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Point of view

Does minocycline have antidepressant effect?

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Abstract

Only one-third of patients undergoing monotherapy with an antidepressant achieve remission of their depressive symptoms and gain functional recovery. Therefore, further exploration of antidepressant mechanisms of action is important in order to facilitate the development of antidepressants with new modes of action. Preclinical and clinical studies have demonstrated that major depression is associated with impaired inflammatory responses and deficient neuroprotection. In this regard, we propose that the second-generation tetracycline ''minocycline'' may hold a potential as a new treatment for major depression. Emerging findings in animal and human studies of minocycline reveal that it has antidepressant-like neuroprotective and anti-inflammatory actions, and minocycline has been shown to perform as an antidepressant in an accepted animal model (forced swimming test). Anecdotal evidence supports minocycline's efficacy for augmentation of antidepressants in major depressive disorder. The following review describes the evidence supporting the consideration of minocycline as a potential antidepressant. We suggest that minocycline may be particularly helpful in patients with depression and comorbid cognitive impairment, as well as depression associated with organic brain disease. We also describe the antinociceptive effect of minocycline and propose a role for minocycline in the treatment of patients with major depression and prominent somatic discomfort and somatoform spectrum disorders. The lack of clinical studies of minocycline for depression is noted. Further studies of the potential therapeutic mechanism of minocycline and its therapeutic implications for major depression are warranted, and may substantially contribute to the development of newer and more effective antidepressants.

Keywords: Minocycline; Depression; Neuroprotection; Anti-inflammatory effect

1. Introduction

For several decades, the accepted pathogenesis of major depression has involved the dysfunction of neurotransmitters such as serotonin, norepinephrine, and dopamine. The monoamine hypothesis in part stems from the observation that drugs which enhance monoamine function show efficacy for depression, and subsequent drug design has focused primarily on promoting serotonergic and norepinephrinergic neurotransmission. Antidepressants with monoamine-based mechanisms have prevailed in clinical practice since the mid-twentieth century, and for the most part have demonstrated efficacy and safety in the treatment of major depression. However, such drugs are associated with major limitations. For example, only one-third of patients undergoing monotherapy with an antidepressant achieve complete remission of depressive symptoms and gain functional recovery [1]. Therefore, further exploration into alternative mechanisms of action of antidepressants has the potential to facilitate the development of antidepressants with new mechanisms of action to overcome the limitations of current antidepressants.

Recently, the concept of the pathogenesis of major depression has been extended to include alterations in brain

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inflammatory mediators and disruption of neuroprotection in the limbic system. Preclinical and clinical studies have demonstrated that major depression is accompanied by systemic immune activation or inflammatory response [2]. Subsequent research has also indicated that increased production of pro-inflammatory cytokines may play a role in the pathophysiology of major depression [3,4]. Recent evidence also suggests that impaired neuroprotection is highly involved in the pathogenesis of major depression. For example, decreased neuronal survival and disordered neurogenesis in the hippocampus have been repeatedly found in patients with major depression and are now considered to be potential pathophysiological factors and therapeutic targets for major depression [5,6].

In this regard, the second-generation tetracycline, minocycline, has powerful anti-inflammatory and neuroprotective effects and is a potential new agent for the treatment of major depression. Minocycline effectively crosses the blood–brain barrier. It has shown neuroprotective effects in amyotrophic lateral sclerosis [7] and Parkinson's disease [8] in preclinical and clinical studies. In animal studies, minocycline has been shown to significantly mitigate 3,4-methylenedioxymethamphetamine (MDMA)-induced neurotoxicity of serotonin and dopamine systems in the cerebral cortex and hippocampus, and to promote neurogenesis as well [9]. Minocycline has a regulatory effect on pro-inflammatory agents such as nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) [10], which are consistently reported to be increased in patients with major depression and to normalize after antidepressant treatment [2,11].

Hence, we propose that minocycline may exert potential antidepressant effects through its robust neuroprotective activities which include neurogenesis, antioxidation and anti-glutamate excitotoxicity, and direct regulation of pro-inflammatory agents. The therapeutic implications of this idea are discussed.

Based on findings from animal and human studies with minocycline, several lines of evidence support the hypothesis that minocycline may treat major depression through anti-inflammatory activity and neuroprotection (neurogenesis, antioxidation, and anti-glutamate excitotoxicity).

2. Possible antidepressant effect of minocycline through neuroprotection

2.1. Neurogenesis

The hippocampus is an important limbic structure that modulates mood, anxiety, learning, and memory, which are commonly disrupted in depression [12]. Preclinical and clinical studies have demonstrated that major depression results in a reduction in the total number of neurons in the hippocampus by inducing a prolonged decrease in the rate of cell proliferation [13]. In contrast, antidepressant treatment enhances hippocampal neurogenesis and can thereby block or reverse the atrophy and damage caused by major depression; this process has been demonstrated with antidepressants such as fluoxetine [14] and tianeptine [15], as well as the mood stabilizer lithium [16]. Similarly, administration of minocycline significantly mitigated MDMA-induced neurotoxicity of the serotonin and dopamine neuronal systems in the cerebral cortex and hippocampus in an animal study, resulting in increased neurogenesis [9]. In particular, systemic administration of minocycline restored hippocampal neurogenesis more markedly in severe brain injury than in mild-to-moderate brain injury [17]. We postulate that minocycline may have the potential to directly attenuate or reverse neuronal atrophy in the context of major depression by upregulating hippocampal neurogenesis.

2.2. Antioxidation

Several studies have demonstrated derangements in antioxidant defense systems in major depression. Patients with major depression have been shown to exhibit increased serum levels of lipid peroxidation, superoxide dismutase, and malondialdehyde, as well as decreased serum levels of ascorbic acid and vitamin E; these abnormalities corrected after successful antidepressant treatments in a number of studies [18,19]. This evidence conjures the question of whether antidepressant efficacy is linked to antioxidant effects. Minocycline has been shown to be an antioxidant via a direct radical scavenging property very similar to that of vitamin E, according to data from rat brain homogenate lipid peroxidation and 2,2-diphenyl-1-picrylhydrazyl radical scavenging assays [20]. In addition, the chemical structure of minocycline includes a multiply-substituted phenol ring similar to that of vitamin E [20]. These antioxidant properties of minocycline support the premise that it may have antidepressant efficacy similar to traditional antidepressant medications.

2.3. Anti-glutamate excitotoxicity

Glutamate excitotoxicity has been considered as another pathway in the development of major depression. The plasma and frontal cortex levels of glutamate in patients with major depression have been reported to be higher than those in normal control subjects [21,22], while antidepressant treatment significantly reduces serum glutamate levels [23]. Furthermore, it has recently been shown that anti-glutamatergic agents have antidepressant effects [24]. Therefore, the direct and robust neuroprotective effect of minocycline against glutamate excitotoxicity, through regulation of p38 and Akt pathways, raises the possibility of another antidepressant mechanism [25].

3. Possible antidepressant effect of minocycline through anti-inflammatory effect

A growing body of evidence also suggests that dysregulation of inflammatory processes may be a major pathophysiological mechanism of major depression (e.g., cytokines play a major role in bridging the nervous and immune systems). Pro-inflammatory agents have been implicated in the pathogenesis of major depression, through their direct effects on neural cells or by modulating neurotransmitters and neuropeptides [2]. A recent preclinical study showed that stress-induced

depressive symptoms in mice were associated with increased hippocampal interleukin-1 (IL-1) and that mice altered by deletion or antagonism of the IL-1 receptor were not prone to depressive symptoms when subjected to stress; the study authors assert that elevated brain IL-1 is linked to depression and that reduction or inhibition of brain IL-1 has potent antidepressant effects [26]. Furthermore, the pro-inflammatory cytokine levels (e.g., TNF-α and IL-1β) were found to be consistently higher in patients with major depression than in controls [3,4], and antidepressants reversed these altered levels, demonstrating the immunomodulatory effect of antidepressants (TNF-α and IL-1β directly cause depression in animal models) [2]. Nitric oxide (NO) is another pro-inflammatory agent that has been shown to be increased in patients with major depression, a finding that is reversed by antidepressant treatment [11]. Consistent with a potential antidepressant role, minocycline has demonstrated a direct inhibitory effect on the pro-inflammatory cytokines TNF-α, IL-1β, and NO in a preclinical study. More specifically, minocycline suppressed the hypoxic upregulation of these pro-inflammatory agents in cultured rat microglial and neuronal cells [10].

4. Proven antidepressant effect of minocycline in forced swimming test

A recent study in mice evaluated the potential antidepressant activity of minocycline alone or in combination with traditional antidepressant drugs or glutamate receptor antagonists using the time sampling method in the forced swimming test (FST). Minocycline demonstrated antidepressant-like actions in that it reduced immobility by increasing climbing behavior, and a subthreshold dose of minocycline synergized the antidepressant actions of subthreshold doses of desipramine and glutamate receptor antagonists [27]. The FST is one of the most commonly used animal models to evaluate antidepressant activity, and it is sensitive to all of the major classes of antidepressant drugs [27,28]. Of note, antidepressant drugs with predominantly noradrenaline or dopamine enhancing effects reduce immobility by increasing climbing behavior in the time sampling method in the FST. Conversely, antidepressant drugs with predominantly serotonin enhancing effects reduce immobility by increasing swimming [27,29]. Hence, the finding by Molina-Hernandez and colleagues [27] suggests that minocycline produces antidepressant effects through modification of the noradrenergic system in the brain. Interestingly, minocycline did not synergize the antidepressant-like actions of fluoxetine, indicating that minocycline may not directly impact the serotonergic system [27]. Accordingly, as the authors propose, minocycline may be of use for the augmentation of noradrenergic antidepressant drugs [27].

5. Therapeutic implication

Physiological studies demonstrate the similarity of minocycline to traditional antidepressant drugs, and minocycline has shown antidepressant properties in animal models of antidepressant activity. However, to what extent minocycline is clinically useful for depression remains unclear, and the appropriate target population has yet to be determined. Studies showing minocycline's various anti-inflammatory and neuroprotective properties have not correlated physiological changes with efficacy measures of depression, such as the Hamilton Depression Rating Scale (Ham-D), and this may be an appropriate next step. Minocycline has been shown to have neuroprotective effects against various brain insults, and perhaps minocycline should be particularly useful in older patients with major depression, as well as depression comorbid with organic brain diseases, such as Parkinson's disease, stroke, traumatic brain injury, and Alzheimer's disease. In fact, minocycline's potential utility in cognitive disorders is suggested by an animal study in which minocycline protected basal forebrain cholinergic neurons from mu p75-saporin immunotoxic injury, mitigating against cognitive impairment [30]. Minocycline has also been found to exert potent and consistent antinociceptive activity in models of tissue injury and inflammation-evoked pain [31], which points to its potential effectiveness in treating somatic symptoms commonly found in patients with major depression and functional somatoform disorders such as pain disorder and fibromyalgia. Finally, an anecdotal case report describes an antidepressant effect of minocycline. This report describes that the addition of minocycline 150 mg/day to clomipramine led to significant improvement of depressive symptoms in 3–4 days and a decrease in Ham-D from 25 to 8. This effect reportedly persisted after minocycline was discontinued (2 weeks of treatment) and was also associated with the resolution of facial pain [32]. This report suggests that minocycline has clinically useful antidepressant effects when used to augment a serotonergic antidepressant; of note, this contrasts with data from the FST animal model in which minocycline worked synergistically with a noradrenergic antidepressant (desipramine) but not a serotonergic agent (fluoxetine) [27]. The clinical utility of minocycline monotherapy has not been reported, but study of minocycline is warranted in both monotherapy and combined therapy conditions.

6. Conclusion

Minocycline may exert antidepressant effects based on its known physiological properties of neuroprotection and anti-inflammation. In vitro and in vivo animal studies are important to further clarify the physiological properties of minocycline in an effort to better understand the pathophysiology of depression. Clinical studies should be conducted to elucidate whether minocycline has clinical efficacy as an antidepressant, and such studies will hopefully link antidepressant efficacy with biological markers of minocycline's neuroprotective and anti-inflammatory effects.

7. Conflicts of interest

None.

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