Casual Friday Series

When Blood Pressure Boils Over

A Biogenetix Clinical Presentation

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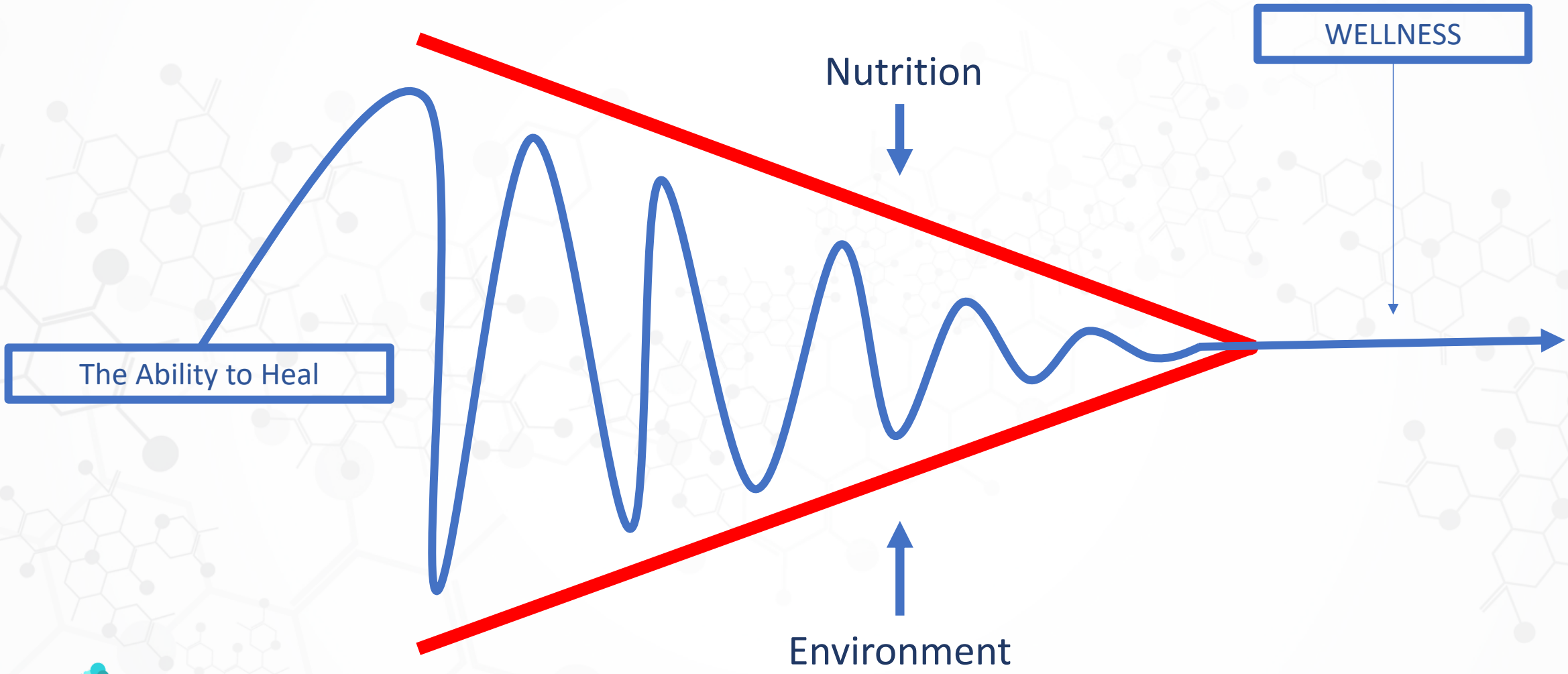
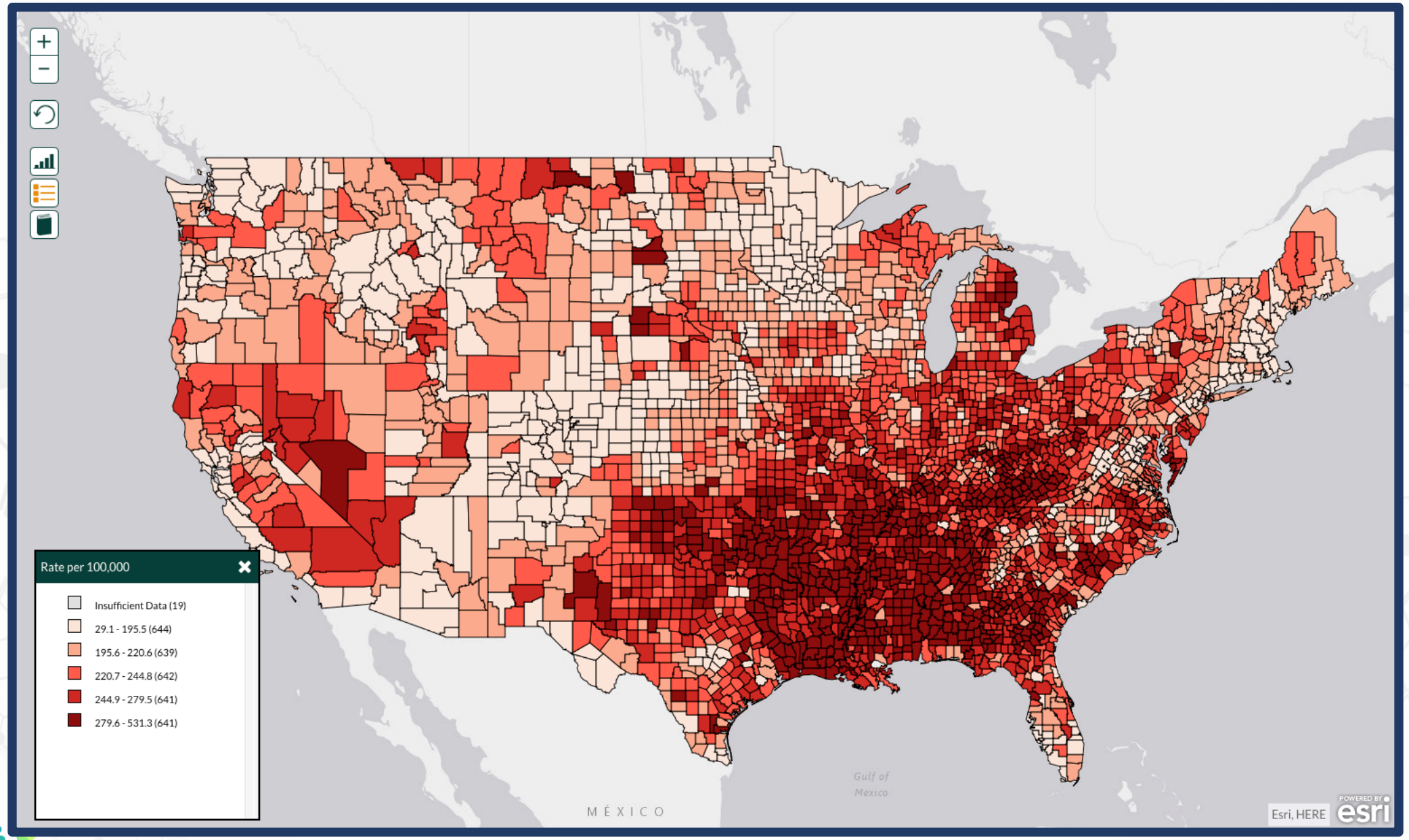
Lifestyle + Genetics = Chronic Health IMPROVEMENT

Protocols





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Roles of Inflammation, Oxidative Stress, and Vascular Dysfunction in Hypertension

Quynh N. Dinh,[1] Grant R. Drummond,[1] **Christopher G. Sobey**,[1] and Sophocles Chrissobolis[1]

Hypertension is a complex condition and is the most common cardiovascular risk factor, contributing to widespread morbidity and mortality. Approximately 90% of hypertension cases are classified as essential hypertension, where the precise cause is unknown. Hypertension is associated with inflammation; however, whether inflammation is a cause or effect of hypertension is not well understood. The purpose of this review is to describe evidence from human and animal studies that inflammation leads to the development of hypertension, as well as the evidence for involvement of oxidative stress and endothelial dysfunction—both thought to be key steps in the development of hypertension. Other potential proinflammatory conditions that contribute to hypertension—such as activation of the sympathetic nervous system, aging, and elevated aldosterone—are also discussed.

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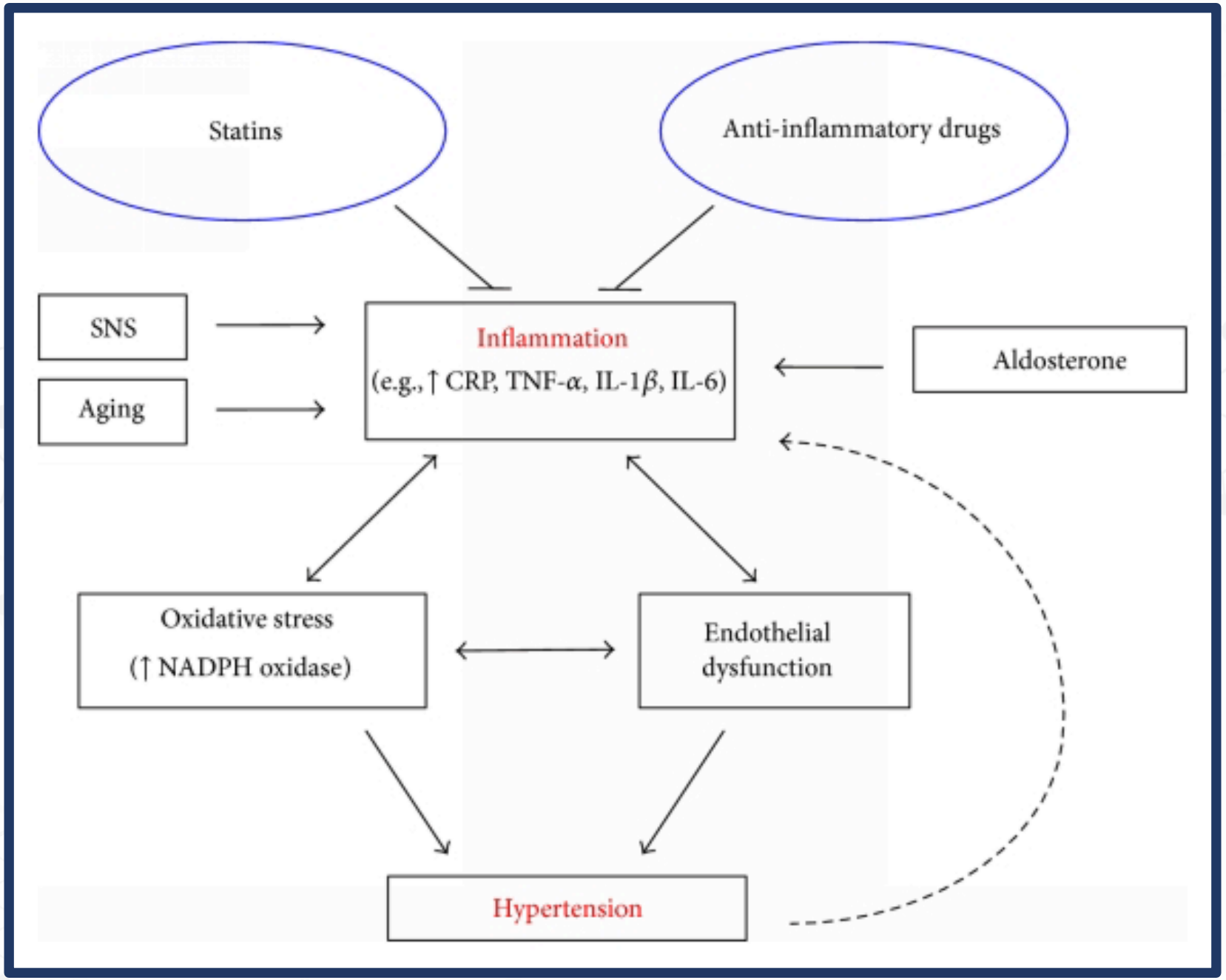
precise cause is unknown [3]. A small minority of hypertensive patients have secondary hypertension, in which a known factor is specifically responsible for raising blood pressure. Many secondary causes of hypertension include primary aldosteronism, obstructive sleep apnea, and renovascular disease [4]. An association between


Statins
Anti-inflammatory drugs
SNS
Aging
Inflammation
(e.g., ↑ CRP, TNF-α, IL-1β, IL-6)
Aldosterone
Oxidative stress
(↑ NADPH oxidase)
Endothelial
dysfunction
Hypertension

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Current therapies for human hypertension include angiotensin II (Ang II) type 1 receptor (AT1R) inhibitors, angiotensin converting enzyme (ACE) inhibitors, diuretics, calcium channel antagonists, and β-blockers. Treatment with commonly used antihypertensives reduces the risk of total major cardiovascular events, and importantly, it appears that the larger the reduction in blood pressure, the larger the reduction in cardiovascular risk [5]. Insulin resistance contributes causally toward the pathogenesis of hypertension [6, 7]. Indeed, hypertension has been found to be associated with hyperinsulinemia and insulin resistance in humans [8]. Yet, while the above-mentioned therapies successfully lower blood pressure in most individuals, there are a group of patients who are resistant to such treatments. Furthermore, even when blood pressure targets are achieved, many hypertensive patients remain at risk for a cardiovascular event, which may be due to underlying inflammation.

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The acute phase protein, C-reactive protein (CRP), is involved in innate immune responses and has roles that include activating the complement system and enhancing phagocytosis [13]. CRP can stimulate monocytes to release proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumour necrosis factor alpha (TNF-α) [14] and also endothelial cells to express intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 [15], effects which will further promote inflammation.

CRP is considered the inflammatory marker with the strongest association with hypertension. It has been demonstrated in numerous clinical trials that hypertensive patients commonly have increased plasma CRP levels [16–21]. Both males and females

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One potential mechanism by which inflammation may promote hypertension is by causing endothelial dysfunction. The endothelium is a single cell layer that lines the luminal surface of blood vessels and is involved in regulation of vascular tone and structure. Nitric oxide (NO) derived from endothelial nitric oxide synthase (eNOS) is a signalling molecule important in regulating vascular tone. When NO is released from endothelial cells it causes smooth muscle relaxation and subsequent vasodilation (Figure 2) [63]. Endothelial dysfunction may contribute to increased systemic vascular resistance and thus lead to the development of hypertension and is commonly manifested as impaired endothelium-dependent vasodilation due to an imbalance between vasoconstrictors and vasodilators [64]. Inflammation can alter the rates of synthesis and

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Chronic inflammation can also trigger oxidative stress, which has been associated with hypertension [77]. As mentioned, inflammation is the primary immune response to eliminate pathogens or to repair tissue damage. Innate immune cells, such as neutrophils and macrophages, produce reactive oxygen species (ROS) such as superoxide and hydrogen peroxide in order to kill pathogens [77]. Nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidase is a major source of ROS in immune cells and also in the vasculature [78]. Inflammatory processes continue until the pathogens are destroyed or the tissue repair process has been completed. However, sustained inflammation can lead to an overproduction of ROS. Oxidative stress (defined as an

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The kidney is an important organ involved in regulating blood pressure, and chronic kidney disease is one of the most common causes of secondary hypertension [86]. Elevated renal oxidative stress can be seen in the early stages of chronic kidney disease [87], and inflammation [88] and oxidative stress [87] increase as renal dysfunction progresses. Prehypertensive SHR from 2-3 weeks of age have elevated renal inflammation and oxidative stress compared to age-matched WKY rats [89]. Renal artery

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Sympathetic nervous system (SNS) activation is a common feature of hypertension and can contribute to the development of hypertension [94]. Essential hypertension patients are reported to have increased renal sympathetic outflow [95]. Autonomic dysfunction is characterised by increased sympathetic and decreased parasympathetic activity, and the SHR has been shown to be a good rodent model of human autonomic dysfunction [96]. The SNS innervates primary and secondary lymphoid organs and most immune cells express receptors for catecholamines such as noradrenaline [97]. The SNS can enhance inflammatory responses. For example, deletion of extracellular superoxide dismutase in the circumventricular organs of mice increased sympathetic outflow, modestly elevated

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Patients with primary aldosteronism have elevated aldosterone levels, and as mentioned earlier, primary aldosteronism is a common secondary cause of hypertension. More than 10% of hypertensive patients have raised aldosterone levels [111], and drugs that block the mineralocorticoid receptor (MR), the main target receptor of aldosterone, are used to treat hypertension that is resistant to ACE inhibition and AT1R antagonism [112]. Aldosterone is involved in the RAAS whereby a fall in blood pressure under physiological conditions leads to Ang II generation which, through its action on the AT1R in the adrenal zona glomerulosa, stimulates the release of the mineralocorticoid, aldosterone. Aldosterone activates the MR in the distal renal tubule of the kidney to increase sodium and water retention, and potassium excretion, leading to an increase in blood volume and thus blood pressure [113]. Actions of aldosterone were, until recently, believed to be restricted to the kidney, but it is now understood that aldosterone can target other tissues relevant to blood pressure control, including the brain [114], vasculature [115], and heart [116].

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1. Inflammation
2. Endothelial dysfunction
3. Oxidative stress
4. Renal dysfunction
5. Sympathetic overdrive
6. Hyperaldosteronism

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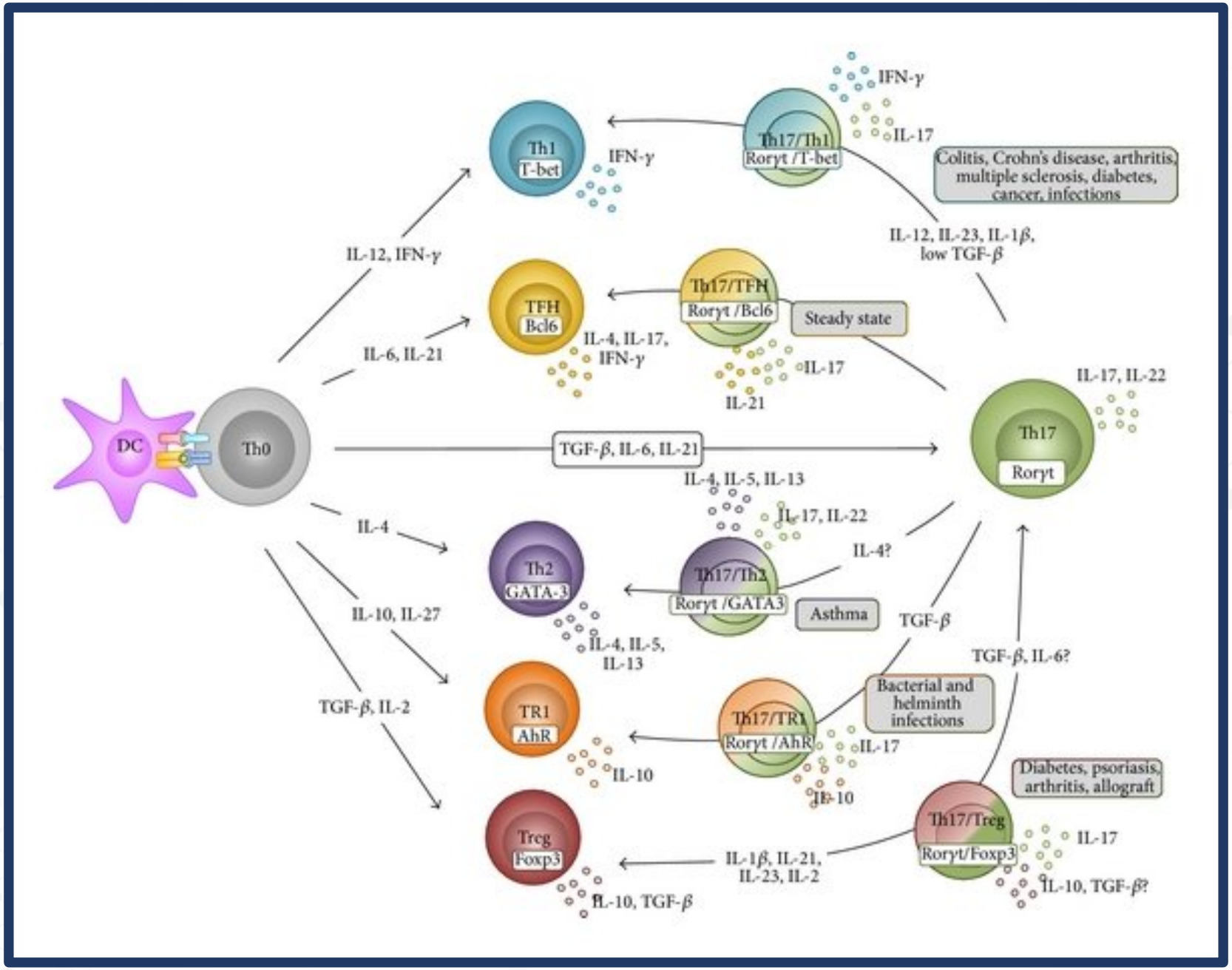

https://www.researchgate.net/publication/283965918/figure/fig2/AS:329918396289024@1455670083081/Th17-cell-plasticity-T-helper-cells-differentiate-from-naive-T-cells-Th17-cells-are.png

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Inflammation and hypertension: new understandings and potential therapeutic targets

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Tregs and Th17 cells

Experimental studies have focused upon the pathophysiological role of individual T-cell subsets. Specific experimentation is elucidating the functions of two T-cell subtypes distinct from the classical Th1 and Th2 paradigm – regulatory T-cells (Tregs) and Th17 cells. The development, differentiation, and plasticity of these cell types are still under intense scrutiny among immunologists, but many researchers hypothesize therapeutic benefit for inflammatory disorders by altering the dynamics of Tregs and Th17 cells. In the past few years, studies have shown that Tregs attenuate hypertension and target organ damage, while Th17 cells exacerbate the pathology.

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Th17 cells are a recently described subset of T-cells characterized by the expression of the master transcription factor retinoic acid-related orphan receptor (ROR)γt and by the production of interleukin 17 (IL-17) [9]. In contrast to the anti-inflammatory role of Tregs, Th17 cells are proinflammatory, and exacerbate tissue damage and disease in conditions of chronic inflammation and autoimmunity [10]. This appears to be the case in hypertensive pathology as well, and blunting Th17 signaling may alleviate the inflammation associated with hypertension and target organ damage. For instance, the consequences of angiotensin II

Summary

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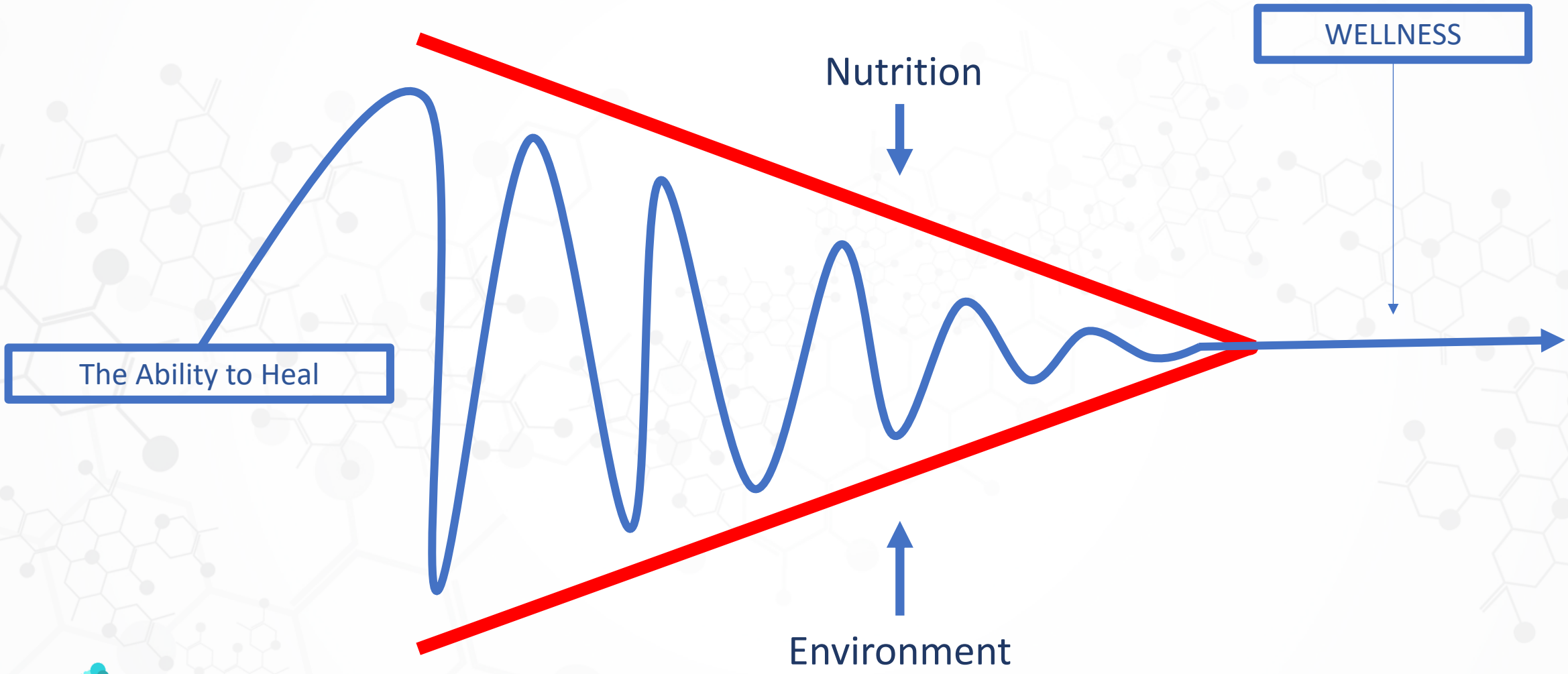
2. Endothelial dysfunction
3. Oxidative stress
4. Renal dysfunction
5. Sympathetic overdrive
6. Hyperaldosteronism

Protocols



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