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Review

Novel therapeutic targets in depression: Minocycline as a candidate treatment

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HIGHLIGHTS

- Regional cell loss and brain atrophy in mood disorders may be a consequence of impaired neuroplasticity.
- Neuroplasticity is regulated by neurotrophic, inflammatory, oxidative, glutamatergic pathways.
- Abnormalities in these systems are implicated in the pathophysiology of mood disorders.
- Minocycline exerts effects on neuroplasticity and targets these interacting systems.
- Evidence indicates that minocycline may be a viable treatment option for mood disorders.

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ABSTRACT

Mood disorders are marked by high rates of non-recovery, recurrence, and chronicity, which are insufficiently addressed by current therapies. Several patho-etiological models have been proposed that are not mutually exclusive and include but are not limited to the monoamine, inflammatory, neurotrophic, gliotrophic, excitatory, and oxidative stress systems. A derivative of these observations is that treatment(s) which target one or more of these mechanistic steps may be capable of mitigating, or preventing, disparate psychopathological features. Minocycline is an agent with pleiotropic properties that targets multiple proteins and cellular processes implicated in the patho-etiology of mood disorders. Moreover, preclinical and preliminary clinical evidence suggests that minocycline possesses antidepressant properties. Herein, we provide the rationale for conducting a randomized, controlled trial to test the antidepressant properties of minocycline.

Contents

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1. Introduction

Mood disorders, notably major depressive disorder (MDD) and bipolar disorder (BD), are leading causes of disability and premature mortality in developed and developing nations [1,2]. Notwithstanding the availability of over a dozen conventional antidepressants, manual-based psychotherapies and neuromodulatory approaches for the treatment of major depressive episodes, most individuals with mood disorders exhibit high rates of non-recovery, recurrence, and illness chronicity [3–8]. Moreover, no available treatments have demonstrated efficacy in mitigating cognitive deficits, a common feature of mood disorders [9,10]. Most treatments for mood disorders (e.g. conventional antidepressants, lithium), with the exception of some neuromodulatory approaches (e.g. deep brain stimulation) [11], were discovered by serendipity, and no drug therapy has been developed based on *a priori* disease model [12]. While substantial progress has been made in improving the antidepressant safety and tolerability profile, the canonical target of all available antidepressants remains the monoaminergic system. Although the monoamine hypothesis is supported by depletion, genetic polymorphism, and radioligand studies, there is no consistent evidence that disturbance in monoamines is the principal pathological process in mood disorders [12–15]. Less than 50% of individuals achieve remission after an index antidepressant treatment and approximately one third of patients fail to achieve remission following four systematically applied treatments [16]. Taken together, the available evidence advocates a need for novel modeling of mood disorder pathophysiology and proposing new viable targets for the development of disease-modifying treatments.

Accumulated evidence indicates that mood disorders are marked by disturbances in neural circuitry, neural and synaptic plasticity, and dendritic pruning [17–22]. These processes are influenced by a wide range of molecules and systems, including neurotransmitters, neurotrophic factors, hormones, immune mediators, neuropeptides and oxidative species [23,24]. Abnormalities in these systems have been implicated in the pathophysiology of mood disorders, and provide the basis for hypothesizing that targeting these systems may offer neurotherapeutic effects [17,25].

Herein, we propose a multi-factorial model for mood disorders based on evidence of dysfunctional interacting systems that are critical to the regulation of neuronal and glial plasticity. In keeping with this model, we present minocycline, a tetracycline antibiotic with anti-inflammatory, anti-oxidant, anti-glutamatergic and neuroprotective actions, as a prototype of a multi-target antidepressant.

2. Impairments in plasticity as core pathophysiological mechanisms in mood disorders

The term 'neuroplasticity' was introduced by Konorski in reference to the notion that neuronal interconnections adapt in response to environmental interactions [26,27]. This concept was modified to describe the phenomenon of the brain's ability to change in structure and function in response to environmental demands [28,29]. Neuroplasticity occurs at several levels, including intracellular processes (e.g. gene transcription, cell metabolism), intercellular interactions (e.g. synaptic plasticity, dendritic arborization, axonal growth, connectivity), neural circuits, and brain structures. One of the key processes of neuroplasticity is synaptic pruning, the constant remodeling of connectivity through the activity of neurons and synapses. Active synaptic connections will be maintained and reinforced, while others will be inhibited or eliminated. Optimal balance between reinforcement and removal of synaptic connections is critical for neuroplasticity. In this regard, processes regulating cell death and survival are key determinants of brain adaptation [30,31].

Mood disorders are marked by abnormalities in brain structure and function, as well as impairments in cognition (see for review [32,33]). Given the complexity and heterogeneity of these conditions, intricate interacting networks that incorporate diverse cellular/molecular systems and neural circuits are likely involved [24,34–36]. Postmortem studies document decreased neuronal and glial density, neuronal size, synapses, and synaptic proteins in frontal and subcortical brain regions in individuals with MDD and BD [37–40]. These findings corroborate the volume loss in both gray and white matter often observed in these brain regions [24,36].

An important corollary of the neuroplasticity model of mood disorders is the co-occurrence of cognitive deficits. Since cognitive processes and affect regulation are subserved by overlapping neurobiological substrates, regions such as the prefrontal cortex contribute both to executive function/cognitive flexibility and mood regulation [41], while the anterior cingulate and the hippocampus play a role in emotional salience of experience as well as memory formation [42,43]. It is therefore unsuprising that cognitive deficits are a common feature in mood disorders [9,10].

Dysregulation and acceleration of apoptotic pathways have been hypothesized to contribute to the brain structural changes evident in mood disorders [44]. Disturbances in various factors [e.g. intracellular calcium levels, circulation of hormones, toxins, reactive oxygen species (ROS), neurotrophic factors and cytokines], often evident in these individuals, can contribute to accelerated

apoptosis; left unresolved may result in tissue atrophy [45]. Increased pro-apoptotic factors in serum [46] and in *postmortem* human prefrontal cortex mRNA (e.g. caspase-3, Bcl-2-associated X protein, Bcl-2-associated death promoter) [47] along with reduced levels of anti-apoptotic factors [e.g. B-cell lymphoma 2 (Bcl-2) mRNA, Heat Shock Protein 70 (HSP70)] [47,48], have been reported in some individuals with BD. Given the role of Bcl-2 in inhibition and activation of caspase and neurotrophic pathways, respectively, decrements in this protein may increase cell death and reduce neurite sprouting/outgrowth as well as axonal regeneration [35,49]. Increased expression of pro-apoptotic genes such as perforin, TRAIL and caspase-2 has also been reported [50]. Disparate psychotropic agents such as lithium have been shown to reduce apoptotic activity, possibly via caspase-3 suppression, increased Bcl-2 expression [51], and glycogen synthase kinase 3 (GSK-3) beta inhibition (a key regulator of apoptosis and cellular plasticity/resilience) [52,53] (reviewed in [35]). Notwithstanding the conceptual, preclinical, postmortem, and molecular/cellular evidence indicating that apoptosis is a salient aspect of the patho-etiology of mood disorders, these changes are not universal across all individuals nor replicated in all studies.

Hence, it could be hypothesized that the regional cell loss and brain atrophy in mood disorders are a consequence of impairments in neuroplasticity, that are mediated by interacting neurotrophic, oxidative, inflammatory, and glutamatergic pathways. Collectively, abnormalities in this network along with genetic, developmental, and environmental influences compromise the ability of the brain to respond and adapt to different stimuli, ultimately manifesting as a mood disorder [35,54].

3. Mediators of neuroplasticity in mood disorders

3.1. Neurotrophic factors

Several neurotrophic factors [e.g., brain derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF), glial cell line-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF), nerve growth factor (NGF)] are implicated in the growth, survival, differentiation, and maturation of neuronal and glial populations [55]. Reduced concentration of peripheral circulating BDNF is a well replicated finding in MDD and BD [56,57], which increases following treatment with several conventional treatments [58–62]. The neurotrophic and neuroprotective effects of BDNF are primarily mediated through its activity on neuronal tropomyosin related kinase B (TrkB) receptors; which activate intracellular cascades [e.g. phosphoinositide 3-kinase (PI3K)/Akt pathway] involved in neuronal growth and survival [35,63]. BDNF can also act via its low-affinity cognate p75 neurotrophin receptor (p75NTR) to prune axons and regulate functional connectivity [64]. Preclinical experiments suggest that peripheral infusion of BDNF or direct infusion of BDNF to the dentate gyrus can produce antidepressant-like effects [65,66]. Antidepressants from the tricyclic and selective serotonin reuptake inhibitors (SSRIs) class have been shown to increase TrkB activity in a BDNF dependent manner, which is associated with behavioral effects in animal models [67].

Abnormalities in other neurotrophic factors such as IGF-1 [68], GDNF [69,70], VEGF [71,72], and NGF [73,74] have also been reported in MDD and BD, and are likewise influenced by psychotropic medications [75,76]. Not all studies however, have been able to replicate these findings and these changes likely affect only a subset of individuals. Taken together, these studies suggest that neurotrophic factors constitute a class of salient contributors to mood disorder pathophysiology, and are compelling putative targets for therapeutic intervention.

3.2. Oxidative stress

Under physiological conditions, cellular respiration results in the production of free radicals such as ROS and reactive nitrogen species (RNS), which are counterbalanced by antioxidant defense pathways [77]. Compromised antioxidant capacity results in oxidative stress, which can lead to accelerated apoptosis or necrosis [78]. Oxidative stress has been hypothesized to play a role in the pathophysiological processes of BD and MDD. In both disorders, increased levels of ROS and RNS including peroxide [79] and nitric oxide (NO) have been reported [80–82].

Studies in individuals with mood disorders have also identified reduced or overactive antioxidant defenses. For example, alterations in antioxidant enzymes including reduced or increased activities of superoxide dismutase (SOD) [83–87], catalase [83,87,88], and glutathione peroxidase [83,89,90] have been reported in MDD and BD. Whereas increased antioxidant enzyme activity may represent a compensatory mechanism to attenuate increased ROS and RNS activity; a reduction in antioxidant defenses may reflect a decline of compensatory mechanisms with illness progression [77].

Markers of lipid peroxidation are likewise elevated in mood disorders. Increased levels of malondialdehyde (MDA), a byproduct of polyunsaturated fatty acid peroxidation and arachadonic acid, have been detected in MDD [44,87,91], and thiobarbituric acid reactive substances (TBARS) have been shown to be increased in all phases of BD [83,88]. Furthermore, *postmortem* studies have identified a down-regulation of several mitochondrial genes (e.g. the ATP synthase, cytochrome-*c* oxidase) in the hippocampus [92] and dorsolateral prefrontal cortex of individuals with BD [93], which could result in mitochondrial dysfunction, shifting metabolism toward anaerobic energy production, and greater production of ROS [94]. For review of oxidative stress pathways in mood disorders see suggested reference [77].

In keeping with this view, substances with antioxidant properties have been evaluated as potential treatments for mood disorders. N-acetylcysteine (NAC) is a glutathione precursor that directly scavenges oxidants such as hydroxyl radicals and hypochlorous acid [95]. In a 24-week, randomized, double-blind, placebo-controlled trial, adjunctive NAC (1 g bid) significantly mitigated depressive symptoms in individuals with BD in the maintenance phase ($n = 75$), with results becoming significant after 20 weeks of treatment [96]. Significant improvement in depressive symptom severity was also reported in an 8-week, open-label trial with adjunctive NAC (1 g bid) in individuals with BD in the maintenance phase ($N = 149$) [97]. N-acetylcysteine, via its antioxidant properties, may be a viable treatment for bipolar depression. To our knowledge, no published studies have evaluated NAC in MDD.

3.3. Inflammatory mediators

Cytokines are a heterogeneous family of regulatory proteins produced by immune cells, which influence the survival, proliferation, differentiation, and effector function of target tissues and cells [98]. Pro-inflammatory cytokine-induced 'sickness behavior' in animal models provided the first evidence for cytokine involvement in mood disorders. This syndrome is characterized by decreased sucrose consumption, motivation, cognitive impairment, and neurovegetative symptoms that collectively resemble the phenotypic presentation of depressive symptoms in humans [99]. Pro-inflammatory cytokine activation in healthy individuals is likewise associated with disturbances in affective and cognitive function [100,101]. In healthy volunteers, increased circulating interleukin-6 (IL-6) concentrations following *Salmonella typhi* vaccine are associated with mood deterioration, which correlates with enhanced activity in the subgenual anterior cingulate cortex

during processing of emotional facial expressions [101]. The subgenual cingulate cortex is implicated in MDD pathophysiology and is a target of deep brain stimulation for treatment resistant MDD [11]. Moreover, Capuron et al. reported that 45% of patients treated with IFN-α develop a major depressive episode during a 12-week follow-up period [102]. The association between inflammation and depressive symptoms in both human and animal populations provides the basis for hypothesizing that inflammatory activity may play a role in the pathophysiology of mood disorders.

Abnormal cytokine concentrations are now well documented in MDD and BD, with elevations in circulating TNF-α, IL-6 and IL-1β being the most replicated findings [103–107]. Preliminary evidence indicates that circulating IL-6 concentrations may be associated with depression severity [108]. Preliminary studies also document elevated IL-1β and reduced concentrations of IL-6 and its soluble receptor in the cerebrospinal fluid (CSF) of individuals with MDD and BD [109,110]. Aberrant mRNA expression [111,112] and genetic polymorphisms of these inflammatory proteins are also evident [113,114]. C-reactive protein (CRP), a pro-inflammatory acute phase reactant activated by IL-6, is often increased in BD [115–118] and MDD [105]. Elevated levels of IL-2 and the soluble IL-2 receptor (sIL-2R), which play a role in T cell expansion and proliferation, are also reported [103,104,107,119].

It has been hypothesized that inflammation in mood disorders may arise from an imbalance between pro- and anti-inflammatory cytokines and their associated T cell subsets [i.e. pro-inflammatory T helper 1 (Th1) and Th17 versus anti-inflammatory Th2 and regulatory T cells (Treg)] [120]. Increases in pro- to anti-inflammatory cytokine ratios have been reported in mood disorders [121–123]. Abnormalities in the function of T cell subsets have largely been imputed from circulating concentrations of the cytokine signals between these cells. Evidence points toward increased Th1 (e.g. TNF-α, IL-2) activity, while both increased and decreased Th2 (e.g. IL-4, IL-10) or Treg (e.g. transforming growth factor-beta [TGF-β], IL-10) activity is reported in both conditions [103,124–127]. The discrepant findings in Th2 and Treg activity may reflect differences in cytokine concentrations between early and late stages of the illness. Preliminary evidence in BD indicates that pro-inflammatory cytokine levels (i.e. IL-6 and TNF-α) are increased during early and late stages of the illness while the anti-inflammatory cytokine IL-10 is increased only during early but not late stages, suggesting reduced anti-inflammatory capacity with illness progression [128]. Preliminary evidence also suggests that the proportion of Treg is decreased in individuals with MDD [122] and increased in BD [104].

A prominent mechanism by which cytokines influence neurotransmitter metabolism is via the indoleamine 2,3-dioxygenase (IDO), an enzyme induced by pro-inflammatory cytokines (e.g. IFN-γ, TNF-α) and ROS. This enzyme catabolizes the serotonin precursor tryptophan to kynurenine (KYN) [99]. Quinolinic acid (QUIN), a primarily microglia-derived KYN metabolite, acts as an agonist of the glutamate N-methyl-D-aspartate (NMDA) receptor, and may contribute to increased extracellular glutamate concentrations in this patient population [129,130]. These findings are suggestive of a plausible link between inflammation and a downstream neurodegenerative process. Another metabolite of KYN, kynurenic acid (KYNA), is produced primarily by astrocytes and can inhibit excitatory neurotransmission in the hippocampus and frontal cortex, affecting memory and cognitive flexibility [131,132]. Therefore, aberrant brain KYN metabolism may be involved in the cognitive symptoms of mood disorders (see Fig. 1).

Decreased peripheral circulating tryptophan and increased KYN, as well as a polymorphism (rs9657182) of the IDO gene, have been associated with IFN-α-induced depression [133,134]. Preliminary evidence suggests that microglial QUIN is elevated in subregions of the anterior cingulate gyrus of suicide victims with MDD, but not BD [130], while plasma levels of KYNA may be reduced in MDD [135]. The BD profile may be similar to that of schizophrenia, with increased KYN and KYNA levels being observed in CSF and *post-mortem* brain, respectively [136,137]. Results however, have not always been unanimous between studies [138]. See Steiner et al. for review [139].

Conventional pharmacological treatments for mood disorders including antidepressants, mood stabilizers and antipsychotics act in varying capacities to down-regulate the production of pro-inflammatory cytokine mRNA and proteins [111,140–142]. Moreover, double-blind, randomized, placebo-controlled studies have documented significant antidepressant effects following adjunctive treatment with the anti-inflammatory agent, celecoxib, in individuals with BD and MDD [143,144]. Although favorable results have been reported with non-steroidal anti-inflammatory drugs (NSAIDs) in mitigating depressive symptoms across disparate populations, not all studies have been positive and the effect sizes are of questionable clinical significance [145]. In addition, TNF antagonists may have antidepressant effects as is suggested by improvements in secondary measures of depression and quality of life in individuals with inflammatory disorders [146–151]. No existing study has primarily evaluated the antidepressant effects of TNF antagonists in individuals with mood disorders.

3.4. Glutamate

Glutamate is a major excitatory neurotransmitter in the CNS, and a major player in learning and memory processes [54]. Plasticity occurring at glutamate synapses (e.g. long-term potentiation and depression) enables encoding of new information [54]. The glutamatergic system is an implicated mediator of mood disorder pathology, a possible final common pathway for antidepressant medications, and a novel therapeutic target [54]. Abnormalities in glutamate levels have been demonstrated in plasma, CSF, and brain tissues of individuals with mood disorders [152,153] (reviewed in [54]). Magnetic resonance spectroscopy (MRS) studies have documented that levels of glutamate-related metabolites are reduced in MDD and elevated in BD [154] (for review see [154]). In MDD these abnormalities are most consistently evident in the frontal cortex and cingulate regions, and in various brain regions in BD [54,155,156]. State dependent abnormalities in glutamine/glutamate ratio have also been demonstrated, with reductions and elevations reported during depressive and manic states, respectively [154]. Improvement in depressive symptom severity has also been associated with decreases in cerebral glutamate/glutamine levels [157]. Since, the glucose metabolic signal is dominated by glutamatergic transmission, amplified glutamate effects could be inferred from the hypermetabolism, notably in limbic-cortical-striatal-pallidal-thalamic circuits, often observed with functional neuroimaging in this population [40]. Antidepressants have also been shown to modulate glutamate receptor function, and reduce the presynaptic release of glutamate (see Sanacora et al. [54] for review).

The glutamatergic disturbances in some individuals with mood disorders may be the consequence of abnormal levels of KYN metabolites, QUIN and KYNA, endogenous modulators of the NMDA receptor (see Fig. 1 and Section 3.3); as opposed to a direct dysfunction in glial glutamate transporters or membrane receptors [139]. A disturbance in the QUIN/KYNA ratio in favor of QUIN may contribute to excitotoxicity [40,41,158]. Furthermore, prolonged synaptic activation by glutamate may ensue in the context of astrocyte loss, impairing glutamate reuptake from the extracellular space by transporters located primarily on these cells [159,160].

Glutamate is a promising target for novel drug development [161]. In particular, the noncompetitive antagonist of the NMDA glutamate receptor (NMDA-R), ketamine, has been evaluated clinically for its antidepressant effects. A single dose of

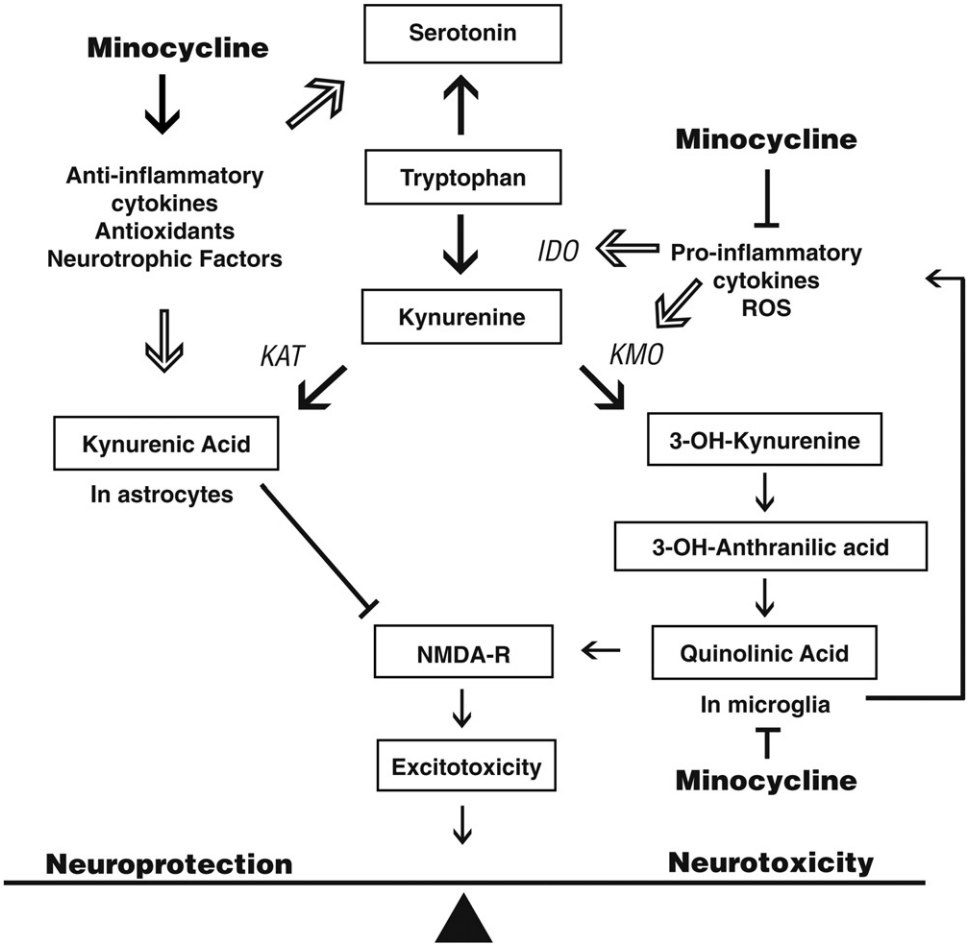

Fig. 1. The Kynurenine pathway as a possible mechanism linking several systems implicated in the pathophysiology of mood disorders. The indoleamine 2,3-dioxygenase (IDO) enzyme, induced by pro-inflammatory cytokines and ROS catabolizes the serotonin precursor tryptophan to kynurenine. Quinolinic acid, a primarily microglia-derived kynurenine metabolite, acts as an agonist of the glutamate NMDA-R, and may contribute to increased extracellular glutamate concentrations. On the other hand, kynurenic acid, a primarily astrocyte-derived kynurenine metabolite, acts as an antagonist of the NMDA-R. It is hypothesized that minocycline via its effects on other mediators of the kynurenine pathway (e.g. inflammatory cytokines, neurotrophic factors, etc.) can ultimately influence the equilibrium between neuroprotection and neurotoxicity in the brain. Black arrows indicate upregulation, black lines with bar indicate inhibition/downregulation, green arrows indicate activation from modulatory pathways. ROS: reactive oxygen species, IDO: indoleamine 2,3-dioxygenase, KAT: kynurenine aminotransferase, KMO: kynurenine monoxygenase. N-methyl-D-aspartate receptor (NMDA-R). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)
This figure has been adapted with permission from Steiner et al. [139].

adjunctive intravenous ketamine has been shown to exert a rapid antidepressant response in three randomized, double-blind, placebo-controlled, crossover trials in individuals with bipolar and unipolar depression (including treatment-resistant) [162–164]. Ketamine as compared to placebo significantly mitigated depressive symptoms in individuals with BD and MDD in less than 2 min, and remained significant up to days 3 and 7, respectively [162–164]. Other glutamate modulating agents such as riluzole, when used as monotherapy or augmentation to conventional therapy, have also been shown to possess antidepressant effects in patients with treatment resistant depression or bipolar depression [165–167].

Taken together, a substantial body of evidence supports the involvement of interacting apoptotic, neurotrophic, inflammatory, oxidative, and glutamatergic pathways, in mood disorders (see Fig. 2). Nevertheless, the directionality of these abnormalities is not always concordant between studies, and non-significant findings are reported. Considering that not all individuals will manifest abnormalities in these pathways, different combination of factors will likely differentiate distinct disorder subtypes. In keeping with this multi-factorial model, we present evidence that minocycline based on its ability to target the manifold neurobiological perturbations implicated in the pathophysiology of mood disorders may be a potential antidepressant.

4. Minocycline as a regulator of neuroplasticity

Minocycline is a broad-spectrum tetracycline antibiotic, with a long half-life of 12–18 h [168]. It is the most lipid-soluble of the tetracycline antibiotics and as such it has the greatest penetration into the CSF and central nervous system (CNS) [169]. It has low propensity to produce antibiotic resistance and is commonly used to treat acne and other infections of the skin and respiratory tract [169]. In addition, the anti-inflammatory properties of minocycline have led to its recognition as a disease-modifying anti-rheumatic drug by the American College of Rheumatology, which recommends its use for mild rheumatoid arthritis [170]. In preclinical and early clinical trials, minocycline has demonstrated neuroprotective properties in neurological disorders including ischemia, multiple sclerosis, spinal cord injury, Huntington's disease, Parkinson's disease, and Alzheimer's disease [171].

In addition to its neuroprotective properties, minocycline may directly promote neurogenesis. It was shown to increase the number of integrated newborn hippocampal neurons by promoting the survival of newly divided cells [172], and to increase the survival of CA1 pyramidal neurons from 10.5% to 77% in animal models of ischemia [173]. This agent has also been shown to restore a population of neural stem/progenitor cells in a murine model of Japanese

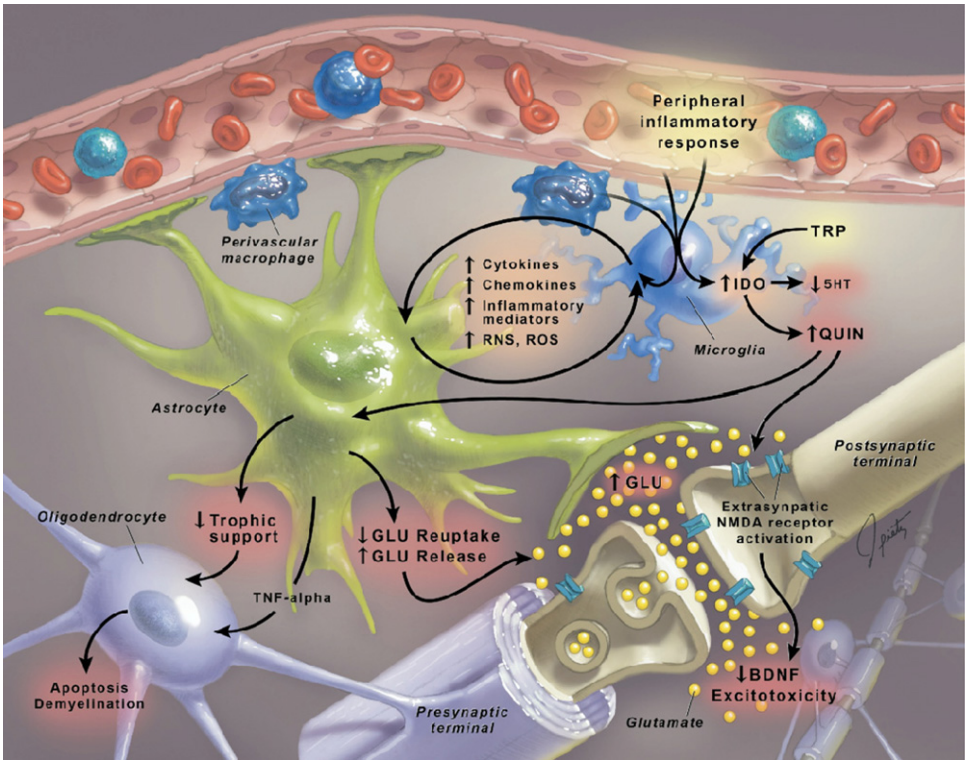

Fig. 2. Interacting systems implicated in the pathophysiology of mood disorders. Effects of the CNS inflammatory cascade on neural plasticity. Microglia are primary recipients of peripheral inflammatory signals that reach the brain. Activated microglia, in turn, initiate an inflammatory cascade whereby release of relevant cytokines, chemokines, inflammatory mediators, and reactive nitrogen and oxygen species (RNS and ROS, respectively) induces mutual activation of astroglia, thereby amplifying inflammatory signals within the CNS. Cytokines, including IL-1, IL-6, and TNF-alpha, as well as IFN-alpha and IFN-gamma (from T cells), induce the enzyme, IDO, which breaks down TRP, the primary precursor of 5-HT, into QUIN, a potent NMDA agonist and stimulator of GLU release. Multiple astrocytic functions are compromised due to excessive exposure to cytokines, QUIN, and RNS/ROS, ultimately leading to downregulation of glutamate transporters, impaired glutamate reuptake, and increased glutamate release, as well as decreased production of neurotrophic factors. Of note, oligodendroglia are especially sensitive to the CNS inflammatory cascade and suffer damage due to overexposure to cytokines such as TNF-alpha, which has a direct toxic effect on these cells, potentially contributing to apoptosis and demyelination. The confluence of excessive astrocytic glutamate release, its inadequate reuptake by astrocytes and oligodendroglia, activation of NMDA receptors by QUIN, increased glutamate binding and activation of extrasynaptic NMDA receptors (accessible to glutamate released from glial elements and associated with inhibition of BDNF expression), decline in neurotrophic support, and oxidative stress ultimately disrupt neural plasticity through excitotoxicity and apoptosis. 5-HT, serotonin; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; GLU, glutamate; IDO, indoleamine 2,3 dioxygenase; IFN, interferon; IL, interleukin; NMDA, *N*-methyl-D-aspartate; QUIN, quinolinic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; TNF, tumor necrosis factor; TRP, tryptophan.
Figure is adapted with permission from Miller et al. [272].

encephalitis [174], and to prevent nigral cell loss after a toxic insult in an animal model of Parkinson's disease [175]. Other animal studies have reported that minocycline reduces tissue damage and cavitation after spinal cord injury [176], and restores impaired hippocampal neurogenesis after lipopolysaccharide (LPS)-induced inflammation [177]. Oligodendrocyte preservation and decreased myelin impairment after excitotoxic damage has also been reported with this agent [178,179].

Evidence from multiple models suggests that minocycline, while reducing inflammatory injury, does not reduce BDNF concentrations [180–182], suggesting a favorable balance of neurotrophic support. In one study, the combination of minocycline and prednisone prevented the reduction of BDNF and NGF in experimental autoimmune encephalomyelitis mice [180]. In vitro, minocyline potentiated the effects of NGF-induced neurite outgrowth [183] and reversed oxidative stress-induced impairment in the neuroprotective effects of IGF-1 [184].

Brain imaging studies have also demonstrated in vivo neuroprotective effects of minocycline. A study using positron emission tomography (PET) in conscious monkeys showed that minocycline administration can protect against methamphetamine-induced neurotoxicity in the striatum, attenuating the reduction of dopamine transporters (DAT) [185]. A separate MRS study with rhesus macaques indicated that minocycline reversed the simian immunodeficiency virus-induced decline in neuronal integrity, as evidenced by declining N-acetylaspartate/creatine (NAA/Cr) ratio [186]. In individuals with multiple sclerosis, minocycline decreased contrast enhancing lesions, a marker of disease activity, in magnetic resonance imaging (MRI), and also reduced the measures for local brain atrophy indicating preservation of brain volume [187]. A case report of an individual with schizophrenia showed that minocycline, along with symptomatic improvement, was associated with normalization of regional cerebral blood flow (rCBF) in the posterior cingulate gyrus [188]. Although the exact mechanisms by which this agent affects neurogenesis, neuroprotection and neuroradiological signs remain unknown, it is documented to modulate systems (e.g. apoptosis, inflammation, glutamate and oxidative stress) that influence neural and glial plasticity (reviewed [171,189,190]). In keeping with this view Pae et al. hypothesized that minocycline may exert antidepressant effects [191]. For a summary of minocycline's proposed mechanisms of action see Table 1.

5. Minocycline's pleiotropic mechanisms of action

5.1. Anti-apoptotic

Minocycline exerts anti-apoptotic effects through caspase-dependent and caspase independent pathways. The caspase-dependent effects include reducing mitochondrial calcium overload, stabilizing the mitochondrial membrane, and inhibiting the

Table 1
Minocycline's mechanisms of action.

Neuroplasticity ↑ number of newborn neurons ↑ survival of neurons/prevent neuronal loss ↓ white matter damage	Inflammation	↓ Microglial activation Cytokines: e.g. ↓ IL-1β, IL-6, IL-2, TNF-α, IFN-γ; ↑ IL-10 Chemokines: e.g. ↓ MIP-1, RANTES, CXCR3 ↓ IDO activity and production of kynurenine and QUIN ↓ MMPs ↓ T-cell migration into CNS ↓ lipid mediators e.g. ↓ phospholipase A2 ↓ Prostaglandin E2 ↓ COX-2
	Oxidative stress	↓ Free radical generation Directly scavenges free radicals ↓ ROS and RNS ↓ Lipid peroxidation ↓ NADPH ↑ catalase
	Apoptosis	Caspase dependent ↓ Mitochondrial calcium overloading ↓ Apoptotic factors (e.g. cytochrome c, Smac/DIABLO) ↓ Caspase activation Caspase independent ↑ Bcl-2 ↓ BID, AIF ↓ ASK-1
	Glutamate excitotoxicity	↓ glutamate release ↓ glutamate transmission ↓ toxicity associated with NMDA receptor antagonism
	Monoaminergic modulation	Attenuates decreases in 5-HT, DA, 5-HTT and DAT associated with psychotomimetic substance administration Attenuates decreases in levels of dopamine, norepinephrine and serotonin associated with 3-nitropropionic acid treatment

IL-1β: interleukin 1-beta; IL-6: interleukin 6; IL-2: interleukin 2; TNF-α: tumor necrosis factor-alpha; IFN-γ: interferon-gamma; IL-10: interleukin 10; MIP-1: macrophage inflammatory protein-1; RANTES: Regulated upon Activation, Normal T-cell Expressed, and Secreted; CXCR3: chemokine (C-X-C motif) receptor 3; MMP: matrix metalloproteinase; COX-2: cyclooxygenase-2; NO: nitrix oxide; iNOS: inducible nitric oxide synthasase; NADPH: nicotinamide adenine dinucleotide phosphate; Smac: small mitochondria-derived activator of caspases; DIABLO: direct IAP binding protein with low p1; Bcl-2: B-cell leukemia-2; AIF: apoptosis inducing factor; BID: BH3 interacting domain death agonist; ASK-1: apoptosis signaling kinase-1; NMDA: N-methyl-D-aspartate; 5-HT: 5-hydroxytryptamine; DA: dopamine; 5-HTT: 5-HT transporter; DAT: dopamine transporter; IDO: indoleamine 2,3-dioxygenase; QUIN: quinolinic acid.

release of apoptotic factors (e.g. cytochrome *c*, Smac/DIABLO) into the cytoplasm with resultant decrease in caspase (e.g. caspase-1, caspase-3, caspase-9) activation and nuclear damage [169,171,192,193]. Through caspase independent pathways, minocycline upregulates the anti-apoptotic factor Bcl-2 [171,194], reduces the activation of the pro-apoptotic protein BH3 interacting domain death agonist (BID), and inhibits the release of apoptosis inducing factor (AIF) [169,189,190]. Inhibitory effects on apoptosis signaling kinase-1 (ASK-1) have also been reported with minocycline [169]. Thus minocycline exerts dual anti-apoptotic effects, both by reducing the release of apoptotic agents from mitochondria and enhancing the release of anti-apoptotic factors.

5.2. Anti-inflammatory

Microglial cells are capable of rapid activation in response to pathological changes in the CNS, imbalances in ion homeostasis, and peripheral immune activation [195,196]. Microglial activation can impair neuroplasticity by inhibiting the proliferation of neural progenitor cells via cognate cytokine receptors [197], and by inhibiting neurite outgrowth in cortical neurons [198]. These effects can be mitigated by minocycline [199], via direct suppression of microglial activation/proliferation, and inhibition of subsequent inflammatory mediator synthesis. For example, minocycline reduces the expression of pro-inflammatory cytokines (e.g. IL-1β, IL-6, IL-2, TNF-α, IFN-γ) [169,173,200–202], and up-regulates the anti-inflammatory cytokine IL-10 [203]. Additionally, neuroprotective actions of minocycline may be enacted via suppression of chemokine production [e.g. macrophage inflammatory protein 1α (MIP-1α), Regulated upon Activation, Normal T-cell Expressed and Secreted (RANTES)] and chemokine receptor expression [e.g. chemokine (C-X-C motif) receptor 3 (CXCR3)] [204]. Down-regulation of these chemokines and their receptors by minocycline may reduce the deleterious neuroinflammatory consequences of peripheral T-cell activation [171,189].

Matrix metalloproteinases (MMPs) have also been shown to enhance the effects of pro-inflammatory cytokines and regulate chemokine activity. Matrix metalloproteinases (e.g. MMP-9) disrupt the blood brain barrier by degrading the extracellular matrix proteins of the basal lamina that surround blood vessels [190]. Both in vitro and in vivo studies have shown that minocycline can reduce inflammation by inhibiting MMPs [205,206]. Interestingly, the functional −1562C/T polymorphism of the MMP-9 gene has been associated with BD [207]. Minocycline has been shown to functionally suppress activated T cells and inhibit T cell proliferation in a dose-dependent manner [208]. In keeping with this view, minocycline's inhibitory actions on MMPs may result in reduced neuroinflammation by suppressing T cell infiltration and migration into the CNS [189].

Down-regulation of lipid mediators of inflammation is also associated with minocycline treatment. The enzyme phospholipase

A2 which catalyses release of arachidonic acid in prostaglandin production pathways, is downregulated in response to minocycline [189,209]. Prostaglandin E2 and cycloxygenase-2 (COX-2) expression and production are also reduced by minocycline treatment in vitro and in vivo [201,210].

5.3. Anti-oxidative

Minocycline exerts antioxidant properties by suppressing free radical generation [211,212] and directly scavenging free radicals [213]. Pretreatment with minocycline prevented the generation of 6-hydroxydopamine-induced free radicals in cultured rat cerebellar granule neurons and attenuated hydrogen peroxide neurotoxicity [212]. In a separate study, Japanese encephalitis virus-induced ROS generation in mouse neuroblastoma cells was inhibited by treatment with this agent [214]. Treatment with minocycline at concentrations comparable to therapeutic blood levels reduced hydrogen peroxide and hydroxyl radical generation from zymosan-stimulated polymorphonuclear leukocytes [211]. Treatment with minocycline also reduces hypoxia- and endotoxin-induced NO production in cultured microglial cells [202,215]. Free radical scavenging properties of minocycline are comparable to those of vitamin E [213,216], and it has been shown to scavenge peroxynitrite at submicromolar concentrations [217].

Evidence further indicates that pretreatment with minocycline attenuates decreases in the antioxidant enzyme catalase and mitochondrial complex II enzyme succinate dehydrogenase activities in rats treated with 3-nitropropionic acid (an irreversible inhibitor of succinate dehydrogenase) [218]. It also attenuates increases in lipid peroxidation (i.e. MDA) levels [216,218] and inhibits nicotinamide adenine dinucleotide phosphate (NADPH) oxidase which participates in ROS generation [219].

5.4. Glutamatergic

Although the precise mechanisms are unknown, minocycline does not appear to directly target NMDA receptors but may indirectly modulate glutamatergic transmission [220,221]. In rats, minocycline treatment ameliorated the down-regulation of glial glutamate transporter proteins (i.e. glutamate transporter 1 and glutamate aspartate transporter), therefore preventing impaired glial glutamate uptake and normalizing NMDA receptor activation in spinal sensory synapses [222]. Minocycline has also been shown to increase spinal cord glutamate transport, protecting mice from virally-induced motor neuron death [223]. Preliminary evidence suggests that the effects of minocycline in glutamatergic transmission may be dose-dependent. At lower concentrations (10 μM), minocycline increases phosphorylation and membrane insertion of neuronal glutamate receptor 1 (GluR1) both in vitro and in vivo, thereby increasing glutamate excitability [224]. At higher concentrations (>50 μM), glutamate release is reduced and glutamatergic neurotransmission is depressed in hippocampal neurons [225,226].

Minocycline's influence on glutamate transmission may be secondary to its anti-inflammatory and anti-oxidative effects, which result in reduced production of the NMDA agonist QUIN via the KYN pathway (see Fig. 1) [158]. Pretreatment with minocycline has been reported to attenuate LPS-induced increases in IDO mRNA expression and KYN/tryptophan ratio in plasma and in the brain [227]. Moreover, in an animal model of Huntington's disease, this agent has been shown to counteract the neurotoxic effects (behavioral, inflammatory and oxidative) induced by intrastriatal administration of QUIN [228,200]. Glutamate excitotoxicity may also be attenuated by inhibiting the p38 mitogen activated kinase (MAPK) pathway: this signal transduction pathway mediates inflammation, apoptosis, and oxidative stress [229] (see Stirling et al. [189] for review). Cerebellar granular neurons exposed to toxic glutamate levels support the role of minocycline in suppressing p38 MAPK activation and also indicate enhancement of the neuroprotective PI3K/Akt pathway, which promotes cell growth, survival and proliferation [229].

The NMDA antagonist KYNA is considered protective against the neurotoxic effects of QUIN, however, since it exerts this effect in all ionotropic excitatory amino acid receptors, elevated levels of KYNA could induce glutamatergic hypo-functioning and disturb cognition [158]. Although the effect that minocycline has on KYNA remains to be investigated, it has been demonstrated that cognitive deficits induced with NMDA antagonists (i.e. phencyclidine), an animal model of schizophrenia, improve following subchronic (14 days) minocycline treatment (40 mg/kg) [230]. Similarly, pretreatment of rats with minocycline (35 mg/kg) can also reverse cognitive deficits induced by MK-801 [231]. Dizocilpine (MK-801)-associated increases in extracellular dopamine levels in the mouse frontal cortex and striatum are also attenuated with minocycline (40 mg/kg) pretreatment [232]. Although this effect may be counterintuitive considering minocycline's inhibitory role in microglial activation, and by extension QUIN production, the reversal of the cognitive deficits may occur via a non-glutamatergic mechanism (e.g. anti-apoptotic) and/or may reflect modulation rather than just antagonism of the glutamatergic system.

These studies provide putative mechanisms by which minocycline can ameliorate dysfunction of the systems that regulate extracellular glutamate concentrations. This regulation may be beneficial as stimulation of extrasynaptic neuronal NMDA receptors can lead to excessive neuronal excitation, increasing ROS generation and transition of neurons into apoptotic pathways.

5.5. Monoaminergic

Minocycline may exert neuroprotective and psychotropic effects by indirectly targeting the monoaminergic system. Studies have demonstrated that minocycline is capable of antagonizing the effects of psychotomimetic substances. For example, pretreatment and subsequent administration of minocycline (40 mg/kg) in a murine model significantly attenuated the reduction of 5-hydroxytryptamine (5-HT) and dopamine as well as density of 5-HT transporter (5-HTT) and DAT following repeated administration of 3,4-methylenedioxymethamphetamine (MDMA) [233]. Pretreatment with minocycline has also been shown to attenuate MDMA-induced reduction in the density of 5-HT uptake sites in rat frontal cortex at high but not low doses (45 mg/kg bid on day 1 and 90 mg/kg bid day 2 vs. 45 mg/kg bid on both days) [234]. In a separate study, minocycline pretreatment and subsequent administration attenuated methamphetamine-induced reduction in dopamine and its metabolite 3,4 dihydroxyphenyl acetic acid (DOPAC) in a dose dependent manner (10, 20, 40 mg/kg), and in DAT at 40 mg/kg in the mouse striatum [235]. In vivo pretreatment with minocycline (40 mg/kg) attenuated increased extracellular dopamine levels after administration of methamphetamine [235]. In a postnatal day 3 rat model of preterm hypoxia-ischemia, 1 week of minocycline treatment (22.5 mg/kg, i.p.) prevented the associated decrease in serotonin transporter levels in the frontal cortex, thalamus and brainstem, 5-HT levels in the frontal cortex and thalamus, as well as number of 5-HT-positive raphe neurons ipsilateral to the carotid ligation [236]. Decreases in levels of dopamine, norepinephrine and serotonin in forebrain homogenates are also prevented with minocycline (50 and 100 mg/kg) pretreatment in 3-nitropropionic acid-treated rats [218].

6. Preclinical and clinical efficacy trials with minocycline in psychiatric disorders

6.1. Minocycline's antidepressant-like properties in preclinical trials

Minocycline's antidepressant-like properties are supported by several animal studies. Adult male Wistar rats ($N = 42$) were randomly assigned to minocycline monotherapy (50, 60, 80 mg/kg) or combination treatment of subthreshold doses of minocycline (50 mg/kg) and subthreshold doses of fluoxetine (15 mg/kg), desipramine (5.0 mg/kg) or glutamate receptor antagonists (i.e. EMQMC: 0.6 mg/kg, MTEP: 2.5 mg/kg, and dizolcipine: 0.5 mg/kg). The rats received the respective drug treatments at 23 h, 5 h, and 1 h prior to the forced swim test (FST). Minocycline monotherapy (60 and 80 mg/kg) and combination treatment with minocycline and desipramine or dizolcipine significantly reduced immobility by increasing climbing behavior on the FST test as compared to vehicle treated rats [237]. Reduced immobility by increased climbing suggests that minocycline may produce antidepressant action via modification of noradrenergic mechanisms [237,238]. Behavioral effects predictive of antidepressant activity have also been documented with central administration of minocycline into the nucleus accumbens [239]. In a learned helplessness (LH) rat model of depression, bilateral infusion of minocycline (160 μg/side) into the cerebral ventricle resulted in significantly improved performance on the conditioned avoidance test (i.e. less escape failures and shorter latency to escape) relative to saline treated rats. This antidepressant-like effect was not observed in LH rats treated with 20 μg/side of minocycline or naive rats. Further investigation of the mechanisms of action suggests that minocycline may exert its antidepressant-like effects by increasing DA and DOPAC levels in the amygdala, as no significant changes were found in other brain regions or molecular targets (i.e. 5HT, norepinephrine, their metabolites, and BDNF) following minocycline infusion [241]. However, a separate study with minocycline monotherapy (20 and 40 mg/kg) administered 60 min prior to the FST on day 1 and day 2, did not find any significant effects on immobility [240].

A few studies have also demonstrated that minocycline can block LPS-associated depressive-like behavior. For example, pretreatment with minocycline (50 mg/kg) or saline daily for 3 days attenuated LPS-associated increased duration of immobility on the FST and the Tail Suspension Test. Interestingly, these effects were observed at a time when LPS-induced sickness behavior was no longer apparent [227]. In a separate study, pretreatment with minocycline has been shown to attenuate LPS-induced anhedonic and social exploratory behaviors. Recovery from LPS-induced sickness behavior with minocycline pretreatment was associated with reduced microglial activation and reduced expression of IL-1β, IL-6, and IDO in the cortex and hippocampus [242]. Taken together, these preclinical studies suggest that minocycline may exert its antidepressant-like effects by targeting both monoaminergic and inflammatory pathways.

It has also been suggested that tetracycline antibiotics may possess lithium-like activity [243,244]. Amphetamine-induced hyperactivity is a longstanding model of mania [245], and like lithium, minocycline has been has been shown to reverse this effect [243,244]. This model does have a number of limitations, as hyperactivity is common to several psychiatric conditions, and does not account for the broad spectrum of symptoms that characterize BD [245]. As such, minocycline is reported to reduce hyperactivity in animal models of traumatic brain injury, drug abuse, and schizophrenia [230–232,235,246]. Counter to this evidence is a reported rare risk of antibiotic-induced mania. The most common causative antibiotics are clarithromycin, ciprofloxacin, and ofloxacin, nevertheless close monitoring of minocycline-treated individuals with BD is warranted (for a review see Abouesh et al. [247]).

6.2. Minocycline's effects on depressive symptoms and quality of life in non-psychiatric populations

Several clinical trials with minocycline administered depression and quality of life (QOL) metrics to non-psychiatric populations but have yielded mixed results. A three-arm, multi-center, open-label, randomized, parallel-group control trial in acne patients ($N = 150$) found that 4 weeks of antibiotic treatment [minocycline (100 mg/d or 50 mg bid), roxithromycin (150 mg bid), or faropenem (200 mg bid)] significantly improved inflammatory lesion counts as well as emotional and overall QOL; these effects were maintained 4 weeks after treatment discontinuation. On the other hand, a non-randomized study, did not find any significant within-group or between-group changes in depressive symptoms or QOL in individuals with acne vulgaris treated with minocycline and topical therapy or isotretinoin [248]. Likewise, no significant effects on depressive symptoms were reported with adjunctive minocycline (100 mg bid) in HIV-1-infected individuals with progressive neurocognitive decline enrolled in a 24-week, randomized, placebo-controlled trial [249]. Quality of life also remained unchanged in adult asthmatic patients ($N = 17$) treated with minocycline (150 mg bid) as part of an 8-week randomized, double-blind, placebo-controlled cross-over trial [250]. A major limitation of these studies is that depression was either exclusionary or not systematically evaluated at enrollment.

Improvement in psychiatric symptoms as well as neuropsychological function has been reported in a small ($N = 14$) open-label study with adjunctive minocycline (100 mg/day) in individuals with Huntington's disease. Significant improvement in motor and neuropsychological function was evident at 6 months while psychiatric symptoms were not ameliorated until 24 months of therapy [251,252]. These findings however, were not replicated in a 6-month open-label study or an 8-week, randomized, double-blind, placebo-controlled trial; the latter actually reported worse performance on the Stroop Interference Test [253,254]. An open -label clinical trial in Fragile X syndrome, has also reported significant improvements in behavior including irritability, hyperactivity, stereotypy, and inappropriate speech after 8 weeks of adjunctive minocycline therapy (50 mg or 100 mg bid) [255].

6.3. Minocycline's efficacy on symptoms of depression and schizophrenia

To our knowledge, there is one published clinical trial that reported on minocycline's antidepressant effects in individuals with MDD [256], and one case report that provides only suggestive evidence for its utility in bipolar depression. Within a week of adjunctive minocycline (150 mg/day) treatment a 66-year-old female with BD experienced a reduction in symptom severity, as evidenced by a 17 point drop on the Hamilton Rating Scale for Depression rating scale (HAMD); an effect that was maintained 2 weeks after treatment initiation [257]. Several clinical trials are underway testing the effects of minocycline in individuals with unipolar (NCT01574742) and bipolar depression (NCT01429272, NCT01514422, NCT01403662) [258,259].

The efficacy of adjunctive minocycline in mitigating depressive and psychotic symptoms of individuals with DSM-IV-TR-defined unipolar depression with psychotic features ($N = 25$) has been evaluated in a 6-week, multicenter, open-label study. Minocycline was initiated at 50 mg bid for the first week and 50 mg tid thereafter. Adjunctive medication included a stable dose of SSRIs. Significant reduction in the mean 21-item Hamilton Rating Scale for Depression (HAMD-21) total score was identified

from baseline to week 6, with significant reductions being evident from the first post-baseline assessment (week 2). Antidepressant response (>50% reduction in HAMD-21 total score) was noted in 80% of participants. Adjunctive minocycline also significantly mitigated psychotic symptoms as evidenced by a reduction in the Brief Psychiatric Rating Scale total score from baseline to week 6. Minocycline was well tolerated and no severe or serious adverse events were recorded during the study [256]. No significant changes however, were reported on secondary depressive symptom measures, in a study that primarily aimed to evaluate the effects of adjunctive minocycline in treatment resistant obsessive compulsive disorder (OCD) [260].

Moreover, results from clinical trials evaluating the efficacy of minocycline in treating symptoms of schizophrenia may presage its utility in mood disorders. The shared putative pathophysiological abnormalities and therapeutic efficacy of antipsychotics for mood disorders and schizophrenia point to possible overlapping pharmacologic targets in both conditions. A 4-week, open-label study with adjunctive minocycline (150 mg tid) enrolled DSM-IV-defined individuals with schizophrenia ($n = 22$) who were non-responsive to conventional pharmacotherapy. Minocycline was initiated at 100 mg bid for the first week, and 150 mg tid from week 2 to week 4. Subjects demonstrated significant improvement on measures of positive and negative symptoms as well as general psychopathology. The symptomatic reduction observed at study endpoint was maintained at a 4-week follow-up visit [261].

These results have been replicated in a 22-week, double-blind, randomized, placebo-controlled trial that evaluated the efficacy of adjunctive minocycline (200 mg/day) in DSM-IV-defined individuals with schizophrenia ($N = 70$). All participants enrolled were in the early-phase of their illness (i.e. within 5 years of their first exposure to an antipsychotic) and treated with an atypical antipsychotic. After a 2-week, single-blind, placebo lead-in, subjects were randomized to minocycline or placebo. Individuals receiving minocycline exhibited a significant improvement in negative symptoms, as measured with the Scale for Assessment of Negative Symptoms (SANS) total score, and global improvement as measured by the Clinical Global Impression (CGI) score starting at week 14, although significant improvement in measures of positive symptoms was not observed [262].

6.4. Minocycline's effects on cognitive symptoms

Minocycline has been reported to reduce signs of cognitive impairment in preclinical and preliminary clinical trials. For example, reducing microglial activation with minocycline prevents an exaggerated hippocampal IL-1β response and prevents memory impairment on the Contextual Fear Condition task in adult rats infected with *Escherichia coli* as neonates. This effect was also evident when minocycline was administered prior to fear conditioning but after the LPS challenge [263]. In a separate study, minocycline (50 mg/kg/day) ameliorated performance on the Morris Water Maze and Open Field Tasks in a rat model of vascular dementia [264]. In a rat model of traumatic brain injury, minocycline (45 mg/kg) improved active place avoidance learning that required memory lasting less than 2 h. Minocycline in combination with NAC synergistically prevented cognitive deficits by improving learning and memory spanning at least 24 h in the active place avoidance task [265]. Improvements in spatial learning have also been demonstrated in a mouse model of Alzheimer's disease following 4 weeks of minocycline therapy (50 mg/kg every other day) [266]. Similarly, amyloid precursor protein transgenic mice fed minocycline-containing food (0.5 g/kg) for 3 months starting at 5 months of age also exhibited better performance on the Morris Water Maze task as compared to untreated animals [267].

Preliminary, clinical evidence from randomized placebo-controlled trials suggests that minocycline exerts significant effects on some cognitive functions. In a study with healthy males ($N = 49$), 4 days of minocycline treatment (100 mg bid) did not significantly influence trust or altruistic behavior, but may have led to more rational decision-making. In a trust game with an anonymous partner, minocycline but not placebo-treated individuals made their decisions based on their general trust of others, which the authors speculate to signify that the first group attended more to the lack of information about their partner, while the latter group attended more to the uncertainties and fears regarding their unknown partner [268]. In individuals with schizophrenia, 22 weeks of adjunctive minocycline (200 mg/day) was associated with significant improvement in executive functions, including the executive function composite score, spatial recognition memory, cognitive planning, and intradimensional/extradimensional set shifting. Significant improvement was also noted in spatial recognition memory but not pattern recognition memory, psychomotor speed or attention [262]. In a 24-week trial, adjunctive minocycline (100 mg bid) significantly improved manipulative dexterity, but did not exert significant effects on most primary or secondary measures of cognitive function in individuals with HIV-associated cognitive impairment ($N = 107$) [249]. To our knowledge, no study has evaluated the effects of minocycline on cognitive symptoms in individuals with a primary mood disorder diagnosis.

6.5. Minocycline's anxiolytic effects

Studies with animal models suggest that minocycline could be effective in mitigating anxiety symptoms. Mice pre-exposed to chronic stress (3 weeks of daily restraint for 3 h) and then subjected to 8 min of cardiac arrest/cardiopulmonary resuscitation (CA/CPR) exhibit anxiety-like behavior as assessed in the open field test. Intracerebroventricular infusion of minocycline (10 μg/day) reduced anxiety-like behavior among CA/CPR versus sham operated mice [269]. Minocycline (45 mg/kg) administered to postnatal day 4 rats after bilateral carotid artery occlusion followed by exposure to hypoxia significantly attenuated the hypoxia–ischemia induced anxiety-like behavior on the elevated plus maze [179]. A study of 3-week-old fragile X mental retardation gene knock out (*Fmr1* KO) mice exhibited significantly less anxiety in the elevated plus maze when nursed by mothers that received minocycline in their drinking water (30 mg/kg/day for 21 days) [270]. In humans, it has been suggested that minocycline may improve symptoms of OCD. In a 12-week, open-label study with adjunctive minocycline (100 mg bid), two out of nine patients (22%) with early onset of OCD symptoms exceeded treatment response criteria (40% and 46% reduction on the Yale–Brown Obsessive Compulsive scale) although no significant effect was observed in the full group. No significant changes were reported in symptoms of depression and anxiety, as measured with the HAMD-17 and Hamilton Anxiety Rating Scale, respectively; 44% of participants however, met criteria for symptomatic remission at baseline (total score of ≤ 7) [260].

7. Perspectives

The pathophysiology of mood disorders is heterogeneous, with no single encompassing explanation. A coherent comprehensive disease model would integrate observations from clinical studies and animal models into a common framework for understanding their impact on mood and cognitive symptoms. Novel and preferably disease-modifying therapies are more likely to stem from an a priori disease model rather than serendipity. Minocycline is a pleiotropic agent that exerts effects on multiple interacting systems (e.g. anti-inflammatory,

anti-oxidant, anti-apoptotic, anti-glutamatergic, monoaminergic) implicated in the pathophysiology of mood disorders. It could be conceptualized that the totality of these effects converges on impaired neuroplasticity. Notwithstanding the pleiotropic effects of minocycline in animal and cellular models, its antidepressant effects in individuals with mood disorders are not established. There are several examples wherein the conceptual and preclinical evidence base is more compelling than the therapeutic proof of concept research [271]. Minocycline's putative neuroprotective effects are currently under exploration for improving outcomes in several neurological conditions. If the potential benefits of minocycline are to be realized in psychiatry, rigorous clinical trials evaluating its efficacy as an alternative or adjunctive therapy for symptoms of mood disorders are suggested.

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