Review

Gut dysbiosis dysregulates central and systemic homeostasis via decreased melatonin and suboptimal mitochondria functioning: pathoetiological and pathophysiological implications.

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ABSTRACT

Two important hubs have emerged as cutting edge areas of research across a diverse array of medical conditions, the gut microbiome and mitochondria. This article highlights the role of melatonin in modulating changes in both the gut and mitochondria. The gut microbiome, especially via its production of the small chain fatty acid, butyate, can have a significant impact on immune inflammatory processes. Lower levels of butyrate producing bacteria can increase gut permeability, thereby increasing immune-inflammatory activity. Butyrate may also modulate immune and other cells via the regulation of the content of exosomes from intestinal epithelial cells. Butyrate also induces N-acetylserotonin and melatonin synthesis in the gut, suggesting that some of the effects of butyrate may be mediated via its induction of the melatonergic pathway. The induction of melatonin by butyrate may feedback on the microbiome via melatonin increasing gut bacteria swarming, as well as melatonin optimizing gut barrier and mitochondria functioning. As butyrate readily crosses into the circulation it is likely that the immune- and glia-dampening effects of butyrate also involve the induction of melatonin in these reactive cells. Butyrate also positively modulates mitochondria functioning, suggesting that butyrate, both directly and via melatonin, will have significant impacts on gut, immune, glia and other cells, via mitochondria regulation. Other factors that act to regulate melatonin, including dietary factors and stress, will therefore act to modulate many of butyrate's effects. The regulation of melatonin at these two important hubs has significant treatment and classification implications across a wide array of medical conditions. Overall, gut dysbiosis has a significant impact on central and systemic homeostasis, via decreased butyrate and melatonin driving suboptimal mitochondria functioning. This has implications for the pathoetiology and pathophysiology of a host of medical conditions associated with gut dysbiosis and decreased melatonin production.

Keywords: melatonin, butyrate, gut, microbiome, mitochondria, immune, homeostasis, inflammation, depression.

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1. INTRODUCTION

A growing body of data shows that alterations in the gut microbiome and changes in mitochondria functioning may be intimately linked to a plethora of diverse medical conditions, including multiple sclerosis, Alzheimer's disease, Parkinson's disease, autistic spectrum disorders, schizophrenia, bipolar disorder, depression, rheumatoid arthritis, inflammatory bowel disease and metabolic syndrome (1-8). Such a diverse array of clinical presentations have significant alterations in mitochondria and the gut microbiome as important aspects of their pathophysiology, as well as

being important sites for treatment interventions.

Recent work now shows melatonin to have a significant role in the regulation of key processes in mitochondria as well as in the interactions of the gut microbiome with intestinal epithelial cells and the mucosal immune system. Many of the benefits associated with a diverse gut microbiome are mediated by an increase in the short-chain fatty acid (SCFA), butyrate, which has effects both locally in intestinal epithelial cells as well as crossing into the general circulation, where it can regulate many cells, including immune cells (9-12). One of the benefits of butyrate is its induction of the melatonergic pathways, indicating that melatonin may be an important mediator of many of butyrate's beneficial effects (13).

This article looks at the physiological processes overlapping changes in the gut and mitochondria functioning, hypothesizing that variations in the levels of melatonin synthesis may be important in determining how the inter-connected changes at these two hubs regulate a diverse array of medical presentations.

1.1. Gut and microbiome.

Alterations in the gut microbiome are at the cutting edge of a host of medical conditions, including psychiatric, neurodegenerative, cancers, cardiovascular, and metabolic disorders (1,2). Interest in the gut arises from the influence of gut microbiome alterations, which can increase gut permeability, thereby allowing gut bacteria or fragments of partially digested food to drive an immune-inflammatory response. Such increases in immune-inflammatory processes are thought to significantly contribute to the pathophysiology of a diverse array of medical conditions (1), including to the heightened risk of comorbid conditions, such as depression, obesity, dementia and arthritis (3-5). Alterations in vagal interactions with the gut may also contribute to this, including via the retrograde transport of alpha-synuclein in Parkinson's disease (6, 7). As such, the gut microbiome may influence host health by a number of different routes.

Although gut bacteria are necessary for the supply of many factors crucial to the host's survival, variations in the production of the three SCFAs, butyrate, propionate and acetate, are important mediators of the gut alterations underpinning immune-inflammatory activity. Decreases in the bacterial families producing butyrate seem of particular importance, with butyrate not only maintaining the integrity of the gut barrier, but also crossing the gut barrier where it can dampen immune and glia cell inflammatory processes (8, 9). Butyrate has direct effects on mitochondria functioning (10) and also acts as a histone deacetylase inhibitor (HDACi), Nod-like receptor family pyrin domain containing (NLRP)3 inflammasome inhibitor and regulator of autophagy (11). Interestingly, all of these effects of butyrate are replicated by melatonin (12).

Such overlapping effects of butyrate and melatonin may be partialy explained by butyrate's induction of aralkylamine N-acetyltransferase (AANAT) and acetylserotonin O-methyltransferase (HIOMT) protein and mRNA, leading to N-acetylserotonin (NAS) and melatonin synthesis, as shown in gut epithelial cells (13). Consequently, gut bacteria derived butyrate may be mediating some of its many beneficial effects via its induction of melatonin, including effects on mitochondrial functioning, sirtuin induction and autophagy, as well as immune regulation and NRLP3 inflammasome dampening. It is also of note that the release of melatonin in the gut increases the swarming of some gut bacteria. Recent work by Paulose and colleagues suggests that “the human circadian system may regulate its microbiome through the entrainment of bacterial clocks”, with melatonin increasing the swarming of some gut bacteria (14). As well as a decrease in the circadian release of pineal melatonin over age, there is also a significant decrease in gastro-intestinal melatonin release over the course of aging, as evidenced by faecal levels in rodents (15). Given that the heightened risk of most medical conditions rises with age, such conditions are intimately associated with cellular aging processes, which may be importantly negatively regulated by butyrate and melatonin.

The gut microbiome is now modelled as forming a number of axes, including gut-brain, gut-

liver, and gut-kidney axes (16), highlighting the importance of the gut microbiome in the regulation of different organs and body systems, with implications for wider homeostatic regulation. However, many of the changes that are occuring in these interacting body systems are mediated via alterations in mitochondria functioning.

1.2. Mitochondria.

Almost all body cells contain mitochondria, which are crucial for cellular energy production as well as reactive oxygen species (ROS)-driven plasticity and cellular signalling. Mitochondria are also important hubs for many intra- and extra-cellular signalling processes and receptors, including sirtuins, tryptophan metabolites, anti- and pro-apoptotic molecules as well as alpha 7 nicotinic (α7nAChR), melatonin, and the aryl hydrocarbon receptors (AhR) (17). Such mitochondrial interations of these physiological pathways are crucial to the functioning of all cells, including those of the gut, and therefore in the regulation of gut permeability and inflammatory responses. It is important to note that alterations in mitochondria functioning will modulate the cellular responses and inter-cellular signalling of reactive cells, including immune and glia cell reactivity thresholds and inflammatory responses (18, 19). Mitochondria are clearly a crucial hub for the regulation of cellular responses, with such mitochondrial alterations intimately linked to systemic changes, including in the immune system and various gut axes.

Many of butyrate's effects seem mediated via mitochondria, with butyrate enhancing mitochondria functioning under oxidative stress (20). Data from diverse areas of research show the microbiome to be in close interaction with host mitochondria, especially via the release of butyrate (21, 22). Butyrate increases peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and mitochondrial DNA copy number, modulates energy metabolism and mitochondrial function, β-oxidation, the tricarboxylic acid cycle, oxidative phosphorylation, mitochondrial manganese-superoxide dismutase and glutathione peroxidase activity, whilst decreasing glycolysis (23). It should be noted that this is a two-way interaction with mitochondria, especially in intestinal epithelial cells and mucosal immune system, where mitochondria act to regulate the composition of the microbiome and levels of butyrate production.

It should also be noted that many of the factors associated with wider health benefits may be acting to modulate the interactions of the gut microbiome with host mitochondria, such as the green tea polyphenol, epigallocatechin-3-gallate (24), curcumin (25) and taurine (26). Taurine is the most common amino acid in the brain and is known for its anti-inflammatory, gut-regulatory and antioxidant effects (27), with taurine increasing butyrate production (28), suggesting that it will, at least indirectly, increase melatonin synthesis (13). Taurine also has a number of positive effects on mitochondrial functioning (26, 29), whilst alterations in the murine gut microbiome significantly modulates brain taurine levels (30). Such data suggests that alterations in the gut microbiome may act to modulate brain mitochondrial and neuronal functioning, at least in part, via alterations in taurine. Taurine can also significantly modulate immune cell inflammatory activity, including that of macrophages (31) mast cells (32) and microglia (33). It is also of note that astrocytes release taurine, which regulates the neuronal glycine receptor, when neurons are under challenge (34). Taurine can then act to regulate GABAergic and glycine currents, thereby acting as a neuromodulator of the balance of excitatory and inhibitory neuronal activity (35).

Importantly, taurine can regulate AANAT and therefore melatonin synthesis (36), suggesting that some of the effects of taurine on gut and mitochondria functioning, like those of butyrate, may be mediated by the regulation of local melatonin synthesis.

2. MELATONIN IN MITOCHONDRIA & MICROBIOME MODULATION OF IMMUNITY

2.1. Melatonin and immunity.

It is widely accepted that many of the alterations that arise from an increase in gut permeability are mediated by an increase in immune-inflammatory responses, especially from increases in circulating pro-inflammatory cytokines. As well as direct impacts in cells, interleukin (IL)-1β, IL-6, IL-18, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ can all increase indoleamine 2,3-dioxygenase (IDO), leading to the driving of tryptophan to kynurenine pathway products and away from serotonin and melatonin synthesis (37). Likewise stress induced cortisol and oxidative stress may increase tyrptophan 2,3-dioxygenase (TDO) and therefore the kynurenine pathway. As many of the kynurenine pathway products, such as quinolinic acid and kynurenic acid, significantly modulate neuronal activity, changes in gut butyrate and melatonin can have significant impacts on brain and peripheral neuronal activity. This has a number of consequences, including as to how the gut microbiome may link to depression and dementia, as well as to the levels of melatonin that may be available for the modulation of mitochondria and gut functioning (Figure 1).

A plethora of data over many decades show melatonin to significantly modulate immune responses, both at single cell and system levels (38). Melatonin can increase t-helper (Th)1 and Th2 differentiation, whilst shifting macrophages from a M1 to M2-like phenotype (39), the latter effect via the autocrine release of melatonin by macrophages. Melatonin can also decrease the differentiation of the more damaging Th17 cells, lowering the heightened autoimmune responses that are linked to many disorders (40). Melatonin also decreases the recruitment and degranulation of mast cells, which are important cells at many barrier interfaces, including the gut barrier. Some of melatonin's effects are mediated via its HDACi capacity (41) and positive regulation of sirtuins (42).

Many of these effects can be replicated by butyrate, which promotes Th1 cell development whilst inhibiting Th17 cell development. Butyrate also upregulates IL-10 production in T cells both under Th1 and Th17 cell conditions. Butyrate's promotion of Th1 cells is mediated via HDACi and seems independent of the G-protein coupled receptor (GPR) (43). Like melatonin, butyrate promotes an M2-like phenotype in macrophages (44) and induces sirtuin-1 (45) as well as dampening intestinal mast cell recuitment and degranulation (46).

Butyrate may also imprint an anti-microbial programme in macrophages via the inhibition of mammalian target of rapamycin (mTOR), thereby restricting bacterial growth and enhancing the host's immune defense (47). Melatonin also acts to inhibit mTOR (48, 49) and promotes antimicrobial responses in plants, suggesting that its effects on macrophage antimicrobial responses will be important to determine. Butyrate's ability to regulate the melatonergic pathways will important to determine not only in the gut, but in other body cells and systems, particularly immune cells. It will also be important to determine what cellular factors modulate butyrate's induction of melatonin.

Circadian melatonin is an important modulator of immune responses. As indicated above, both exogenous and endogenous melatonin can have dramatic impacts on immune cell responses. Recent work by Regina Markus and colleagues have highlighted this by their work showing an immune-pineal axis (50), whereby the presence of higher levels of pro-inflammatory cytokines, such as following surgery, act to suppress pineal melatonin synthesis. Such work suggests that the necessary initial inflammatory response allows the immune system to deal with systemic challenges, which, when resolved, allows pineal melatonin to contribute to circadian regulation, including the dampening of immune responses. However, the dampening of immune responses following initial inflammation involves local melatonin production by immune-inflammatory cells (39). As such, melatonin synthesis in different cells and tissues at different time-points may be intimately co-ordinated in the regulation of immune system homeostasis. Such increased levels of systemic inflammation, if prolonged, would also modulate gut processes and mucosal inflammasome activity, in turn driving down the levels of butyrate producing gut bacteria (51), whilst also increasing gut permeability (52). It requires investigation as to whether such prolonged, and perhaps low-level, immune-inflammatory activity, also drives down levels of gut melatonin. Overall, melatonin is intimately involved in the regulation of cellular and systemic immune responses, including as to

how the gut microbiome may modulate immunity.

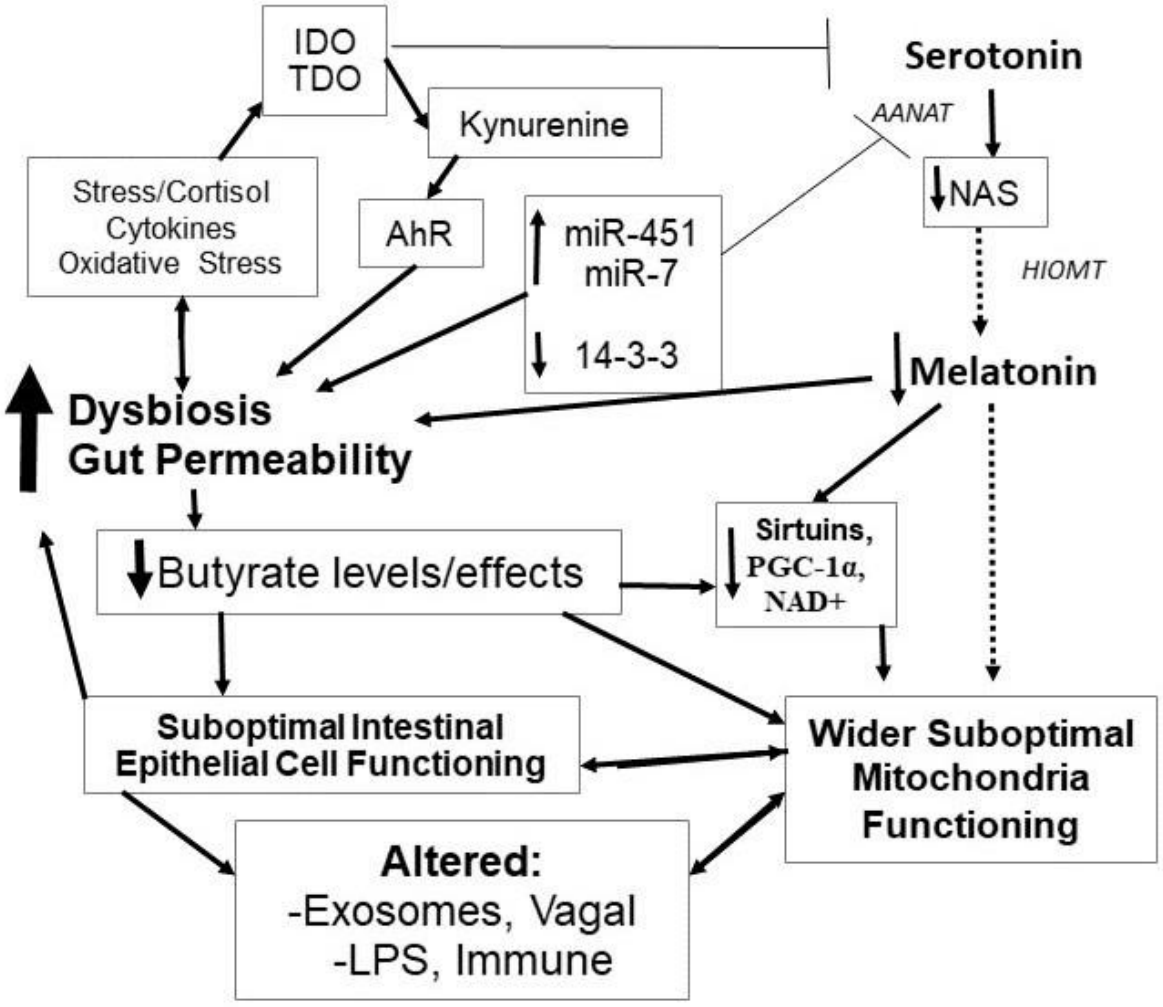

Fig. 1. The potential impacts of melatonin on gut microbiome and mitochondria.

Stress, diet and cytokines can increase gut dysbiosis and gut permeability as well as decreasing microbiome-derived butyrate. Decreased butyrate leads to suboptimal mitochondria functioning in intestinal epithelial cells, contributing to continued gut and immune dysregulation as well as alterations in the contents of released exosomes. The ensuing increase in pro-inflammatory cytokines, along with cortisol and oxidative stress, activate IDO and TDO, decreasing tryptophan availability for the serotonergic and melatonergic pathways. The increase in microRNAs, miR-7 and miR-451, and decrease in 14-3-3 lead to a further decrease in melatonin synthesis, further contributing to mitochondria dysfunction. Increased kynurenine activates the AhR, contributing to gut dysbiosis and alterations in mitochondria functioning. The dysregulation of gut mitochondria functioning may then spread, via decreased butyrate and melatonin, to other mitochondria in other tissues and organs. Ongoing gut dysbiosis acts to inhibit any compensatory feedback regulatory effects, leading to a new homeostatic state with ongoing deficits in sirtuins, PGC-1α and NAD+. Decreased butyrate production can influence other sites, including the CNS via alterations in exosomes, vagal nerve activity, circulating LPS and increased immune-inflammatory cytokines. All changes impact on mitochondria functioning. The AhR has constitutive effects, with its activation by induced kynurenine and exogenous ligands and toxins compromising such regulatory effects, including in the gut. AANAT: aralkylamine N-acetyltransferase; AhR; aryl hydrocarbon receptor; HIOMT: N-Acetylserotonin O-methyltransferase; LPS: lipopolysaccharide; NAD+: nicotinamide adenine dinucleotide; NAS: N-acetylserotonin; PGC: peroxisome proliferator-activated receptor-γ co-activator.

2.2. Melatonin, mitochondria and immunity.

There is a growing appreciation of the importance of mitochondria in the regulation and modulation of immune cells and their responsivity (53-55). As such, factors that act to alter mitochondria functioning can have significant impacts on innate and adaptive immune responses. Work over many decades shows melatonin to modulate mitochondrial functioning, as recently reviewed by Tan and Reiter (56), with recent data showing melatonin and its sulfation metabolites to be actively transported into mitochondria via the oligopeptide transporter (PEPT) 1/2 and organic anion transporter (OAT)-3, respectively (57). It is also of note that melatonin is produced within mitochondria (58).

The presence and synthesis of melatonin in mitochondria is of some importance, including for its anti-oxidant effects, given there is no histones-mediated protection of human mitochondrial DNA (mtDNA), which increases the susceptibility of human mtDNA to ROS-mediated damage (59). Melatonin has long been known to accumulate on mitochondria, with some data indicating that melatonin may improve the membrane fluidity of the mitochondria membrane (60), with possible consequences for the composition of the many important complexes that form on the mitochondria membrane, including apoptotic and anti-apoptotic proteins as well as the α7nAChR, kynurenine pathways products [3-hydroxykynurenine (3-OH-Kyn) and 3-hydroxyanthranillic acid (3-OH-ANA)], and AhR. The mitochondria regulatory effects of 3-OH-Kyn and 3-OH-ANA (61) indicate that the activation of the kynurenine pathways will not only decrease tryptophan availability for melatonin synthesis, but will also provide products with direct consequences for mitochondria functioning.

Melatonin may also have indirect effects on mitochondria functioning, including via the α7nAChR, which is present on mitochondria and mediates about 40% of the protection afforded by melatonin in cells under hypoxia challenge (62). As to how relevant the presence of the α7nAChR on mitochondria is to the powerful regulatory effects of the α7nAChR on immune cell functioning requires investigation (63, 64). Clearly the regulation and effects of melatonin in mitochondria are closely intertwined with a wide array of other important processes and their receptors, with significant consequences for the regulation of immune cells and systems.

Adenosine monophosphate-activated protein kinase (AMPK) is a highly-conserved serine/threonine kinase. AMPK is a crucial regulator of intracellular energy homeostasis, being activated under challenge when ATP declines. AMPK is an important modulator of immune responses (65). AMPK is also closely linked to an array of factors known to modulate mitochondrial and wider cellular functions, including mTOR and sirtuin-3 (66). Interestingly, AMPK is significantly inhibited by microRNA (miR)-451 (67), as are AANAT and HIOMT and therefore melatonin synthesis (68), suggesting that melatonin synthesis may be closely aligned to AMPK induction, at least in part via the regulation of miR-451. Melatonin can also increase AMPK, with consequences for mitochondria functioning (69, 70).

2.3 Melatonin, microbiome and immunity.

Interestingly, gut microbiome-derived butyrate increases AMPK levels (71), including in intestinal epithelial cells (72, 73). It requires investigation as to whether butyrate decreases miR-451 in different cell types, thereby contributing to an increase in AMPK and melatonin as well as more optimized mitochondria functioning (68). Increasing gut epithelial cell AMPK contributes to the maintenance of gut barrier integrity (74). This may be of some importance as there seem to be three way interactions of the gut microbiome, intestinal epithelial cells and mucosal immune cells, with the consequences of these interactions modulating the content of exosomes released by intestinal epithelial cells (75). Such exosomes can have direct impacts on immune cell functioning (75, 76), including via exosomal miR-451, which can increase Th17 cell differentiation (77), contributing to the heightened pro-inflammatory activity and autoimmunity, as well as decreasing AMPK,

melatonin and NAS synthesis. As such, miR-451 may link important mitochondria regulators, including melatonin and AMPK as well as shaping the nature of inflammatory immune responses, highlighting the importance of determining as to whether it is modulated by butyrate.

Clearly alterations in mitochondria functioning are relevant to epithelial cell-microbiome-mucosal immune interactions at the gut barrier. In the gut, as elsewhere, both melatonin and butyrate can increase levels of PGC-1α, which is a powerful regulator of cellular and mitochondria functioning, including via PGC-1α-induced nuclear respiratory factor 1 (NRF1) and mitochondrial transcription factor A (TFAM) (78). Consequently, PGC-1α is often referred to as the master mitochondrial regulator, (79). PGC-1α is positively modulated by the nicotinamide adenine dinucleotide (NAD+) dependent sirtuin-1, which deacetylates and activates sirtuin-3. Sirtuin-3 is a significant regulator of mitochondria-related genes (80). Both butyrate and melatonin can positively regulate these mitochondria optimizing factors. Suboptimal mitochondria functioning is associated with increased oxidative stress, which is directly or indirectly linked to decreases in sirtuins, ATP and PGC-1α, with such oxidative stress-linked changes ameliorated by melatonin (78, 81-82). Of note, a decrease in intestinal epithelial cell sirtuin-1 is associated with alterations in the gut microbiome, suggesting an associated decrease in sirtuin-3 and mitochondria functioning, with implications for a number of human diseases (83).

Such data indicates some of the cellular and mitochondria factors that modulate how intestinal epithelial cells interact with the microbiome and gut immune cells, and thereby contribute to changes in the gut that are common across a host of medical conditions. It requires investigation as to whether such alterations in gut functioning driven by variations in gut epithelial cell sirtuin-1 are mediated via alterations in local melatonin synthesis, with impacts on epithelial cell mitochondria functioning, including sirtuin-3 levels and activity (84). It is also of note that impaired autophagy in intestinal epithelial cells alters the murine gut microbiome and immune responses (85), with data in hepatic cells indicating significant interactions of sirtuin-1 and mitochondria functioning with levels of autophagy (86). As such, factors that act to regulate intestinal epithelial cell mitochondrial functioning may play a crucial role in determining the composition of the microbiome as well as the immune functioning of the host.

Such data highlights a growing appreciation of the importance of intestinal epithelial cells in the regulation of immune responses, suggesting a role considerably greater than one of a simple barrier function. It also highlights the importance of local gut melatonin and how this may interact with variations in the gut microbiome, in turn having consequences for the regulation of immune responses. As well as modulating key intracellular processes, melatonin is a significant modulator of the exosomal content in an array of different cell types (87), which then have consequences for any subsequent immune activation (88) and wider inflammatory processes (89).

3. CLINICAL AND CLASSIFICATION IMPLICATIONS

Some currently defined clinical conditions, such as depression, cirrhosis and arthritis, show high levels of comorbidity across a wide array of other diverse medical conditions (90-92). Such data point to overlapping pathophysiologies that are not represented in current classification systems (17). In this section, the role of melatonin in the gut and within mitochondria are proposed as overlooked factors that better clarify such overlaps, as exemplified by depression. This has both clinical and classification implications (17).

3.1 Depression and depression-associated conditions.

Depression is a common comorbidity, and risk factor, for a host of diverse medical presentations, including dementia (93), schizophrenia (94), cardiovascular disorders (95), type II diabetes (96), fibromyalgia (97), multiple sclerosis (98), Parkinson's disease (7), migraine (99), polycystic ovary syndrome (100), endometriosis (99), and inflammatory bowel disease (5). All of

these conditions have been associated with alterations in the gut microbiome, suboptimal mitochondria functioning and alterations in, or modulation by, melatonin (101). As such, the alterations in mitochondria functioning, and the gut microbiome/permeability-driven increase in immune inflammatory activity will contribute to the etiology of these diverse conditions, whilst also mediating their association with depression. It is likely that the putative decrease in mitochondria and gut melatonin may be an important aspect of how depression biologically links to such a wide array of medical conditions.

There is a growing body of data showing a role for alterations in the gut microbiome in the etiology and treatment of depression, reviewed in (102), whilst alterations in mitochondria functioning have long been associated with depression (103), as have alterations in melatonin regulation (17, 104). As indicated above, a compromised gut barrier increases immune-inflammation, leading to an increase in IDO and the activation of the neuro- and immuno-regulatory effects of the kynurenine pathway, in association with a decrease in the availability of tryptophan for the syntheis of serotonin, NAS and melatonin. Although these pathways may be variably regulated by distinct genetic and epigenetic factors across the various depression-associated conditions above, there is some evidence to indicate that the above pathways are relevant to the pathophysiologies of these disorders and how they associate with heightened levels of depression (17).

regulation of the gut may act to determine not only the severity of a given condition but also how that condition modulates the risk of other medical conditions. Suboptimal mitochondrial functioning Under stress challenge, high doses of melatonin administration recovers barrier integrity following the increase in gut permeability (105), suggesting that factors acting to regulate intestinal and pineal melatonin's is an important aspect of gut permeability (106-107), suggesting that some of the benefits of melatonin may be mediated via the processes that maintain more optimal mitochondria functioning within intestinal epithelial cells. Such processes require clarification under different conditions and challenges. Some data indicates that the beneficial effects of melatonin on gut barrier maintenance may be mediated via the activation of the α7nAChR (108), perhaps involving regulation of the vagal nerve and ACh production. It is also of note that the α7 nAChR can be located on the mitochondrial membrane, suggesting that the known positive circadian regulation of the α7nAChR by melatonin (109) may allow melatonin to have mitochondria impacts via the α7nAChR (17). It should also be noted that melatonin may also be metabolized by IDO under some inflammatory conditions (110), the relevance of which will be important to determine, including regarding mitochondria and α7nAChR regulation.

It is also important to note that mitochondria dysfunction is evident not only in intestinal epithelial cells, but also in many other cells and tissues across these various depression-associated conditions. This would suggest that gut dysbiosis and associated decreases in butyrate production has an impact on wider central and systemic homeostasis, in part via a decrease in the effects of butyrate and melatonin in mitochondria. It is such processes that underpin conceptualizations of gut-brain, gut-liver, gut-lung, gut-pancreas and gut-kidney axes. Alterations in the gut, via decreased butyrate and melatonin, change mitochondria functioning in a wide array of tissues and organs, leading to changes in the various gut axes, which underpin wider body homeostasis alterations.

Factors acting to regulate local melatonin production will also be relevant to such gut-linked axes, including via its autocrine effects on mitochondria functioning. In this context, it will be important to determine as to whether the effects of mitochondria-released melatonin are mediated via 'autocrine' effects at the mitochondria-located MT1 receptor in intestinal epithelial cells, as well as other cell types (111).

Such a conceptualization of the importance of melatonin at these two hubs has relevance to classification, especially for psychiatric, but also other medical conditions. All of the above mentioned medical conditions are generally perceived to be poorly managed, primarily as a consequence of a lack of knowledge as to their pathoetiology and the biological underpinnings of

their clinical course. This has arisen due to classification systems where pathophysiological processes are seen as organ specific, by-passing the complexity of inter-related systemic and central systems. Melatonin generally has significant utility in the management of most medical conditions, usually attributed to its antioxidant and anti-inflammatory effects coupled to its optimization of mitochondria functioning. However, it is likely that the beneficial effects of melatonin could be better utilized if placed within the context of gut-linked axes and systemic systems, with deficits in mitochondria functioning across a host of disorders and sites framed within the context of altered systemic homeostasis. Overall, gut dysbiosis highlights the importance of the gut and mitochondria as important hubs for understanding the wider changes and comorbidities of a host of poorly conceptualized and poorly managed medical conditions. The regulation of melatonin at both of these hubs is important to this.

4. CONCLUSIONS

It would seem clear that the gut microbiome and mitochondria are important hubs for systemic and cellular organization. Melatonin is an important factor in how changes at these hubs modulate the complex interactions of cellular and systemic processes. Research directed at the role of melatonin in mitochondria and in the gut should significantly improve the treatment and classification of a host of medical presentations that are currently poorly managed.

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AUTHORSHIP

The manuscript was conceived and written by G. Anderson

CONFLICT OF INTEREST

The author declares no conflicts of interest in relation to this work

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