Review

Why are aging and stress associated with dementia, cancer, and other diverse medical conditions? Role of pineal melatonin interactions with gut microbiome butyrate in HPA axis and cortisol awakening response regulation. Possible role of BAG-1

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ABSTRACT

Pineal melatonin and the cortisol awakening response (CAR) are integral aspects of the circadian rhythm. Pineal melatonin release during sleep is proposed to optimize mitochondrial function and dampen any residual oxidant and inflammatory activity. Little is known about CAR, which is generally thought to prepare the body for the coming day, primarily through the activation of the glucocorticoid receptor (GR). Melatonin, like the gut microbiome-derived butyrate, suppresses GR nuclear translocation, indicating that pineal melatonin and night-time butyrate may interact to modulate CAR effects via the GR, including CAR priming of immune and glia cells that underpin the pathogenesis of most medical conditions. Cutting edge research shows that the GR can be chaperoned by bcl2-associated athanogene (BAG)-1 to mitochondria, where GR can have significant and diverse impacts on mitochondrial function. A number of lines of evidence indicate that melatonin indirectly increases BAG-1, including via epigenetic mechanisms, such as derepressing miR-138 inhibition of BAG-1. The dramatic decrease in pineal melatonin production over aging will therefore have significant impacts on GR nuclear translocation, but also possibly the levels of BAG-1 mediated mitochondrial translocation of the GR. This may have dramatic consequences for how CAR 'prepares the body for the coming day', via the differential consequence of GR location in the cytoplasm, nucleus or mitochondria, with differential effects in different cell types. The interactions of melatonin/butyrate/BAG-1/GR are especially important in the hypothalamus, where a maintained heightened melatonin concentration occurs over the night due to the direct release of pineal melatonin, via the pineal recess, into the third ventricle. The interaction of melatonin/butyrate/BAG-1/GR will have differential effects in different cell types, thereby altering the intercellular homeostatic interactions in a given microenvironment that will contribute to the pathogenesis of many aging-associated conditions, including neurodegenerative conditions and cancer. This reframes the nature of the circadian rhythm as well as how stress-associated hypothalamus-pituitary-adrenal (HPA) axis may modulate both the pathogenesis and course of diverse medical presentations. This has a number of research and treatment implications across a host of current medical conditions.

Key words: Melatonin, cortisol, HPA axis, BAG-1, mitochondria, circadian, immunity, hypothalamus. aging

1. INTRODUCTION

Aging increases the risk of most medical conditions, including dementia, cardiovascular disorders and cancer (1). The association of aging with emergent medical disorders are traditionally attributed to raised levels of oxidative stress, oxidant-induced DNA damage, suboptimal mitochondrial function and the dysregulation of wider systemic processes, such as the circadian rhythm, gut microbiome/permeability and immune system (2). Stress, in all its different manifestations, is another factor associated with accelerated aging, mediated at a cellular level by factors suppressing mitochondrial function, such as oxidant-induced DNA damage (3). Psychological and physiological stress are typically associated with hypothalamic-pituitary-adrenal (HPA) axis dysregulation, with stress being importantly mediated and modulated by glucocorticoids, predominantly via glucocorticoid receptor (GR) activation (4). Stress, including social/racial discrimination stress (5), can contribute to accelerated aging (6), including immune aging (7), being partly mediated by raised HPA axis activation and cortisol exposure-linked telomere shortening (8). Such data underpin the classical identification of cortisol as the 'stress hormone' that drives stress-linked aging and aging-linked medical conditions. Research across aging-linked medical conditions highlights the role of mitochondrial dysfunction, including suppressed mitophagy, leading to the accumulation of suboptimally functioning mitochondria, further contributing to oxidative stress, metabolic dysregulation, accelerated aging and susceptibility to aging-linked medical conditions (9).

Suppressed mitophagy is a core aspect of the end-point changes driving many 'autoimmune'/'immune mediated' disorders, including Alzheimer's disease, Parkinson's disease, neuropsychiatric disorders and cancer. The pathoetiology of these diverse medical presentations is proposed to arise from mitochondria-driven alterations in the intercellular interactions of cells in a given microenvironment, leading to changes in homeostatic interactions partly determined by intercellular regulation of the tryptophan-melatonin pathway (10-13). As to how the HPA axis and cortisol levels contribute to the intercellular metabolic interactions driving homeostatic dysregulation has still to be determined. Cortisol significantly regulates mitochondrial function across cell types (14-15), as well as regulating mitophagy (16-17), with raised CNS GR levels and activation evident in aging-linked conditions and neuropsychiatric disorders (18). The HPA axis and GR activation can therefore be an important aspect of alterations in mitochondrial function and intercellular homeostasis that underpin many aging-linked medical conditions.

As well as the HPA axis and mitochondrial dysfunction, aging is associated with circadian dysregulation, including in the pathoetiology of dementia (19-20). The circadian dysregulation associated with aging is importantly determined by the 10-fold decrease in pineal gland melatonin production from adolescence to the ninth decade of life (21). This is attributed to the powerful antioxidant, anti-inflammatory, antinociceptive and mitochondria-optimizing effects of melatonin, the loss of which with aging increases cell susceptibility to challenge (22). Pineal melatonin also acts to dampen any residual daytime inflammatory activity at night via its suppression of reactive cells, such as immune cells and CNS glia cells, thereby 'resetting' immune cell responses, with consequences for wider homeostatic interactions. The suppression of night-time melatonin levels leads to the loss of melatonin's optimizing of mitochondrial function, which has recently been proposed to contribute to cancer pathoetiology (23-24). The dramatic decrease in pineal melatonin during aging can therefore have direct impacts on the pathogenesis of many aging-associated medical conditions.

Mitochondrial dysfunction is often associated with dysregulated mitophagy. A number of factors can suppress mitophagy, including oxidative stress, which is partly mediated via the inhibition of PTEN-associated kinase (PINK)1/parkin (25). By suppressing oxidative stress (25), melatonin prevents the major histocompatibility complex (MHC)-1 upregulation that

underpins the chemoattraction of natural killer (NK) cells and CD8+ T cells that mediate cell destruction in the final stages of 'autoimmune'/'immune-mediated' disorders, including type 1 diabetes mellitus (T1DM) and neurodegenerative disorders (11, 25). Recent work indicates that the suppression of mitophagy and autophagy is intimately linked to aging via telomere shortening arising from the suppression of AMP-activated protein kinase (AMPK)-Unc-51 like autophagy activating kinase 1 (ULK1) (26). Under conditions of suppressed autophagy and mitophagy, melatonin increases PINK1/parkin and AMPK-ULK1, thereby suppressing MHC-1 driven cytolytic cell attraction, whilst optimizing mitochondrial function and cell survival (27). Overall, the suppression of the pineal, and possibly local, melatonergic pathway is strongly associated with aging, including aging-linked changes in mitochondrial metabolism and immune cell function/activation.

This article proposes that the suppression of pineal (and possibly local cellular) melatonin over aging dysregulates the effects of the HPA axis, including the 'cortisol awakening response' (CAR). Melatonin's suppression of cortisol/GR effects were pioneered by the work of Maestroni and colleagues in the 1980s, including in the regulation of immune responsivity (28) and anti-stress induced aging (29, 30). Melatonin's suppression of the GR may be mediated by a number of mechanisms, including direct binding to the GR and/or hsp90 (31) as well as by epigenetic mechanisms as detailed below. In addition to receptor promiscuity and epigenetic processes, melatonin is proposed here to suppress the GR via the epigenetic regulation, and possible direct induction, of bcl2-associated athanogene (BAG)-1, which prevents GR translocation to the nucleus, as first shown in 1999 (32). Subsequent data indicates that the prevention of GR nuclear translocation can be mediated by BAG-1 chaperoning the GR to mitochondria (33). The attenuation of melatonin's direct and/or indirect induction of BAG-1 over aging is therefore linked to distinct cortisol effects at the nucleus compared to mitochondria, with consequences for systemic cell function and patterned immune responses as well as intercellular homeostatic interactions due to the differential effects of melatonin/BAG-1/GR in different cell types within a given microenvironment.

Given the importance of melatonin to GR effects, the tryptophan-melatonin pathway and HPA axis are briefly reviewed next, before looking at the importance of their interactions in the regulation of 'core' physiological processes that contribute to how aging associates with a wide array of diverse medical conditions.

2. TRYPTOPHAN-MELATONIN PATHWAY

The tryptophan-melatonin pathway is evident in all human cells so far investigated and is crucial to most human medical conditions (22, 34, 35). The essential amino acid, tryptophan, is predominantly diet-derived, although some contribution to tryptophan availability comes from the gut microbiome's shikimate pathway, which may be powerfully regulated by the availability of *Akkermansia muciniphila* (11). Tryptophan availability may also be limited by pro-inflammatory cytokine induced indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). IDO and TDO convert serotonin to kynurenine thereby depleting tryptophan availability. Following IDO induction, kynurenine can be metabolized to a number of immune and neuronal regulatory products, such as kynurenic acid and quinolinic acid, with kynurenine and kynurenic acid also activating the aryl hydrocarbon receptor (AhR). AhR activation is an important modulator of the tryptophan-melatonin pathway as AhR activation alters the ratio of melatonin to its immediate precursor, N-acetylserotonin (NAS).

Dietary or shikimate pathway derived tryptophan is taken up from the circulation by the large amino acid transporters, whereupon tryptophan is converted by tryptophan hydroxylase (TPH) to 5-hydroxytryptophan (5-HTP). 5-HTP is rapidly converted to serotonin (5-HT) by aromatic-L-amino acid decarboxylase (AADC). TPH1 is expressed in body organs, with TPH2

expressed in brain cells. TPH2, and likely TPH1, requires stabilization by 14-3-3, including 14-3-3ε and possibly other 14-3-3 isoforms (36). Serotonin can also be provided to cells from serotonergic neuronal inputs and circulating platelets. Serotonin is converted to NAS by 14-3-3ζ (and possibly other 14-3-3 isoforms)-stabilized aralkylamine N-acetyltransferase (AANAT), in the presence of acetyl-coenzyme A (acetyl-CoA). The requirement of acetyl-CoA links the initiation of the melatonergic pathway to mitochondrial function given that acetyl-CoA availability is largely dependent upon the conversion of pyruvate to acetyl-CoA by the pyruvate dehydrogenase complex (PDC). PDC is an important determinant of ATP production by the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS). PDC is deacetylated and disinhibited by sirtuin-3, which is decreased over aging. Finally, NAS is converted to melatonin by acetylserotonin methyltransferase (ASMT). As melatonin increases sirtuin-3, the aging-associated decrease in pineal melatonin will contribute to the suppression of sirtuin-3/PDC/acetyl-CoA over the circadian rhythm during the course of aging (37, 38, 39). As well as melatonin, other factors upregulate sirtuin-3 including the gut microbiome-derived short-chain fatty acid, butyrate. Butyrate optimizes mitochondrial function by enhancing sirtuin-3, PDC activation and acetyl-CoA thereby upregulating the mitochondrial melatonergic pathway, allowing the gut microbiome to have significant impacts on systemic mitochondrial function (40, 41). See Figure 1.

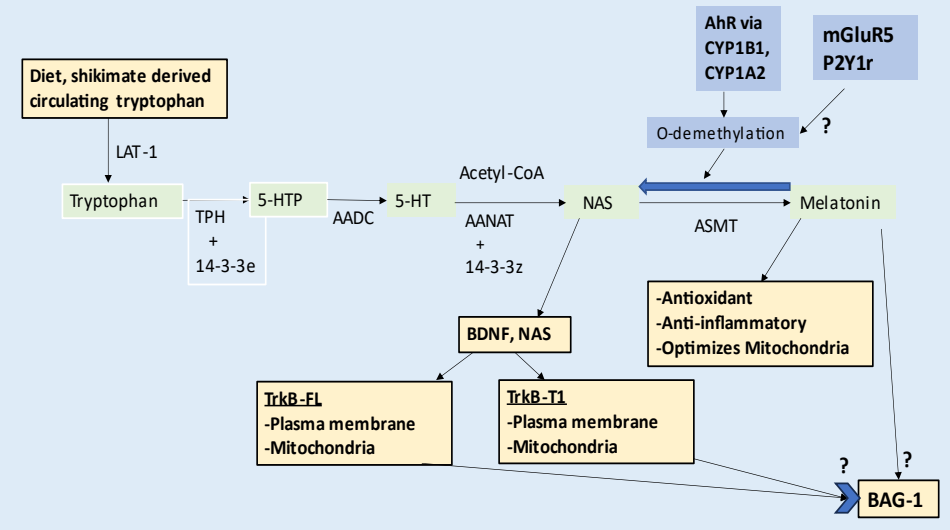


Fig. 1. The tryptophan-melatonin pathway (green shade)

This pathway is initiated by tryptophan uptake into cells, usually via the large amino acid transporter (LAT)-1. Tryptophan is converted to 5-HTP by tryptophan hydroxylase (TPH), with TPH2 and likely TPH1 requiring stabilization by 14-3-3eta. 5-HTP is converted to 5-HT by AADC, with 5-HT metabolized by 14-3-3zeta stabilized AANAT, in the presence of acetyl-CoA, to N-acetylserotonin (NAS). NAS is converted to melatonin by ASMT. The AhR, via CYP1B1 and CYP1A2, (as well as possibly mGluR5 and P2Y1r) 'backward' converts melatonin to NAS via O-demethylation, whilst the AhR/CYP1B1/CYP1A2 may also hydroxylate melatonin to 6-hydroxymelatonin, thereby impacting on the NAS/melatonin ratio. This is relevant as NAS activates the BDNF receptor, TrkB, as well as inducing BDNF in some cells, with BDNF or NAS activating the truncated (TrkB-T1) and full-length (TrkB-FL), both of which may be present on the mitochondrial and plasma membranes. Melatonin and NAS have similar antioxidant and anti-inflammatory effects, although only NAS mimics BDNF via TrkB activation. Melatonin is highly likely to upregulate BAG-1. It is unknown whether NAS at TrkB regulates BAG-1. Abbreviations: 5-HT: serotonin; 5-HTTP: 5-hydroxytryptophan; AADC: aromatic-L-amino acid decarboxylase; AANAT: acetyl-CoA: acetyl-coenzyme A; aralkylamine

N-acetyltransferase; AhR: aryl hydrocarbon receptor; ASMT: N-acetylserotonin O-methyltransferase; BAG-1: bcl2-associated athanogene 1; BDNF: brain-derived neurotrophic factor; LAT-1: large amino acid transporter 1; mGluR: metabotropic glutamate receptor; NAS: N-acetylserotonin; P2Y1r: purinergic P2Y1 receptor; TrkB-FL: tyrosine receptor kinase B-full length; TrkB-T1: tyrosine receptor kinase B-truncated.

As evident in Figure 1, the tryptophan-melatonin pathway can be regulated by factors modulating tryptophan availability and uptake, as well as 14-3-3 isoforms, TPH, AADC, ASMT, acetyl-CoA, sirtuin-3, pineal melatonin, and gut microbiome-derived butyrate. Consequently, the tryptophan-melatonin pathway is intimately integrated with, and influenced by, important systemic and local processes. The tryptophan-melatonin pathway also affords plasticity in response to different cell states, including via the 'backward' conversion of melatonin to NAS via O-demethylation and the hydroxylation of melatonin. The O-demethylation of melatonin by AhR-induced cytochrome P450 (CYP)1A2 and CYP1B1 'backward' converts melatonin to NAS, thereby increasing the NAS/melatonin ratio (42, 43). Other receptors may also increase the NAS/melatonin ratio, including the purinergic receptors ($P2Y_1r$ and $P2X_7r$) and the metabotropic glutamate receptor (mGluR)5 (44-46). NAS, as well as its metabolite N-(2-(5-hydroxy-1H-indol-3-yl) ethyl)-2-oxopiperidine-3-carboxamide (HIOC), activate the brain-derived neurotrophic factor (BDNF) receptor, tyrosine receptor kinase B (TrkB) (47, 48). NAS may also increase BDNF, as shown in the rodent hippocampus (49), thereby further enhancing TrkB activation. Although, melatonin and NAS have many similar antioxidant and anti-inflammatory effects, the BDNF mimicking effects of NAS at TrkB is not replicated by melatonin. An increase in the NAS/melatonin ratio may therefore be problematic in proliferative conditions, such as cancer (50) and endometriosis (51, 52), where melatonin's differentiation and antiproliferative effects (53) may contrast with NAS proliferative effects via TrkB activation. Such distinct effects of NAS are further complicated by TrkB-full length (TrkB-FL) and TrkB-truncated (mostly TrkB-T1) receptors, as well as the presence of these receptors on the plasma membrane and/or mitochondrial membrane (54). Other receptors interacting with the melatonergic pathway, including the alpha 7 nicotinic acetylcholine receptor (α7nAChR), which melatonin induces (55), and the AhR, which is reciprocally antagonistic with melatonin, further implicate and complicate the association of the tryptophan-melatonin pathway with mitochondrial function as part of cellular and intercellular plasticity responses. The presence of melatonergic pathway-linked receptors (α7nAChR, AhR, TrkB-FL, TrkB-T1) on the mitochondrial membrane highlight the potential influence that local and pineal mitochondrial melatonergic pathway can have on core aspects of mitochondrial function.

Importantly, data shows pineal melatonin to be directly released into the cerebrospinal fluid (CSF) via the pineal recess [22]. Released pineal melatonin therefore shows heightened, and maintained, concentrations in the third ventricle at night, compared to systemic circulating melatonin levels (22). Such heightened and maintained melatonin levels in the third ventricle will act upon the tanycytes that line much of the third ventricle, and thereby regulate hypothalamic function. This may be of some importance as hypothalamic tanycytes, and associated astrocytes, are crucial determinants of core hypothalamic function, including systemic metabolism, reproduction, and survival responses, as well as modulating the initiation of the HPA axis (56). The heightened concentrations of pineal melatonin have effects in tanycytes and astrocytes that modulate hypothalamic function with relevance to the course of many aging-and stress-linked medical conditions. Alterations in hypothalamic function and the tryptophan-melatonin pathway are also associated with local aging-linked changes in many medical conditions, such as polycystic ovary syndrome (PCOS) (57, 58) and bipolar disorder (59), highlighting the importance of the hypothalamus in the regulation of systemic

metabolism. Variations in pineal melatonin in the third ventricle may also be important to a wide array of diverse stress/HPA axis linked medical conditions (10). The dramatic decrease in pineal melatonin over aging (21) is therefore of particular importance to the dysregulation of core hypothalamic processes that are crucial to systemic functions. The interactions of the HPA axis and the cortisol awakening response (CAR) with suppressed pineal melatonin in the third ventricle and systemically, may therefore be an overlooked circadian dysregulation in the pathoetiology of a host of diverse medical conditions, including the growing number of conditions that would be classed as 'immune-mediated' disorders (10).

3. HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The HPA axis arises from hypothalamic corticotrophin releasing hormone (CRH) acting in the pituitary to increase adrenocorticotropic hormone (ACTH), which then acts on the G_s-coupled melanocortin-2 receptor on the zona fasciculata cells of the adrenal cortex to drive cortisol production and release. CRH is also released by the amygdala, with amygdala and hypothalamic CRH also having HPA axis independent effects, including inducing tumor necrosis factor (TNF)α release by mucosal mast cells, which increases gut permeability (60). Such data would indicate that the association of the HPA axis with stress may be coordinated with wider systemic changes. Cortisol effects are predominately mediated via the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MCr), with the stress and immune-suppressive effects of cortisol mainly driven by GR activation. As well as being responsive to acute stress, the HPA axis is classically associated with the induction of the 'late sleep/early wakening' cortisol awakening response (CAR) surge. As with melatonin, CAR is an intimate aspect of the circadian rhythm. Also, like melatonin, cortisol can be locally produced via 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), with corticosteroid medications, which are a widely prescribed anti-inflammatory despite long-recognized significant detrimental consequences (61), acting to increase local cortisol via 11β-HSD1 (62).

Immune suppression is another parallel between melatonin and cortisol/GR effects. The immune-suppressive effects of cortisol were popularly highlighted during the COVID-19 pandemic where the use of the GR agonist, dexamethasone, provided some clinical efficacy, although its dampening of natural killer (NK) cell and CD8+ T cell responses also led to the emergence of dormant fungal infections, which often proved fatal (63). This clearly contrasts to melatonin effects in severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) management during the COVID-19 pandemic, where melatonin increased patient survival as well as NK cell and CD8+ T cell antiviral efficacy (64, 65). Such data highlight how cortisol/GR, vs melatonin, differentially regulates different immune cells. GR activation dampens mast cell (66), macrophage (67) and microglia activation (68), whilst GR activation can also attenuate the capacity of dendritic cells to induce regulatory CD4+ and CD8+ T cells (Treg) (69), thereby significantly impacting on the wider patterned immune response. The powerful effects of cortisol/GR activation on the patterned immune response highlight the importance of HPA axis and CAR effects via the GR, and therefore the importance of factors acting to regulate such GR responses. Melatonin has distinct immune effects to that of cortisol at the GR, with melatonin generally acting to suppress the inflammatory response of the immune system 'first responders', such as neutrophils and macrophages, whilst enhancing the cytotoxicity of NK cells during the later immune response. These differential effects of melatonin and cortisol/GR activation on different immune cells are likely to be of some importance in how melatonin and cortisol/GR interact over the circadian rhythm to regulate patterned immune responses on awakening, including in aging-associated medical conditions.

Many 'immune-mediated'/'autoimmune' conditions, such as rheumatoid arthritis, are treated with glucocorticoids. Morning symptom exacerbation in rheumatoid arthritis patients

is linked to raised night-time inflammation in association with an attenuated CAR surge (70), with treatment utilizing delayed release GR agonists targeting the replacement of the lost CAR surge (71). Importantly, CAR is generally accepted as being poorly understood, with extrapolations from rodent data indicating CAR correlations with cognition, especially hippocampal function (72). This correlation is also given some support in human investigations, which show correlations of cognitive function, stress and CAR (73). Decreased cortisol levels correlate with decreased pain thresholds and enhanced pain sensitivity, with a blunted CAR also correlating with suppressed cognitive function (73-76). Much of HPA axis and CAR research seems shaped by the association of cortisol with 'stress' and the impact of stress in the regulation of cognition and mood in affective disorders (77). Clearly, clarification as to how CAR regulates cellular function, including patterned immune responses, will have important consequences for understanding the pathoetiology and pathophysiology of a host of neuropsychiatric and aging-linked medical conditions.

3.1. Cortisol/GR at the nucleus and mitochondria.

GR effects are classically modelled as being mediated via nuclear translocation and the consequent induction of genes with a promotor containing the glucocorticoid response element (GRE). The GR can also act via a plasma membrane GR and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB)/activator protein 1 (AP1)/ signal transducer and activator of transcription 3 (STAT3) pathway as well as showing differential effects via repeated exposure transrepression (78). The GR also interacts with other transcription factors within the nucleus, highlighting how its absence and presence in the nucleus can have wide and complex consequences (78, 79). Recent data shows that bcl2-associated athanogene (BAG)-1 not only prevents GR nuclear translocation but can also chaperone the GR to mitochondria (79). Emerging data shows the GR to have dramatically distinct consequences at mitochondria, compared to the nucleus, including in the regulation of mitochondrial OXPHOS and apoptotic susceptibility (80). BAG-1 driven GR translocation to mitochondria and away from the nucleus is relevant to a wide array of diverse medical conditions, including depression susceptibility and stress resilience (79).

The interaction of BAG-1 with the GR translocation is an active area of cutting-edge research. Preliminary attempts to integrate data on GR nuclear versus mitochondria translocation across different cell types indicate: 1) Short-term high/low dose glucocorticoids increase a GR/Bcl-2 complex that leads to mitochondria translocation. In contrast, high-dose, long-term glucocorticoids attenuate GR mitochondrial translocation, which in the cells investigated increased apoptosis, with apoptosis and suppressed mitochondrial translocation prevented by BAG-1 over-expression; 2) High-dose, short-term glucocorticoids enhance the formation of the GR/BAG-1 complex, thereby increasing GR mitochondrial translocation (81). Although clearly requiring further investigation across different cells types such data has highlighted the importance of BAG-1 in determining GR site of translocation and the differential consequences that can arise from GR nuclear, versus mitochondria, translocation. The GR is also regulated by epigenetic factors, including by histone deacetylase inhibitors (HDACi) (82), which counteracts GR induction of HDAC6. GR-induced HDAC6 increases mitochondria translocating proteins on the outer (TOM20) and inner (TIM23) mitochondrial membranes, which enhances GR mitochondria matrix translocation and the neuronal apoptosis induction by high dose GR activation (81, 83). HDAC6 also potentiates GR binding to heat shock protein (hsp)70/hsp90 (81, 83).

The involvement of HDAC-driven epigenetic processes in GR site of translocation indicates that the gut microbiome-derived short-chain fatty acids, especially the pan-HDACi, butyrate, will impact on GR translocation and the seemingly diverse effects of the GR at the nucleus,

versus mitochondria, in different cell types. Data in neurons shows butyrate to regulate GR effects on anxiety and hyperalgesia as well as on preadipocyte differentiation, which is mediated via butyrate driven acetylation of the GR (82-84). Such data would indicate a role for the gut microbiome/permeability in the epigenetic regulation of GR translocation site and effects, with butyrate having concurrent effects on mitochondrial function via sirtuin-3/PDC/acetyl-CoA and therefore the mitochondrial melatonergic pathway, as indicated in Figure 1. Clearly, factors impacting on gut dysbiosis/permeability, including as driven by psychosocial stressors and GR activation in the gut, will then impact on the diverse GR effects in different cells. The contrasting effects that may arise in different cell types would then change the intercellular interactions within given microenvironments, which recent work proposes to underpin the pathoetiology of 'autoimmune'/'immune-mediated' disorders, including aging-associated dementia and cancer (10).

Overall, stress-linked HPA axis activity and CAR activation of the GR will have their effects differentially determined by variations in melatonin, butyrate and BAG-1 levels. This has significant implications for how the circadian rhythm interacts with aging-linked medical conditions, which may be powerfully determined by variations in pineal melatonin levels.

4. MELATONIN, HPA AXIS, CORTISOL AWAKENING RESPONSE AND BAG-1

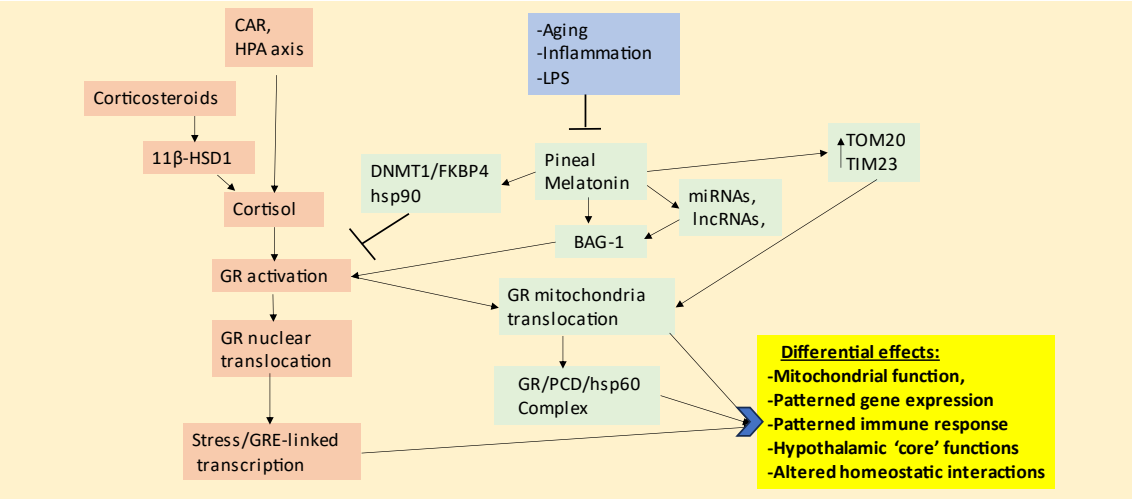
Numerous studies show melatonin modulates GR effects in different cells, with differential consequences under different experimental conditions (28-31). Melatonin attenuates GR effects, including dexamethasone effects on humoral and cell-mediated immune responses (85), and breast cancer initiation (86), as well as stress/GR effects on ovarian damage (87), and placental angiogenesis impairment (88). Melatonin also suppresses the hyperactivated HPA axis in type 2 diabetes mellitus (T2DM) with effects modelled via enhancing GR levels and decreasing hippocampal 11β-HSD1 activity, thereby enhancing GR sensitivity and negative feedback to the HPA axis (89).

Importantly, melatonin suppresses GR nuclear translocation (90). It is proposed that this is mediated by a number of processes, including: 1) via melatonin maintaining the GR in a cytoplasmic complex with hsp90, whilst increasing nuclear factor erythroid 2–related factor 2/hemeoxygenase-1(Nrf2/HO-1)/Bcl-2 expression, as shown in peripheral blood mononuclear cells (PBMCs) (91); 2) via melatonin enhancing DNA methyltransferase 1 (DNMT1)-mediated FKBP52 promoter hypermethylation, leading to the suppression of the GR co-chaperone, FKBP prolyl isomerase 4 (FKBP4), thereby reducing GR nuclear translocation and GR-driven mitochondrial dysfunction and neuronal apoptosis (92). These authors also propose that melatonin will therefore limit GR suppression of mitophagy, with consequences for neurodegenerative disorders (92). Melatonin's upregulation of DNMT1, will also increase BAG-1 via insulator protein DNA-binding by Brother of regulator of imprinted sites (BORIS) as well as by chromatin dynamics via histone demethylation regulation (93). 3) BAG-1 is suppressed by a number of microRNAs, including miR-138 (94), which melatonin suppresses (95), thereby allowing melatonin to derepress BAG-1. miR-138 upregulation is closely associated with a diverse array of aging-linked medical conditions (96), which is parsimonious with an aging-linked alterations in how CAR and the stress-associated HPA axis may differentially regulate circadian and stress modulation of different cells over the course of aging and in the pathoetiology of aging-associated conditions. Overall, melatonin can suppress GR nuclear translocation via a number of processes, including by a number of processes leading to BAG-1 upregulation.

It is proposed here that interactions of pineal melatonin, local melatonin and CAR across the circadian rhythm determine the patterning and efficacy of the immune/glia responses, primarily via impacts on mitochondrial function and patterned gene expression and, in some

circumstances BAG-1 upregulation. Night-time pineal melatonin, local melatonin, butyrate and BAG-1 will interact to differentially prime the consequences of GR activation in the course of the morning CAR. The suppression of melatonin over aging as well as by systemic inflammation and gut permeability-induced circulating LPS, will therefore have impacts not only on melatonin levels and effects but also on the consequences arising from CAR and stress-induced HPA axis activity. Such systemic and circadian variations during aging/inflammation/gut permeability may be especially important in the circadian regulation of reactive cells, such as glia and immune cells, by altering how reactive cells modulate the homeostatic interactions of cells in a given microenvironment across body tissues and organs (10). See Figure 2.

Fig. 2. The interactions of CAR and the HPA axis (orange shade) with the melatonin/BAG-1 pathway (green shade), with differential impacts (yellow shade) of pineal melatonin influenced CAR and HPA axis.



CAR (and stress activated HPA axis) lead to cortisol activation of the GR, which when translocated to the nucleus induces stress-linked genes expressing the GRE in their promotor. Corticosteroid medications do likewise, typically via the induction of local 11β-HSD1. Pineal melatonin (green shading), and possibly local melatonin, in the early night can induce BAG-1 indirectly via miRNAs and lncRNAs regulation (and possibly directly). Melatonin's epigenetic upregulation of BAG-1 prevents CAR induced GR nuclear translocation by translocating the GR to mitochondria, whilst melatonin via DNMT1/FKBP4 and hsp90, prevents GR nuclear translocation. Melatonin's upregulation of TOM20 and TIM23 allows GR translocation into the mitochondrial matrix, where the GR can form a complex with PDC and hsp60, thereby regulating mitochondrial metabolism. The dramatic decrease in pineal melatonin over aging as well as from raised LPS and pro-inflammatory cytokines suppressing pineal melatonin, thereby attenuates the epigenetic upregulation of BAG-1, with a diverse array of metabolic consequences in different cell types. Aging, by decreasing pineal melatonin and changing GR nuclear, versus mitochondria, translocation will therefore change the consequences arising from CAR and stress linked HPA axis activation. Abbreviations: 11β-HSD1: 11β-hydroxysteroid dehydrogenase type 1; BAG-1: bcl-2 associated athanogene 1; CAR: cortisol awakening response; DNMT1: DNA methyltransferase 1; FKBP4: FKBP prolyl isomerase 4; GR: glucocorticoid receptor; GRE: glucocorticoid receptor element; HPA: hypothalamic-pituitary-adrenal; hsp: heat shock protein; lnc: long non-coding; PDC: pyruvate dehydrogenase complex; TIM: mitochondrial import inner membrane translocase subunit; TOM: mitochondrial import outer receptor subunit.

The melatonin regulation of GR effects via BAG-1 will be subject to differential modulation in different cell types, at least partly influenced by variations in other BAG-1 regulators, such as miRNAs and long non-coding (lnc)RNAs, with miR-342, (97), miR-138 (94) and lncRNA XIST (98) modulating BAG-1 levels. LncRNAs, including lncRNA-H19 (H19) (99) and NCK1 Antisense RNA 1 (NCK1-AS1) (100), suppress miR-138, thereby derepressing BAG-1. Melatonin generally increases H19 by enhancing the transcription efficiency of the H19 promoter (101) and therefore may suppress miR-138 via H19. However, melatonin can also decrease H19 (102), indicating that the wider cell state determines melatonin's regulation of H19. Such data highlights melatonin's homeostatic regulatory functions and how 2.5 billion years of evolution that have maintained the association of the melatonergic pathway with the ancient bacteria that evolved into mitochondria allow melatonin effects to be coordinated with mitochondrial and cellular plasticity (103). The differential effects of melatonin on H19 levels may indicate the hierarchical relevance of mitophagy, which melatonin increases under conditions of oxidative stress (25). As H19 suppresses mitophagy by hindering eukaryotic translation initiation factor 4A, isoform 2 (eIF4A2) binding to PINK1 mRNA, thereby suppressing PINK1 translation and mitophagy (104), melatonin effects on H19 would seem dependent upon wider, core aspects of mitochondrial function and regulation. It requires investigation as to whether other miRNAs and lncRNAs modulate BAG-1, including across different cell types and the implications that this could have for the intercellular homeostatic interactions in a given microenvironment, including over the circadian rhythm.

As noted, miR-138 is associated with aging-linked changes across different organs and tissues, including bone thinning (96) and skin aging (105), with effects at least partly mediated via decreases in sirtuin-1, sirtuin-6 and sirtuin-7 (96,106,107). The suppression of sirtuin-1 by miR-138 is also relevant in preclinical models of Parkinson's disease (108). miR-138 also dysregulates insulin release in BAG-1 expressing pancreatic β-cells (109,110,111). As GR activation induces apoptosis in pancreatic β-cells (112) partly via raised glycogen synthase kinase (GSK)3β levels and GR nuclear translocation (113), any miR-138 suppression of BAG-1 in pancreatic β-cells will contribute to the GR-mediated insulin dysregulation and apoptosis in T1DM (11). Interestingly, the dexamethasone treatment of inflammatory conditions often induces diabetes and pancreatic β-cell loss. Whether the suppression of the endogenous mitochondrial melatonergic pathway in pancreatic β-cells contributes to increased miR-138 and miR-138 suppression of BAG-1, thereby enhancing GR nuclear translocation, will be important to determine. Whether this would be further exacerbated by the loss of local melatonin production in pancreatic β-cells, via the attenuation of melatonin's capacity to induce BAG-1 and/or a maintained cytoplasmic hsp90/GR complex will also be important to determine. This is parsimonious with the induction of T1DM in rodents by streptozotocin (11), which suppresses the endogenous melatonergic pathway, as shown in the retina (114), indicating that local, as well as pineal, melatonin may be relevant to BAG-1 and GR regulation. The interactions of melatonin/BAG-1/GR in the regulation of T1DM and T2DM highlight the importance of alterations in metabolism evident in many medical conditions, as well as the importance of local aging-linked changes in different tissues and organs across all age ranges.

Pineal and local melatonin will also regulate the consequences of GR translocation to mitochondria via melatonin's capacity to increase TOM20 and TIM23 levels, whilst preserving TOM20 and TIM23 levels in cells under challenge (115-117). This would indicate that melatonin, as well as suppressing miR-138 and increasing BAG-1, may also optimize GR uptake into the mitochondria matrix, thereby biasing the mitochondria, versus nuclear, GR effects. Under conditions of suppressed mitophagy, the capacity of melatonin to upregulate mitophagy is partly determined by increased TOM20 and TIM23 levels and function (116), indicating that the maintenance of mitophagy may be intimately linked to the site of GR translocation. Interestingly, preserving TOM20 and TIM23 levels is coupled to the

maintenance of hsp60 in the mitochondrial matrix and mitochondrial biogenesis upregulation (117). Hsp60 is also a GR mitochondrial binding partner, indicating that melatonin will influence the mitochondrial matrix complex formed following GR translocation to mitochondria (118). Notably, the dramatic decrease in pineal melatonin with age correlates with suppressed BAG-1 levels over aging, as shown in rodents (119), highlighting how aging-associated changes in melatonin and BAG-1 levels can be intimately linked to GR translocation site, interaction partners in mitochondria and consequent metabolic effects.

4.1 Pineal melatonin, third ventricle, hypothalamic function and CAR.

Pineal melatonin is released into the cerebrospinal fluid through the pineal recess into the posterodorsal aspect of the third ventricle (22). This is proposed to allow pineal melatonin to have a heightened influence on the circadian rhythm via enhanced melatonin effects in the hypothalamus, classically attributed to effects at the hypothalamic suprachiasmatic nucleus (22). However, melatonin released into the third ventricle will have direct and immediate effects on the cells that predominantly line this ventricle, namely tanycytes. This suggests that the decrease in pineal melatonin over aging, as well as in many diverse medical conditions, such in PCOS (120), bipolar disorder (121), endometriosis (122), dementia (123), obesity/T2DM [124] and amyotrophic lateral sclerosis (125), will modulate hypothalamic function. Tanycytes and their mitochondrial function are important regulators of the hypothalamic function, with implications for many systemic processes and metabolism (124). It is unknown, although highly likely, as to whether tanycytes express the melatonergic pathway or indeed whether BAG-1 is expressed in tanycytes with consequences for GR and other receptors translocation to mitochondria, versus the nucleus.

The capacity of pineal melatonin to suppress GR nuclear translocation and indirectly, and perhaps directly, to upregulate BAG-1 will determine the impact of CAR on hypothalamic tanycytes, astrocytes and neurons, thereby allowing pineal melatonin, BAG-1 and CAR interactions to modulate the consequences of CAR on cellular and metabolic function. The role of CAR in physiological function is unknown, other than being widely believed to ‘prepare the body for the challenges of the upcoming day’, by increasing blood pressure and respiration. The above would indicate that CAR and GR activation may be important mediators of suppressed pineal melatonin over aging and across medical conditions, via the differential GR effects at the nucleus, versus mitochondria. The prolonged fourfold increase in melatonin concentration in the third ventricle would indicate that pineal melatonin effects may be most important in the hypothalamus, especially given the hypothalamic regulation of core functions related to reproduction, feeding, stress and aggression/survival behaviors. These core hypothalamic functions are all regulated by cortisol and GR activation (126-128), highlighting the importance of pineal, and perhaps local, melatonin in the regulation of GR effects on core aspects of survival.

Importantly, pineal releases over the circadian rhythm include NAS as well as melatonin, with NAS having some distinct effects via its capacity to mimic BDNF via TrkB activation (47). BDNF, TrkB-FL and TrkB-T1 are expressed in tanycytes and adjacent hypothalamic astrocytes (129), suggesting that pineal NAS, as well as the O-demethylation of melatonin to NAS by AhR-induced CYP1A2 and CYP1B1 in the hypothalamus, will activate TrkB-FL and TrkB-T1. Both TrkB-FL and TrkB-T1 can be expressed in the plasma membrane and mitochondrial membrane (see Figure 1), indicating diverse effects on mitochondrial function and patterned gene transcription that may be dependent upon the chaperoning of TrkB to mitochondria. It will be important to determine whether pineal NAS and melatonin have differential effects on BAG-1 and GR translocation, especially in the hypothalamus, given the importance of the hypothalamus in the regulation of core systemic processes and crucial

behaviors. Overall, the presence of TrkB-FL and TrkB-T1 in tanycytes and adjacent astrocytes will allow variations in the pineal NAS/melatonin ratio to modulate core aspects of hypothalamic function, possibly involving the differential regulation of BAG-1 and GR translocation site in response to morning CAR, thereby differentially priming systemic and CNS processes for the coming day.

5. CLINICAL IMPLICATIONS

As indicated throughout the document, the suppression of pineal, and local melatonin production will have pathophysiological consequences across a host of diverse medical conditions, including as to how these conditions associate with alterations in the circadian rhythm, CAR, and HPA axis activity. Ultimately, the interactions of melatonin, BAG-1 and the GR will be mediating their effects on patterned gene transcription and alterations in mitochondrial function. However, the differential effects of melatonin/BAG-1/GR in different cell types and states, such as increased miR-138, will not only impact on single cell function but also on the intercellular homeostatic interactions in a given microenvironment. Recent work has conceptualized the interactions in a given microenvironment as a form of evolutionary modified bacteria (99) in the form of mitochondria interacting with each other (130). Such a perspective highlights the importance of core metabolic processes determined by mitochondrial function and powerfully influenced by the capacity of a given cell to maintain the tryptophan-melatonin pathway. Alterations in the homeostatic interactions of cells in a given microenvironment, as exemplified in the tumor microenvironment (130), will be powerfully determined by the capacity of interacting cells to modulate the mitochondrial melatonergic pathway in other cells. The circadian effects of melatonin/BAG-1/GR, and factors modulating melatonin/BAG-1/GR in individual cells (such as miR-138), will be powerful determinants of the dyshomeostasis that may ultimately lead to cell elimination from a given microenvironment, as exemplified in 'immune-mediated' conditions such as Parkinson's disease and T1DM (10). It is also important to highlight that the gut microbiome is an integral aspect of the circadian rhythm, with butyrate production acetylating both the GR and hsp90 (82, 131), thereby preventing GR nuclear translocation, whilst concurrently increasing sirtuin-3, PDC and the mitochondrial melatonergic pathway. See Figure 3.

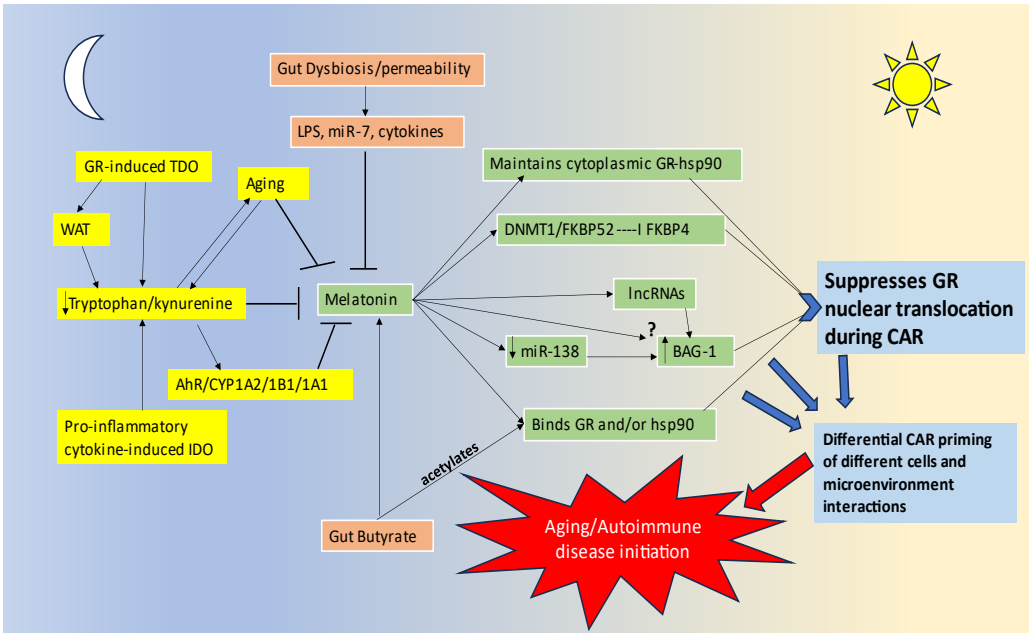


Fig. 3. Shows how different systemic factors modulate the GR directly and via melatonin regulation, with consequences for autoimmune and aging-linked disorders.

Systemic factors, including pro-inflammatory cytokine-induced IDO, cortisol/GR/TDO potentiation of white adipocyte and wider aging processes can increase conversion of tryptophan to kynurenine, thereby activating the AhR (yellow shade) and suppressing pineal and/or local melatonin. Suppressed melatonin enhances GR nuclear translocation, with melatonin proposed to suppress GR nuclear translocation via a variety of mechanisms, including via indirect (miRNAs, lncRNAs) and possibly direct BAG-1 upregulation (green shade). The gut microbiome regulates melatonin availability, with gut derived butyrate increasing the melatonergic pathway, whilst gut dysbiosis and increased gut permeability decreases butyrate and raises factors suppressing melatonin, including LPS, miR-7 and pro-inflammatory cytokines (orange shade). The interactions of these factors over the night result in variable GR nuclear translocation in different cell types during the course of the cortisol awakening response (CAR), thereby altering the nature of the patterned interactions within a given microenvironment. The differential priming by night-associated processes of morning CAR in the different cells of a given microenvironment alters microenvironment interactions across the body and brain, thereby priming pathoetiological changes linked to aging and 'autoimmune'/'immune mediated' conditions, including dementia and cancer. Abbreviations: AhR: aryl hydrocarbon receptor; BAG-1: bcl2-associated athanogene-1; CAR: cortisol awakening response; CYP: cytochrome P450; DNMT1: DNA methyltransferase 1; FKBP: FK506 binding protein; GR: glucocorticoid receptor; hsp: heat shock protein; IDO: indoleamine 2,3-dioxygenase; lnc: long noncoding; LPS: lipopolysaccharide; miR: microRNA; TDO: tryptophan 2,3-dioxygenase; WAT: white adipocyte.

6. FUTURE RESEARCH IMPLICATIONS

1. Does melatonin directly and/or indirectly upregulate BAG-1 levels? What are the consequences of BAG-1 mediated GR mitochondria translocation in different cell types and does this change with aging?

2. Are the maintained higher melatonin levels in the third ventricle mediating effects in hypothalamic tanycytes, astrocytes and neurons that suppress HPA axis and CAR effects at the GR? Does this involve BAG-1 upregulation? Are some hypothalamic cells relatively resistant to BAG-1 upregulation due to heightened levels of miRNAs, such as miR-138 and miR-342, leading to an altered patterning of hypothalamic peptides following CAR/HPA axis activation with consequences for systemic regulation?

3. Under conditions of suppressed pineal melatonin, perhaps especially if gut butyrate is also suppressed, are there differential consequences of melatonin/butyrate/BAG-1/GR alterations in different cell types that change the nature of intercellular homeostatic interactions that underpin the emergence of aging-associated medical conditions, including 'autoimmune'/'immune-mediated' disorders involving cell elimination, like T1DM and dementia?

4. Do increases in the pineal and local NAS/melatonin ratio change the regulation of GR and BAG-1 and therefore the consequences of CAR and stress-linked HPA axis activity, especially in the hypothalamus? Does NAS modulate BAG-1 levels?

5. Is the mitochondrial melatonergic pathway evident in hypothalamic tanycytes? If so, is the tanycyte mitochondrial melatonergic pathway regulated by AhR-induced CYP1B1 and CYP1A2, leading to the O-demethylation of melatonin to NAS? Is NAS released from tanycyte mitochondria to activate TrkB-FL and/or TrkB-T1 on mitochondrial and/or plasma membranes?

6. Does the induction of BAG-1, including indirectly and perhaps directly by melatonin, modulate the presence of melatonergic pathway-linked mitochondrial membrane receptors, namely α7nAChR, AhR, TrkB-FL, TrkB-T1? The presence of the AhR at mitochondria reciprocally interacts with translocator protein (TSPO) at the mitochondrial membrane, with consequences for mitochondrial function and mitophagy (132,133). Is TSPO regulation linked to alterations in the mitochondrial melatonergic pathway driven by the AhR induction of CYP1A2 and CYP1B1? There is a growing interest in the roles of different tryptophan-melatonin pathway linked receptors at mitochondria, including the GR.

7. As well as miR-138, miR-342 and lncRNA XIST, do other miRNAs and lncRNAs modulate BAG-1 levels, and therefore CAR and GR effects in different cell types, including over the circadian rhythm?

7. TREATMENT IMPLICATIONS

1) The investigation of the above research directions should provide wider treatment targets involving the regulation of hypothalamic melatonin/BAG-1/GR activation. A plethora of clinical investigations have highlighted the clinical utility of melatonin in wide array of different cancers, including leukemia (134), breast cancer (135), and renal carcinoma (136), with a growing appreciation that aging and circadian dysregulation, including by night-shift work, increase cancer risk by suppressing pineal melatonin (137). In contrast, the effects of stress and heightened GR activation heighten cancer risk and poor outcomes (138). Likewise in dementia, dramatic decreases in melatonin are evident, including in hippocampal neurons (139), with melatonin showing some efficacy in the management of circadian and cognitive symptoms in Alzheimer's disease (140) and mild cognitive impairment (141), where dysregulated GR activation is often evident. Clearly, the interactions of pineal melatonin and local mitochondrial melatonergic pathway regulation in the modulation of CAR/stress linked GR effects, including possibly via BAG-1 regulation, will be important to clinically determine. The interactions of night-time melatonin and fasting-driven heightened butyrate at night (142) in the pathoetiology of such diverse medical conditions should provide clinically relevant targets based on research-derived physiological processes, such as night-time processes modulating CAR. This would seem preferable to utilizing and conceptualizing treatments based on the pathophysiological changes evident at the 'end-point chaos' of most current medical classifications. The research indicated above should provide a framework in which to place data relevant to aging-linked medical conditions.

2) The utilization of melatonin will benefit from the concurrent monitoring of the gut microbiome and the optimization of butyrate producing bacteria and/or the use of sodium butyrate as a readily available nutraceutical. Both melatonin and butyrate inhibit GR nuclear translocation, with potentially significant consequences as to how the morning CAR "prepares the body for the coming day." The timing and speed of release of melatonin and sodium butyrate administration will be important to determine clinically in shaping the consequences of the morning CAR.

3) The development of pharmaceuticals or nutraceuticals that target the tryptophan-melatonin pathway, especially in specific cells, will shape treatments to core physiological processes. Clearly, the capacity to maintain pineal melatonin production over aging will suppress many of the aging-linked pathoetiological changes occurring in many medical conditions. This will be an important treatment target, with implications for hypothalamic function and CAR regulation as driven by night-time processes.

4) Loneliness and little physical contact are aspects of social stressors for many people over the course of aging, the detrimental impacts of which are at least partly mediated via HPA axis activation (143). This would indicate targeted suppression of the GR with melatonin and

butyrate over the circadian rhythm may be able to attenuate the consequences of deprived social contact over aging.

8. CONCLUSIONS

The capacity of melatonin to suppress GR nuclear translocation including indirectly, and perhaps directly via BAG-1 upregulation, thereby modulating the site of GR nuclear, versus mitochondria, translocation significantly changes how the circadian rhythm is conceptualized to regulate cell function and intercellular interactions across the body. This has relevance to a diverse range of medical conditions, many of which are widely recognized as being poorly conceptualized and consequently poorly treated, including aging associated conditions such as Alzheimer's disease and cancer, as well as other medical conditions with an 'autoimmune'/'immune-mediated' aspect to their pathophysiology, such as PCOS, T1DM, Parkinson's disease and bipolar disorder. The interactions of melatonin/butyrate/BAG-1/GR in the regulation of CAR may be of particular importance in the pathoetiology of these diverse medical conditions via changes in the intercellular homeostatic interactions in particular microenvironments. This has a number of research and treatment implications, the investigation of which should better clarify relevant pathophysiological processes and treatment targets.

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AUTHORSHIP

GA conceptualized and wrote the article.

CONFLICT OF INTEREST

The author declares no competing interests.

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
ACTH	adrenocorticotropic hormone
AhR	aryl hydrocarbon receptor
AMPK	AMP-activated protein kinase
ASMT	N-acetylserotonin O-methyltransferase
BAG-1	bcl-2 associated athanogene 1
BDNF	brain-derived neurotrophic factor
CAR	cortisol awakening response
CRH	corticotrophin releasing hormone

CSF	cerebrospinal fluid
CYP	cytochrome P450
DNMT1	DNA methyltransferase 1
FKBP4	FKBP prolyl isomerase 4
GR	glucocorticoid receptor
GRE	glucocorticoid receptor element
HDAC	histone deacetylase
HPA	hypothalamic-pituitary-adrenal
hsp	heat shock protein
IDO	indoleamine 2,3-dioxygenase
lnc	long non-coding
LAT-1	large amino acid transporter 1
mGluR	metabotropic glutamate receptor
MHC	major histocompatibility complex
NAS	N-acetylserotonin
NK	natural killer
OXPHOS	oxidative phosphorylation
P2Y1r	purinergic P2Y1 receptor
PCOS	polycystic ovary syndrome
PDC	pyruvate dehydrogenase complex
PINK1	PTEN-associated kinase 1
T1DM	type 1 diabetes mellitus
TCA	tricarboxylic acid
TDO	tryptophan 2,3-dioxygenase
TIM	mitochondrial import inner membrane translocase subunit
TOM	mitochondrial import outer receptor subunit.
TrkB-FL	tyrosine receptor kinase B-full length
TrkB-T1	tyrosine receptor kinase B-truncated
ULK-1	Unc-51 like autophagy activating kinase 1

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