Minocycline as a potential treatment in the early stages of schizophrenia: a translational approach

Cristiano Chaves1,2, Antônio W. Zuardi1,2, Jaime E. C. Hallak1,2

1Department of Neuroscience and Behavior, Division of Psychiatry, Ribeirão Preto Medical School, University of São Paulo, Brazil
2National Science and Technology Institute for Translational Medicine (INCT-TM, Brazil)

Correspondence: Cristiano Chaves
E-mail: crischaves01@yahoo.com.br
Received: January 31, 2015
Published online: March 01, 2015

Despite the wide variety of currently available antipsychotics, their efficacy is limited only to the improvement in positive symptoms. In addition, longitudinal cohort studies of patients with first episode psychosis show worsening in different psychopathological domains and progressive loss of brain gray matter volumes. Beyond changes in neurotransmitter systems, most notably in the dopaminergic and glutamatergic systems, there is growing evidence of an immune and inflammatory component in the pathophysiology of schizophrenia, indicating an increase of cytokines (e.g., interleukin 1β, interleukin 6 and TNF-α) and microglial activation in patients with this disorder. Growing evidence indicates that minocycline may enhance the antipsychotic treatment and may prevent some brain changes observed in the early stages of schizophrenia. Minocycline is a tetracycline with broad anti-inflammatory activity and with evidence of neuroprotective action. However, the precise effects of minocycline in the CNS are still elusive. In the other hand, several points can be addressed, providing rational hypotheses for understanding how minocycline can improve symptoms and modulate brain structure and function in schizophrenia. In this article, relevant data about minocycline action are reviewed, linking bench to bedside. The potent inhibition of brain microglia activation and the broad anti-inflammatory effects of minocycline, in addition to indirect modulation of dopaminergic and glutamatergic systems, may mediate the effects of minocycline in schizophrenia. Further longitudinal studies with larger samples and measurement of inflammatory markers are needed to evaluate the potential of minocycline as adjunctive treatment in schizophrenia.

To cite this article: Cristiano Chaves, et al. Minocycline as a potential treatment in the early stages of schizophrenia: a translational approach. Ther Targets Neurol Dis 2015; 2: e580. doi: 10.14800/ttnd.580.

Minocycline is a semisynthetic tetracycline introduced in 1967, with efficacy against both gram-positive and gram-negative bacteria [1]. In addition to its antibiotic effect, both basic and clinical studies have shown that minocycline has broad anti-inflammatory properties [1,2], mainly through modulation of microglial activity and the subsequent release of pro-inflammatory cytokines, such as IL1β, IL6 and TNF-α [3-5]. Due to its anti-inflammatory effects, it is also used for the treatment of rheumatoid arthritis, cutaneous sarcoidosis, common acne, perioral dermatitis, and difficult-to-control asthma [2,6]. In addition, minocycline is a highly lipophilic molecule, easily crossing the blood-brain barrier [2,6]. Translational scientific data indicate that this drug may have neuroprotective effects in several neurodegenerative diseases, including cerebral ischemia, traumatic brain injury, Alzheimer's disease and Huntington's disease [2,6].

Increasing evidence points out that minocycline can be an adjuvant treatment of schizophrenia. Miyaoaka et al. (2007 and 2008) [7,8] published a case report and an open trial of minocycline add-on treatment, indicating global improvement in patients with schizophrenia. Additionally,
two case reports also showed benefits of minocycline in addition to clozapine in treatment-resistant schizophrenia [9, 10]. Over recent years, five randomized double-blind placebo controlled trials [11-15] have evaluated the efficacy of minocycline add-on treatment, observing improvement of schizophrenia symptoms, particularly the negative symptoms.

A recent study published by our group evaluated the effects of minocycline on brain morphometry and cerebral perfusion in recent-onset schizophrenia after 12 months of a randomized double-blind, placebo-controlled clinical trial of minocycline adjuvant therapy [16]. In this study, minocycline add-on treatment significantly improved positive and negative symptoms in comparison with placebo. In addition, the analysis of MRI scans indicated that patients in the placebo group had significant lower gray matter volumes in the midposterior cingulate cortex and in the precentral gyrus. [99m-Tc]-ECD SPECT brain images indicated a decreased ECD uptake in the minocycline group in frontotemporal areas. However, despite the abovementioned findings, the precise mechanisms of minocycline’s action in the SNC are still elusive. In the other hand, several points can be addressed, providing rational hypotheses for understanding how minocycline can improve symptoms and modulate brain structure and function in schizophrenia.

It is noteworthy that minocycline does not exert significant direct effects on different neuroreceptors, including monoaminergic and NMDA receptors [17]. However, minocycline can regulate several processes associated with neural plasticity. This drug affects the downstream signaling of NMDA receptors and has opposing effects on p38 MAPK activation and PO3/Akt kinase pathway suppression. These signaling pathways are substrates for the neurotoxic effects of glutamate [18]. In addition, minocycline treatment reverses or prevents the effects of NMDA antagonists in animal models [19-21]. These effects are in accordance with the NMDA hypofunction hypothesis of schizophrenia, since NMDA hypofunction might be related to an excessive release of glutamate at non-NMDA receptors, underlying clinical deterioration and neurodegeneration in schizophrenia [22-24]. Moreover, Moghaddam et al. (2003) [23] suggested that NMDA receptor dysfunction in schizophrenia is possibly due to changes in downstream signaling pathways of NMDA receptors, rather than gross alterations in the NMDA receptor levels.

Another relevant point is that minocycline has broad anti-inflammatory effects, reduces microglia activation and can inhibit a wide range of cytokines [2, 6]. These effects may corroborate the action of minocycline in the CNS, since increasing evidence points out that neuroinflammation is involved in neurodevelopment and in neural plasticity, playing an important role in the development and progression of schizophrenia [25]. Furthermore, growing evidence indicates that patients in first episode psychosis show increased levels of cytokines [26, 27] even in antipsychotic-naïve patients [28]. In addition, there may be interactions between cytokines and dopaminergic function [29]. In accordance, IL-6 administration in mice led to behavioral and locomotor hyperactivity, which are similar to the changes observed in animal models of psychosis by administering dopamine agonists [30]. Another study also indicated that repeated administration of IL-6 in mice produced a sensitization to the effects of amphetamine-induced locomotor hyperactivity [31], reinforcing the hypothesis that there is an interaction between IL-6 and the dopaminergic system. In addition, the minocycline pre-treatment of mice significantly reduced the increase of extracellular dopamine in the striatum after repeated administration of methamphetamine [32]. Pre-treatment with minocycline also significantly reduced the dopamine increase in the striatum as well as in the frontal cortex of mice that received the NMDA-antagonist dizocilpine [21]. Moreover, neuroinflammation can modulate glutamatergic function through the cytokine-induced activation of the kynurenine pathway of tryptophan metabolism, since elevated levels of kynurenic acid can inhibit NMDA receptors [33-35].

A major finding in recent schizophrenia genetics research is that immune-related genes of the Major Histocompatibility Complex (MHC) are associated with schizophrenia [25, 36-41]. Further evidence indicates significant correlations between gene variants in the MHC region and cerebral ventricular size in schizophrenia [42]. In addition, Fillman et al. (2012) [43] observed increased inflammatory markers (including different cytokines and inflammatory RNA expression) in the dorsolateral prefrontal cortex of schizophrenia patients. Neuroinflammation can also impact neurogenesis and thereby neural plasticity in schizophrenia [35]. Accordingly, Das et al. (2011) [44] observed that minocycline can inhibit neuroinflammation and restore neurogenesis in a murine model of Japanese encephalitis. Moreover, Rueger et al. (2012) [45] suggested a positive effect of minocycline in neurogenesis independently of neuroinflammation.

Furthermore, the potent inhibition of microglia activation by minocycline may play a key role in the effects of this drug in schizophrenia. A study by van Berckel et al. (2008) [46] evaluated microglia activation in recent-onset schizophrenia through a quantitative (R)-[11C] PK11195 PET study. The authors observed increased microglia activation in patients with recent-onset schizophrenia (within 5 years of illness onset), suggesting that neuronal injury occurs and may be...
implicated in the reduction of gray matter volume in the initial phase of schizophrenia. This finding was replicated by Doorduin et al. (2009) [47], indicating that microglia activation is a potential target for preventing gray matter reduction and clinical deterioration in schizophrenia. Thus, the potent inhibition of microglia activation by minocycline may have a protective effect against gray matter volume reduction in recent-onset schizophrenia. In accordance, a previous (R)-[11C] PK11195 PET neuroimaging study of microglial activation in zymosan-treated rats observed that minocycline treatment reduced zymosan-induced microglial activation in brain by 46% [48].

In view of the growing evidence on the importance of neuroinflammation in schizophrenia and the broad anti-inflammatory effects of minocycline, further studies that directly assess the effects of this medication in inflammatory markers will be important for better clarification. For example, blood levels of cytokines can be measured and brain microglia activation can be assessed by (R)-[11C] PK11195 PET scans. Moreover, the neuroinflammatory process may play a larger role in a subset of patients. Consequently, a subgroup with evidence of inflammation may respond better to minocycline treatment in comparison with a subgroup without an increase in inflammatory markers.

References


33. Anderson G, Maes M. Schizophrenia: Linking prenatal infection to cytokines, the tryptophan catabolite (TRYCAT) pathway, NMDA receptor hypofunction, neurodevelopment and neuroprogression. Prog Neuropsychopharmacol Biol Psychiatry 2012.


36. Irish Schizophrenia Genomics C, the Wellcome Trust Case Control C. Genome-wide association study implicates HLA-C*01:02 as a risk factor at the major histocompatibility complex locus in schizophrenia. Biol Psychiatry 2012; 72:620-628.


