Research Paper

Minocycline Improves Memory by Enhancing Hippocampal Synaptic Plasticity and Restoring Antioxidant Enzyme Activity in a Rat Model of Cerebral Ischemia-Reperfusion

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Article info:
Received: 25 Jan 2021
First Revision: 23 Feb 2021
Accepted: 26 Dec 2021
Available Online: 01 Mar 2022

ABSTRACT

Introduction: Oxidative stress plays a crucial role in the impairment of synaptic plasticity following cerebral ischemia, ultimately resulting in memory dysfunction. Hence, the applying antioxidant agents could be beneficial in managing memory deficits after brain ischemia. Minocycline is a tetracycline antibiotic with antioxidant effect. The main objective of this work was to assess the minocycline effect on the impairment of synaptic plasticity and memory after cerebral ischemia-reperfusion in rats.

Methods: Transient occlusion of common carotid arteries was used to induce ischemia-reperfusion injury in rats. Single or multiple (once daily for 7 days) dose(s) of minocycline were administered before (pretreatment) or after (treatment) brain ischemia. Seven days after ischemia-reperfusion, passive avoidance performance, long-term hippocampal potentiation, and the activity of antioxidant enzymes were assessed.

Results: The passive avoidance test showed that minocycline (20 and 40 mg/kg) significantly increased step-through latency while reducing the duration of staying in a dark chamber in the treatment (but not pretreatment) group. In electrophysiological experiments, the rats treated (but not pretreated) with minocycline (40 mg/kg) showed a significant increase in the amplitude of the field excitatory postsynaptic potentials in the dentate gyrus area of the hippocampus. The treatment (but not pretreatment) with minocycline (20 and 40 mg/kg) resulted in a significant increase in the activity of catalase, glutathione peroxidase, and superoxide dismutase in the hippocampus.

Conclusion: It was determined that minocycline attenuates memory dysfunction after cerebral ischemia-reperfusion in rats by improving hippocampal synaptic plasticity and restoring antioxidant enzyme activity.

Keywords:
Brain ischemia, Memory, Minocycline, Synaptic plasticity, Antioxidant enzymes

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Citation
Parvardeh, S., Sheikholeslami, M.A., Ghafghazi, S., Pouriran, R., & Mortazavi, S. E. Minocycline Improves Memory by Enhancing Hippocampal Synaptic Plasticity and Restoring Antioxidant Enzyme Activity in a Rat Model of Cerebral Ischemia-Reperfusion. Basic and Clinical Neuroscience, 13(2), 225-236. http://dx.doi.org/10.32598/bcn.12.6.2062.1

http://dx.doi.org/10.32598/bcn.12.6.2062.1
1. Introduction

Learning and memory disorder is one of the most common outcomes of cerebral ischemia in patients who suffer from stroke, vascular dementia, and cardiac arrest. The administration of fibrinolytic agents is the only approved medication to manage the acute phase of ischemic stroke. However, there is no effective therapeutic approach to attenuate neuronal damage in a long-term period which underlies sensorimotor and cognitive disorders, particularly memory impairment (Zhao & Willing, 2018).

The hippocampus is one of the most important areas of the brain which implicates the formation of memory. It is well established that the formation of long-term potentiation (LTP) is a fundamental process for memory acquisition in hippocampal formations (Lynch, 2004). Nonetheless, the physiological induction of LTP could remarkably get impaired under pathological conditions, particularly oxidative stress. In this regard, it has been demonstrated that the increase in the free radical generation, often concomitant with a reduction in antioxidant enzyme capacity, adversely affects the induction of LTP (Knapp & Klann, 2002). Accordingly, in cerebral ischemia, in which excessive amounts of free radicals are produced (Warner, Sheng, & Batinić-Haberle, 2004), LTP formation in the hippocampus is disrupted and ultimately leads to memory impairment (Xu et al., 2010).

Studies have shown that hippocampal neurons are highly susceptible to oxidative stress and are damaged during ischemia-reperfusion (Baron, Yamauchi, Fujioka, & Endres, 2014). Oxidative stress during cerebral ischemia causes a noticeable generation of reactive oxygen species (ROS), such as peroxide, superoxide, and radical hydroxyl. Oxidative stress occurs when ROS generation predominates over the antioxidant defense system. However, intracellular antioxidant enzymes, including glutathione peroxidase, catalase, and superoxide dismutase, are the most important antioxidant mechanisms in protecting cells against the destructive effects of ROS (Manzanero, Santro, & Arumugam, 2013). Considering the massive production of ROS during cerebral ischemia (Warner, Sheng, & Batinić-Haberle, 2004) and the impairment of synaptic plasticity due to oxidative stress (Serrano & Klann, 2004; Kishida & Klann, 2007), it could be anticipated that the utilization of antioxidant agents results in the attenuation of neuronal damage and...
memory disorders following cerebral ischemia (Karimi, Salehi, Komaki, Sarabi, Zarei, & Shahidi 2013; Chen, Yin, Hwang, Tang, & Yang, 2012).

Minocycline is a tetracycline molecule with anti-apoptotic, anti-inflammatory, and antioxidant effects in addition to its antibiotic effect. Besides, minocycline can act as a free-radical scavenger and efficiently remove several reactive radical molecules (Chen et al., 2012). Moreover, it has been recently reported that pretreatment or treatment with minocycline suppresses the process of lipid peroxidation and neuroinflammation in the brain and attenuates neuronal injury during global ischemia in rat brain (Naderi, Sabetkasaei, Parvardeh, & Moini Zanjani, 2017). Although several mechanisms of action have been reported to describe the protective effect of minocycline against ischemic conditions in the brain (Naderi, Sabetkasaei, Parvardeh, & Zanjani, 2017; Sheng et al., 2018), the neuroprotective effect of this antibiotic has not yet been evaluated on hippocampal synaptic plasticity and enzymatic antioxidant activity following cerebral ischemia. Considering the fundamental role of synaptic plasticity in memory formation (Lynch, 2004) and the enzymatic antioxidant defense system in the restoration of neuronal function (Lalkovičová, & Danielisová, 2016), we hypothesized that the mechanisms mentioned above might underlie the attenuating effect of minocycline on memory impairment during cerebral ischemia.

This study aimed to clarify whether minocycline could enhance memory function through improving synaptic plasticity and restoration of antioxidant enzyme activity in the hippocampus after neuronal injury induced by cerebral ischemia-reperfusion in rats.

2. Materials and Methods

Study animals

In this study, male Wistar rats weighing 200 to 250 g were used. The rats were kept in a standard temperature, light, and humidity conditions and had free access to tap water and food. All experiments and procedures were carried out under the supervision and approval of the Ethics Committee of the School of Medicine, Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.SM.REC.1394.6).

Induction of cerebral ischemia

The cerebral ischemic injury was induced by bilateral occlusion of common carotid arteries in rats, as described previously (Naderi, Parvardeh, Zanjani, & Sabetkasaei, 2018). For the induction of cerebral ischemia, common carotid arteries on both sides of the vertebral column in the neck were exposed in rats under anesthesia induced by chloral hydrate (300 mg/kg, intraperitoneally [IP], Sigma-Aldrich). Then, the blood flow through the common carotid arteries was blocked using micro bulldog clamps. After 20 min, the micro clamps were removed, and the blood flow to the brain was restored.

Study design

The rats were divided into four main groups (n=6). In the treatment group, minocycline (Sigma-Aldrich) was injected IP to the rats immediately after reperfusion. In this group, minocycline was administered at doses of 10, 20, and 40 mg/kg daily for 7 days. In the pretreatment group, a single dose of minocycline (10, 20, and 40 mg/kg, IP) was administered to the rats 60 min before the obstruction of common carotid arteries. The rats in the control group received normal saline. In the sham-operated group, the animals underwent surgery, and their common carotid arteries were exposed but not occluded. Minocycline dosage was selected based on previous studies (Naderi et al., 2017).

Passive avoidance test

Seven days after cerebral ischemic injury, a passive avoidance test was conducted to assess memory performance in rats. The procedure was executed using a shuttle box according to the method described by Arabian et al. (2017). Primarily, the rats were placed in the shuttle box to habituate to the surrounding. Thirty minutes after the habituation trial, the rats were placed in the light chamber of the shuttle box. After 5 seconds, the guillotine door between the light and dark compartments was opened, and the animal was allowed to enter the dark chamber. Immediately after the entrance of the rats to the dark compartment, the door between the two chambers was closed, and an electric shock (1 mA for 2 s) was applied. Twenty seconds later, the rats were transferred to their cages. After 24 hours, a retention trial was performed in which the rats were placed once more in the light compartment, and after 5 seconds, the door between the two chambers was opened. The latency to step through the dark chamber and the time duration in which animals remained in the dark compartment were recorded. At this stage, no shock was given to the animal when it entered the dark chamber. The cut-off limit to enter the dark chamber was considered 300 s in the retention trial.
Recording of LTP in the hippocampus

One day after the passive avoidance test, LTP recording was performed to evaluate the synaptic plasticity in the hippocampus. The animals were first anesthetized by urethane (Merck) with the dosage of 1.5 g/kg, IP, and then placed in a stereotactic device. Two small holes of 1 mm diameter were created in the animal’s skull to enter electrodes into the brain. The stimulating electrode was placed in the hippocampal perforant pathway (PP) zone in accordance with the atlas of the rat’s brain (AP: -8.1 mm, ML: +4.3 mm, and DV: 3.2 mm). The recording electrode was put in the granular cell layer of the dentate gyrus (DG) area in the hippocampus (AP: -3.8 mm, ML: +2.3 mm, and DV: 2.7-3.2 mm) (Paxinos & Watson, 2004). The electrodes were made of Teflon-coated stainless steel 125 μm in diameter (A-M Systems, USA). A two-channel electro module amplifier (R12, Science-Beam, Co., Tehran, Iran) was used to record field excitatory postsynaptic potentials (fEPSPs). The recorded signals were amplified (×1000) and digitized at 1 kHz. A bandwidth filter was set at 1-3000 Hz prior to digitization. The acquisition of biosignal and data analysis was carried out using eTrace software (ScienceBeam, Co., Tehran, Iran). The input-output curve was generated by applying a series of stimulating currents from 100 to 900 mA to obtain the maximum amplitude of field excitatory postsynaptic potentials (fEPSP). Then, the test stimulus with 0.033 Hz frequency and a stimulation intensity that aroused an fEPSP with an amplitude of 40% of the maximum response was applied in the PP area. The recording of fEPSP in the DG area was performed for 30 minutes as the baseline. To induce LTP, a high frequency (100 Hz) stimulation consisting of 10 bursts, each containing 4 shocks at intervals of 200 ms, was applied in the PP area. Immediately after tetanic stimulation, electrical stimulation similar to pre-tetanic stimulation was applied, and fEPSPs were recorded for two hours. The changes in the amplitude of fEPSPs after tetanic stimulation were compared to those of baseline (Moghim, Parvardeh, Zanjani, & Ghaefghazi, 2016).

Measurement of antioxidant enzymes in the hippocampus

To explore the effect of minocycline on oxidative damage in the brain, the activity of antioxidant enzymes, including SOD (superoxide dismutase), catalase, and GPxs (glutathione peroxidase), was determined in the hippocampus. By the end of electrophysiological procedures, the rats were sacrificed under anesthesia, and the whole hippocampus was dissected out of the brain. The activity of antioxidant enzymes in the hippocampal tissue was determined using enzyme activity assay kits (ZellBio GmbH, Ulm, Germany). According to the manufacturer’s instructions, the amount of hydrogen peroxide (H2O2) in 20 μL of samples was measured using a spectrophotometer at 240 nm. GPx activity was evaluated spectrophotometrically at 412 nm based on reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidation to NADP+. SOD activity was determined based on the dismutation of supercarboxide radicals produced by hypoxanthine and xanthine oxidase, which was detected by spectrophotometer at 420 nm (Khoshnazar, Bigdeli, Parvardeh, & Pouriran, 2019).

Statistical analysis

The obtained data were reported as Mean±SEM in each group. One-way ANOVA followed by a post hoc Tukey test was used to analyze the difference in means between groups. If the P value was obtained less than 0.05, the difference between groups was considered significant.

3. Results

Effect of minocycline on passive avoidance performance

Induction of cerebral ischemia-reperfusion in rats caused a significant reduction in step-through latency in the control group while prolonging the duration of remaining animals in the dark chamber (P<0.001). In contrast, the treatment of rats with minocycline (20 and 40 mg/kg) once daily for 7 days resulted in a significant increase in the latency of entrance to the dark chamber (P<0.05 and P<0.01, respectively). Furthermore, treatment of rats with minocycline (20 and 40 mg/kg) significantly shortened the residence time of rats in the dark chamber (P<0.01 and P<0.001, respectively, Figure 1A and 1B). In the pretreatment group, the administration of maximum dosage of minocycline (40 mg/kg, single dose) could significantly prolong the latency of step-through (P<0.05, Figure 1C) and reduce the duration of time spent in the dark chamber (P<0.01; Figure 1D). The mean prolongation of step-through latency in the rats treated with minocycline (40 mg/kg) was more than the time of the pretreatment group (143.3±16.8 vs 107.5±8.6; P=0.3253). Besides, the mean duration of remaining in the dark compartment in the rats treated with minocycline (40 mg/kg) was lower than the time of the pretreated group (130.8±10.2 vs 155.2±12.1; P=0.4636).
Effect of minocycline on synaptic plasticity in the hippocampus

In the electrophysiological recording of LTP in the sham group, tetanic stimulation of nerve fibers in the PP elicited a significant increase in the amplitude of fEPSPs in the DG region of the hippocampus. In contrast, no significant difference was obtained by comparing the amplitude of fEPSPs before and after tetanic stimulation in the control rats (Figures 2 and 3). In the minocycline-treated rats (40 mg/kg, once daily for 7 days), tetanic stimulation of neurons successfully induced LTP in the hippocampus (Figure 2). As shown in Figure 3, parts A and B, a significant increase was observed in the amplitude of fEPSPs which were recorded every 30 seconds during the first 5 min after tetanic stimulation (P<0.01, compared to baseline). A remarkable increase in the amplitude of fEPSPs was also obtained at the time intervals of 25 to 30 min (P<0.01), 55 to 60 min (P<0.05), and 115 to 120 min (P<0.01) after tetanic stimulation in the treatment group (Figure 3A and 3B). Furthermore, statistical analysis revealed a significant difference in the amplitude of fEPSPs between the minocycline-treated rats and control groups at the time intervals of 0 to 5 min, 25 to 30 min, and 55 to 60 min following high-frequency stimulation (P<0.05; Figure 3B). The administration of lower doses of minocycline (10 and 20 mg/kg) once daily for 7 days following cerebral ischemia-reperfusion did not
induce LTP in the hippocampus (data not shown). On the other hand, in the minocycline-pretreated group, tetanic stimulation did not succeed in raising the amplitude of fEPSPs (Figures 2 and 3).

**Effect of minocycline on the activity of antioxidant enzymes in the hippocampus**

The measurement of antioxidant enzyme activity revealed that the induction of cerebral ischemia-reperfusion in rats caused a significant reduction in the activity of the antioxidant enzyme, including catalase, GPx, and SOD in the hippocampus (P<0.001 in Figure 4, parts A–F, except for 4D in which P<0.01; all control groups were compared to the sham group). In contrast, a significant enhancement in the activity of catalase (P<0.01, Figure 4A), GPx (P<0.01, Figure 4B), and SOD (P<0.05, Figure 4C) was observed in the animals which were treated by minocycline at a dose of 20 mg/kg. Besides, treatment with minocycline at the maximum dose of 40 mg/kg resulted in a significant increase in the activity of catalase (P<0.001, Figure 4A), GPx (P<0.001, Figure 4B), and SOD (P<0.01, Figure 4C). Treatment of rats with a lower dose of minocycline (10 mg/kg) did not restore the function of antioxidant enzymes in the hippocampus (Figure 4, parts A–C). Moreover, neither one of the single doses of minocycline, when administered prior to the induction of ischemia, resulted in the enhancement of antioxidant enzyme activity in the hippocampus (Figure 4, parts D–F).

**4. Discussion**

In this study, global cerebral ischemia-reperfusion was induced in rats through bilateral occlusion of common carotid arteries. By this method, the memory function in ischemic rats was successfully impaired, evident in both the behavioral and electrophysiological experiments. The attained results indicated, for the first time, that treatment of rats with minocycline can enhance synaptic plasticity and restore the antioxidant enzyme function in the hippocampus.

The hippocampal formation, which is believed to function as the fundamental structure in the brain for memory formation (Lynch, 2004), is highly vulnerable to brain ischemia and oxidative stress (Baron, Yamauchi, Fujio-ka, & Endres, 2014). Accordingly, oxidative stress plays a pivotal role in causing neuronal damage in the hippocampus.

![Figure 2. Effect of Minocycline on Long-Term potentiation in the Hippocampus](image)
campus and resulting in memory impairment following cerebral ischemia-reperfusion (Manzanero et al., 2013).

Previous studies have shown the excessive amounts of ROS generated during cerebral ischemia along with a remarkable decrease in antioxidant enzyme activity (Chen et al., 2011). In the present study, the induction of ischemia-reperfusion injury in the brain significantly reduced the activity of antioxidant enzymes in the hippocampus, indicating the progression of oxidative stress in the neural tissue. Evidence indicates that oxidative stress-induced neuronal injury in the hippocampus causes apparent impairment in memory performance in behavioral tests, including the Morris water maze (Moghimi et al., 2016) and passive avoidance test (Arajian et al., 2017). Consistently, the results obtained from the present study showed a remarkable impairment in passive avoidance task in the rats subjected to cerebral ischemia-reperfusion injury. This finding suggests that reducing blood flow to the brain and consequent oxidative stress, particularly in the hippocampus, is the primary causative agent of memory deficit following cerebral ischemic events. The reason is that in the sham-operated animals where the induction of oxidative stress is unsuspected, memory impairment was not observed in the passive avoidance performance.

The present study showed for the first time that either pretreatment or treatment of rats with minocycline apparently improved the performance of animals in the passive avoidance test. In this regard, our findings showed that during the memory retention task, the minocycline-treated rats presented a more desirable performance than that of pretreated animals. It might be related to the fact that the pretreated group received single doses of minocy-
Minocycline before the induction of cerebral ischemia, and thus the rats did not receive enough doses of the drug. Accordingly, it is suggested that in future studies, multiple doses of minocycline rather than a single dose are administered for a long enough period before cerebral ischemia.

The results of behavioral tests indicated that the attenuating effect of minocycline on memory impairment was dose-dependent. In other words, a significant improvement in the memory function was obtained in rats that were under treatment with a maximum dosage of minocycline. A similar dose-dependent effect was also observed in minocycline-treated rats in biochemical assays of antioxidant enzyme activity in the hippocampus.

The passive avoidance test is one of the major methods used to investigate the learning and memory mechanisms. This test is widely used to identify chemicals that modify cognitive function. There is evidence suggesting that the function of the hippocampus plays a fundamental role in passive avoidance performance (Arabian et al., 2017). Indeed, this is why the induction of ischemia in the hippocampus disrupts passive avoidance performance. It has been shown that brain ischemia-reperfusion results in memory impairment through the disruption of synaptic plasticity (Xu et al., 2010; Moghimi et al., 2016).

To track the pathological changes in the structure and function of synapses, the properties of baseline synaptic neurotransmission and LTP are evaluated using electrophysiological methods (Nicoll & Schmitz, 2005). There is evidence showing that the formation of the LTP phenomenon in rat hippocampus is impeded after transient cerebral ischemia, which is induced by the occlusion of common carotid arteries (Xu et al., 2010; Moghimi et al., 2016). In line with this evidence, the results obtained from the present study showed that in rats that were subjected to cerebral ischemic-reperfusion injury, tetanic stimulation of nerve fibers in the PP area did not induce LTP in the DG region of the hippocampus. In contrast, the treatment with minocycline could restore the formation of LTP in the hippocampus, which persisted.
for two hours. These findings reinforce the improving effect of minocycline on memory performance which was obtained from the passive avoidance test. This result indicates that the attenuating effect of minocycline on memory dysfunction following cerebral ischemia is at least partly due to facilitating LTP formation in the hippocampus. The enhancement of hippocampal LTP by minocycline was also reported by Hoshino, Hayakawa, and Morimoto (2017) in a mouse model of septic shock. Similar studies have shown that minocycline improves LTP by facilitating neuroplasticity and raising the expression of synapse-associated signaling proteins in mice (Jiang et al., 2015). It should be noted that in the present work, minocycline did not affect the properties of baseline synaptic neurotransmission, such as fEPSP amplitude in the DG area of the hippocampus. These findings are consistent with the findings of recent work by Song, Liu, and Zhuo (2015), in which they reported the lack of minocycline effect on baseline recording from neurons in the anterior cingulate cortex. In contrast to the results obtained from minocycline-treated rats, pretreatment of animals with a single dose of minocycline could not facilitate the synaptic neurotransmission in the hippocampus.

In the process of neuronal damage after ischemia-reperfusion, several mechanisms are involved: the most important are oxidative stress and apoptosis (Chen et al., 2011; Manzanero et al., 2013). Evidence suggests that the production of free oxygen radicals after cerebral ischemia results in neuronal damage in the hippocampus, consequently leading to the impairment of learning and memory (Chen et al., 2011). On the other hand, the pivotal role of antioxidant enzymes, including catalase, GPx, and SOD, in protecting neural cells against oxidative stress has been established (Lalkovičová & Danielisová, 2016). Several studies have shown that during brain ischemia, the function of these enzymes is remarkably disrupted and progressively results in neuronal damage and death (Warner et al., 2004; Lalkovičová & Danielisová, 2016). Consistently, the results obtained from the present work showed a considerable reduction in the activity of catalase, GPx, and SOD in the hippocampus of rats subjected to cerebral ischemia-reperfusion. Nevertheless, treatment (but not pretreatment) of rats with minocycline significantly elevated the level of antioxidant enzyme activity in the hippocampus.

The findings verify a recent study in which minocycline could restore the activity of GPx and SOD enzymes in rat spinal cord following neuronal damage (Abbaszadeh et al., 2018). Additionally, there is evidence indicating that minocycline exerts neuroprotective effects through attenuating lipid peroxidation (Naderi et al., 2017) as well as reducing ROS formation (Réus et al., 2015; Dai et al., 2017). Furthermore, the direct radical scavenging effect of minocycline due to its phenolic structure has been reported (Kraus, Pasieczny, Lariosa-Willingham, Turner, Jiang, & Trauger, 2005). These reports are similar to the current work and further support the role of antioxidant activity and neuroprotective effects of minocycline. Accordingly, the restoration of antioxidant enzyme activity and enhancement of synaptic plasticity in the hippocampus underlie the boosting effect of minocycline on memory performance following cerebral ischemia-reperfusion injury in rats.

Overall, treatment with minocycline improves memory impairment after cerebral ischemia-reperfusion in rats. The obtained results showed that these effects are mediated through the enhancement of enzymatic antioxidant capacity and facilitating synaptic plasticity in the hippocampal formation indeed.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.SM.REC.1394.6)

Funding

This research was supported by the research project (No. 13/963) funded by the Shahid Beheshti University of Medical Sciences.

Authors' contributions

Conceptualization: Siavash Parvardeh; Methodology, Siavash Parvardeh, Mohammad Abbas Sheikholeslami; Investigation and Data collection: Siavash Parvardeh, Mohammad Abbas Sheikholeslami, and Shiva Ghafghazi; Writing - original draft: Siavash Parvardeh, Seyed Erfan Mortazavi; Writing - review & editing: Siavash Parvardeh, Ramin Pouriran; Funding Acquisition: Siavash Parvardeh; Resources: Siavash Parvardeh, Mohammad Abbas Sheikholeslami; Supervision: Siavash Parvardeh; Funding acquisition: Siavash Parvardeh; Resources: Siavash Parvardeh and Mohammad Abbas Sheikholeslami; Supervision: Siavash Parvardeh.

Conflict of interest

The authors declared no conflict of interest.

Parvardeh, S. et al. (2022). Minocycline and Restoring Synaptic Plasticity. BCN, 13(2), 225-236
Acknowledgments

This work was supported by the Research Department of the School of Medicine, Shahid Beheshti University of Medical Sciences (Grant No.: 13/963).

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