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Review

Daily and seasonal mitochondrial protection: Unraveling common possible mechanisms involving vitamin D and melatonin

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ABSTRACT

From an evolutionary point of view, vitamin D and melatonin appeared very early and share functions related to defense mechanisms. In the current clinical setting, vitamin D is exclusively associated with phosphocalcic metabolism. Meanwhile, melatonin has chronobiological effects and influences the sleep-wake cycle. Scientific evidence, however, has identified new actions of both molecules in different physiological and pathological settings. The biosynthetic pathways of vitamin D and melatonin are inversely related relative to sun exposure. A deficiency of these molecules has been associated with the pathogenesis of cardiovascular diseases, including arterial hypertension, neurodegenerative diseases, sleep disorders, kidney diseases, cancer, psychiatric disorders, bone diseases, metabolic syndrome, and diabetes, among others. During aging, the intake and cutaneous synthesis of vitamin D, as well as the endogenous synthesis of melatonin are remarkably depleted, therefore, producing a state characterized by an increase of oxidative stress, inflammation, and mitochondrial dysfunction. Both molecules are involved in the homeostatic functioning of the mitochondria. Given the presence of specific receptors in the organelle, the antagonism of the renin-angiotensin-aldosterone system (RAAS), the decrease of reactive species of oxygen (ROS), in conjunction with modifications in autophagy and apoptosis, anti-inflammatory properties inter alia, mitochondria emerge as the final common target for melatonin and vitamin D. The primary purpose of this review is to elucidate the common molecular mechanisms by which vitamin D and melatonin might share a synergistic effect in the protection of proper mitochondrial functioning.

1. Introduction

The deep understanding of mitochondrial dysfunction is a strategic objective since the decoupling in the generation of cellular ROS, and the associated inflammation contributes inexorably to the development of multiple pathologies that are until now poorly understood. Mitochondrial dysfunction has been related to the etiologies of many complex diseases where the overactivation of the renin-angiotensin-aldosterone system (RAAS), vitamin D deficiency, and the reduction of melatonin synthesis converge. In this sense, experimental and clinical evidence indicates that inflammation, oxidative stress, as in mitochondrial dysfunction, are consistent with low levels of melatonin and vitamin D, and also represent risk factors connected with development and maintenance of prevalent acute and chronic pathologies [1,2].

Multiple sclerosis, a demyelinating inflammatory disease, has been the cornerstone for establishing relationships between melatonin and vitamin D. Ghareghani and colleagues recently published a review summarizing and proposing common mechanisms between sunlight, vitamin D, bacterial infection, and melatonin production in the pathophysiology of multiple sclerosis [3]. A variety of epidemiological and experimental evidence proposes that high circulating levels of vitamin D are linked with a lower risk of multiple sclerosis [4–6], and the supplementation of the vitamin might reduce the relapses [7]. Insufficient sunshine exposure and hypovitaminosis D are widespread in temperate countries, which present the highest incidence for multiple sclerosis [8]. Patients who have multiple sclerosis showed lower bioavailable $25(OH)D_3$ and $1,25(OH)_2D_3$, but no difference in the ratio of other metabolites, *e.g.*, $25(OH)D_3/24,25(OH)_2D_3$ [9]. Miclea and colleagues proved the modulation of seasonal multiple sclerosis disease activity through vitamin D supplementation, showing a notable reduction in the quarterly relapse rate in late winter/early spring [10].

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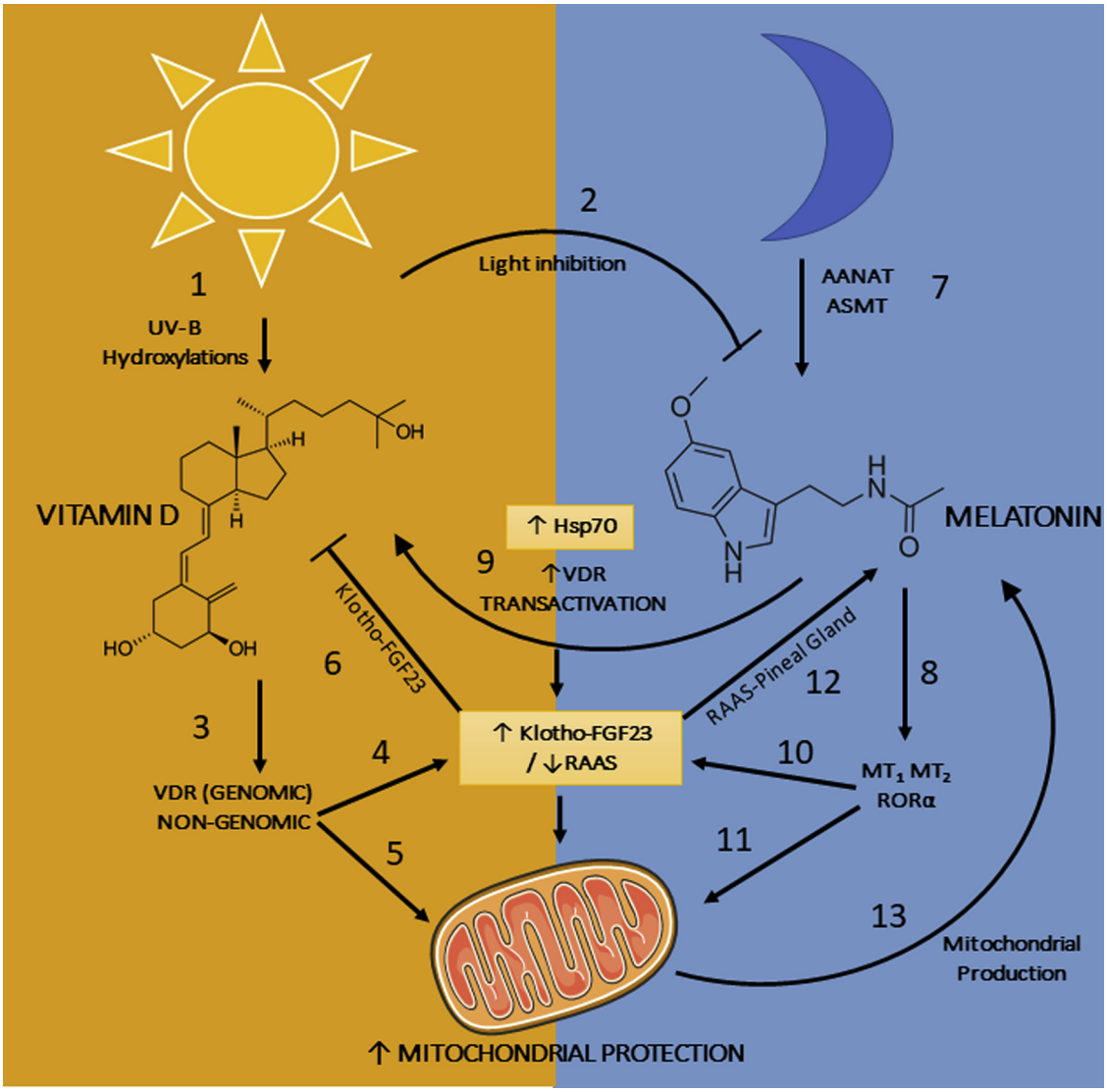

Fig. 1. Graphical overview of common mechanism for mitochondrial protection. (1) Vitamin D3 (cholecalciferol) derives from the UV-B radiation exposure of the cholesterol precursor 7-dehydrocholesterol. To be biologically active vitamin D3 must be hydroxylated in the liver and the kidney, eventually being converted to $1,25(OH)_2D_3$. (2) Light inhibit the synthesis of melatonin. (3) The effects of vitamin D3 are primarily mediated by its interaction with a nuclear vitamin D receptor (VDRn), which acts as a constituent of the nuclear receptor superfamily of ligand-activated transcription factors. (4) One of the main convergent pathways of the mitochondrial protective action of vitamin D seems to be the modulation of the RAAS system. Vitamin D contraregulation of RAAS seems to be also mediated by Klotho. Vitamin D decreases the ratio of Klotho/RAAS levels. (5) Vitamin D exerts protective effect of on mitochondrial function by increasing antioxidant activity and improving the efficiency of the organelle. (6) Klotho and FGF-23 inhibit the synthesis of vitamin D. (7) Melatonin, the chemical expression of darkness, is produces in the pineal gland during the night. The precursor serotonin is N-hydroxylated by the enzyme aralkylamine N-acetyltransferase (AANAT), the product is converted into melatonin by the Acetylserotonin O-methyltransferase (ASMT). (8) Melatonin exerts its effects by melatonin G-protein-coupled receptors in the plasma membrane (*e.g.*, MT1 and MT2); and orphan nuclear receptors (ROR). (9) Melatonin increases the expression of VDR and up-regulates its transcriptional activity. Hsp70, a molecule induced by melatonin and vitamin D interacts with the VDR and plays a role in controlling the concentration of the steroid receptor in cells, facilitates the intracellular localization of active vitamin D metabolites, and might also transactivate the VDR. (10) An angiotensin-melatonin axis linked to mitochondrial function has been proposed. Melatonin antagonizes RAAS and up-regulates Klotho. (11) Melatonin exerts prominent pleiotropic effect resulting in to the modulation of healthy mitochondrial function. See Fig. 2. (12) Vitamin D might have a negative regulatory effect on melatonin. This effect might be mediated by the downregulation of the RAAS, since paracrine angiotensin-II and angiotensin-IV impact on pinealocytes and enhance de synthesis of melatonin. (13) Mitochondria are an intracellular source of melatonin. The enzymes involved in melatonin biosynthesis and degradation have been found in the mitochondrial matrix. *This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License;* https://smart.servier.com.

Melatonin, also a crucial immunomodulatory molecule, presents seasonal fluctuations, and its plasma levels show an inverse correlation with multiple sclerosis clinical relapses [11]. Even more, patients with multiple sclerosis present mitochondrial dysfunction [12], oxidative stress [13], and alteration in the RAAS (as an increase in the activity of angiotensin-converting enzyme) [14,15]; this could explain the beneficial synergism of vitamin D and melatonin against the disease.

The pathophysiology, incidence, and prognosis of other common diseases, including cancer [16,17], neuropsychiatric disorders [18,19], and hypertension [20,21], also show a seasonal fashion. For example, there is a lower diagnosis of cancer during the periods with the highest physiologic levels of vitamin D (summer) or periods of highest levels of melatonin (winter) [22].

Taking together all the current evidence, we illustrate the common pathways by which vitamin D and melatonin interact, exerting mitochondrial protection. To the extent of our knowledge, we describe for

the first time the potential synergic but not redundant effects of vitamin D and melatonin regarding daily and seasonal mitochondrial welfare (Fig. 1).

2. Vitamin D: generalities and mechanism of action on the mitochondria

Vitamin D_3 (cholecalciferol) is a fat-soluble, secosteroid, antioxidant, and an ancient prohormone; it derives from the UV-B radiation exposure of the cholesterol precursor 7-dehydrocholesterol. Given that it is produced non-enzymatically, it occupies an ancestral place in evolution [23]. It acts as a solar radiation scavenging end product that has been preserved in many life forms, which range from the phytoplankton of 750 million years ago to present-day mammals [24]. In humans, although vitamin D can be taken in the diet, the essential source depends on sun exposure, which is influenced by season and latitude. To be biologically active vitamin D_3 must be hydroxylated in the liver and the kidney, eventually being converted to $1,25(OH)_2D_3$ at the end of these processes [25]. The connection between vitamin D and mitochondria begins from its synthesis because the aforementioned hydroxylation occurs in this organelle through a redox process [25,26]. Extrarenal hydroxylation of vitamin D can also be effectuated in many tissues, including the prostate, placenta, lung, brain, and immune cells [27,28]. Despite the fact that it has been frequently associated with the regulation of phosphocalcic metabolism, the relationship between vitamin D deficiency and the incidence of cardiovascular, neuropsychiatric, metabolic, autoimmune, and neoplastic pathologies, among others, emphasizes its pleiotropic action [29,30].

The effects of vitamin D_3 are primarily mediated by its interaction with a nuclear vitamin D receptor (VDRn), which acts as a constituent of the nuclear receptor superfamily of ligand-activated transcription factors. VDR forms a dimer with retinoid X receptor (RXR) and binds to vitamin D response elements (VDRE) in the DNA, thus interacting with various coupling and essential transcription factors to activate promoters and control gene expression [31]. Additionally, vitamin D_3 exerts rapid, non-genomic actions in the activation of signaling molecules, the opening of Ca^{2+} and Cl^- channels, and the interaction with the membrane-associated rapid response steroid (MARRS), among others [32,33].

Interestingly, an interrelation between vitamin D and the circadian system has been demonstrated. Plasma concentration of $1,25(OH)_2D_3$ and Vitamin D Binding Protein (VDP) present circadian oscillations in subjects of different ethnic groups [34]. Further, vitamin D alters the expression of circadian genes in adipose-derived stem cells [35]. It has also been recently described that Clock (a protein involved in the circadian clock) interaction with the vitamin D receptor VDR accelerated its binding to the VDR response element in a circadian fashion [36]. Even more, vitamin D has been proposed as a modulator of the sleep-wake cycle since low levels of the hormone are correlated with poor quality sleep and short sleep duration [37]. Gominak and Stumpf went even further and hypothesized the existence of an anatomic and epidemiological association between sleep disorders and vitamin D deficiency [38].

Of particular interest for the present review, Silvagno and colleagues, have also described the localization of VDR in mitochondria of platelets, megakaryocytes [39], and keratinocytes. Moreover, they showed that the translocation of VDR is associated with proteins of the permeability transition pore [40]. However, the specific functional role of the VDR on the organelle remains unclear.

The effects of vitamin D at the level of mitochondrial metabolism are complex, and the literature on these actions is partially contradictory. In most cases, the impact of the steroid on anabolic and catabolic pathways seems to be tissue and dose-dependent. While most investigations agree on the protective effect of vitamin D on mitochondrial function by increasing antioxidant activity [41], the influence of this compound concerning oxidative phosphorylation activity and oxygen consumption appears to diverge between muscle and the other tissues [42].

Vitamin D deficiency is linked to a decrease in oxygen consumption and disruption of mitochondrial function in skeletal muscle [43–45]. Romeu Montenegro and collaborators recently demonstrated, *in vitro*, an increase in mitochondrial oxygen consumption in myoblasts and myotubules as well as an elevation in maximum respiration and ATP production after the administration of $1,25(OH)_2D_3$ [46]. A plausible explanation for the beneficial effect of vitamin D resulting in the catabolic promotion in muscle mitochondria would be the improvement of lipid metabolism, or "lipid flux," which might avoid lipotoxicity [47]. Vitamin D deficiency has been linked to high oxidative stress, muscle atrophy, and reduced mitochondrial function of patients with chronic low back pain [48]. Supplementation with $1,25(OH)_2D_3$ enhanced the activity of citrate synthase and antioxidant enzymes [49].

Translating the regulatory effect of vitamin D in the skeletal muscle to immunometabolism, Calton and colleagues proposed that the seasonal increase of $25(OH)D_3$ plasma levels is associated with reduced systemic inflammation, immune cells bioenergetic profiles, and whole-body energy metabolism [50]. Low levels of $25(OH)D_3$ during winter might enhance oxidative metabolism and activate peripheral blood mononuclear cells [51].

In different cell models *in vitro*, as well as in the murine model, *in vivo*, the silencing of the VDR gene increased the activity of the respiratory chain and the production of ROS [52]. $1,25(OH)_2D_3$/VDR signaling shows suppressive effects on respiratory chain transcription [52–55]. As a follow-up to the *in vitro* studies, $VDR^{-/-}$ mice showed an elevated basal metabolism, explained by an increase in the total energy expenditure, oxygen consumption, CO_2 production, fatty acid β-oxidation, and uncoupling proteins (UCPs) upregulation compared with those in wild type mice [56,57]. VDR downregulates the transcription of proteins of the respiratory chain and can reduce the mitochondrial membrane potential, thus diverting the metabolism to a biosynthetic route and optimizing energy consumption [41].

Recently, Blajszczak and Nonn reported a biphasic mechanism by which vitamin D modifies the mitochondrial function in prostate epithelial cells through genomic and non-genomic mechanisms. Initially, the treatment with $25(OH)D_3$ generates a transient pro-oxidant effect and a change in mitochondrial membrane potential, but prolonged exposure suppressed mitochondrial respiration, decrease in ATP synthesis, and up-regulation of genes related to the import of substrates and proteins into the mitochondria [58].

Mitochondrial genes related to oxidative phosphorylation (Cytochrome b5 and ATPase, H^+ transporting, V1 B2) as well as redox balance (Mn-containing superoxide dismutase, Catalase, Prolyl 4-hydroxylase, and Branched-chain aminotransferase) have also shown to be downregulated in the adult progeny of vitamin D deficient mothers [59].

One of the main convergent pathways of the mitochondrial protective action of vitamin D seems to be the modulation of the RAAS. Many aspects of the RAAS and the vitamin D systems were described in very primitive animals such as jellyfish, lamprey, and crab, among others. Classically, RAAS is a regulatory cascade that plays a critical role in the modulation of blood pressure and electrolyte and plasma volume homeostasis. Recently, much evidence of actions for the RAAS, which exceed the classically described signaling pathways, have been reported, and they involve inflammation and oxidative stress [60–64]. The RAAS has been identified in many tissues and organs, including those not typically associated with blood pressure and electrolyte and plasma volume homeostasis [65]. Concerning mitochondrial localization, the existence of angiotensin-II receptors type 1 (AT_1) and 2 (AT_2) and a functional RAAS has been probed by Abadir et al., and has been corroborated by our laboratory and others [66–70]. Since $1,25(OH)_2D_3$ suppresses renin gene transcription [71], and VDR ablation stimulates the RAAS and leads to accumulation of angiotensin II [72], we and others have demonstrated several times the attenuation of angiotensin-

II mitochondrial dysfunction through the modulation of vitamin D signaling [67,73–75].

Vitamin D contraregulation of RAAS seems to be also mediated by Klotho, another key mitochondrial protective molecule [76]; since $1,25(OH)_2D_3$ promotes the expression of Klotho [77]. Klotho gene inactivation displays a premature aging phenotype in mice and increased cardiovascular complications [78]. *In vivo* expression of exogenous Klotho reduces RAAS-related proteins, including angiotensinogen, renin, angiotensin-converting enzyme, and AT_1, and also normalizes blood pressure [79,80]. Conversely, angiotensin-II and oxidative stress-induced downregulation of Klotho mRNA [81]. Overexpression of Klotho induces a rise in the transcription of antioxidant enzyme genes, including catalase, superoxide dismutase 1 (SOD1), SOD2, peroxiredoxin 3 (PRDX3), and glutathione peroxidase 1 (GPX1) [82]. Finally, α-Klotho gene inhibition *in vivo* disrupted muscle progenitor cells, drove mitochondrial DNA (mtDNA) damage, decreased cellular bioenergetics [83], and impaired mitochondrial morphology [84]. Klotho, together with Fibroblast growth factor-23 (FGF23), exerts a negative effect on vitamin D synthesis, creating a negative contra-regulatory feedback [85].

The overactivation of the RAAS can lead to a vicious circle of enhanced production of mitochondrial ROS under redox signaling and reduced ATP production [86,87]. When this process persists, the resultant mitochondrial dysfunction activates the transcription factor NF-κB and, thus, the expression of the inducible nitric oxide synthase (iNOS), and other inflammatory molecules, forcing the cell to undergo apoptotic/pyroptotic death [88]. Fortunately, vitamin D antagonized these deleterious effects *via* the induction of NF-kB [89–91], as well as the transcription of iNOS [92–94], both *in vivo* and *in vitro*.

To counteract the mitochondrial dysfunction, and the redox imbalanced originated by the overactivation of RAAS, vitamin D decreases oxidative stress by activating the Sirtuin 1 (SIRT-1)/AMP-activated protein kinase (AMPK) and the nuclear factor E2-related factor 2 (Nrf2)/antioxidant defense pathways [95]. SIRT-1 regulates cell survival, mitochondrial biogenesis, metabolism, and stress responses, among others [96]. Lack of VDR from the genome of kidney cells decreases SIRT-1 expression, both *in vivo* and *in vitro* studies, enhancing the transcription of renin, angiotensinogen, and AT_1 [97]. Supplementation of $1,25(OH)_2D_3$ improves mitochondrial functioning by increasing the expression of SIRT-1 and other proteins of the sirtuin family [98,99]. Interestingly, positive feedback between SIRT-1 and VDR has been established, since SIRT-1 enzymatically enhances $1,25(OH)_2D_3$ signaling *via* VDR deacetylation [100]. AMPK is a serine/threonine kinase that also plays a central role in maintaining cellular metabolic balance by sensing and decreasing mitochondrial ROS [101], and modulating RAAS [102,103]. Vitamin D treatment increases the protein level of AMPK [104] as well as its phosphorylation (p-AMPK) [105].

Another member of the cellular stress defense pathway modulated by vitamin D is Nrf2 [106–108]. Nrf2 is a basic leucine zipper region transcription factor, which exerts antioxidant, anti-inflammatory, anti-aging, and prosurvival genes through antioxidant response elements (ARE), and therefore supports the structural and functional mitochondrial integrity [109,110]. $1,25(OH)_2D_3$ increases the expression of NRF2 in a VDR dependent fashion [111], and also promotes its translocation to the nucleus [112].

Forkhead box O1 (FOXO1) is a transcription factor that belongs to the forkhead box (FOX) family and integrates insulin signaling with mitochondrial function [113]. Over function of this transcription factor is associated with insulin resistance and metabolic abnormalities, both related to the physiopathology of type 2 diabetes mellitus [114,115]. $1,25(OH)_2D_3$ acts as a negative regulator of the FOXO1 activity [116–118]. It has been shown, *in vivo*, that FOXO1 is up-regulated in the skeletal muscle of global VDR-null mice; furthermore, *in vitro*, that the treatment of muscle cells with $1,25(OH)_2D_3$ decreased FOXO1 expression, nuclear translocation, and activity [119]. Chen and colleagues have also recently described that the silencing of the VDR decreased cell survival and increased both FoxO1 mRNA and protein expression, and that FoxO1 overexpression increased the production of ROS and decreased the mitochondrial membrane potential [120].

Another key player in mitochondrial dysfunction is the mammalian target of rapamycin (mTOR), a member of the phosphatidylinositol 3-kinase-related kinase family of protein kinases, which regulates transcription, autophagy, proliferation, growth, motility, survival, and protein synthesis [121]. Blocking mTOR signaling using rapamycin provides mitochondrial protection by decreasing ROS production and activating mitophagy [122–124]. Vitamin D seems to exert antiproliferative and immunomodulatory effects modulating mTOR pathway signaling [125]. It has been illustrated *in vivo*, and *in vitro*, that VDR activation promotes the expression of DNA damaged-induced transcription 4, which then activates tuberous sclerosis 2 (also an action promoted by AMPK), resulting in the inhibition of mTOR [126–130]. Similar to the effects of vitamin D on energy metabolism, the impact of the secosteroid in mTOR signaling differs among the skeletal muscle and other tissues. Insulin resistance and mitochondrial dysfunction are associated with sarcopenia and skeletal muscle integrity; in parallel, the protective role of $1,25(OH)_2D_3$ in muscle health is mediated by antagonizing these processes [48,131]. Muscles from mice lacking VDR present reduced activity of mTOR signaling components, which is related to an atrophic phenotype [132]. Treatment with vitamin D or a VDR receptor agonist, such as elocalcitol, improves insulin signaling and protein synthesis *via* AKT-mTOR induction [133,134]. Another possible indirect inhibitory mechanism of vitamin D on mTOR signaling might be the blockade of RAAS. Angiotensin-II promotes the phosphorylation of the mTOR and other mTOR downstream targets [135–137]. Similar to the effects of VDR agonist, blocking RAAS with losartan in podocytes and glomeruli of streptozotocin-diabetic rats decreased phosphorylated/activated forms of mTOR (Ser2448) [138].

Finally, also as a mechanism of mitochondrial protection, VDR activation induces the expression of heat shock proteins, *e.g.*, Hsp70 [139]. Interestingly Hsp70 is a molecular chaperone that has a critical role in the recovery of cells from stress and in cytoprotection [140] since it regulates a diverse set of signaling pathways for cellular oxidative stress responses [141]. Hsp70 is also localized at the lysosomal membranes, and it is indispensable for the stabilizing of this organelle [142]. We have shown that the induction of Hsp70 by a vitamin D agonist protects the kidneys in a rat model of hypertensive disease [74]. Moreover, Hsp70 interacts with the VDR and plays a role in controlling the concentration of the steroid receptor in cells, facilitates the intracellular localization of active vitamin D metabolites, and may also transactivate the VDR, even in the absence of the ligands [143,144].

Given the enormous number of pathways involved in vitamin D signaling, it is possible to understand the devastating effects of its deficiency in various pathological conditions. While the supplementation of vitamin D might appear as a "panacea" until now, it is only recommended to patients with deficiency, there is a big controversy in the literature about its effets [145,146], and there is still no adequate evidence of established limits of the preventive and therapeutic doses [147,148].

3. Melatonin: generalities and mechanism of action on the mitochondria

Melatonin is a highly functionally diverse molecule that has also been classified as a vitamin. Melatonin is ubiquitously distributed in many species, including algae, fungi, bacteria, plants, animals, and humans [149]. In vertebrates, it responds to a photoperiodic stimulus (day/night cycle) and requires for its synthesis the amino acid tryptophan. Initially, melatonin was described as a pineal regulator of the seasonal reproduction [150], and chronobiological events, such as sleep [151]. Currently is also know that the loss of melatonin is also involved in cardiovascular diseases including hypertension, neurodegenerative

diseases, kidney diseases, cancer, psychiatric disorders, bone diseases, metabolic syndrome, and diabetes, among others [152–154]. The loss of melatonin-dependent pleiotropic effects could explain, at least in part, the appearance of all these pathologies, where latest findings highlight it as a prominent pleiotropic effect to the modulation of healthy mitochondrial function [155,156].

For years, it was believed that melatonin was exclusive of pineal origin; however, it has also been demonstrated in retina, liver, intestine, kidneys, adrenal glands, thymus, thyroid gland, immune cells, among others tissues [157], and, probably exists in every cell of every species [158]. The most relevant finding in this area was identifying the presence of biosynthetic precursors, as well as the biosynthetic enzymes of melatonin in different subcellular compartments and especially within the mitochondria [159–161]. Previously, it was proposed that the presence of melatonin in the mitochondria was as a consequence of its uptake; however, higher levels of intramitochondrial melatonin compared to plasma melatonin levels were recently detected, and these higher values persist after pineal removal consistent with intramitochondrial synthesis [162]. It has been proposed that neither during evolution nor the diversification of species changed its original chemical structure; therefore, melatonin, a ubiquitous/promiscuous molecule, is also a privileged and highly conserved molecule since the bacteria existing billions of years ago as well as currently living plant and animal species contain melatonin. Similarly, multiple studies have reported on the highly conserved nature of RAAS during species evolution.

In the light of the most current knowledge, it could be proposed that both systems (melatonin and RAAS) evolved in parallel as adaptive-evolutionary defense mechanisms in which mitochondria appear to be a common final pathway. Accordingly, there is evidence from mitochondrial studies that reinforce the notion of how melatonin modulates the inflammatory and oxidative processes consistent with the involvement of the RAAS. An angiotensin-melatonin axis linked to mitochondrial function has been proposed, and since melatonin and angiotensin interact at multiple levels to regulate circadian function [163,164], we propose that mitochondria are a critical site of mechanistic interactions. Consistently, our laboratory demonstrated an antiarrhythmic effect linked to melatonin's cardiorenal protection due to a decrease in oxidative stress/fibrosis/apoptosis associated with AT_1 reduction [165], as well as mitochondrial edema; also dilated crests were prevented. Similar results were demonstrated in another model of kidney disease where melatonin, in addition to reducing AT_1 expression, normalized angiotensin-II levels, as well as oxidative stress [166]. These changes were accompanied by reduced blood pressure, fibrosis, and free radical damage. Reduction in oxidative stress is an essential mechanism for melatonin in mitochondria [167,168] and, consistent with mitochondrial ultrastructural findings, Prado et al. demonstrated that NADPH oxidase activity was significantly decreased and heat shock protein 70 (Hsp70) was induced as a result of melatonin treatment. The results from Prado and colleagues were replicated, in a hypertension rat model, by using a RAAS inhibitor, where enalapril enhanced Hsp70 expression and prevented fibrosis, apoptosis, mitochondrial damage, and NADPH oxidase activity. Thus, data suggest that AT_1 modulated during renal protection could be a consequence of Hsp70-mediated cell protection [74].

Melatonin increases heat shock proteins (HSPs) as part of its antioxidant protective effect [169], and more specifically, the activation of melatonin receptors MT1/MT2 increases the expression of HSPs [170]. Mitochondria express receptors for melatonin [160,171,172], and therefore, it is assumed that this canonical route mediates most of the melatonin's effects. Nonetheless, melatonin exerts some actions not mediated by its typical receptors, such as inhibition of TLR9-triggered proinflammatory cytokine production in macrophages by suppressing ERK1/2 and AKT activation [173]. Therefore, melatonin exhibits effects by binding to membrane receptors, nuclear receptors, intracellular proteins, and in a receptor-independent action [155,158,174,175]. Indeed, mitochondrial protection has been proved by the introduction of melatonin, heat shock factor 1 (HSF-1), an Hsp70 transcription factor, and glutamine, an Hsp70 inductor amino acid, each of which increases the levels of Hsp70 [176]. Also, Hsp70 supports an additional mechanism that involves translocase of the outer mitochondrial membrane 70 (Tom70), with the mitochondrial function being required to correct Hsp70 interaction with Tom70 [177]. Tom70-Hsp70 interaction is required for the recognition, unfolding, and translocation of amino acids into the mitochondria. The Tom70 protein is a crucial member of the mitochondrial outer and inner membrane transport systems.

Melatonin provides cardioprotection against ischemia/reperfusion injury by activating a vast array of signaling pathways such as sirtuins, and nuclear factor E2-related factor 2 (Nrf2), and the previously mentioned Tom70 [178]. Thus, another mechanism to consider is the co-induction of both Hsp70 and Nrf2-dependent antioxidant genes as a coordinated adaptive cytoprotective system for oxidative stress modulation [179]. Indeed, melatonin upregulates the endogenous antioxidant Nrf2 and heme oxygenase-1 (HO-1), which consequently reverses acute ethanol-induced elevated ROS and oxidative stress [180].

Melatonin is also linked to the upregulation of the expression of antioxidant proteins, including Nrf2 and HO-1, reduced ROS, increased SOD and GSH activities, and downregulation of iNOS [181–183] and tumor necrosis factor-α (TNF-α) activities. Also, melatonin reduces the stress-induced activation of the NF-κB signaling pathway by limiting the phosphorylation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα), and p65 nuclear translocation [184]. The NF-κB signaling pathway is a crucial target for mitochondrial dysfunction [185], and melatonin has demonstrated broad benefits with oxidative stress reduction, lower inflammation, and elevated mitochondrial integrity [186–188].

NF-κB signaling pathway is closely related to the cellular/mitochondrial cytotoxic effects of nitric oxide (NO) [189]. NO is implicated in cellular stress response since it is now well known that it inhibits components of the mitochondrial respiratory chain leading to cellular energy deficiency, and eventually, apoptosis [190]. To protect themselves from such injuries, cells have evolved integrated responses (so-called longevity assurance processes), composed of several genes termed vitagenes and including, among others, HSP members, such as Hsp70 and HO-1, to detect and control diverse forms of stress [191,192]. Interestingly, melatonin exerts a neuroprotective effect related to the vitagenes system as an increased expression of SIRT-1 and SIRT-2, Hsp70, and HO-1 activity [193].

To further elucidate the signaling pathways decoupled during mitochondrial dysfunction, de Cavanagh and colleagues reviewed how angiotensin-II blockade modulates molecular targets in mitochondria and how it slows aging [194]. Zhang et al. recently described the same processes, and remarkably both groups have identified several key signaling pathways that converge in mitochondrial dysfunction [195]; these include (as in the case of vitamin D) NF-κB, FOXO, mTOR, Nrf-2, Klotho/fibroblast growth factor 23 (FGF23), and sirtuins (Fig. 2). In brief, mTOR inhibition, enhanced sirtuin, and Klotho signaling contribute to mitochondrial integrity. Likewise, the transcription factor FOXO is strongly associated with mitochondrial function and longevity [196]. Of particular interest in the present review, melatonin modulates all these cell-signaling pathways. Thus, FOXO1 promotes apoptosis and plays a role in the intrinsic mitochondrial apoptotic pathway [197], while melatonin induces FOXO1 suppression by phosphatidylinositol 3-kinase (PI3K)-AKT axis linked to activation of SIRT-1 signaling, which increases granulosa cell resistance to oxidative stress and abolishes the autophagic response [198]. In parallel, León and colleagues demonstrated positive effects when they used melatonin in colon cancer cells, where melatonin diminishes endothelin-1 expression through the inactivation of FOXO1 and NF-κβ [199]. Furthermore, melatonin prevents the injury-induced depletion of AKT/forkhead transcription factors phosphorylation [200].

The mTOR alteration with mitochondrial dysfunction, protein

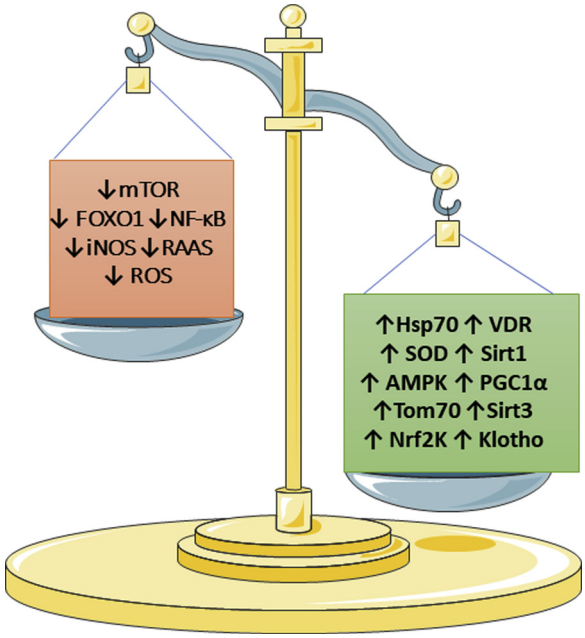

Fig. 2. vitamin D and melatonin exert mitochondria protection by modulating the following pathways. Downregulated pathways in red (RAAS, mTOR, FOXO1, iNOS, NF-κB); upregulated pathways in green (Klotho, SIRT-1, AMPK, Nrf2, Hsp70, Tom70, SOD, PGC1α). *This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License;* https://smart.servier.com.

misfolding, and aggregation was correlated with neurodegeneration, while melatonin increases neurogenesis and protects against neurodegeneration by mTOR modulation [201]. The primary role of melatonin in modulating mTOR and mitochondrial dysfunction has been recently highlighted. Indeed, melatonin modulates apoptosis through modifying mitochondrial-related oxidative stress and the modulation of Bcl-2, NF-κB, mTOR, and Wnt signaling pathways [202]; it is established that melatonin suppresses the mTOR signaling pathway [203].

As previously mentioned, Klotho, like FOXO, signaling, contributes to mitochondrial function, and consequently, abnormalities in the phosphate-Klotho axis have been related to inflammation and premature aging [204]. However, melatonin reduces inflammatory and oxidative stress processes through the positive induction of Klotho [205,206]. Additionally, melatonin protective effects have been robustly documented since previously, they have been associated with a double modulation of Klotho, such as sirtuin genes in mitochondrial dysfunction [207]. Melatonin protects cardiovascular toxicity by enhancing the expression of SIRT-1 with anti-inflammatory, antioxidant, and antiapoptotic effects [208]. Concerning mitochondrial dysfunction, melatonin prevents mitochondrial fission and mitochondria-derived superoxide production in diabetic hearts through SIRT-1 induction [209]. Also, melatonin treatment, in a rat model of cognitive impairment, increased hippocampal SIRT-1 expression and prevented amyloid β-induced neurotoxicity mediated by mitochondrial biogenesis [210]. However, the benefits of melatonin are not restricted to modulating the SIRT-1 signaling pathway. Melatonin, also upregulated SIRT-3 expression by increasing the transcription efficiency of the SIRT-3 promoter in human glioma cell lines U87 and U251 [211].

Shukla and colleagues have discussed the role of melatonin in targeting cell signaling pathways linked to mitochondrial dynamics [212]. Mitochondrial dynamics is a control system related to survival or apoptosis and involves fusion and fission processes, biogenesis, and mitophagy [213]. In this complex context, it has been established that melatonin diminishes myocardial ischemia-reperfusion injury *via* enhancing mitochondrial fusion/mitophagy and stimulating the AMPK-OPA1 signaling pathways [185]. Li and colleges also documented melatonin protection in cardiac injury *via* activating the AMPK/Nrf2 pathway [214]. Also, melatonin diminishes renal fibrosis by activating the AMPK/Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC1α) signaling pathway and rescuing mitochondrial function [215].

Collectively, the most current evidence illustrates the multiple signaling pathways that converge in the mitochondria and their vital functions, such as the maintenance of cellular integrity. As a consequence, in-depth knowledge of mitochondrial dysfunction and the molecular mediators involved will permit an understanding of the primary pathogenic mechanisms and propose possible new therapeutic alternatives. In this regard, the latest findings suggest that melatonin, and accurately, its interaction with the multiple signaling pathways altered during mitochondrial dysfunction, represents an attractive therapeutic alternative.

4. Common signaling mechanisms

In 1988 Dr. Walter Stumpf published a paper entitled: *"The Endocrinology of Sunlight and darkness Complementary Roles of Vitamin D and Pineal Hormones,"* describing the possible synergic mechanisms of both molecules on endocrine, autonomic, sensory, skeletal, and motor functions [216]. More than thirty years later, we propose -in the present review- that the mitochondria would act as a common nexus for the complementary action of these molecules.

Given the importance of mitochondria as the cell powerhouse and its role as a cellular signaling platform [217], evolution is likely to have provided defense system organisms that sustain the correct mitochondrial functioning during circadian and seasonal fluctuations [158]. Multiple studies have demonstrated the effect of circadian variation on important events related to mitochondria, including morphology, biogenesis, fission/fusion processes, and mitophagy [218–220]. Therefore, since the levels of melatonin and vitamin D are strongly influenced by sunlight exposure, and they interact with the circadian molecular machinery, we hypothesize that both molecules play an essential role as modulators of mitochondrial function and adaptation to circadian and seasonal variations.

The combination of melatonin and vitamin D results in strong synergistic effects, including cytostatic and apoptotic effects on breast cancer cells [221], protection against apoptotic ischemia-reperfusion injury in the rat kidney [222,223], and counteraction on adipogenic differentiation [224,225].

Melatonin seems to enhance the signaling of vitamin D. We demonstrated that chronic treatment with melatonin increases the expression of VDR in a rat model of unilateral ureteral-obstruction [165]. In agreement with our previous report, it has been shown, in vitro, that melatonin up-regulates the transcriptional activity of the VDR in human breast cancer cells [226].

However, vitamin D could have a negative regulatory effect on melatonin. In a clinical study, Golan and colleagues found that the overnight secretion of melatonin decreased after three months of high dose vitamin D supplementation in patients with multiple sclerosis. Consequently, a decrease in serum 25(HO)D_3 levels was associated with an increase in melatonin secretion [227]. This regulatory mechanism might be needed to inhibit redundancy and enhance the homeostasis of the system (Fig. 1). Regarding the mechanism involved in the inhibitory effects of vitamin D on melatonin production, it could be mediated by two mechanisms. VDR is expressed in several brain areas [228], which are related not only to the sleep-wake cycle but also to the innervation of the pineal gland, as the case of the superior cervical ganglia [229]. A second explanation might be the downregulation of the RAAS since paracrine angiotensin-II and angiotensin-IV impact on pinealocytes and enhance the synthesis of melatonin [164,230].

As mentioned before, both molecules intervene in common signaling pathways related to the protection and maintenance of an appropriate mitochondrial function. In Fig. 2, the common downregulated

pathways (RAAS, mTOR, FOXO1, iNOS, NF-κB), as well the upregulated pathways (Klotho, SIRT-1, AMPK, Nrf2, Hsp70) are presented.

5. Perspectives

Mitochondria are central to the optimal function of cells, organs, and organisms. The evidence that both vitamin D and melatonin focus a significant portion of their actions on these organelles portends their essential roles in maintaining proper molecular dynamics and cellular physiology. Throughout many eons of evolution, vitamin D and melatonin have co-habituated in organisms where they have developed mutually beneficial interactions in limiting inflammation, corralling oxidative stress, and reducing premature autophagy and apoptosis, among others.

In the present-day environment, however, most humans are likely relatively deficient in both vitamin D and melatonin. Based on current standards, a high percentage of humans suffer from suboptimal 25(OH) D_3 levels in part related to their significantly reduced exposure to sun light-derived ultraviolet B radiation. Similarly, humans are rendered hypomelatoninemic because of excessive light exposure at night (420-nm light is sufficient for plasma melatonin suppression in humans) [231], which compromises both the quantity of pineal melatonin secreted as well as perturbing the circadian influences of the melatonin rhythm, which are dependent of the regular recurring periods of light and darkness as determined initially by the rising and the setting of the sun [232]. Additionally, exposure to inappropriate wavelengths of visible radiation from manufactured light sources (*e.g.*, energy-efficient lighting -LEDs- and electronic devices) during the day has been reported to seriously jeopardize the amplitude of pineal melatonin production and secretion at night [233].

The chronic combined deficits of vitamin D and melatonin surely have pathophysiological consequences. The published data clearly show that hypovitaminosis D has detrimental effects that contribute to bone loss, osteoporosis, cancer, cardiovascular disease, inflammation, among others [234–236]. Likewise, low/altered melatonin levels are accompanied by a reported increase in cancer risk, seasonal depression, sleep disturbances, bone loss, and elevated oxidative damage (the pathological consequences of which are numerous), among others [237–239].

The collective findings should alert us to the need to pay more considerable attention to our photoperiodic environment, which has been profoundly corrupted in current so-called developed societies. The proper management of the quality of light to which humans are exposed could aid in restoring more normal levels of vitamin D and a regular and high amplitude melatonin rhythm, both of which may enhance disease resistance and improve well-being.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Not applicable.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest with the contents of this article.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jsbmb.2020.105595.

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