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LEADING ARTICLE

Role of Immune-Inflammatory and Oxidative and Nitrosative Stress Pathways in the Etiology of Depression: Therapeutic Implications

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Abstract Accumulating data have led to a re-conceptualization of depression that emphasizes the role of immune-inflammatory processes, coupled to oxidative and nitrosative stress (O&NS). These in turn drive the production of neuroregulatory tryptophan catabolites (TRYCATs), driving tryptophan away from serotonin, melatonin, and *N*-acetylserotonin production, and contributing to central dysregulation. This revised perspective better encompasses the diverse range of biological changes occurring in depression and in doing so provides novel and readily attainable treatment targets, as well as potential screening investigations prior to treatment initiation. We briefly review the role that immune-inflammatory, O&NS, and TRYCAT pathways play in the etiology, course, and treatment of depression. We then discuss the pharmacological treatment implications arising from this, including the potentiation of currently available antidepressants by the adjunctive use of immune- and O&NS-targeted therapies. The use of such a frame of reference and the treatment benefits attained are likely to have wider implications and utility for depression-associated conditions, including the neuroinflammatory and (neuro)degenerative disorders.

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1 Introduction

Historically, depression has been variously conceptualized, from a psychoanalytical entity to a neuronal disorder dependent on monoamine dysregulation. The serotonin hypothesis of depression was mainly based on the findings that compounds with clinical antidepressant effects, e.g., iproniazid and imipramine, increase available serotonin [1]. Following the launch of selective serotonin reuptake inhibitors (SSRIs), the blaze of publicity undoubtedly enhanced the placebo effects that are relevant to all psychotropic medications [2]. Although the use of these agents has led to significant improvements in treatment outcomes, many patients continue to have depression-related morbidity, stressing the need for new treatments based on an evolving understanding of depression pathogenesis.

More recent conceptualizations of depression's biological underpinnings emphasize the role of oxidative and nitrosative stress (O&NS) coupled to immune-inflammatory pathways [3–5]. A large body of data shows that depression is associated with increased levels of immune-inflammatory processes as well as genetic and epigenetic changes in redox status [1, 3]. The changes driven by immune-inflammatory and O&NS pathways incorporate many disparate aspects of depression, including: decreased serotonin, dopamine, and norepinephrine; circadian and melatonin dysregulation; transition to O&NS-induced

damage and autoimmunity; decreased neurogenesis and neurodegenerative processes; reduction in brain volume with progression and changes over the course of depressive episodes; and chronicity and treatment resistance [6]. Activated immune-inflammatory and O&NS pathways also explain the high association of chronic fatigue and somatization with depression [7] and suicide attempts, and the association of depression with neuroinflammatory and neurodegenerative disorders [8], general medical conditions especially immune- and O&NS-mediated disorders [8, 9], and other psychiatric disorders [10]. As such, immune-inflammatory and O&NS processes provide a conceptual framework in which to better incorporate the diverse range of data linked to depression.

The objectives of this article are: (1) to review the role that immune-inflammatory and O&NS pathways play in the etiology, course, and treatment of depression; and (2) to discuss the pharmacological treatment implications, including the use of combination treatments, whereby immune- and/or O&NS-targeted therapies may be used to enhance the efficacy of conventional antidepressants.

2 Immune-Inflammatory and O&NS Pathways in the Etiology and Course of Depression

There is now evidence that depression is accompanied by signs of activated immune-inflammatory and O&NS pathways, including signs of a low-grade inflammatory response and cell-mediated immunity (CMI) activation, increased O&NS damage to lipids, proteins, DNA, and mitochondria, and autoimmune responses directed against oxidatively or nitrosatively damaged epitopes. The available evidence is summarized in the following sections.

2.1 Immune Activation

Increased levels of immune activation occur in depression, evidenced by increased interferon-gamma (IFN-γ) and neopterin [11] from associated T-helper (Th)-1 activation [12]. Th-1 immune activation increases interleukin (IL)-2 as well as IFN-γ, with IL-2 inducing immune cell proliferation, differentiation, and activation [13]. As a consequence of such indicators of CMI, depression can be conceptualized as a CMI-mediated disorder, driven by increased O&NS [5]. Many CMI indicants occur in depression, including increased soluble IL-2R (sIL-2R), sCD8 [14, 15], neopterin [5], and IL-12 [16] as well as decreased tryptophan [3, 5]. While potentially confounded by variations in co-morbid somatization and changes in the biological underpinnings during recurrent depression, increased CMI is a robust finding in depression [17]. The mechanisms driving the influence of systemic immune activation on central processes is partly mediated by indoleamine 2,3-dioxygenase (IDO) activation by CMI products, especially IFN-γ, but also IL-1β, IL-6, IL-12, IL-18, and tumor necrosis factor-alpha (TNF-α) [18, 19]. In inducing IDO, IFN-γ and other cytokines that are elevated in depression, including IL-1 and TNF-α, may drive tryptophan to the production of kynurenine (kyn) and subsequent tryptophan catabolites (TRYCATs), such as the neuroregulatory kynurenic acid (KYNA) and quinolinic acid, and away from serotonin, *N*-acetylserotonin, and melatonin production. Decreased plasma tryptophan and increased kyn are robust findings in depression [20, 21], especially in association with somatization [22]. Peripheral kyn is readily transported over the blood-brain barrier (BBB) where it is taken up by CNS cells especially astrocytes and microglia, which subsequently produce a range of neuroregulatory TRYCATs, including quinolinic acid by microglia [23]. This allows factors acting on systemic immunity to impact on central processing.

Further CMI changes common in depression include increased Th-17 cells and IL-17 production. IL-6 levels are increased in depression [24], which in the presence of transforming growth factor-beta1 (TGF-β1) promotes Th-17 cell differentiation and proliferation. The CMI-driven increase in kyn and KYNA, via their activation of the aryl hydrocarbon receptor can also induce Th-17 differentiation [25]. Autoimmunity is highly associated with the relatively more prolonged and damaging effects of activated Th-17 cells, with autoimmunity in depression [26] thought to contribute to alterations in the biological underpinnings of recurrent depression, and thereby with the emergence of treatment resistance [3]. Together, these findings highlight the significant impacts of CMI products on the central changes driving depression, contributing to its progressive biological underpinnings over time.

2.2 Low-Grade Inflammation

Further indicants of immune inflammation are also evident in depression, both peripherally and centrally. In a post-mortem study of medication-free depressed patients, increased levels of the proinflammatory cytokines IL-2, IL-6, IL-12A, IL-18, IFN-γ, and TNF-α were found in the prefrontal cortex coupled to increased indicators of apoptotic processes [27, 28]. Peripheral proinflammatory cytokines were also raised, with increases in IL-1β and its counteracting IL-1 receptor antagonist (IL-1RA), generally indicative of monocyte/macrophage activation in depression [12]. Single nucleotide polymorphisms (SNPs) in immune-inflammatory genes, such as IL-1 [29], IL-6 [30], TNF-α [31], monocyte chemoattractant protein-1 [32], and T-cell regulatory function genes [33], modulate depression susceptibility and support the role of immune inflammation

in the etiology of depression. These genetic susceptibility SNPs code for a wide range of immune-inflammatory factors and further highlight the importance of CMI and inflammation in depression.

Proinflammatory cytokines in depression increase production of the positive acute-phase proteins such as haptoglobulin, ceruloplasmin, and C-reactive protein, whilst decreasing production of the negative acute-phase proteins such as albumin and transferrin [34, 35]. Changes in acute-phase proteins co-occur with other alterations to inflammatory responses, including changes in the complement system in depressed patients, where increases in C3C and/or C4 have been shown [35, 36].

Further possible consequences of the low-grade inflammatory status in depression are hypothalamic-pituitary-adrenal (HPA)-axis hyperactivity including glucocorticoid resistance and increased baseline activity of the HPA axis [37]. Indeed, proinflammatory cytokines, such as IL-1β, may activate the HPA-axis and downregulate glucocorticoid receptors, thus elucidating the positive association between indicants of inflammation and HPA-axis hyperactivity in depression [37]. In contrast to acute stress, chronic stress/cortisol exposure increase monoamine oxidase levels, in turn increasing the metabolism of monoamines including serotonin [38]. Prolonged exposure to IL-1, TNF-α, or IL-6 increases the uptake of serotonin by the serotonin transporter [39]. This decreases serotonin availability, thereby decreasing melatonin and *N*-acetylserotonin production. Low-grade inflammation also reduces the neurotrophin brain-derived neurotrophic factor (BDNF) and nerve growth factor at both mRNA and protein levels [40].

2.3 Activated O&NS Pathways

2.3.1 O&NS

Increased O&NS levels are evident in depressed individuals, contributing to increased levels of lipid peroxidation, protein carbonylation, DNA damage, telomere shortening, and related O&NS damage [5, 41]. Given that mitochondria are significant sources of reactive oxygen species (ROS), coupled to the brain's high metabolic rate, O&NS is particularly evident in the brain. Damage can be driven by relatively minor stressors such as examination stress, which increases the susceptibility to DNA damage and lipid peroxidation, and leads to reduced lymphocyte proliferation to mitogens and antigens [42, 43]. Malondialdehyde, a lipid peroxidation maker, is increased in acute and recurrent depressed patients versus controls [44]. Increased 8-hydroxy-deoxyguanosine is found in depression, an indicant of DNA damage [45], in turn inducing the DNA repair response. The DNA repair response increases poly(ADP-ribose) polymerase (PARP), which decreases nicotinamide (NAD+), leading to suboptimal mitochondria functioning [46], which further contributes to mitochondrial ROS production. 4-Hydroxynonenal (4-HNE) is another oxidant that is elevated in those with mood disorders [47] and is produced via lipid peroxidation, as a result of the effects of peroxides and ROS on omega-6 polyunsaturated fatty acids (PUFAs) [48]. In depression, nitrosative stress is driven by protein nitrosylation, leading to nitric oxide (NO) adducts such as NO-tyrosine and NO-tryptophan [49, 50]. The latter findings in depression indicate chronic hyperproduction of NO, damage to proteins by nitrosative stress, and the genesis of autoimmune responses against the newly formed (neo)epitopes.

2.3.2 Decreased Antioxidant Levels

Coupled to increased O&NS levels in depression is a lowering of endogenous antioxidants, including alpha-tocopherol, independent of dietary intake [51], glutathione (GSH) [52], co-enzyme Q10 (CoQ10) [53], glutathione peroxidase (GPx) [54], zinc [55], melatonin [56], selenium [57], and total antioxidant capacity [58]. Decreased antioxidant levels contribute to O&NS damage in depression, as well as modulating many wider cellular processes and system functions, including immune system regulation [59]. Coupled to decreased endogenous antioxidants is a decreased omega-3/6 PUFA ratio in depressed patients [60], contributing to the proinflammatory environment and oxidant levels. There is a bidirectional relationship in this regard, with lower dietary omega-3 PUFA intake a risk factor for depression, with oxidative stress and secondary lipid peroxidation further depleting stores [61].

2.3.3 Mitochondrial Pathways

Mitochondrial dysfunction is commonly found in depression [62] and correlates with depressive clinical presentations [63]. When mitochondrial deletions occur, they are often associated with severe depression [64]. In addition, in many other depression-associated conditions, particularly bipolar disorder, mitochondrial dysfunction is evident [3, 8, 65]. As well as being a major contributor to levels of cellular ROS, mitochondrial dysregulation decreases adenosine triphosphate, lowering cellular energy. The antioxidants compromised in depression, including alpha-tocopherol, GSH, and superoxide dismutase, are crucial to mitochondrial functioning, contributing to depressive symptoms and an association with neurodegenerative disorders [66]. Oxidant-driven DNA damage, leading to increased PARP and decreased NAD+ and sirtuins will also modulate mitochondrial functioning. Sirtuins are a group of seven NAD+ induced histone deacetylases, of

which sirtuin-1 and sirtuin-3 have been most extensively investigated, with sirtuin-1 alleles showing a genetic association with depression [67]. Some sirtuins show an association with increased longevity, in part via the inhibition of the pro-apoptotic factor, p53, but also by other means, including their regulation of mitochondria [68]. Sirtuin-1 is a significant regulator of peroxisome proliferator-activated receptor gamma coactivator-1alpha, the master mitochondrial co-ordinator. 4-HNE can change the configuration of sirtuin-3, decreasing mitochondria-located sirtuin-3 function [69]. With peroxides and ROS driving 4-HNE production via omega-6 products, the decreased omega-3/6 PUFA ratio in depression contributes to mitochondrial dysregulation. As well as having antioxidant effects, zinc also regulates PUFA metabolism, thereby also modulating mitochondrial function [70]. As such, O&NS drives mitochondrial dysregulation, which in the absence of adequate antioxidants further contributes to O&NS and wider cellular and system dysregulation.

2.3.4 Secondary Autoimmune Responses to O&NS Damage

O&NS-driven membrane damage exposes the immune system to fragments not recognized as self. Such neoepitope induction may generate IgM- or IgG-mediated autoimmune responses [49], including IgG autoantibodies against low-density lipoprotein, and this is believed to contribute to an association of depression with atherosclerosis [71]. O&NS may also drive autoimmune responses to serotonin [72], further dysregulating serotonergic activity. The induction of autoimmunity is important in changing the biological underpinnings of long-standing and recurrent depression driving neuroprogression (see Sect. 2.5).

2.4 Gut Permeability and Inflammatory Disorders

Increased gut permeability and associated bacterial translocation may contribute to immune responses in depression [73]. Gut permeability, in driving immune inflammation and O&NS, is proposed to contribute to cytokine-induced IDO and TRYCAT production, leading to increased kyn transfer over the BBB and thereby contributing to central changes driving depression [3]. Increased gut permeability may contribute to treatment resistance and chronicity in depression by contributing to immune activity and autoimmunity. There is considerable interest in the role of the microbiome, which has many immune modulatory effects. Some identified gut commensals produce molecular hydrogen, which has in vitro and in vivo antioxidant properties, that may have treatment implications in mood disorders [74].

Many other medical conditions, including inflammatory bowel diseases, psoriasis, and many cancers [75], as well as neurodegenerative and other psychiatric conditions [8] are associated with heightened levels of immune inflammation and O&NS. All of these medical conditions have high rates of concurrent depression, the biological underpinnings of which, in the case of central disorders, may be an integral part of degenerative processes [9].

2.5 Neuroprogression

As a consequence of the changes induced by O&NS and immune-inflammatory processes [76], recent conceptualizations of depression have emphasized its changing nature over time, a process termed neuroprogression [5, 77]. Neuroprogression incorporates many related changes occurring over the course of recurrent depressive episodes, including neuronal apoptosis, decreased neurogenesis, and increased autoimmune responses [78, 79]. Immune-inflammatory and O&NS facilitated changes in mitochondrial functioning and membrane damage-driven autoimmune responses, including to serotonin, are thought to drive depressive neuroprogression. These neuroprogressive processes lead to alterations in brain structure and cognition, and may be associated with reduced treatment response over time, although data are mixed [80]. The changes occurring over the course of neuroprogression result in the understanding of depression to be more intimately aligned to the etiology and course of many neurodegenerative disorders [8].

3 Immune Inflammation and O&NS: Antidepressant Interactions

Reconceptualizing the biological underpinnings of depression provides new insights informing novel treatment approaches.

3.1 Immune Inflammation, O&NS, and Treatment-Resistant Depression

Serum sIL-2R and IL-6 are generally increased in depression, especially when treatment resistance is evident [81]. Increased TNF-α, as well as an elevated CD4+/CD8+ T-cell ratio, is associated with treatment-resistant depression [21]. BDNF genotypes also modulate the susceptibility to treatment resistance [82], suggesting that immune inflammation-induced decreases in BDNF contribute to treatment resistance. Decreased serum coQ10 and zinc [51, 83, 84] are associated with treatment resistance. The potent redox modulator melatonin regulates CoQ10 levels [85], suggesting that decreased serotonin availability for melatonin production, including in astrocytes, may also modulate treatment resistance [86].

Reciprocal relationships between the immune-inflammatory and O&NS pathways may confer risk of treatment resistance, given that peripheral TNF-α decreases pineal melatonin production [87] and melatonin can increase CoQ10 as well as afford wider mitochondria protection [85].

3.2 Immune Inflammation, O&NS, and Depression Chronicity

Treatment resistance is intimately associated with chronicity and recurrent episodes. Increased gut permeability and autoimmune responses directed against multiple O&NS-modified epitopes contribute to immune activation and thereby modulate depression chronicity. Some chronicity effects are driven via aging-associated processes, including decreases in longevity-associated sirtuins and also in telomere length [88]. Such impacts on aging processes contribute to the association of depression with neurodegenerative disorders. Given the induction of sirtuin-1 by melatonin and the wider antioxidant and anti-inflammatory effects of melatonin coupled to increasing mitochondrial functioning and oxidative phosphorylation [89], it is of note that the melatonin receptor (MT2r) is a susceptibility gene for chronicity in depression [90]. Melatonin and the activation of its receptors are dependent on serotonin availability, including in astrocytes [86], suggesting that local central melatonin and its receptor activation may be decreased in depression.

3.3 Immune-Inflammatory Pathways and Sensitization

CMI biomarkers such as neopterin, and cytokines such as TNF-α, correlate positively with the number of depressive episodes, suggesting that immune-inflammatory pathways contribute to sensitization in depression [91]. This is also supported by the increased serum sIL-1RA and IL-6 evident in women, postpartum, who had previously experienced a depressive episode [92]. A consequence of increased levels of immune-inflammatory processes and O&NS is neuronal sensitization to other stimuli; such as IFN-γ-mediated sensitization to the effects of the Alzheimer disease-associated amyloid-β peptide [93]. Sensitization is another factor contributing to neuroprogression, aging, and neurodegenerative disorders. As to whether sensitization differentially occurs in some neurons, making it a process akin to competitive weakening or elimination, requires investigation.

4 Immune-Targeted Therapies to Enhance Antidepressant Efficacy

Attempts to accelerate and potentiate the effects of antidepressants, including the adjunctive use of pindolol (a serotonin 5-HT_{1A} antagonist) with SSRIs, have demonstrated some success [94]. However, a conceptualization of depression as driven by O&NS and immune-inflammatory processes supports the targeting of these factors in efforts to improve depression management, including risk of recurrence, chronicity, treatment resistance, and neuroprogression. In the treatment of immune-inflammatory processes by etanercept in psoriasis [95] and Crohn disease [96], there is a concurrent significant decrease in depression levels, strengthening the role of immune inflammation in depression. The comparative efficacy of agomelatine, a melatonin MT1&2r agonist and a serotonin 2Cr antagonist, versus a range of SSRIs and serotonin and norepineprhine reuptake inhibitors [97] is likely to reflect the enhanced antioxidant, anti-inflammatory, and immune regulatory benefits of melatonin.

4.1 Useful Combination Treatments

A number of immune and O&NS regulatory treatments have been tried adjunctively to conventional antidepressants, including acetylsalicylic acid [98], which decreases multiple oxidant markers, and, in an open-label trial, decreased the time to effective antidepressant response [99]. *N*-acetylcysteine (NAC), a precursor of GSH [100], improves the efficacy of antidepressants in depressed bipolar disorder participants [101], as well as anhedonia in rodents with chronic unpredictable mild stress (CUMS), suggesting preventative efficacy [102]. Ebselen, a GPx mimetic, likewise prevents CUMS-induced depression, whilst attenuating CUMS-induced IL-1 and cyclooxygenase (COX)2 as well as preventing cortex apoptosis [103]. The effects of Ebselen include increasing dopamine and norepinephrine levels [104].

Generally, fruit and vegetable intake is lower in people with depression [105, 106], increasing depression risk, while a range of dietary anti-oxidants show antidepressant efficacy in animal models, including curcumin, tumeric, resveratrol, quercetin, and green tea's epigallocatechin gallate, reviewed in [3]. Augmentation of SSRIs with omega-3 fatty acids enhances prevention of depressive-like symptoms in rodents [107], whilst a meta-analysis of double-blind, placebo-controlled trials of the omega-3 eicosapentaenoic acid (EPA) found EPA to have antidepressant efficacy per se [108], partly via proinflammatory cytokine inhibition [40]. Zinc also heightens antidepressant efficacy, although only significantly in treatment-resistant depression [109].

Preliminary data demonstrate minocycline, an anti-inflammatory tetracycline derivative shown to inhibit microglial activation, can also improve antidepressant efficacy [110], including sub-effective doses of desipramine [111]. Although the clinical utility of minocycline needs

balancing against its adverse effects, it does support the role of O&NS and immune inflammation in the course and treatment of depression. Likewise, some evidence supports the anti-inflammatory COX2 inhibitors as antidepressants [112], although their long-term use may theoretically exacerbate depression, including by exacerbating Th-1-driven responses, lipid peroxidation, neuroinflammation, bacterial gut translocation, and neuroprogression, as well as decreasing key antioxidants [113]. Pioglitazone, an insulin-sensitizing agent with anti-inflammatory properties that include the inhibition of the microglial inflammatory response [114], has efficacy in depression, a therapeutic effect not shared by metformin, a comparable insulin-sensitizing agent without clear effects on immunity [115]. Given the role of oxidants and controlled inflammatory processes in normal physiological functioning and given the role of autoimmune processes in depression, the dampening of O&NS and immune-inflammatory processes in depression may not necessarily find a straightforward solution in the administration of simple anti-inflammatories.

4.2 Multi-targeting

Given the limitations imposed by the inhibition of single immune-inflammatory or O&NS factors on normal physiological functioning, it is likely that greater benefit might be attained from a multi-targeted dampening of the pathways and processes outlined. Such multi-targeting is attained to some degree by factors such as NAC, acetylsalicylic acid, zinc, melatonin, and omega-3. All of these substances target multiple pathways, including O&NS, immune-inflammatory processes, and mitochondrial functioning, and are potentially efficacious in augmenting prescribed antidepressants. Most conventional antidepressants have antioxidant, anti-inflammatory, and negative immune regulatory effects [1, 55, 116]. It will be interesting to determine if specific adjunctive treatments, such as melatonin or NAC, have any particular useful interactions with specific antidepressants, as suggested for valproate with melatonin and vitamin D in multiple sclerosis treatment [117].

4.3 Other Possible Treatment Targets

Targeting other pathways may also prove useful, including IL-1 [91, 93]. Given that both IL-1 and IL-18 are increased in depression and modulate significant O&NS and immune-inflammatory pathways, their coordinated induction by the inflammasome requires investigation in depression [118]. With cellular plasticity-associated O&NS and ceramide driving inflammasome induction [119] and IL-1β and IL-18 (formerly called the IFN-γ inducing factor) being important inducers of IDO and the TRYCATs, the exploration of the inflammasome may be an important bridge between O&NS and immune inflammation, and the investigation of its regulation in depression will be important to initiate. Increased IL-6 trans-signaling is another treatment target, given its induction of IDO [18] and its intimate association with autoimmune and epigenetic processes, including its inhibition by methyl-CpG-binding protein 2 (MeCP2) [120]. Melatonin induces a trend increase in MeCP2 [121], which epigenetically silences IL-6 transcription [122], suggesting that, perhaps for subsets of patients with decreased local and/or pineal melatonin and raised IL-6, the regulation by melatonin of MeCP2 may be of particular benefit, including via the inhibition of IL-6-induced IDO and TRYCATs. IL-6 interactions with MeCP2 and local melatonin at the glia-neuronal interface at sites of local inflammation [120] require testing. Targeting IDO is a feasible target, given the development of IDO inhibitors. However, activation of IDO and the TRYCAT pathway serves as a negative feedback CIRS (a compensatory anti-inflammatory reflex system) attenuating the primary immune response [5, 21]. Thus, targeting IDO may theoretically dysregulate this beneficial CIRS response [21], while the wide immune dysregulation, including autoimmune responses, that occur in depression would not make this a practicable treatment choice. Targeting central TDO may prove useful, given the 20-fold increase in central serotonin, increased neurogenesis, and decreased anxiety in TDO knockout rodents [123], with central TDO suggested to significantly modulate human depression [21].

With increased gut permeability contributing to the immune inflammation-driven TRYCAT production that modulates central changes in depression, the targeting of gut permeability, including with dietary modification, zinc, NAC, and glutamine [124] is another feasible treatment target readily screened at assessment. The microbiome is also emerging as an intriguing treatment opportunity [125]. Targeting secondary autoimmunity to neoepitopes may be another immune-linked screening target, with particular relevance to neuroprogression and chronicity prevention.

5 Conclusions

A conceptualization of depression that emphasizes the role of O&NS and immune-inflammatory processes in driving changes in neuroregulatory TRYCATs, neuroprogression, and secondary autoimmune responses, in turn damaging serotonin, provides a more encompassing perspective on the nature of depression. This also provides treatment targets, whilst explaining the antidepressant efficacy of nutritional factors. Future benefits may accrue from a better

understanding of the role of systemic immune-inflammatory pathways, including as activated by gut permeability, the microbiome, and mechanisms underlying the central glia-neuronal interface at sites of inflammation. This will have wider benefits for depression-associated conditions, especially the neuroinflammatory and neurodegenerative disorders.

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