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Mechanisms underlying the effects of caloric restriction on hypertension

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ABSTRACT

Hypertension is a major risk factor for cardiovascular disease (CVD) as well as a major contributor to all-cause mortality and disability worldwide. The pathophysiology of hypertension is highly attributed to a dysfunctional endothelium and vascular remodeling. Despite the wide use of pharmacological therapies that modulate these pathways, a large percentage of patients continue to have uncontrolled hypertension, and the use of non-pharmacological interventions is increasingly investigated. Among these, caloric restriction (CR) appears to be a promising nutritional intervention for the management of hypertension. However, the mechanisms behind this effect are not yet fully understood, although an evolving view supports a significant impact of CR on vascular structure and function, specifically at the level of vascular endothelial cells, vascular smooth muscle cells along with their extracellular matrix (ECM). Accumulating evidence suggests that CR promotes endothelium-dependent vasodilation through activating eNOS and increasing nitric oxide (NO) levels through multiple cascades involving modulation of oxidative stress, autophagy, and inflammation. Indeed, CR diminishes phenotypic shift, and suppresses proliferation and migration of VSMCs via pathways involving NO and mTOR. By regulating transforming growth factor-β and matrix metalloproteinases, CR appears to reduce ECM and collagen deposition in vascular walls. Here, we offer a detailed discussion of how these mechanisms contribute to CR's influence on reducing blood pressure. Such mechanisms could then provide a valuable foundation on which to base new therapeutic interventions for hypertension.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide accounting for 17.9 million deaths each year, an estimated 31% of global deaths [1]. This disease is intimately associated with many risk factors such as smoking, obesity, high cholesterol, diabetes, family history, and hypertension. Among all others, hypertension is the single leading contributor to all-cause mortality and disability worldwide [2]. It is estimated that 874 million people suffer from hypertension globally, with an associated mortality of 9.4 million deaths per year [2]. Moreover, hypertension is associated with many CVDs such as coronary artery diseases, heart failure, and peripheral artery disease [3,4]. It increases steadily with age, excessive sodium and low potassium intake, obesity, alcohol intake, and physical inactivity [5]. The pathophysiology of hypertension is related to impaired control of blood pressure determinants, including dysfunctional endothelium, sodium homeostasis, renin-angiotensin-aldosterone system, natriuretic peptides, sympathetic nervous system, and inflammation [6].

Several classes of drugs have been employed to reduce blood pressure. These include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, thiazide-type and thiazide-like diuretics, and beta adrenergic blockers [6]. Despite the

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wide use of these efficacious drugs, a large percentage of patients continues to have uncontrolled hypertension [7]. While poor adherence may partly explain this, it is becoming evident that, in patients taking at least three anti-hypertensive drugs at the maximum tolerated dose, resistance is a key player in the failure to reduce blood pressure [7].

It is becoming increasingly clear that concomitant adoption of non-pharmacological interventions or lifestyle modifications is crucial for managing high blood pressure and improving patients' quality of life [8]. One approach that appears to favorably modulate many cardiovascular parameters, including hypertension, is caloric restriction (CR), which is defined as a decrease in caloric intake compared to *ad libitum* diet, without causing malnutrition [9]. Despite various reports on the role of CR in reducing blood pressure and the underpinning mechanisms, a unified context for the effect of CR on blood pressure reduction at the level of the vascular wall in specific has not been forthcoming. This review, thus, aims to put together and reconcile the various molecular and cellular players involved in such an effect on the vasculature and consequently on blood pressure.

2. CR and blood pressure

A considerable body of evidence implicates CR in reducing blood pressure and ameliorating hypertension. Indeed, studies show that calorie-restricted diets cause significant reductions in both systolic and diastolic blood pressure (SBP and DBP) in rats [10-13] and humans [14-16]. Importantly, this significant effect of CR in humans was reported in studies of different designs including cross-sectional [14-16] randomized controlled [17,18] and non-randomized [19-23] studies in both men and women with variable baseline characteristics with subjects being obese, overweight, diabetic, having metabolic syndrome, or healthy non-obese [14-23].

The effect of fasting and energy restriction on blood pressure in adults has also been studied [24]. A recent meta-analysis of 23 studies with a total of 1397 participants revealed that fasting and calorie-restricted diets could reduce both SBP and DBP [24]. These findings are cemented by The CALERIE study, a phase 2, multi-center randomized controlled trial carried for two years in young and middle aged (21–50 years old), healthy non-obese men and women in three clinical centers in the USA [25]. Patients were randomly allocated to a control *ad libitum* diet group and a CR group, which sustained a 11.9% reduction in caloric intake. The results showed that compared to baseline, CR induced a significant and persistent reduction in several conventional cardio-metabolic risk factors, including SBP and DBP [25]. Another randomized controlled study, The ENCORE, enrolled 144 subjects that were grouped intro healthy, pre-hypertensive or stage 1 hypertensive subgroups. This study determined how DASH diet (Dietary Approaches to Stop Hypertension) alone, or in combination with weight loss and exercise can affect blood pressure [26]. Compared to control diet, DASH diet significantly reduced both SBP and DBP [26]. However, when DASH was accompanied with 500-calories-per-day deficit, further significant reduction in SBP and DBP was noticed [26]. Importantly, a one-year follow up of the ENCORE study showed that the reduced blood pressure persists for 8 months after the conclusion of the 16-week ENCORE program, albeit with some changes in the benefits [27]. Another multi-arm parallel, randomized, single-blind controlled experimental trial, The EXERDIET-HTA Randomized Trial Study, was conducted on 167 primary hypertensive, overweight/obese, or non-physically active subjects for 16 weeks. This study revealed that a DASH diet with 25% reduced energy intake accompanied with aerobic exercise significantly decreased SBP in both men and women [25]. Taken together, it is becoming increasingly evident that CR is effective as a behavioral intervention for reducing blood pressure. The mechanisms that contribute to this effect are variable and multiple players come to play at the cellular and molecular levels.

3. Vascular endothelial function and hypertension

The vascular endothelium plays a critical role in maintaining the function and health of blood vessels, as well as the surrounding tissues [28]. In addition to being a structural barrier, the endothelium synthesizes and secretes an array of vasoactive molecules in an autocrine and/or paracrine manner. These molecules play vital roles in vascular hemodynamics and vasotone. Indeed, blood flow and pressure are regulated by the balance between vasodilators such as nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF) or prostacyclin (PGI_2), and vasoconstrictors such as endothelin (ET), platelet-activating factor (PAF), angiotensin II and thromboxane-A_2 (TXA_2) [29]. While each of these mediators is implicated in modulating vasoreactivity, this paper focuses on NO and, to a lesser extent, ET as important mediators between CR and hypertension.

3.1. NO, hypertension, and CR

NO is a gasotransmitter that is synthesized from the amino acid L-arginine by the endothelial nitric oxide synthase (eNOS) [30,31]. Once produced, NO diffuses from the endothelium into the surrounding smooth muscle cells where it activates the soluble guanylyl cyclase (sGC) which catalyzes the formation of the intracellular second messenger cGMP from GTP [31,32]. cGMP activates protein kinase G (PKG) which phosphorylates ion channels and downstream mediators that subsequently decrease intracellular calcium concentrations. PKG also phosphorylates myosin light chain kinase (MLCK), which then decreases its activity and ability to phosphorylate myosin light chain (MLC), thereby leading to VSMC relaxation [32-34]. By modulating vascular tone, NO plays an important role in the regulation of blood pressure.

Any imbalance in the vasodilators and vasoconstrictors released by the endothelium, particularly the reduction in NO bioavailability, can impair endothelium-dependent vasodilation in response to chemical (e.g. acetylcholine, bradykinin) or mechanical (e.g. shear stress) stimuli [35]. In fact, an association between endothelial dysfunction and high blood pressure is well-established [35,36], especially in patients with essential hypertension [37-39]. The Framingham heart study cohort suggests that the degree of impairment of endothelial function is positively associated with the severity of hypertension [40]. Similarly, a significant development of systemic hypertension was observed in rats with 2 months NO-blockade by the NO synthase inhibitor N^{ω}-nitro L-arginine methyl ester (L-NAME) [41].

Considerable experimental evidence has shown that CR upregulates eNOS, increases NO production, and improves endothelial dysfunction in animal models as well as in humans [42-45]. As such, the first part of this review will investigate the various signaling mechanisms through which CR increases NO production and bioavailability.

3.1.1. Adiponectin – AMPK – eNOS pathway

Adiponectin, an adipokine family hormone, is released by the adipose tissue [46] and is known to be elevated following CR [10,47]. Although many of the adipokines (leptin, resistin, tumor necrosis alpha (TNF-α), interleukin (IL)-6, transforming growth factor beta (TGF-β), plasminogen activator inhibitor (PAI)-1, among others) mediate various vascular and metabolic complications of adiposity [48], adiponectin in particular is an important anti-inflammatory, anti-atherosclerotic, and anti-diabetic hormone [48-51].

Several studies report that adiponectin levels are significantly decreased in patients with coronary artery disease, suggesting a correlation between reduced adiponectin and vasculopathies [52,53]. Moreover, hypoadiponectinemia is an independent risk factor for the development of hypertension [54,55]. Similarly, after a high salt-diet, adiponectin knockout (KO) mice have higher systemic blood pressure than their wild-type (WT) counterparts, and adenoviral replenishment of adiponectin in these mice reverses hypertension [56].

Accumulating evidence supports the notion that adiponectin prevents hypertension through an endothelium-dependent vasodilatory mechanism [56-58]. For instance, human studies show a positive association between plasma levels of adiponectin and the forearm vasodilator response to a reactive hyperemia [57]. No significant correlation is noted between adiponectin levels and nitroglycerin-induced hyperemia [57]. Similarly, adiponectin-KO mice had significantly reduced acetylcholine-induced vasorelaxation compared to WT, but no difference was documented between both groups upon administration of sodium nitroprusside, an endothelium-independent vasodilator [57]. This suggests an endothelium-dependent mechanism that is further confirmed by an impaired eNOS activation and NO production in aortic rings isolated from adiponectin-KO mice [59]. These changes were also reversed upon treatment with recombinant adiponectin [59]. Likewise, eNOS activity and total NO levels are also increased in response to recombinant adiponectin administration in rats with dietary obesity [58].

Most of the cardio-protective and vasodilatory mechanisms mediated by adiponectin are related to the activation of the AMP-activated protein kinase (AMPK) [10,47,60-62]. AMPK, a ubiquitously expressed serine/threonine kinase, is an integral cellular energy sensor that is activated by low energy status. The rise in the AMP:ATP ratio, such as occurs in CR, activates AMPK independently from adiponectin, and stimulates many cellular catabolic pathways in order to increase ATP levels [63,64]. Furthermore, the expression of AMPK in endothelial cells plays a role in improving vascular functions through the regulation of eNOS activity, lipid metabolism and redox status [65,66]. The signaling pathway through which adiponectin stimulates eNOS phosphorylation through AMPK has not been fully elucidated. Evidence shows that adiponectin induces AMPK phosphorylation at Threonine^{172} [58,67] which in turn leads to eNOS phosphorylation at Serine^{1177} [58,68] or at Serine^{1179} [67]. In line with this, PI3-kinase inhibitors (e.g. Wortmannin) block the adiponectin/AMPK-induced eNOS phosphorylation and NO production [67,69], suggesting that AMPK functions upstream of PI3-kinase. However, a discordance in the literature pertaining to whether Akt (protein kinase B) acts downstream of the AMPK-PI3-kinase axis or not is noted. Few studies argue that the AMPK signaling pathway is

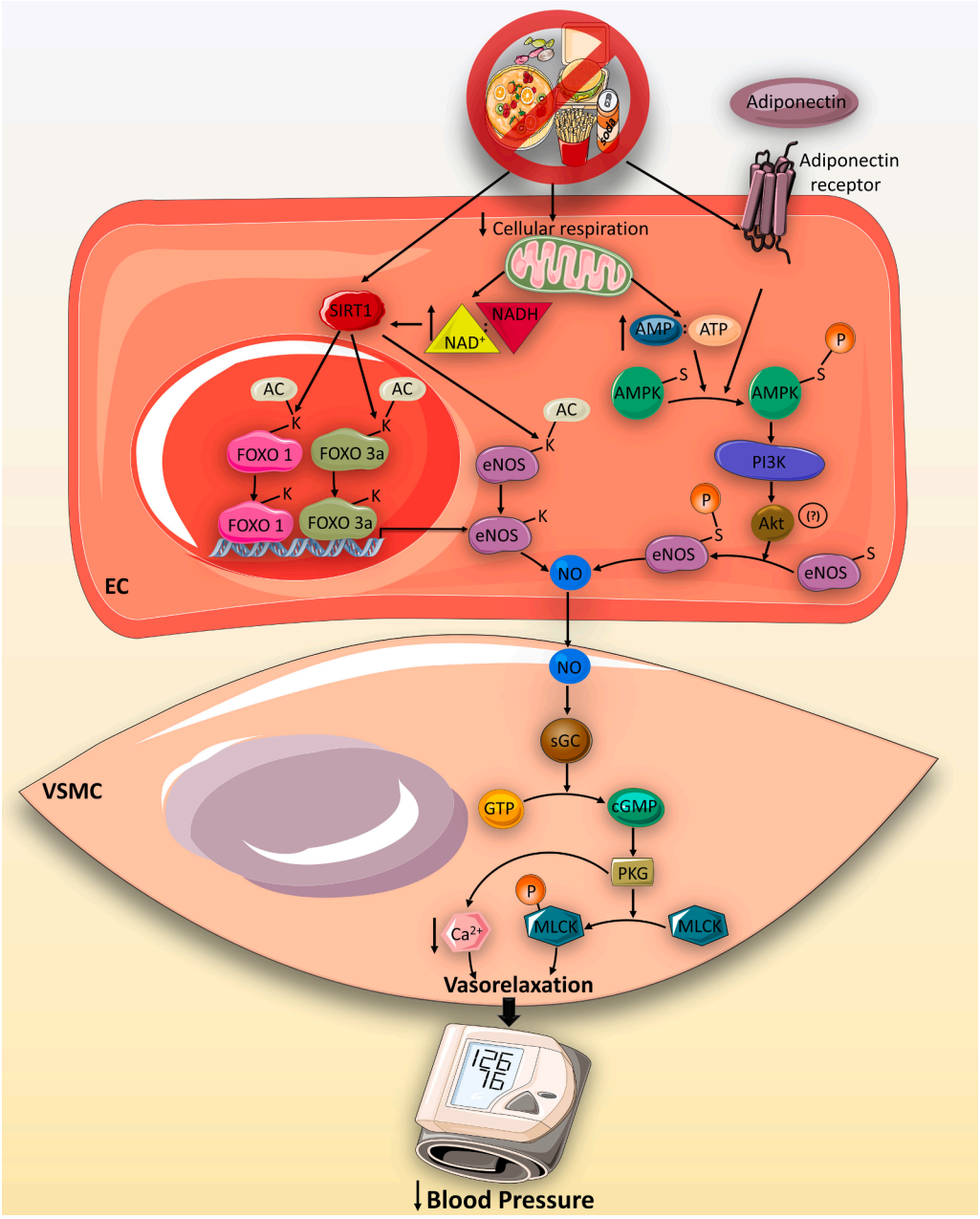

Fig. 1. The integrated signaling pathway linking adiponectin, AMPK and SIRT-1 to the biological effects of caloric restriction on nitric oxide (NO) production in the cardiovascular system. CR reduces energy state of cells by exhausting cellular respiration, thus increasing NAD^+ and AMP levels, which in turn activate SIRT-1 and AMPK, respectively. CR also increases the expression of SIRT-1 protein in endothelial cells, as well as the circulating adiponectin levels. In the cytosol of endothelial cells, activated SIRT-1 deacetylates eNOS at lysine (K) residues 496 and 506. This promotes eNOS activation and NO production. In parallel, SIRT-1 deacetylates the transcription factors FOXO1 and FOXO3a in the nucleus leading to a rise in eNOS mRNA expression thereby increasing NO availability. On the other hand, increased levels of adiponectin and AMP independently stimulate the phosphorylation of AMPK at threonine172. This activated AMPK in turn phosphorylates PI3-K and possibly Akt leading to the phosphorylation of eNOS at serine1177/1179 and subsequently NO production. NO diffuses from the endothelium into nearby vascular smooth muscle cells (VSMCs) where it activates the soluble guanylyl cyclase (sGC) responsible for GTP to cGMP conversion. Subsequently, cGMP stimulates protein kinase G (PKG) to decrease intracellular Ca^{2+} concentrations and to phosphorylate myosin light chain kinase (MLCK) decreasing MLC phosphorylation, leading smooth muscle cells relaxation. This mechanism portrays the enhanced endothelial-dependent vasodilation mediated by CR which contributes to the reduction of blood pressure.P: phosphorylation, AC: acetylation, K: lysine, S: serine.

independent of Akt [58,67,68] as the expression of dominant-inhibitory mutant of Akt does not significantly affect adiponectin-induced NO production [67]. In contrast, other studies confirm the involvement of an adiponectin-AMPK- PI3k- Akt- eNOS axis, since dominant negative AMPK suppresses the activating Akt phosphorylation at Ser^{473} in endothelial cells [69,70]. Similarly, the reduction in blood pressure in obese (fa/fa) Zucker rats subjected to mild CR is also linked to the involvement of PI3-k/Akt downstream of AMPK in activating eNOS [11].

Perhaps it is more solid to argue that Akt functions downstream of AMPK as this is consistent with data obtained from other signaling pathways involving AMPK, independent of adiponectin. For example, vascular endothelial growth factor [71], sphingosine-1-phosphate [71], as well as propionyl-L-carnitine [72] are shown to have a protective effect on the vasculature by stimulating eNOS activity through the same AMPK-PI3k-Akt signaling pathway described above (Fig. 1). As such, CR exhibits one of its cardioprotective effect through an adiponectin/AMPK-mediated increase in the phosphorylation of eNOS, which is followed by increases NO bioavailability. This NO is integral to the vasodilatory effect that improves endothelial dysfunction and consequently hypertension.

3.1.2. *Sirt1 – eNOS pathway*

The mammalian sirtuins family are nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylases that activate energy preserving pathways in response to metabolic stress or an increase in the cellular NAD^+: NADH ratio [73]. SIRT-1, one of the seven sirtuin enzymes, plays a critical role in regulating vascular functions by deacetylating various proteins including histones, and transcription factors. It modulates genomic and non-genomic mechanisms in endothelial cells [74], and as an energy sensor, it also contributes to the vasculoprotective effects of CR [75,76].

CR evokes elevation in the NAD^+: NADH ratio which subsequently increases levels and activates SIRT-1 [42,75,77]. In the cytosol of endothelial cells, SIRT-1 deacetylates eNOS at lysine residues 496 and 506 in the eNOS calmodulin-binding domain, thereby promoting eNOS activation and NO production [45]. In parallel, SIRT-1 acts in the nucleus to deacetylate the forkhead box O (FOXO) transcription factors FOXO1 and FOXO3a. This deacetylation increases mRNA levels of eNOS and indirectly increases NO bioavailability [78,79] (Fig. 1). Moreover, inhibiting SIRT-1 in the endothelium of mice arteries prevents endothelial-dependent vasodilation and reduces NO production, further supporting the premise of CR-precipitated SIRT1-mediated NO production [45,80] (Fig. 2). Interestingly, pharmacologic or genetic inhibition of NO by L-NAME or eNOS knockout, respectively, decreases SIRT-1

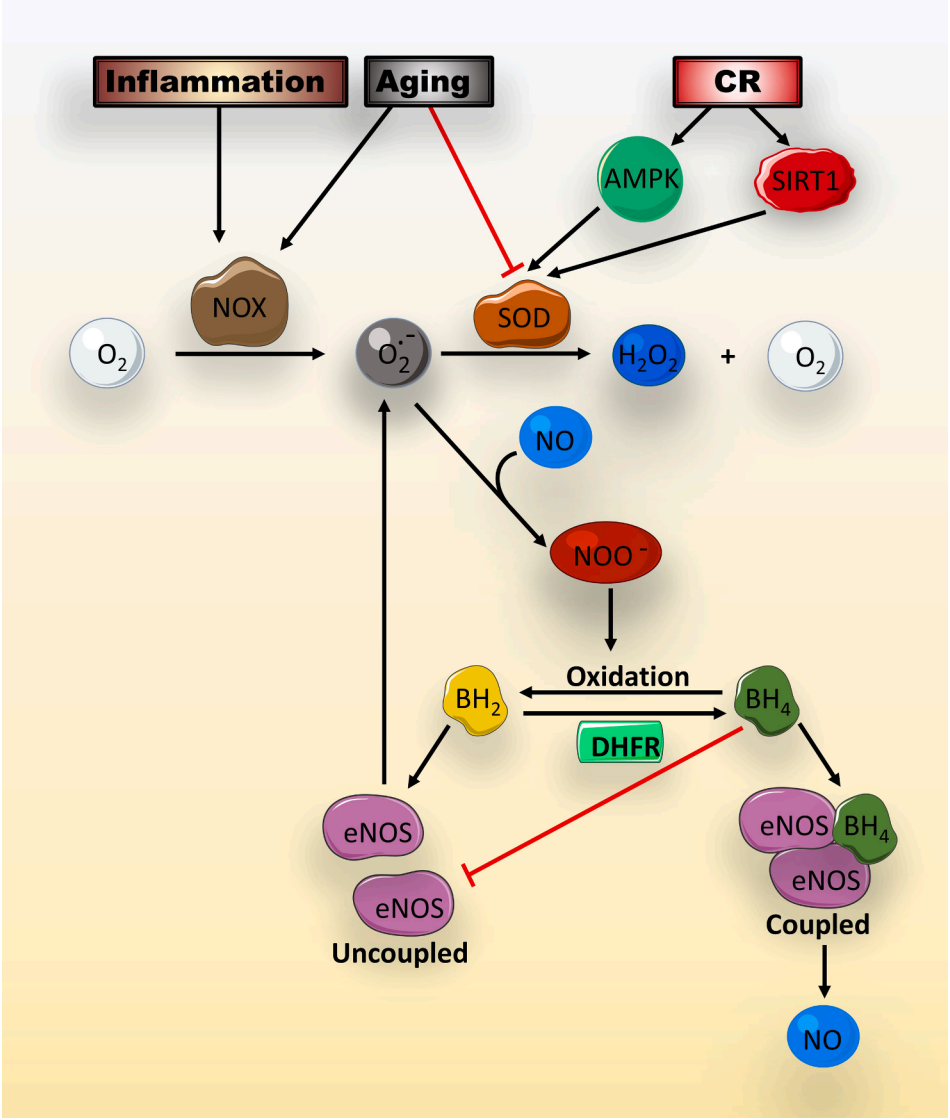

Fig. 2. Caloric restriction inhibits superoxide formation and increases its clearance. NADPH oxidase (NOX) is the main generator of reactive oxygen species, producing superoxide ($O_2^{\cdot-}$). Superoxide, which can be cleared by the enzyme superoxide dismutase (SOD), reacts with nitric oxide (NO) non-enzymatically to form peroxynitrite ($ONOO^-$). Peroxynitrite promotes the oxidation of eNOS cofactor tetrahydrobiopterin (BH_4) resulting in an uncoupled enzyme that produces superoxide instead of NO. The oxidized form of BH_4 is dihydrobiopterin, it can be reduced back into BH_4 through the enzyme dihydrofolate reductase (DHFR). Aging is reported to stimulate NOX and inhibit SOD. Similarly, Inflammation stimulates NOX. Caloric restriction, however, through Sirt and AMPK activatiom, stimulates SOD activity.

expression in white adipose tissue of mice [42] as well as in endothelial cells [81]. Therefore, a positive feedback loop involving eNOS, NO and SIRT-1, amplifies the beneficial effects of CR in the vasculature.

3.1.3. Inflammation and endothelial dysfunction

The correlation between inflammation and hypertension is well-established. Inflammation causes endothelial dysfunction and oxidative stress, both of which contribute to hypertension [82]. Inflammation involves recruitment of leukocytes that adhere to endothelium and cross the capillaries into the site of immune reaction. These leukocytes produce various chemokines and factors that mediate inflammatory processes, such as TNF-α, IL-1β, and IL-6 [83]. Although inflammation protects the body from pathogens and promote tissue repair, prolonged inflammatory insults contribute to, or even mediate, the progression of many chronic diseases such as atherosclerosis [84], rheumatoid arthritis [85], and systemic lupus erythematosus [86].

The relationship between inflammation and hypertension has been delineated in various studies. Indeed, elevation of the plasma level of C-reactive protein (CRP), an inflammatory marker, is noted in hypertensive [87-92] and prehypertensive patients [93]. Moreover, in non-hypertensive individuals, elevated CRP levels are associated with increased risk of hypertension [94-96]. Similarly, hypertensive patients exhibit significantly higher plasma levels of IL-6 [97-99], IL1-β [100,101], and TNFα [97,102,103] than non-hypertensive individuals. These inflammatory mediators can downregulate eNOS expression by different mechanisms. For instance, CRP [104] and TNF-α [105] destabilize eNOS mRNA resulting in lower translation of the enzyme, while IL-17 activates Rho kinase which phosphorylates (at threonine 495) and inhibits eNOS [106]. IL-17 levels have also been known to increase after infusion of angiotensin II, a hypertensive hormone [107]. Similarly, salt was found to promote the differentiation of $CD4^+$ T-cells into IL-17 secreting cells (T_H17) [108]. Together, these observations show how inflammation could impair endothelial-dependent vasodilation by reducing NO production resulting in an increased blood pressure (Fig. 2).

Many studies demonstrate the effect of CR on decreasing inflammation and its markers especially in the adipose tissue. Two-month (short-term) 40% CR in Fischer 344 rats reduces plasma CRP levels by 61% compared to age-matched controls [109]. Similarly, long-term 40% CR attenuates the age-related increase in plasma CRP levels by 60% [109]. In addition, lower levels of CRP and IL-6 in plasma or adipose tissue, respectively are achieved following 6-month CR in obese mice [110]. Similarly, CR evoked a decrease in TNFα, IL-1β and IL-6 expression in white adipose tissues (WAT), namely epididymal, subcutaneous, and perirenal (eWAT, sWAT, and pWAT respectively) as well as brown adipose tissue (BAT) in Wistar rats [111]. By suppressing these inflammatory mediators, CR might attenuate their inhibitory effect on eNOS expression, possibly playing a role in NO-dependent vasodilation and to the consequent drop in blood pressure. However, further studies establishing a clear causative relationship are still needed to cement this argument.

3.1.4. Reactive oxygen species

The effect of inflammation on endothelial cells can be direct as discussed above, or indirect via an oxidative milieu (Fig. 2). Inflammation is indeed a major instigator of oxidative stress, especially when immune cells synthesize and release large amounts of reactive oxygen species (ROS) such as superoxide and hydrogen peroxide to kill pathogens [112]. The major source of ROS is the enzyme nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidase, also known as NOX, expressed in both immune and endothelial cells. NADPH oxidase transfers electrons from NADPH to molecular oxygen to produce superoxide ($O2^{\bullet-}$), a reactive free radical [113]. The enzyme superoxide dismutase (SOD) acts as an antioxidant enzyme that transforms superoxide into molecular oxygen (O_2) and hydrogen peroxide (H_2O_2) [114]. Superoxide can also be produced from mitochondria through electron transport chain, especially complex I; this production is augmented in cases of high proton motive force and high NADH:NAD^+ ratio [115]. Here, we discuss the effects of oxidative stress as pertains to both inflammation and mitochondria.

Oxidative stress becomes more pronounced with age, mainly due to increased production and decreased breakdown of ROS [116] (Fig. 2). Superoxide and hydrogen peroxide generation by mitochondria indeed increase with age, likely following increased expression of NOX2 [111]. Such increased levels of superoxide react with NO to produce peroxynitrite (ONOO–) [117], thus consuming the NO that is much needed for vasodilation. This reaction takes place at a faster rate than superoxide clearance by dismutase (SOD) [118]. Peroxynitrite further inhibits NO production by inhibiting eNOS through the oxidation and inactivation of its cofactor 4-tetrahydrobiopterin (BH4) resulting in a defective uncoupled eNOS that produces superoxide instead of NO [119]. This further promotes a cycle of NO consumption and superoxide production, and consequently abolishes eNOS-dependent endothelium-evoked relaxation [120] (Fig. 2).

CR slows this age-related increase in mitochondrial superoxide and hydrogen peroxide [121]. Indeed, animal studies show that long term CR decreases mitochondrial ROS in the heart [121,122], brain [121,123], kidneys [121], liver [124], skeletal muscles [125,126], and aorta [76]. In line with this, expression of NOX2 is suppressed in adipose tissues of Wistar rats subjected to CR [111]. Moreover, CR increases liver NO, glutathione (an anti-oxidative agent) and mitochondrial SOD activity in rats [127]. Contextually, life-long CR in mice reduces aortic NADH oxidase (NOX) activity and increases aortic levels of catalase, the enzyme responsible for breakdown of hydrogen peroxide [128].

In humans, a randomized clinical trial shows that 25% caloric reduction significantly decreases oxidative stress in obese women in 5 days [129]. Another clinical trial shows that CR for 12 weeks improves redox status evident by decreased thiobarbituric acid reactive substances (TBARS) and increased total antioxidant capacity [130]. Similarly, moderately overweight volunteers subjected to 6 months of low glycemic dietary load CR exhibit increased plasma glutathione peroxidase activity, a cytosolic antioxidant enzyme that reduces hydrogen peroxide to water and oxygen [131]. Further, obese subjects with type 2 diabetes mellitus subjected to 12-week moderate energy-restricted diet with or without exercise show reduced plasma levels of malondialdehyde, an oxidative stress marker [132]. Together, these and other studies show how CR increases NO bioavailability by suppressing accumulation of ROS [128].

The mechanisms by which CR decreases oxidative stress are still under investigation. NAD^+ is hypothesized to be an important link between aging, inflammation and oxidative stress. Importantly, it is depleted with aging and increased with CR, indicative of how CR could indeed reverse or counteract aging-induced oxidative stress. Part of its effects could be attributed to its role as a substrate for SIRT family of transcription factors as discussed previously [133]. Interestingly, high-calorie diet feeding decreases SIRT3 levels in rat hippocampus while also increasing neuronal ROS and apoptosis [134]. Contrarily, CR upregulates SIRT3 expression in neuroendocrine cells and protects them from H_2O_2-induced apoptosis [135]. In line with these findings, knockdown of SIRT1 abolishes the anti-oxidant and anti-inflammatory effects of CR serum [76]. CR-induced SIRT1 activation deacetylates the forkhead box O (FOXO) transcription factors that upregulate MnSOD, catalase, periredoxins, and thioredoxins, all functioning as anti-oxidant enzymes [136] (Fig. 1). CR-induced AMPK can also mitigate oxidative stress by upregulating MnSOD in endothelial cells [137]. Taken together, these findings highlight the possible mechanisms that could underpin a role for CR in the NO-mediated vasculo-protective and antihypertensive effects.

3.2. Vascular aging and autophagy

Autophagy is a natural cellular mechanism in which cellular

components such as proteins and organelles are engulfed into membranous vesicles forming autophagosomes. These subcellular structures fuse with lysosomes so that degradation of the engulfed material ensues. The process is initiated by the formation of a phagophore, a precursor membrane that expands then seals off to form an autophagosome [138]. Phagophore formation is induced through one of two pathways: (i) the activation of unc-51 like autophagy activating kinase 1, also known as ULK1 or Atg1 (Autophagy related gene 1), which is otherwise inhibited by mTORC1 (mammalian target of rapamycin complex 1), and (ii) the formation of beclin-1/Vsp34 complex, with Vsp3 being a class III phosphatidyl inositol 3 kinase (PI3K) and beclin-1 being its positive modulator, also known as Atg6 (Fig. 3). This induction step is followed by the expansion of the phagophore, a step that acquires lipids through many Atg proteins to form a complete vesicular membrane. It finally fuses with the lysosome to form an autolysosome [139-143].

Autophagy is closely linked to aging; while autophagic markers decrease with age, inhibiting autophagic pathways induces cellular senescence [144]. Defects in autophagic pathways are indeed correlated with many chronic diseases such as neurodegenerative disorders, metabolic syndrome, cancer, kidney diseases, and CVD [145-147]. Autophagy is rather viewed as an important anti-aging mechanism that reduces cellular injury and protects cells from oxidative stress, glycation end products and lipotoxicity. It mediates the clearance of cytotoxic glycation end products, protects the cell from lipid overload-induced toxicity, and increases overall cell survival [148,149]. Indeed, expression of autophagy markers is dramatically decreased in older subjects, and this decrease significantly impaired arterial endothelium-dependent dilatation [150]. In this context, primary hypertension is aggravated when autophagosomes are decreased [151], clearly indicative of the important role for autophagy in maintaining a physiologic blood pressure.

Autophagy promotes pro-survival stress response in endothelial cells. Although the outcome of autophagy depends on the nature of the stress imposed on endothelial cells, most responses are cytoprotective.

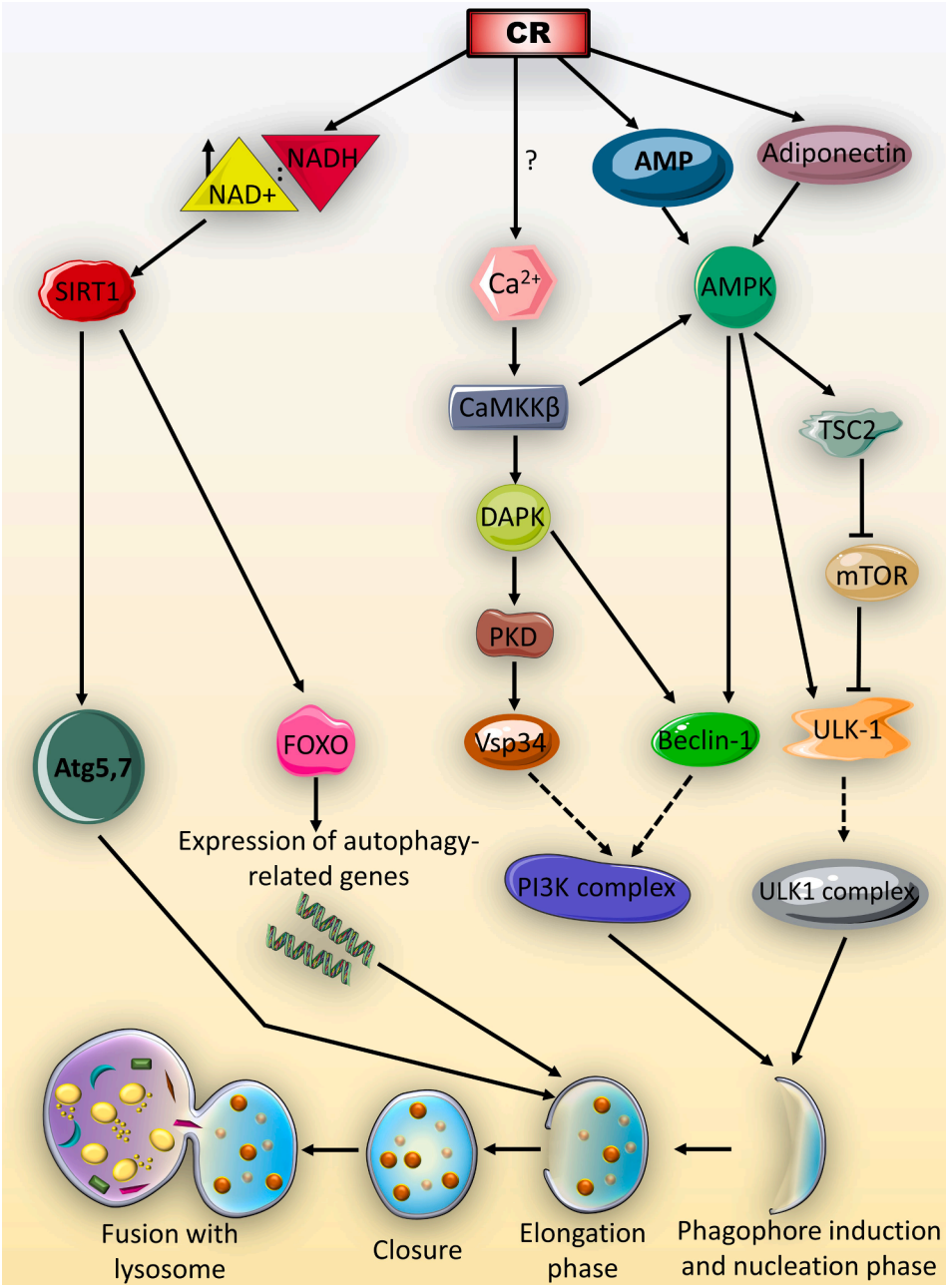

Fig. 3. Caloric restriction promotes autophagy through different pathways. CR or low energy state results in increased [NAD^+]/[NADH] and AMP levels. AMP, in addition to adiponectin, stimulates AMPK which phosphorylates tuberous sclerosis 2 (TSC2) that inhibits mTORC1, thus releasing the inhibition from ULK1. Calcium/calmodulin-dependent protein kinases β (CaMKKβ) activates DAPK (death activated protein kinase) which phosphorylates and activates beclin-1 directly, and Vsp34 through protein kinase D (PKD). ULK1 is part of ULK1 complex, and beclin-1/Vsp34 is part of PI3K complex, each of which can initiate the formation of phagophores. NAD^+ stimulates Sirt1, which deacetylates and activates autophagy related proteins (Atg5 and 7) and FOXO transcription factor. FOXO promotes autophagy-related gene expression. The products of these genes, in addition to Atg5 and 7 promote the elongation of the phagophore, which then closes and fuses with the lysosome.

Albeit via unknown mechanisms, autophagy also appears to augment eNOS expression [152,153], thereby promoting vasodilation. And vice-versa, inhibiting autophagy reduces NO production resulting in reduced arterial endothelium-dependent dilatation [150]. In this context, agents that promote autophagy have been reported to ameliorate hypertension in spontaneously hypertensive rats [154]. Importantly, reduced caloric intake or CR increases autophagy [155-163], via three different pathways: AMPK, Sirt-1, and possibly increased intracellular calcium (Fig. 3), as discussed below.

3.2.1. AMPK and autophagy

Following reduced ATP levels resulting from CR, levels of the cellular energy sensor AMPK increase. AMPK phosphorylates tuberous sclerosis 2 (TSC2) which inhibits mTORC1, thus releasing the inhibition from ULK1. AMPK can also phosphorylate and activate ULK1 and beclin-1, thus activating both pathways of autophagy induction [164,165]. Interestingly, the activity of AMPK decreases under conditions of high concentrations of glucose and fatty acids [166].

3.2.2. Sirt1 and autophagy

Sirt-1, activated by the CR-elevated levels of high [NAD^+]/[NADH] ratio, can deacetylate and activate the FOXO family of transcription factors, which upregulate the expression of autophagy related genes [167-170]. Sirt1 can also deacetylate and activate autophagy related proteins Atg5 and Atg7 which may contribute to increased autophagy [171,172] (Fig. 3).

3.2.3. Increased intracellular calcium and autophagy

Amino acid starvation has been reported to increase intracellular calcium levels [173]. This increase in calcium activates calcium/calmodulin-dependent protein kinases β (CaMKKβ) which in turn stimulates AMPK, thus inducing autophagy as discussed before (Fig. 3). CaMKKβ can also activate DAPK (death activated protein kinase) which phosphorylates and activates beclin-1 and Vsp34, also inducing autophagy [174].

3.3. Endothelins, hypertension, and CR

Endothelins represent a family of endothelial-derived vasoactive agents that cause sustained vasoconstriction [175]. Three isopeptides of endothelin, namely endothelin-1 (ET-1), ET-2, and ET-3, have been recognized with ET-1 being the most potent vasoconstrictor and the most predominantly expressed in vasculature [176,177]. In addition to its vasoconstricting effects, ET-1 modulates salt and water homeostasis, stimulates the renin–angiotensin–aldosterone and sympathetic nervous systems, and plays an ionotropic and mitogenic roles [178]. ET-1 acts on two receptor subtypes, ET_A and ET_B [179,180]. ET_A receptors are most highly expressed in the aorta, heart, kidney, but not endothelial cells, whereas ET_B receptors are mostly expressed on endothelial cells [181,182]. Importantly, these receptors have opposing effects. Upon activation, ET_A receptors of the vascular smooth muscles cause vasoconstriction and blood pressure elevation whereas endothelial and renal ET_B activation causes vasodilation and natriuresis thus depressing blood pressure. The resultant effect of ET-1 thus depends on the balance between ET_A and ET_B mediated effects [178]. Combined blockage of both ET_A and ET_B receptors proves to decrease peripheral vascular resistance and also blood pressure but to a lower extent, which hints that the overall physiological effect of endothelin is to elevate blood pressure [183].

The literature dissecting the possible effect of CR on endothelin levels or function is rather scant. Animal studies show that rats which fasted up to 48 h, or were on 40% CR diet for 2 weeks had lower levels of ET-1 and 2 compared to *ad libitum* fed rats [184]. Several other human studies hint to the possible effect of CR on lowering ET-1 levels, although this decrease may not be sufficient to dramatically lower blood pressure. Indeed, in a study involving 15 obese hypertensive men following a diet of 800 kcal/day for 12 weeks, it was found that 7 out of the 15 had a significant decrease in their blood pressure, a drop that was accompanied by decreased ET-1 levels [185]. While the remaining 8 did not have their blood pressure normalized, their ET-1 levels nonetheless significantly decreased [185]. Similar results were reported in another report utilizing a protocol of 12 weeks of CR [186]. Furthermore, another study following 14 people who exercised for 40 min daily, 3 days per week, for 3 weeks with their daily caloric intake reduced by 500 kcal/day shows significantly decreased endothelin levels [187]. In another study, following a 3-month program of CR and weight loss in seven obese men, a linear relation that reaches statistical significance is found between reduction of blood pressure and reduction in plasma ET-1 levels [188]. Taken together, these results suggest that a decrease in endothelin is associated with CR, and could be part of the mechanism by which CR decreases blood pressure. However, further mechanistic studies are warranted before a conclusive notion can be observed.

4. Vascular smooth muscle cells (VSMCs) and hypertension

VSMCs play important roles in phsyiology and pathology of the vasculature. They greatly control tissue perfusion and blood pressure. VSMC hypertrophy, proliferation, and migration, in addition to ECM deposition are well established contributors to vessel wall structure alterations that are associated with elevated blood pressure. Under normal physiologic conditions, VSMCs assume a quiescent non-proliferative phenotype, also referred to as contractile phenotype. This phenotype is characterized by expression of proteins like α-isoform of actin, the SM-1 and SM-2 myosin heavy chain isoforms, and others, which are all involved in the contractile apparatus [189-191]. However, VSMCs retain high plasticity that allows them to de-differentiate into a synthetic, migratory phenotype in response to mechanical/biochemical signals which are associated with CVDs like atherosclerosis and hypertension [192,193]. Upon de-differentiation, VSMCs migrate from tunica media to the tunica intima, where they further proliferate as well as increase synthesis and deposition of ECM [194,195].This pathophysiologically-driven phenotypic shift from the contractile phenotype to a synthetic phenotype occurs via loss in contractile molecules and increase in protein synthesis-related organelles [194]. Increased proliferative and migtatory capacities of synthetic VSMCs drive intimal thickening, alter vessel wall structure and mechanics, and decrease vessel lumen diameter, all contributing to the onset or exacerbation of hypertension. Indeed, early physiological and morphometric studies show an increase in both large and small artery wall thickness in hypertensive animals [196-200] and humans [201], and attribute this increase partly to an increase in smooth muscle mass. This increase in muscle mass is mediated by an increase in hypertrophy, hyperplasia, or both.

CR and its effects on the molecular and cellular levels can contribute to changes in vascular smooth muscle functions and phenotype which could lead to reversal or attenuation of their role in hypertension. In this section, we attempt to delineate some of the mediators and mechanisms that could govern this effect on the cellular and molecular level.

4.1. Phenotype switch

Curbing VSMC phenotypic switch could be one of the mechanisms by which CR lowers blood pressure. Phenotypic switching can be incited by various stimuli including growth factors, mitogens, inflammatory mediators and mechanical stimuli [192,193]. By virtue of its ability to suppress inflammation and its mediators, CR could be also indirectly contributing to the decrease in VSMC phenotypic switch and the consequent effects on vessel wall and hypertension. Aging, for example, is associated with increased inflammation as a key event on the molecular and cellular level. This inflammatory environment contributes to arterial intimal thickening by promoting phenotypic shift, where platelet-derived growth factor (PDGF) being an essential signaling

molecule in the process [202,203]. In this context, a 40% CR is capable of decelerating age-associated proliferation, migration, matrix deposition and by retarding phenotypic shift of VSMCs and governing PDGF-B signaling [204]. Indeed, CR could retard the age-associated arterial remodeling including the increased intimal wall thickness, fragmentation of elastin lamina, increased collagen deposition in all vascular wall layers, and increased VSMCs number in intima [204]. CR also decreased the level of PDGF and its intima-media gradient which is usually elevated in old rats [204]. Apart from PDGF, a two-week CR regimen on rats that were previously fed a high-calorie diet suppresses vascular IL-1β level, ERK1/2 phosphorylation, and medial hypertrophy, as well as reduces sensitivity to contractile agonists [205] and the pressor response to phenylephrine [206]. Together, these studies suggest an important role for CR in abolishing phenotypic shift, thus potentially ameliorating the pathogenesis or decelerating the onset of hypertension.

4.2. NO and VSMC proliferation

NO plays a pivotal role in maintaining homeostasis in the vasculature. In addition to mediating vasodilation by relaxing VSMCs, NO contributes to vascular remodeling by a dose-dependent inhibition of VSMC proliferation. This is observed in VSMCs of different vascular beds both in humans and rats [207-209]. NO affects cell cycle progression, particularly at the G1/S checkpoint [208,210,211], by upregulating the cyclin-dependent kinase inhibitor $p21^{Waf1/Cip1/Sdi1}$ [208,209,212], while also downregulating cyclin A and cyclin-dependent kinase 2 [208,212]. Moreover, NO appears to modulate cell proliferation through targeting important mitogenic tyrosine kinase receptors and their downstream signaling cascades, such as the epidermal growth factor receptor [212-214]. As discussed in previous sections, amongst the major effects of CR is to increase NO production. Therefore, it is

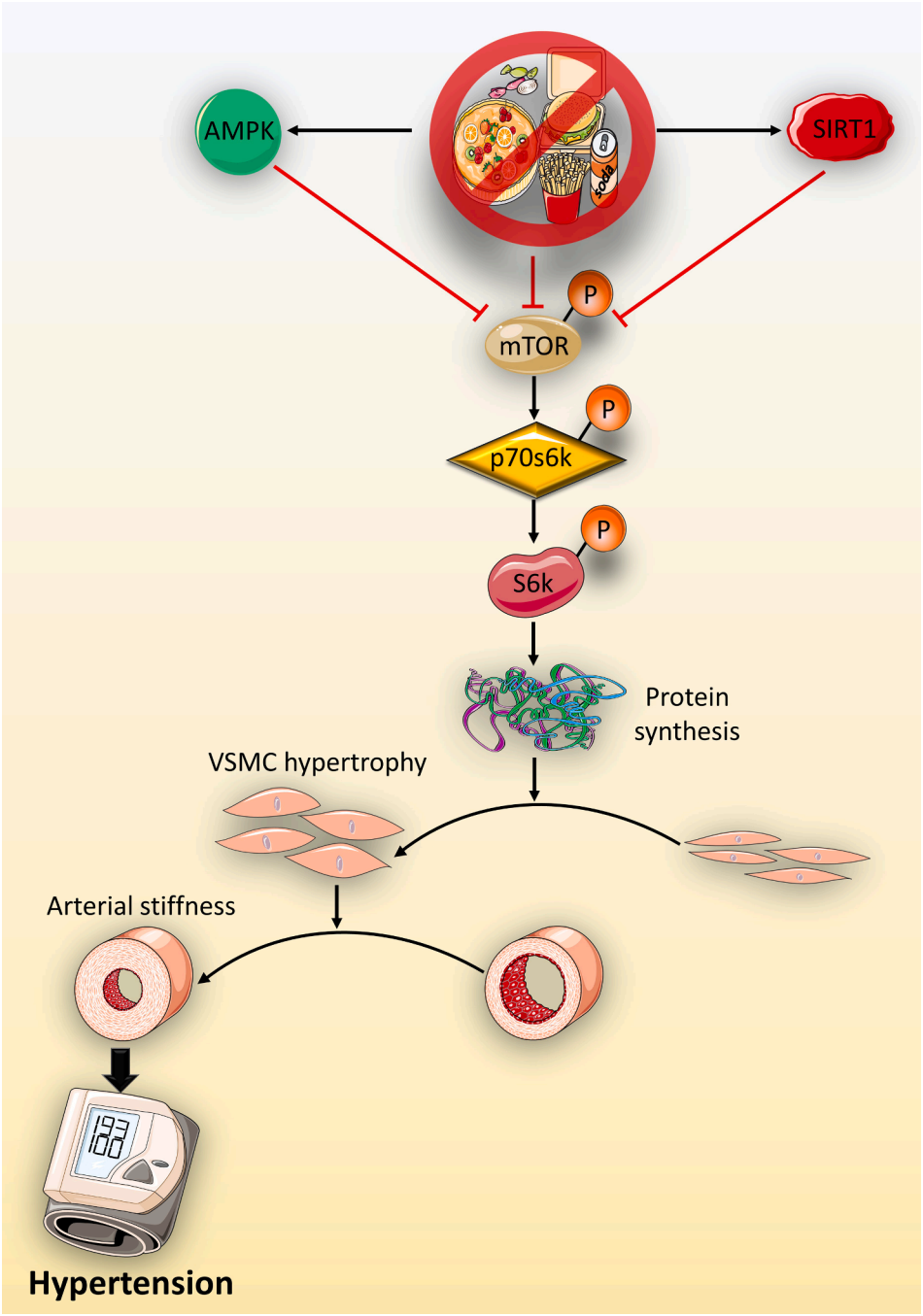

Fig. 4. Caloric restriction inhibits mTOR-mediated VSMC hypertrophy. mTOR activity, predominantly regulated by nutrient availability, stimulates cellular growth and protein synthesis pathways. In vascular smooth muscle cells (VSMCs), mTOR and its downstream p70s6 ribosomal protein kinase (p70s6k) enhance growth and protein translation leading to VSMC hypertrophy. CR leads to a state of decreased nutrient availability, which inhibits mTOR/p70s6k signaling. This pathway is also inhibited by SIRT-1 and AMPK, both of which stimulated by CR.

tempting to speculate that CR mediates part of its anti-hypertensive effect a NO-mediated suppression of VSMC proliferation.

4.3. mTOR and VSMC hypertrophy

mTOR is a conserved threonine/serine kinase that regulates cellular metabolism and growth by integrating multiple environmental cues and energy states. In contrast to other energy sensing metabolites like SIRT-1 and AMPK, mTOR activity is inhibited, rather than activated, by reduced nutrient availability since it is usually involved in cellular growth and protein synthesis [215]. In fact, SIRT-1 and AMPK can also inhibit mTOR and regulate its activity in low energy status [216,217] (Fig. 4).

An interesting interplay between CR and mTOR has been receiving increased attention. Apparently, long term CR in rats and mice decreased the phosphorylated levels of arterial mTOR and its downstream p70 S6 ribosomal protein kinase [128,218]. Aside from the enhanced autophagy discussed previously, inhibition of mTOR/P70S6K signaling decreases protein synthesis and thus affects vascular remodeling by decreasing aortic vascular smooth muscle cell hypertrophy [219]. VSMC hypertrophy, which involves elevated p70S6K activity [219,220], is commonly seen in hypertension, which partly explains why spontaneously hypertensive rats have higher aortic mass than their wild type controls [221]. In contrast, a reduction in p70S6K phosphorylation, consistent with a reduced hypertrophy of VSMCs and decreased arterial wall thickness, is observed in spontaneously hypertensive rats subjected to CR [10]. Therefore, we postulate that CR could relieve vascular resistance, and thus hypertension, by decreasing VSMC hypertrophy, and that this effect of CR occurs via suppressing the activity of mTOR/P706K and the anabolic cellular signaling pathways (Fig. 4).

5. ECM deposition and hypertension

The extracellular matrix (ECM) is a cardinal component of the connective tissue surrounding cells. Structural proteins like collagens, elastin, fibronectin, and proteoglycans make up the lion's share of this matrix. In the vasculature, the ECM plays a substantial role in the maintenance of the structural and mechanical integrity of the vessels, and in the regulation of cell-cell signaling and interaction. The balance between the different structural proteins greatly determines the biomechanical properties of vessels. Under physiologic conditions, deposition and turnover of collagen as well as the collagen/elastin ratio are kept under control. However, increased disintegration of elastin fibers and/or excess desposition of collagen and fibronectin, remininescent of a pro-inflammatory microenvironment, contribute to ECM remodeling, fibrosis and increased arterial stiffness [222,223], which consequently alter vessel biomechanics. Diminished elasticity/compliance or increased stiffness often lead to elevated systolic blood pressure and increased cardiac work load, thus precipitating cardiac hypertrophy and increased risk of cardiovascular complications. [224,225] (Fig. 4). At the molecular and cellular level, ECM deposition and remodeling are mediated by many paramaters, prime of which are TGF-β and matrix metalloproteases (MMPs).

The TGF-β superfamily of proteins encompasses more than 40 members that play important roles in many physiologic and pathophysiologic processes. Disruption of the TGF-β signaling has been associated with vascular fibrosis and arterial aging [226]. Indeed, TGF-β1, the isoform expressed in endothelial cells, VSMCs, myofibroblasts, and vascular adventitial macrophages, is usually upregulated during fibrotic processes and ECM remodeling [227]. Indeed, TGF-β1 and its downstream SMADs augment the expression of collagen, fibronectin, and PAI-1 and connective tissue growth factor (CTGF) [226,228,229]. TGF-β is also involved in regulating collagenases and tissue inhibitors of metalloproteinases (TIMPs), which in turn affect ECM [230]. It is important to mention that other non-SMAD pathways are also involved in the profibrotic signaling pathway of TGF-β. These pathways involve c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), p38 MAPK, and phosphoinositide 3-kinase/Akt signaling [231].

Matrix metallopeptidases (MMPs) are a family of endopeptidases that play a major role in ECM degradation and remodeling [232]. Degradation of collagen, elastin, and other ECM proteins by MMPs is linked to a pro-inflammatory microenvironment that prompts a direction of secretion, proliferation, migration, and senescence in endothelial cells and vascular smooth muscle cells. This contributes to increased intima thickness and arterial stiffness through fibrosis, calcification, and further endothelial dysfunction [227]. The effect of MMPs on vascular fibrosis as pertains to hypertension remains to be fully elucidated as both stimulatory and inhibitory modulation has been described for different MMP isoforms [233]. MMP9 potentiates fibrosis and DNA damage [234], and MMP2 increases collagen deposition and fibronectin secretion [235,236]. Furthermore, an association between elevated blood pressure and increased levels of MMP-2 and MMP-9 has been reported [237-240]. Inconsistent results have, however, been shown in hypertensive patients with reported unchanged [241-243], increased [244], or decreased [245] MMP-2 levels. Variable study designs, hypertension severity and comorbidities, and other analytic factors in the studies might be at the basis of such discrepancies [246], hence the need for further studies.

Several animal studies emphasize the effect of CR on the vascular ECM deposition and hints to the modulation that happens in the processes at the molecular level. Increased stiffening of large elastic arteries with aging is thought to be driven by alterations in the major structural proteins involving collagen deposition and elastin fragmentation as we have alluded to earlier [247-250]. In rodents, lifelong CR was shown to prevent stiffening of large elastic arteries by abolishing the age-related increase in collagen deposition or elastin degradation [128,204,251]. Recently, it was reported that moderate CR potentiates exercise-induced improvements in proximal aortic stiffness [252]. Consistent with this, the fibrotic process in the aortae of aging rats was markedly reduced in rats subjected to CR compared to *ad libitum*, evident by a remarkable decrease in TGFβ1 and collagen levels [253]. This study also revealed that CR decreased the activity of Jun-N-terminal kinase (JNK) and p38 [253], both of which are implicated in the non-SMAD fibrotic signaling pathways of TGF-β as mentioned earlier. It appears that the anti-fibrotic effect of CR occurs via a reduction in TGF-β1, PDGF-BB, and MMP2 signaling. [254,255].

MMP-9, which has a role in vascular fibrosis, elastin degradation, and blood pressure elevation, also mediates the effect of CR on ECM composition. Indeed, lifelong CR prevents the increase in MMP-9 expression, thus curbing the effects of this enzyme on vascular stiffening and the consequent elevation in blood pressure [128]. The link between CR and MMP-9 is mediated by SIRT-1 deacetylase activity, which is increased in lifelong CR as discussed above. MMP-9 transcription is enhanced by the acetylation of its promoter region at the NF-κB binding site, and the direct acetylation of NF-κB at lysine residue 310 also increases its affinity for the MMP-9 promoter, which together result in increased expression of MMP-9 and subsequent adverse alterations in the arterial ECM [256] (Fig. 5). Contextually, overexpression of SIRT-1 deacetylase enzyme in isolated macrophages, known to be a major source of MMP-9 secretion into vascular tissue [257], could decrease the facilitatory effect of acetylation of NF-κB and MMP-9 gene promoter on MMP-9 expression. The increased SIRT-1 deacetylase activity that happens in lifelong CR could thus contribute to decreased MMP-9 activity and subsequent reduction of ECM adverse changes and arterial stiffening [128], thus possibly ameliorating to the pathology of hypertension (Fig. 5). By reducing arterial stiffness through this MMP-9 activity modulation in addition to the reduction of oxidative stress and inflammation, CR could thus contribute to an overall protection from cardiovascular disease morbidity and mortality risk factors (Fig. 6). Patients on restricted calorie diets had decreased levels of TGF-β1 along with the reduced blood pressure when compared to subjects on western diet [15]. Data from both animal and human models provide evidence that CR can modulate ECM deposition in vascular walls. Favorable alterations in the

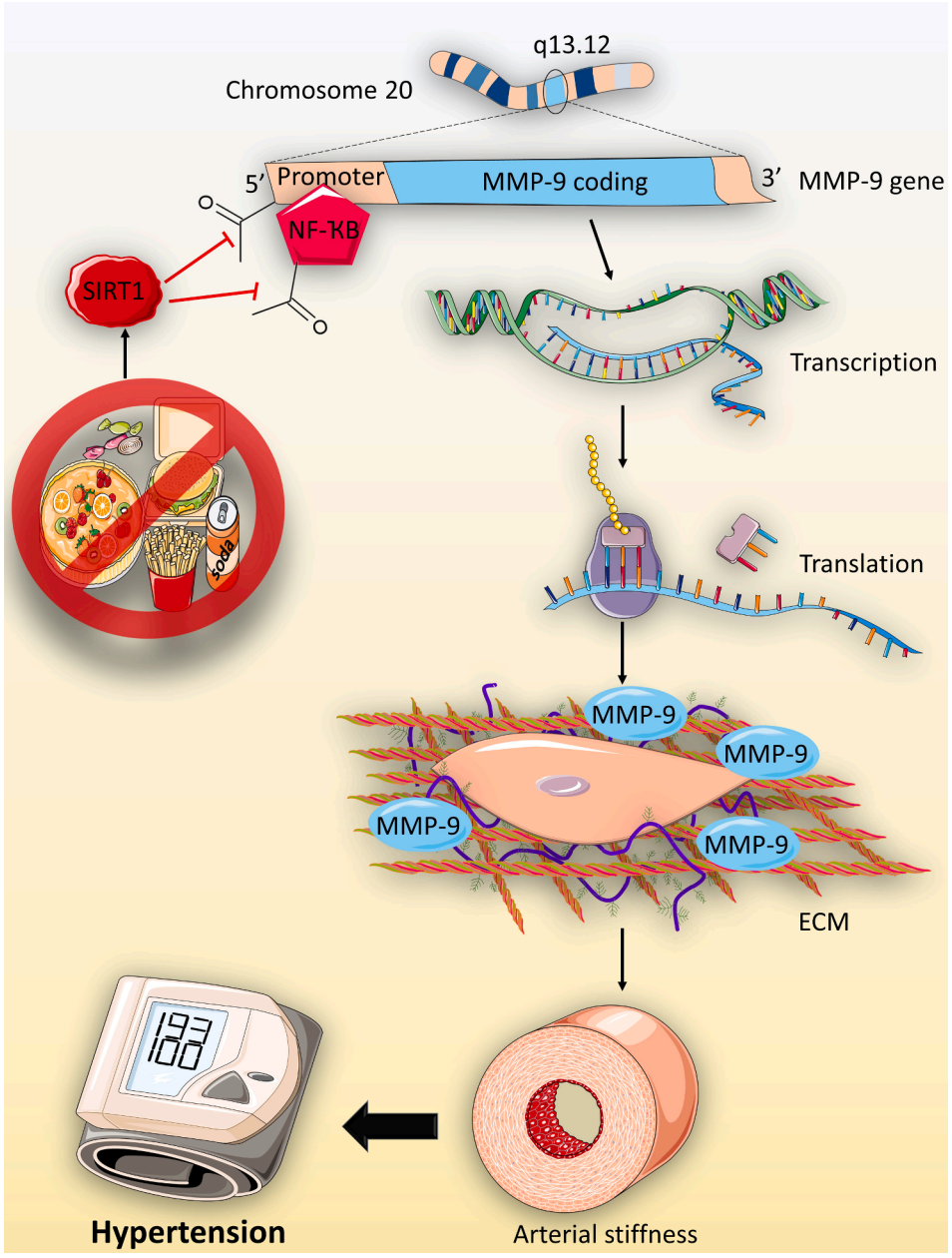

Fig. 5. The link between caloric restriction and MMP-9 through SIRT-1 deacetylase activity. MMP-9 transcription is enhanced by the acetylation of its promoter region at the NFκB binding site. Direct acetylation of NFκB at lysine residue 310 also increases its affinity for the MMP-9 promoter. This results in increased expression of MMP-9 and subsequent adverse alterations in the arterial ECM that contributes to blood pressure elevation. With CR, SIRT-1 deacetylase activity is increased which reverses the promoting effects of NFκB acetylation and MMP-9 expression. Increased SIRT-1 deacetylase activity that occurs in lifelong CR could thus contribute to decreased MMP-9 activity, and the consequent reduction in adverse ECM changes, thereby ameliorating arterial stiffening and alleviating hypertension.

matrix may greatly improve arterial compliance, and thus possibly contribute to the decrease in blood pressure (Figs. 5 and 6).

6. Conclusion

Despite significant advances in medicine and pharmacotherapeutics, the burden of CVD on the healthcare sector remains high. The positive effects of CR on cardiovascular health parameters prove to be promising means of non-pharmacological intervention that could mitigate CVD progression and complications. The effect of CR in reducing high blood pressure by reversing the vascular dysfunction is of unique importance especially with the absence of complete success of traditional antihypertensive medication in controlling hypertension in some cases. We have dissected the different mechanisms that mediate CR's effect by linking different pathways involving inflammation, ROS, ECM deposition, NO, and others. However, it is important to mention here that further studies are still needed to establish causal relationships. Finally, the question whether weight loss is required to achieve the beneficial effects of CR requires further observation and analysis. Controlled studies are thus necessary to isolate the major effects of fasting, in absence of body weight variation, hence verifying whether the sole activation of the energy-sensing pathways is sufficient to mimic the effects of CR on the vasculature.

CRediT authorship contribution statement

Ahmad A. Al Attar: Conceptualization, Project administration. **Gracia I. Fahed:** . **Malak M. Hoballah:** . **Shona Pedersen:** Formal analysis. **Ahmed F. El-Yazbi:** . **Suzanne A. Nasser:** Investigation. **Alessandra Bitto:** . **Alexander N. Orekhov:** Data curation. **Ali H. Eid:** Resources, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

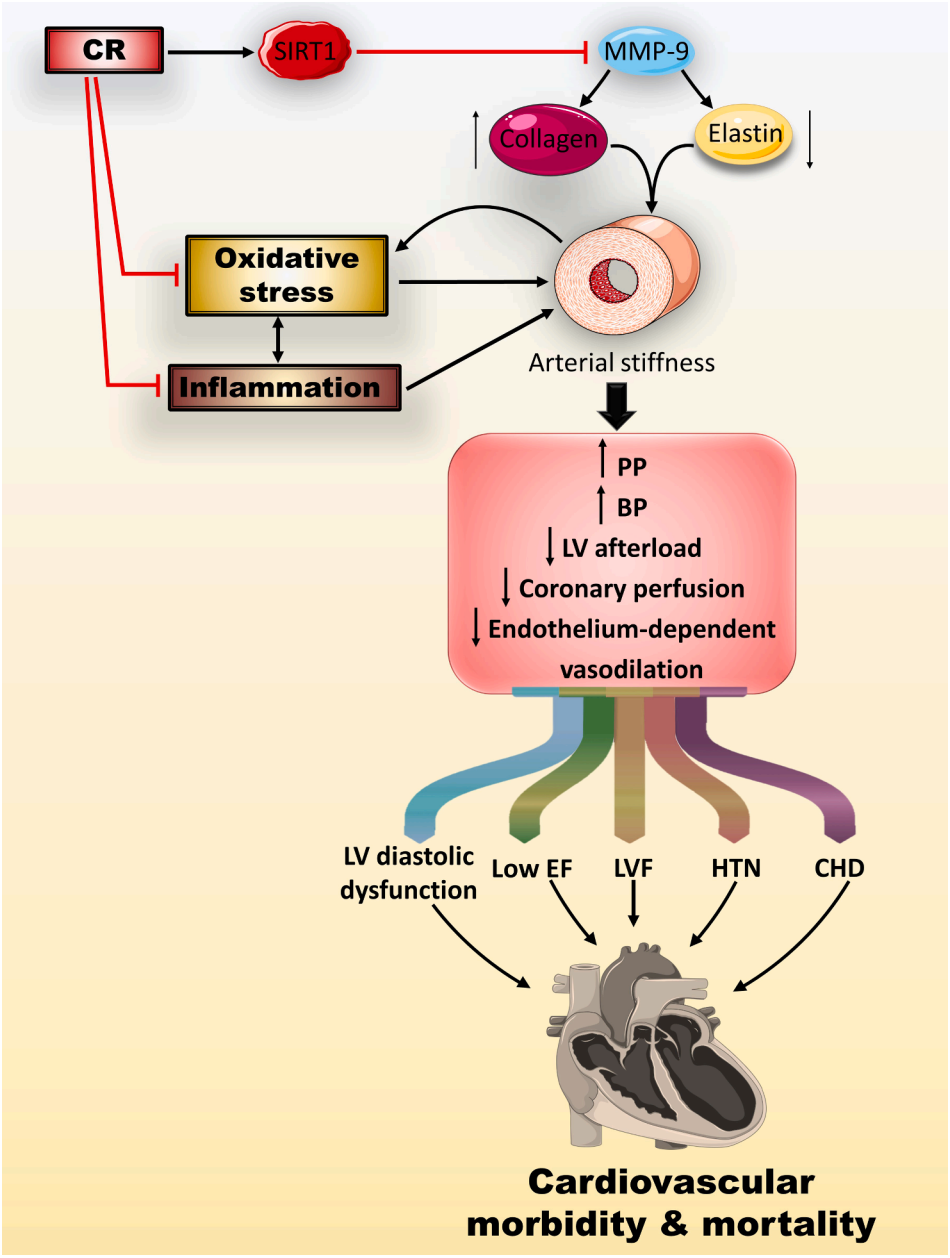

Fig. 6. Effect of caloric restriction on protection from arterial stiffening. Oxidative stress and inflammation, both of which contribute to stiffening of arteries, are attenuated by CR. Increased expression of SIRT-1 by a caloric restricted diet also produces inhibitory effects on the expression of MMP-9, an enzymes that promotes arterial stiffening through increasing collagen and decreasing elastin levels. By suppressing stiffening of the arteries through these mechanisms, CR could thus contribute to preventing the detrimental effects of arterial stiffening on cardiovascular parameters like the increased blood pressure (BP), increased pulse pressure (PP), increased Left ventricle afterload (LV afterload), decreased coronary perfusion, and decreased endothelium dependent vasodilation. This in turn leads to protection from known cardiovascular disease morbidity and mortality risk factors like left Ventricle diastolic dysfunction (LV diastolic dysfunction), low ejection fraction (EF), Left Ventricular Hypertrophy (LVH), Hypertension, and Coronary Heart Disease (CHD).

the work reported in this paper.

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