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Review

Diabetic cardiomyopathy: Role of the cardiac mitochondrial melatonergic pathway

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Abstract: Although cardiovascular diseases, especially diabetic cardiomyopathy (DCM), account for up to 80% of deaths in diabetic patients, the pathophysiological changes driven by diabetes on cardiovascular function are poorly defined and treated. As with many medical conditions, increased levels of Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Signal transducer and activator of transcription (STAT)3 are significant aspects of DCM pathophysiology. Research indicates that NF-κB dimer composition and nuclear (canonical) and mitochondrial (noncanonical) STAT3 interact across human cells to regulate the melatonergic pathway. Given the beneficial effects of melatonin across almost all cardiovascular diseases, including DCM, it is amiss that the melatonergic pathway has not been investigated in cardiomyocytes, cardiac fibroblast, or endothelial cells. In this article, we reviewed DCM pathophysiological factors/processes and link these to wider bodies of data on the regulation of the melatonergic pathway, providing a framework that better integrates previous disparate bodies of data on DCM, while indicating clear future research and treatment implications.

Keywords: diabetic cardiomyopathy; melatonin; NF-κB; STAT3; mitochondria; treatment; diabetes; methylglyoxal; RAGE; butyrate

Abbreviations

11β-HSD1: 11β-hydroxysteroid dehydrogenase type 1
5-HT: serotonin
5-HTTP: 5-hydroxytryptophan

α7nAChR: alpha 7nicotinic acetylcholine receptor
AADC: aromatic-L-amino acid decarboxylase
AANAT: aralkylamine N-acetyltransferase
acetyl-CoA: acetyl-coenzyme A
AhR: aryl hydrocarbon receptor
ASMT: N-acetylserotonin O-methyltransferase
BAG-1: bcl-2 associated athanogene 1
BDNF: brain-derived neurotrophic factor
CAR: cortisol awakening response
CTGR: connective tissue growth factor
CYP: cytochrome P450
DCM: diabetic cardiomyopathy
GR: glucocorticoid receptor
HDAC: histone deacetylase
HPA: hypothalamic-pituitary-adrenal
IDO: indoleamine 2,3-dioxygenase
LETM1: Leucine Zipper EF-hand containing Transmembrane protein 1
LAT-1: large amino acid transporter 1
MAMs: mitochondria-associated membranes
MHC: major histocompatibility complex
NAS: N acetylserotonin
NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3: NLR family pyrin domain containing 3
OXPHOS: oxidative phosphorylation
PDC: pyruvate dehydrogenase complex
PVN: paraventricular nucleus
RAGE: receptor for advanced glycation end products
SPMs: specialized proresolving mediators
STAT3: signal transducer and activator of transcription 3
T2DM: type 2 diabetes mellitus
TDO: tryptophan 2,3 dioxygenase;
TGF-β1: transforming growth factor-beta1
TPH: tryptophan hydroxylase

1. Introduction

Complications of diabetes can arise in many organs and tissues, including diabetic retinopathy and diabetic nephropathy. We look at the consequences of diabetes in the heart that lead to a diagnosis of diabetic cardiomyopathy (DCM). Given the worldwide rise in diabetes, DCM prevalence is increasing, with an estimated 30% of diabetic patients showing the presence of DCM [1], highlighting the importance of defining the pathophysiological processes driving DCM and therefore refining its treatment [2]. DCM is characterized by alterations in the structure and function of cardiomyocytes as well as cardiac fibroblasts and endothelial cells that are not caused by other current cardiovascular

disease (CVD) classifications. The clinical importance of this is highlighted by data showing that 50-80% of deaths from diabetes are due to CVD, especially DCM [3].

The pathophysiological processes underpinning DCM are many and various, being typically linked to alterations in cardiomyocyte metabolism, structural changes and Ca^{2+} regulation as well as hyperglycemia-induction of methylglyoxal as a precursor for advanced glycation end-products (AGEs) to activate the receptor for AGEs (RAGE) coupled with enhanced oxidative stress and inflammation, which all contribute to inducing myocardial fibrosis [4]. Numerous factors typically associated with most medical conditions are also evident in DCM, including increased Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Signal transducer and activator of transcription (STAT)3, and suboptimal mitochondrial function, coupled to the suppression of sirtuins and endogenous antioxidants/antioxidant enzymes [5,6]. Many of the detailed cellular changes, like most medical conditions, arise from data derived from preclinical models.

As with most medical conditions, there is a growing appreciation of the roles of systemic and circadian processes in the pathophysiology of a given condition in a particular organ/tissue [7], including DCM [8]. DCM pathogenesis is therefore not only associated with local myocardial metabolic disorders but is also co-influenced by systemic factors such as circadian rhythms, immune inflammation, and gut microbiota [7,8]. Diabetes mellitus can directly or indirectly interfere with cardiac function by altering gut microbiota and intestinal barrier function, thereby complicating DCM pathophysiology. Such data highlight the importance of a holistic perspective, further complicating an organ-specific understanding of DCM.

Research indicates that most medical conditions, especially aging-associated medical conditions, may be powerfully determined by alterations in night-time dampening and resetting by pineal melatonin in the first half of sleep and its interaction with the cortisol rise in the second half of sleep that peaks in the cortisol awakening response (CAR) [9]. As well as aging, pineal melatonin suppression is typically associated with aging-accelerating conditions, such as type 2 diabetes mellitus (T2DM) [10,11], indicating that alterations in night-time dampening and resetting are relevant aspects of the circadian and systemic alterations driven by T2DM, which changes the night-time regulation of DC cardiomyocytes, cardiac fibroblasts, and endothelial cells. Consequently, T2DM mimics aging by dysregulating how pineal melatonin and circadian cortisol dampen and reset body cells and systems for the coming day [9].

The capacity of circadian processes to optimally dampen and reset at night seems dependent upon local melatonergic pathway upregulation in a given organ/tissue, as indicated by vagal nerve stimulation only having efficacy if local melatonin can be increased in an inflamed organ, as shown in preclinical [12] and clinical [13] studies. A growing body of data indicates that local melatonergic pathway regulation across diverse human cells is determined by the interactions of STAT3 and NF-κB dimer composition [14,15], with STAT3 and NF-κB being intimate aspects of DCM pathophysiology [5,6].

Here, we review how circadian/systemic interactions in the modulation of local melatonin production may be core aspects of DCM, especially as driven by STAT3 interactions with NF-κB dimer composition. First, night-time processes of dampening and resetting are briefly reviewed.

2. Night-time dampening and resetting

There is a growing appreciation of the role of alterations in night-time dampening and resetting in the pathoetiology and pathophysiology of a host of diverse medical conditions, especially aging

associated conditions such as Alzheimer's disease [16] and cancer [17]. This is also pertinent to conditions linked to accelerated aging, such as T2DM [18], where the suppression of night-time pineal melatonin production changes the nature of the interactions of melatonin and cortisol over the course of sleep in preparation of body cells, microenvironments, and systems for the coming day. The night-time changes in pineal melatonin and cortisol at night and their alterations over aging and in T2DM are shown in Figure 1.

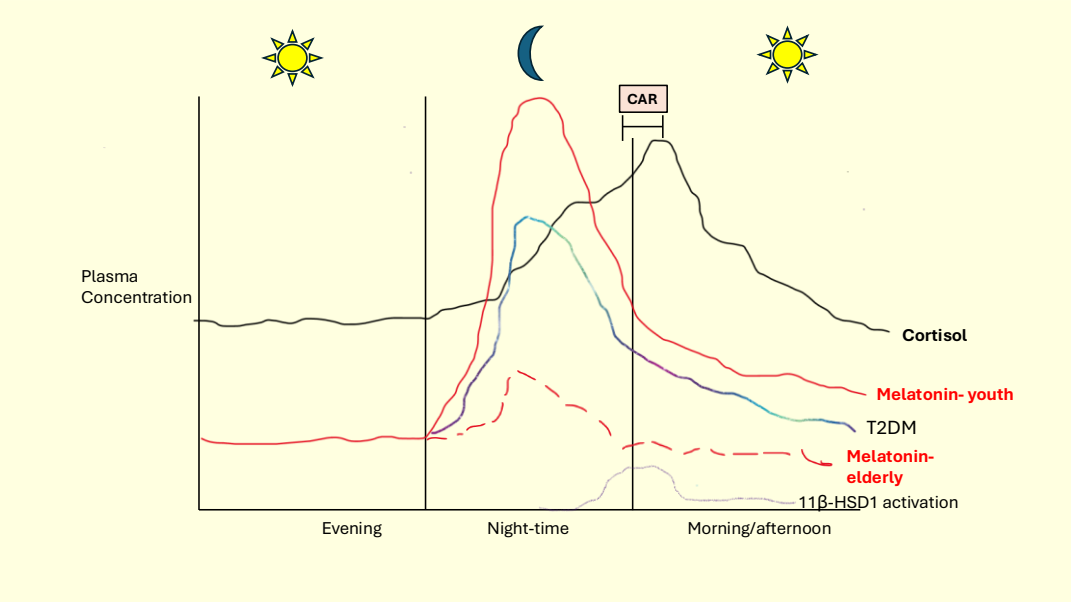

Figure 1. Melatonin and cortisol circadian variations over age and T2DM.

Figure 1 shows how pineal melatonin can dramatically decrease over time, with T2DM showing a suppression of pineal melatonin that accelerates aging driven changes. Cortisol levels overnight and during the morning CAR tend to remain similar over aging, although in some condition's cortisol levels may be enhanced during the day. Importantly, the changes in melatonin and cortisol are interactive, as melatonin suppresses the nuclear translocation of the glucocorticoid receptor (GR)-α, upon which most of the cortisol effects have been investigated. The suppression of pineal melatonin over aging and in T2DM may therefore act to disinhibit the influence of cortisol on how body cells and systems are prepared for the coming day. Both enhanced GR-α activation and pro-inflammatory cytokines can increase local cellular cortisol production by 11 beta hydroxysteroid dehydrogenase 1 (11β-HSD1), enabling local cortisol to have a heightened influence on cell function and intercellular interactions in the microenvironment in which all cells exist. Other factors pertinent to aging and T2DM, including gut microbiome derived butyrate and bcl2 associated athanogene (BAG)1, can also prevent GR-α nuclear translocation but are not included for clarity. Abbreviations: 11β-HSD1: 11 beta hydroxysteroid dehydrogenase; BAG-1: bcl2-associated athanogene 1: CAR: cortisol awakening response; GR: glucocorticoid receptor; T2DM: type 2 diabetes mellitus.

As highlighted in Figure 1, melatonin suppression over time and T2DM significantly modulates how night-time dampening and resetting regulates cellular and systemic processes over aging and aging-accelerating conditions, such as T2DM. This has implications for wider dampening processes, such as vagal nerve activation, which may be induced by melatonin both directly and via melatonin's

induction of oxytocin [19–21]. Oxytocin is often decreased in T2DM [22], while hypothalamic paraventricular nucleus (PVN) oxytocin neurons are significantly decreased in T2DM in association with decreased astrocytes and altered debris collection by the glymphatic system [23]. Oxytocin has complex interactions with T2DM, with data indicating positive impacts of oxytocin on hyperglycemia and pancreatic β-cell function in people in the normal weight range [24] but with relatively little efficacy in obese/T2DM patients [25]. Such mixed results may be complicated by oxytocin stimulation of the vagal nerve (see figure 2), which can dampen inflammation only when local melatonin can be upregulated, as shown in the gut [12]. This would indicate that the promising impacts of oxytocin in diabetes regulation may be determined by the availability of the local tryptophan-melatonin pathway in a given organ/tissue/cell. Consequently, the beneficial effects of oxytocin in preclinical models of DCM may require the capacity of oxytocin stimulated vagal nerve activation to induce the melatonergic pathway in heart tissue. This requires further investigation.

In contrast, cortisol activation of the GR-α can have complex effects on the vagal nerve, including its suppression [26]. Heightened cortisol level is a major driver of left ventricular diastolic dysfunction, an important pathophysiological feature of DCM, with raised cortisol levels in T2DM positively correlating with age and glycated hemoglobin [27], as well as with elevated fasting glucose, total cholesterol levels, and ischemic heart disease [28]. Such data and contrasting results [29] highlight the complex effects of cortisol in the interface of T2DM with DCM. Whether suppressed pineal melatonin disinhibits GR-α effects to upregulate GR-β and/or alter the site(s) of the GR localization (not only in cytoplasm, but can be present on the plasma membrane, mitochondrial membrane, and mitochondrial matrix), with consequent diverse effects [30,31], will be important to clarify. Heightened GR activation can also increase local cortisol production via 11β-HSD1 [30,31], further contributing to cortisol's complex effects. As such, many of the differential effects of cortisol, including in DCM, may be in the absence of raised cortisol levels per se when the inhibitory effects of melatonin on the GR-α are attenuated.

The dampening effects of the vagal nerve over the circadian rhythm are mediated by acetylcholine (ACh) release that activates ACh receptors, especially the alpha 7 nicotinic acetylcholine receptor (α7nAChR). The α7nAChR generally suppresses immune cell activation, partly mediated by the upregulation of specialized pro-resolving mediators (SPMs) [32] that are proposed to drive a shift in NF-κB dimer composition leading to an NF-κB dimer that interacts with nuclear pSTAT3 to upregulate the melatonergic pathway [14,33]. Pineal melatonin increases the α7nAChR [34], indicating another route whereby the suppression of pineal melatonin decreases the capacity to achieve resolution from inflammation. Consequently, the suppression of pineal melatonin (and melatonin induced oxytocin) can modulate vagal nerve activity and the capacity to achieve resolution of inflammation locally across body organs and tissues. This interacts with the availability of local melatonin, which can be suppressed e.g., by hyperglycemia induced methylglyoxal that binds tryptophan to attenuate the initiation of the tryptophan-melatonin pathway [35], as shown in Figure 2. Levels of circadian and local/systemic mitochondrial melatonergic pathway availability therefore interact to modulate systemic as well as organ-specific inflammation.

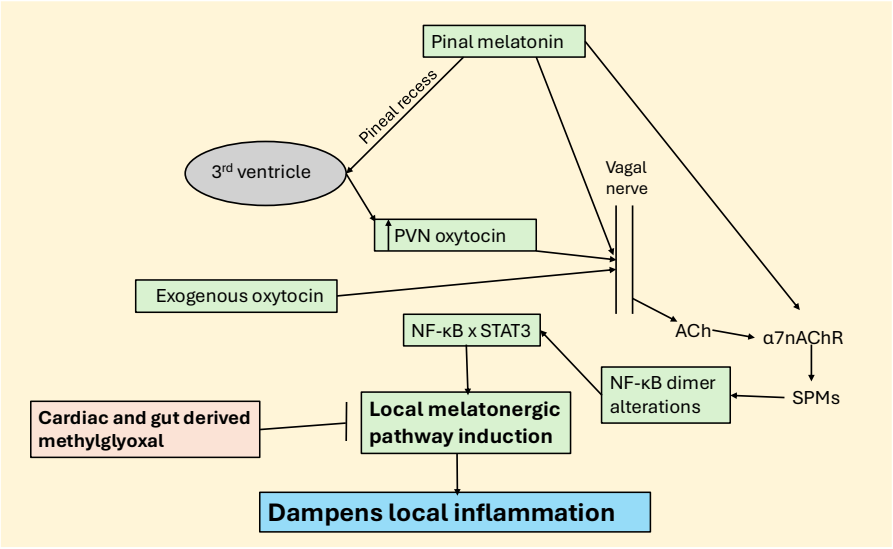

Figure 2. Pineal melatonin and oxytocin modulation of vagal driven inflammation resolution.

Pineal melatonin may directly, and indirectly via oxytocin induction, activate the vagal nerve, which releases acetylcholine (ACh), including to the α7nAChR, thereby inducing specialized proresolving mediators (SPMs). Pineal melatonin may further contribute to vagal efficacy in dampening inflammation by upregulating the α7nAChR [34]. Suppressed pineal melatonin may therefore not only decrease endogenous oxytocin induction but also modulate the consequence of oxytocin activation of the vagal nerve via α7nAChR activation. α7nAChR activation induces specialized proresolving mediators (SPMs) that can alter the NF-κB dimer composition by switching from a pro-inflammatory NF-κB dimer composition, such as p65/p50 to a resolution inducing NF-κB dimer composition, such as c-Rel/p50, thereby upregulating the local melatonergic pathway in the course of local inflammation resolution. Oxytocin effects via the vagal nerve in DCM may therefore be intimately dependent upon the capacity to upregulate the local melatonergic pathway, including in cardiomyocytes, cardiac fibroblasts and/or endothelial cells. Factors suppressing tryptophan availability for the tryptophan-melatonin pathway in these cardiac cells, such as local and/or gut microbiome derived methylglyoxal, will attenuate the capacity of melatonin and oxytocin to achieve local resolution via vagal nerve activation. Suppressed vagal activity coupled with lower oxytocin and pineal melatonin levels in DCM and raised methylglyoxal levels can therefore interact to attenuate local inflammation resolution in cardiac tissue. Abbreviations: α7nAChR: alpha 7 nicotinic acetylcholine receptor; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; STAT3: signal transducer and activator of transcription.

The integration of pineal and local melatonin into DCM pathophysiology requires an understanding of the tryptophan-serotonin-N-acetylserotonin (NAS)-melatonin pathway and its interactions with the kynurenine pathway, which are briefly covered next.

3. Tryptophan-melatonin and kynurenine pathways

The regulation of the tryptophan-serotonin-N-acetylserotonin (NAS)-melatonin pathway and its interaction with the kynurenine pathway are important aspects of the pathophysiology of a host of

diverse medical conditions, including neurodegenerative diseases [36], cancer [37], and cardiovascular diseases, such as DCM [38]. Tryptophan levels are typically decreased in T2DM, partly via an enhanced conversion of tryptophan to kynurenine [39] by pro-inflammatory cytokine induction of indoleamine 2,3-dioxygenase (IDO) and cortisol/GR-α induction of tryptophan 2,3-dioxygenase (TDO) [40]. Tryptophan-melatonin pathway suppression may therefore be intimately linked to kynurenine pathway upregulation, as is typically evident in many medical conditions showing heightened pro-inflammatory cytokines and raised cortisol levels/effects [41], as shown in Figure 3.

Kynurenine activates the aryl hydrocarbon receptor (AhR), which is generally detrimental in cardiovascular diseases. The kynurenine/AhR pathway initiation is proposed to be mediated by the IL-6/Janus kinase (JAK)/STAT3 pathway leading to IDO induction and increased kynurenine as well as raising AhR levels, which is followed by enhanced AhR activation by kynurenine [42]. AhR induction by IL-6/JAK/STAT3 may therefore be coupled to the suppression of the putative cardiac mitochondrial melatonergic pathway, which, in other cell types, is dependent on the NF-κB dimer components and whether STAT3 is nuclear translocated (canonical pathway) or mitochondria translocated (non-canonical pathway) [14]. The IL-6/JAK/STAT3 pathway is pathophysiologically relevant in DCM [6], where AhR activation can be detrimental [43], although AhR knockout is also detrimental [44], suggesting complex AhR effects in DCM. AhR activation may also suppress melatonin availability via AhR induced cytochrome P450 (CYP)1B1 and CYP1A2, which can hydroxylate melatonin as well as 'backward convert' melatonin, via O-demethylation, to its precursor, NAS [45,46]. AhR activation may therefore also contribute to decreased melatonin availability in cells. As NAS is a brain-derived neurotrophic factor (BDNF) mimic via its activation of the BDNF receptor, tyrosine receptor kinase (Trk)B [47], some of the protective effects of the AhR may be mediated by increasing the local NAS/melatonin ratio, although this may be a problem in other CVDs, such as Left ventricular hypertrophy [48], and requires experimental investigation in DCM. The interactions of the tryptophan-melatonin pathway and kynurenine pathway may provide a framework to better integrate the diverse, and sometimes contrasting, data on DCM.

The interactions of the tryptophan-melatonin and kynurenine pathways are likely to be evident in all body cells. Tryptophan is taken up into cardiomyocytes by the large amino acid transporter (LAT)1 and is converted to serotonin by cardiomyocyte tryptophan hydroxylase (TPH), while serotonin can also be taken up into cardiomyocytes by the serotonin transporter (SERT) [48]. However, the conversion of serotonin to NAS and melatonin in cardiomyocytes needs to be investigated. A Russian language article seems to indicate the active presence of melatonin production in approximately 20% of cardiomyocytes at a given time, with this being decreased over age and decreased in dilated cardiomyopathy patients, vs controls [49]. This needs to be experimentally investigated in DCM. However, this does suggest the presence of the melatonergic pathway in cardiomyocytes, with alterations in cardiomyocyte melatonergic pathway evident over the course of aging and in wider cardiomyopathy presentations.

The interactions of the tryptophan-melatonin and kynurenine pathways with the AhR are shown in Figure 3.

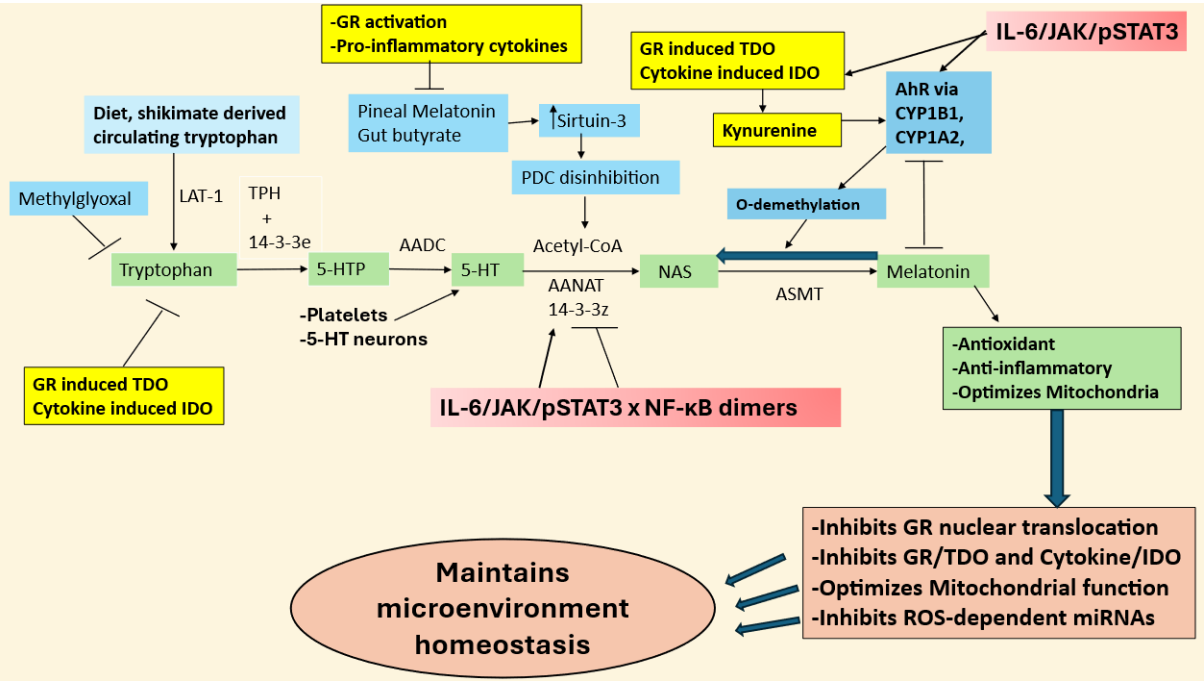

Figure 3. Tryptophan-melatonin and kynurenine pathways interact with IL-6/JAK/STAT3/AhR.

The mitochondrial melatonergic pathway of the tryptophan-melatonin pathway (green shade) seems to occur in all cells. The tryptophan-melatonin pathway can be regulated by an array of circadian and systemic processes as well as by interactions within a given cell's microenvironment, including: 1) Tryptophan availability from diet and possibly the gut microbiome shikimate pathway derived tryptophan; 2) Cortisol/GR induced TDO and pro-inflammatory cytokines induced IDO, suppress tryptophan availability by conversion to kynurenine; 3) Kynurenine and its metabolite, kynurenic acid, activate the AhR (blue shade), which decreases melatonin via O-demethylation of melatonin to N-acetylserotonin (NAS) by AhR induced CYP1B1 and CYP1A2 as well as by hydroxylating melatonin; 4) pro-inflammatory cytokines and GR activation also inhibit pineal melatonin, including via gut permeability that increases circulating LPS levels, typically in association with gut dysbiosis-linked suppression of butyrate; 5) the suppression of butyrate decreases its induction of the cellular melatonergic pathway, as does the LPS/TNF-α suppression of pineal melatonin, leading to a decrease in mitochondria-located sirtuin-3 and, therefore, the sirtuin-3 inhibition of mitochondrial ROS at three points of the electron transport chain, coupled to a attenuation of sirtuin-3 induction of mitochondrial ATP and acetyl-CoA production by the pyruvate dehydrogenase complex (PDC). Acetyl-CoA is a necessary cosubstrate for the initiation of the mitochondrial melatonergic pathway; 6) GR-α nuclear translocation can regulate routes to suppress the mitochondrial melatonergic pathway, thereby modulating mitochondrial function and patterned cell responses; 7) IL-6 not only activates the JAK/pSTAT3 pathway but concurrently induces IDO, and therefore IDO/kynurenine/AhR/CYP1B1/CYP1A2 to suppress the tryptophan-melatonin pathway; 8) IL-6/JAK/pSTAT3^{Tyr705} can interact with NF-κB dimers in the nucleus to induce or repress the melatonergic pathway, possibly via the suppression of kinases that phosphorylate pSTAT3^{Ser727} and the mitochondrial translocation of pSTAT3; 9) IL-6/JAK/pSTAT3^{Ser727} translocates pSTAT3 to mitochondria where it modulates Ca^{2+} influx via mitochondria-associated membranes (MAMs) and

binds and regulates 14-3-3 availability to limit the 14-3-3 stabilization of mitochondrial AANAT, while increasing NLRP3 inflammasome mitochondrial translocation and activation coupled to an increased NF-κB and p65 mitochondrial translocation (not detailed for clarity); 10) hyperglycemia induced methylglyoxal suppresses tryptophan availability via protein-protein interactions; and 11) other tryptophan melatonin pathway factors, such as LAT-1, 14-3-3 isoforms and TPH may be regulated by genetic, epigenetic, circadian, systemic and microenvironmental processes, with consequences for melatonin production in the course of cellular and intercellular inflammation resolution. The regulation of the tryptophan-melatonin pathway and its interactions with the kynurenine pathway therefore modulate a wide array of diverse factors and processes linked to DCM. Abbreviations: 5-HT: serotonin; 5-HTP: 5-hydroxytryptophan; AADC: aromatic-L-amino acid decarboxylase; AANAT: Aralkylamine N-acetyltransferase; AhR: aryl hydrocarbon receptor; ASMT: N-acetylserotonin O-methyltransferase; CYP: cytochrome P450: GR: glucocorticoid receptor; HPA: hypothalamus-pituitary-adrenal; IDO; indoleamine 2,3-dioxygenase; JAK: Janus kinase; IL: interleukin; LAT-1: large amino acid transporter 1; LPS: lipopolysaccharide; miRNAs: microRNAs; NAS: N-acetylserotonin; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; ROS: reactive oxygen species; STAT; signal transducer and activator of transcription; TDO: tryptophan 2,3-dioxygenase; TLR: toll-like receptor**.**

4. Integrating the IL-6/JAK/STAT3 pathway interactions with NF-κB dimer components

Increased Signal transducer and activator of transcription (STAT)3 is intimately associated with diverse medical conditions [50–55], including DCM [56], as well as the regulation of diverse systemic cells [57–60], including cardiac fibroblasts [61], endothelial cells [62], and cardiomyocytes [63,64]. STAT3 effects across medical conditions and cell types are proposed to be mediated by a diverse array of signaling pathways and factors. As with STAT3, NF-κB is intimately linked to almost all medical conditions where it seems invariably to be associated with the induction of inflammatory processes [65], although the NF-κB dimer composition determines whether it induces inflammatory or resolution associated transcription [66]. It is proposed here that the complex interactions of STAT3 with NF-κB dimer components to activate or suppress the mitochondrial melatonergic pathway [14] is a core cellular process that is subject to dysregulation when factors and processes over the course of aging and aging-accelerating conditions, such as T2DM, limit the availability of the tryptophan-melatonin pathway and, therefore, the capacity of pSTAT3 interactions with NF-κB dimer components to achieve cellular resolution and intercellular homeostasis via melatonin upregulation and efflux. Figure 4 shows how sites of STAT3 phosphorylation interact with NF-κB dimer composition to modulate the melatonergic pathway, including via the release of IL-6 to initiate the IL-6/JAK/STAT3 pathway in neighboring cells in the local microenvironment to suppress or stimulate the mitochondrial melatonergic pathway, the suppression of which is proposed to drive the initiation of many autoimmune/'immune-mediated' disorders [67].

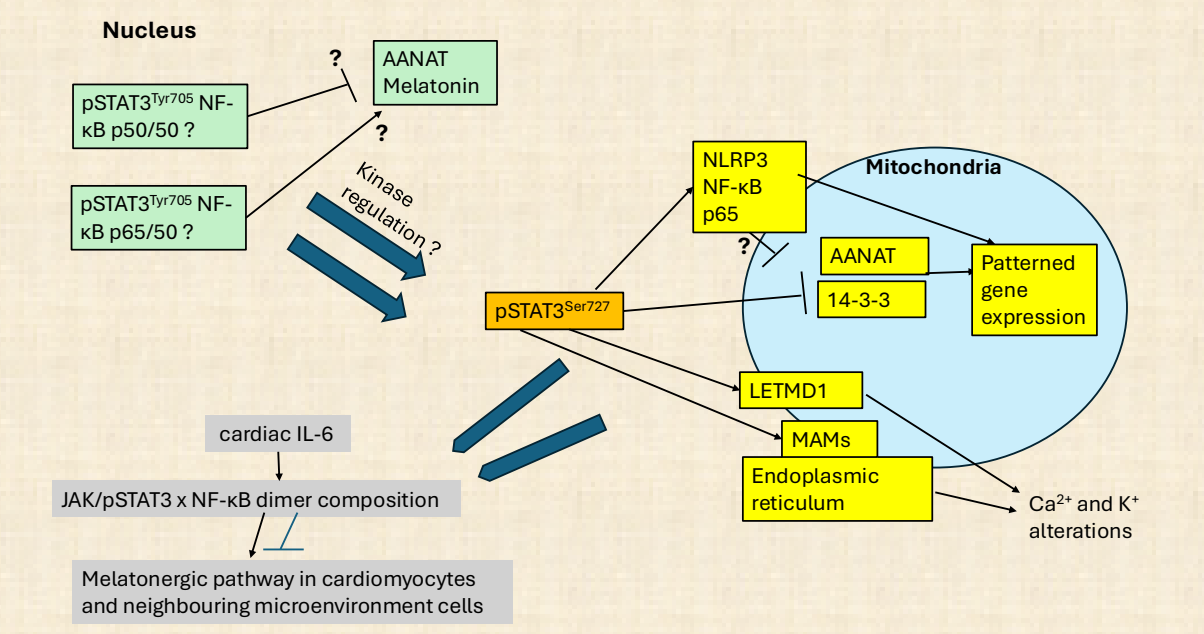

Figure 4. STAT3 interacts with NF-κB dimer composition in melatonergic pathway regulation.

STAT3 interacts with NF-κB dimer composition to modulate the cellular melatonergic pathway. $STAT3^{Tyr705}$ provides the canonical pSTAT3 pathway that takes $STAT3^{Tyr705}$ to the nucleus where it can differentially interact with NF-κB dimer components (such as p65/50 and p50/p50) to stimulate or inhibit the melatonergic pathway. Data indicate that the differential effects of NF-κB components may be dependent on cell type [14]. The nuclear (green shade) interactions of $STAT3^{Tyr705}$ and NF-κB dimer components in modulating the melatonergic pathway may be directly in the nucleus and/or via nuclear STAT3-NF-κB inducing/suppressing kinases that regulate the mitochondrial $STAT3^{Ser727}$ where $STAT3^{Ser727}$ can 1) regulate MAMs, and thereby endoplasmic reticulum derived Ca^{2+} mitochondrial influx to modulate core aspects of mitochondrial function; 2) bind and regulate 14-3-3 availability, thereby modulating 14-3-3 stabilization of AANAT and therefore melatonergic pathway initiation; 3) form a positive feedback loop with LETM1 domain-containing protein 1 (LETMD1) to modulate mitochondrial Ca^{2+} and K^{+} regulation; and 4) drive the mitochondrial translocation of the NLRP3 inflammasome, NF-κB and p65 to modulate mitochondrial patterned gene expression and mitochondrial function as well as possibly attenuating the melatonergic pathway initiation via AANAT binding to the LETM1/LETMD1 14-3-3 like matrix motif [68] and/or inducing 14-3-3 dimer formation with this 14-3-3 like motif. Via these processes, mitochondrial $pSTAT3^{Ser727}$ may modulate cardiomyocyte IL-6 release that drives the IL-6/JAK/pSTAT3/NF-κB in other cell types to stimulate or suppress the melatonergic pathway. The plethora of factors regulating STAT3 and NF-κB dimer components can therefore modulate core cellular processes, including those in cardiomyocytes, cardiac fibroblasts, and cardiac endothelial cells, as well as any other cells in the cardiomyocyte microenvironment, such as platelets and macrophages. Abbreviations: LETM1: Leucine Zipper EF-hand containing Transmembrane protein 1; MAMs: mitochondria-associated membranes; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells.

The above provides a novel perspective of the pathophysiological underpinnings of DCM that better integrate pre-existing data.

5. Integrating wider DCM data

Figures 1–4 provide a conceptualization of DCM that better integrates the diverse bodies of data collected on DCM, including its association with diabetes and hyperglycemia.

5.1. Hyperglycemia and methylglyoxal

Hyperglycemia is an important driver of the pathophysiological changes occurring in prediabetes, T2DM and T1DM. Hyperglycemia is classically associated with endothelial alterations and blood vessel damage that can impact on an array of diverse organs and tissues typically damaged in the course of T2DM and T1DM, including retinopathy [69], diabetic kidney injury [70], and DCM [71]. Many of the effects of hyperglycemia are mediated via methylglyoxal upregulation [72]. Methylglyoxal can inhibit the tryptophan-melatonin pathway by different mechanisms. Methylglyoxal directly binds tryptophan via protein-protein interactions, which suppresses tryptophan availability and TPH induction [35], thereby decreasing tryptophan availability for the tryptophan/serotonin/NAS/melatonin pathway. This is one route where hyperglycemia induced methylglyoxal suppresses the capacity to induce autocrine and paracrine effects of melatonin in the course of resolution of inflammation and oxidative stress.

Methylglyoxal is classically modeled as mediating its effects by being a precursor for advanced glycation end products (AGEs) that activate the receptor for AGEs (RAGE) [73]. RAGE is a treatment target in a host of diverse medical conditions, including DCM [74]. RAGE activation upregulates pSTAT3 [75], indicating that the hyperglycemia/methylglyoxal/RAGE/pSTAT3 pathway is another route where methylglyoxal can regulate the melatonergic pathway, thereby influencing the capacity of cells to achieve resolution of inflammation. This also has consequences for the intercellular interactions of a given cell within its local microenvironment and attenuates the capacity of circadian melatonin to dampen and reset at night as well as potentially suppressing the capacity of the vagal nerve to dampen and resolve inflammation via the vagal ACh/α7nAChR/SPMs/NF-κB dimers/pSTAT3 pathway that resolves local inflammation by upregulating local melatonin production and efflux [12,13]. Methylglyoxal may, therefore, suppress the capacity of pineal melatonin and vagal nerve stimulation to achieve inflammation resolution via local melatonergic pathway upregulation in a given organ/tissue. Numerous factors inhibit RAGE to afford protection in DCM, including cannabinoid 2 receptor agonism [74], tetrahydroberberrubine (THBru) [76], and the traditional Chinese medicine, Shexiang Tongxin Dropping Pills (STDP) [77]. A number of downstream factors and processes are proposed to mediate the efficacy of RAGE suppression in DCM, including the suppression of RAGE induced High Mobility Group Box-1 (HMGB-1) [78] and NLRP3 inflammasome [74]. This is parsimonious with RAGE induced $pSTAT3^{Ser727}$ phosphorylation and the mitochondrial translocation of $pSTAT3^{Ser727}$ [79] that increases the mitochondrial translocation and activation of the NLRP3 inflammasome, NF-κB and p65, while suppressing the mitochondrial melatonergic pathway, as shown in other cell types.

Every cell has the capacity to increase methylglyoxal, typically downstream from enhanced glycolysis. However, a dysregulated gut microbiome also produces methylglyoxal, which may have local and/or systemic effects via a ‘leaky gut’, thereby linking gut methylglyoxal with host aging and longevity [80]. Increased gut permeability and gut dysbiosis are evident in DCM [81], including a decrease in the short-chain fatty acid, butyrate [82]. Butyrate is a histone deacetylase inhibitor (HDACi)

and therefore epigenetic regulator and activates the G-protein coupled receptor (GPCR)-41, GPCR-43, GPCR-109A. Butyrate also upregulates the melatonergic pathway, as shown in intestinal epithelial cells [83], suggesting that some of the efficacy of butyrate in DCM treatment may involve melatonergic pathway upregulation. Increased gut methylglyoxal may, therefore, coordinate gut dysregulation with wider systemic dysregulation in DCM pathophysiology.

5.2. Gut dysbiosis/permeability in DCM pathophysiology

Alterations in the gut microbiome/dysbiosis/permeability are linked to most medical conditions, with effects partly mediated by suppressed butyrate levels that contribute to suboptimal mitochondrial function systemically [84]. Alterations in gut dysbiosis/permeability are also strongly associated with DCM [81,85], at least partly mediated by the upstream effects of hyperglycemia and T2DM [86].

Butyrate's capacity as a HDACi modulates the IL-6/JAK/STAT3 pathway [87]. Butyrate effects on STAT3 seem cell dependent and can be inhibitory [87] and stimulatory [88]. However, further investigation is needed regarding how butyrate acts on the canonical and non-canonical STAT3 pathways. The effects of butyrate are likely to be complex regarding this, given its likely epigenetic regulatory effects on the downstream products induced by nuclear and mitochondrial STAT3. Butyrate, in other cell types, has long been known to modulate NF-κB dimer composition [89], indicating that butyrate may influence the induction of the melatonergic pathway via canonical, nuclear STAT3 interactions with different NF-κB dimer components. The seemingly ubiquitous beneficial effects of butyrate may, therefore, involve melatonergic pathway upregulation, at least partly mediated by butyrate's regulation of nuclear STAT3 and NF-κB dimer composition. Butyrate effects on canonical and noncanonical STAT3 interactions with NF-κB dimer composition is important to determine in cardiomyocytes, cardiac fibroblasts, and endothelial cells. Overall, gut permeability/dysbiosis in DCM may be intimately linked to alterations in mitochondrial function, including the mitochondrial melatonergic pathway, both in the heart and systemically, with consequences for the capacity to achieve inflammation resolution.

5.3. Wnt/β-catenin in DCM pathophysiology

The Wnt/β-catenin pathway is an important regulator of cardiomyocyte and coordinated heart development as well as having a significant role in T2DM-induced DCM [90], especially hyperglycemia-induced DCM [91]. The Wnt/β-catenin pathway is coupled with NF-κB [92,93] and STAT3 upregulation [94]. Notably, there is a positive cross-regulation between the NF-κBp65 and Wnt/β-catenin pathways that potentiates IL-6 upregulation, as shown in human macrophages [95]. This may be of relevance as it indicates the importance of NF-κB dimer composition interactions with Wnt/β-catenin/(pSTAT3?) in the upregulation of IL-6, a significant driver of the JAK/STAT3 and NF-κB pathways, which is possibly indicative of a positive feedback loop between Wnt/β-catenin and IL-6/JAK/STAT3 and NF-κBp65 that maintains inflammation while inhibiting resolution by the melatonergic pathway. The inhibition of NF-κB and Wnt/β-catenin ameliorates DCM induced by streptozotocin in a T1DM model [96]. Interestingly, streptozotocin suppresses the retinal melatonergic pathway, at least transiently [97], suggesting a possible role for streptozotocin, via NF-κB and Wnt/β-catenin induced pSTAT3, in the suppression of the melatonergic pathway across cell types in T1DM [98], T2DM [99], and in diabetes linked Alzheimer's disease [100], where the suppression of the astrocyte

melatonergic pathway may be of overlooked significance [101]. The interactions of STAT3 and NF-κB with other DCM associated transcription factors and intracellular signaling pathways in the modulation of the mitochondrial melatonergic pathway requires future investigation.

Methylglyoxal, via its conversion to the advanced glycation end product, methylglyoxal-derived hydroimidazolone-1 (MG-H1), activates RAGE to enhance Wnt/β-catenin pathway driven fibrosis, as shown in the kidney [102]. As methylglyoxal also binds tryptophan, via protein-protein interactions [35], to suppress the initiation of the tryptophan-melatonin pathway, and RAGE activation increases pSTAT3 [75] and NF-κB [103], hyperglycemia induced methylglyoxal may contribute to melatonergic pathway suppression by a number of routes to inhibit a core process underpinning the association of diabetes with Alzheimer's disease, amyotrophic lateral sclerosis, retinopathy, nephropathy, and DCM [104,105]. Whether this underpins the prolonged inflammatory activity and lack of inflammation resolution in these conditions will be important to determine.

5.4. Transforming growth factor-beta1 (TGF-β1)

Hyperglycemia induced Transforming growth factor-beta1 (TGF-β1) is a significant driver of the fibrosis underpinning DCM pathophysiology. Raised levels of TGF-β1, TGF-β receptor II, and its intracellular mediator, connective tissue growth factor (CTGF), are typically increased in DCM and drive myocardial fibrosis, with proposed effects via the Smad pathway [106]. Prolonged hyperglycemia stimulates cardiac fibroblasts, which can induce fibroblast differentiation into myofibroblasts, culminating in raised levels of myocardial collagen and extracellular matrix (ECM) dysregulation in the course of myocardial fibrosis [106]. Myocardial fibrosis drives ventricular wall 'stiffness' and is a major contributor to heart failure in DCM. Hyperglycemia induced TGF-β1 is accompanied by upregulation of a number of kinases, including Extracellular signal regulated protein kinase 1/2 (ERK1/2), p38 MAPK, and c-Jun N-terminal kinase (JNK) [107], which can phosphorylate STAT3 at Serine 727, as can PKCε and cyclin dependent kinase 1 (CDK1) [108], indicating that TGF-β1 may be accompanied by the non-canonical $pSTAT3^{Ser727}$ mitochondrial translocation and accompanying increase in NF-κB, p65, and NLRP3 inflammasome translocation to mitochondria. TGF-β1 has complex interactions with STAT3 in different cell types but pSTAT3 typically increases TGF-β1, collagen, and CTGF levels [109], especially in cancer and fibrosis [110,111]. The interactions of TGF-β1 with canonical and non-canonical STAT3 and NF-κB dimer composition in the modulation of the mitochondrial melatonergic pathway in the course of fibrosis in DCM will be important to clarify. Notably, treatment with melatonin, which can inhibit $pSTAT3^{Ser727}$, suppresses TGF-β1, NF-κB, and NLRP3 levels and activation in models of cardiac fibrosis [112], indicating the likely relevance of local melatonin production in DCM and how it interfaces with TGF-β1, collagen, CTGF, NF-κB, and the NLRP3 inflammasome in the course of cardiac fibrosis.

6. Future research implications

The above has a number of future research implications:

(1) Is the melatonergic pathway evident in cardiomyocytes, cardiac fibroblasts, and cardiac endothelial cells? Is the melatonergic pathway in these cells regulated by STAT3 interactions with NF-κB dimer composition? Does methylglyoxal bind tryptophan via protein-protein interactions in these cells to limit tryptophan-melatonin pathway availability? Does the suppression of the melatonergic

pathway underpin the prolonged inflammatory activity and lack of inflammation resolution in DCM and wider diabetes associated pathologies in other organs/tissue?

(2) Does the association of gut microbiome derived methylglyoxal with aging and longevity across species [85] derive from the capacity of methylglyoxal to both bind tryptophan [35] and induce RAGE regulation of STAT3 [75] and NF-κB [103] and, therefore, pSTAT3 and NF-κB dimer interactions [14], indicating that methylglyoxal acts on core cellular processes in cells involving the regulation of the tryptophan-melatonin pathway and, therefore, mitochondrial melatonin? Does this provide a set of core processes linked to aging and aging-associated conditions, including DCM? Is the gut microbiome derived methylglyoxal evident in T1DM, T2DM, and DCM, enabling gut microbiome derived methylglyoxal to regulate the tryptophan-melatonin pathway via protein-protein interactions with tryptophan and methylglyoxal/RAGE/STAT3/NF-κB pathway, both of which may suppress the melatonergic pathway?

(3) Does butyrate modulate the canonical and/or non-canonical STAT3 pathways, as well as the NF-κB dimer composition [89], to regulate the melatonergic pathway in DCM?

(4) Since alterations in thyroid function, including subclinical hypothyroidism and Hashimoto's thyroiditis, show an association with cardiomyopathy [113], obesity and metabolic dysregulation are risk factors for these thyroid conditions, and thyroid aging linked to changes in pineal melatonin production [114], does this indicate that aging-associated alterations in dampening and resetting at night (see figure 1), modulate DCM pathophysiology, at least partly, via alterations in thyroid function mediated by changes in the thyroid tryptophan-melatonin pathway? Would this be more widely applicable in different thyroid cells and not simply the C-cells where an active melatonergic pathway has been shown [115], thereby impacting on thyroid-heart interactions?

(5) Does melatonin treatment of DCM upregulate the cardiomyocyte, fibroblast, and endothelial cell melatonergic pathway via $pSTAT3^{Ser727}$ suppression?

(6) Is the AhR present and physiologically relevant in the cytoplasm and/or mitochondrial membrane of cardiomyocytes, cardiac fibroblasts, and/or cardiac endothelial cells? Does AhR activation regulate the local melatonergic pathway in these cells, including the NAS/melatonin ratio [116]?

(7) Does mitochondrial AANAT bind to the LETM1/LETMD1 14-3-3, like matrix motif [68], and/or does 14-3-3 form a dimer with this 14-3-3, like motif? Does mitochondrial $pSTAT3^{Ser727}$, by increasing LETMD1 via a positive feedback loop, thereby modulate mitochondrial melatonergic pathway availability?

(8) Do the beneficial effects of oxytocin in the regulation of glucose dysregulation in obesity/T2DM act via vagal nerve activation and, therefore, require the capacity of the vagal nerve to stimulate local melatonin production in a given organ/tissue, as shown in preclinical [12] and clinical [13] studies?

Moreover, cell death in DCM can be driven by a number of processes, including apoptosis, pyroptosis, necroptosis, and ferroptosis, which are all intimately intertwined with oxidative stress and inflammation [117,118]. The failure to dampen and reset these processes at night, arising from suppressed pineal melatonin and a dysregulated cortisol system (see figure 1), seems significant to DCM associated cell death, given the capacity of melatonin, in cardiomyocytes to inhibit apoptosis [119], pyroptosis [120], necroptosis [121], and ferroptosis [122]. The association of diverse routes to cell death with oxidative stress and inflammation is intimately linked to alterations in mitochondrial function [123–125], given that suboptimally functioning mitochondria are the main source of oxidants and the caspases that cleave NLRP3 derived pro-IL-1β and pro-IL-18 into their active forms (see

Figure 4). Suboptimal mitochondrial function includes the suppression of the mitochondria-derived peptides (MDPs), including humanin, which is produced in cardiomyocytes [126] to suppress pro-apoptotic Bcl2-associated proteins, Bax and Bid, intracellularly, as well as being released to dampen inflammatory activity and optimize mitochondrial function in neighboring cells, including in DCM preclinical models [127]. It has been proposed that pineal melatonin increases humanin, which is proposed to modulate intracellular cell death pathways and the altered homeostatic interactions occurring in inflammatory environments, including by upregulating the mitochondrial melatonergic pathway [128]. This will be important to determine in the DCM microenvironment.

7. Treatment implications

(1) As melatonin suppresses TGF-β1, NF-κB, and NLRP3 levels and activation in models of cardiac fibrosis [112] and suppresses gut dysbiosis/permeability [129,130] and the consequences of hyperglycemia in diabetes [131], melatonin has utility in the management of DCM [112,132].

(2) Numerous factors have been proposed to inhibit the myocardial fibrosis that is intimately linked to DCM pathoetiology, including epigallocatechin gallate (EGCG), curcumin, and resveratrol, which are proposed to inhibit TGF-β1 induced oxidative stress and inflammation in the induction of myocardial fibrosis during DCM pathoetiology [106]. Interestingly, all three nutriceuticals can directly increase the endogenous melatonergic pathway (e.g., via monoamine oxidase inhibition [133]) and indirectly via AhR inhibition [134], thereby increasing the local availability of the melatonergic pathway. Clinical studies investigating alterations in melatonergic pathway regulation in DCM associated cells should better refine targeted treatment.

(3) Nanoparticle encapsulated curcumin may be of particular interest if targeted to mitochondria, where it has been shown to inhibit mitochondrial STAT3 and associated increases in ROS, like other inhibitors of mitochondrial STAT3 [135].

(4) Given the role of methylglyoxal in driving many of the pathophysiological processes in DCM, it is notable that quercetin quenches methylglyoxal [136] and shows significant clinical efficacy in preclinical DCM models [137]. The quenching of methylglyoxal by quercetin may prevent/attenuate many of the initial changes driving DCM pathoetiology, including the methylglyoxal/AGEs/RAGE/pSTAT3 pathway and the tryptophan suppression arising from methylglyoxal protein-protein interactions with tryptophan, as shown in preclinical studies of physiological processes [35], suggesting that incorporation of the mitochondrial melatonergic pathway may provide important routes to DCM prevention.

(5) The relevance of melatonin in the regulation of DCM pathophysiology and treatment is highlighted by the protective effects of the melatonin regulated nuclear retinoic acid-related orphan receptor-α (ROR-α) [138], including in affording protection against high glucose induced cardiac fibroblast proliferation [139]. Whether melatonin binds and activates the ROR-α is the subject of some debate, although it is clear that pineal melatonin regulates ROR-α [140]. Interestingly, data in T-cells indicates that the local production of melatonin in these cells also modulates the ROR-α [141], suggesting that the regulation of the local melatonergic pathway in cardiomyocytes, cardiac fibroblasts, and endothelial cells may have significant impacts on DCM pathophysiology via melatonin regulation of ROR-α. This requires future investigation. The development of recent ROR-α agonists, such as SR1078, is hoped to have significant treatment implications for DCM, as indicated by preclinical

studies [139]. Whether the adjunctive use of melatonin and/or melatonin upregulation in cardiac cells modulates the efficacy of SR1078 will be important to determine.

8. Conclusions

By incorporating the presence and regulation of the mitochondrial melatonergic pathway by canonical and noncanonical pSTAT3 interactions with NF-κB dimer composition in DCM, a wide array of disparate data can be integrated into a distinct pathophysiological framework with novel future research and treatment implications. The roles of circadian processes (melatonin and cortisol), aging, T2DM (methylglyoxal and RAGE), the AhR, and kynurenine may be more plausibly inter-related in DCM pathoetiology and pathophysiology by incorporation of the mitochondrial melatonergic pathway in cardiomyocytes, cardiac fibroblasts, and endothelial cells, as are the treatment benefits derived from quercetin, EGCG, mitochondria-targeted curcumin, and resveratrol. As 50-80% of diabetic patients die from heart failure driven by CVDs, especially DCM, the investigation of the presence and regulation of the cardiac melatonergic pathway is of clinical importance.

However, it is important to note that the presence and regulation of the mitochondrial melatonergic pathway in cardiomyocytes, cardiac fibroblast, and endothelial cells need to be investigated. Although the beneficial effects of melatonin have been extensively researched in DCM and other CVDs, and the melatonergic pathway is evident in all cells where it has so far been investigated, the data and pathways highlighted remain hypothetical and await data collection. The presence of the cardiac melatonergic pathway will be important to determine given the treatment implications arising for this poorly managed condition.

Use of Generative-AI tools declaration

The author declares that no Artificial Intelligence (AI) tools were used in the creation of this article.

Conflicts of interest

The author declares that there are no conflicts of interest.

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