Melatonin: A Natural Homeostatic Regulator – Interactions with Immune Inflammation and Tryptophan Catabolite Pathways in the Modulation of Migraine and Endometriosis

George Anderson¹,* and Michael Maes²

¹CRC Scotland & London, Eccleston Square, London, UK and ²Deakin University, Department of Psychiatry, Geelong, Australia

Abstract: An increase in oxidative and nitrosative stress, pro-inflammatory cytokines, depression and stress, are common in a number of medical conditions, with these factors mediating many of their effects via the induction of indoleamine 2,3-dioxygenase, leading to tryptophan catabolite production, in turn decreasing levels of serotonin availability as a precursor for the melatoninergic pathways.

Here we look at the role of these biological processes and their interactions in the etiology, course and management of migraine and endometriosis. Both conditions are considerably improved by melatonin, although the role of local melatonin production in non-pineal cells in these disorders still requires clarification. In both migraine and endometriosis, increased levels of brain-derived neurotrophic factor (BDNF) may be detrimental, suggesting that the immediate precursor of melatonin, N-acetylserotonin, which is a BDNF mimic, may also have regulatory, if not negative effects in these disorders.

As such, the regulation of the NAS/melatonin ratio in an array of cell types and tissues may be of some importance to the genesis, course and treatment of a number of poorly managed medical disorders, including migraine and endometriosis.

Keywords: Migraine, Endometriosis, Melatonin, N-Acetylserotonin, Tryptophan, Kynurenine, Tryptophan catabolites, Oxidative stress, Immune-inflammation.

1. INTRODUCTION

1.1. Melatoninergic Pathways

N-acetyl-5-methoxytryptamine, commonly referred to as melatonin, is a methoxyindole that is evident in most plants and animals and possibly all mitochondria containing cells, indicating an evolutionary conserved utility [1]. In mammals, melatonin has mainly been investigated in the context of its night-time release by the pineal gland, which is driven by pineal levels of norepinephrine (NE). The interest in pineal melatonin release stems from its role in circadian rhythm regulation. However, melatonin has much more to provide than simple circadian regulation, being a powerful anti-oxidant, anti-inflammatory and antinociceptive, as well as a significant immune regulator and modulator of mitochondrial functioning, thereby regulating most key defense and cellular energy processes [2,3].

As well as being a powerful antioxidant per se, melatonin is also a significant endogenous anti-oxidant inducer, which is mediated via its induction of the transcription factor NF-E2-related factor 2 (Nrf2) [4]. Furthermore, melatonin increases levels of neurogenesis [5] as well as the longevity protein, sirtuin-1, which, when coupled to its optimization of mitochondrial functioning, indicates a powerful role in the inhibition of the plethora of ageing associated medical conditions, including Alzheimer's disease [6] and cancers [7], as well as in bipolar disorder [8] and an array of other medical conditions. Many of melatonin effects seem to be via its contribution to the maintenance of homeostatic processes, as indicated by its apoptotic effects in cancer cells [9], in contrast to its capacity to increase neurogenesis under physiological conditions. Consequently, melatonin has clinical utility across a wide range of medical conditions, including neurodegenerative and psychiatric disorders.

The immediate precursor of melatonin is N-acetylserotonin (NAS), which is also a powerful anti-oxidant as well as being a significant immune regulator and modulator of mitochondria functioning. As with melatonin, neurogenesis is increased by NAS, although its mode of action may be significantly different, given that NAS is a brain derived neurotrophic factor (BDNF) mimic, via its activation of the BDNF receptor, tyrosine kinase receptor-B (TrKB) [10]. Importantly, NAS and melatonin levels and synthesis are highly dependent on the availability of serotonin, which is the immediate precursor of NAS. The enzyme, aralkylamine N-acetyltransferase (AANAT) converts serotonin to NAS, with...
hydroxyindole O-methyltransferase (HIOMT), which is also referred to as acetylseryotonin methyltransferase, converting NAS to melatonin.

As such, given the dependence of these melatonergic pathways on serotonin availability, a decrease in serotonin, for example during episodes of depression or in the course of immune activation, restricts the levels of NAS and melatonin produced. As a result, the modulation of the melatonergic pathways is common across a host of medical conditions, including the many disorders that are associated with increased levels of depression, such as multiple sclerosis (MS) [11], migraine [12] and endometriosis [13]. It is important to note that, being amphiphilic, both melatonin and NAS readily diffuse through the extracellular space and across cell membranes, meaning that they are not entirely dependent on plasma membrane receptors for their effects in cells. Consequently, melatonin commonly accumulates around intracellular organelles, particularly mitochondria.

When metabolized, many of melatonin’s metabolites also show similar effects to that of melatonin, including anti-inflammatory and anti-oxidative, coupled to significant immune system modulation, reviewed in [4]. These melatonergic metabolites include N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK). Consequently, such research derived data clearly show that the activation of the melatonergic pathway produces an array of anti-oxidants, coupled to melatonin, via Nrf2, inducing endogenous anti-oxidants. Such melatonergic pathway induction of antioxidants is of some importance, given that a growing number of medical conditions, including neurodegenerative disorders [14], psychiatric conditions [15] and wider medical conditions [16] show evidence of oxidative and nitrosative stress (O&NS), which may be intimately associated with the etiology, course and treatment of such a diverse array of medical disorders [17].

Being amphiphilic, only some of the protection afforded by melatonin across such medical conditions and pathophysiological processes can be attributable to melatonin receptors (MT1r and MT2r) activation, with many of melatonin’s protective effects being melatonin receptor independent [18]. However, single nucleotide polymorphisms (SNP) in MT1r, MT2r and the melatonergic pathway enzymes increase the susceptibility/risk of a wide array of medical conditions, including cancer [19], depression [20], MS [21] and bipolar disorder [22].

As well as decreased serotonin availability modulating the melatonergic pathways, it is the subject of intense investigation as to what factors may act to modulate NAS and melatonin synthesis, including in the pineal gland, but also at other sites, such as the gut, where melatonin is highly expressed and acts to maintain the integrity of the gut barrier, thereby decreasing the influence of a ‘leaky gut’ on a host of medical conditions that show evidence of a clinically relevant gut-brain axis [23]. Data on pineal gland melatonin regulation indicate that some 14-3-3 isoforms may regulate the melatonergic pathways by increasing the stability and transcription of AANAT [24], whereas tumor necrosis factor-alpha (TNFa) can decrease pineal melatonin production [25].

As indicated above, the melatonergic pathways are active in many, if not all mitochondria-containing cells, including astrocytes [26], retina [27], fibroblasts [28] and macrophages [29]. AANAT is also present in neurons [30], indicating that neurons may also be a significant source of melatonin, with intracrine, autocrine and paracrine effects. Such local melatonin production and its likely differential regulation by a plethora of factors, will have consequences, both centrally and systemically, including via the regulation of mitochondrial functioning, as well as immune and glia reactivity regulation [17].

A number of consequences arise from serotonin availability being a prerequisite for melatonergic pathway activation. Numerous of biological factors act to regulate serotonin availability, including levels of monoamine oxidase (MAO), which degrades monoamines such as serotonin; stress-induced hypothalamus-pituitary-adrenal (HPA) axis activation and cortisol production, which may induce tryptophan 2,3-dioxygenase (TDO), thereby driving tryptophan to tryptophan catalobite (TRYCAT) synthesis and away from serotonin synthesis; and pro-inflammatory cytokine induced indoleamine 2,3-dioxygenase (IDO), which, similar to TDO, drives tryptophan to TRYCATs synthesis [31]. Such serotonin availability regulators not only decrease activation along the melatonergic pathways, but also link changes in these pathways to alterations in many key biological processes, with relevance across a host of medical conditions and pathophysiological processes.

Astrocyte and microglia, as well as immune cells’ induction of the melatonergic pathways, with autocrine and paracrine melatonin effects in these reactive
cells, is likely to be relevant to neuronal vulnerability regulation, across a host of medical conditions [17]. Given the seemingly controlling role of astrocytes in the regulation of neuronal activity and energy provision, coupled to their wider regulation of vasodilation and oxygen/glucose provision, the presence of melatoninergic enzymes in astrocytes may be of particular importance. The important localization of astrocytes, with astrocytic end-feet covering blood vessels and astrocytic processes enclosing many synapses, has led to astrocytes being conceptualized as an important hub that integrates central and systemic/peripheral processes and fluxes [32]. As such, the autocrine effects of melatonin that dampen astrocyte reactivity, may be a significant determinant of the nature of central and systemic interactions, in turn being an important treatment target across a host of medical conditions, including glioblastoma [7].

NAS, in comparison to melatonin, has been relatively little investigated, being generally seen to be similar to melatonin, given its antioxidant effects. However, being a BDNF mimic [10], NAS effects are not the same as those of melatonin. Consequently, modulators of the NAS/melatonin ratio may differentially impact on a wide array of central and systemic processes, and has been proposed to be of some importance in glioblastoma [7]. Factors that act to regulate the NAS/melatonin ratio may be of clinical importance and need investigation.

The growing evidence indicating that melatonin is synthesized in a variety of cell types, and possibly in all mitochondria-containing cells [1], suggests that the regulation of local melatonin synthesis in different cell types may be intimately linked to all intercellular interactions, including in the regulation of O&NS and immune-inflammatory responses [33]. Over the course of evolution it is generally accepted that mitochondria have evolved from melatonin-synthesizing bacteria, particularly rhodospirillum rubrum, which is still evident today and produces melatonin in a circadian rhythm [34]. As such, evolutionary forces may have shifted the synthesizing capacity of bacteria/mitochondria to the nuclear genome [1], although mitochondria may still have some residual melatonin synthesizing capacity, as indicated the presence of the MT1r [35] and AANAT in mitochondria [1]. Given the importance of mitochondria dysregulation and sub-optimal functioning across a host of medical conditions, such mitochondrial localization of melatoninergic synthesizing enzymes will be important to investigate.

1.2. An Immune-Pineal Axis?

One of the consequences of the melatoninergic pathways being activated in different cell types, is that melatonin regulation may not necessarily be ubiquitously produced in all cell types at any given moment. For example, the reinstatement of melatonin synthesis in astrocytes may lead to a decrease in reactivity in microglia that includes the induction of microglia melatonin synthesis, with autocrine effects that induce a microglia M2-like phenotype [29,36]. A similar process has been shown to occur in the interactions of systemic immune inflammatory activity, which increases TNFα, leading to a decrease in the pineal gland's circadian melatonin production [25]. This research group have developed this, leading to their proposal of an immune-pineal axis (IPA) [37], whereby systemic pro-inflammatory processes, including TNFα, switch off pineal melatonin production, thereby preventing melatonin's generally immune-suppressive effects, including from melatonin's suppression of lymphocytes adhesion to endothelial cells and vessels. As such, the suppression of pineal melatonin allows the immune system to optimize its response. When the immune challenge subsides at peripheral sites, including by the release of local melatonin from immune cells [29], there is a subsequent re-instatement of pineal circadian melatonin synthesis. As such, melatonin regulation may be subject to differential spatio-temporal regulation.

Similar effects to TNFα have also been shown in response to lipopolysaccharide (LPS), which acts via the toll-like receptor (TLR)4 complex on microglia, which leads to increased microglia TNFα release, which, in turn, acts to decrease pineal circadian melatonin synthesis [38]. Given that circulating bacteria usually arise from an increase in gut permeability, which melatonin prevents, variations in gut melatonin may then also act to regulate levels of pineal NAS and melatonin production. The IPA hypothesis, therefore, suggests a two-way interaction of immune cells with pineal melatonin synthesis, which may be determined via the differential regulation of melatonin at different sites, e.g. the gut, and in different cells e.g. macrophages [20]. As to how the often chronic, but low, levels of immune inflammatory activity in medical conditions such as endometriosis acts to impact on pineal melatonin production requires investigation.

Overall, melatonin has many effects, including being: a powerful antioxidant; an optimizer of mitochondria functioning; an endogenous antioxidants inducer; an anti-inflammatory; a reactivity regulator of immune and
glia cells; as well as a circadian rhythm regulator. The melatonergic pathway is present in many cell types and tissues/organs, as well as possibly being synthesized in mitochondria. Melatonin also has significant effects at important 'hubs', including astrocytes and the gut, as well as regulating inter-area immune communications, as indicated by work on the IPA.

We now briefly review the data on the interactions of the melatonergic and TRYCAT pathways, before looking at the relevance to these pathway interactions in migraine and endometriosis.

2. MELATONINERGIC PATHWAYS INTERACTIONS WITH TRYCAT PATHWAYS

As indicated above, the availability of serotonin is an important determinant of melatonergic pathway activation. The induction of the TRYCATs pathway, following the activation of TDO and/or IDO, significantly influences the availability of tryptophan for serotonin synthesis, and therefore of melatonergic pathway activation. We shall briefly review the TRYCATs pathways, before looking at how these pathways may interact with the melatonergic pathways.

The kynurenine pathway is activated when cytokines-induced IDO and/or cytokines/stress-induced TDO, act to drive tryptophan to TRYCATs synthesis, including neuroregulatory TRYCATs, such as kynurenic acid (KYNA) and quinolinic acid (QUIN) [39]. A number of pro-inflammatory cytokines can activate IDO, particularly interferon-gamma (IFN-\(\gamma\)), but also interleukin (IL)-1, IL-6, IL-18 and TNF-\(\alpha\). Cytokines may also induce TDO, although its induction may be predominantly via stress-induced cortisol, allowing both stress and immune-inflammatory cytokines to modulate levels of melatonergic pathway activity. Such driving down of serotonin availability and melatonergic pathway activation, will then commonly be associated with increased levels of particular TRYCATs, including KYNA, which acts to regulate glutamatergic receptor channels as well as inhibiting the alpha 7 nicotinic receptor. Another TRYCAT, QUIN, is excitotoxic via increased Ca\(\text{2+}\) influx via the N-methyl D-aspartate (NMDA) receptor [40].

Many medical conditions, including neurodegenerative [41] and psychiatric [42] disorders, as well as migraine [43] and endometriosis [44] are associated with an increased level of depression. Depression is classically associated with lower levels of serotonin that is coupled to an increase in the ratio of kynurenine/tryptophan, with the increased O&NS and immune-inflammatory cytokines in depression driving down tryptophan-serotonin-NAS-melatonin levels and increasing TRYCATs, with consequences, centrally and systemically, on the patterning of activation of different receptors. Consequently, depression and its biological underpinnings are less a co-morbidity of this wide array of depression-linked medical conditions, but rather may be an intimate part of the biological underpinnings of these medical disorders, which invariably show increased O&NS and immune-inflammatory cytokine production that is coupled to increased stress levels.

Overall, the interactions of the TRYCATs and melatonergic pathways is intimately linked to changes in serotonin and increased levels of depression that are evident across a host of medical conditions. Changes in the levels of melatonin's regulation of the blood-brain barrier (BBB), gut permeability, glia reactivity and immune cell reactivity, as well as changes in the circadian rhythm are all closely associated with, and to a great extent driven by, O&NS and cytokine driven up-regulation of TRYCATs and down-regulation of the melatonergic pathways.

Before looking at the role that the melatonergic pathways play in migraine and endometriosis, we will briefly review these two common but poorly managed conditions.

3. MELATONINERGIC PATHWAYS IN MIGRAINE AND ENDOMETRIOSIS

3.1. Migraine

Migraine is characterized by recurrent headaches that are usually moderate to severe, often coupled to an array of autonomic nervous system symptoms. Most typically, headache is experienced in only one hemisphere, with the headache being of a 'pulsating' nature, and with a duration typically between a couple of hours to 3 days. Not uncommonly, an array of other symptoms are also present, including vomiting and nausea, as well as sensory sensitivity. Around 30% of migraineurs perceive an 'aura', which predates, and predicts, the headache. There is a significant genetic susceptibility to migraine, with about 65% of cases being familial [45]. Hormonal factors are thought to influence the increased emergence of migraines in females after puberty, with migraine frequency decreasing during pregnancy [46].

Although the pathophysiology of migraine has still to be fully determined, it is clearly a very common (15% of population) and highly disabling condition, which is
generally regarded as a neurovascular disorder that is coupled to alterations in nociceptive neurons in the brainstem’s trigeminal nucleus. Migraine is highly associated with increased levels of depression, including increased migraine levels in patients with bipolar disorder [47]. Migraine is also associated with decreased levels of melatonin, in line with reduced levels of serotonin [48] and increases in the kynurenine/tryptophan ratio [49].

The pathophysiology of migraine is classically seen as driven by increased brain levels of the excitatory neurotransmitter, glutamate, especially in the cortex and brainstem's trigeminal nucleus, [50]. Glutamate is proposed to increase hyperexcitability via increased NMDAr activation, as evidenced from data derived from transcranial magnetic stimulation and visual evoked potentials, which suggest heightened responses to sensory stimuli in migraineurs [51,52]. Later neuroimaging studies also supported enhanced sensory driven cortical activation [53,54]. Migraine with an aura is associated with cortical spreading depression, which is also thought to be driven by the effects of glutamate at the NMDAr that drive increased calcium entry, in a process involving astrocyte-neuronal interactions [55]. Activated microglia are also thought to play a role in cortical spreading depression [56]. Following this activity burst, cortex blood flow in the affected site is decreased for two to six hours, with the spreading depolarization suggested to modulate nociceptive nerves in the head and neck [55].

Increases in pro-inflammatory cytokines are evident in migraineurs, including levels of C-reactive protein, which can increase BBB permeability [57], as well as the risk of migraine being genetically associated with single nucleotide polymorphisms in TNFα and IL-1β [58]. This suggests that an increase in pro-inflammatory cytokines is relevant to the etiology of migraine. Migraine is also associated with a number of gastrointestinal disorders, likely in association with increased gut permeability [59], which would be another source of increased immune-inflammatory factors, including bacteria crossing over a compromised gut barrier. Migraine may also be associated with autoimmune disorders [60], suggesting that the increase in the pro-inflammatory cytokine, IL-17, that is most strongly associated with autoimmune disorders, may also have a role to play in migraine.

O&NS is increased in migraine, whilst endogenous antioxidants are decreased [61], with genetic variations in the endogenous antioxidants, superoxide dismutase and catalase, associating with an increased risk of paediatric migraine [62]. As such, migraine is linked to increases in immune-inflammatory processes and O&NS that are strongly associated with the induction of IDO, TDO and TRYCATs pathways, that, in turn, contribute to decreased levels of melatoninergic pathway activation. In addition to this, the increased morning levels of cortisol in chronic migraineurs, suggests that a dysregulated stress/cortisol response may occur in migraine [63], further contributing to decreased serotonin availability, via increased monoamine oxidase degradation of serotonin [64] and cortisol induced TDO that further enhances TRYCATs induction [65].

It is also of note that estrogen increases migraine associated nociceptive processes, linking to the increased risk of migraine in women after the hormonal changes of adolescence [66]. It is of note that melatonin negatively regulates estrogen and its effects at the estrogen receptor alpha [67].

3.2. Migraine and Melatoninergic Pathways

Given the increases in stress, depression, O&NS, pro-inflammatory cytokines and kynurenine in migraineurs, it is not surprising that melatonin levels are often found to be decreased in migraine [68], perhaps especially during an acute migraine episode [1]. It is important to note that melatonin has wider antinociceptive efficacy across a range of pain associated conditions [69]. As such, its efficacy in migraine treatment would be expected, which a number of studies have shown to be the case.

Treatment of migraine by melatonin has proved of significant clinical utility in adult migraineurs, with evidence for this dating back over some decades [70,71]. Melatonin has been shown to decrease the duration of migraines, as well as their severity and frequency in adult migraineurs, coupled to aiding sleep [70]. A number of review articles on melatonin utility in adult migraineurs have found melatonin to have clinical efficacy [72,73], although melatonin seems to have been considerably under-utilized in the everyday management of adult migraine.

In fact, not only has treatment with melatonin proved useful in the treatment of adult migraineurs, but also in paediatric migraine treatment. In a study of boys and girls presenting with migraine, Fallah and colleagues have recently shown melatonin to have prophylactic effects [74]. This study is of some importance, as no current pharmaceuticals have been approved for
migraine preventive therapy to date. These authors found that the monthly frequency and severity, as well as the duration of headache were significantly reduced by approximately 50% across all of these migraine measures in children using melatonin [74]. These authors conclude that melatonin can be considered as an effective prophylaxis, without significant side effects, with its utilization encouraged also by its ready availability and low costs. Other studies have also supported the utility of melatonin in decreasing the frequency, severity and duration of migraine in children [75].

The relatively recent development of a melatonin-based antidepressant, agomelatine, which acts as an agonist at the MT1r and MT2r, whilst also antagonizing the serotonin 2C receptor, has provided another possible pharmaceutical option for the management of migraine [76]. As with melatonin, agomelatine is well tolerated and with few side effects and requires further investigation as to its utility in migraine management.

It is unknown as to whether the immediate precursor of melatonin, NAS, has any modulatory effects in migraine, although its action as a BDNF mimic suggest that it could have regulatory, and perhaps even detrimental, effects, given an increase in BDNF is found during migraine attacks [77]. This could suggest that variations in the NAS/melatonin ratio could have some relevance to the biological underpinnings of migraine, as in other medical conditions [7], and requires investigation.

Overall, an increase in levels of O&NS, pro-inflammatory cytokines, stress and depression in migraine allows ready links to the modulation of the melatoninergic pathways. This is supported by data showing decreased melatonin in migraineurs, especially during acute attacks, with melatonin having significant prophylactic efficacy in both adult and paediatric migraineurs. As to whether agomelatine, NAS and the NAS/melatonin ratio have any relevance to the etiology, course and/or management of migraine requires investigation.

3.3. Endometriosis

In endometriosis, endometrial tissue that is normally restricted to the uterus, grows in other locations, most often in the ovaries and fallopian tubes, as well as in nearby tissue. These areas of endometriosis also bleed over the monthly menstrual cycle, leading to inflammation and scarring [78]. The main presenting symptom is pelvic pain, being chronic in 50% of patients and in 70% during menstruation. Infertility also occurs in approximately 50% of cases [79]. Endometriosis occurs in approximately 6–10% of women, with most presentations being by women aged 30-40 years [78]. Endometriosis is a benign gynaecological disease that is also typically associated with chronic immune-inflammatory activation, as well as high stress and depression levels [80]. In a study of Brazilian women with endometriosis, an 86% depression rate was found in women with chronic pelvic pain versus 36% in pain free women with endometriosis [81]. Most typically, endometriosis shows raised levels of estrogenic activity and progesterone resistance [78].

Endometriosis is associated with increased levels of O&NS [82,83], with recent studies on the pathological characteristics of endometriosis revealing a vicious cycle, whereby generated O&NS has been shown to facilitate implantation of the ectopic endometrium [82]. A variety of different antioxidants and antioxidant inducers, including vitamins C, vitamin E, melatonin, resveratrol, xanthohumol and green tea’s epigallocatechin-3-gallate (EGCG) have all been shown to have a positive impact on endometriosis, reviewed in [82]. High levels of O&NS in endometriosis may be associated with raised levels of iron [84], suggesting that oxidative stress may be triggered by the Fenton reactions.

Pro-inflammatory cytokines are also increased in endometriosis, including IL-1β, which contributes to increased IL-6 and IL-8 in endometriosis, as well as the induction of TDO, thereby contributing to the heightened levels of immune tolerance that are often present [85]. Immune tolerance under inflammatory conditions and increased O&NS often associates with increases in autoimmune raised levels of T helper (Th)17 cells and the cytokine IL-17, which are all increased in endometriosis [86]. The taking of tryptophan to TRYCAT’s production, in turn increasing kynurenine, may also be relevant to this, given that kynurenine activates the aryl hydrocarbon receptor (AhR), which can induce IDO and associated immune tolerance, as well as contribute to the induction of Th17 cells [87]. Recent data shows that the dioxin and environmental toxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), may have a role to play in endometriosis [88]. TCDD activates the AhR, leading to increased IDO as well as Th17 cells [87], and may further deplete serotonin availability for melatoninergetic pathways activation. Such heightened levels of IDO will also increase the invasiveness of endometrial stromal cells [89].
Although there is no doubt as to the role of estrogen at the estrogen receptor alpha in the etiology and exacerbation of endometriosis [90], there does not seem to be any genetic association of single nucleotide polymorphisms in the estrogen receptor alpha that increases the risk of endometriosis [91]. It is of note that melatonin has inhibitory effects on this estrogen receptor [67].

Overall, many of the factors associated with the inhibition of the melatonergic pathways, including via O&NS, cytokines and stress-induced IDO, TDO and the TRYCATs, are increased in endometriosis, suggesting that alterations in the melatonergic pathways are of relevance in this still poorly treated condition.

3.4. Endometriosis and Melatonergic Pathways

As with migraine, many of the biological factors associated with endometriosis, including O&NS, pro-inflammatory cytokines, stress and depression, are all associated with the up-regulation of the TRYCAT pathway, leading to the deprivation of serotonin for the melatonergic pathways. A role for TCDD, via the activation of the AhR, will also induce TRYCATs, via AhR induction of IDO, in turn contributing to decreases in melatonergic pathway activity.

Surprisingly, melatonin has not been experimentally investigated in endometriosis, although indications of altered pineal efflux have been published [92]. Given the clinical utility of melatonin in the treatment of endometriosis, the lack of investigation of circadian melatonin production requires urgent rectification, including the monitoring of melatonin at different phases of the menstrual cycle [93].

The efficacy of melatonin in the treatment of endometriosis has been shown in both clinical studies as well as in vitro experimental models. In a phase II, randomized, double-blind placebo-controlled trial of melatonin in endometriosis patients, Schwertner and colleagues showed melatonin to have relevant analgesic, antioxidant, and antiinflammatory effects in endometriosis-associated chronic pelvic pain, which presents with an intense pro-inflammatory reaction. Interestingly, this trial compared melatonin (10mg) with placebo over 8 weeks, comparing not only on aspects of endometriosis-associated pain, but also with levels of BDNF. Results showed that there was a significant interaction (time vs group) in regard to the major pain score outcomes, as indicated by a visual analogue scale measuring daily pain, dysuria, dysmenorrhea and dyschezia [93]. These results indicated that melatonin, versus placebo, lowered daily pain scores by 39.80% and dysmenorrhea scores by 38.01%. As well as improving sleep, melatonin also reduced the risk of analgesic use by 80%, whilst also lowering BDNF levels, with the latter occurring independently of melatonin’s antinociceptive effects. As well as clearly highlighting the utility of melatonin in the management of endometriosis, this work also showed that melatonin modulates BDNF secretion via mechanisms that seem distinct from its regulation of pain.

Interestingly, some of the exacerbating effects of estrogen in endometriosis seem mediated by its increase in levels of BDNF [94]. Again this could suggest that NAS, as a BDNF mimic that can also induce BDNF [95], may have negative effects in endometriosis. It is very likely that the melatonergic pathway enzymes are expressed in endometrial cells, suggesting that variations in local levels of NAS and melatonin, and therefore the NAS/melatonin ratio may have significant impacts in endometriosis. Given that melatonin may also decrease the levels of estrogen activity at the estrogen receptor-alpha, it is likely that melatonin, including if locally induced, would have impacts on estrogen-regulated aspects of endometriosis.

Overall, alterations in the melatonergic pathways are likely to have relevance to the genesis, course and treatment of endometriosis, with likely effects arising from changes in the local NAS/melatonin ratio.

3.5. Melatonergic Underpinnings of Other Treatments

A number of pharmaceuticals and nutriceuticals have been shown to have utility in migraine and endometriosis, including green tea's EGCG [82;96], selenium [97,98] and taurine [99,100]. These, and many other factors that impact on both of these medical conditions, may all be mediating their effects via the regulation of the local melatonergic pathways [101].

As such, as well as melatonin having direct clinical utility across a host of medical conditions, including migraine and endometriosis, it is likely that the biological underpinnings of both of these disorders may involve alterations in the regulation of local melatonergic pathways in a variety of cell types and tissues. This is in urgent need of investigation as it may provide an important and achievable pharmaceutical target.
4. CONCLUSIONS

The activation of immune-inflammatory and O&NS pathways across a host of medical conditions, including migraine and endometriosis, is associated with the driving of tryptophan down the kynurenine pathway to TRYCATs production and away from the melatoninergic pathways. Melatonin is a useful treatment for both of these conditions, with the bonus of having little side-effects. The melatoninergic pathways, including alterations in the NAS/melatonin ratio may be an important treatment target for the management of these still relatively poorly treated conditions, especially given the role of BDNF in both of these conditions and the BDNF-mimicking effects of NAS. It requires investigation as to whether the many pharmaceutical and nutriceutical products that have shown utility in management of migraine and endometriosis are mediating their effects via the regulation of the NAS/melatonin ratio. In the meantime, the under-utilized, cheap, readily-available and efficacious melatonin should be more extensively used to manage poorly-treated conditions such as migraine and endometriosis.

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