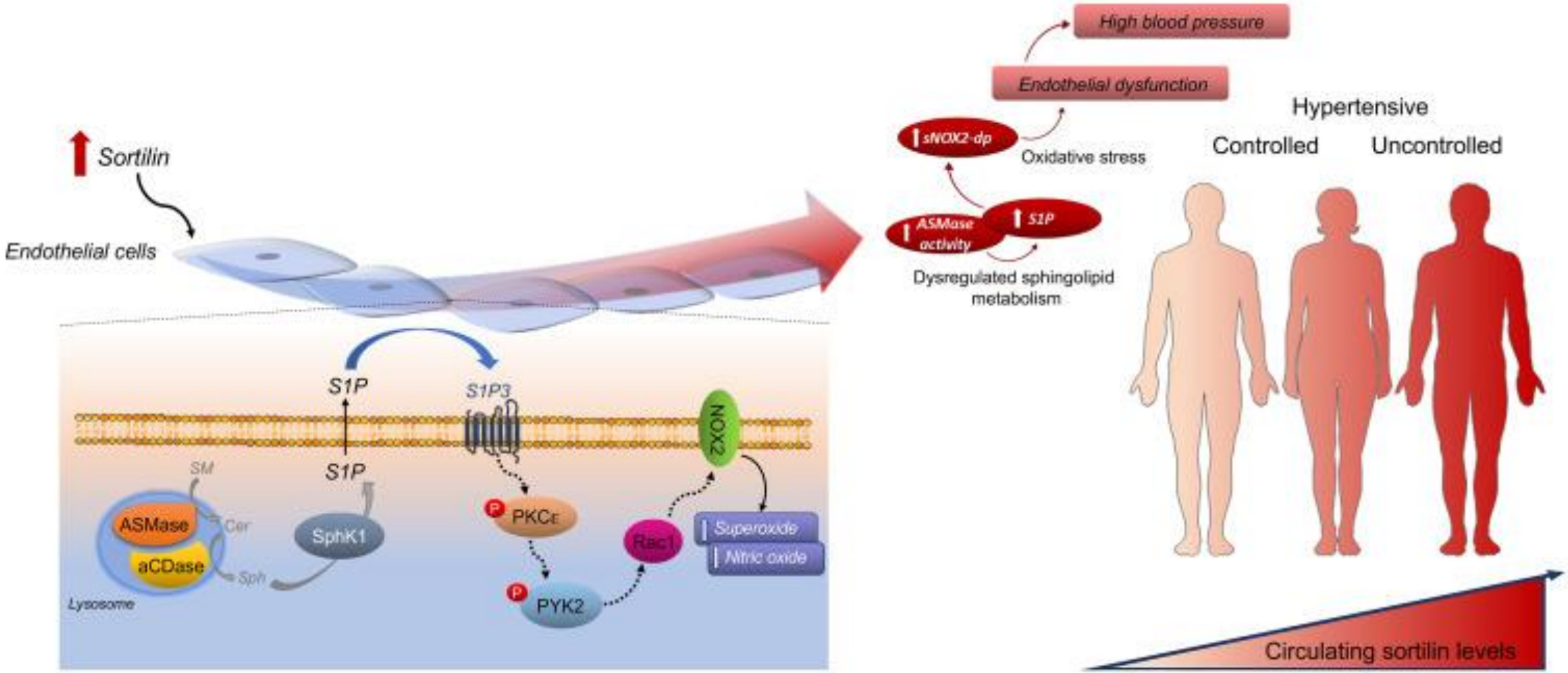
Sortilin: endothelial dysfunction of mesenteric arteries through NADPH oxidase 2 (NOX2) isoform activation

plasmacid sphingomyelinase (ASMase) or sphingosine kinase 1 activity and plasma levels of sortilin increased in hypertensive subjects, especially in those with uncontrolled blood pressure and resistant hypertension

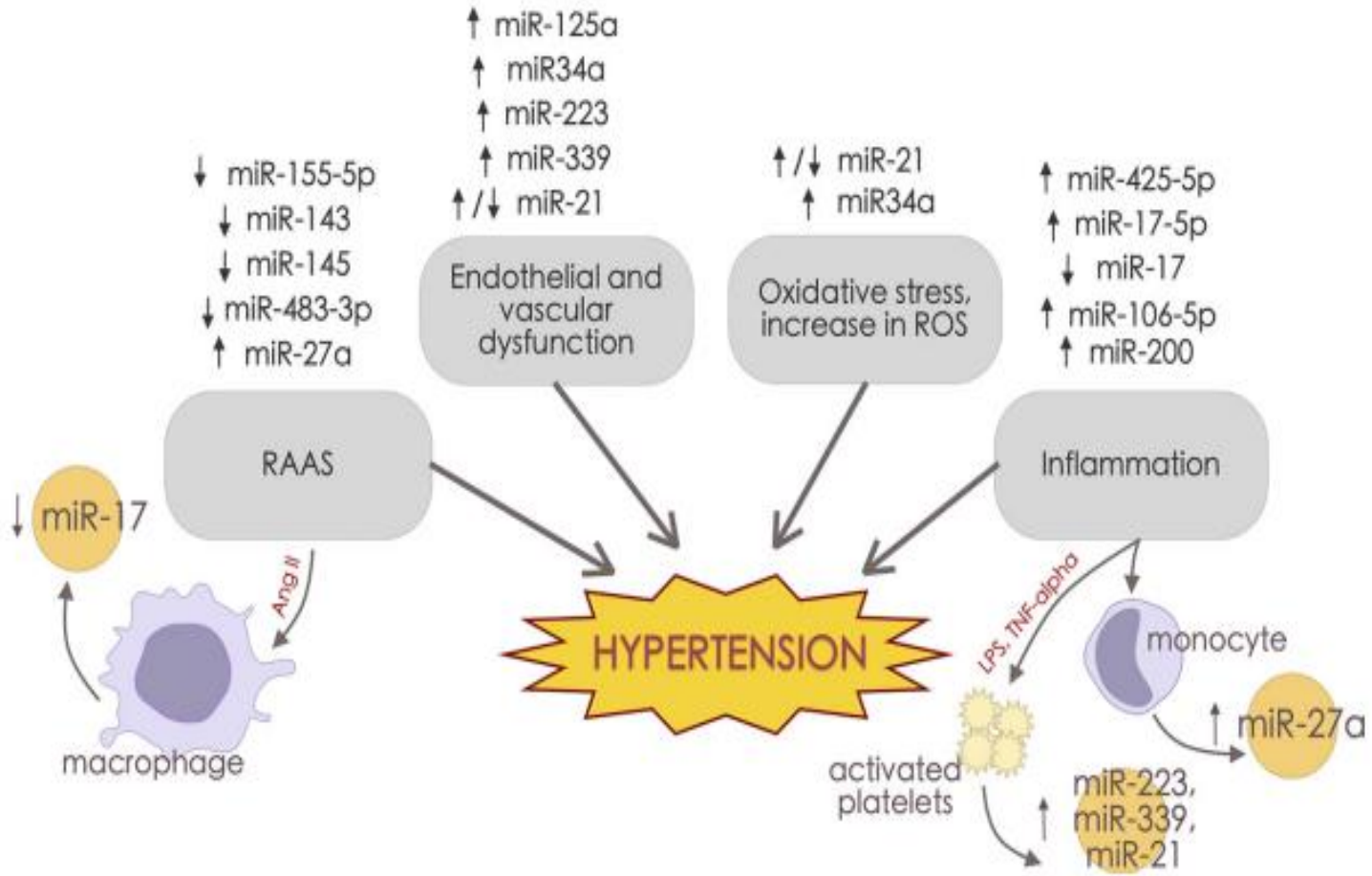
Some other biomarkers: Sphingosine-1-phosphate, bactericidal/permeability-increasing fold-containing family B member 4 (BPIFB4), klotho, exosomal microRNAs (such as miR-130a, miR-195.), and SUV420H1

These markers have the potential to classify essential hypertension due to biomarkers' specificity: PTX3 or Sortilin is related to vascular dysfunction, SUV420H1 is identified as a potential biomarker for the early diagnosis of salt-sensitive hypertension

provide guidance for targeted treatment of hypertension



Targeting the ASMase/S1P pathway protects from sortilin-evoked vascular damage in hypertension, Reference information: J Clin Invest. 2022;132(3):e146343. https://doi.org/10.1172/JCI146343



Am J Physiol Heart Circ Physiol 320: H1486–H1497, 2021. First published February 12, 2021; doi:10.1152/ajpheart.00888.2020

Awasthi *et al. Clinical Hypertension* (2023) 29:5
https://doi.org/10.1186/s40885-022-00229-y

Clinical Hypertension

REVIEW Open Access

Fok I and *Bsm I* gene polymorphism of vitamin D receptor and essential hypertension: a mechanistic link

Richa Awasthi[1], Priyanka Thapa Manger[1*] and Rajesh Kumar Khare[2]

Abstract

The vitamin D receptor (*VDR*) gene serves as a good candidate gene for susceptibility to essential hypertension. The gene regulates the renin angiotensin system by influencing blood pressure regulation. Around 3% of the human genome is regulated by the vitamin D endocrine system. Several studies have reported mixed results with respect to relationship of *VDR* gene and hypertension. Observational evidence supports the concept that vitamin D plays a role in the pathogenesis of cardiovascular disease and arterial hypertension which is further supported by meta-analysis and case control studies reporting how *VDR* polymorphism leads to the onset and development of hypertension. In this review, we summarize the existing literature on the link between VDR and hypertension, including mechanistic studies, observational data, and clinical trials showing relationship of vitamin D level and hypertension with a focus on recent findings related to genetic studies that showed the relationship of *VDR* gene polymorphism with vitamin D level in hypertensive and normotensive groups. As a result, determining the association of *VDR* polymorphisms with essential hypertension is expected to aid in the risk assessment for the condition.

Keywords: Essential hypertension, Renin angiotensin system, Single nucleotide polymorphism, Calcitriol receptors, Cyclic adenosine monophosphate

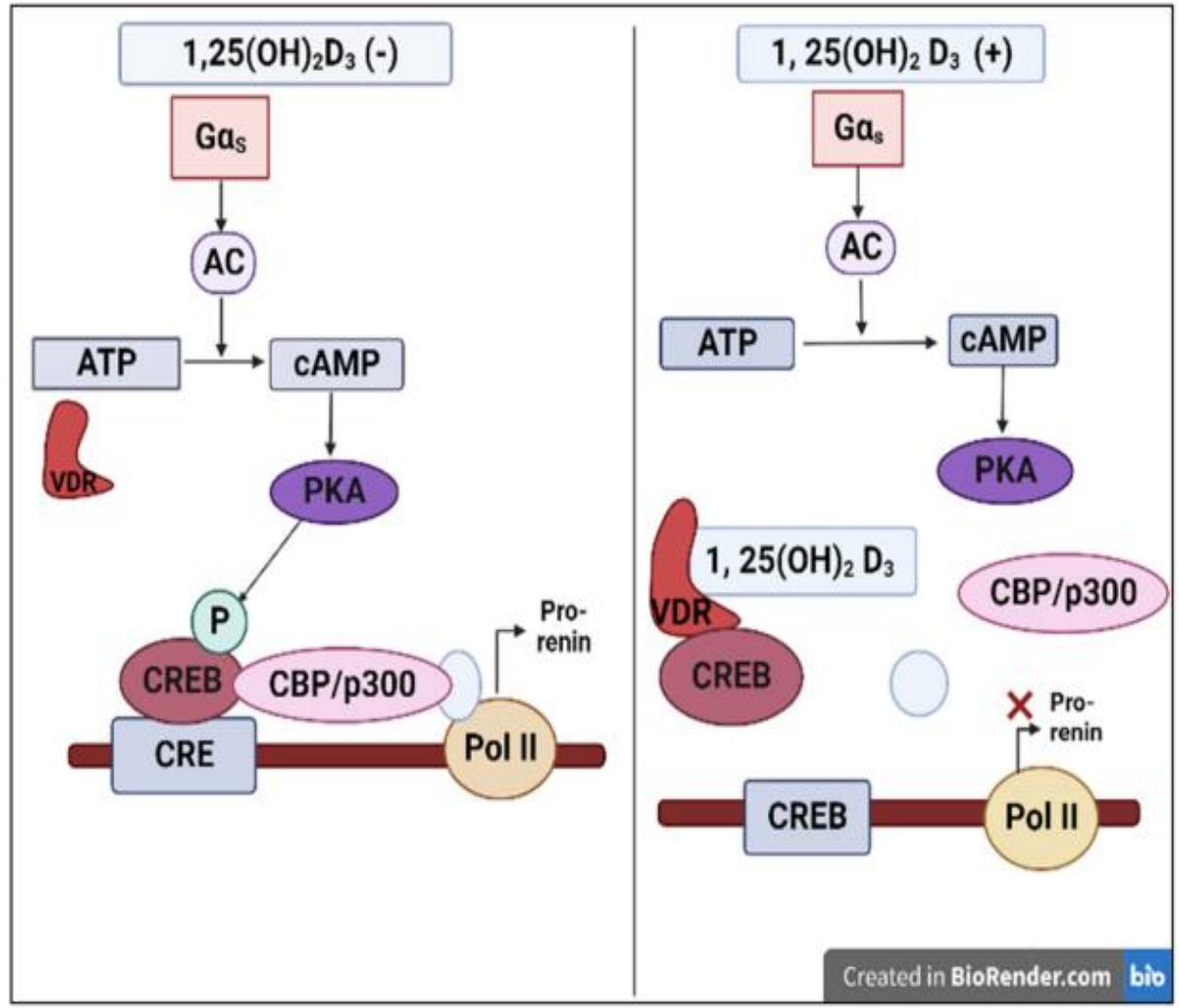


Fig. 2 Proposed mechanism for action of vitamin D on renin expression. $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D; $G\alpha_s$, G_s protein α subunit; AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; VDR, vitamin D receptor; PKA, protein kinase A; P, phosphate; CREB, cyclic adenosine monophosphate dependent response element binding protein; CRE, cyclic adenosine monophosphate response element; CBP, cyclic adenosine monophosphate binding protein; Pol, polymerase. Created with BioRender (Toronto, Canada; https://biorender.com/). Adapted from Legarth et al. [12] according to the Creative Commons Attribution License

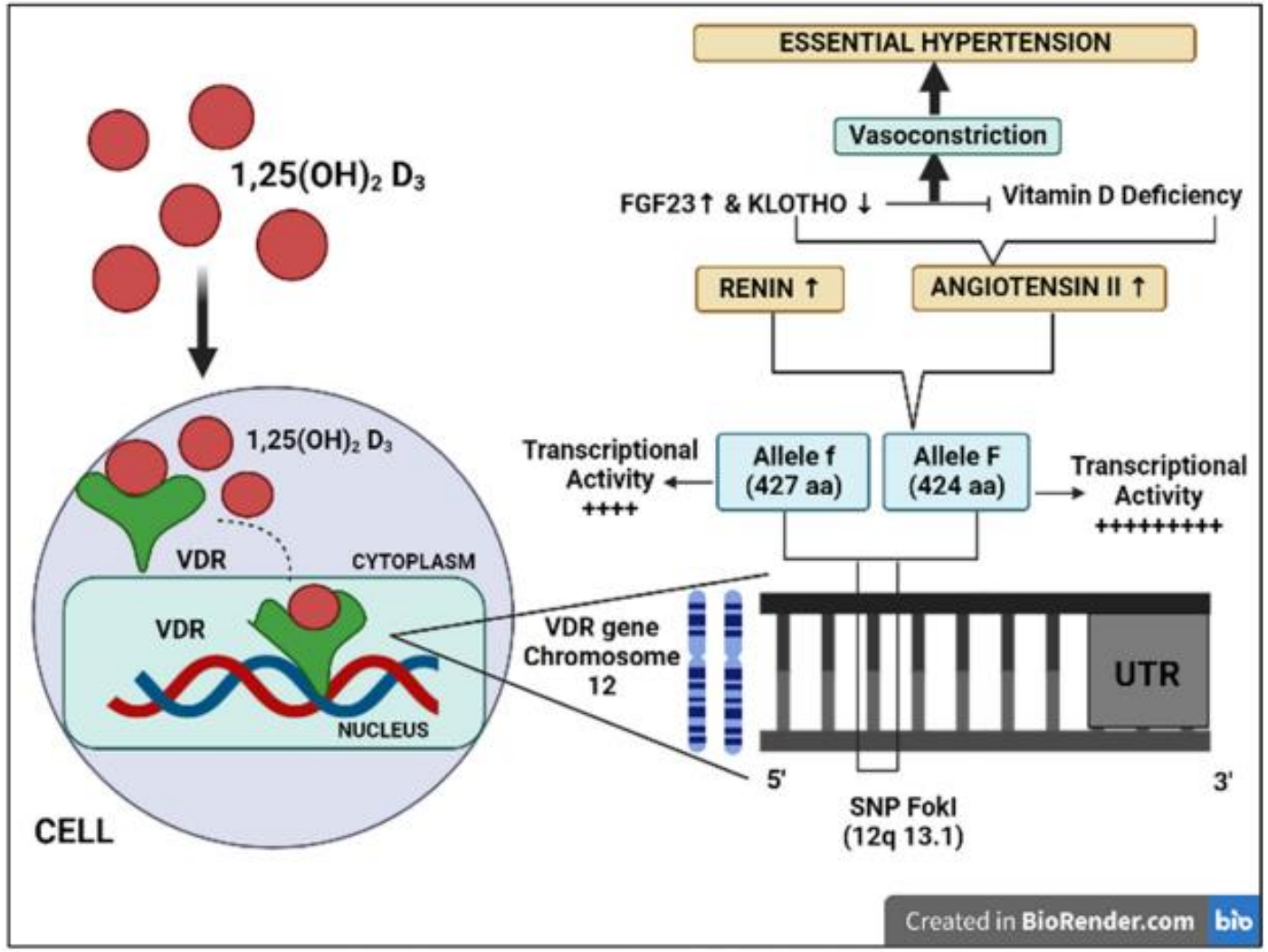


Fig. 4 Proposed mechanism of vitamin D receptor (VDR; *Fok I*) polymorphism in susceptibility to essential hypertension. $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D; SNP, single nucleotide polymorphism; UTR, untranslated region. Adapted from Nunes et al. [47] with permission from Oxford University Press

- To the original theory (70 years ago), modern research has added not only new mechanisms but also, strong evidence for the existence of reciprocal influences between different CV control systems, as a result of which alteration of one system may favor or reinforce alterations of the other systems and vice versa
- Combination of mechanistically different drugs lowers BP much more effectively than monotherapy
- Provide possibility to targeted therapy