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Review

Tetracycline antibiotics: Emerging roles in neuropsychiatric disorders

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ABSTRACT

Tetracyclines are broad-spectrum antibiotics used primarily for bacterial infections and various other conditions. Experimental studies have demonstrated their neurogenesis-inducing, neuroprotective, antioxidant, antinociceptive, antiapoptotic, and anti-glutamate-induced excitotoxicity properties. Due to these attributes, it is believed that when combined with antipsychotic medications used in psychiatric disorders, tetracyclines may facilitate the treatment of conditions such as autism spectrum disorder (ASD), major depressive disorder (MDD), and schizophrenia. This review article examines the biochemical structure, pharmacokinetic, and pharmacodynamic properties of the tetracycline group of antibiotics, as well as their uses in various diseases. It particularly focuses on the neuroprotective, antioxidant, antinociceptive, antiapoptotic, and anti-glutamate-induced excitotoxicity properties of minocycline. Additionally, the potential use of minocycline in the treatment of psychiatric disorders such as ASD, MDD, and schizophrenia is discussed.

Keywords: Autism spectrum disorder, depression, major depressive disorder, minocycline, schizophrenia, tetracycline.

Tetracyclines are a broad-spectrum group of antibiotics effective in inhibiting protein synthesis and are frequently used in the treatment of bacterial infections. This group includes therapeutics obtained naturally, such as tetracycline, oxytetracycline, and chlortetracycline, as well as semi-synthetic agents like minocycline (7-dimethylamino-6-demethyl-6-deoxytetracycline), doxycycline, and methacycline.[1]

Tetracycline antibiotics are indicated for a wide range of bacterial infections, including rickettsial infections, leptospirosis, amebiasis, actinomycosis, acne, nocardiosis, brucellosis, chlamydial infections, tularemia, Legionnaires' disease, syphilis, Lyme disease, and Whipple's disease. Beyond bacterial infections, they are also indicated for numerous other conditions such as rosacea, bullous dermatitis, Kaposi's sarcoma, sarcoidosis, pyoderma gangrenosum, hidradenitis suppurativa, alpha-1 antitrypsin deficiency, scleroderma, and rheumatoid arthritis.[1-4]

The tetracycline group is generally administered orally, but intramuscular, intravenous, and topical forms are also available. Only oxytetracycline and tetracycline can be used intramuscularly. This drug group has excellent tissue distribution, but its penetration into cerebrospinal fluid is poor. When taken with metals such as calcium, magnesium, or aluminum, chelation occurs, which reduces absorption.[5,6]

The use of tetracycline can cause side effects such as discoloration of the teeth, epigastric pain, nausea, vomiting, anorexia, photosensitivity, delayed bone development in children, and Clostridium difficile infection, which is a common side effect seen with many antibiotics.[7,8] Additionally, tetracyclines are contraindicated in pregnant women due to their potential to cause discoloration of the fetus's teeth, impairment of fetal long bone growth, and hepatotoxicity.[9-11] Tetracyclines also pass into breast milk; however, the calcium present in breast milk chelates the drug, preventing its transfer to the infant.

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Therefore, tetracyclines are considered safe therapeutic agents for breastfeeding mothers and their infants.[12]

Minocycline is a second-generation, semi-synthetic, potent tetracycline analog with neuroprotective and anti-inflammatory effects.[13] Its lipophilic structure allows it to cross the blood-brain barrier and be readily absorbed by the body.[14] Although its immunomodulatory mechanism has not been fully elucidated, minocycline affects multiple pathways.[15] It reduces microglial activation,[16] inhibits matrix metalloproteinase-9 activity, and modulates the secretion of cytokines and chemokines involved in neuroinflammation, such as interleukin-6 and tumor necrosis factor-alpha (TNF-α).[17]

Minocycline increases the expression of the anti-apoptotic B cell lymphoma 2 (Bcl-2) and reduces the expression of pro-apoptotic proteins such as Bax and Bid, thereby balancing the Bax/Bcl-2 ratio.[18] This results in the suppression of apoptotic factors such as caspase-1 and caspase-3 activation and cytochrome c.[19,20]

Although minocycline is actively used in the treatment of acne vulgaris or as an antiviral agent, its anti-inflammatory, antioxidant, and anti-apoptotic effects have led scientists to investigate its potential beyond these usage targets. Research has been directed towards exploring its potential in neuro-psychiatric conditions such as Alzheimer's, Parkinson's, and Huntington's diseases.[21-28]

Minocycline, as an inhibitor of microglial activation, possesses anti-inflammatory, antioxidant, and antiapoptotic properties, and it can modulate glutamate-dependent excitotoxicity. Its therapeutic potential has been demonstrated through various animal experiments.[28-35] In addition to these findings, recent experiments have shown that minocycline, when used in combination with antipsychotic medications, particularly improves negative symptoms.[36-41]

THE POTENTIAL ANTIDEPRESSANT EFFECTS OF MINOCYCLINE

Depression treatment

Both clinical and preclinical studies indicate that major depressive disorder (MDD) stems from inadequate inflammatory responses and impaired neuroprotection. Researchers suggest that minocycline, a second-generation tetracycline antibiotic, could play a role in the treatment of major depression by virtue of its identified antinociceptive effects. Moreover, it is proposed that minocycline could be utilized in the treatment of both MDD and somatoform disorders, as well as certain prominent somatic disorders. Results from various studies conducted on humans and animals also indicate that minocycline possesses antidepressant-like and anti-inflammatory effects on the nervous system. Its antidepressant properties have also been evidenced through the 'forced swim test'.[42]

In light of recent research and findings, the pathogenesis of MDD has been expanded to encompass limbic system damage and alterations in inflammatory mediators in the brain. This includes disrupted neuroprotection. Examples of this include the repeated findings of decreased neuronal survival and impaired neurogenesis in the hippocampus in patients with MDD. This situation strongly supports the consideration of the aforementioned findings as possible elements of the disorder's pathophysiology.[43,44]

Another characteristic of minocycline is its ability to effectively cross the blood-brain barrier. Neuroprotective effects of minocycline have been observed in clinical and preclinical studies in amyotrophic lateral sclerosis and Parkinson's disease.[45,46] In animal experiments, it has been understood that minocycline significantly increases neurogenesis and markedly reduces 3,4-methylenedioxymethamphetamine-induced serotonin and dopamine system neurotoxicity in the cerebral cortex and hippocampus.[46] Minocycline has a regulatory effect on proinflammatory agents such as TNF-α, nitric oxide, and interleukin-1 beta.[47] Additionally, it has been reported that these agents increase in patients with MDD and return to normal levels after antidepressant treatment.[43,48] It is also suggested that minocycline may exert potential antidepressant effects through its strong neuroprotective activities, which include neurogenesis, antioxidation, anti-glutamate-induces excitotoxicity, and direct regulation of proinflammatory agents.[42]

Neurogenesis, antioxidation, and anti-glutamate-induced excitotoxicity

The hippocampus, a crucial part of the limbic system, is predominantly affected in depression

and regulates activities such as mood, anxiety, learning, and memory.[47] Clinical and preclinical studies indicate that another consequence of MDD is a reduction in the total number of neurons in the hippocampus, mainly due to a prolonged decrease in cell proliferation rate.[49] In contrast, antidepressant treatments accelerate hippocampal neurogenesis; thus, they can prevent or reverse the atrophy and damage caused by major depression. These mechanisms have been demonstrated with fluoxetine, tianeptine, and lithium.[50-52] In light of these findings, it is assumed that the second-generation tetracycline antibiotic minocycline may directly attenuate or reverse neuronal atrophy caused by MDD by up-regulating hippocampal neurogenesis.[42]

Levels of lipid peroxidation and oxidative damage markers such as superoxide dismutase are observed to increase in the serum of major depression patients, while antioxidants such as vitamins E and C decrease. However, after effective antidepressant treatment, these levels return to normal.[53,54] It has been shown that minocycline possesses a direct radical scavenging property similar to vitamin E, and upon examination of the drug's chemical structure, it becomes apparent that minocycline contains multiple phenolic rings similar to vitamin E.[55]

Plasma and frontal cortex glutamate levels have been found to be higher in patients with MDD compared to the normal control group.[55,56] Antidepressant treatment, on the other hand, significantly increases glutamate levels.[57] In recent times, it has been understood that anti-glutamatergic agents also have antidepressant effects.[58] Therefore, the direct and potent neuroprotective effect of minocycline against glutamate excitotoxicity increases the possibility of another antidepressant mechanism through the regulation of the p38 and Akt pathways.[59]

The proven antidepressant effect of minocycline with the forced swim test

Minocycline has demonstrated antidepressant-like actions by increasing climbing behavior, reducing immobility, and synergizing with subthreshold doses of desipramine and glutamate receptor antagonists. Molina-Hernández et al.[60] suggested that the antidepressant effect of minocycline may involve modification of the noradrenergic system in the brain. Interestingly, minocycline did not synergize with fluoxetine's antidepressant-like effects, indicating that minocycline may not directly affect the serotonergic system. In light of this information, it can be said that minocycline may be used to enhance the effect of noradrenergic antidepressant drugs in this regard.

Minocycline has been shown to have neuroprotective effects in various regions of the brain, and it is thought that it may be used not only in older patients with MDD but also in comorbid conditions associated with organic brain pathologies such as Parkinson's disease, stroke, traumatic brain injury, Alzheimer's, and others.[61] It has also been shown that minocycline has a strong and consistent antinociceptive effect, demonstrated in pain models associated with tissue damage and inflammation. This suggests that minocycline has been effective in treating somatic symptoms commonly found in patients with major depression and pain disorders such as fibromyalgia, where functional somatoform disorders are often present.[62] According to the results of another study, the addition of minocycline to clomipramine (150 mg/day) has led to significant improvements in depressive symptoms within 3-4 days, with the Hamilton Depression Rating Scale score decreasing from 25 to 8. It was reported that this effect continued after minocycline was discontinued (after a 2-week treatment) and was also associated with the resolution of facial pain.[63] Briefly, this study demonstrates that minocycline can be highly beneficial in producing antidepressant effects when used in conjunction with a serotonergic antidepressant to enhance its effects. However, this information contradicts the synergy study conducted with desipramine, a noradrenergic antidepressant, rather than fluoxetine, a serotonergic antidepressant agent used in the forced swim test animal model.[60]

Tetracycline use in the treatment of schizophrenia

Schizophrenia is a psychiatric disorder characterized by delusions, hallucinations, disorganized speech, decreased motivation, and cognitive impairments. Affecting approximately 1% of the world population, this illness ranks among the top 10 leading causes of global disability.[64]

The results of studies so far suggest that neuroinflammation affecting microglial cells plays a significant role in the etiology of schizophrenia, and appropriately controlling microglial activation holds promise in the therapeutic strategy for schizophrenia.[65,66]

The second-generation tetracycline antibiotic minocycline, which inhibits microglial activation, has shown neuroprotective effects in many different neurodegenerative diseases. Mechanisms overlapping with neuropathological pathways are being investigated for minocycline's role as an adjunctive treatment in schizophrenia and its potential use in treatment for its ability to improve negative symptoms of the disease.[67]

Until now, the effective treatment of schizophrenia has been limited to antipsychotic medications with antidopaminergic effects, which regulate dysfunctional neurotransmitter systems to alleviate symptoms of the disease.[68] Additionally, while antipsychotic medications are the most effective drug class for positive symptoms, they are not sufficiently effective for negative and cognitive symptoms.[69] In recent years, the results of studies have strengthened the concept of microglial neuroinflammation in etiology. Particularly, the appropriate control of microglial activation holds great promise for the treatment of the disease.[70-73]

Minocycline has a distinct neuroprotective profile independent of its antibacterial properties.[13] Almost all of it is absorbed when taken orally, and it penetrates the brain tissue very well. These properties, along with the beneficial effects observed in animal experiments related to neurological disorders, have prompted scientists to investigate the potential role of the drug in the treatment of schizophrenia.[13,28] Subsequent studies have reported many beneficial effects of minocycline in treatment when used in combination with antipsychotic medications.[30,38,74,75]

Preclinical studies

Preclinical studies indicate the potential neurotherapeutic effects of minocycline in mental illnesses.[28-31] Another reported finding is that similar to its benefits in dopaminergic terminal neurotoxicity, minocycline can also induce behavioral changes related to hallucinations and delusions.[29]

According to Hashimoto's animal experiments with monkeys, minocycline protects the brain from methamphetamine-induced neurotoxicity in the monkey brain.[32] In Levkovitz et al.'s[30] study, the effects of minocycline and haloperidol on schizophrenia were compared in animal experiments. Rats were administered minocycline at a dose of 35 mg/kg/day for three days, followed by injection of MK-801 (N-methyl-D-aspartate receptor agonist), and evaluated using behavioral tests. The findings showed that MK-801 caused cognitive visual-spatial memory impairments and significantly disrupted sensorimotor gating, similar to schizophrenia, and minocycline reversed these cognitive impairments like haloperidol. Similarly, Zhang et al.[33] suggested that minocycline might have a potential therapeutic role in schizophrenia by reducing behavioral abnormalities like acute hyperactivity in mice following dizocilpine administration.

Clinical studies

Interestingly, some studies have shown that minocycline has significant effects on negative symptoms and contributes to impaired cognitive function and weakened vocational and social skills in schizophrenia patients. Case reports demonstrate the effective role of minocycline when added to antipsychotic medications for treating negative symptoms of schizophrenia.[36,37]

According to a randomized, double-blind, placebo-controlled clinical trial, the addition of minocycline (200 mg/day) to the treatment of patients with early psychosis for one year was reported to reduce negative symptoms of schizophrenia without detectable adverse effects on cognition.[38]

Sofuoğlu et al.[76] demonstrated in their study that minocycline improved subjective reward effects in dextroamphetamine-dependent individuals.

Tetracyclines in Autism

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by symptoms such as difficulties in socialization and highly repetitive patterns of behavior.[77] The prevalence of the disorder, which is observed in 1% of the world's population, is rapidly increasing day by day.[78,79] Although many environmental

factors such as socioeconomic status, race, and culture influence the etiology of the disease, genetic factors are among the most important factors in the etiology of ASD.[80,81] Autism is more prevalent in males than in females, and comorbid conditions are also more frequently observed in males (70% concurrent conditions).[82] In addition, large-effect rare mutations or numerous small-effect mutations also play a significant role in the etiology of the disease.[77]

Individuals with ASD have atypical social perceptions, executive dysfunctions, and unusual cognitive behaviors, which are believed to be associated with abnormal neuronal development.[83] Due to these behaviors, individuals with ASD can be easily distinguished within social communities. Although ASD can be diagnosed easily in the preschool years, early diagnosis and intervention are extremely important for the patient's quality of life. Evaluations should be multidisciplinary and transformative in light of the Diagnostic and Statistical Manual of Mental Disorders-5 diagnostic criteria.[84] Following an early diagnosis, interventions aimed at treatment goals can enhance social communication and reduce aggressive behaviors. Although therapeutic agents prescribed after diagnosis can alleviate comorbid symptoms, being in a supportive environment that respects the differences of individuals with ASD and makes them feel safe is also extremely valuable for their quality of life.[85]

Studies conducted with minocycline have primarily focused on Fragile X syndrome, an X-chromosome-linked disorder, which is one of the most common causes of ASD.[86,87] In Fragile X syndrome, mutations occurring in the Fragile X mental retardation 1 (FMR1) gene on the X chromosome result in cognitive dysfunction, changes in visual and auditory capabilities, hyperactivity, communication problems, and ASD in affected individuals.[88,89] In an open-label study, it has been demonstrated that minocycline significantly increases sensitivity in Fragile X syndrome patients, as measured by the Aberrant Behavior Checklist-Community (ABC-C) sensitivity subscale.[90] In another study, it was observed that dendritic maturation increased with minocycline, and the performance of FMR1 gene-silenced mice decreased.[86] Based on clinical trials conducted with individuals with Fragile X syndrome, minocycline has been observed to be a safe therapeutic agent for improving autistic behaviors.[91-93]

After administering minocycline (1.4 mg/kg/day) for six months to 11 autistic children, along with vitamin B6 (0.6 mg/kg) treatment to reduce vestibular side effects, the experiment was completed with 10 children. Among them, while the severity scores remained stable on the Clinical Global Impression (CGI) scale for eight children, only minimal improvement was observed in the severity score of CGI for two children, and clinical improvements remained negligible. The composite scores of the Vineland Adaptive Behavior Scale showed very little change, and several side effects were reported by parents. While a significant decrease in cytokine release was observed only in interleukin-8, there was no increase in colony-stimulating factor.[94]

In a randomized, double-blind, placebo-controlled study conducted over 10 weeks with 50 children with ASD, the administration of minocycline in addition to the most prescribed atypical antipsychotic, risperidone, resulted in a significant decrease in sensitivity, hyperactivity, and irritability subscales of the ABC-C. Based on these results, minocycline has been reported as an effective therapeutic target in the treatment of ASD.[95]

In a study conducted using mouse models of autism, it was observed that adding minocycline to the drinking water from the 17th day of pregnancy to the 21st day after birth resulted in improvement in microglial activation and anxiety behaviors.[96] Another study conducted with a rat model of autism induced by valproic acid also showed that minocycline use improved autistic behaviors.[92]

After 10 days of minocycline treatment (oral gavage, 30 mg/kg per day) given to adult mice with silenced FMR1 gene, it was observed that the treatment increased gamma-band phase-locking in response to auditory stimuli and decreased gamma power in resting state electroencephalogram.[93]

In conclusion, in light of the studies conducted, especially with minocycline, this broad-spectrum

antibiotic group, which is used in many diseases besides its primary therapeutic target of bacterial diseases, is now seen as promising for psychiatric disorders as well. In addition to its known neuroprotective and anti-inflammatory effects, minocycline, which has been shown to have antidepressant effects *in vivo* and *in vitro* animal experiments, can be suggested to enhance the effects of noradrenergic antidepressant drugs in the treatment of MDD. For ASD, more extensive studies across age groups are needed to demonstrate the effects of the drug in different age groups. Furthermore, research should be intensified on the positive effects of the combination of risperidone and minocycline. The use of minocycline in the treatment of schizophrenia is recommended by scientists based on studies and meta-analyses. Clinical trials do not provide definitive information due to high dropout rates, but preclinical animal experiments provide promising results for the use of tetracycline group antibiotics as a new alternative in the treatment of psychiatric disorders.

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