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HYPERTENSION AND OBESITY (E REISIN, SECTION EDITOR)

Hypertension and Insulin Resistance: Implications of Mitochondrial Dysfunction

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Abstract Mitochondria are the primary generators of cellular reactive oxygen species (ROS); their pathophysiological roles in hypertension and insulin resistance are but imperfectly understood. Mitochondrial dysfunction has been linked to the etiologies of many complex diseases, but many other factors, including the upregulation of the renin-angiotensin system (RAS) and vitamin D deficiency, have also been implicated in hypertension pathogenesis. Hypertension resulting from the disruption of the RAS contributes to the risk of cardiovascular disease. Likewise, experimental and clinical evidence indicate that RAS stimulation and low vitamin D levels are inversely related and represent risk factors associated with the pathogenesis of hypertension. Furthermore, RAS activation induces insulin resistance, resulting in increases in ROS levels. High levels of ROS are harmful to cells, having the potential to trigger both mitochondrial-mediated apoptosis and the degradation of the mitochondrial DNA. Diabetes risk is also associated with high levels of oxidative stress; taking vitamin D, however, may reduce that risk. The finding that mitochondria possess both a functional RAS and vitamin D receptors is the starting point for improving our understanding of the interaction of mitochondria and chronic disease states, which understanding should lead to decreases in the chronic disease burden attributable to hypertension, diabetes, or both.

Keywords Mitochondrial dysfunction · Hypertension · Insulin resistance · Vitamin D · Angiotensin II · Heat-shock protein 70

Introduction

The mitochondrion is a membrane-bound organelle found in most eukaryotic cells [1]. Not only do mitochondria supply cellular energy, but they are also involved in signaling, cell differentiation, and control of the cell cycle—this last including both cell growth and cell death [2]. Mitochondria—and mitochondrial dysfunction—have been linked to various complex human diseases (e.g., mitochondrial [3] and cardiac pathologies) and have been implicated in the human aging process [4]. It is worth noting that while mitochondria are known to be significant sources of reactive oxygen species (ROS), the generation of cardiac ROS, the pathophysiological role of its formation in hypertension, and the molecular mechanisms of the process itself have yet to be determined [5••]. Further implicated in the pathophysiology of hypertension are the activation of the sympathetic nervous system, the upregulation of the renin-angiotensin system (RAS), the dysregulation of G protein-coupled receptor signaling, increased levels of inflammation, altered T cell function, and decreased levels of vitamin D [6••, 7••, 8•], and the single element common to all of these processes is the bioavailability of ROS. Excess ROS levels promote oxidative stress, as do the concomitant reduced antioxidant capacities in the renal, nervous, and cardiovascular systems, of which the last is of particular importance as the incidence of cardiovascular disease (CVD) is more closely linked to vitamin D deficiency than it is to any other risk factors: The disruption of the RAS by lack of

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vitamin D leads to hypertension and endothelial dysfunction, both potential precursors to CVD [7••], and playing an essential role in the functional changes associated with and resulting from CVD is angiotensin II (Ang II), a peptide hormone.

A product of the RAS, Ang II is significantly involved in regulating both cardiac homeostasis and nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase activation. When activated by Ang II, NAD(P)H oxidase is the primary source of ROS [9]. Marked increases in the incidences of such ROS-related maladies as hypertension, hyperlipidemia, myocardial infarction, and stroke as well as of chronic kidney disease and type 2 diabetes mellitus (T2DM) have been linked to vitamin D deficiency. Low vitamin D levels also are related to the upregulation of the RAS, increased inflammation, and endothelial dysfunction [10•]. Moreover, experimental and clinical evidence has determined that low vitamin D levels and the associated RAS stimulation—each individually playing a role in the induction of hypertension—are inversely related and that the two combined have a significant impact on the pathogenesis of hypertension [7••, 11•, 12••, 13]. Of particular relevance is the fact that the mitochondrial localization of vitamin D receptors (VDRs) as well as of angiotensin II type 1 (AT_1) and 2 (AT_2) receptors has been established [14, 15••, 16••]. In addition, the vitamin D analog calcitriol protects renovascular function during hypertensive episodes by down-regulating the AT_1 receptors and thereby reducing oxidative stress [17•]. We have been able to demonstrate—at the mitochondrial level—that VDR-modulated heat-shock protein 70 (Hsp70)/AT_1 is involved in the mechanism that paricalcitol manifests to provide renal protection in hypertension. We therefore propose that heat-shock response-induced Hsp70-mediated cell protection might lead to low AT_1 expression via VDR induction [18••].

The activation of the RAS and the resulting increases in ROS induce insulin resistance, itself leading to T2DM [19, 20]. Though the exact roles of AT_1 in the modulation of redox signaling, mitochondrial function, and cardiac oxidative stress remain unclear, existing data link AT1 receptor-mediated Nox2 activation to each, further evidence that any or all may be linked to the metabolic syndrome, a multiplex risk factor for CVD [21]. Further, mitochondrial apoptosis and degradation, altered energy balance, and the accumulation of lipids in the heart can all arise from enhanced RAS activation and associated increases in ROS levels. Continuing in that vein, the inhibition of mitochondrial biogenesis and mitochondrial dysfunction are both linked to a number of genetic and environmental factors, the process of aging, hyperglycemia, and hypertension as well as to oxidative stress and impairments in metabolic signaling [22]. It should be noted that growing evidence suggests that diabetes risk is modified by vitamin D: pancreatic beta cell dysfunction, insulin resistance, and systemic inflammation, multiple factors involved in the pathophysiology of T2DM, are all directly and indirectly affected by vitamin D [23]. As demonstrated by a previous double-blind clinical trial, obesity-associated inflammation might be mitigated by treatment with alfacalcidol and insulin resistance lessened through the enhancement of relative VDR expression [24]. A different study determined that a deficiency or insufficiency of serum vitamin D may be predictive of insulin resistance in individuals with prediabetes [25]. Empirical evidence further links low levels of 25-hydroxyvitamin D with CVD and a number of its risk factors, such as diabetes, metabolic syndrome, insulin resistance, hypertension, microalbuminuria, and inflammation, all of which suggest that vitamin D replacement therapy might positively affect diabetic patients at risk for CVD [26]. More studies are needed—and those performed with less heterogeneous populations—to determine whether vitamin D deficiency causes or aggravates (or both) hypertension and to determine, as well, whether vitamin D supplementation provides one or more cardioprotective effects [27].

According to recent findings, the metabolic pathways of the age-related chronic diseases hypertension and diabetes are remarkably similar, and each disease's etiology and progression are susceptible to comparable environmental and genetic factors. An intriguing hypothesis has been put forth that insulin resistance and, ultimately, diabetes and/or hypertension might result from mitochondrial dysfunction, endoplasmic-reticulum stress, inflammation, metabolic alterations, or any one or combination of the previous.

Lastly, mitochondria's possessing of both a functional RAS and vitamin D receptors provides a basis for beginning to understand how mitochondria and chronic disease states interact and, consequently, should engender reductions in the burdens that attend hypertension- and diabetes-associated chronic disease.

Hypertension Linked to Mitochondrial Dysfunction

First linked to hypertension in 1961 [28], mitochondria are the primary source of ROS in cells. Today, neither the pathophysiological role of ROS in hypertension nor the regulation of mitochondrial ROS generation in the cardiovascular system is yet clear. Further complicating matters, the molecular mechanisms underlying the previously mentioned regulatory process have yet to be concretized [5••]. Oxidative stress is defined as an imbalance between antioxidant defenses and the production of ROS. High levels of ROS production cause cell damage but at lower levels induce subtle changes in intracellular signaling pathways (termed redox signaling). Sources of ROS include uncoupled nitric oxide synthases, xanthine oxidase, NAD(P)H oxidases, and mitochondria. The first three are critical to redox signaling, as they are implicated in the pathophysiology of hypertension [29]. ROS generation, then, has an important role in the vasoconstrictor and vasodilator

responses, in vascular remodeling, and in the altered vascular mechanics associated with hypertension. What is particularly interesting is the presence of crosstalk (theorized as being a kind of feed-forward vicious cycle [30]) between the two main sources of ROS in hypertension—mitochondria and NAD(P)H oxidase. Oxidative stress—mitochondrial oxidative stress in particular—is a key factor in the development of cardiac hypertrophy. Hypertrophy signaling kinases and transcription factors such as mitogen-activated protein (MAP) kinase and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) are, among others, activated by ROS. Further, translocator protein (TSPO) in the outer mitochondrial membrane is involved in oxidative stress and cardiovascular pathology [31]. When a condition of oxidative stress exists, the crosstalk between mitochondria and NAD(P)H oxidases can be targeted pharmacologically. Mitochondrial-targeted antioxidants have been demonstrated to break the aforementioned vicious cycle resulting from such crosstalk, thus inhibiting mitochondrial ROS production and reducing NAD(P)H oxidase activity. This novel strategy of specifically targeting antioxidants may prove effective in the treatment of diabetes, hypertension, and any number of degenerative neurological disorders in which mitochondrial oxidative stress plays a role [32].

As was stated previously, several processes and components are thought to be involved in the pathophysiology of hypertension, examples of which include the upregulation of the RAS, sympathetic nervous system activation, the dysregulation of G protein-coupled receptor signaling, inflammation, altered T cell function, and vitamin D deficiency [6••, 7••, 8•]; common to all of them is the increased bioavailability of ROS caused by reduced antioxidant capacity in the cardiovascular, nervous, and renal systems and, as should be apparent, excess ROS generation. Such increased bioavailability disrupts the RAS, with the resulting hypertension and endothelial dysfunction contributing to CVD risk [7••]. The peptide hormone Ang II is critical to the pathophysiological modulation of cardiovascular function. Ang II is the principle effector of the RAS and is a hormone having a critical role in hypertension; it is involved in regulating cardiac homeostasis and is a potent stimulator of (NAD(P)H) oxidase, the major source of and primary trigger for ROS generation [9]. Indeed, recent data suggest that Ang II induces mitochondrial dysfunction, which, in turn, promotes excessive amounts of ROS, e.g., superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO^-$) from mitochondria [33]. Similarly, by activating endothelial cell NAD(P)H oxidases and forming peroxynitrite, Ang II induces the disruption of mitochondrial function via a protein kinase C-dependent pathway. Disrupting mitochondrial function leads to the modulation of endothelial nitric oxide (NO) generation, and such modulation has ramifications in terms of the development of endothelial dysfunction [34]. By inducing mitochondrial dysfunction, Ang II contributes to the aging process, and because Ang II is a pleiotropic peptide, the protective effects (on age) of blocking the RAS are expected to be various. Calorie restriction (CR)—a dietary strategy for extending human lifespan—and RAS blockade share several characteristics, in that both have been shown to ameliorate or retard such age-related conditions as hypertension, diabetes, and renal and cardiovascular diseases [35]. CR's effect on age retardation appears to be linked to the actions of peroxisome proliferator-activated receptors (PPARs) and is at least partly accomplished by regulating mitochondrial activity. The downregulation of transforming growth factor-beta (TGF-β) and the upregulation of Klotho and sirtuins are other mechanisms that may benefit from the RAS blockade. Numerous investigations have confirmed that Ang II excites the generation of mitochondrial oxidants, consequently leading to the depression of energy metabolism. Alternately, inhibiting Ang II lowers mitochondrial oxidant generation, thereby protecting the mitochondrial structure and enhancing energy production [36]. RAS inhibition yields renal and cardiac benefits beyond the mere reduction of blood pressure; these benefits are ostensibly linked to mitochondrial function. Moreover, RAS inhibition has been shown to prevent mitochondrial dysfunction in the kidneys of spontaneously hypertensive rats (SHRs) [18••, 37]. New details regarding the therapeutic role of the RAS blockade in hypertension might be revealed with human testing.

Strikingly, altered vitamin D metabolism in the kidneys of SHRs has been seen. Data suggest that serum 1,25(OH)2D is inappropriately low in relation to the elevated parathyroid hormone (PTH), and this may be due, at least in part, to the impaired responsiveness to PTH of renal 1-hydroxylase and to the enhanced metabolism of 1,25(OH)2D, and elevated PTH or other agents may stimulate the 1-hydroxylase in the kidney even before the onset of hypertension [38]. As previously reported herein, our efforts have led to our demonstrating that VDR-modulated Hsp70/AT1 expression is involved, at the molecular level, in the mechanism by which the VDR inducer paricalcitol provides renal protection in hypertension [18••]. Hsp70 chaperone proteins possess ATP-binding and ATPase domains; further, the interaction of these proteins with intracellular substrates is ATP dependent, and the conversion of ATP to ADP causes Hsp70 to have a greater affinity for protein substrates [39]. Immunoreactivity to Hsp70 expressed in the kidney causes salt-sensitive hypertension, with autoimmunity playing a role in this particular brand of hypertension and with the following key antigen being identified: Hsp70 expressed in the kidney [40••]. In addition, Hsp70 promotes the biogenesis of the epithelial sodium channel (ENaC) as well as its trafficking to the apical surface of epithelial cells. Because the ENaC's role in blood pressure homeostasis is essential, its under-regulation leads to refractory hypertension [41]. Moreover, the thiazide-sensitive NaCl cotransporter (NCC), responsible for renal salt reabsorption, is targeted by

thiazide diuretics. NCC is commonly prescribed in the treatment of hypertension and, interestingly, is linked to the degradation of chaperone proteins associated with the endoplasmic reticulum [42].

Finally, because the chaperone protein Hsp70 modulates several signaling pathways via their interactions with proteins and because caveolin is required to traffic the AT_1 receptor through the exocytic pathway, we examined the effect of losartan, an AT_1 receptor, on the association of caveolin-1 and Hsp70 in the proximal tubules of SHRs; we also looked at Hsp70's involvement in the regulation of oxidative stress by losartan. After losartan administration, the interaction of caveolin-1 and Hsp70 was shown in the proximal tubules of SHRs. The translocation of Hsp70 to the proximal tubule membranes in SHRs being treated with losartan might exert a cytoprotective effect by downregulating NAD(P)H subunit Nox4 [43]. Then, Hsp70 is necessary to improve mitochondrial bioenergetics [44••], and indeed, mitochondrial Hsp70 expression has been shown [45, 46]. We mentioned previously that mitochondria possess a functional RAS, Hsp70, and vitamin D receptors, the recognition of which should lead to a better understanding of the interaction of mitochondria and chronic disease states. Such an understanding should reveal potential therapeutic targets for enhancing mitochondrial function and, thereby, helping to alleviate the multiple burdens of chronic diseases that are associated with hypertension and diabetes.

Insulin Resistance Linked to Mitochondrial Dysfunction

The activation of the inflammation cascade, endothelial dysfunction, and oxidative stress are all implicated in insulin resistance as well as in the vascular complications associated with diabetes. Aggravating these processes are obesity, insulin resistance, hyperglycemia, hypertension, and dyslipidemia, each of which is a comorbidity of diabetes. Of these, insulin resistance and its associated conditions (obesity and T2DM) have been linked to changes in oxidative metabolism, indicating that mitochondria, a key player in cellular function, may have a role in the onset and progression of insulin resistance [47]. Inherited or acquired (or both) mutations in either the number or quality of the mitochondrial DNA (mtDNA) are possible causes for the variability of baseline mitochondrial function that is seen in insulin's primary target tissues, skeletal muscle cells, adipocytes, and hepatocytes. Such abnormalities—and their quantitative aspects—though known to cause insulin deficiency and resistance and, thusly, diabetes mellitus, have not been well addressed [48], a lack that needs rectifying owing to the importance of mitochondrial oxidative stress in the etiology of CVD associated with T2DM. Hyperglycemia and insulin resistance are both linked to excess ROS production. ROS, in turn, are known to damage sundry mitochondrial macromolecules, of which damage one important result is mitochondrial dysfunction [49]. Accumulating evidence supports the notion that mitochondrial dysfunction may be an intermediary between cardiovascular risk factors and the eventual formation of vascular lesions, an idea that is further bolstered by the fact that mitochondria are both sources and targets of ROS [50]. Interestingly, insulin resistance is also induced by the activation of the RAS and resulting increases in ROS. At least one factor involved in the complex etiology of insulin resistance (and the subsequent development of T2DM) is the overabundance of oxidants [19, 20]. Still not well understood, however, are the effects of AT_1 on mitochondrial function and oxidative stress in the heart as well as this receptor's precise role in mediating redox signaling, but data suggest that AT1 receptor-mediated Nox2 activation may lead to impaired redox signaling and altered mitochondrial activity, metabolic dysregulation, and other cardiovascular complications associated with metabolic syndrome [21]. Furthermore, mitochondrial apoptosis and degradation, altered bioenergetics, and lipid accumulation in the heart can all result from enhanced RAS activation and associated increases in ROS. It should be noted that not only do genetic and environmental factors, aging, hyperglycemia, and hypertension contribute to reduced mitochondrial biogenesis and mitochondrial dysfunction, but they also cause impairments in metabolic signaling and increase oxidative stress levels [22]. Reductions in insulin signaling are linked to multiple components, including the expansion of adipose tissue and the increase of pro-inflammatory adipokines, an overactive RAS, decreases in the oxidative capacity of skeletal muscle mitochondria and increases in intramuscular lipids, and the overproduction of ROS [51]. A recent report summarized the effects of RAS on the energy-producing metabolic pathways of the heart and detailed the role of Ang II in inducing cardiac insulin resistance and mitochondrial dysregulation; the function of ROS and that of sirtuins in these processes were also revealed [52]. Another finding of this report was that CR ameliorates Ang II-induced mitochondrial remodeling and cardiac hypertrophy [53]. Additionally, therapies combining AT_1 antagonists and vitamin D analogues have succeeded in markedly reducing the biological markers of diabetic nephropathy. Vitamin D and its receptors play important roles in the cardiovascular system and insulin resistance since one of vitamin D's pleiotropic effects is its interaction with components of the RAS [54•]. Indeed, in combination with an insufficiency of vitamin D, the upregulation of islet RAS genes can result in the impairment of islet function. Independently of vitamin D status, such upregulation can, as well, increase insulin resistance [55•].

We have already touched on the notion that vitamin D might modify diabetes risk and that evidence exists supporting this notion. The direct and indirect effects of vitamin D on the various mechanisms related to the pathophysiology of T2DM include pancreatic beta-cell dysfunction, impaired insulin

action, and systemic inflammation [23]. A double-blind clinical trial demonstrated that treatment with alfacalcidol could reduce obesity-associated inflammation. The supplement might, as well, be used to reduce insulin resistance by enhancing the expression of VDR and its downstream genes, which last have been confirmed as being associated with the glucose homeostasis pathway [24]. Furthermore, insulin resistance can be predicted by a deficiency or insufficiency of serum vitamin D in individuals with prediabetes [25]. Finally, observational data suggest that low levels of 25-hydroxyvitamin D are associated with CVD and might be risk factors for diabetes, metabolic syndrome, insulin resistance, hypertension, microalbuminuria, and inflammation. The replacement of vitamin D may mitigate some of the risk factors of CVD in diabetic patients [26]. As mentioned before, more studies—and in a greater number of more homogeneous populations—are necessary if we are to reach a firm conclusion regarding vitamin D deficiency and its associated potential outcomes [27].

The VDR is a member of the steroid/retinoid receptor superfamily of nuclear receptors that interacts with and is regulated by BAG1L, a nuclear protein that binds Hsp70 family molecular chaperones [56]. Though the role of stress proteins in diabetes yet remains unclear, newly acquired data point to their playing an important part in the development of both diabetic metabolic disturbances and the associated complications of same. Recent studies have found a positive correlation between the expression of the 72-kDa heat-shock protein in skeletal muscle and metabolic status in T2DM patients. In fact, diabetics whose levels of 72-kDa activity are 10 times lower than are those levels in non-diabetics have reduced insulin-stimulated glucose uptake, storage, and oxidation, with the lipid oxidation being correspondingly less sensitive to the effects of insulin [57]. Taken together, the data suggest that stimulating heat-shock protein genes might lessen insulin resistance, a notion that could lead to the development of new pharmacological interventions. In agreement with the previous, the positive association of plasma Hsp70 and insulin was confirmed in a study of a group of elderly patients; this study also concluded that high levels of Hsp70 protect against the development of insulin resistance during aging [58].

The loss of mitochondrial Hsp70, an element vital to the protein import process, has been linked to alterations to the mitochondrial proteome, and these alterations to the impairment of the mitochondrial-protein import machinery, which impairment is implicated in the pathogenesis of diabetic cardiomyopathy [59]. The heat-shock response (HSR) was originally recognized as a mechanism for cellular defense. When inhibited, its defensive activities are curtailed, giving rise to metabolic abnormalities. In addition, activating the HSR leads to a lessening of insulin resistance and improvements in glucose homeostasis in both rodents and humans, as doing so increases the expression of heat-shock protein 72 [60]. Inducers of heat-shock protein synthesis share exercise-associated metabolic pathways with 5′ adenosine monophosphate-activated protein kinase (AMPK), peroxisome proliferator-activated receptor-alpha coactivator (PGC1-a), and sirtuins [61], all of which reduce inflammatory cytokine levels, insulin resistance, visceral obesity, and body weight, while at the same time increasing mitochondrial function, regulating lipid composition, normalizing the structure of the mitochondrial membrane, and maintaining organ function. Restoring the stress response is a critical step in addressing insulin resistance and its associated clinical manifestations.

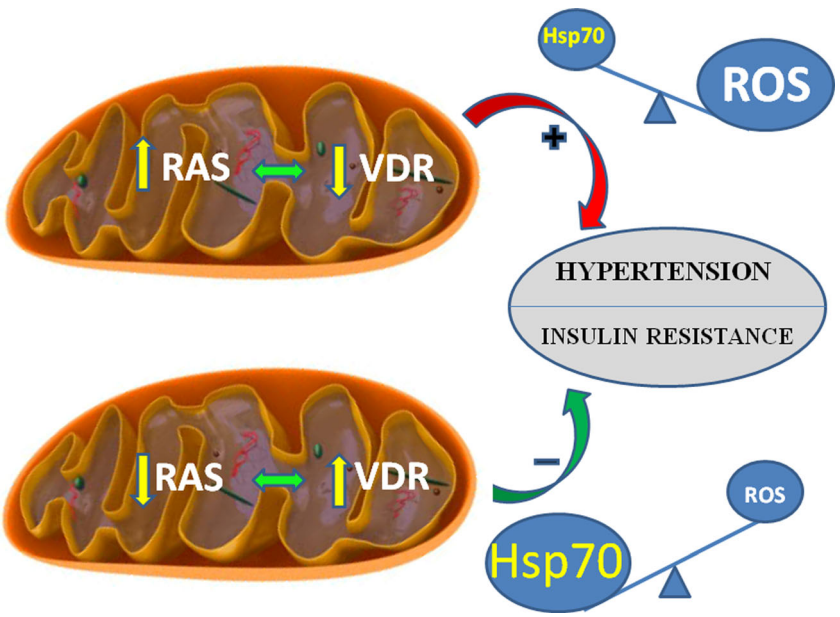

Fig. 1 Hypertension and insulin resistance linked to mitochondrial dysfunction. A representative overview of the potential interaction between RAS and VDR in the mitochondrion: The proposed ROS-Hsp70 interaction may occur throughout the mitochondria

Conclusions

According to the collected evidence, the dysregulated pathways of the age-related chronic diseases hypertension and diabetes are quite similar, in that environmental factors and genetic susceptibility are both implicated in the etiology and progression of each disease. A recent and thought-provoking hypothesis holds that mitochondrial dysfunction may be a precursor to insulin resistance and, thus, to diabetes, hypertension, or both (see Fig. 1).

Compliance with Ethics Guidelines

Conflict of Interest Walter Manucha, Bob Richie, and León Ferder declare no conflicts of interest.

Human and Animal Rights and Informed Consent The animal experiments described herein were not performed by any of the authors, signifying that no animals were harmed in the course of preparing this manuscript.

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AUTHOR QUERIES

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Q1. Please check provided address for affiliation 2 if correct.
Q2. Please check if the section headings are assigned to appropriate levels.
Q3. "Ethics Statement" has been changed to "Human and Animal Rights and Informed Consent". Please check if correct.
Q4. Please provide annotations for bulleted references.