The gut–brain axis: The role of melatonin in linking psychiatric, inflammatory and neurodegenerative conditions

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1. Introduction

Recent conceptualisations of psychiatric conditions have highlighted the role of oxidative and nitrosative stress (O&NS) and inflammatory processes, especially in depression [1], but also across a range of other psychiatric conditions. The emerging biological underpinnings of depression show depression to be more than a common, often prodromal, psychological comorbidity to neurodegenerative conditions, but rather to be an important biological contributor to neurodegenerative processes [2]. A number of factors can contribute to inflammatory conditions. Here we focus on the role of melatonin in gut permeability, especially via its regulation of the inflammasome. This has important consequences across a host of medical conditions, including Alzheimer’s disease, non-alcoholic fatty liver disease, obesity, fibromyalgia and alcoholism, as well as in the aetiology and course of depression. Such work emphasises the importance of central and systemic interactions, and has implications for the etiological conceptualisation, classification, course and treatment of a diverse array of medical conditions.
to how bacteria or pathogens in other organs and tissues can influence central activity.

Gut permeability arises as a consequence of a loosening of the tight junctions that closely link the cells lining the gut. A number of factors have been shown to increase gut permeability, including dietary fats [7], stress [6] and alcohol [8], including binge alcohol drinking [9], whilst a number of factors can decrease permeability or help to maintain gut tight junction integration, including dietary whole grains [10] and melatonin [4], with the latter preventing the effects of alcohol on gut permeability [8]. Recent work on the role of gut permeability in other medical conditions has focussed on its impact in the aetiology and course of depression, in turn driving the association of recurrent depression with other medical conditions, including Alzheimer's disease [11]. As such, we will first look at the role of gut permeability in depression, linking this to the aetiology of depression-associated conditions.

2.1. Gut permeability and depression

By increasing gut permeability, stress and other factors allow the transfer of a variety of commensal, gram-negative bacteria (as well tiny fragments of partially digested food), which can trigger an immune response. Lipopolysaccharide (LPS) is part of the bacterial wall of gram-negative bacteria and mediates its effects by activating the toll-like-receptor-2/4 (TLR2/4)–CD14 complex, which is an important activator of the innate immune response. Many gram-negative bacteria are part of the normal gut flora [12]. Depressed patients show a significant increase in the plasma levels of such bacteria [13,14]. This suggests that in depressed patients there is a heightened IgA- and IgM-mediated immune response directed against LPS as a consequence of increased gut bacteria translocation. Activating the CD14–TLR2/4 complex increases the production of a number of inflammatory processes, including nuclear factor k-light-chain-enhancer of activated B cells (NF-kB), which is a transcription factor that drives many inflammatory genes and processes, including the pro-inflammatory cytokines, tumour necrosis factor alpha (TNFα) and interleukin (IL)-1β, as well as cyclo-oxygenase-2 (COX-2) [15,16]. Increased gut permeability enhances gram-negative bacteria translocation into the mesenteric lymph nodes (MLNs) and occasionally into the blood [17,18]. IgM and IgA responses can be mounted in the blood, whilst IgA responses may be mounted even when bacterial translocation is limited to the MLNs.

As well as immune-inflammatory processes, LPS, as a consequence of increased gut permeability, heightens O&NS levels, including inducible nitric oxide (iNOS) and thereby NO [16]. LPS also activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase resulting in enhanced levels of superoxide and peroxides [19,20]. Generally increased O&NS enhances immune-inflammatory processes and vice versa [14]. As such, the LPS driven systemic IgA and IgM-mediated immune response in depressed patients contributes to both the increases in immune-inflammatory and O&NS processes, with consequences for the aetiology and course of depression and depression-associated medical conditions. A vicious cycle may then be formed with immune-inflammatory processes and O&NS further contributing to increased gut permeability [13].

It is of note that recent work shows that the IgM responses directed against LPS are significantly enhanced in chronic or recurrently depressed patients [21]. This may be of importance to the changing nature of depression, termed neuroprogression [22,23], as well as to changes in the course of depression-associated medical conditions [1]. Heightened immune-inflammatory activity and increased O&NS can lead to damage to membranes that results in the exposure of neo-epitopes, thereby triggering an autoimmune response. Increased autoimmune responses, including to serotonergic pathways [24], are important to the changing nature of depression over the course of neuroprogression, with likely consequences for the course of depression-associated conditions.

By raising immune inflammatory processes and O&NS, increased gut permeability will also activate indoleamine 2,3-dioxygenase (IDO), leading to decreases in tryptophan availability for serotonin, N-acetylseryton and melatonin synthesis. Centrally, IDO is predominantly induced in microglia by pro-inflammatory cytokines, especially interferon-gamma (IFN-γ). IDO drives tryptophan down the kynurenine pathways that produce tryptophan catabolites (TRYCATs) that have neuroregulatory effects, which is reviewed in [1]. This is one means by which gut permeability, bacterial translocation and immune activation can lead to changes centrally that influence neuronal survival and excitability, as well as inter-area neuronal patterning within the CNS [1]. It is likely that stress-induced cortisol also contributes to this, both via increasing gut permeability and by increasing tryptophan 2,3-dioxygenase (TDO), which like IDO results in tryptophan depletion and the induction of neuroregulatory TRYCATs. As such the classical association of stress with depression and depression-associated conditions may be mediated, at least in part, via increases in gut permeability and the downstream consequences arising from this.

3. Depression-associated conditions: inflammation and O&NS

3.1. Depression and other psychiatric conditions

Many, if not most, other major psychiatric disorders, are associated with high levels of stress and depression, as well as with heightened levels of O&NS and immune-inflammatory activation, including mania in bipolar disorder, schizophrenia [25] and post-traumatic stress disorder (PTSD) [26]. The autoimmune consequences arising from this suggest that there are neuroprogressive changes to the biological underpinnings of such depression-associated disorders, which recent work supports [27,28].

The role of inflammation and O&NS in a variety of depression-associated psychiatric conditions has a long history, with the earliest work showing increased pro-inflammatory cytokines, including IL-6 and acute phase proteins [29,30], coupled with immune activation, as indicated by increased levels of the soluble IL-2Rs levels [29,31], in acute and euthymic manic patients, being published in the early 1990s, which is supported by a recent meta-analysis [32]. In 1995 Smith and Maes published the monoocyte-T lymphocyte theory of schizophrenia, whereby immune inflammatory processes were proposed to underlie the neurodevelopmental pathology in schizophrenia that is driven by gestational infections, reviewed in [33]. A recent meta-analysis also supports this [34]. PTSD is another depression-associated condition that shows elevations in pro-inflammatory cytokines, including IL-1 [35], IL-6 [36] and TNFα [37], especially when comorbid with depression [38]. An array of other depression-associated conditions classically seen in psychiatric settings, such as fibromyalgia and chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), likewise show increases in immune inflammation and O&NS [24].

3.2. Gut permeability in other depression-associated psychiatric conditions

Recent work is beginning to show associations of these depression-associated conditions with changes in the gut. PTSD has a long historical association with alterations in the gut [39], although direct investigation of the role of gut permeability and gut microbiota in PTSD has still to be investigated. However, the association of PTSD with depression, stress and early life events suggests a role for gut microbiota [40]. Discordant patterns of
bacterial translocation markers are evident in people with schizophrenia and bipolar disorder [41], suggesting a role for variations in gut bacteria and increased gut permeability in psychotic disorders. Both fibromyalgia and CFS/ME are associated with increased gut permeability, with treatment targeted to the gut leading to symptom improvement [13]. Also in CFS/ME patients the increase in autoimmunity against serotonin is associated with increased gut permeability [21].

3.3. Depression and other inflammatory conditions

Many other non-psychiatric medical conditions associate with increased levels of depression, including obesity [42], type II diabetes [43], cardiovascular disease [44], chronic obstructive pulmonary disorder [45], non-alcoholic fatty liver disease (NAFLD) [46] and a variety of different cancers [47,48]. As with depression-associated psychiatric conditions, the increased rates of depression in general medical inflammatory conditions have classically been attributed to a psychological reaction to an often long-term, chronic condition. However, as highlighted above the increased immune-inflammation and O&NS in depression may play an intimate role in the aetiology and course of these inflammatory conditions.

3.4. Gut permeability in other inflammatory conditions

Obesity is linked to increased gut permeability and circulating levels of LPS [49], as is type II diabetes [50]. Targeting gut microbiota has been proposed as a new line of treatment for type II diabetes [51], with the association of obesity with cancers being thought to mediate, in part, by the specifics of the gut microbiome [52]. Likewise variations in gut bacteria and gut permeability are now recognised as significant factors in the aetiology and course of cardiovascular disorders [53]. As well as specific lung airway bacteria being associated with asthma in adults, there is a growing appreciation that gut bacteria play a role in pulmonary conditions, including COPD [54]. The emerging role of gut bacteria in the aetiology and course of NAFLD has led to a gut–liver axis being proposed [55].

3.5. Depression and neurodegenerative conditions

Neurodegenerative conditions such as Alzheimer’s disease, Parkinson’s disease and multiple sclerosis have long been associated with increased rates of depression [56–58], with depression classically thought to masquerade cognitive symptoms in dementia [59]. Increased immune-inflammatory processes and O&NS evident in depression, coupled to decreased endogenous antioxidants, also occur in Alzheimer’s disease, Parkinson’s disease and multiple sclerosis [1,60], with increased TRYCATs and decreased tryptophan, serotonin, N-acetylserotonin and melatonin also common in these neurodegenerative conditions [60–62]. The driving of TRYCAT pathways by O&NS and immune-inflammatory processes is increasingly being recognised as important to depression-associated conditions, including Alzheimer’s disease [63], Parkinson’s disease [60], and multiple sclerosis [62]. Overall, the association of depression with neurodegenerative disorders is intimately linked to the processes by which increased gut permeability contributes to depression. In this context, it is worthy of note that recurrent depression increases the risk of dementia [11].

3.6. Gut permeability and neurodegenerative conditions

Changes in the function of the gut are intimately associated with Parkinson’s disease, including increased gut permeability [64]. These authors found that levels of gut permeability correlated with levels of alpha-synuclein and O&NS in early stage Parkinson’s disease patients, suggesting that increased gut permeability may be an integral part of the Parkinson’s disease aetiology. Likewise there is increasing interest in the role of gut bacteria and increased gut permeability in white matter demyelination in the CNS [65], including in multiple sclerosis [66]. Changes in white matter are relevant to many psychiatric as well as neurodegenerative conditions such as the dementias [67], being another process by which gut permeability, immune inflammation and O&NS may contribute to a wider variety of medical conditions [68].

3.7. Summary: gut permeability and depression-associated conditions

Undoubtedly gut permeability and depression significantly associate with a wider range of medical conditions, with likely reciprocal interactions and influences. Many of these effects and interactions are driven by increases in immune inflammatory activity, O&NS and TRYCATs, allowing these common underlying biological processes to link a diverse array of medical presentations. However, it should be borne in mind that depression is very likely to be a set of heterogenous pathophysiological conditions, with classification, as in psychiatry generally, still based on subjective phenomenology as well as signs and symptoms. As such many depression presentations may have a wide and distinct range of biological processes that are changed in a particular individual, suggesting that subtypes of depression, with distinct biological underpinnings may exist. This requires further study, but is indicated by data showing the differentiation of somatisation and depression on the basis of the ratio of the TRYCAT products kynurenine and kynurenic acid, as well as the kynurenine/tryptophan ratio [69]. This exemplifies the importance and interconnectedness of O&NS, immune inflammation and TRYCATs in driving a more refined understanding of the different aspects of depression, and, as a consequence, how these different biological aspects of depression pertain to its association with wider medical conditions. As highlighted above, gut permeability and depression provide biological threads across many diverse and poorly treated medical conditions. One important connection across this diverse array of conditions is melatonin (Fig. 1).

4. Melatonin

Melatonin is widely known as the hormone released by the pineal gland at night, with a role in entraining circadian rhythms. Melatonin is also a powerful anti-inflammatory, antioxidant and analgesic that significantly optimises mitochondrial functioning, thereby contributing to energy production in all cells. In fact, mitochondria are evolutionarily derived from melatonin producing bacteria, suggesting that all mitochondria-containing cells may produce melatonin to some degree [70]. As well as being a powerful antioxidant melatonin also induces the synthesis of endogenous antioxidants, thereby making a significant contribution to cellular oxidant status across a range of organs and tissues. Pineal melatonin is commonly decreased across a wide range of medical disorders, including depression-associated conditions, such as schizophrenia [71] and Alzheimer’s disease [72], with melatonin proposed to have some efficacy in the management of such conditions [25]. Single nucleotide polymorphisms in the molecules and receptors of the melatoninergic pathway are modelled as mediating their disease susceptibility effects predominantly via pineal melatonin dysregulation.

Melatonin treatment has wide treatment efficacy across a host of medical conditions, including bipolar disorder, Alzheimer’s disease, Parkinson’s disease, depression and fibromyalgia, which all show evidence of increased immune inflammation and O&NS [73], although a small meta-analysis of its anti-depressant effects in depressed and non-depressed samples found mixed anti-depressant
efficacy but no overall significant clinical effect [74]. However, it should be noted that this meta-analysis included studies with a melatonin dose from 0.5 to 6.0 mg, which is likely to include doses that are below any clinical efficacy [74]. During the course of inflammation, it is proposed that peripheral cytokines, such as TNF-α, shut down pineal melatonin production, contributing to the decreased pineal circadian melatonin synthesis across many medical conditions. This can be mediated by TNF-α effects directly in pinealocytes or indirectly via TLR-4 activation in microglia around the pineal gland, which drives local TNF-α production and release [75]. This is based on data in women who have undergone caesarean section, where inflammation induced TNF-α switched off pineal melatonin production for 14 days on average, with pineal melatonin circadian synthesis being reinstated once the peripheral inflammation was resolved [76]. This would suggest that evolutionary processes have acted to suppress pineal melatonin in the presence of peripheral inflammation, indicating that the frequently attenuated melatonin release over a host of central and systemic medical conditions may be part of a controlled response to inflammation [2].

Exogenous or circadian melatonin has been shown to have a broad range of effects across many immune cell types. Generally, melatonin increases the more beneficial T helper (Th)-1 responses, including IL-2 and IL-6 cytokines in T-cells [77], whilst likely suppressing the more prolonged and damaging inflammatory activity generated by Th-17 cells [78]. Melatonin also increases the cytotoxicity of natural killer cells that contributes to melatonin’s efficacy in cancers [79]. Melatonin regulates many, if not all, immune cells, generally decreasing their reactivity and increasing phagocytosis [80]. As a consequence, the loss of circadian melatonin will have significant immune and oxidative consequences. Much of this research has been carried out by Regina Markus and colleagues, who recently proposed an immune-pineal axis [81], linking peripheral inflammation with decreased pineal melatonin synthesis. This requires investigation in the context of depression and depression-associated conditions.

4.1. Local melatonin synthesis

Melatonin is synthesised by many, if not all mitochondria containing cells [70]. This includes immune and glia cells, such as macrophages [82] and astrocytes [83]. A phagocytic, anti-inflammatory macrophage phenotype is induced by the initial activation of NF-κB in macrophages, leading to melatonin release and autocrine effects [82]. As melatonin is synthesised and released by many, if not all, immune cells it is likely to have a wide range of impacts on immune-inflammatory activity and O&NS that drives immune cell activation. This suggests that many medical conditions shown to have melatonin SNP genetic susceptibilities will have this association with the melatonergic pathways via changes in immune system and glia responses, and not necessarily as a result of altered pineal melatonin synthesis [2]. This may also be important to wider regulatory systems as melatonin also has a number of epigenetic effects [84]. Similar epigenetic processes are known to be relevant in many depression-associated conditions, including Alzheimer’s disease [85], Parkinson’s disease [86] and schizophrenia [87], suggesting that local, as well as pineal, melatonin may be relevant to a wide array of relevant processes across a host of medical conditions. Such work suggests that targeting local melatonin synthesis in glia and immune cells may be relevant to many medical conditions that are currently poorly treated [2].

Many disorders show an association with increased blood brain barrier permeability (BBBp). This would seem to be at least partly driven by increased reactivity levels in astrocytes and mast cells, leading to the efflux of a number of BBBp regulating factors, including TNF-α, IL-1β and vascular endothelial growth factor (VEGF) [88,89]. Given that local paracrine and autocrine, as well as circadian, melatonin dampens astrocyte and mast cell reactivity, melatonin would also decrease BBBp and therefore the infiltration of invading leukocytes. It should be noted that melatonin is also a significant inducer of the alpha 7 nicotinic acetylcholine receptor (α7nAChr) [90], which, when activated, is a significant regulator of mitochondrial functioning and inflammasome activation [91], as well as being an inhibitor of glia and mast cell reactivity [92,93]. Mast cells are also a significant determinant of increases in human gut permeability to stress/cortisol [6]. Overall, variations in melatonin synthesis from a variety of cellular sources are likely to have significant impacts on processes important to BBBp and thereby on CNS inflammatory responses.

4.2. Gut melatonin

Melatonin is very highly synthesised in the gut in a non-photocircadian manner, where it is released at levels that are up to...
400-fold higher than levels released by the pineal gland [94], being highest after food intake [95]. Although many cell types may contribute to such gut melatonin, the majority is derived from enterochromaffin cells [96]. Given melatonin’s effects on immune-inflammatory activity, O&NS, mitochondrial functioning and barrier permeability, it is likely to have beneficial impacts on a host of gut related disorders. Recent work suggests that this is indeed the case, with melatonin decreasing Escherichia coli induced increases in gut permeability and associated immune activation [97], with melatonin being proposed as something of a panacea for gut related disorders [98], including inflammatory bowel disorders and their sensitisation of gastrointestinal cancer susceptibility [99,100]. There is increasing interest in the role of increased gut permeability and altered gut microbiota in the aetiology and course of depression, and thereby with many other conditions. This could suggest that some of the efficacy of melatonin is mediated via changes in the gut as well as centrally.

Much has still to be investigated as to how different gut bacteria interact with the gastrointestinal tract and the host’s immune system. Indeed it is unknown as to whether different gut bacteria produce melatonin or differentially induce its production by enterochromaffin cells or immune cells. Although it should be noted that the specificity of gut bacteria determines the tryptophan availability [101], suggesting upstream effects on the availability of tryptophan for serotonin and subsequent melatonin synthesis. Such direct effects of gut bacteria on the host melatoninergetic pathways and the question of bacterial melatonin synthesis will be important to determine. Given the importance of tryptophan availability and its regulation of serotonin and melatonin, as well as glia and immune responses, it is likely that gut bacteria will have a significant impact on key processes driving changes in neuroinflammation [1,2,25]. The role of gut melatonin in neuroinflammatory conditions such as Alzheimer’s disease is urgently in need of investigation.

However, known important effectors of gut permeability and its interaction with gut bacteria are the inflammasomes, especially the NOD like receptor 3 (NLRP3) and NOD like receptor, pyrin domain containing 6 (NLRP6). These inflammasomes are important in gut homeostasis [102], including a role in gut permeability [103]. NLRP6 is a significant regulator of murine gut microbiota and gut permeability, mediating the effects of stress induced corticotrophin releasing hormone (CRH) [104]. Also, α7nAChR activation [105] or melatonin [106] decrease sepsis by decreasing NLRP3 activation in LPS models. As highlighted above, melatonin is a significant positive regulator of the α7nAChr [90], suggesting that some of melatonin’s effects in gut regulation may be mediated by its induction of the α7nAChr. Recent work shows that melatonin’s protection against induced gut permeability is mediated, at least partly, by the α7nAChr [8]. Factors regulating inflammasome activation are the subject of intense investigation, with known regulators including ROS and oxidised mitochondrial DNA release [107]. The α7nAChr inhibits NLRP3 activation by released oxidised mitochondrial DNA [90], with melatonin inhibiting mitochondrial DNA release [108]. As to whether some of the effects of gut melatonin are mediated via its regulation of the mitochondrial α7nAChr and/or oxidised mitochondrial DNA release requires investigation. The inflammasomes are crucial to IL-1β and IL-18 release. Both cytokines are commonly increased in depression and depression-associated conditions [109,110], with rodent data showing a role for the inflammasome in LPS induced depressive-like behaviours [111]. It is also worthy of note that there is a circadian variation in the inflammatory response to LPS/sepsis that is regulated by melatonin [112].

4.3. Melatonin based medications

Given with wide-ranging benefits of melatonin, pharmaceutical companies have put in a lot of effort in a bid to develop melatonin-based medications. As a result, a number of melatonin-based and melatonin receptor agonist pharmaceuticals are now available, including agomelatine. Agomelatine is a 5HT1r and MT2r agonists that also has antagonistic effects at the 5-HT2Cr. Agomelatine has well-proven anti-depressant and anxiolytic effects [113]. Serotonin is a significant regulator of gut function, although this is predominantly attributed to its effects at the 5-HT3 and 5-HT4 receptors [114]. It remains to be determined as to whether agomelatine has any impact on gut permeability that is relevant to its therapeutic efficacy in some depressed patients.

5. Conclusions

The gut–brain axis is the subject of extensive investigation and has been extensively reviewed elsewhere [115–117]. Here, we have focussed on the role of melatonin in regulation of the gut–brain axis, with effects both centrally and peripherally. Melatonin is an important regulator of a number of key processes underlying the associations of depression and depression-associated conditions, including via gut regulation. Melatonin’s effects are mediated via a wide range of processes across distinct physiological systems, involving immune-inflammation, O&NS, mitochondria and, as highlighted here, gut homeostasis and gut permeability. It will be important to investigate a number of such melatonin influenced processes, including its role in gut permeability in the aetiology and/or course of Alzheimer’s disease and other depression associated neurodegenerative conditions. As to whether melatonin is produced by different gut bacteria will also be important to determine, and perhaps not unlikely, given that the bacteria that eventually evolved into mitochondria were melatonin producing organisms [70]. As such, melatonin has a long evolutionary association with the human condition and with the other organisms that are crucial to our existence as well as health.

References


