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

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ABSTRACT

Recent work has highlighted the importance of immune inflammatory processes, oxidative and nitrosative stress (O&NS) and tryptophan catabolites (TRYCATs) in the aetiology of depression and many depression-associated disorders, including other psychiatric, neurodegenerative and wider medical disorders. A recently researched aspect of the aetiology and course of depression has focussed on the role of gut permeability and gut microbiota. Increased gut permeability is evident in many medical conditions, contributing to increased immune inflammatory cytokines, O&NS and neuroregulatory TRYCATs. By driving tryptophan down the kynurenine pathways and away from serotonin, N-acetylserotonin and melatonin synthesis, such processes alter the nature of central processes, but also contribute to changes in gut permeability regulation. Here we look at the role of decreased 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.

1. Introduction

Recent conceptualisations of psychiatric conditions have highlighted the role of oxidative and nitrosative stress (O&NS) and immune-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 gut permeability in increasing immune-inflammatory activity, in turn contributing to depression and depression-associated conditions such as the neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease and multiple sclerosis, as well as obesity and non-alcoholic fatty liver disease (NAFLD). As such, the gut–brain axis is now emerging as an important driver of a range of medical conditions, allowing these conditions to be etiologically integrated, in turn challenging the nature of current pharmaceutical targets and classification systems.

Within this context, factors that regulate the gut will have significant pharmaceutical, complementary and general integrative significance. Dietary factors [3], alcohol [4], variations in gut microbials [5] and stress [6] can all regulate gut permeability, thereby having an impact via the immune system on a wide range of medical disorders. Here, we focus on the role of melatonin in the gut, highlighting its role in gut permeability and treatment.

2. Gut permeability and gut microbials

Many sites of peripheral inflammation have now been shown to have consequences for central processing, including periodontal and lung tissues. It is generally accepted that this arises from environmental bacteria driving changes in the immune response, which in turn can have an impact in the brain, as well as in other organs. As such, gut permeability is part of wider investigations as

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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 gram-negative bacteria, with resultant increases in plasma levels of immunoglobulin (Ig) A and/or IgM that are directed against 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 κ-light-chain-enhancer of activated B cells (NF-κB), 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-acetylserotonin 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 monocyte-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