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Review

The melatonergic pathway and its interactions in modulating respiratory system disorders

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ABSTRACT

Melatonin is a key intracellular neuroimmune-endocrine regulator and coordinator of multiple complex and interrelated biological processes. The main functions of melatonin include the regulation of neuroendocrine and antioxidant system activity, blood pressure, rhythms of the sleep-wake cycle, the retardation of ageing processes, as well as reseting and optimizing mitochondria and thereby the cells of the immune system. Melatonin and its agonists have therefore been mooted as a treatment option across a wide array of medical disorders. This article reviews the role of melatonin in the regulation of respiratory system functions under normal and pathological conditions. Melatonin can normalize the structural and functional organization of damaged lung tissues, by a number of mechanisms, including the regulation of signaling molecules, oxidant status, lipid raft function, optimized mitochondrial function and reseting of the immune response over the circadian rhythm. Consequently, melatonin has potential clinical utility for bronchial asthma, chronic obstructive pulmonary disease, lung cancer, lung vascular diseases, as well as pulmonary and viral infections. The integration of melatonin's effects with the alpha 7 nicotinic receptor and the aryl hydrocarbon receptor in the regulation of mitochondrial function are proposed as a wider framework for understanding the role of melatonin across a wide array of diverse pulmonary disorders.

1. Introduction

Pineal melatonin (N-acetyl-5-methoxy tryptamine; MT) is a key regulator of circadian rhythm homeostasis in humans, with important consequences for many systemic processes and systems, including via optimizing immune function. Although widely known as an antioxidant and anti-inflammatory, MT's effects on the circadian rhythm and metabolism allow it to have clinical utility across an extensive range of medical conditions since its discovery in 1958 [1].

MT is a product of the tryptophan pathway, with tryptophan-derived serotonin being converted to N-acetylserotonin (NAS) by aralkylamine N-acetyltransferase (AANAT). NAS is enzymatically converted to MT by acetylserotonin methyltransferase (ASMT). Tryptophan and serotonin availability may therefore limit melatonergic pathway induction, as do a number of factors. AANAT requires stabiliization by 14–3–3 protein to be transcriptionally active. AANAT also requires acetyl-coenzyme A (acetyl-CoA) as a cosubstrate for activation. As such, factors acting to regulate 14–3–3 and acetyl-CoA availability can modulate the melatonergic pathway. It is also of note that a number of factors can act to 'backward' convert MT to NAS, including cytochrome P450 (CYP)1b1, the metabotrobic glutamate receptor (mGluR5), the purinergic receptor (P2Y1r) and O-demethylation. Increasing the NAS/MT ratio can have

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dramatic impacts across a host of medical conditions, especially proliferative conditions, including across a number of pulmonary disorders. This arises from NAS being a brain-derived neurotrophic factor (BDNF) mimic via TrkB activation [2–4]. Clearly, the melatonergic pathway can be regulated by an array of crucial physiological processes, allowing it to be an integral aspect of most medical conditions [5]. Fig. 1 shows the melatonergic pathway and its regulatory factors.

Such wide impacts of the melatonergic pathway arise from studies showing MT to be produced by seemingly all mitochondria containing cells, including within mitochondria as well as in the cytoplasm. Clearly, MT has impacts both locally, as well as from its nighttime release by the pineal gland [6–9]. Importantly, MT is synthesized in all immune cells investigated to date, including macrophages, mast cells, natural killer (NK) cells, eosinophilic leukocytes, thrombocytes, and endotheliocytes. Pineal MT can increase local MT via the induction of the circadian gene, Bmal1, allowing pineal MT to modulate the melatonergic pathway in systemic cells. Pineal MT-induced Bmal1 in immune cells leads to the dampening of immune activation, via oxidative phosphorylation (OXPHOS) upregulation and the suppression of glycolytic metabolism, the latter crucial to immune cell activation [10,11]. Such immune dampening is achieved by MT release and its autocrine effects [12]. This wide MT distribution reflects its key role as an intracellular neuroimmune-endocrine regulator and coordinator of multiple complex and interrelated biological processes. This seems to arise from MT production by the very first proteo archaeal bacteria that eventually became a mitochondrion over the course of cell evolution [13]. As such, MT has been an intimate aspect of cellular life, including plant, animal and fungal from its first inception. Consequently, alterations in pineal and extra-pineal MT can have significant consequences across a host of diverse medical conditions [14], including ageing-associated conditions [15].

MT shows clinical efficacy in many conditions, including endometriosis [16], migraine [17] and an array of treatment-resistant cancers [18], as well as in obesity and type II diabetes [19]. MT is a powerful antioxidant as well as inducer of endogenous antioxidants and antioxidant enzymes, with significant effects on the oxidative status of mitochondria [20–22] and thereby on a host of medical conditions and common pathophysiological processes [23–25].

This review focuses on the role of MT in regulation of respiratory system function under normal and pathological conditions. It is proposed that the effects of MT may be intimately linked to its induction of the alpha 7 nicotinic acetylcholine receptor (α7nAChR) across a host of diverse pulmonary conditions. An integrated model is produced proposing that as well as its interactions with the α7nAChR, MT's reciprocal negative interactions with the aryl hydrocarbon receptor (AhR), have consequences for the regulation of both immune and pulmonary cells, as well as their interactions. Mitochondria are highlighted as an important site for the interactions of MT, α7nAChR and AhR, both directly on mitochondrial function, as well as indirectly via signalling pathways.

2. Melatonin and bronchial asthma

Bronchial asthma (BA) is a serious problem across all age groups. It is a chronic disease, with bronchospasm (narrowing of of bronchial lumen) caused by specific immune (hypersusceptibility and allergy) or non-specific mechanisms being key aspects. Blood MT levels are significantly lower in BA patients [26], which may arise from the raised levels of tumor necrosis factor (TNF)α, which can act on TNF receptor 1 on

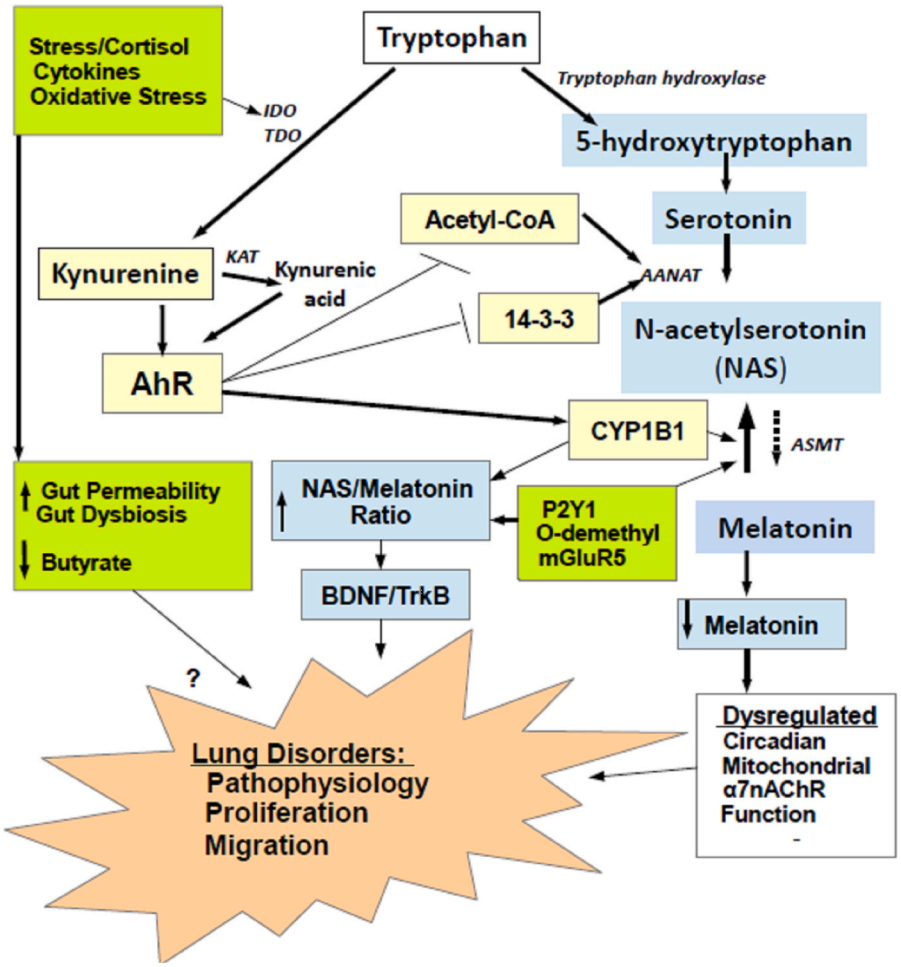

Fig. 1. Stress, pro-inflammatory cytokines and oxidative stress, by increasing IDO and TDO, drive tryptophan down the kynurenine pathway and away from the serotonergic and melatonergic pathway. The serotonergic/melatonergic pathway is highlighted in blue, the kynurenine/AhR pathway in pale yellow and factors acting on the interactions of these pathways in green, with consequences for the pathophysiology of a number of lung disorders. Kynurenine and kynurenic acid activation of the AhR, may further reduce melatonin by increasing its backward conversion to NAS. Activation of P2Y1 receptor or mGluR5 or O-demethylation can also drive the backward conversion of melatonin to NAS. As NAS is a BDNF mimic via activation of the BDNF receptor, TrkB, NAS will be detrimental in proliferative conditions, such as cancers, as well as in fibrosis. AhR activation may also suppress 14–3–3 and acetyl-CoA, which are necessary for AANAT stabilization and as a cosubstrate, respectively. A decrease in pineal and local melatonin production will significantly dysregulate circadian and mitochondrial function, as well as the levels of the α7nAChR, contributing to wider systemic, metabolic and immune dysregulation across an array of distinct lung disorders. Stress and cytokines also increase gut dysbiosis and permeability, leading to decreased butyrate and increased LPS, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

pinealocytes to suppress MT production, thereby being an important aspect of the immune-pineal axis [27], whereby the presence of ongoing immune-inflammatory activity and heightened pro-inflammatory cytokines, as well as circulating lipopolysaccharide (LPS) and amyloid-beta (Aβ), can suppress pineal MT production. Proinflammatory cytokines, including TNF-α and interleukin-1 (IL-1), are released in the early stage of allergic inflammation. In endothelial and epithelial cells, TNF-α induces an inflow of eosinophils to tissues due to the increased expression of adhesion molecules [28]. As such, the suppression of pineal MT may be an early aspect of immune inflammatory conditions, including BA.

As well as neutrophils, eosinophils are important effector cells in asthmatic airway inflammation, accumulating in the peripheral blood, bronchoalveolar lavage fluid, and airways of patients with asthma or allergen-sensitized animals. Eosinophil number is regulated by a wide range of chemotactic factors [29]. Eotaxin and RANTES (chemokine expressed and secreted by T-cells upon activation) are C-C-chemotaxins which can recruit eosinophils to airways in asthma [30]. Various types of cells, including epithelial lung cells, produce eotaxin and RANTES, which play an important role in the functioning of the respiratory system [31]. Oral MT acts to dampen induced lung inflammatory activity, including decreasing the levels and activity of eosinophils [32].

Circadian changes in airway inflammation and pulmonary function have been observed in asthmatic patients [26]. Prenatal data shows that pinealectomy decreases the total number of inflammatory cells in the lungs of asthmatic rats, which can be reversed by the application of exogenous MT [33]. In the lung epithelial cell line, A549, the addition of MT and TNF-α increase the mRNA and protein of eotaxin and RANTES [34]. Such early preclinical and in vitro data raised concerns as to the utility of MT in the regulation of asthma, including regarding its relevance to 'nocturnal' BA, versus BA with daytime symptoms [28,35,36].

However, a predominantly neutrophil-driven airway inflammation occurs in BA patients, which correlates with symptom severity. MT inhibits neutrophil infiltration and oxidant production that underpins the pathogenesis of BA nocturnal symptoms [35], with antioxidants more generally having some clinical utility in the management of BA [37]. Recent work has highlighted the utility of MT in the treatment of BA, with MT significantly attenuating airway hyperresponsivity and airway smooth muscle cell remodeling [38]. Preclinical data shows allergens to activate TLR2, leading not only to NLRP3 induction, but also to the inhibition of the melatonergic pathway, thereby decreasing local MT production. This is likely to have wider impacts on pulmonary cell function, given the role of local MT in the optimization of mitochondrial function and endogenous antioxidant regulation [39]. Such data is highly suggestive of a significant role for a decrease in local MT production in the pathoetiology and pathophysiology of BA.

As BDNF, via TrkB activation, is a significant contributor to BA pathophysiology by inducing airway hyperresponsiveness [40,41], it would seem that ASMT may be suppressed or MT backward converted to NAS, a TrkB ligand, in BA. Clearly, this requires further investigation, including the relevance of AhR-induced CYP1b1 in the production of NAS and thereby TrkB activation, coupled to a decrease in MT production. This is parsimonious with the decreased levels of MT in bronchoalveolar lavage fluid in BA [42]. The raised levels of plasma BDNF in asthma are irrespective of severity, or of subtypes, such as Type-2, allergic, and eosinophilic asthma, but with higher BDNF in aspirin sensitivity and aspirin-exacerbated respiratory disease, would also highlight an important role for TrkB activation, including from an increase in the NAS/MT ratio [43]. As some early preclinical studies indicate that MT may contribute to BA pathophysiology, it will be important to determine as to whether this arises from MT conversion to NAS, and therefore to TrkB activation, thereby mimicking the known effects of BDNF at TrkB in asthmatic conditions.

As prenatal nicotine as well as cigarette smoke can induce BA in the offspring [44], it will be important to determine the relative effects of MT-induced α7nAChR in the pathoetiology and pathophysiology of BA. As α7nAChR is an immune suppressor and is generally protective in pulmonary epithelial cells, it will be important to investigate as to whether it has any differential effects in the regulation of BA. For example, the α7nAChR is expressed in lipid rafts, where its activation will modulate the longevity and composition of rafts, thereby potentially impacting on a wide array of signalling processes in immune and pulmonary epithelial cells. Likewise, MT can significantly modulate lipid raft fluidity and may form a thin 'film' over lipid rafts [45], including binding to an array of different receptors and channels [46]. This is also likely to happen in the mitochondria bilipid membrane, where the α7nAChR is also expressed [47], suggesting that MT and the α7nAChR may have effects that are wider than their classical downstream pathway signalling. The relevance of this to the etiology and pathophysiology of BA, as well as other lung conditions, will be important to determine. It is also of note that local MT is present in the lung and is decreased during allergy, where there is an increase in NLRP3 inflammasome activation coupled to a decrease in MT in the bronchoalveolar lavage fluid [42]. These authors also showed that the decrease in local endogenous MT and the enzymes of the melatonergic pathway (AANAT and ASMT) underpin the heightened levels of NLRP3 and pro-inflammatory cytokines, highlighting importance of local melatonergic pathway regulation in BA. The influence of such local MT on α7nAChR levels will be important to determine. Clearly, the role of MT and its interactions with the α7nAChR will be an important avenue for future research in BA.

3. Melatonin and chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a progressive disease which is characterized by irreversible restriction of airflow through airways caused by an abnormal inflammatory reaction of the lung tissue to irritation with various pathogenic particles and gases. The increasing COPD morbidity rate is primarily associated with the continuing impact of risk factors, such as tobacco smoke, air pollutants, and hazardous environments, which may be mediating effects via accelerated ageing [48]. COPD is a growing global problem as well as a major drain of limited health care system resources. Investigations of COPD pathophysiology have highlighted a number of potential treatment targets, including raised plasma BDNF [49]. MT shows efficacy in COPD management [50], although most studies on the utility of MT in COPD have focussed on the beneficial effects of MT on sleep disruption, which is common in this condition [51].

In a randomized double-blind placebo-controlled study, the efficacy of MT was investigated on sleep and respiratory function in 25 COPD patients with various degrees of severity. The exclusion criteria were the following: disease aggravation during the last month, obstructive sleep apnea, psychiatric disorder, oxygen therapy at night, recent occupational change, administration of oral glucocorticosteroids, methylxanthines, or hypnotic sedating medications. Patients received oral MT or placebo in a single 3 mg dose, one hour before sleep, for 21 days. Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI), and daytime sleepiness was measured with the Epworth Sleepiness Scale. Pulmonary function and exercise performance level were assessed with spirometry and 6-minute walk testing. The MT treatment significantly improved the PSQI scors, especially sleep waiting time and sleep duration. No differences were found in daytime sleepiness, pulmonary function, and exercise performance levels. It was concluded that MT administration improved sleep quality in COPD patients [51,52].

Another study investigated the utility of the 8 mg MT_1/MT_2 receptor agonist, ramelteon, versus placebo, in the treatment of insomnia in COPD over the course of 5–10 nights. Polysomnographic monitoring, including oxygen saturation measurement and respiratory function, were assessed. No significant changes were observed between ramelteon and placebo, although total sleep time and sleep efficiency increased, while sleep waiting time decreased in the ramelteon group [53]. Such data would suggest that ramelteon is not as efficacious as MT for sleep regulation in COPD patients.

COPD patients who received MT 3 mg/day for three months showed

a 1.6-fold decrease in 8-isoprostane levels, as well as a decrease in dyspnea without significant changes in pulmonary function while doing physical exercises. Non-enzymatic oxidation of phospholipids in cell membranes produces 8-isoprostane which serves as a reliable marker of oxidative stress. Increased IL-8 levels were observed in patients who received placebo. Consequently, it was concluded that MT administration reduced the oxidative stress intensity and dyspnea in COPD patients [54]. Acrolein-induced IL-8 production in human lung fibroblasts is suppressed by MT via the PI3K / AKT signaling pathway, thereby impacting on the cell proliferation, growth, and survival [55], and suggesting that some of the utility of MT may be mediated via PI3K/Akt inhibition of IL-8 in COPD.

Preclinical studies of MT benefits in COPD show MT to increase pulmonary sirtuin-1, and therefore suppress classical ageing-associated pathways [56], as well as suppress levels of transforming growth factor (TGF)-β1 [57], and improve mitochondrial and endoplasmic reticulae function, at least in part via the suppression of the NLRP3 inflammasome [58]. MT also inhibits excessive mucus production (from MUC5AC-driven mucin activation) and associated neutrophil infiltration in preclinical models, which the authors show linked to alterations in the extracellular-related kinase (Erk) pathway [59]. Such effects of MT are linked to a decrease in oxidants and increase in antioxidant in pulmonary cells [57]. MT also reduces the pulmonary hypertension that is clinically relevant in COPD and which arises as a result of chronic hypoxia [60]. Overall, preclinical data indicates the importance of raised TGF-β1, BDNF, NLRP3, oxidants and mucus production, coupled to decreased sirtuin-1 and antioxidants, suboptimal mitochondria and dysfunctional endoplasmic reticulae in COPD pathophysiology. All of these factors may be significantly improved by MT treatment.

Activation of the α7nAChR suppresses key pro-inflammatory fluxes from peripheral blood mononuclear cells, viz nitric oxide and IL-6, which are increased in COPD and contribute to lung impairment [61]. Such data would indicate that MT's upregulation of the α7nAChR and MT's potentiation of vagal nerve acetylcholine will contribute to its anti-inflammatory effects in COPD. The relevance of MT-induction of the α7nAChR in the pathophysiology of COPD requires further investigation.

Extracellular ATP has an important role in pulmonary disorders, especially in COPD and cough generation [62]. As the P2Y1 receptor is highly expressed in pulmonary epithelial cells and other cells within the pulmonary microenvironment, this raises the possibility that the P2Y1 receptor-induced 'backward' conversion of MT to NAS may be relevant to COPD pathophysiology. As in BA, this would contribute to BDNF mimicking effects via TrkB activation, coupled to a decrease in local MT availability. ATP also acts on the PX2/3 receptors to increase bronchoconstriction and cough, with cigarette smokers and COPD patients exhibiting a hypersensitivity to extracellular ATP [63]. Whether such clinical consequences of increased levels of pulmonary ATP include effects on the NAS/MT ratio will be important to determine. As the effects of ATP are partly mediated via alterations in vagal nerve acetylcholine release, it is likely that there will be concurrent effects on vagal nerve regulation of α7nAChR activity, as well as on muscarinic ACh receptor, that contribute to bronchioconstriction [64]. Overall, the pathophysiological effects of extracellular ATP in COPD will have a number of consequences, including vagal nerve regulation and cholinergic activation of muscarinic receptors as well as on local MT availability and perhpas MT-induced α7nAChR.

4. Melatonin and type II diabetes lung pathophysiology

Type II diabetes is the most common metabolic disease worldwide and is a significant contributor to mortality, both directly and indirectly via its impacts across multiple organs and tissues as well as on the vascular and immune systems [65]. Diabetic patients can develop pulmonary dysfunction, which contributes to reduced exercise performance and decreased quality of life [66]. Diabetes is associated with, and complicates, many pulmonary disorders, including asthma and COPD [67,68].

A number of pulmonary pathophysiological changes arise as a consequence of poorly controlled diabetes, including a lower pulmonary microvascular reserve and heightened risk of chronic hypoxia [69]. Collagen accumulation in lung tissue may result in tissue stiffness, which occurs inside the pulmonary parenchyma and around the chest wall [70,71]. Such pathological changes can worsen the prognosis for lung infections which often occur in diabetic patients [72], being driven by alterations in the immune response, including to the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus that underpins the COVID-19 pandemic [73].

Type II diabetes is often associated with an increase in gut permeability and gut dysbiosis, thereby increasing levels of circulating LPS and lowering levels of the short-chain fatty acid, butyrate [74,75]. Butyrate is an epigenetic regulator via its capacity as a histone deacetylase inhibitor (HDACi), and optimizes mitochondrial function and immune system activity. This can complicate type II diabetes. For example, the changes in neutrophils in diabetic patients result in a heightened sensitivity to TLR4 activation by LPS [64], indicating that the gut permeability-derived LPS will interact with diabetes to modulate neutrophil effects in the lung. Such processes contribute to the heightened sensitivity to infection in diabetic patients, as well as wider alterations in immune responses.

It is also important to note that the increase in pro-inflammatory cytokines associated with type II diabetes increases indoleamine 2,3-dioxygenase (IDO), which drives tryptophan down the kynurenine pathway and away from serotonin and MT synthesis [76]. Such processes also seem important to the etiology and progression of type II diabetes [77]. As well as directly decreasing serotonin and MT, this has a number of immune-regulatory implications, including via raised levels of kynurenine and kynurenic acid, which activate the AhR. Increased AhR ligands are significantly associated with the development of type II diabetes [78], highlighting the relevance of such factors in driving some of the important changes underpinning type II diabetes.

Pineal MT is decreased in type II diabetes, leading to the conceptualization of a mutually inhibitory interaction between MT and insulin, which is supported in a number of studies, and contrasts to the changes seen in type I diabetes [79,80]. The raised levels of pro-inflammatory cytokines and higher circulating LPS arising from increased gut permeability may contribute to this via direct effects on pinealocytes and/or pineal microglia, thereby decreasing pineal MT release [27]. This is likely to have wider circadian implications, including an attenuation of the MT resetting of immune cells and their mitochondrial metabolism at night, as well as the attenuation of the antioxidant effects of nighttime pineal MT [81]. The roles of MT in the changes associated with obesity and type II diabetes are highlighted by genetic data showing that alleles of the MT2 receptor modulate weight gain as well as weight loss and response to dietary alterations [82].

As in other organs and tissues, MT reduces lung injury by lowering pulmonary oxidative stress markers and increasing the endogenous enzymatic antioxidant capacity, including glutathione peroxidase, catalase, and superoxide dismutase [83]. Preclinical data shows MT to significantly decrease malondialdehyde levels in the type II diabetic lung [59]. This is supported by other data showing MT to bring down lung inflammation and myeloperoxidase levels to that of the control group [65]. Some of MT effects have been proposed to be mediated via the inhibition of IL-33 [84]. However, it is the homeostatic regulation of oxidant status and mitochondrial function, including via the regulation of the local melatonergic pathway, that seems to form the basis of the wide-ranging beneficial effects of MT [85].

Preclinical data also indicates an important role for MT in the regulation of diabetes-associated lung disorders. Diabetic rats show hyperplasia in bronchial-associate lymphoid tissue (BALT), which was significantly reduced by MT administration. These authors also showed MT to lower the levels of the pro-apoptotic caspase 3, highlighting the

utility of MT in the treatment of diabetes-associated lung disorders [65,86].

Besides, high-fat diet alters the levels of α7nAChR, with differential effects on α7nAChR levels in pulmonary and immune cells, including following activation by LPS [87]. Like MT, α7nAChR is an important regulator of obesity pathophysiological across different organs [88,89], indicating that it will modulate more systemic inflammatory processes that contribute to alterations in immune responses and lung regulation [90]. Heightened immune cell activity invariably leads to an increase in circulating daytime MT, arising from the release of MT from de-activating immune cells. Whether such local MT release, like circadian MT can induce the α7nAChR will be important to determine. Invariably an increase in pro-inflammatory cytokines, via IDO induction in an array of different cells, will drive tryptophan to the production of kynurenine pathway products and away from serotonin and MT synthesis. As to whether this then influences the levels of local MT production from immune and pulmonary cells requires investigation [42].

Overall, most data would indicate that MT plays an important role in the regulation of type II diabetes, with effects that are mediated via its homeostatic regulation of mitochondrial function, at least in part via the upregulation of the antioxidant/oxidant ratio. The relevance of the MT induction of the α7nAChR in the diabetic lung requires further investigation, given the beneficial effects of the α7nAChR in both pulmonary and immune cells.

5. Melatonin and pulmonary fibrosis

Pulmonary fibrosis is a progressive disease characterized by epithelial cell damage, fibroblast proliferation, excessive extracellular matrix accumulation, and lung tissue scarring. An array of factors can contribute to diffuse alveolar damage, which increases alveolar-capillary membrane permeability, thereby contributing to pneumonia and alveolar epithelial cell apoptosis [91]. Moreover, excessive apoptosis of alveolar epithelial cells of type II (AECIIs) destroys the epithelial barrier, leading to ageing-associated changes and inflammation of the alveolar tissue [92]. As in many ageing-associated conditions, mitochondrial dysfunction and heightened ROS hyperproduction are important aspects of the pathophysiological changes occuring in pulmonary fibrosis.

Alterations in mitochondrial function are crucial to cellular plasticity across a variety of challenges, including via variations in the levels of oxidants and antioxidants produced. However, unrestrained ROS production may ultimately lead to cytochrome C release and cellular apoptosis [93]. Many factors can influence mitochondrial function, including the pineal MT/Bmal1-driven increase in acetyl-CoA and associated upregulation of OXPHOS, TCA cycle and the mitochondrial melatonergic pathway, as noted above and detailed below. It should also be noted that the growing interest in the role of the gut microbiome, especially production of the HDACi, butyrate, is at least partly driven by the mitochondrial optimizing effects of butyrate in body cells [81]. Some of the effects of butyrate are mediated via its upregulation of the melatonergic pathway, as shown in intestinal epithelial cells [94]. There is a growing realization that the gut-lung axis is a relevant aspect of pulmonary fibrosis pathophysiology [95,96], with the melatonergic pathway being relevant both in the gut as well as in how alterations in gut influence mitochondrial function within other organs and tissues, including the changes occuring in pulmonary fibrosis.

Although, the above would indicate a more 'holistic' perspective in the understanding of pulmonary fibrosis and the relevance of the melatonergic pathway, it should be noted that most MT data to date has been restricted to looking at changes directly in pulmonary cells. In the bleomycin model of pulmonary fibrosis, MT can significantly decrease mortality and restore alveolar epithelial function, with effects driven partly by reduced ROS production and the prevention of AECIIs senescence, via raising mitochondria number. MT also improves pulmonary function, by upregulating poly-[ADP-ribose] polymerase (PARP)1 activity, and therefore the DNA repair pathway [97] and by attenuating pulmonary hypertension, as shown in rats exposed to chronic hypoxia [98]. The protection afforded by MT is at least partly mediated via the MT receptors [99].

Further data indicates that MT affords protection in pulmonary fibrosis via the upregulation of apelin-13, leading to the activation of its G protein-coupled receptor, APJ [100]. Apelin-13/APJ are widely expressed in various tissues, where they act to regulate an array of physiological processes, including angiogenesis, homeostasis, and energy metabolism regulation [101]. In pulmonary disorders, apelin reduces lung tissue inflammation, increases cyclic guanosine monophosphate (cGMP) levels, promotes alveolarization, stimulates pulmonary angiogenesis [102], promotes mitochondrial biogenesis [103], increases mitochondrial oxidative capacity [104], and inhibits senescence [99], thereby affording protection against a number of lung diseases [105]. Clearly, the ability of MT to upregulate apelin-13 significantly contributes to its beneficial effects in pulmonary fibrosis.

As in asthma and other lung conditions, pulmonary fibrosis pathophysiology is associated with increased BDNF and other neurotrophins that can activate TrkB [106]. As noted above, this would suggest that factors biasing an increase in the NAS/MT ratio will enhance the BDNF mimicking effects of NAS at TrkB. It should also be noted that NAS can increase BDNF transcription, as shown in the brain [107], suggesting that the release of pulmonary NAS may contribute directly and indirectly to TrkB activation. Importantly, TrkB activation contributes to the epithelial-mesenchymal transition, promoting the acquisition of (myo) fibroblast cell phenotype in idiopathic pulmonary fibrosis [108].

Exogenous activators of the AhR, including air pollutants and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in cigarette smoke, can constribute to pulmonary fibrosis [109,110], as well as upregulating the NAS/MT ratio. However, it should be noted that endogenous AhR activators, such as 6-formylindolo (3,2-b) carbazole (FICZ), may afford protection via the upregulation of regulatory T-cells and associated suppression of inflammation by CD4+IFNγ+ and γδ+IL-17A+T-cells [111]. As such, variations in exogenous and endogenous AhR ligands and cells activated may produce differential effects, which is parsimonious with the typically complex effects of AhR activation. AhR activation, via CYP1b1, can backward convert MT to NAS, and thereby contribute to TrkB activation. Clearly, such differential effects of the AhR in pulmonary fibrosis require further investigation, especially as this could have treatment implications by AhR antagonists, such as the readily available nutraceutical supplements, epigallocatechin gallate (EGCG) and resveratrol. Resveratrol has shown some efficacy in the treatment of pulmonary fibrosis. However, its mode of efficacy is complicated by its induction of sirtuin-1, and inhibition of the NLRP3 inflammasome as well as its inhibition of the AhR [112].

As in other organs, MT induction of the α7nAChR will have significant impacts on lung function and response to challenge. The α7nAChR is an important regulator of patterned gene expression in pulmonary epithelial cells, both basally and under challenge [113]. This would indicate that the suppression of MT's induction of the α7nAChR is a significant modulator of basal and challenged pulmonary epithelial cell patterned gene expression. Coupled to the α7nAChR regulation of the immune response, it is clear that suppression of MT's induction of α7nAChR will impact on key processes that underpin pulmonary disorders, including pulmonary fibrosis. In a preclinical model, these authors show that the α7nAChR attenuates pulmonary hypertension, at least in part by suppressing the induction of the NLRP3 inflammasome [114].

6. Melatonin and lung tumors

Lung cancers are the most common malignant tumor and the most common cause of death from cancers. According to data of the International Agency for Research on Cancer (IARC), around one million new cases of lung cancer are registered annually throughout the world, with

60% of lung cancer patients dying from this disease [115]. Histologically, there are two types of lung cancer: small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Approximately 85% of lung cancer cases are classified as NSCLC, and most of these patients are in the late stages of the disease at diagnosis [116].

Numerous physiological, biological, and immunological factors may influence the occurrence and development of tumors. The nervous, endocrine, and immune systems act to provide protection of the organism from such pathological process. MT acts to regulate endocrine glands, the immune system function, and nervous system, as well as exhibit antioxidant and oncostatic properties [117–119]. The lower nocturnal MT level and decreased MT/cortisol ratio in lung cancer patients [120], will therefore have significant impacts on diverse body systems acting to regulate lung cancer etiology and pathophysiology. MT1 and MT2 receptors decrease as NSCLC stage/severity increase [121], indicating a significant role for variations in MT effects in the regulation of NSCLC progression [122]. Consequently, there is an exponential interest in the utility of MT in the management of lung cancers as well as for an array of other cancers [123].

Classically, cancer cells are associated with an increase in pro-survival and proliferative signalling pathways and factors, including an increase in the epidermal growth factor (EGF) receptor, Erk, and PI3K/Akt pathways in association with an increase in Bcl2, nuclear factor erythroid 2-related factor 2 (Nrf2) and human telomerase reverse transcriptase (hTERT), coupled to a decrease in pro-apoptotic Bax and p53. All of these processes show alteration in NSCLC and SCLC [124–126]. Cancer cells also show significant changes in metabolism, including an increase in glycolytic metabolism, usually coupled to maintained OXPHOS [127]. The relative balance of aerobic glycolysis and OXPHOS in lung and other tumour cells seems important not only to processes occuring within tumours, but also in how tumours act to regulate the immune cells of the tumour microenvironment [128]. The interactions of OXPHOS and glycolysis in tumours cells are proposed to regulate their efflux of kynurenine, which activates the AhR in NK cells and CD8 + T-cells, leading to a state of 'exhaustion' and immune suppression [73,129]. Such interactions of fundamental processes in tumour cells and immune cells adds a further layer of complexity in understanding MT utility in clinical studies.

Although, MT usually enhances survival and proliferation of cells, as in CNS neurogenesis [130], it has opposing effects in cancer cells, leading to a decrease in survival, proliferation and metastasis [116]. MT usually increases sirtuins, Bcl2 and decreases pro-apoptotic Bax, with the direction of effects in these factors being reversed in cancer cells. MT effects have been proposed to be mediated by a variety of processes, including the inhibition of HDAC9 [131] and the induction of cell cycle arrest in the S-phase [132] in NSCLC, or by its differential effects on metabolism, including increasing OXPHOS and inhibiting the upregulation of glycolysis [133]. This would indicate that MT is having fundamental effects on key aspects of tumour cell metabolism, with its differential effects on pro/anti-apoptotic/survival pathways being downstream of its impact on more fundamental processes [11,134].

Alterations in MT are evident in lung cancers as well as in the MT/cortisol ratio [120], with MT treatment decreasing metastasis [135,136], increasing tumour apoptosis and decreasing proliferation [137]. MT increases the expression of the intercellular tight junction, occludin, in human lung carcinoma cells (line A549) [137], thereby decreasing the likelihood of metastasis. EGFR mutation or its overexpression is present in 43–89% of NSCLC patients [138]. Various inhibitors of EGFR tyrosine kinase are used as standard treatment for advanced NSCLC patients [139]. MT was found to inhibit the growth of circadian-dependent tumor cells by suppressing the EGFR receptor regulation [140]. MT also suppresses the mitochondria-located Bcl-2 expression, whilst enhancing pro-apoptotic Bax in lung adenocarcinoma cells [141,142], as well as enhancing cyto c release from a NSCLC line [142]. MT also inhibits the pro-migration, growth, and angiogenesis effects of cyclooxygenase-2 (COX-2) in lung cancer cells [143], partly via the suppression of the Akt/ERK pathway [142]. These authors also showed MT to inhibit hTERT and its induced regulator, enhancer-binding protein 2β (AP-2β), thereby limiting telomerase maintenance [142]. MT can also increase the survival time of NSCLC patients, as well as decrease the side-effects of radio- and chemo-therapy [144].

Perhaps more importantly, MT can significantly improve the immune response to cancers, with its antioxidant and anti-inflammatory effects limiting the damage that can initiate tumour development, as well as enhancing cytotoxic efficacy of NK cells and CD8 + T-cells [145]. However, it is the presence of the melatonergic pathway in these immune cells, as well as in NSCLC and SCLC, that may be more important to understanding the role of MT in lung cancers.

As noted above for asthma and other lung conditions, activation of the BDNF receptor, TrkB, can be highly damaging in conditions involving a proliferative pathophysiology, such as lung cancers. Cancer cells induce immune suppression via pro-inflammatory cytokine-induced IDO, leading to kynurenine that then activates the AhR in NK cells and CD8+T-cells, as well as intracrinally in cancer cells, thereby inducing immune suppression [73,129]. AhR activation, via CYP1b1 and the 'backward' conversion of MT to NAS, allows cancer cells to drive trophic effects via TrkB activation. As such, the cells capable of eliminating cancers cells may be persuaded to provide trophic support. AhR activation also induces COX-2/prostaglandin (PG)E2/EP4 receptor activation, which also contributes to 'exhaustion'. By inhibiting acetyl-CoA production, the AhR prevents the acetylation, and inhibition of COX-2, whilst preventing the acetylation of Raptor on the mTORC1 complex, leading to its mislocalization and thereby preventing the mTORC1-driven upregulation of glycolysis, which is necessary for NK cell and CD8+T-cell cytotoxic activation [73]. Potentially, this allows both cytolytic cells and cancer cells to provide trophic support for the survival and proliferation of cancer cells, via NAS activation of TrkB, coupled to the suppression of cytotoxic immune cells. As such, the local regulation of the melatonergic pathway, including by pineal MT and the AhR will have consequences for the metabolic interactions of OXPHOS and glycolysis, with crucial consequences for tumour survival [3].

Clearly MT has utility in the management of NSCLC and SCLC. However, it should be noted that activation of the α7nAChR can have trophic effects in lung cancers, with α7nAChR antagonists being proposed as a treatment in NSCLC [146]. It requires clarification whether the beneficial effects of MT in lung cancers are modulated by its induction of the α7nAChR, including as to whether the addition of MT changes the nature of the α7nAChR influence on lung tumour initiation, survival and proliferation. In this context, the limited data on the α7nAChR influence on lung cancer progression is linked to the presence of nicotine in cigarette smoke. However, the major lung cancer modulating factor in cigarette smoke is TCDD via its activation of the AhR. The interactions of the AhR with MT and the α7nAChR are highlighted below in the context of respiratory infections. Such wider interactions are likely to have relevance to the lung disorders highlighted in this article, and may be seen as an integrative model to generate future research.

7. Melatonin and respiratory infections

Recent work on bacterial and viral respiratory infections highlight the complex effects that MT has on lung physiology and pathophysiology. As well as effects of pineal or exogenous MT on pulmonary epithelial cells, MT is also produced in many, if not all, lung cells, as well as within immune cells. MT also upregulates the α7nAChR, with the α7nAChR being an important regulator of pulmonary epithelial cell and immune cell responses to respiratory infection [113]. Many of the priming effects of air pollutants across a host of lung conditions are mediated via AhR activation [147]. The AhR is also intimately linked to the pathophysiology of most lung conditions, including within cancer cells and in driving the immune suppression within the tumour microenvironment, via AhR-driven exhaustion in natural killer (NK) cells and

CD8+T-cells [73]. As MT and the AhR have negative reciprocal interactions, the regulation of MT in the lung and in surrounding immune cells can only be understood in relation to AhR levels and ligands [148]. Data on viral and bacterial lung infections highlight the importance of alterations in immune cell function in driving lung pathophysiology.

8. Melatonin, AhR, α7nAChR and kynurenine pathway interactions

As well as reciprocal negative interactions of the AhR and MT, AhR activation leads to the induction of CYP1b1, and therefore to the 'backward' conversion of MT to NAS. Consequently, the AhR can determine MT levels as well as the NAS/MT ratio. As NAS is a BDNF mimic by activating TrkB [2], the AhR driven increase in NAS can result in trophic support for proliferative conditions, including an array of different cancers [149]. The effects of exogenous or pineal MT may therefore be dependent on the levels of AhR activation. Most lung conditions are associated with an increase in pro-inflammatory cytokines, which induce IDO, thereby taking tryptophan away from serotonin, NAS and MT synthesis and driving it to the production of kynurenine, and other kynurenine pathway products, including kynurenic acid and quinolinic acid. As both kynurenine and kynurenic acid can activate the AhR, and kynurenic acid may act to inhibit the α7nAChR [150], it is clear that raised pro-inflammatory cytokines will change the nature of MT, α7nAChR and AhR interactions. AhR ligands include cigarette smoke component TCDD, air pollutants and numerous endogenous ligands, such as FICZ. ROS and RNS, as well as psychological stressors, can increase IDO or tryptophan 2,3-dioxygenase (TDO) to increase kynurenine and kynurenic acid, and thereby to activate the AhR. Clearly, an array of diverse biochemical and psychological stressors can then act to modulate the interactions of MT, NAS, α7nAChR and the AhR, considerably adding to the complexity of changes arising across lung infections and the lung disorders highlighted in this article.

The AhR regulates all of the above lung conditions, including brochial asthma [151], pulmonary fibrosis, COPD, diabetic/aged lung [152], NSCLC [153] and SCLC [154]. It should be noted that the AhR can have complex effects, due to differential responses in different cells and variations in effects that are ligand and circadian regulated [155]. It is also important to note that the AhR can be present on the mitochondrial membrane [47], as well as regulating mitochondrial function, including via increased CYP1b1 and the backward conversion of MT to NAS, as well as the suppression of 14–3–3 in some cells, leading to the loss of 14–3–3 mediated stabilization of AANAT, and thereby inhibiting the initiation of the melatonergic pathway [156]. As mitochondrial and cytoplasmic MT are important determinants of optimized mitochondrial function, including via the upregulation of sirtuins and superoxide dismutase (SOD)2, the AhR suppression of MT will have wider consequences for cellular function. Importantly, the activation and levels of AhR has been proposed to be a major driver of cellular and whole-body ageing [157], indicating the importance of its interactions with MT and the α7nAChR over the course of ageing and damaged-induced alterations in lung function. This is supported by data showing that a high-fat diet potentiates AhR signalling, including via increased macrophage pro-inflammatory cytokine production [158] and thereby contributing to inflammatory processes across body organs. As such, AhR signalling is important to ageing-associated changes, which is clearly seen in an Alzheimer's disease model, where air pollutant activation of the AhR leads to an increase in disease associated factors, including potentiated oxidative stress, AhR, CYP1b1, beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), angiotensin converting enzyme (ACE)1, and amyloid-beta (Aβ) [159]. As Aβ also inhibits pineal MT release [160], the AhR-induction of Aβ will contribute to how the AhR acts to suppress MT.

The interactions of MT, AhR, α7nAChR and the kynurenine pathway in the lung are most clearly seen in data on pulmonary viral and bacterial infections.

9. Melatonin, AhR, α7nAChR in viral and bacterial infections

There has been an increasing interest in the role of MT in the modulation of viral infections following the COVID-19 pandemic arising from the SARS-CoV-2 virus [73,161,162]. Data on repurposed medications indicate that MT is the only currently widely used medication/nutraceutical that decreases the risk of COVID-19, with a decreased risk ranging from 28% to 64% [163]. It is also proposed that MT would prevent the 'cytokine storm' that arises from most pulmonary viral infections, including influenza and SARS-CoV-2 [73,161]. This is proposed to be mediated via the anti-inflammatory effects of MT on the neutrophils, macrophages and mast cells that drive the increase in pro-inflammatory cytokines underpinning the 'cytokine storm' [73; 161]. MT also affords protection against viral and bacterial infection via effects in pulmonary epithelial cells [164], with some of these effects mediated via MT's ability to upregulate the α7nAChR. α7nAChR activation affords protection to pulmonary epithelial cells during viral and bacterial infection [113].

Although MT may increase the efficacy and cytotoxicity of the body's endogenous anti-viral/cancer cells, especially NK cells and CD8 + T-cells, it is widely appreciated that AhR antagonism is more important to optimizing NK cell and CD8+ T-cell cytotoxicity and anti-viral/cancer efficacy [129]. SARS-CoV-2, both directly [165], and via the induction of kynurenine [161], activates the AhR, thereby paralleling the processes underpinning 'immune suppression' in the cancer microenvironment [73,129]. AhR activation can also increase the 'cytokine storm' by potentiating cytokine release from macrophages, neutrophils and mast cells [73]. Importantly, it would seem that one of the major consequences of AhR activation in immune cells is its suppression of MT production, both via 14–3–3 inhibition and the CYP1b1-driven backward conversion of MT to NAS [73]. Many of the AhR effects in cytolytic cells are via COX-2 activation, leading to prostaglandin (PG)E2 and activation of the PGE2 receptor, EP4. The AhR-COX-2/PGE2/EP4 pathway is classically associated with an 'exhausted' state in NK cells and CD8+T-cells [73].

In NK cells and CD8+T-cells, pineal MT acts via the circadian gene, Bmal1, to reset these cells, thereby leading to an enhanced cytotoxicity of these cells in the early daytime period [73]. MT acts via Bmal1, to inhibit pyruvate dehydrogenase kinase (PDK) and thereby disinhibit the pyruvate dehydrogenase complex (PDC). Such PDC disinhibition leads to an increase in the conversion of pyruvate to acetyl-CoA, thereby increasing ATP production from OXPHOS and the TCA cycle. Importantly, acetyl-CoA is also a necessary co-substrate for AANAT and therefore the initiation of the cytoplasmic and mitochondrial melatonergic pathway. Acetyl-CoA, like aspirin, acetylates COX-2, thereby inhibiting COX-2 mediated 'exhaustion' in these cytolytic cells. As all immune cells need both an optimized metabolism from mitochondrial OXPHOS coupled to an upregulation of glycolytic metabolism in order to become activated, it is crucial to note that acetyl-CoA, via Raptor acetylation, appropriately locates the mTORC1 complex, thereby allowing these cytolytic cells to increase glycolytic metabolism. Clearly the interactions of the AhR and the melatonergic pathway are crucial to optimization of the anti-viral/cancer cell response.

This contrasts to the effects of the AhR and MT in neutrophils, macrophages and mast cells. AhR activation can increase immune activation in these cells, whilst the effects of endogenous MT in the cytoplasm and mitochondria, upon its release, is to act in an autocrine manner to switch these cells from an M1-like to M2-like phenotype. This would seem partly mediated by the concurrent upregulation of specialized pro-resolving mediators (SPMs), reviewed in [73].

As such, the preventative and treatment utility of MT in viral infections involves its interactions with the AhR and α7nAChR, in the regulation of mitochondrial function and metabolism, with differential effects in the initially responding immune cells, versus the anti-viral/cancer cell responses.

Pulmonary bacterial infection parallels some of the changes seen in

the initial pro-inflammatory phase of viral infections. The effects of LPS in pulmonary epithelial cells [113] and immune cells [166] are inhibited by MT and the α7nAChR, with the AhR effects on the melatonergic pathway and α7nAChR modulating the consequences of bacterial infection in these cells.

Overall, it is clear that the effects of MT across a host of diverse pulmonary conditions involve interactions with a diverse array of other factors and processes, with the AhR, α7nAChR, circadian genes and cellular metabolism being important determinants of both disease processes and MT effects. Data derived from viral and bacterial infections indicate the importance of the AhR, and α7nAChR interactions with MT and the melatonergic pathway. The AhR and α7nAChR effects on COPD, NSCLC, SCLC, bronchial asthma, pulmonary fibrosis, and the diabetic lung indicate the importance of these factors across diverse conditions. Future research on the clinical utility and pathophysiological regulation of MT in these diverse conditions will require investigation on the role of epigenetic and genetic changes in the AhR and α7nAChR in the modulation of mitochondrial metabolism in pulmonary and immune cells. This is likely to have clinical relevance to ageing and immune senescence, and therefore to a wider array of medical conditions. It is also of note that the AhR, like MT and its induction of the α7nAChR, is differentially regulated over the circadian rhythm, indicating a significant role for wider circadian factors in the regulation of immune responses to respiratory conditions [167]. The utilization of nebrolyzed MT, with and without AhR and α7nAChR regulators, should better define the clinical utility of MT and its interactions with these receptors across diverse pulmonary conditions.

10. Future research

10.1. Neuroepithelial bodies

Although MT seems to be produced by all mitochondria-containing cells, thereby allowing MT to have regulatory effects on mitochondrial function, oxidant status and the dampening of immune inflammatory activity via autocrine effects [12], it is clear that MT is more highly produced and released by specific cells. The release of MT by pinealocytes underpins MT's influence on the circadian rhythms, whilst the even higher release of MT in the gut by enterochromaffin cells seems crucial to bacterial swarming following food intake. It will be important to determine whether the neuroepithelial bodies (NEBs) of the bronchial epithelium [168], are relevant sources of MT in the lung, either directly and/or via their known release of serotonin [169].

Serotonin is present in the lungs of all studied animals [170,171]. Although the role of pulmonary NEB serotonin in the lung is unknown, it is released after acute hypoxia [172–174], and is proposed to regulate bronchoconstriction, vasomotor tonus [175], and hypoxia signalling [174,176]. Whether serotonin release by NEBs contributes to heightened melatonergic pathway activity will be important to determine. NEBs may be a significant hub in the lung, given their contact with afferent nerve fibers in the autonomic nervous system [177] and their regulation of responses to alterations in air quality [178,179].

NEBs also regulate stem cell niches (Clara cells) in the bronchioloalveolar junction of the lungs [180]. These stem cells are crucial to the repair of chronic lung diseases [181]. The role of the melatonergic pathway and the perhaps differential regulation of the NAS/MT ratio in such processes will be important to investigate, especially as to whether NEBs have their melatonergic pathway regulated to increase NAS activation of TrkB, thereby mimicking the pathophysiological effects of BDNF in asthma [41] or whether NEBs release of serotonin is converted primarily to NAS in other pulmonary cells.

10.2. Mitochondria and ageing

As decrements in mitochondrial function occur over the course of ageing, in association with raised mitochondria-derived ROS and AhR levels, coupled to suppressed endogenous antioxidant enzymes, and pineal MT, it is clear that ageing-associated processes will impact on pulmonary and immune responses across a range of pulmonary disorders [182–184]. Although MT has shown utility in preventing such ageing-associated changes in mitochondrial function [185], the interactions of the melatonergic pathway, AhR and α7nAChR, which are all expressed on or within mitochondria [47], will be important to determine. The α7nAChR also regulates mitochondrial mass and metabolism in immune-type cells [186], highlighting the importance of its role in the regulation of immune cell metabolism and inflammatory processes.

10.3. Melatonergic pathway

Some important issues regarding melatonergic signaling deserve to be addressed by scientific research in consideration of possible clinical corollary:

- Is the NAS/MT ratio relevant to proliferative lung conditions, such as BA, COPD and lung cancers, via heightened TrkB activation?
- Do MT and the α7nAChR modulate the composition of complexes and activity within pulmonary epithelial cell lipid rafts, on both the plasma membrane and mitochondrial membrane?
- Does locally released MT form a film over lipid rafts that modulates their function [45], at least in part via its promiscuous receptor binding [46]?
- How much local MT and NAS are released in the lung and would this be sufficient to regulate Bmal1 and the α7nAChR?
- Do the increased levels of, and sensitivity to, ATP in COPD contribute to the 'backward' conversion of MT to NAS via P2Y1r activation?

11. Conclusion

MT is a biogenic amine (indoleamine) possessing powerful multifunctional biological and pharmaceutical effects, including antioxidant, antitumor, anti-inflammatory, anti-aging, anti-diabetic, antiviral, and neuroprotective activities. MT promotes normalization of the structural and functional organization of damaged tissues by paracrine and neuroendocrine regulation of local homeostasis through cascading metabolism of various signaling molecules. MT also mediates its effects on, and its production within, mitochondria. Investigations on the interactions of MT with the AhR and α7nAChR in pulmonary and immune cells should help to better define relevant pathophysiological processes and treatment targets, including for bronchial asthma, COPD, NSCLC, SCLC, diabetic lung conditions and pulmonary fibrosis, as well as pulmonary viral and bacterial infections. The safety profile of MT, as well as that of the nutraceutical inhibitors of the AhR, such as resveratrol and epigallocatechin gallate, and α7nAChR activators, such as nicotine and vagal nerve stimulation, would indicate the ready utility of research in this area.

Ethics approval and consent to participate

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Data availability

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